A

ABC Transporters

Definition

Adenosine triphosphate (ATP)-binding cassette (ABC) transporters constitute a superfamily of primary active transport systems that are present from prokaryotes to humans. ABC transporters hydrolyze ATP to transport various substrates across cellular membranes. 48 ABC transporters are present in humans and are classified in seven subfamilies. The human ABCB1 or P-glycoprotein is responsible for multiple drug resistance (MDR) in pumping chemotherapeutic drugs out of the cell. A few ABCC members, also known as MRP (multiple drug resistance associated protein), and ABCG2 or BCRP (breast cancer resistance protein) are like, P-gp, expressed at the BBB where they play a protective role for the brain against xenobiotics.

Abeta

► Amyloid-Beta

Abridged Somatization

► Somatoform and Body Dysmorphic Disorders

Absorption

Definition

Absorption is the process of a drug entering the general circulation.

Cross-References

► Distribution
► Excretion
► Liberation
► Metabolism
► Pharmacokinetics

Abstinence

Definition

The act or practice of refraining from indulging in appetitive behaviors, typically relating to substance use.

Abstinence Syndrome

► Withdrawal Syndromes

Abuse

Definition

Abuse of something is the use of it in a wrong way or for a bad purpose.

Abuse Liability

Synonyms

Abuse potential

Definition

Abuse liability is a term used to denote properties of a drug that would lead to abuse and dependence in humans if it were to become available as a prescription medication or through illicit routes. It is assessed primarily from the ability of a drug to produce positive outcomes in laboratory tests predictive of abuse and dependence in humans. Clinical and epidemiological data are also taken into account when available. Abuse liability also depends upon other factors such as the formulations in which the drug becomes available, its cost, and the ease of synthesizing it.

Cross-References

► Drug Discrimination
► Drug Self-Administration
► Withdrawal Syndromes

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Abuse Liability Evaluation

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Synonyms

Abuse potential

Definition

The abuse liability of a drug or a class of drugs is their propensity to be abused and produce adverse public health consequences. Although much of what constitutes abuse liability of a drug arises from the pharmacological properties of the drug itself (i.e., its ability to produce psychoactive effects associated with risk for abuse and/or addiction, also known as abuse potential), it can also be affected by social and cultural factors and may change from time to time as one drug or class of drug gain popularity in a particular culture. Individual products, even those containing the same generic drug, can differ in abuse liability, which may be determined by the specific formulation, the indication for which it is used and such things as its market penetration.

Current Concepts and State of Knowledge

Background

One of the principal strategies for drug abuse prevention is to place regulatory controls on the manufacture, distribution, sales, and possession of drugs with abuse liability. This strategy is embodied in international treaties and in the drug abuse control laws of individual countries. The simplest level of control for medications is to require a physician prescription for their use. Drug abuse control treaties and laws place additional requirements on drugs that have demonstrated abuse liability. Consequently, it is essential for the function of this drug abuse prevention strategy that there be a means of establishing which drugs have abuse liability and should be subjected to such regulations. In addition, the existing regulations call for differential restrictions on drugs based on differences in their abuse liability; therefore, it is also necessary to have a means of ranking this propensity.

At the international level, drug abuse control resides in two treaties, the Single Convention on Narcotic Drugs and the Convention on Psychotropic Substances (http://www.unodc.org/unodc/en/treaties/index.html). The United Nations has been given the authority to implement these treaties. Most countries are signatory to these treaties and among their obligations are to control manufacture, distribution, sale and possession of drugs at least as strictly as called for in the treaties. The drug abuse control laws differ somewhat among countries, so to illustrate how abuse liability impacts on drug abuse control, we will use as an example the ▶ Controlled Substances Act (CSA) in the US (http://www.usdoj.gov/dea/pubs/csa.html).

Under the CSA, drugs with abuse liability are placed in one of the five schedules (I-V), with Schedule I having the most restrictions and Schedule V the least. The intent is for the drugs with the greatest abuse liability and potentially causing the greatest public health concerns to be in Schedule I, with successively lower Schedules used for progressively less dangerous drugs. There is controversy about whether or not the existing classifications of drugs are consistent with this intent.

The remainder of this article will focus on how abuse liability is measured scientifically. The CSA specifies eight factors which should be assessed in determining abuse liability, but these factors do not easily translate into specific scientific assessments, so we will use a more scientifically based analysis. In this regard, it is important to distinguish between the assessment of abuse liability of drugs which are widely available to the public already and new drugs or medications, where data on actual abuse are not available but assessments of their abuse potential need to be made prior to their approval or a scheduling decision. In the former, methods from epidemiology are of paramount importance in assessing the actual abuse of the drugs. For new products, data from laboratory and clinical testing are usually the main source of information on abuse liability. Several regulatory agencies and scientific organizations have proposed strategies for abuse liability assessment (Balster and Bigelow 2003), which include chemical properties, animal test procedures (Negus and Fantegrossi 2008), human laboratory testing (Preston and Walsh 1998), and information that can be obtained from clinical efficacy trials.

Chemical Properties and Formulation

New medications that are based on analogs of existing drugs of abuse are often presumed to have abuse liability. Knowledge of structure-activity relationships can also be used to predict sites of action in the brain that might mediate abuse-related effects of drugs. Medications that are metabolized to known drugs of abuse or that can be

easily converted to an abusable drug can be considered to have abuse potential. Water soluble drugs and formulations are at increased risk for injection use. In some cases, it is possible to formulate drugs in ways that reduce their abuse liability and that are relatively tamper proof. Delayed or sustained formulations may have less abuse liability than their immediate release counterparts.

Animal Laboratory Testing of Abuse Liability

Knowledge of the pharmacological properties of a novel medication is an important first step in predicting their abuse potential. Indeed, binding assays and other means of determining a drug's cellular sites of action in the brain are typically used to assess if the drug acts on receptor systems or neural circuitry known to mediate the abuse-related effects of known drugs of abuse.

In general, the more similar a new drug is to known drugs of abuse the more likely it is to have abuse liability. The concept has often been referred to as pharmacoequivalence, and standard pharmacological tests of the properties of drugs can be used to establish pharmacoequivalence. For example, opioids, depressants, amphetamine-like stimulants, hallucinogens, and other classes of abused drugs can produce typical, class-specific profiles of pharmacological properties in animal tests. Often, developers of new medications are attempting to retain therapeutic properties (e.g., analgesia, sedation, etc), while reducing abuse potential.

► Drug discrimination testing in animals is a useful means of assessing pharmacoequivalence particularly because the discriminative stimulus effects of drugs are related to the nature of their acute subjective effects (Holtzman 1990). For abuse liability testing, novel drugs are typically tested in animals that have been trained to discriminate one or more known drugs of abuse from placebo. For example, animals trained to discriminate morphine from vehicle could be used to test a novel analgesic for morphine-like discriminative stimulus effects employing ► stimulus generalization procedures. With the use of appropriate training drugs, it is possible to characterize discriminative stimulus effects with high specificity. For example, mu and kappa opioids can be distinguished from one another, as can the various subtypes of GABA agonists.

Drug ► self-administration is also widely used for abuse liability assessment in laboratory animals. This procedure directly measures the reinforcing effects of drugs using standardized procedures, and has been used in rodents and nonhuman primates. One commonly used form of self-administration is the drug substitution procedure in which animals are trained to self-administer a known drug of abuse under limited access conditions, typically using fixed-ratio schedules of reinforcement and the intravenous route of drug administration. When rates of self-administration become reliable from day to day, a test drug is substituted to determine if animals will maintain responding. It is essential to test a range of doses of the test drug. More advanced self-administration procedures have also been used to measure reinforcement efficacy to compare the relative abuse liability of various drugs. For example, in progressive ratio procedures animals are required to make more lever presses for subsequent injections, and the maximal number of presses they make is used as the measure of reinforcement efficacy.

Testing for the development of a ► physical dependence syndrome can also be done in animals (Aceto 1990). Physical dependence is a feature of many, but not all, drugs of abuse. It is related to abuse potential because it may increase the likelihood of further drug-taking as well as being an adverse consequence of drug use. Physical dependence testing is used predominantly for opioids and depressants because the withdrawal syndromes are most pronounced with these classes of drugs. Cross-dependence can also be used to determine the extent to which a novel drug resembles a known drug of abuse. There are two primary models. One, which is often referred to as single dose suppression, utilizes animals that have already been made dependent on a known drug of abuse, such as morphine or pentobarbital, and then a test drug is administered during withdrawal to see if it suppresses the withdrawal signs that would normally emerge. If a test drug exhibits ► cross dependence in this procedure, it is very likely to produce dependence by itself. For example, a drug that suppresses withdrawal signs in morphine-withdrawn animals will probably produce dependence of the opiate type. The other common methodology is the assessment of primary physical dependence in which the test drug is administered repeatedly (or continuously by infusion) for a week or more. During treatment, animals can be injected with an antagonist (e.g., naloxone) to determine if precipitated withdrawal occurs or the drug administration can be discontinued and animals observed for spontaneous withdrawal signs.

Other animal test procedures that have been used for abuse liability assessment include the assessment of ► tolerance or ► cross tolerance, ► conditioned place preference, and altered thresholds for electrical self-stimulation of the brain.

Human Laboratory Testing of Abuse Liability

Abuse liability assessment studies conducted with humans typically occur prior to approval and marketing of a novel compound and/or new formulation of an existing

compound, but only after comprehensive safety evaluations of the new agent have been conducted in nonhumans and humans (Phase 1). Whether specific abuse liability testing in humans is needed depends on existing knowledge of the abuse potential for the test compound and pharmacologically related compounds, and the outcomes of animal abuse liability screening.

Standardized laboratory-based procedures have been developed to assess abuse potential in humans (Preston and Walsh 1998). Typically these studies are conducted using paid volunteers who are experienced with the class of drug under evaluation. Experienced drugs users provide a sensitive indicator of the positive mood effects of their drug of choice. When appropriate, abuse liability studies are sometimes conducted in normal (i.e., nondrug using individuals) and patient populations. Participants in these studies are screened for physical and mental health, cognitive ability to provide consent and answer questionnaires, and for recent drug use that would interfere with testing.

The most widely used approach for human abuse liability testing is the controlled assessment of the subjective experience of drug effects through structured and unstructured questionnaires (i.e., subjective effect reports). Key design elements for these studies include (1) testing a broad range of doses of the study agent in a controlled environment, (2) inclusion of a placebo control, (3) testing multiple doses of a positive control drug (i.e., a known drug from the same class with well characterized abuse potential), and (4) randomized dosing and double-blind procedures. Questionnaires are presented before and at regular intervals after the drug is administered (typically as an acute dose) in order to capture the onset, magnitude, and duration of drug action. The procedure produces a dose-effect of subject-reported responses associated with the test drug relative to a drug with known abuse potential.

Several standardized self-report measures are used to assess abuse liability. One measure is the visual analog scale, which allows subjects to rate their state in relation to specific questions or descriptors on a line labeled "not at all" and "extremely." Typical questions are for example, "How much do you like the drug?" "How strong is the drug?" or "Do you feel nauseous?" Other measures are adjective-rating scales, which employ a Likert-rating (e.g., ratings on a 0–10 scale), such as an opioid rating scale with effects such as nodding and itchy. The Single Dose Questionnaire (Fraser et al. 1961) is an opioid-specific questionnaire originally developed at the ►Addiction Research Center located at the ►U.S. Narcotics Prison Farm in Lexington, Kentucky where much of the seminal work in this research area was originally developed. Another widely used questionnaire (also developed at the Addiction Research Center) was a large empirically-derived battery known as the ►Addiction Research Center Inventory (ARCI; Haertzen 1966). This battery was derived after administration of drugs from a wide array of pharmacological classes, including ►opioids, ►alcohol, ►sedatives, ►psychostimulants, and ►hallucinogens. The original version has 550 true–false items subdivided into numerous subscales, with each sensitive to a specific drug-induced subjective state (e.g., the Morphine–Benzedrine Group scale (MBG) is used as a proxy for the euphoric effects produced by opioids and amphetamines; the Weak Opioid Withdrawal scale is sensitive to withdrawal symptomatology). A shortened version with only 49 items of the ARCI is most commonly employed in contemporary studies (Martin et al. 1971). Numerous other validated or locally developed questionnaires are also used.

Observer-rated measures yield additional information on observable signs of drug intoxication of which the subject may be unaware and are free of the potential bias/experimental noise that can result from drug intoxication. Cognitive and psychomotor test procedures may also be used to evaluate the impairing effects of the study drugs. These tests may include simple assessments such as balance, reaction time, and standard sobriety tests or more sophisticated cognitive measures which capture direct effects on cognitive processing and memory.

Drug discrimination and self-administration procedures have been adapted from the animal laboratory for use in humans. While these procedures are not typically used for abuse liability screening, they may provide additional relevant information. Human drug discrimination outcomes are generally concordant with those from the animal studies. Drug self-administration procedures are used most commonly with marketed agents to compare abuse liability among drugs or to evaluate potential pharmacotherapies for drug abuse treatment (Comer et al. 2008).

Evaluation of physical dependence capacity in humans was historically conducted using direct addiction studies. In early studies, subjects were exposed to repeated dosing with the test drug and then tested for signs of a withdrawal syndrome. However, these direct addiction studies are no longer conducted for ethical reasons. Instead, physical dependence is studied in currently dependent humans using substitution and withdrawal suppression procedures. For example, methadone-maintained subjects may be enrolled to examine the ability of another opioid to substitute for their maintenance dose or marijuana-dependent individuals may be maintained experimentally on equivalent oral THC doses during study participation.

Abuse Liability Assessment in Clinical Trials

Abuse liability is not typically assessed in clinical trials, which are usually designed to assess efficacy on a specified therapeutic outcome. Nevertheless, ► Phase I trials can produce information about the nature of the intoxication after administration of high doses (Brady et al. 2003). The adverse events in ► Phase II and ► Phase III trials can be a source of information about drug liking or other abuse-related phenomena, and escalation of use, or missing test medication might indicate a propensity for diversion.

Cross-References

► Addiction Research Center
► Addiction Research Center Inventory
► Conditioned Place Preference and Aversion
► Controlled Substances Act
► Cross Dependence
► Cross Tolerance
► Drug Discrimination
► Phase I, II and III Clinical Trials
► Physical Dependence
► Self-administration of Drugs
► Stimulus Generalization
► Tolerance
► US Narcotics Prison Farm

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Abuse Potential

► Abuse Liability
► Abuse Liability Evaluation

Acamprosate

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Synonyms

Calcium acetylhomotaurinate; Campral

Definition

Acamprosate, marketed under the brand name Campral, is an orally administered drug approved in the USA and throughout much of the world for treating ► alcohol abuse and dependence.

Pharmacological Properties

History

Alcohol-use disorders, which include both alcohol abuse and dependence, make up one of the most prevalent categories of substance use disorders in the USA, affecting almost 18 million Americans. The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV; APA 1994) characterizes alcohol dependence as a maladaptive pattern of drinking leading to clinically significant impairment, as manifested by a compulsion to drink, a lack of control over the amount of alcohol consumed and continued drinking, despite a realization of the problems associated with it. Physiological symptoms of tolerance and withdrawal may also be present. One of the most challenging aspects of recovering from alcohol dependence is maintaining abstinence after acute withdrawal and avoiding

subsequent relapse to drinking (Koob and Le Moal 2006). The goal of maintaining abstinence can be undermined by acute stressors like anger, loneliness, or hunger or by more chronic conditions such as cognitive impairment, polysubstance abuse, and mood and sleep disturbances. Supplementing counseling approaches with medications targeted to treat the biological aspects of drinking behavior can help in the maintenance of abstinence.

Three medications are currently approved for the treatment of alcohol dependence – ► disulfiram, ► naltrexone (oral and injectable extended release), and acamprosate (Koob and Le Moal 2006). A number of other therapeutic agents are under investigation; these include serotonergic agents, anticonvulsants, GABA receptor agonists, cannabinoid receptor antagonists, and corticotrophin-releasing factor antagonists. Disulfiram has been available for decades; however, high rates (up to 80%) of nonadherence to this aversive medication have contributed to its decreased use by the treatment community. Naltrexone has been available since 1994; however, it has not been readily adopted by practitioners to treat alcohol dependence. The recent Food and Drug Administration (FDA) approvals of acamprosate (2004) and an injectable extended formulation of naltrexone (2006) offer new pharmacologic options for treating this disorder.

Acamprosate is a safe and well-tolerated pharmacotherapy that has been studied in numerous clinical trials worldwide. It has been used successfully for over 15 years in 28 countries and has been prescribed for more than 1.5 million alcohol-dependent patients. Clinical trials have consistently shown that acamprosate is effective in maintaining abstinence in recently detoxified patients, especially when patients are motivated to be abstinent (Mason and Crean 2007). Current research also indicates that acamprosate has a unique mechanism of action, which may have implications for its therapeutic use (De Witte et al. 2005). In contrast to disulfiram, which causes aversive behavior through negative physical effects, or naltrexone, which tempers the pleasurable effects of alcohol, acamprosate acts to normalize dysregulation in neurochemical systems that have been implicated in the biological mechanisms of alcohol dependence.

Mechanism of Action

Acamprosate is an analog of amino acid neurotransmitters such as taurine and homocysteic acid and it has been demonstrated that acamprosate binds to a specific spermidine-sensitive site that modulates the NMDA receptor in a complex way. The NMDA receptor is one of the ► glutamate receptor subtypes. This work suggests that acamprosate acts as a "partial co-agonist" at the NMDA receptor, such that low concentrations enhance activation when receptor activity is low, and high concentrations inhibit activation when receptor activity is high. This may be particularly relevant to the success of acamprosate as a pharmacotherapy given that chronic exposure to ethanol results in an upregulation of ► NMDA receptors and an upregulation in the density of ► voltage-dependent calcium channels (Littleton 2007). Thus, sudden alcohol abstinence causes the excessive numbers of NMDA receptors to be more active than normal, and to produce the symptoms associated with acute ► alcohol withdrawal, such as ► delirium tremens and seizures and with the more persisting symptoms associated with early abstinence, such as craving and disturbances in sleep and mood (Tsai and Coyle 1998). Withdrawal from alcohol induces a surge of excitatory neurotransmitters like glutamate, which in turn activates the NMDA receptors (Tsai and Coyle 1998). Conversely, acamprosate promotes the release of taurine in the brain (Dahchour and De Witte 2000). Taurine is a major inhibitory neuromodulator/neurotransmitter and an increase in taurine availability would also contribute to a decrease in hyperexcitability. Thus, each of these changes produced by acamprosate may contribute to a decrease in the neuronal hyperexcitability commonly observed following acute alcohol withdrawal and that may underlie symptoms associated with relapse, like craving, negative affect and insomnia. Therefore, it has been hypothesized that acamprosate may promote abstinence by minimizing or normalizing some of the physiological changes produced by chronic heavy ethanol exposure.

Animal Models

Acamprosate has been shown to reduce ethanol consumption in rodents that have an extended history of ethanol exposure or are ethanol-dependent (Spanagel et al. 1996). It also has been shown to reduce the increased ethanol consumption associated with a period of enforced abstinence from ethanol (the alcohol deprivation effect) in rats (Heyser et al. 1998; Spanagel et al. 1996). In contrast, acamprosate appears to have less of an effect on alcohol consumption in alcohol naïve and nondependent rats (Heyser et al. 1998). Acamprosate also has been reported to attenuate some of the behavioral and neurochemical events associated with ethanol withdrawal (Dahchour and De Witte 2000). For example, acamprosate reduces the hyperactivity and elevated glutamate levels observed during the first 12 h of ethanol withdrawal. However, not all aspects of withdrawal are reduced by acamprosate, such as withdrawal-induced hypothermia. In addition to the direct effects on ethanol consumption, acamprosate

has been shown to inhibit cue-induced ► reinstatement of alcohol-seeking behavior in an operant conditioning model (Bachteler et al. 2005). Taken together, these results provide support for the use of acamprosate specifically as an anti-relapse medication following acute alcohol withdrawal.

Pharmacokinetics

The recommended dosage of acamprosate is two 333-mg tablets taken three times daily, with no dose adjustment required for body weight or gender (Campral package insert, 2005). Acamprosate is absorbed via the gastrointestinal tract, with pharmacokinetic linearity in terms of dose and time. Absolute bioavailability of acamprosate under fasting conditions is approximately 11%; after food intake, bioavailability decreases by approximately 20%, but this decrease lacks clinical significance (Wilde and Wagstaff 1997). Plasma protein binding is negligible. Importantly, acamprosate is not metabolized in the liver and approximately 90% of the drug is excreted unchanged in the urine (Wilde and Wagstaff 1997). Therefore, the pharmacokinetics of acamprosate are not altered in patients with mild to moderate hepatic impairment and no dose adjustment is required in such patients. Since there is a risk of accumulation of acamprosate with prolonged administration of therapeutic doses in renally impaired patients, the use of acamprosate is contraindicated in patients with severe renal impairment. The pharmacokinetics of acamprosate have not been evaluated in pediatric or geriatric populations.

Because acamprosate is not metabolized by the liver, it is unlikely to cause drug–drug interactions via cytochrome P450 inhibition. Its pharmacokinetics are not altered by co-administration with ► diazepam, ► disulfiram, ► antidepressants, or ► alcohol – substances that are often taken by patients with alcohol dependence. In pharmacokinetic studies with human subjects, co-administration with naltrexone increased the rate and extent of acamprosate absorption. These results suggest that combination therapy may improve the ► bioavailability of acamprosate without compromising its tolerability (Mason and Crean 2007).

Efficacy

Acamprosate was initially studied in Europe, and more recently, in Brazil, Korea, Australia, and the USA. The acamprosate double-blind, placebo-controlled clinical trial database included over 6500 outpatients from 15 countries and is reported in 23 published studies (Mason and Crean 2007). Nineteen of these trials used relatively equivalent methodology in terms of entry criteria, treatment, handling of drop-outs, outcome measures, and assessment of compliance. Patients received the psychosocial intervention typical of their treatment setting. Treatment duration ranged from 2 to 12 months with 13 trials 6 months or longer in duration. Patients were generally recently detoxified and typically had been abstinent for about 5 days at entry into the trials. In these studies, the principal ► efficacy measure was abstinence, which was assessed as the rate of patients completing the trial with no consumption of alcohol at all, the cumulative proportion of the study duration when the patients remained abstinent, and/or the time to first drink.

The results have been consistent in the majority of published studies, and generally show a significant beneficial effect of acamprosate on abstinence outcomes relative to placebo. A factor of 2 in the difference in the proportion of patients achieving stable abstinence was observed in approximately one-third of studies. A beneficial effect on the time to first drink was also frequently observed.

Overall, the published placebo-controlled studies demonstrate the efficacy of acamprosate for supporting abstinence over a broad range of patients in association with a variety of different psychosocial interventions. A number of these studies assessed the persistence of a treatment benefit after the study medication was stopped, and found acamprosate efficacy was maintained for up to 12 months post-treatment relative to placebo. In addition, the result of a recent multi-center, ► double-blind, ► placebo-controlled clinical trial of acamprosate conducted in the United States showed that the benefits of acamprosate were optimized in patients who had a clearly identified goal of abstinence at the start of treatment (Mason and Crean 2007).

Safety and Tolerability

The safety profile of acamprosate appears favorable. The only adverse event consistently reported across trials more frequently in acamprosate-treated patients with respect to placebo-treated patients was mild and transient diarrhea. Across clinical trials, the rate of early terminations due to drug-related adverse events did not differ between acamprosate and placebo-treated patients. Pharmacovigilance subsequent to the commercialization of acamprosate in 1989 has not identified any health risk associated with acamprosate use in over 1.5 million patients. Clinical investigations show no evidence of ► tolerance, ► dependence, or the emergence of a ► withdrawal syndrome or rebound drinking when treatment is ceased (Mason and Crean 2007). Comprehensive safety guidelines may be reviewed in the package insert for acamprosate (Forest Pharmaceuticals, Inc. 2005).

Conclusion

Acamprosate appears to be useful in the treatment of alcohol dependence above and beyond the effects of counseling alone. Acamprosate appears to work by normalizing the dysregulation of NMDA-mediated glutamatergic neurotransmission that occurs during chronic alcohol consumption and withdrawal, and thus attenuates one of the physiological mechanisms that may prompt relapse. Acamprosate requires around a week to reach steady-state levels in the nervous system and its effects on drinking behavior typically persist after the treatment is completed.

Studies into the efficacy of acamprosate in alcohol-dependent patients are generally favorable. Clinical studies and post-marketing experience indicate that acamprosate is typically safe when used as approved by the FDA in alcohol-dependent patients, including those dually diagnosed with psychiatric disorders. The majority of randomized controlled trials of acamprosate given in conjunction with counseling show significantly improved alcoholism treatment outcome relative to counseling administered with placebo. This evidence base suggests that acamprosate should be routinely considered by medical professionals for patients entering alcoholism treatment, taking into account the patient's treatment goals and preferences as well as the safety considerations outlined above.

Cross-References

- ► Alcohol Dependence
- ► Alcohol Withdrawal
- ► Disulfiram
- ► Glutamate Receptors
- ► Naltrexone
- ► Voltage-Gated Calcium Channels (VDCC)

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Acetaldehyde

Synonyms

ADH; Ethanal

Definition

Acetaldehyde is an intermediate by-product in normal carbohydrate metabolism. It is known to psychopharmacologists as the first metabolite of alcohol that is eliminated primarily through oxidation by the enzyme alcohol dehydrogenase in the liver. Acetaldehyde, in turn, is converted to acetate by aldehyde dehydrogenase. Acetaldehyde has pharmacological effects on the cardiovascular system, the liver, monoamine neurotransmitter metabolism, brain function, and behavior. At high levels, it can be toxic, causing headache, facial flushing, nausea and vomiting, tachycardia, headache, sweating, dizziness, and confusion.

Acetylcholine

Definition

A neurotransmitter in the brain and peripheral nervous system involved in the mediation of motor and autonomic functions, and in the mechanisms of cognitive events such as memory functions.

Acetylcholinesterase and Cognitive Enhancement

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Synonyms

Anti-Cholinesterases

Definition

Acetylcholinesterase inhibitors are molecules that inhibit the acetylcholinesterase enzyme from metabolizing (hydrolyzing) acetylcholine, thus increasing both the level and duration of action of the neurotransmitter acetylcholine.

Pharmacological Properties

Cholinergic System Effects on Cognitive Functioning

Several decades of research support the critical role of CNS cholinergic systems in cognition in humans, particularly in learning and memory formation and attention. Beginning with studies by Drachman (1977), temporary blockade of ▶ muscarinic receptors produced impairments of learning and memory that resembled changes associated with normal aging and was proposed as a model of the cognitive deficits in ▶ Alzheimer's disease (AD). Such findings were supported by animal studies showing that cognitive performance of younger animals after the administration of ▶ scopolamine was similar to older untreated animals (Bartus et al. 1982). These studies were extended by Newhouse et al. (1988) who showed that when elderly normals and depressed patients were given scopolamine, their performance declined to a level similar to AD patients. There is thus an age- and disease-related functional decline in muscarinic cholinergic system resources that matches the decline in cell number and other cholinergic markers seen in autopsy studies. Investigations of CNS nicotinic cholinergic receptors have shown qualitatively similar findings. Newhouse et al. (1994) have shown that blocking CNS ▶ nicotinic receptors with the antagonist ▶ mecamylamine in humans produces measurable cognitive impairment with a similar age- and disease-related increase in sensitivity. These studies showed that cognitive impairment followed the blockade of central nicotinic receptors, which partially modeled cognitive impairment that occurs with aging and degenerative disorders (e.g., AD). Studies of both nicotinic agonists and antagonists (Newhouse et al. 2004) have helped to establish the importance of CNS nicotinic receptors in human cognitive functioning and justified efforts to develop therapeutic agents aimed at these receptors. Thus, the effects of acetylcholinesterase inhibitors on cognitive functioning must be contextualized with an appreciation of effects on both cholinergic receptor systems (muscarinic and nicotinic).

In humans, the cholinergic system has been implicated in many aspects of cognition, including the partitioning of attentional resources, ▶ working memory, inhibition of irrelevant information, and improved performance on effortful tasks. Warburton and Rusted (1993) have proposed that the cholinergic system modulates processes that are supported by a limited capacity central executive and that the cholinergic system influences information processing during tasks that engage the control processes for the allocation of attentional resources. Cholinergic system manipulation appears to affect performance on resource demanding tasks as well as during the allocation of attention.

More recently, advances in basic animal research, cognitive pharmacology, and functional imaging have allowed a reformulation of the cholinergic hypothesis of cognitive functioning. Sarter et al. (2005) proposed that the cholinergic system modulates attentional functioning in two ways: first it serves to optimize bottom-up, signal-driven detection processes. Second, the cholinergic system also optimizes top-down, knowledge-based detection of signals, and the filtering of irrelevant information. Thus, the cholinergic system will be involved whenever a task is difficult or relevant and/or irrelevant information is difficult to discriminate, requires partitioning of attentional resources, inhibition of irrelevant information, or increased cognitive effort.

Human functional brain imaging studies have shown that cholinergic stimulation increases cortical activity in extrastriate and intra-parietal sensory areas during encoding and facilitates visual attention-associated activity in extrastriate cortex. Nicotinic cholinergic stimulation enhances reorienting of attention and alters parietal lobe activity associated with this process (Thiel et al. 2005) and may enhance the activity of a distributed neural network. Nicotinic cholinergic stimulation also specifically improves inhibitional attentional functioning (Potter and Newhouse 2004). By contrast, muscarinic cholinergic blockade reduces learning-related activity in the hippocampus (Sperling et al. 2002) and alters prefrontal and perirhinal cortical activity specifically associated with novelty. Studies have shown that muscarinic and nicotinic receptor-specific antagonists cause task-related alterations in activation in frontal and parietal areas during working memory tasks (Dumas et al. 2008).

These data support the concept that cholinergic system activation is phasic rather than tonic and serves to interrupt ongoing activity in the cortex in the context of an attentional requirement (top-down) or a signal requiring reorienting (bottom-up). A hypothesis suggested by

prior neuroimaging studies suggests that nicotinic and muscarinic systems may be responsible for different aspects of task performance; e.g., nicotinic stimulation may affect attentional modulation, rather than simply acting as a general signal gain enhancing system, whereas muscarinic effects may be more tied to stimulus processing or encoding (Thiel et al. 2005).

Studies of ► acetylcholinesterase inhibitors support these hypotheses regarding cholinergic functioning. Studies have shown that during the attentionally demanding N-back task, subjects with ► mild cognitive impairment (MCI) had increases in frontal activation after donepezil treatment relative to control subjects without MCI. In these patients with MCI, frontal regions were recruited during this task with the aid of the pro-cholinergic drug. Other pharmacological functional magnetic resonance imaging (fMRI) studies investigating the treatment of MCI with galantamine have found increased recruitment of task-related brain areas, including bilateral frontal areas and the hippocampus during semantic association, attention, and spatial navigation tasks following treatment. Donepezil treatment in AD subjects improved performance on an attention task of target cancelation while showing no effects on memory tasks (Foldi et al. 2005). Studies of the acetylcholinesterase inhibitor physostigmine have shown increased cortical activity after physostigmine compared to placebo while performing a working memory task in extrastriate and intraparietal areas during encoding but not during retrieval. Physostigmine administration also facilitates visual attention by increasing activity in the extrastriate cortex during a repetition priming task.

Thus, experimental studies using acetylcholinesterase inhibitors suggests that cholinergic system activity modulates stimulus-specific processing of sensory information in selected cortical areas. In addition, the activity of brain regions involved in memory processing such as the hippocampus and frontal lobe may be modulated by cholinergic system activity. The effects of acetylcholinesterase inhibitors on sensory areas may reflect the role of the cholinergic system in modulating attentional processes, and effects on memory-related processing areas similarly suggest effects of cholinergic modification of encoding-related activity for long-term storage.

Neuroimaging methods such as ► functional magnetic resonance imaging (fMRI) have increasingly been used by investigators as a tool to study neural processes involved in human cognitive function. Several functional imaging studies using healthy volunteers have found that enhancing acetylcholine activity via acetylcholinesterases can enhance the effect of selective attention within the extrastriate visual cortex, but not all stimulus processing regions or stimulus types are affected in a similar fashion. Based on the findings that brain activity related to both selective attention and emotional processing can be independently enhanced with physostigmine in the fusiform gyrus, and that physostigmine decreases differential activation due to attention in the posterolateral occipital cortex, cholinergic projections may modulate attention-related and emotion-related activity in distinct parts of the extrastriate and frontoparietal cortices. It has been found that physostigmine effects stimulus-selectivity and attention-related brain activation differently in patients with AD compared to healthy controls. Physostigmine partially reversed impaired stimulus activity in extrastriate visual cortices in AD patients, but negatively affected face-selectivity in the right fusiform cortex in both patients and controls. In contrast to physostigmine's reversal of impairment seen in the Alzheimer's patients, it was found to impair stimulus-related and task-related activity in controls. This finding may reflect a region-specific loss of functional cholinergic inputs in AD and/or regional variations in cortical AD neuropathology. Patients classified as cholinesterase inhibitor (ChEI) responders (based on changes in Clinical Interview Based Impression of Change and Mini Mental State Exam scores) showed a restoration of regional brain function using fMRI in the same areas used by elderly controls while performing semantic association and working memory tasks following 20 weeks of ChEI treatment (Vanneri et al. 2009). In those patients classified as nonresponders, activation patterns appeared less like the elderly controls and there was a reduction in task-related activation. Thus, recent studies tend to suggest that cholinergic stimulation with ChEI agents appears to increase task-related activation and decrease activity in areas of cortex that are unrelated to normal task activity.

Current Acetylcholinesterases

Cholinesterase inhibitors can be described as being either reversible (tacrine, ► donepezil, huperzine, and ► physostigmine), pseudoirreversible (► rivastigmine, metrifonate), or irreversible (soman, sarin, and VX). The latter class has not generally been found to have clinical applications, and are primarily toxic nerve agents or used as pesticides. Four cholinesterase inhibitors have been approved for the symptomatic treatment of AD (see Table 1): tacrine (an aminoacridine), donepezil (a benzylpiperidine), rivastigmine (a carbamate), and ► galantamine (a tertiary alkaloid). Physostigmine was the cholinesterase inhibitor most studied in the early phases of antidementia drug development, but is now generally used only as an investigational tool and for the treatment of glaucoma and myasthenia gravis. Another inhibitor of clinical

Acetylcholinesterase and Cognitive Enhancement. Table 1. Pharmacologic characteristics of cholinesterase Inhibitors.

Name	Class	Reversibility	Inhibition	Elimination half-life (h)
Tacrine	Acridine	Reversible	Noncompetitive	2–4
Donepezil	Piperidine	Reversible	Mixed	73
Rivastigmine	Carbamate	Pseudo-irreversible	Noncompetitive	5
Physostigmine	Carbamate	Reversible	Competitive	0.5
Galantamine	Phenathrene alkaloid	Reversible	Competitive	4.4–5.7
Huperzine A	Lykopodium alkaloid	Reversible	Mixed	4.8

importance is huperzine, a lykopodium alkaloid isolated from the Chinese herb Huperiza serrata.

Tacrine was the first reversible acetylcholinesterase inhibitor to be studied and approved for the treatment of AD, and is about four times more potent in its action on butyrylcholinesterase than on acetylcholinesterase. The therapeutic effects of tacrine do not seem to be correlated closely with its anticholinesterase activity, so it is thought that other neurochemical actions of the drug may be contributing to its behavioral activity. Tacrine is also known to produce problematic side effects in many patients, including hepatotoxicity.

Physostigmine is an alkaloid isolated from the seed of a perennial plant of West Africa (the Caliber bean), and is classified as a carbamate acetylcholinesterase and reversible inhibitor (Giacobini 2000). Physostigmine is the most potent of the carbamate derivatives, which also includes rivastigmine. Both of these agents are more selective for butyrylcholinesterase than for acetylcholinesterase.

Rivastigmine is a pseudo-irreversible cholinesterase inhibitor, and is found to specifically inhibit the acetylcholinesterase subtype found primarily in the hypothalamus and cortex. This particular subtype is implicated in the accumulation and maturation of amyloid plaque.

Donepezil was approved as a treatment for AD in 1996, and is known to be more selective for acetylcholinesterase versus butyrylcholinesterase (Giacobini 2000). Donepezil is a reversible inhibitor but due to its long pharmacokinetic half-life (about 100 h), it produces long lasting inhibition. The rate of onset of pharmacodynamic activity, however, is slow because the drug is relatively slowly absorbed.

Galantamine is a reversible acetylcholinesterase and competitive inhibitor, but unlike other agents, can also act on nicotinic receptors by allosteric modulation. As it is a weak cholinesterase inhibitor, this allosteric modulation of nicotinic receptors has been postulated to be a significant contributor to the activity of the drug. It has been proposed that modulation as opposed to agonism may protect against down regulation of post-synaptic receptors and thus allow the drug to have a more sustained action.

Huperzine is a potent, highly specific, reversible inhibitor of acetylcholinesterase. It has been found that the potency of Huperzine A is similar or superior to other inhibitors currently being used in the treatment of AD, based on in vitro and in vivo comparison studies.

Behavioral Effects of Acetylcholinesterase Inhibitors

Due to the extensive distribution of cholinergic pathways in the brain, anticholinesterase activity affects a wide range of behavior in animals and in humans. Although acetylcholine was not identified as a brain transmitter until 1914, physostigmine was isolated as a natural product and used as clinical therapy as early as 1877 (Giacobini 2000). The most recent neuropharmacological application of these agents has been as antidementia drugs. Tacrine was the first drug approved for the treatment of AD and was shown to improve memory, language, praxis, and activities of daily living.

In patients with AD, it is thought that cholinergic deficits in limbic and paralimbic structures contribute to the development of abnormal behavior, and human pharmacology data support the concept that stabilization of cholinergic function could improve both behavioral symptoms and cognitive deficits (Giacobini 2000). Most clinical trials have shown that acetylcholinesterase inhibitors improve scores on cognitive subscales of the AD Assessment Scale, the Mini-Mental State examination, and global scales such as the Clinical Interview-Based Impression of Change (CIBIC). For noncognitve domains, scales such as the AD Assessment Scale (ADAS-noncog) and the Neuropsychiatric Inventory (NPI) scale have most consistently demonstrated the ability of AChEIs to improve noncognitive behavioral problems including apathy, disinhibition, abberant motor behaviors, and anxiety. These agents temporarily improve, stabilize, or reduce the rate of decline in memory and other intellectual functions relative to placebo.

Comparison Between Acetylcholinesterase Inhibitors

In a meta-analysis done by Hansen et al. the affects of three major acetylcholinesterase inhibitors on behavior and cognition in 26 different studies were reviewed. Two trials directly comparing donepezil and galantamine showed conflicting results; the longer 52-week, fixed dosed trial found no significant differences between the agents in cognition for treated patients, while the shorter 12-week trial using flexible doses of drug showed significant differences in cognition and function favoring donepezil. In a 2-year double blinded randomized trial comparing flexible doses of donepezil and rivastigmine, treated patients had similar favorable changes in cognition and behavior as measured by Severe Impairment Battery (SIB) and Neuropsychiatric Inventory (NPI). Patients treated with rivastigmine had significantly better functional and global assessment outcomes. In a shorter, 12-week open label trial comparing flexible doses of donepezil and rivastigmine, no statistically significant differences were seen in cognition. For donepezil, rivastigmine, and galantamine, Hansen et al. concluded that the meta-analyses of placebo-controlled data support modest overall benefits for stabilizing or slowing decline in cognition, function, behavior, and clinical global change (Hansen et al. 2008). In another review of 24 trials, it was found that donepezil improved cognition and global functioning for patients with AD and ► vascular dementia. In 10 studies investigating galantamine versus placebo, there was consistent evidence that patients being treated with galantamine showed a positive effect on cognition and global assessment. There is less consistent evidence for a significant difference in cognition for tacrine versus placebo.

Treatment with cholinergic agents may also show beneficial behavioral and cognitive responses in other disorders with cortical cholinergic abnormalities such as ► Lewy body dementia, Parkinson's disease with dementia, olivopontocerebellar atrophy, vascular dementia, Down's syndrome, and traumatic brain injury. It has also been hypothesized that the cognitive deficits seen in ► schizophrenia could be in part secondary to dysfunction within the cholinergic system. Although findings have been negative, this concept is under investigation with the use of cholinergic agents, e.g., nicotinic agonists, as possible treatments.

Cholinesterase inhibitors have also been reported to prevent and/or reduce common behavioral disturbances seen in patients with AD, including apathy, agitation, and ► psychosis (hallucinations and delusions). Visual hallucinations and apathy are the most commonly reduced symptoms. Anxiety, disinhibition, agitation, depression, delusions, and aberrant motor behavior are also found to improve in some studies but not all.

Factors that may Affect Acetylcholinesterase Effect

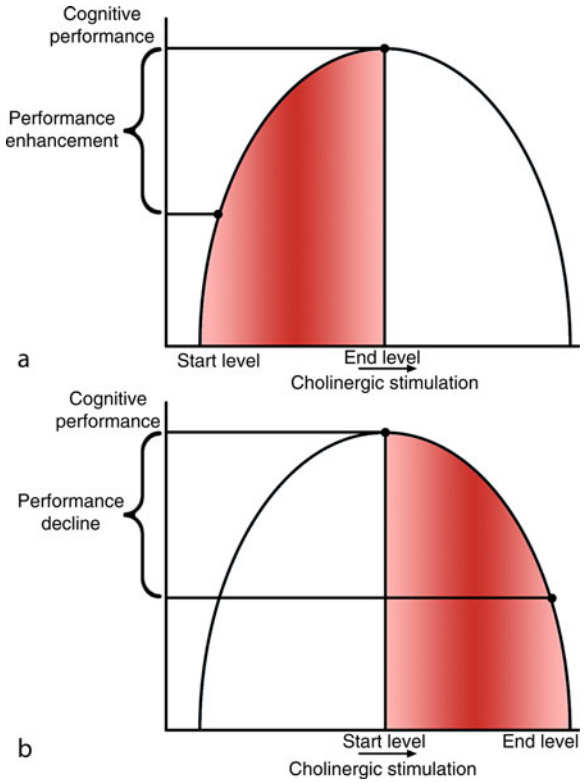
For procholinergic drugs, as the dose is increased, efficacy increases. However, side effects may become a limiting factor more rapidly than loss of efficacy, with an upside down U-shaped curve describing the relationship between cholinergic stimulation and cognitive benefit. Also, due to the phasic properties of cortical acetylcholine function, it is often difficult for increased acetylcholine in the synaptic cleft to result in stimulation of post-synaptic receptors independently from pre-synaptic activity. The ability of pre-synaptic neurons to respond to signaling may also be reduced by excessive autoreceptor stimulation. A wide range of response to treatment is seen, and may be due to variations in cholinergic deficit between patients. There may be a potential role for the ► apolipoprotein E4 genotype, as its presence is linked with late-onset AD, though the effect of this allele on the degree of Alzheimer neuropathology is not clearly understood. These individuals have less brain ► choline acetyltransferase and nicotinic receptor binding, which may contribute to developing cognitive dysfunction from cholinergic deterioration. It is clear that differences in age, disease severity, and genotype may all influence ► cholinergic deficits, and thus, the response to acetylcholinesterase therapy will vary between individuals.

Contradictions Regarding Effects of Acetylcholinesterase Inhibitors on Human Cognitive Functioning

A review of the effects of acetylcholinesterase inhibitors on cognitive functioning and performance in humans demonstrates both performance enhancement and impairment. A careful look at the nature of these disparate studies reveals clues to understanding the seemingly contradictory nature of research in this area.

Studies which tend to show impairment generally use normal unimpaired subjects. These studies tend to conclude that blocking acetylcholinesterase does not improve cognitive functioning and may impair it. By contrast, studies which tend to show improvement generally utilize clinical populations or normal subjects who have been artificially impaired. These studies generally demonstrate and/or conclude that acetylcholinesterase inhibitors have cognitive-enhancing effects. These disparate results can be resolved by considering that the findings reflect the differing populations utilized for the experiments. These populations can be expected to show quite different responses to nicotine based on principles of rate dependency or

baseline effects of cholinergic agents (e.g., the Yerkes-Dodson principal) (Fig. 1). Cognitive performance can be envisioned as a parabolic function related to cholinergic stimulation with intermediate levels of stimulation producing optimal performance and either low or high levels of stimulation impairing performance. If an individual subject who is performing suboptimally due to a disease state or impairment (e.g., AD), his performance will be enhanced by increased cholinergic stimulation via acetylcholinesterase inhibition (Fig. 1a). However, if an individual subject is already performing at or near their optimal level of performance, increasing cholinergic stimulation following acetylcholinesterase inhibitor administration will produce deterioration in cognitive functioning (Fig. 1b). The same analysis may apply if the individual is normal but the task demands are severe.



Acetylcholinesterase and Cognitive Enhancement. Fig. 1. Effects of cholinergic stimulation through acetylcholinesterase blockade are dependent on baseline performance and are subject to nonlinear effects. (**a**) Baseline performance is low and cholinergic augmentation through produces improvement in performance. (**b**) Baseline performance is normal/high and cholinergic augmentation impairs performance.

If the task is demanding enough in terms of attention, especially over a period of time, then the individual may move back to the left in terms of the performance curve and optimal performance may require enhanced cholinergic stimulation.

Studies of normal volunteers are thus unlikely to show cognitive improvement with cholinergic stimulation due to the fact that these individuals are likely to be operating at or near their optimal level of performance, particularly in the setting of experimental paradigms with pre-training for cognitive tasks, financial incentives, etc.

The preponderance of evidence is that stimulation of cholinergic receptors is most easily detected by effects on attentional systems and to some extent psychomotor speed. The most well-documented effect of cholinergic augmentation is on intensifying or sustaining attention to stimuli or tasks over a prolonged period of time. In addition, there is evidence from studies of individuals with disorders such as schizophrenia and ADHD that nicotinic cholinergic stimulation enhances selective attention, sensory detection, and inhibitional processes in attention. Positive effects of nicotinic stimulation, via acetylcholinesterase inhibitors on learning in memory may be mediated by effects on attentional functioning. Learning and memory require acquisition, encoding, storage, and retrieval. However, attention is the "front end" of this process, and adequate attentional functioning is a primary requirement for higher order processing.

Attention and related processes may be thought of as an endophenotype for cholinergic stimulation and consequently drug development. Attention, central processing impairment, and executive dysfunction may be orthogonal to the underlying neuropsychiatric diagnoses and should be considered as an independent target for drug development across diagnostic categories. Particular attentional deficits in different diagnoses may still respond to cholinergic stimulation with acetylcholinesterase inhibitors, however, the parameters for assessing improvement may be quite different between disease states and will require careful attention to particular specific agents, dosing regimens, and outcome measures for experimental studies. Paying careful attention to the issue of baseline dependency in treatment response will be vital to ensuring appropriate interpretation of experimental results, both for studies of normals and individuals with disease states. Targeting specific populations that are already impaired is much more likely to reveal potential benefits of cholinergic stimulation. Studies of normal or unimpaired individuals with acetylcholinesterase inhibitors are unlikely to show cognitive benefits except under extreme task demands.

Cross-References

► Cognitive Enhancers: Role of the Glutamate System
► Dementias and other Amnestic Disorders
► Mild Cognitive Impairment
► Muscarinic Agonists and Antagonists
► Nicotinic Agonists and Antagonists

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Acetylcholinesterase Inhibitors

Definition

These drugs prevent the breakdown of acetylcholine by inhibiting the action of the enzyme acetylcholinesterase. Their action therefore leads to an increase in the concentration of acetylcholine at the synapse.

Cross-References

► Acetylcholinesterase and Cognitive Enhancement

N-Acetylcysteine

Definition

It is the *N*-acetyl derivative of the amino acid L-cysteine, and is a precursor in the formation of the antioxidant glutathione in the body. Furthermore, it is used as a mucolytic agent and in the management of acetaminophen overdose. *N*-acetylcysteine increases cystine–glutamate exchange activity and thereby restores inhibitory tone on presynaptic metabotropic glutamate receptors. Clinically, it has reduced both cocaine use and the desire for cocaine.

Acquired Tolerance

► Tolerance

Action Inhibition

► Behavioral Inhibition

Action Potentials

Synonyms

Nerve impulse; Nerve spikes

Definition

Action potentials are pulse-like waves traveling along excitable membranes. Action potential initiation occurs when the voltage of the membrane increases sufficiently (depolarizes), thus activating (opening) voltage-gated sodium channels. Since the concentration of sodium channels outside the cell is much larger than the inside, sodium ions rush into the cell and represent the fast upstroke portion of the action potential wave. The Na channels close as the voltage peaks, and potassium channels then open allowing potassium ions to flow out of the cell since the concentration of potassium ions is much larger on the inside of the cell than the outside. This represents the falling phase of the action potential

waveform, and thus repolarizes the membrane ready for the next action potential.

Activation

Definition

The stimulation of a receptor by a ligand that stabilizes the receptor in the open conformation.

Activational Effects of Hormones

Definition

Immediate (temporary) effects of hormones that "come and go" with the presence and absence of the hormone.

Cross-References

► Sex Differences in Drug Effects

Active Avoidance

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Synonyms

Conditioned avoidance response; two-/one-way active avoidance

Definition

Active avoidance refers to experimental behavioral paradigms where subjects (mainly rodents) are trained to, following the onset of a conditioned stimulus (CS), move from a starting position to another position in the testing apparatus within a fixed amount of time (avoidance). Failure to move within the given time frame, results in the onset of a negative reinforcer, usually a weak electric shock in a grid floor, until a correct move is performed (escape). In animals performing at a high level of correct response following training, drugs that are effective as antipsychotics, but not other classes of drugs, show a unique ability to selectively suppress the avoidance behavior, within a clinically relevant dose range, while leaving escape behavior intact. Because of this robust marker for the prediction of antipsychotic activity, the active avoidance test is primarily used, and considered an important screening tool, for the detection of novel potentially ► antipsychotic drugs.

Principles and Role in Psychopharmacology

Background

It was found early that antipsychotic drugs for the treatment of ► schizophrenia had the ability to produce a selective suppression of active avoidance/conditioned avoidance behavior in rats (Cook and Weidley 1957). Later, as more antipsychotic drugs came on the market, it was found that this was a unique property among antipsychotics that was not shared by other classes of pharmacological agents, and that the selective suppression of conditioned avoidance response (CAR) produced by the antipsychotic drugs correlated with their main therapeutic mechanism of action namely brain dopamine D2 receptor blockade (Arnt 1982).

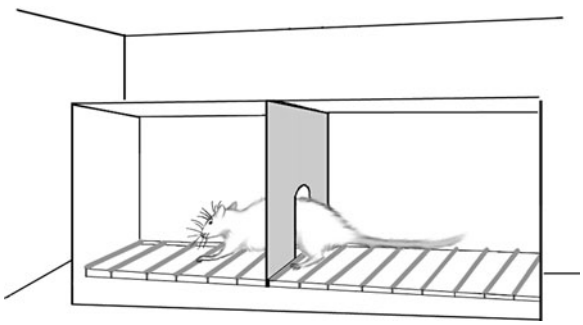
History and Procedures

The active avoidance procedure has connections back to classical conditioning (as first presented by I.P. Pavlov in 1927) (► Classical (Pavlovian) conditioning). The concept was further developed by the experimental psychologist B.F. Skinner. Skinner showed that a certain behavior could be maintained by the consequences it produced, and called this type of behavior operant behavior (► Operant behavior in animals). Thus, operant behavior (such as active avoidance response) can be defined as behavior that is maintained by its consequences.

The basic principle of active avoidance is that an animal (usually rodent) is trained (conditioned) to make a specific response within a fixed time interval when presented with an auditory, or visual, stimulus (CS). During training, incorrect responses (i.e., late responses) will trigger a negative reinforcer (unconditioned stimulus; UCS), usually a weak electric footshock presented in a grid floor, that will be active together with the CS until a correct response occurs. Thus, the animal terminates the negative reinforcer (together with the CS) by making the appropriate response. If the response, expected to be performed by the animal, is to move from one place to another upon presentation of the CS, the procedure is said to be using the active avoidance paradigm. Active avoidance procedures using a negative reinforcer typically record three dependent variables: avoidance (correct move within stipulated time frame), escape (correct, but late, move following onset of negative reinforcer), and escape failure (failure to perform a correct move despite the onset of negative reinforcer within a certain cut-off time) (see e.g., Wadenberg et al. 2007).

The active avoidance paradigm can be carried out mainly in two different ways: (1) one-way active avoidance; (2) two-way active avoidance. The one-way active avoidance procedure has the experimenter placing the animal in a chamber with a metal grid floor (for the electric shock, UCS), and upon presentation of the CS, the animal is required to move from the starting chamber into another (safe) compartment of the experimental box or jump onto a wooden pole hanging down from the ceiling of the box. The experimenter then has to move the animal back into the starting chamber for the next trial. In the two-way active avoidance procedure on the other hand, the animal moves back and forth (shuttles) between two compartments of equal size and appearance in the box via an opening in the partition dividing the box into the two compartments (shuttle-box) (Fig. 1). Here, the animal has to learn that upon presentation of the CS, it is always supposed to cross over to the other empty compartment in the box. Training and experimental sessions typically consist of a fixed number of trials over a certain time interval. The two-way active avoidance procedure has over time become the most commonly used procedure, most likely in part because this procedure can be set up as a computer-assisted apparatus with several boxes run simultaneously by one computer, thus saving time and money.

The training phase (typically needing three to four consecutive training days) in the active avoidance paradigm can be considered an acquisition phase (i.e., acquisition of avoidance performance), while, following training, animals that perform well show retention (over time) of the acquired avoidance performing ability. Screening for novel, potentially antipsychotic drugs uses well-trained, high avoidance performing animals. The marker for potential antipsychotic activity thus is the ability of an acutely administered drug to selectively, and temporarily, suppress the retention of avoidance performance in the animals.



Active Avoidance. Fig. 1. The figure shows a conventional two-way active avoidance apparatus (schematic drawing by Sofia I Wadenberg).

Evaluation and Use of the Active Avoidance Test

Animal behavioral tests (so-called animal models), used in the development of novel drugs for pharmacological treatment of diseases, are typically evaluated and rated for their fulfillment of validity criteria such as (1) predictive, construct and face validity; (2) their reliability; and (3) how they fare in terms of producing false positives or negatives. The active avoidance test is commonly considered to have high predictive validity, since all clinically effective antipsychotics, but not other classes of drugs, show the ability to selectively suppress avoidance behavior with a positive correlation between doses needed for the selective suppression of avoidance and their clinical potency for the effective treatment of schizophrenia (Seeman et al. 1976). More recently it was also found that antipsychotics produce selective suppression of avoidance in doses that result in a brain striatal dopamine D2 receptor occupancy around 65–75% in the rat (Wadenberg et al. 2001), which is also the percentage of dopamine D2 receptor occupancy usually needed for therapeutic response to occur in schizophrenic individuals following antipsychotic treatment. In other words, the active avoidance test identifies potential antipsychotic activity of new drugs tested with high predictive certainty. The active avoidance test has also been shown to have some construct validity (i.e., selective suppression of avoidance may mimic a blockade of some pathophysiological mechanisms in schizophrenia). Thus, the local application of an antipsychotic-related dopamine D2 receptor blocking agent, (-)sulpiride, into various brain areas in the rat, produced selective suppression of avoidance only when injected into the nucleus accumbens/ventral striatum (Wadenberg et al. 1990), a brain area that has a prominent role in the dopamine mesolimbic pathway that is commonly thought to be involved in the psychotic symptoms in schizophrenia (Laruelle et al. 1996) (► Aminergic hypotheses for schizophrenia). The active avoidance test has, however, no face validity, as it does not mimic any behavioral core symptoms of schizophrenia. The active avoidance test also shows high reliability, as there is a high degree of agreement between laboratories as to which compounds produce antipsychotic-like effects and in what dose range that occurs. Finally, to the best of the Author's knowledge, the active avoidance test produces few, if any, false positives or negatives. Thus, there is no antipsychotic, known to be clinically effective, that does not produce a selective suppression of active avoidance within a clinically relevant dose range. In addition, drugs

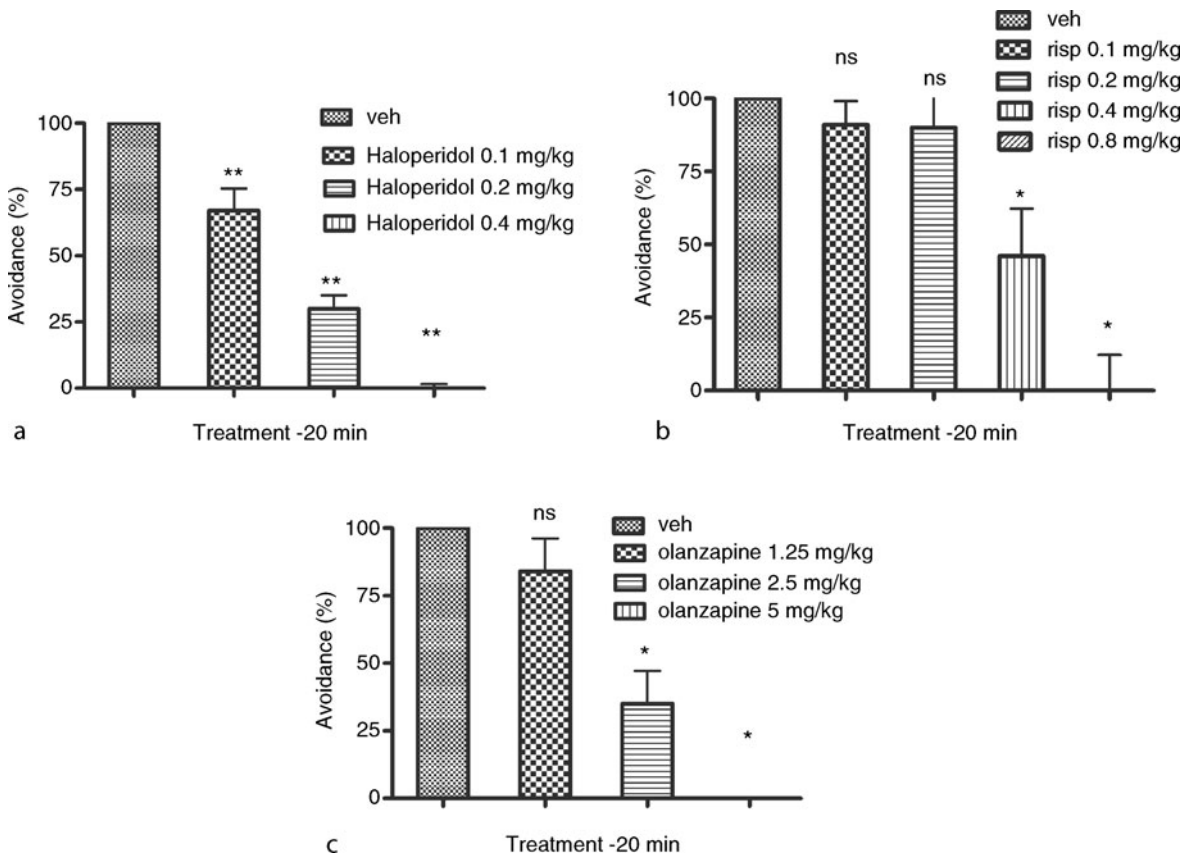
that have failed in clinical trials, or studies, for antipsychotic activity (such as for example, selective serotonin2A antagonists, selective dopamine D1 or D4 receptor antagonists) also, either showed no effect on active avoidance, or failed to produce a dose dependent suppression of avoidance without concomitant inhibition also of the escape variable (i.e., producing failures).

Based on the properties listed above, the active avoidance test falls into the category of so-called screening tests. A screening test is used by drug companies to evaluate synthesized molecules for a specific therapeutic property. When the screening test is an animal behavioral test, drug companies usually label the procedure in vivo pharmacology. Effects in these tests should occur following an acute administration of test drug, and only molecules that are effective against a particular disease should produce the specific effect that constitutes the marker for clinical activity – in this case selective suppression of avoidance within a clinically relevant dose range is produced.

The Active Avoidance Test and Identification of Drug Pharmacological Properties

There is no doubt that active avoidance behavior is strongly associated with brain dopamine neural transmission, and that the suppression of avoidance performance correlates significantly with the degree of striatal dopamine D2 receptor occupancy produced by D2 receptor blocking antipsychotic drugs. However, the active avoidance test not only identifies traditional, mainly dopamine D2 blocking antipsychotics such as haloperidol (Fig. 2a), but is also equally sensitive in detecting the antipsychotic activity of the newer, so-called atypical, antipsychotics with a different mechanism of action such as combined lower dopamine D2/high serotonin2 receptor blockade (e.g., olanzapine, risperidone) (Fig. 2b,c), or being partial agonists at dopamine D2 receptors rather than pure D2 antagonists (i.e., aripiprazole).

In addition, data from clinical studies (Litman et al. 1996; Schubert et al. 2006) are in line with, and support,



Active Avoidance. Fig. 2. Shown are typical dose-response effects on active avoidance response (selective suppression of avoidance) by the typical antipsychotic haloperidol (**a**), and the atypical antipsychotics risperidone (**b**), and olanzapine (**c**) in rats. Data are presented as medians ± semi-interquartile range (n=6–9).

experimental data showing that the active avoidance test also reliably detects sufficient antipsychotic activity obtained by adjunct treatment with some non-D2 blocking agents (such as alpha2 adrenoceptor antagonists or acetylcholinesterase inhibitors) to a low dose of an antipsychotic not giving sufficient dopamine D2 occupancy alone to produce antipsychotic activity (Wadenberg and Karlsson 2007; Wadenberg et al. 2007). Thus, the ability of the active avoidance test to detect antipsychotic activity does not seem to be solely limited to the detection of drugs with direct dopamine D2 receptor blocking properties. This certainly increases the value of this test as a screening tool in further development of new antipsychotic drugs, since many current development strategies, in order to minimize side effects and improve therapeutic efficacy, aim at moving away from molecules with mainly strong dopamine D2 receptor blocking properties.

Alternative Use of the Active Avoidance Test

The active avoidance test is primarily a test for detecting antipsychotic activity, that is, the ability of tested compounds to counteract psychotic symptoms in patients. However, since there is an element of training and learning (acquisition) associated with this test, there have been attempts to investigate if the test may be used also as a model for the detection of compounds that will enhance learning (effects on acquisition) or memory (effects on retention). Such attempts have overall not produced any consistent data. In fact, drugs that normally would impair memory (such as for example, drugs blocking brain neural transmission of acetylcholine) do not suppress avoidance behavior. Furthermore, the administration of a dopamine D2 receptor blocking antipsychotic to the animals during the training/acquisition phase does not impair the final outcome of avoidance performance in the absence of drug. This would suggest that suppressive effects on avoidance performance are not related to the impairment of memory, but rather to a temporary attenuation of the conditioned reflex, or urge, to hurry over to the other side in order to avoid getting a footshock. Indeed, gross observations of the behavior in animals given an antipsychotic drug strongly indicate that upon presentation of the CS, these animals still remember exactly what they are supposed to do; they just do not care enough to move within the time frame. Another way of explaining this phenomenon, although somewhat speculative, could be that the reason why active avoidance does not seem to work as a memory test, is because the acquisition and retention performance of active avoidance seem to primarily involve the brain subcortical mesolimbic system in general considered to be mediating behavior associated with basic reward and survival factors (i.e., survival reflexes), rather than recruiting higher order brain structures, such as for example, the prefrontal cortex, that are involved in memory processes of higher order events (Wadenberg et al. 1990).

Advantages and Limitations of the Active Avoidance Test

The active avoidance test has proven to be a unique and very useful screening test for the detection of drugs with antipsychotic activity with high predictive validity as well as excellent reliability. However, individuals suffering from schizophrenia do not only present with psychotic symptoms, but also have features of social withdrawal and cognitive impairment. These symptoms have a crucial impact on the quality of life for these individuals, and unfortunately, many of the currently used antipsychotics do not adequately improve these symptoms. Therefore, novel compounds showing antipsychotic-like effects in the active avoidance test, need to be tested also in an animal model of cognition as a complementary investigation of their potential cognitive enhancing activity compared with currently used antipsychotics. A major improvement in the field would be the development of an animal behavioral screening test that identifies both antipsychotic and cognitive enhancing activity of tested drugs.

Cross-References

- ▶ Aminergic Hypotheses for Schizophrenia
- ▶ Animal Models for Psychiatric States
- ▶ Antipsychotic Drugs
- ▶ Classical (Pavlovian) Conditioning
- ▶ Operant Behavior in Animals

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Active Immunization

► Vaccination

Activities of Daily Living

Definition

The activities of daily living (ADLs) are a defined set of activities necessary for normal self-care. The activities are movement in bed, transfers, locomotion, dressing, personal hygiene, and feeding. These six activities are defined as follows:

1. Movement in bed (sitting in, rising from, and moving around in bed)
2. Transfers (moving from one seat to another, changing position from sitting to standing, and transferring to and from the toilet and bed)
3. Locomotion (walking on the level, on gentle slopes, and downstairs)
4. Dressing (putting on socks, stockings, and shoes, as well as clothing the upper and lower trunk)
5. Personal hygiene (grooming, and washing of face, trunk, extremities and perineum)
6. Feeding (eating and drinking, but not the preparation of food)

Activities of Living Scales

► Impairment of Functioning; Measurement Scales

Acute Brain Failure

► Delirium

Acute Brain Syndrome

► Delirium

Acute Confusional State

► Delirium

Acute Disappointment Reaction

Definition

A syndrome involving lowered or dysphoric mood, which occurs in response to a perceived unpleasant experience such as a loss, rejection, or insult to one's self-concept or self-esteem. The person having the acute disappointment reaction may or may not be fully aware of, or fully able to explain, the issue to which the reaction is in response. Acute disappointment reactions are usually relatively brief – generally lasting at most a week or two – unless the insult to which the response is attached is of a repetitive or continuing nature.

Cross-References

► Depressive Disorder of Schizophrenia

Acute Tolerance

Definition

Acute tolerance is a diminution of effect either during a single drug-taking episode such that the drug produces greater effects as blood concentration increases compared to when blood concentration decreases, or if the effect is less on the second time that the drug is taken.

Acute Tyrosine/Phenylalanine Depletion

► Phenylalanine and Tyrosine Depletion

AD-5423

► Blonanserin

Adaptability

► Behavioral Flexibility: Attentional Shifting, Rule Switching and Response Reversal

Add on Therapy

► Drug Interactions

Addiction

Definition

The condition of a human or an animal where a drug is sought after and taken in spite of negative consequences to the individual. It is a state of obsession and compulsion in which the body depends on a substance for normal functioning, characterized by a loss of control over its consumption. The use of the term is usually restricted to the most serious and severe forms of drug abuse.

Addiction Research Center

Synonyms

ARC; NIDA IRP

Definition

The Addiction Research Center (ARC) began as the research component of the U.S. Narcotics Prison Farm located in Lexington, Kentucky. It was a very important site for early clinical pharmacology studies of opioids and other drugs of abuse. Methods for assessing the physiological and subjective effects of drugs of abuse were refined here, and include such instruments as the Addiction Research Center Inventory and the Single Dose Questionnaire. The ARC eventually became the intramural research unit of the National Institute on Drug Abuse and moved to Baltimore, Maryland.

Cross-References

► Abuse Liability Evaluation
► Addiction Research Center Inventory
► U.S. Narcotics Prison Farm

Addiction Research Center Inventory

Synonyms

ARCI

Definition

A true/false questionnaire developed at the Addiction Research Center used to assess the subjective effects of various drugs of abuse. Items include such statements as:

I have a pleasant feeling in my stomach.
I am sweating more than usual.
I have a floating feeling.
My movements seem slower than normal.

The original version had 550 such statements, but newer and shorter versions have been developed and validated as well. The most widely used version today includes only 49 items. Responses on the ARCI yield scores on various scales (five for the short form) that were empirically derived by administering known drugs of abuse and establishing the pattern of responses. For example, the Morphine-Benzedrine Group scale (MBG) is used as a proxy for the euphoric effects produced by opioids and amphetamines.

Cross-References

► Abuse Liability Evaluation
► Addiction Research Center
► Opioids

Addiction Stroop Test

► Attentional Bias to Drug Cues

Addictive Disorder: Animal Models

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Synonyms

Experimental drug dependence

Definition

Animal model: Experimental preparation developed for studying a given phenomenon found in humans. It is at the basis of experimental medicine, with its two sides: physiology and pathology.

Individual differences: Refer to the concept of differential psychology, personality, and temperament. Each individual is unique in terms of genetic and environmental backgrounds, and of life events and history.

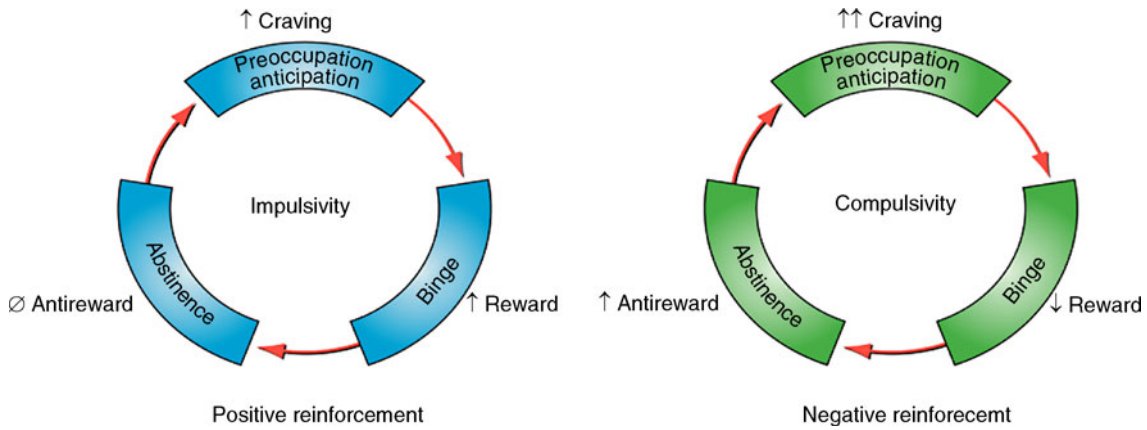
Vulnerability or frailty: A construct inherent to medical practice, for genetic or environmental reasons. It represents a biological state at the limits of homeostasis.

Current Concepts and State of Knowledge

Introduction: A Model of What?

In behavioral pathology and comparative psychiatry a precondition for an animal model is to be informed about what will be modeled. The poor awareness of the complexity of such human conditions is the origin of misunderstanding between clinicians and neurobiologists. This is particularly true in the field of drug abuse. Drug ► addiction, also known as substance dependence, is characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (Koob and Le Moal 1997). The terms addiction and substance dependence (as currently defined by the American Psychiatric Association (1994)) are used interchangeably and refer to a final stage of a misusage process that moves from drug use to a chronic relapsing disorder. This point is critical. It is referred here to a brain pathology from which a recovery is questionable. In other words, the occasional but limited or controlled use of a drug with a potential for abuse or dependence is distinct from the emergence of a chronic drug-dependent state. An important goal of current neurobiological research is to understand the molecular and neuropharmacological neuroadaptations within specific neurocircuits that mediate the transition from occasional, controlled drug use to the loss of behavioral control over drug seeking and drug taking. A key element of the addiction process is the underactivation of natural motivational systems such that the reward system becomes compromised and that an antireward system becomes recruited to provide the powerful motivation for drug seeking associated with compulsive use (Koob and Le Moal 2008).

The process of drug addiction involves elements of both ► impulsivity and compulsivity (Fig. 1), where impulsivity can be defined by an increasing sense of tension or arousal before committing an impulsive act and by a sense of pleasure, gratification, or relief at the time of



Addictive Disorder: Animal Models. Fig. 1. "The addiction cycle." Diagram describing the addiction cycle that is conceptualized as having three major components: preoccupation/anticipation ("craving"), binge/intoxication, and withdrawal/negative affect. Note that as the individual moves from the impulsivity stage to the compulsivity stage, there is a shift from positive reinforcement associated with the binge/intoxication component to negative reinforcement associated with the withdrawal/negative affect component. Craving is hypothesized to increase in the compulsivity stage because of an increase in the need state for the drug that is driven not only by loss of the positive reinforcing effects of the drugs (tolerance), but also by generation of an antireward state that supports negative reinforcement. (Reproduced with permission from Koob and Le Moal 2008.)

committing the act. Compulsivity can be defined by anxiety and stress before committing a compulsive repetitive behavior and relief from the stress by performing the compulsive behavior. Collapsing the cycles of impulsivity and compulsivity yields a composite addiction cycle comprised of three stages: preoccupation/anticipation, binge/intoxication, and withdrawal/negative effect, where impulsivity often dominates at the early stages and compulsivity dominates at terminal stages. As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior. These three stages interact with each other, becoming more intense, and ultimately leading to the *final pathological state*: addiction. Here it is important to realize that the main symptoms correspond to different structural–functional entities including large systems in the brain.

Classic Validation of Animal Models of Drug Addiction

- General typology of animal models

Animal models are critical for understanding the neuropharmacological mechanisms involved in the development of addiction. While there are no complete animal models of addiction, animal models may exist for elements of the syndrome. An animal model can be viewed as an experimental preparation developed for studying a given phenomenon found in humans (McKinney 1988; Geyer and Markou 2002). The most relevant conceptualization of validity for animal models of addiction is the concept of *construct validity*. Construct validity refers to the interpretability, "meaningfulness," or explanatory power of each animal model and incorporates most other measures of validity where multiple measures or dimensions are associated with conditions known to affect the construct. An alternative conceptualization of construct validity is the requirement that models meet the construct of functional equivalence, defined as assessing how controlling variables influence outcome in the model and the target disorders and the most efficient process for evaluating functional equivalence has been argued to be through common experimental manipulations, which should have similar effects in the animal model and the target disorder (Katz and Higgins 2003). This process is very similar to the broad use of the construct of *predictive validity*. *Face validity* often is the starting point in animal models where animal syndromes are produced, which resemble those found in humans in order to study selected parts of the human syndrome but is limited by necessity. *Reliability* refers to the stability and consistency with which the variable of interest can be measured and is achieved when, following objective repeated measurement of the variable, small within- and between-subject variability is noted, and the phenomenon is readily reproduced under similar circumstances. The construct of *predictive validity* refers to the model's ability to lead to accurate predictions about the human phenomenon based on the response of the model system. Predictive validity is used most often in the narrow sense in animal models of psychiatric disorders to refer to the ability of the model to identify pharmacological agents with potential therapeutic value in humans. However, when predictive validity is more broadly extended to understanding the physiological mechanism of action of psychiatric disorders, it incorporates other types of validity (i.e., etiological, convergent or concurrent, discriminant) considered important for animal models, and approaches the concept of construct validity. Some animal models have been shown to be reliable and to have construct validity for various stages of the addictive process will be described.

- Animal models and the stages of the addiction cycle

Table 1 summarizes the models used in most laboratories according to the stages of the addiction cycle.

1. Animals models for the Binge/Intoxication Stage

According to the evolution of the process defined above (Fig. 1), the individual moves from impulsivity to compulsivity with the development of preoccupation-anticipation and when he or she is in abstinence, negative effect and withdrawal symptoms progressively appear as signature of addiction. The procedures used have proven reliability and to have predictive validity in their ability to understand the neurobiological basis of the acute reinforcing effects of drugs. If one could reasonably argue that drug addiction mainly involves counteradaptive mechanisms that go far beyond the acute reinforcing actions of drugs, understanding the neurobiological mechanisms for positive reinforcing actions of drugs of abuse also provides a framework for understanding the motivational effects of counteradaptive mechanisms. Many of the operant measures used as models for the reinforcing effects of drugs of abuse lend themselves to within-subjects designs, limiting the number of subjects required. Indeed, once an animal is trained, full dose-effect functions can be generated for different drugs, and the animal can be tested for weeks and months. Pharmacological manipulations can be conducted with standard reference compounds to validate any effect. In addition, a rich literature on the experimental analysis of behavior is available for exploring the

Addictive Disorder: Animal Models. Table 1. Stages of the addiction cycle and models.

Stage	Source of reinforcement	Animal models
Binge/ intoxication	Positive reinforcement	Conditioned place preference
		Drug self-administration
		Decreased reward thresholds
		Intracranial self-stimulation
Withdrawal/ negative affect	Negative reinforcement	Conditioned place aversion
		Increased self-administration in dependence
		Increased reward thresholds
		Intracranial self-stimulation
Preoccupation/ anticipation	Conditioned positive and negative reinforcement	Drug-induced reinstatement
		Cue-induced reinstatement
		Stress-induced reinstatement
		Protracted abstinence

hypothetical constructs of drug action as well as for modifying drug reinforcement by changing the history and contingencies of reinforcement. The advantage of the intracranial self-stimulation (ICSS) paradigm as a model of drug effects on motivation and reward is that the behavioral threshold measure provided by ICSS is easily quantifiable. ICSS threshold estimates are very stable over periods of several months. Another considerable advantage of the ICSS technique is the high reliability with which it predicts the abuse liability of drugs. For example, there has never been a false positive with the classic discrete trials threshold technique. The advantages of place conditioning as a model for evaluating drugs of abuse include its high sensitivity to low doses of drugs, its potential utility in studying both positive and negative reinforcing events, the fact that testing for drug reward is done under drug-free conditions, and its allowance for precise control over the interaction of environmental cues with drug administration.

2. Animal Models for the Preoccupation/Anticipation Stage

Each of the models outlined above has face validity to the human condition and ideally heuristic value for understanding the neurobiological bases for different aspects of the craving stage of the addiction cycle. The DSM-IV criteria that apply to the craving stage and loss of control over drug intake include any unsuccessful effort or persistent desire to cut down or control substance use. The extinction paradigm has predictive validity, and with the reinstatement procedure, it can be a reliable indicator of the ability of conditioned stimuli to reinitiate drug-seeking behavior. The conditioned-reinforcement paradigm has the advantage of assessing the motivational value of a drug infusion in the absence of acute effects of the self-administered drug that could influence performance or other processes that interfere with motivational functions. For example, nonspecific effects of manipulations administered before the stimulus drug pairings, do not directly affect the assessment of the motivational value of the stimuli because the critical test can be conducted several days after the stimulus drug pairings. Also, the paradigm contains a built-in control for nonspecific motor effects of a manipulation by its assessment of the number of responses on an inactive lever.

The animal models for the conditioned negative reinforcing effects of drugs are reliable measures and have good face validity. Work in this area, however, has largely been restricted to the opiate field where competitive antagonists precipitate a withdrawal syndrome. There is consensus that the animal reinstatement models have face validity. However, predictive validity remains to be established. To date, there is some predictive validity for the stimuli that elicit reinstatement in the animal models, but little evidence of predictive validity from studies of the pharmacological treatments for drug relapse. Very few clinical trials have tested medications that are effective in the reinstatement model, and very few anti-relapse medications have been tested in the animal models of reinstatement. From the perspective of functional equivalence or construct validity there is some evidence of functional commonalities. For example, drug re-exposure or priming, stressors, and cues paired with drugs all produce reinstatement in animal models and promote relapse in humans.

3. Animal Models for the Withdrawal/Negative Affect Stage

It has been proposed by some authors that the motivational measures of drug withdrawal have much the

same value for the study of the neurobiological mechanisms of addiction as procedures used to study the positive reinforcing effects of drugs. ICSS threshold procedures have high predictive validity for changes in reward valence. The disruption of operant responding during drug abstinence is very sensitive. Place aversion is hypothesized to reflect an aversive unconditioned stimulus. Drug discrimination allows a powerful and sensitive comparison to other drug states. The use of multiple dependent variables for the study of the motivational effects of withdrawal may provide a powerful means of assessing overlapping neurobiological substrates and to lay a heuristic framework for the counteradaptive mechanisms hypothesized to drive addiction.

Individual differences, the concept of vulnerabilities and animal models

(a) Individual differences: a central problem in addiction medicine

For all the paradigms presented above and in consequence for these animal models used, all the subjects (rodents) are equal. The data are presented by means with their standard errors. In clinical practice, huge individual differences exist for the proneness to take drugs, for their perceived reinforcing effects and above all for the propensity to continue to misuse them and enter in a spiral of addiction. In other words, one of the most important problems in drug addiction today is to understand why an enormous amount of people take drugs according to the various circumstances of social life whereas only a small percentage of them will become addicted. Some individuals can stop their misusage without noticeable withdrawal syndrome. It is also reported that some get hooked with the first usage. Some individuals are vulnerable, other not. Vulnerability refers to a construct that covers all the fields of medicine. After a period devoted to the description of symptoms and diagnostic, then to identify the pathophysiological bases of the disease, then to find the causes, then to cure, predictive medicine will be the next step, i.e., to discover markers and prodromic states of vulnerabilities. Some vulnerabilities are specific for a given class of diseases, other are, in the state of knowledge, nonspecific. It is a strange phenomenon that while the problem of vulnerability in addiction medicine is abundantly discussed in clinical literature, it is almost completely absent in experimental and animal research.

Needless to say, drugs also have their own pharmacological effects that depend on intrinsic and differential dangerousness of the products. However, a drug is addictive because a specific individual in a given social environment uses it. Moreover, a vulnerable phenotype and vulnerability are revealed a-posteriori.

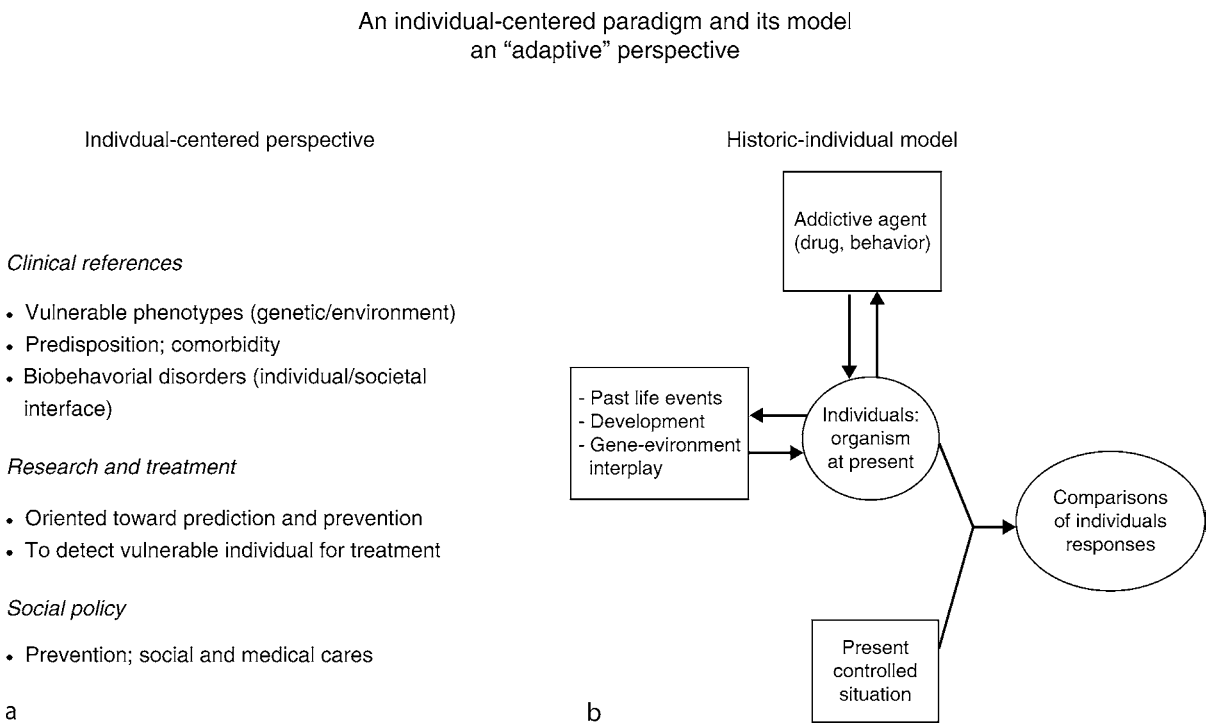
The origins of vulnerability are numerous and interacting: genetic, environmental, aversive life events and stress, age and gender. All these factors have left traces in the organism. Vulnerability participates to psychopathological syndromes and to comorbid factors diagnosed in most of the psychiatric disorders. Each individual has his own history that participates in a unique way to the entrance in addiction process. These factors, each or associated, contribute to psychobiological traits. However, such a view, based on clinical observations and studies is at variance with most of the experimental investigations and raised methodological considerations about animal and biological models and the neuroscience of addiction in general.

(b) Vulnerability and transition to addiction: two opposite views

The first one, adaptive or individual-centered, places the subject with his own characteristics at the center of research and interest. The adaptive perspective (Fig. 2) is based on a predisposition, on the fact that explains why subjects are at risk and why their intrinsic predisposed state determines the neuroplasticity induced by drugs.

To detect the sources of vulnerability would lead to predictive medicine and toward psychosocial interventions. A translation from the real world and from clinical psychiatry to the laboratory must discover and develop models that will present (1) gradual individual differences from the resilient to the most vulnerable phenotypes, (2) a transition from use to misuse for some animals prone to enter in the disease spiral and, (3) the main symptoms of the disease as defined by the DSM IV at the end of the process. An individual-centered approach is basically a historic approach. Patients and animals are considered different and more or less vulnerable because of their past, of developmental characteristics or genetic background. The sequences of the process are represented in Fig. 3.

This paradigm opposes classic pharmacological approaches, i.e., drug-centered, or exposure model, based on drug-induced neuroplasticity and on acquired vulnerability. Here, drug abuse is a iatrogenic disorder and both research and therapeutics are oriented toward understanding drug pharmacological properties and toxicological actions on brain substrates, and toward counteracting these effects by other pharmacological means. This paradigm is largely dominant in laboratory research; animals are considered not in relation with their past (a-historic models) but with the amount of drug taken (Fig. 4).



Addictive Disorder: Animal Models. Fig. 2. "An individual-centered research paradigm (**a**) for an historic-individual animal model (**b**)." Individuals are considered as different from the point of view of their past life events, developmental characteristics, and genetic background. Individual comparisons require nonparametric statistics. (Reproduced with permission from Le Moal (2009) Drug abuse: vulnerability and transition to addiction. Pharmacopsychiatry 42:S42–S55, © Georg Thieme Verlag Stuttgart, New York.)

Individual differences are hidden under statistical standard errors or considered as protocol artifacts.

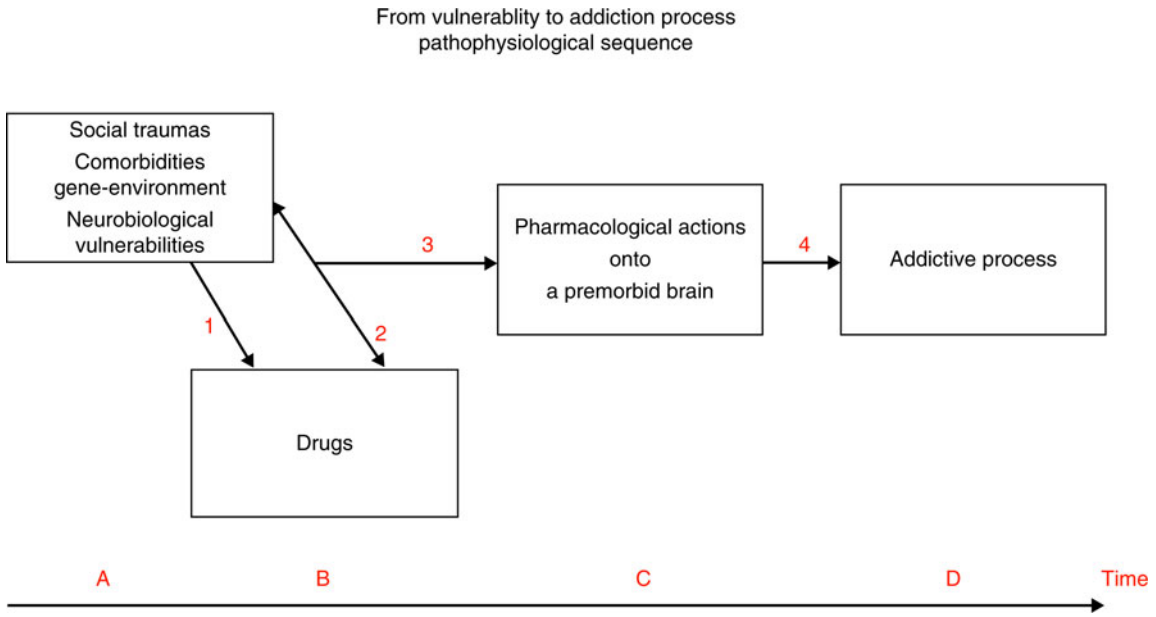
These two different research interests and practices have their own logic and necessities and are sometimes complementary. It is important to discover the neurotoxic damages and neuroplasticities induced by drugs. These neurobiological changes explain the transition from impulsive to compulsive behaviors and loss of control. Drugs of abuse have different addictive properties. It is a trivial observation that frequent usage of a drug, or the repetition of specific behaviors, combined with the intrinsic dangerous state of each drug (gambling, eating, sex...) are dangerous by themselves and lead progressively to loss of control.

(c) Two recent models: drug-centered versus individual centered

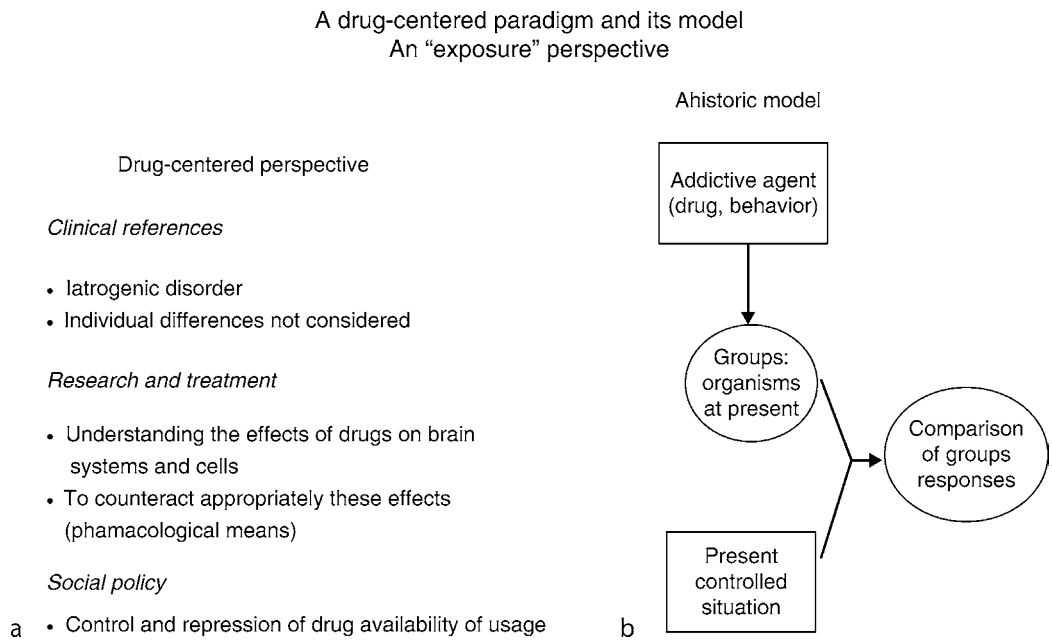
A conceptual framework upon which animal models can be directly related to the compulsive behavior and loss of control over intake, that is the hallmark of addiction, is to specifically relate a given animal model to a specific symptom of the DSM-IV criteria for addiction. Recent studies have emphasized animal models that contribute to specific elements of the DSM-IV criteria with strong face validity, and at the same time may represent specific endophenotypes of the compulsive nature of the addiction process.

1. Ahistoric model: escalation in drug self-administration with prolonged access

A progressive increase in the frequency and intensity of drug use is a behavioral phenomena often characterizing the development of addiction and has face validity with the DSM-IV criteria. A framework with which to model the transition from drug use to drug addiction is found in a recent animal model of prolonged access to intravenous cocaine self-administration. Historically, animal models of cocaine self-administration involved the establishment of stable behavior from day to day to allow the reliable interpretation of data provided by within-subject designs aimed at exploring the neuropharmacological and neurobiological bases of the reinforcing effects



Addictive Disorder: Animal Models. Fig. 3. "Vulnerability to addiction process." A given drug or behavior (e.g., eating, gambling, sex) is "addictive" because of its exposure to a vulnerable individual (1) who will be prone to repeat the drug use (2). Drug use then will induce neuropharmacological and neurotoxicological effects and profound neuronal changes (3) and then addiction (4). A, B, C, D: Process sequence. (Reproduced with permission from Le Moal (2009) Drug abuse: vulnerability and transition to addiction. Pharmacopsychiatry 42:S42–S55, © Georg Thieme Verlag Stuttgart, New York.)



Addictive Disorder: Animal Models. Fig. 4. "A drug-centered research paradigm (**a**) for a ahistoric animal model (**b**)." Group comparisons require parametric statistics. The subjects are not considered from their individual characteristics – they are considered equal or similar. (Reproduced with permission from Le Moal (2009) Drug abuse: vulnerability and transition to addiction. Pharmacopsychiatry 42:S42–S55, © Georg Thieme Verlag Stuttgart, New York.)

of acute cocaine. Typically, after the acquisition of self-administration, rats allowed access to cocaine for 3 h or less per day establish highly stable levels of intake and patterns of responding between daily sessions. These models do not fit with the concept of addiction.

To explore the possibility that differential access to intravenous cocaine self-administration in rats may produce different patterns of drug intake, rats were allowed access to the intravenous self-administration of cocaine for 1 or 6 h per day. One hour access (short access or ShA) to intravenous cocaine per session produced low and stable intake as observed previously. In contrast, with 6 h access (long access or LgA) to cocaine, drug intake gradually escalated over days (Ahmed and Koob 1998). It is observed in the escalation group, there was increased intake during the first hour of the session as well as sustained intake over the entire session and an upward shift in the dose-effect function, suggesting an increase in hedonic set point. When animals were allowed access to different doses of cocaine, both the LgA and ShA animals titrated their cocaine intake, but the LgA rats consistently self-administered almost twice as much cocaine at any dose tested, further suggesting an upward shift in the set point for cocaine reward in the escalated animals. Escalation also is associated with an increase in break point for cocaine in a progressive-ratio schedule, suggesting an enhanced motivation to seek cocaine or an enhanced efficacy of cocaine reward.

This model fits with the drug-centered paradigm. It is a-historic: the subjects are not considered from their individual characteristics but considered at the beginning of the experiment equal or similar. Only the drug parameters (amount taken) change.

2. Historic model: differential vulnerability for a transition to addiction

A second model considers that each individual has different characteristics and vulnerabilities to the pharmacological aspects of drugs. Such differential vulnerabilities had been demonstrated for the propensity to like drugs. A first paper published demonstrated that it was possible to evidence in rats (1) marked individual differences in the development of psychostimulant self administration; (2) that a differential propensity to drug taking was predicted by individual reactivity to novelty, a robust permanent trait; (3) a significant positive correlation between the magnitude of the reactivity and the amount of the drug self-administered during an acquisition session (Piazza et al. 1989). In a recent study explored further the behavioral effects of drug-taking in animals with access to cocaine for 3 months and a number of behavioral tests were administered that were hypothesized to capture DSM-IV criteria of addiction (Deroche-Gamonet et al. 2004). Unsuccessful effort or a persistent desire to cut down or control substance use was linked to the persistence of cocaine seeking during a period of signaled non-availability. A great deal of time spent in activities necessary to obtain the substance was linked to performance on a progressive-ratio schedule, and continued substance use despite knowledge of having a persistent physical or psychological problem was linked to the persistence in responding for drug by animals when drug delivery was associated with punishment. Rats were trained to self-administer cocaine intravenously and then separated by groups based on a test for reinstatement to small doses of cocaine administered after 5 days of extinction. The animals with the high tendency to show reinstatement showed progressively increased responding during signaled nondrug periods, higher break points on the progressive-ratio test, and higher responding after punishment (Deroche-Gamonet et al. 2004). Further study of rats subjected to all three tests above revealed that the animals that met all three positive criteria represented 17% of the entire population, a percentage noted by the authors to be similar to the number of human cocaine users meeting the DSM-IV criteria for addiction while 41% of the rats were resilient (0 criterion). This model highlights the importance of differential vulnerability to addiction. It demonstrates huge individual differences for the propensity to enter in the addiction cycle. It is typically anindividual-centered model and corresponds to what is met in addiction medicine.

Conclusion

Animal models for addiction have progressed from simple drug reinforcement models to sophisticated models with solid face validity. Escalation in drug intake with extended access has been observed in numerous laboratories with all the drugs of abuse. This drug-centered model do not discriminate animals according to potential previous vulnerabilities; here the transition to addiction is linked to compulsivity. More recently, animal models for criteria of addiction that reflect the channeling toward drug seeking at the expense of other environmental contingencies (Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004) have been developed and linked to the compulsive loss of control over intake. The model described above may prove particularly sensitive to the transition to addiction in otherwise vulnerable individuals.

Acknowledgments

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Cross-References

- ► Animal Models for Psychiatric States
- ► Cocaine
- ► Personality: Neurobehavioural Foundation and Pharmacological Protocols
- ► Pharmacokinetics
- ► Phenotyping of Behavioral Characteristics
- ► Psychostimulant Addiction
- ► Sedative, Hypnotic and Anxiolytic Dependence
- ► Self-Administration of Drugs
- ► Stress: Influence on Drug Action
- ► Withdrawal Syndrome

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Add-on Therapy

Definition

Strategy to enhance a therapeutic effect by an additional drug.

Adenine-9-β-D-Ribofuranoside

► Adenosine

Adenine Riboside

► Adenosine

Adenosine

Synonyms

(2R,3R,4R,5R)-2-(6-aminopurin-9-yl)-5-(hydroxymethyl) oxolane-3,4-diol; 9-β-D-ribofuranosyladenine; Adenine-9-β-D-ribofuranoside; Adenine riboside

Definition

Endogenous nucleoside made up of the purinic base adenine and the pentose carbohydrate ribose linked through an N-9 bound. Adenosine is present in all mammalian tissues at both the intra- and extracellular level, and takes part in important physiopathological phenomena (e.g., modulation of inflammation, regulation of heart rhythm). At the level of the central nervous system, adenosine promotes a generalized inhibition of neuronal functionality, a reason why it is often referred to as "endogenous neurodepressant."

Cross-References

- ► Caffeine

Adenosine A_1 Receptors

Definition

Protein G-coupled receptors whose stimulation inhibits the signal cascade mediated by adenylyl cyclase. A_1 receptors have a widespread distribution in the brain, being enriched at significant levels in almost every cerebral area. A_1 receptors are mostly located at the presynaptic level, where they inhibit the release of ► neurotransmitters. Postsynaptic A_1 receptors have also been described on medium-sized spiny neurons projecting from the caudate nucleus to the substantia nigra. These receptors may co-localize with D_1 receptors at the neuronal level, and opposite functional interactions between these receptors

exist (e.g., stimulation of A_1 receptors depresses D_1 receptors-mediated effects).

Cross-References
► Caffeine

Adenosine A_{2A} Receptors

Definition
Protein G-coupled receptors whose stimulation activates adenylyl cyclase-mediated signal cascade. The large majority of A_{2A} receptors (about the 95%) are enriched in the caudate-putamen, where they are located at the postsynaptic level on medium-sized spiny neurons projecting to the globus pallidus. Presynaptic A_{2A} receptors have been detected, in the cortex, basal ganglia, and hippocampus, which participate in the regulation of neurotransmitter release. A_{2A} receptors usually co-localize at the neuronal level with D_2 receptors and opposite functional interactions between these receptors have been described (e.g., stimulation of A_{2A} receptors attenuates D_2 receptors-induced effects). A_{2A} receptors also display a similar modulatory activity on the function of D_1 receptors that is exerted through cross-talk mechanisms involving the basal ganglia network.

Cross-References
► Caffeine

ADH

► Acetaldehyde
► Alcohol Dehydrogenase
► Arginine-Vasopressin

ADHD

► Attention Deficit Hyperactivity Disorder

Adherence

Definition
Adherence refers to taking a drug in the way it has been prescribed, related to both dose and length of time.

Cross-References
► Agoraphobia

Adjunctive Behavior

► Schedule-Induced Polydipsia

Adjunctive Drinking

► Schedule-Induced Polydipsia

Adjustability

► Elasticity

Adjustment Disorders

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Synonyms
Anxiety or mixed states; Reactive depressions; Stress-related mood disorders; Subthreshold diagnoses

Definition
In DSM-IV, the adjustment disorders comprise a distinct group of subthreshold states that emanate from a known stressor that is not of an unusual or catastrophic type, and that can result in maladaptation at work, at school, or at the social level (e.g., interpersonal functioning), all within 3 months of the stressor (in the ICD-10, onset must occur within 1 month of exposure to an identifiable stressor). They can be further defined by the accompanying mood state, e.g., depressed, anxious, or mixed; by the presence of a disturbance of conduct; or by the absence of these predominating features, in which case they are considered unspecified. They can be acute (less than 6 months) or chronic (lasting 6 months or more). The criteria for diagnosing adjustment disorders are compromised in that there is no *specification of*, or *symptom checklist for*, (1) the stressor(s), (2) the maladaptation, or (3) the

accompanying behavior, mood state, or symptoms – the three components in the algorithm for this diagnosis. This characteristic of the adjustment disorder diagnosis means that its classification is more subjective than that of most of the other psychiatric disorders, thereby raising issues of validity and reliability. In addition, adjustment disorders need to be differentiated from normal dysphoric states, acute stress disorders, bereavement, and other problems that may be the focus of the mental health worker's attention. They are not solely the result of a psychosocial problem requiring medical attention, e.g., noncompliance, phase of life problem, etc. Although the upper threshold for diagnosing adjustment disorders is established by the specific criteria for the minor and major psychiatric disorders, the entry threshold between the adjustment disorders and psychosocial problems or normality is not sufficiently demarcated by operational criteria. This lack of specificity and questionable reliability and validity are the hallmarks of interface disorders and subthreshold phenomena, whether they are in diabetes mellitus, hypertension, or depression. Maercker et al conceptualize adjustment disorders as a stress response syndrome in which intrusions, avoidance of reminders, and failure to adapt are the central processes and symptoms. Empirical investigations have shown that the symptom profiles of adjustment disorders are very different in children and adolescents when compared with adults. The future evolution of this and other psychiatric diagnoses will need to consider the effect of developmental epochs, gender, and medical comorbidity on symptom profiles.

The subthreshold disorders present major taxonomical and diagnostic dilemmas, since they are poorly defined, overlap with other diagnostic groupings, and have indefinite symptomatology. However, the advantage of the "indefiniteness" of these subthreshold disorders is that they permit the classification of early or prodromal states when the clinical picture is vague and indistinct, and yet the morbid state is in excess of that expected in a normal reaction, and treatment at this stage is indicated.

Role of Pharmacotherapy

Clinical Features, Etiology, and Pathogenesis

Adjustment disorder with depressed mood: Predominant symptoms are depressed mood, tearfulness, or feelings of hopelessness.

Adjustment disorder with anxious mood: Predominant symptoms are nervousness, worry, or jitteriness or, in children, fears of separation from major attachment figures.

Adjustment disorder with mixed anxiety and depressed mood: Manifestations of depression and anxiety.

Adjustment disorder with disturbance of conduct: Predominant manifestation is a disturbance in conduct, in which there is violation of the rights of others or of major age-appropriate societal norms and rules (e.g., truancy, vandalism, reckless driving, fighting, and defaulting on legal responsibilities).

Adjustment disorder with mixed disturbance of emotions and conduct: When the predominant manifestations are both emotional symptoms (e.g., depression, anxiety) and a disturbance of conduct (see earlier subtype).

Adjustment disorder unspecified: Maladaptive reactions (e.g., physical complaints, social withdrawal, or work or academic inhibition) to psychosocial stressors that are not classifiable as one of the specific subtypes of adjustment disorder.

Etiology

As stated earlier, the adjustment disorders are a product of stressor(s) in a person's life, that is, the precipitating event for this psychiatric disorder is one or more exogenous stressor. It is one of those psychiatric disorders for which an etiology is known. It is assumed that once the stressor is terminated or the patient adjusts to the stressor, the adjustment disorder symptoms, e.g., disturbance of mood or conduct, will also terminate. However, some stressors do not abate, e.g., chronic medical illness, joblessness, financial distress, etc., and the patient may continue to have an adjustment disorder in excess of 6 months. Thus, adjustment disorders join that group of disorders that also have exogenous stressors as the key etiological agent, e.g., acute stress disorder and posttraumatic stress disorder. These stress-related disorders, the organic mental disorders and the substance abuse disorders, for all of which an etiology can be identified, are thus differentiated from the majority of psychiatric disorders in the primary psychiatric taxonomy, the DSM-IV, for which definitive etiologies are not known. Furthermore, since the stressor and symptom profiles in adjustment disorders have not been specified and therefore cannot be measured in a reliable and valid way, these disorders remain a subjective diagnosis.

This also means the adjustment disorders are difficult to study to ascertain their actual frequency in various populations. For similar reasons, it is difficult to study cohorts receiving various interventions in randomized controlled trials: it is uncertain whether one has comparable patient groups when attempts are made to observe outcomes. Adjustment disorders have been diagnosed in over 60% of burn patients, greater than 20% of patients with multiple sclerosis, and over 40% of poststroke

patients. This is the most common psychiatric diagnosis in medically ill inpatients in acute care general hospitals referred for consultation, with rates ranging from 11.5% to 21.5%. Fabrega et al, at the University of Pittsburgh, observed that 2.3% of patients in a walk-in clinic had adjustment disorder only, while in those with other psychiatric or personality disorder comorbidity, the rate was 20%. Mezzich et al, from the same institution, observed that 29% of the patients in the adjustment disorder group had a positive response on indicators for suicide risk, whereas such indicators were seen in 9% of the normal (no illness) group. This emphasizes that a subthreshold diagnosis may be associated with serious symptomatology and mortality as an outcome. Obviously, suicidality is not subthreshold. Adjustment disorder patients with suicidality had lower platelet monoamine oxidase (MAO) activity, higher activity of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), and higher cortisol levels than controls. Although these findings differ from the lower MHPG and cortisol levels found in some studies of patients with major depressive disorder and suicidality, they are similar to findings in other major stress-related conditions.

One must always be on the alert for the symptom profile seen in a patient with an adjustment disorder evolving over time to that of a minor or major depressive disorder, or to a generalized anxiety disorder; the maturation of symptoms over time can easily reach the criteria for these major psychiatric entities.

Treatment

The use of psychopharmacological interventions for adjustment disorders has not been agreed upon, and guidelines usually recommend that talking therapies be applied initially – psychotherapy or counseling. The Cochrane Database reveals only two randomized controlled trials of psychotherapeutic treatment for this condition. Gonzales-Jaimes and Turnbull-Plaza demonstrated that "mirror psychotherapy" for adjustment disorders with depressed mood secondary to a myocardial infarction was both an efficient and effective treatment. Mirror therapy is described as a type of therapy with psychocorporal, cognitive, and neurolinguistic components, with a holistic focus. Mirror therapy was compared to Gestalt psychotherapy or medical conversation in addition to a control group. An "activating intervention" (emphasizing the acquisition of coping skills and the regaining of control) was employed specifically for patients with adjustment disorder associated with occupational dysfunction. In comparison with the control group, the activating intervention decreased sick leave and shortened absenteeism. In a mixed study group of minor depression and adjustment disorders, brief psychodynamic therapy demonstrated greater improvement than brief supportive therapy in a 6-month follow-up. In an unpublished study of eye movement desensitization and reprocessing (EMDR), patients with adjustment disorder and anxious or mixed features, but not those with depressed mood, had significant improvement.

If talking therapy has not been successful in relieving symptoms, then a trial with a selective serotonin reuptake inhibitor (SSRI) (for adjustment disorder, depressed type) or benzodiazepine (for adjustment disorder, anxious type) is warranted. In a retrospective chart review, it appeared that adjustment disorder patients were twice as likely to respond to typical antidepressant therapy in contrast to depressive patients. In another study, the efficacy of etifoxine, a non-benzodiazepine anxiolytic drug, and lorazepam were compared in a primary care setting. Those on etifoxine had less rebound after stopping the medication.

Research is not conclusive on the use of psychopharmacological agents in patients with adjustment disorder. It would be preferred that cautious psychotropic drug administration is employed to avoid subjecting the patient to the risk of unfavorable medical drug-psychotropic drug adverse interactions. Psychotropic medication will not be necessary if the adjustment disorder resolves. If it evolves into a minor or major psychiatric disorder, then appropriate psychopharmacological agents should be employed. If the adjustment disorder does not respond to psychotherapy or the symptoms are significantly uncomfortable or disabling, then small doses of antidepressants and/or anxiolytics may be appropriate. This is especially true for patients with severe life stress(es) and an unrelenting depressed or anxious mood. Tricyclic antidepressants or buspirone are recommended in place of benzodiazepines for adjustment disorder patients with current or past excessive alcohol use, because of the greater risk in these patients of abuse of, or dependence on, the prescribed medications. The use of antidepressants is important for those patients with debilitating maladaptation and in whom the mood is pervasive, especially if a trial of psychotherapy has been shown to be ineffective. Psychopharmacological interventions can be started concurrently with psychotherapies in severe cases of adjustment disorders.

Cross-References

- ▶ Acute Stress Disorder
- ▶ Anxiety
- ▶ Benzodiazepines

▶ Depression and Related Compounds
▶ SSRIs
▶ Stress Disorders
▶ Subthreshold Diagnoses

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Adolescence and Responses to Drugs

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Synonyms

Adolescent neurodevelopmental vulnerability; Peri-adolescent psychopharmacology

Definition

Adolescence is a major developmental phase in which the body, brain, mind, and behavior of the child progress to those of an adult. Although it has long been known that mental functioning and behavior differ significantly between children and adults, an emerging body of evidence indicates that these changes are driven by changes in brain architecture and function. To the extent that these changes are the most robust in, or exclusive to, adolescence, this phase may also represent a context in which drugs impacting the central nervous system produce especially potent and long-lasting alterations.

Current Concepts and State of Knowledge

Adolescent Neurodevelopment

Adolescence encompasses the growth and alteration of many neural and somatic systems and spheres of function that evolve with differing developmental timelines both within and between individuals (Cicchetti and Cohen 2006). Given this complexity, precise definitions of its start and end are elusive. Adolescence is a phase of continuous change within a lifespan of continuous change, while cultural–legal demarcations of the onset of adulthood vary widely. Behavioral neuroscience assumes a general concept of peri-adolescence as the passage of the individual from characteristics of mind, brain, and behavior specific to, and shared among, children of different ages (i.e., from birth to ages 10–15), to characteristics shared among healthy adults (i.e., from age 18–25 and older) (Erickson and Chambers 2006; Romer and Walker 2007). Fundamentally, children are the recipients of teaching and caretaking; their role is to learn about their environment through instruction and play while inviting and acquiescing to caretaking. Adults are the providers of teaching and caretaking; their role is to manipulate, and work within, the environment in the service of caretaking. Between these age ranges (from approximately 13–23 years), adolescent neurodevelopment revises the brain from a design best adapted to play, learning, experimentation, and receiving care, to one best adapted to acting on what has been learned and delivering care.

Changes in Mind and Behavior

Adolescent neurodevelopment involves changes spanning multiple spheres of higher order central nervous system function and anatomy, including those that subserve cognition, emotion, and motivation (Romer and Walker 2007). Cognition in childhood, initially dependent on concrete interpretations of the physical world, and yet prone to fantasy and make-believe, becomes increasingly efficient and accurate with respect to classifying and predicting complex contingencies. Emotions are used less unidimensionally for engendering caretaking or exploring relationships with specific caregivers. They become more complex,

and at times volatile, both for asserting independence from caregivers, and for experimenting with and learning effective emotional conduct across a potentially large variety of peer and other social relationships spanning diverse personal and occupational domains (Nelson et al. 2004). Motivation becomes extremely sensitive to novelty and social competition, especially with respect to stimuli or situations that characterize adult social, sexual or occupational roles, and skill sets (Chambers et al. 2003). Reflecting a desire to achieve adult abilities, and even adult levels of power, the adolescent is motivated to act as an adult, even though prior experience has been largely limited to imaginative play and verbal or role-modeled instruction. Instead of playing with toy cars, the adolescent is suddenly motivated to drive real ones.

Changes in Brain Form and Function

Profound changes involving multiple brain regions underlie the adolescent transformation. Those changes occurring in the ► prefrontal cortex (PFC) are currently the best characterized (Erickson and Chambers 2006; Romer and Walker 2007). The PFC functions as the brain's closest analogue to the central processing unit of a computer; it governs decision making and regulates cognitive working memory, attention, and emotional awareness. Its central functional role and high degree of connectivity with a diversity of cortical and subcortical brain regions, which are more directly specialized in memory formation, emotion, and motivation, probably relate to its keystone position as the last cortical structure to undergo significant micro- and macrostructural revision prior to adulthood. Within the PFC, both excitatory and inhibitory neurons undergo shifts in patterns of connectivity, in which many short-range connections are eliminated (e.g., ► synaptic pruning), and long-range (e.g., transcortical) connections undergo final stages of ► myelination, rendering them more efficient for transferring information. Macrostructurally, these changes correspond to overall declines in PFC energy demands and PFC gray matter thickness. In totality, these changes correspond to the development of greater computational efficiency, adult cognitive styles, and the ability of PFC cognitive processes to intervene in or regulate complex emotional and motivational processes.

While research on developmental changes within subcortical regions primarily involved in memory formation (e.g., ► hippocampus), emotion (e.g., ► amygdala), and motivation (e.g., ► nucleus accumbens/mesolimbic ► dopamine system) is itself in an early developmental stage, growing evidence indicates that, like the PFC, all of these regions undergo peri-adolescent developmental revision (Cicchetti and Cohen 2006; Nelson et al. 2004). Changes spanning these areas include alterations in intrinsic and extrinsic neural connectivities involving multiple neurotransmitter, neuropeptide and neurohormonal systems that collectively change the way these regions process information and communicate with each other and the PFC. For example, parameters of dopamine neurotransmission into the PFC and nucleus accumbens undergo peri-adolescent maturational changes implicated in the particularly robust aspects of adolescent motivation, such as behavioral sensitivity to novel stimuli (Romer and Walker 2007). While both the hippocampus and the amygdala are richly endowed with neurohormonal receptors related to stress responsivity (e.g., corticosteroids) and sexuality (e.g., estrogens and androgens), peri-adolescent changes in the levels and regulation of these hormones can have profound effects on cellular and local circuit functions (Chambers et al. 2003; Nelson et al. 2004). These changes in turn contribute to adolescent-age alterations in emotional, social, and sexual behavior and related motivational programming, as mediated in part via the connectivity of the hippocampus and the amygdala with the nucleus accumbens and prefrontal cortex.

An important aspect shared among these modulatory neurotransmitters and neurohormonal factors is that they are powerful inducers and facilitators of ► neuroplasticity. While the information-processing and learning and memory functions of neurons and local neural connections throughout the central nervous system are most directly carried by changes in the way excitatory and inhibitory transmitters (e.g., ► glutamate and ► GABA) send signals between individual neurons, these modulatory factors (e.g., dopamine and corticosteroids) can produce more broadly distributed influences on the manner, scope, quality, and depth of local neuroplastic changes. These effects are observable on the molecular, cellular, and physiological as changes in cellular mechanisms that govern glutamatergic/GABA transmission, neural firing properties, dendritic arborizations of individual neurons, birth of new neurons, and stimuli-induced activation patterns spanning whole neural networks. Thus, by hierarchically influencing mechanisms of local plasticity in a way that is broadly distributed throughout multiple brain regions in a coordinated fashion, these modulatory systems likely play a key role in the global theme of structural revision in adolescent neurodevelopment. Understanding how these neuromodulatory factors are themselves changed during adolescence, as a result of developmentally timed and environmentally triggered changes in gene expression, will increasingly form the focus of future research on adolescent neurodevelopment.

Impact of Drugs During Peri-Adolescent Neurodevelopment

Peri-adolescent changes in neural systems function, architecture, and plasticity, unparalleled by neural events in middle childhood or adulthood, may reflect a transition that relates to the flexibility–stability dilemma, a fundamental concept of theoretical neuroscience. In this concept, neural systems are thought to operate optimally in the service of one of two goals: learning new information (flexibility) vs. acting on what has been learned (stability) (Liljenstrom 2003). Importantly, while the brain is capable of serving both of these goals to some extent, it cannot serve them both to the highest degree possible simultaneously. The vast yet limited biological resources of the brain, and physical rules of ▶ neuroinformatics, would require that the brain operate in a way that optimizes one goal at the expense of the other. By developmental design, flexibility is favored in childhood, while stability is most adaptive in adulthood. In adolescent neurodevelopment, the brain must undergo a considerable revision of architecture and function to shift the brain toward the stability goal. During this phase, the artificial (e.g., pharmacological) perturbation of neural processes and systems, particularly those that impact the neuroplasticity of cognitive, motivational, and emotional substrates, could produce effects that are thereafter "locked-in," in a semipermanent way, as the brain shifts its design toward the stability goal.

Impact of Drug Exposure on Motivation and Addiction Vulnerability

The most clear and broad-based evidence for such a pharmacological effect is the heightened capacity of addictive drug exposure during adolescence for determining future motivational programming with respect to the acquisition of addictive disorders (Chambers et al. 2003). The vast majority of adult-age addictions begin in adolescence (ages 15–25). Greater accumulated dose of drug exposure, earlier exposure, and the extent of multidrug experimentation during adolescence are all risk factors for adult addictions.

The advancement in our understanding of this developmental age vulnerability to addictions has been informed in part by research on ▶ dual diagnosis in mental illnesses such as ▶ schizophrenia, which involve both peri-adolescent developmental onset and high rates of addiction comorbidity. Adolescence is a normative period of heightened novelty seeking, behavioral disinhibition, and risk taking, all serving as component manifestations of the more general construct of impulsivity (Erickson and Chambers 2006). ▶ Impulsivity, whether occurring in normative adolescence or as an abnormal feature of adult mental illness, is a general trait-marker of addiction vulnerability (Erickson and Chambers 2006; Redish et al. 2008). Moreover, it is often a manifestation of those immature or dysfunctional PFC substrates that are responsible for decision making and response inhibition. As reviewed earlier, during adolescence the PFC is normally immature and thus incapable of adult levels of decision making and behavioral control. At the same time, subcortical motivational systems (e.g., the nucleus accumbens/dopamine system) are operating in a particularly robust manner. This not only allows motivational programming to be relatively sensitive to novel or other reinforcing stimuli that promote dopamine transmission. By virtue of the capability of dopamine itself to regulate neuroplastic events in the PFC and nucleus accumbens, this robustness of function may also facilitate changes governing maturational plasticity underlying the installment of stable, long-lasting, motivational repertoires (Chambers et al. 2003, 2007). In adolescence, this scenario may be viewed simplistically as a car acquiring an accelerator before it acquires adequate brakes. Of course, only the accelerator can make the car go, and give the driver cause for needing, and learning how and when, to apply the brakes. In normative adolescent neurodevelopment, this developmental plan, in which the PFC matures under conditions of robust motivational function, is thought to be a necessary aspect of initiating experiential-action learning, with all of its hazards (Chambers et al. 2003). With addictive drug exposure, and by virtue of the shared pharmacological effect of addictive drugs to further augment dopamine transmission and exert neuroplastic effects, motivational–behavioral repertoires (and underlying neural systems) are potently and more semipermanently sculpted to include drug-seeking and – taking as frequent behavioral options (Chambers et al. 2007).

Impact of Drug Exposure on Cognition and Emotion

The centrality of dopamine in both natural motivation and in the reinforcing properties of drugs with diverse psychoactive and pharmacological profiles (e.g., nicotine, alcohol, cocaine, amphetamine, cannabinoids, and opiates) has rendered progress in our understanding of the responsiveness of adolescents to the motivational properties of drugs a relatively straightforward process. Expanding outward from this core of knowledge, research is beginning to explore the more complex task of understanding how adolescent neurodevelopmental change involving spheres of function other than motivation, and encompassing other neurotransmitter systems and brain regions, may make adolescents particularly vulnerable to long-lasting cognitive and emotional effects of drug

exposure. In essence, this exploration is a contemporary variant of the long-pursued notion that drug use can cause or predispose to permanent acquisition of psychiatric illness or illness features. For many recreational drugs frequently used in the general population, this thesis has not proven easy to support with firm clinical and epidemiological data. However, new evidence detailing the unique and profound neurodevelopmental revision of the brain during adolescence, along with the recognition of the capacity of drugs to modulate cognitive and emotional functions during this developmental period, has renewed interest in this area. For instance, new findings indicate that peri-adolescent ► nicotine exposure can have an enduring impact on acetylcholine neurotransmission in the brain, while producing long-lasting cognitive and emotional dysfunction potentially consistent with features of mental illness (Slotkin 2008). Similarly, ► alcohol as a drug active at glutamatergic and GABAergic synapses, and in a host of other neurotransmitter systems, may produce semipermanent cognitive and emotional changes (Clark et al. 2008). Since endogenous ► cannabinoids are robustly active in PFC and hippocampal networks as modulators of glutamatergic and GABAergic transmission and plasticity, marijuana smoking in adolescence could have particularly profound and long-lasting effects toward changing thresholds for developing mental disorders that involve these regions, including ► schizophrenia and ► depression.

Conclusion

As research on adolescent drug effects continues to evolve, it is expected that animal modeling, involving developmentally timed drug exposures in peri-adolescence, will play an especially crucial role in advancing understanding in this field, given the ethical boundaries, time and cost expenses, and lack of environmental control inherent to longitudinal prospective human studies. Examining adolescent developmental effects of recreational drugs is also expected to inform and inspire investigations that may reveal properties of therapeutic agents that may semipermanently ameliorate or abort illness trajectories for varieties of mental disorders of peri-adolescent onset or worsening.

Cross-References

► Alcohol
► Attention
► Cannabinoids
► Cocaine
► Excitatory Amino Acids and Their Antagonists
► Glutamate
► Impulsivity
► Inhibitory Amino Acids and Their Receptor Ligands
► Long-Term Potentiation and Memory
► Neurogenesis
► Neurosteroids
► Nicotine
► Protein Synthesis and Memory
► Schizophrenia
► Synaptic Plasticity (paired with neuroplasticity)

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Adolescent Neurodevelopmental Vulnerability

► Adolescence and Responses to Drugs

Adrenocorticotropic Hormone

Definition

ACTH or corticotrophin is released from the anterior pituitary corticotrophs into the circulation for stimulating adrenal glucocorticoid synthesis and secretion. It is derived from the pro-opiomelanocortin (POMC) precursor.

Adult Neurogenesis

► Neurogenesis

Adventuresome

► Risk Taking

Adverse Effect

Synonyms
Adverse reaction; Adverse side effect

Definition
An adverse event is a harmful effect that is the result of a medication or intervention.

Adverse Reaction

► Adverse Effect

Adverse Side Effect

► Adverse Effect

AEA

► N-arachidonylethanolamine

Affect

► Emotion and Mood

Affective Disorders

► Mood Disorders

Affective Dominant

Definition
Type of schizoaffective disorder dominated by depressive or manic symptomatology.

Affective State

Synonyms
Current mood; Emotional state

Definition
Moods, emotions, and feelings elicited by stimuli in the environment, including interactions with conspecifics. The transient nature of these experiences results in these affective responses being finite, though their duration can range from seconds to weeks.

Cross-References
► Emotion and Mood

Affinity

Synonyms
K_D^{-1}

Definition
A property of drugs that bind to receptors that reflects the attractiveness of the drug to the receptor, or the likelihood that the drug will bind to the receptor when it is in close proximity. Both receptor agonists and antagonists have affinity for receptors. It is equal to the ratio of the concentration of the bound complex to the product of the reactant concentrations at equilibrium, [LR]/([L], and is usually described in terms of its reciprocal, the equilibrium dissociation constant.

Aggression

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Synonyms

Aggressiveness; Aggressive behavior; Agonistic behavior; Violence

Definition

In most general terms, aggression refers to behavior that is harmful to others or expresses the intention to do so.

Impact of Psychoactive Drugs

Types of Aggression

Aggressive acts are shaped by social experiences via action on molecular events in discrete ascending aminergic pathways from the mesencephalon to the limbic and cortical targets, and the cascade of these intracellular events is increasingly understood. Aggressive behavior is an important behavioral adaptation in all phyla of living creatures, mainly serving reproductive purposes. In addition, maladaptive types of aggressive behavior are the focus of human and veterinary medicine and also of the criminal justice system. Types of aggression differ in terms of their ontogenetic and phylogenetic origins, motivations, and functions, and all indications are in their neurobiological mechanisms. Clinicians distinguish between those types of aggression that include hostile, affective, impulsive, and reactive features from those that are characterized by proactive, premeditated, instrumental, controlled, and also predatory elements. Behavioral researchers, by contrast, focus on adaptive types of aggressive behavior, mostly as part of reproductive strategies such as aggression during the formation and maintenance of dominance hierarchies or territories. Animal species that disperse during the reproductively active lifespan as well as those that live cohesively, engage in aggressive behavior in order to secure the resources for reproduction or to protect the offspring.

The classic ethological thesis that ritualized displays are the major means to maintain a dominance hierarchy has been challenged by rare, but repeatedly documented episodes of intensely injurious aggression in chimpanzees that pursue neighboring groups in order to kill them. The significance of lethal raiding parties in hominids constitutes problems, not the least of which for the typology of aggressive behavior, since it focuses on rare events that are carefully planned and coordinated and, at the same time, involve intense autonomic and behavioral excitement. The adaptive purpose of these lethal raids eludes the traditional theoretical framework. Conventionally, once the frequency, duration, and intensity of aggressive behavior escalate beyond the species-typical levels, it is considered maladaptive and may constitute a behavioral pathology in need of intervention.

Much pharmacological, neurochemical, and molecular biology research on aggressive behavior uses laboratory mice, often recombinant inbred strains and transgenic lines. These animals are housed in same-sex groups, preventing the species-typical formation of demes ("breeding units"), and only a small proportion of these mice actually engage in territorial aggressive behavior that is characteristic of this pugnacious species. Under captive laboratory conditions, group-housed animals may develop a despotic social organization, with one male dominating all other group members.

Neurotransmitters

More than any other neurochemical system, brain ▶ serotonin remains the focus for neurobiological studies of mechanisms mediating impulsive, hostile, and intensely violent outbursts as well as predatory-like aggression. Only detectable in trace amounts in mammalian brain, this phylogenetically old transmitter, arising from cells along the center of the neuroaxis and acting in mammals on at least 14 different receptor subtypes, has a significant role in aggression ranging from invertebrates to humans. Several neurotransmitters comprising amines, acids, ▶ neuropeptides, and ▶ neurosteroids interact with serotonin (5-hydroxytryptamine, 5-HT).

Glutamate

▶ Glutamate and ▶ GABA are the extensively distributed excitatory and inhibitory transmitters, and they modulate the cellular and behavioral effects of serotonin at several levels of the ascending mesocorticolimbic pathways. Early research has established an excitatory role of glutamate in violent outbursts during seizures, although the precise role of glutamate activity during ictal and inter-ictal events remains to be defined. Sparse evidence shows how pharmacological manipulations of glutamate receptor subtypes affect aggressive behavior and also suggests a potential role of ▶ NMDA receptors in escalated aggressive behavior. Low-affinity channel blockers such as ▶ memantine or partial agonists to the glycine-binding site on the NMDA receptor may offer potential options in the pharmacotherapeutic management of escalated aggressive behavior due to their favorable side-effect profile. Regulatory changes in NMDA receptor systems occur also in individuals who are repeatedly victimized by aggressors as revealed by prevention of their sensitized response to psychomotor stimulants with protective administration of NMDA receptor antagonists. It will be of considerable interest to learn how glutamate modulates the ascending monoaminergic, especially dopaminergic and serotonergic projections to limbic and cortical target areas. Several

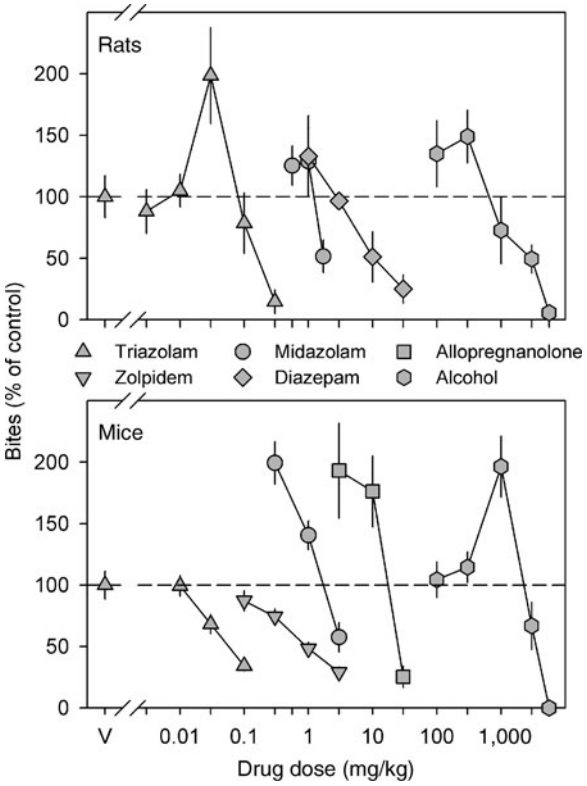
metabotropic glutamate receptors appear to be promising pharmacotherapeutic targets in the management of escalated aggressive behavior.

GABA

By distinction from glutamate, GABA and particularly, the $GABA_A$ receptor complex have been consistently implicated in the neural control of several types of aggressive behavior. Especially positive ► allosteric modulators of the $GABA_A$ receptors such as benzodiazepines, barbiturates, ethanol, and progestin-derived neurosteroids can increase aggressive behavior after low acute doses or after tolerance to the sedative doses has developed (Fig. 1). At moderate and higher doses, the antiaggressive effects of these substances are accompanied by sedation and motor impairment. The bidirectional effects of allosteric positive modulators of the $GABA_A$ receptors depend not only on the dose, but also on the context and the prior experience with aggressive behavior. When social consequences lower the rate of aggressive behavior, benzodiazepines and ethanol are more likely to increase its occurrence. In spite of the consistent epidemiological evidence linking alcohol to two thirds of all violent crimes, the neurobiological mechanism of action for these alcohol effects remains elusive. The current challenge is to understand how an individual's prior experiences with aggressive behavior modify the $GABA_A$ receptor complex so that proaggressive effects of $GABA_A$ positive modulators emerge. The prevalent current hypothesis attributes the divergent effects of $GABA_A$ positive modulators on aggressive behavior to differential expression of genes encoding the subunits that form the pentameric $GABA_A$ receptor complexes. Emerging data from gene deletion and pharmacological antagonism studies suggest a structural dissociation between the anxiety-attenuating, sedative, and aggression-heightening effects of $GABA_A$ receptor positive modulation, primarily due to the differential role of alpha subunits. In addition to the $GABA_A$ receptor, the $GABA_B$ receptors are widely distributed throughout the neuroaxis. The population of $GABA_B$ receptors in the dorsal raphé nucleus modulates serotonin cells, and this may be the mechanism via which $GABA_B$ receptor agonists can increase aggressive behavior in mice.

Norepinephrine

Catecholaminergic and serotonergic pathways contain reciprocal anatomical links which provide the basis for extensive functional interactions. Particularly, intense arousal that is associated with salient life events, among them certain types of aggressive behavior on just observing a fight, is based on elevated activity in noradrenergic cell bodies in locus coeruleus and cortical noradrenergic terminals. Pharmacological blockade of beta receptors may achieve its calming effects in patients with intensely aggressive, hostile outbursts by reducing noradrenergic hyperactivity, although alternatively, beta blockers also act as antagonists at $5\text{-}HT_{1A}$ receptors. Molecular manipulations of the genes encoding for the noradrenergic transporters, or metabolic enzymes such as COMT have so far resulted in inconsistent results with regard to aggressive behavior and traits.



Aggression. Fig. 1. $GABA_A$ positive allosteric modulators and aggression. Biphasic effects of $GABA_A$ receptor positive modulators on aggression in rats (*top*) and mice (*bottom*). Low doses of alcohol (filled hexagon), the benzodiazepines diazepam (filled diamonds, rats only) and midazolam (filled circles), and the neurosteroid allopregnanolone (filled triangles, mice only) increase the mean (±SEM, vertical lines) number of attack bites, expressed as a percentage of vehicle control, while higher doses decrease this measure of aggression. Triazolam (filled upward triangles) increases attack bites in rats but not mice. No increase in aggression was seen after treatment with zolpidem, the alpha1-preferring agonist (filled downward triangles, mice only). The dotted horizontal line represents the baseline at 100%. (From Miczek et al. 2007.)

Dopamine

Specific dopamine (DA) pathways and DA receptor subtypes critically contribute to the neurobiological mechanisms of species-typical and escalated, pathological types of aggressive behavior. Anatomical and pharmacological data provide evidence for serotonergic receptors on soma of DA neurons in the VTA and substantia nigra suggesting modulation of ascending DA pathways by 5-HT.

The most widespread option for pharmacotherapeutic management of aggressive individuals relies on antipsychotic medication that acts via blockade of dopamine (DA) D_2 receptors, although the antiaggressive effects of ► first-generation antipsychotics such as ► haloperidol or ► chlorpromazine are embedded in sedative and motor-incapacitating side effects. At present, the so-called ► atypical antipsychotic drugs with more complex mechanisms appear to be preferred as antiaggressive medication on account of a more favorable side-effect profile. Clearly, there continues to be a need for more satisfactory medication development.

Case studies point to ► amphetamine intoxication as a potentially triggering event for lethal violence. At intermediate doses, amphetamine disrupts many types of social behavior and at lower doses, it may increase aggressive behavior, probably due to its antifatigue and arousing effects. Increased corticolimbic DA can be detected via in vivo measurement and imaging techniques in individuals who react defensively to an aggressive confrontation and who prepare for such an event. Anatomical and temporal analysis with higher resolution may enable a more precise delineation of DA activity in different phases and types of aggressive behavior.

Genetic disruption of the genes that are critically involved in the inactivation of ► catecholamines, COMT, and MAO-A can promote aggressive behavior in male mice. It is tempting to relate these preclinical data to the specific polymorphism in the gene for COMT which is associated with increased aggressive behavior in schizophrenic men.

MAO

Considerable evidence links monoamine oxidase (MAO)-A to traits of violent behavior. It remains to be determined which of the monoamines is primarily responsible for the effects of mutations or deletions of the gene for this enzyme or for the effects of its pharmacological inhibition. An early influential study illustrated how acts of violence by the male members of a Dutch family who were also mentally retarded, appears to be linked to a missense mutation in the gene for this enzyme on the X chromosome. In preclinical research, mice lacking this gene were found to initiate injurious aggressive behavior faster. Probably, the most significant findings link the allelic variant with low activity of MAO-A to the antisocial and violent behavior only in those adult males who were severely maltreated in childhood, whereas the allelic variant with high MAO-A activity or the absence of maltreatment had no such influence in adults. A variable-number tandem repeat polymorphisms of MAO-A may also be associated with the increased probability of a life history of aggressive behavior, particularly aggression involving dysregulated affect. However, there is also evidence that links lower MAO-A activity to aggressive tendencies independent from polymorphisms in MAO-A. While MAO-A is one of the leading candidates, a number of inconsistent findings obscure the causal relationship between the expression of the MAO-A gene, its interaction with early life experiences, and traits of hostile, antisocial, aggressive outbursts.

The differential expression of specific genes for MAO-A in aggressive and nonaggressive individuals is often associated with alterations in the brain serotonin system, based on additional pharmacological studies. A wide array of methodological approaches has implicated the serotonin system in aggressive traits, impulsivity, and also in the initiation and termination of certain types of aggressive behavior. A venerable hypothesis postulated a serotonin deficiency as the characteristic of the trait of ► impulsive aggression, receiving early support from the 5-HT assay data obtained from the hindbrain of isolated aggressive mice and CSF 5-HIAA samples of patients. The significance of CSF 5-HIAA measures is compromised by the uncertainty as to their precise anatomical origin. Direct challenges of brain 5-HT functions with either an agonist or a tryptophan-depleted diet demonstrated a blunted prolactin response in violent patients with various diagnoses, possibly due to actions on 5-HT_{1A} and 5-HT_{2A} receptors. Instead of relying on a single sample of CSF, a peripheral marker, or an endocrine response to a single pharmacochallenge, in vivo microdialysis reveals no changes in cortical 5-HT during the phase of initiating an attack, but then 5-HT begins to decline once the fight is progressing and terminating. The termination of an anticipated aggressive confrontation is accompanied by a decrease in accumbal 5-HT suggesting a potentially significant role for 5-HT in the inhibition of aggressive behavior. Thus, the tonic levels of 5-HT activity have been linked to aggressive traits, and phasic changes in 5-HT may be relevant to the termination of an aggressive burst.

SERT

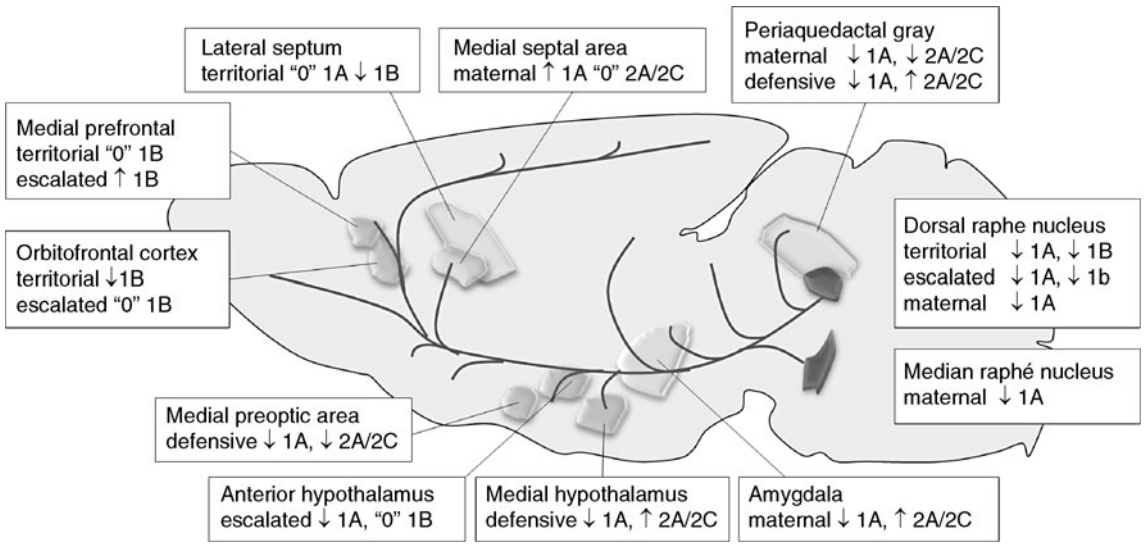
Several receptor families and the 5-HT transporter (SERT) have been characterized in terms of their genetic

basis and molecular features. Pharmacological and molecular genetics studies have begun to implicate the 5-HT_1 and 5-HT_2 receptor families and SERT in different types of aggressive behavior. Agonists of the 5-HT_{1A} and 5-HT_{1B} receptors reduce aggressive behavior; and the antiaggressive effects of the 1B receptor subtype are behaviorally specific and especially, effective in situations that engender escalated levels of aggressive behavior, although these effects remain to be translated to the clinic. Microinjection studies provide evidence that 5-HT_{1A} and 5-HT_{1B} receptor agonists can achieve their antiaggressive effects via action at either somatodendritic autoreceptors in the dorsal raphé nuclei or the presynaptic terminal autoreceptors or the postsynaptic heteroreceptors (Fig. 2). If, in fact, the decrease in extracellular levels of corticolimbic 5-HT after 5-HT_{1A} and 5-HT_{1B} receptor stimulation constitutes a critical mechanism of action for the antiaggressive effects, a significant revision of the serotonin deficiency hypothesis is required. Genetic deletion studies of 5-HT_{1A} and 5-HT_{1B} receptors generate a more complex pattern of results that appears to be influenced by the genetic background of the mouse or by developmental compensations in mutant mice. Similarly, associations between ▶ polymorphisms of 5-HT_{1A} and 5-HT_{1B} receptors and aggressive traits in humans remain inconsistent.

5-HT Receptors

Antagonism of 5-HT_{2A} receptors represents the mechanism via which some atypical antipsychotic compounds achieve their calming effects in patients with diagnoses that range from schizophrenia, dementia, depression, and posttraumatic stress disorders (PTSD). Yet, the side-effect profile of these agents highlights the problematic nature of this new class of antipsychotic agents. Preclinical studies of the 5-HT_{2A} and 5-HT_{2C} receptors have to await the development of more selectively acting molecular tools, since at present it is not possible to differentiate between the antiaggressive effects of agonists and antagonists at these receptor subtypes. Similarly, linkage studies between polymorphisms in the 5-HT_{2A} receptor and impulsive-aggressive or antisocial traits require replication.

Blockade of the reuptake mechanism for 5-HT via the SERT reduces aggressive episodes in most patients, especially when given over extended periods. Large meta-analyses have identified the exceptional nature of the occasional reports of increased aggressivity and suicidal tendencies among those treated with selective serotonin reuptake inhibitors (SSRI). Preclinical studies have shown that acute and chronic treatment with SSRIs reduces aggressive behavior in species ranging from invertebrates to primates. Chronic SSRI administration can also restore competent agonistic



Aggression. Fig. 2. Modulation of aggressive behaviors in rodents by microinjections of 5-HT_{1A}, 5-HT_{1B}, and 5-$HT_{2A/2C}$ receptor agonists. Text boxes show that local injections of 5-HT_{1A} receptor (1A), 5-HT_{1B} receptor (1B), or 5-$HT_{2A/2C}$ receptor (2A/2C) agonist increases (↑), decreases (↓), or has no effect ("0") on territorial, escalated, maternal, and defensive aggressive behaviors. Serotonergic neurons originate from the raphé nuclei and project to several brain areas.

interactions in placid laboratory strains of rats that do not show intact species-typical aggressive behavior.

The short-length allele in the serotonin-transporter gene-linked polymorphic region (5-HTTLPR) leads to lower SERT expression and lower serotonergic activity relative to those with the long-length allele. Some evidence supports the association of the short allele with increased hostility, impulsivity, and aggressiveness, primarily in males. The contribution of the 5-HTTLPR to the variation in aggressive personality traits is relatively small and appears to depend on epistatic influences and on environmental triggers. Early stressful life experiences in monkeys and humans may increase the probability of escalated aggression toward others and themselves, particularly in those individuals who carry the short-length allele. A more adequate understanding of SERT expression in corticolimbic regions promises to be relevant for the display of aggressive personality traits.

Brain serotonin modulates and is modulated by other amines, amino acids, and also neuropeptides and neurosteroids. For example, serotonergic projections in specific hypothalamic nuclei may regulate the release and action of vasopressin (VP), a neuropeptide that is associated with high rates of aggressive behavior in several animal species via action at 5-HT_{1A} and 5-HT_{1B} receptors. Similarly, the modulation of serotonergic neurons by corticotrophic releasing factor (CRF) and opioid peptides provides the anatomical basis for functional interactions that appear relevant to aggressive behavior. The promising information on CRF, GABA, and glutamate in amygdaloid connections with hypothalamic and brainstem structures during displays of intense emotion should prompt a detailed examination of these mechanisms in escalated types of aggressive behavior.

Cross-References

- ▶ Aggression, Clinical
- ▶ Antidepressants
- ▶ Antipsychotics
- ▶ Social Stress
- ▶ SSRI

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Aggressive Behavior

- ▶ Aggression
- ▶ Aggressive Behavior: Clinical Aspects

Aggressive Behavior: Clinical Aspects

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Synonyms

Aggressiveness; Aggressive behavior; Agonistic behavior; Impulsive aggression; Violence

Definition

Behavior by an individual directed at another person or object in which either verbal force or physical force is used to injure, coerce, or express anger.

Role of Pharmacotherapy

Types of Clinical Aggression

Human aggression constitutes a multidetermined act that results in physical or verbal injury to self, others, or objects. It appears in several forms and may be defensive, premeditated (e.g., predatory), or impulsive (e.g., nonpremeditated)

in nature. Defensive aggression is generally seen as dictated by particular external realities and within the normal range of human behavior. Premeditated and impulsive aggressive behaviors are commonly viewed as pathological. Specific acts of aggression may be situational, but the tendency to behave aggressively represents a behavioral trait. While the frequency of aggressive acts tends to decrease with advancing age, numerous studies document that the trait of aggressiveness begins early in life and continues through adulthood. Both impulsive and premeditated aggression represents the potential for significant physical and psychological harm to the individual, to those subjected to the effects and to society in general. However, a converging pattern of empirical data from a variety of studies consistently links *impulsive*, but not premeditated, aggression to biological, environmental, and pharmacological or psychological treatment response factors.

One guiding principle to the consideration of human aggression is that biological and psychological factors contribute significantly to this behavior. Biological factors contribute to aggressive behavior through reduced inhibitory, and/or increased facilitatory, neuronal inputs to behavior. Research in this area has found utmost support for the role of inhibitory behavioral inputs modulated by brain serotonin (5-HT) function. The role of various neurotransmitter systems in increasing facilitatory input for aggressive behavior has received less attention and, in contrast to 5-HT, the results have been somewhat inconsistent. On the other hand, psychotherapy outcome research has successfully focused attention in this general area, vis-a-vis the relationship between the impulsive aggressive individual and his/her external/internal environment as facilitatory in generating impulsive aggressive behavior. Here, the focus is on the hypothesis that vulnerable individuals manifest impulsive aggressive behavior in response to external/internal stimuli perceived as "provocative" or "aversive" in nature which lead to variable states of anger that drive susceptible individuals (e.g., individuals with reduced central 5-HT function) to exceed their "threshold" for effective behavioral inhibition so that an impulsive aggressive outburst is initiated. If so, treatment aimed at increasing central (5-HT mediated) behavioral inhibitory tone and reducing states of high anger (i.e., negative emotionality) should be an effective strategy in treating impulsive aggressive behavior in human subjects. To date, research has shown the potential efficacy of (1) pharmacological approaches to reducing impulsive aggressive outbursts and, (2) psychological approaches to reducing states of acute (and chronic) anger. To date, however, neither approach has been combined or compared in the same study.

Impulsive Aggression Expressed as a Dimension

Behavioral Genetics of Impulsive Aggression

Data from twin, adoption, and family studies suggest genetic influence on aggression. Heritability estimates for measures of aggression are moderately substantial in adults ranging from 44% to 72% and a recent meta-analysis confirmed the presence of a substantial genetic influence for aggression. Heritability estimates were most pronounced for aggression measures reflecting anger and hostility, or anger, impulsiveness, and irritability. It is noteworthy that these same phenomena are associated with the clinical profile of intermittent explosive disorder (IED).

Psychosocial/Environmental Correlates of Impulsive Aggression

The most important psychosocial factors involved in the development of aggression appear to be low socioeconomic status, ineffective parenting style, as well as physical punishment in childhood and exposure to aggression within and outside of the family. Notably, harsh discipline and child abuse (regardless of SES status) have been found to predict the development of *impulsive*, but not nonimpulsive, aggressive behavior in children. In one study, 41% of children abused in the first 5 years of their life became *impulsively* aggressive later in life, compared with 15% of nonabused children; in contrast, none of the nonimpulsively aggressive subjects had a history of child abuse.

Neurochemical Correlates of Impulsive Aggression

Among all of the biological factors potentially involved in aggression, the most studied factors relate to brain neurochemistry, specifically monoamines such as serotonin (5-HT) and other centrally acting neurotransmitters (Brown et al. 1979; Coccaro and Siever 2005; Coccaro et al. 1989). Evidence of a role of brain 5-HT in human aggression is especially strong and points to an inverse relationship between brain 5-HT activity and aggression in animal models, nonhuman primates, and humans. In human studies, various measures reflecting central (as well as peripheral) 5-HT function have been shown to correlate inversely with life history, questionnaire, and laboratory measures of aggression. Most importantly, the type of aggression associated with reduced central 5-HT function appears to be *impulsive*, rather than nonimpulsive aggression (Linnoila et al. 1983). In human studies, there are selective cases where the relationship between 5-HT and aggression is positive in direction or does not exist at all. This may be due to the presence of other factors (e.g., diagnostic group; drug dependence; developmental stage) which may involve differential

contributions from other neurotransmitter systems that also influence the tendency to react aggressively in social contexts. Limited evidence also supports a role for Non-5-HT brain systems and modulators in impulsive aggression. These findings suggest a permissive role for ► dopamine, ► norepinephrine, vasopressin, testosterone, and an inhibitory interaction between neuronal nitric oxide synthase and testosterone in rodents.

Functional Neuroanatomy of Aggression-Related Disorders in Humans

While IED is the only DSM-IV disorder (see later) for which aggression is the cardinal symptom, both borderline personality disorder (BPD) and antisocial personality disorder (AsPD) share a number of attributes associated with aggression as a dimension. At their most basic level, all three disorders are associated with increased anger and irritability as well as self- and other-directed aggression. All three diagnostic groups demonstrate a number of the deficits associated with the orbital ► medial prefrontal cortex (OMPFC)-amygdala tract including deficiencies of executive functions and socioemotional information processing. For IED, a series of PET studies on "impulsive aggressive" patients with both IED and BPD fail to parallel the increase in OMPFC metabolism by normal controls in response to acute administration of serotonin agonists, suggesting an important reduction in OMPFC function in impulsive aggressive individuals (New et al. 2002). Notably, however, chronic administration of a serotonin agonist over 12 weeks can both increase OMPFC metabolism and reduce impulsive aggressive behaviors. A study of temporal lobe epilepsy patients with and without IED, found that a subgroup of 20% of the IED patients (BPD status not assessed) had "severe" amygdala atrophy. In contrast to these studies, the only available imaging data from subjects with IED, demonstrate that IED subjects (even those without BPD or AsPD) have augmented Amygdala (AMYG), and reduced OMPFC, fMRI blood oxygenated level dependent (BOLD) signal activation to angery faces (Coccaro et al. 2007). In contrast to IED, there is a larger imaging literature among patients with BPD and AsPD. Structural MRI studies show only weak support for the existence of reduced frontal volumes for either disorder with equally equivocal support for morphological changes in the amygdala. In contrast, PET and fMRI studies have produced a fairly consistent pattern of altered corticolimbic activation for both disorders. Three PET studies have reported reduced metabolism in the frontal (e.g., OMPFC) cortex in BPD subjects. Both BPD and AsPD populations show decreased OMPFC activation during emotional information processing (e.g., trauma scripts, a conditioned aversive stimulus) compared to control populations. Psychopaths also evidence less activation to abstract words in the right lateral frontal cortex. Both groups show increased amygdala activation to emotional stimuli; BPD subjects display enhanced amygdala activation to unpleasant pictures, as well as fearful and neutral words (viewed as negative by BPD subjects). While psychopaths showed increased amygdala activation when passively viewing negatively valenced pictures, amygdala activation for psychopaths may be attenuated/eliminated during emotional learning/conditioning tasks.

Recurrent, Problematic, Impulsive Aggressive Behavior as a Target for Study and Intervention: Intermittent Explosive Disorder

Although the term IED has only been in the DSM since the third edition (1980), the "construct" of a "disorder of impulsive aggression" has been in the DSM since its inception in 1956. Currently, it describes individuals with recurrent, problematic episodes of aggression not accounted for by other medical or psychiatric factors (Coccaro et al. 2005). While DSM-IV does not specifically refer to the aggression in IED as impulsive in nature, premeditated aggression is typically a characteristic seen in antisocial personality disorder.

Clinical Description

Aggressive outbursts in IED have a rapid onset, often without a recognizable prodromal period. Episodes are typically short-lived (less than 30 min) and involve verbal assault, destructive and nondestructive property assault, or physical assault. Aggressive outbursts most commonly occur in response to a minor provocation by a close intimate or associate, and IED subjects may have less severe episodes of verbal and nondestructive property assault in between more severe assaultive/destructive episodes. The episodes are associated with substantial distress, impairment in social functioning, occupational difficulty, and legal or financial problems.

Epidemiology

In the largest epidemiological study to date, the lifetime prevalence of IED by "Narrow" DSM-IV criteria is estimated at 5.4% with 1-year prevalence estimated at 2.7% (Kessler et al. 2006).

Age of Onset and Demographics

IED appears as early as childhood and peaks in mid-adolescence, with a mean age of onset in three separate studies ranging from 13.5 to 18.3 years. The average

duration of symptomatic IED ranges from 12 to 20 years to the whole lifetime. While initially thought to be more common in males, recent data suggest the gender difference in prevalence of IED may be closer to 1:1. Sociodemographic variables (e.g., sex, age, race, education, marital and occupational status, family income) do not appear to differ meaningfully as a function of IED status.

Laboratory Studies

To date, published data have reported IED subjects as having altered ▶ serotonin function compared with non-IED subjects or healthy controls. Other studies demonstrate a reduction in prolactin responses to ▶ fenfluramine challenge, in the numbers of platelet 5-HT transporters in IED subjects compared with non-IED subjects. Two FDG PET studies report low FDG utilization after D,L-fenfluramine challenge in frontal areas of the brain and low FDG utilization after m-CPP challenge in the anterior cingulate in IED subjects compared with healthy controls. A ligand binding study of the 5-HT transporter also reports reduced low 5-HT transporter availability in the anterior cingulate in IED subjects versus healthy controls. Finally, fMRI study demonstrates increased activation of AMYG, and reduced activation of OMPFC, to angry faces, in IED subjects compared with healthy controls.

Family Study

Family history study of IED subjects demonstrates a significantly elevated morbid risk for IED in relatives of IED, compared with healthy controls, probands (0.26 vs. 0.08, $p < 0.01$). Elevation in morbid risk for IED was not due to the presence of comorbid conditions among IED probands (e.g., history of suicide attempt, major depression, alcoholism, drug use disorder, etc.) and not due to elevations in morbid risk of other non-IED disorders in relatives (e.g., major depression, alcoholism, drug use disorders, anxiety disorder, and any other disorder).

Treatment of Impulsive Aggression and IED

Impulsive Aggression

Several psychopharmacologic agents appear to have effects on impulsive aggression. Classes of agents shown to have "antiaggressive" effects in ▶ double-blind, ▶ placebo-controlled trials of individuals with "primary" aggression (i.e., not secondary to psychosis, severe mood disorder, or organic brain syndromes) include mood stabilizers (e.g., ▶ lithium), 5-HT uptake inhibitors (e.g., fluoxetine) and, anticonvulsants (e.g., diphenylhydantoin, ▶ carbamazepine). While norepinephrine beta-blockers (e.g., ▶ propranolol, nadolol) have also been shown to reduce aggression, these agents have exclusively been tested in patient populations with "secondary" aggression (e.g., mental retardation, organic brain syndromes, etc.). Classes of agents which may have also "pro-aggressive" effects under some conditions include ▶ tricyclic antidepressants (e.g., ▶ amitriptyline), ▶ benzodiazepines, and stimulant and hallucinatory drugs of abuse (e.g., amphetamines, ▶ cocaine, ▶ phencyclidine). Emerging evidence of differential psychopharmacology is of critical importance, and findings from the literature of double-blind, placebo-controlled, clinical trials suggest that antiaggressive efficacy is specific to *impulsive*, rather than nonimpulsive, aggression.

Intermittent Explosive Disorder: Effect of Psychopharmacologic Intervention

▶ Fluoxetine demonstrates clear antiaggressive efficacy for reducing impulsive aggressive behavior in IED subjects compared with placebo (Coccaro et al. 2009). Fluoxetine's antiaggressive effect is most clearly seen on verbal aggression and aggression against objects. Despite this effect, somewhat less than 50% of IED subjects treated with fluoxetine achieve remission. Gains made with fluoxetine typically dissipate within 1 month after discontinuation but can be achieved again when the drug is reinstituted. Notably, fluoxetine has not been shown to increase aggression in IED subjects in placebo-controlled trials. Another placebo-controlled study of IED involving divalporex reported a favorable effect of this agent on overt aggression but only in IED subjects with comorbid cluster B personality disorder.

Intermittent Explosive Disorder: Effect of Psychosocial Intervention

While there are very few studies on the psychosocial treatment of impulsive aggression in adults, the efficacy of treatments that address the related constructs of anger dyscontrol and/or interpersonal aggression have been evaluated and suggest that relaxation training, interpersonal skill training, cognitive therapy, and multicomponent treatments all have moderate to large effects in the treatment of anger, and that the anger-reducing effects of anger treatment remain at follow-up. Of the different approaches for treating individuals with anger and aggression problems, cognitive restructuring, interpersonal skills training, multicomponent treatments, and relaxation skills had the strongest influence on aggression with effect sizes (Cohen's d) for the four types of treatment ranging from 1.06 to 1.87. Recently, a well-controlled study of cognitive behavior therapy in IED focusing on cognitive restructuring, relaxation and coping skills

training has been published, demonstrating significant reduction in impulsive aggressive behavior and in hostile automatic thoughts (McCloskey et al. 2008). The antiaggressive response in this study was similar to that seen with fluoxetine, suggesting the possibility that the two interventions, together, may be very effective in treating the impulsive aggression seen in individuals with IED.

Cross-References

- ► Aggression
- ► Neurotransmitters
- ► Serotonin
- ► SSRIs and Related Compounds

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Aggressiveness

- ► Aggression
- ► Aggressive Behavior: Clinical Aspects

Agomelatine

Definition

A melatonin MT1 and MT2 receptor agonist and 5-HT_{2C} antagonist, known to be effective in acute treatment and relapse prevention in major depressive disorder, it also has proven efficacy in Generalized Anxiety Disorder. It seems better tolerated than some SSRIs and ► venlafaxine, with fewer treatment-emergent side effects and a reduced burden of discontinuation symptoms.

Agonist

Synonyms

Receptor activator

Definition

A substance that binds to a receptor and alters the receptor state, resulting in a biological response. The response mimics the effect of the endogenous activator of the receptor. A compound can be a full agonist, which leads to the maximum possible response of the system under study, or a partial agonist, an agonist that under specified conditions does not elicit as large an effect as a full agonist. This is in contrast to antagonists that have affinity but no efficacy at a receptor, and hence have no observable effects except to modify the actions of an agonist at that receptor. Inverse agonists are compounds that produce a pharmacological response that is opposite in direction to that of an agonist.

Cross-References

- ► Allosteric Modulator
- ► Antagonist
- ► Inverse Agonists
- ► Partial Agonist

Agonistic Behavior

Definition

Refers to aggressive acts, postures, and displays to which the opponent reacts defensively and eventually displays submissive postures or flees.

Cross-References

- ► Aggression
- ► Aggressive Behavior: Clinical Aspects

Agoraphobia

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Synonyms

Avoidance of feared places and situations: Anticipatory anxiety; Fear of being alone; Fear of crowded areas; Fear of public places; Fear reaction to somatic anxiety symptoms; Phobic anxiety

Definition

Agoraphobia is an anxiety syndrome in which patients experience severe anxiety or distress in certain places or situations. This can lead to the avoidance of these situations. The places often represent those from which escape might be difficult or embarrassing e.g., public transport, supermarkets, crowds, or lifts. However, symptoms can also occur when the patient is alone in any place where they anticipate that they will be unable to obtain help should "the worst" happen. It often starts after unexplained spontaneous symptoms of anxiety or ► panic attacks, and the fear of anxiety symptoms rather than the actual attacks becomes predominant leading to a heightened state of anticipation.

Role of Pharmacotherapy

Diagnostic Categories

Currently, ► Panic attacks and agoraphobic avoidance are seen as independent yet closely related anxiety factors. Therefore, two main types of disorder involving agoraphobia are defined according to the major classification systems (APA 2000):

(a) Agoraphobia
(b) Panic Disorder with Agoraphobia

► Panic Disorder in combination with agoraphobia is more common as many patients with Panic Disorder go on to develop agoraphobia eventually. Agoraphobia develops when avoidance behavior intensifies and it results in impairment of personal work and social functioning. Some patients cannot leave the house alone and can become fearful when left alone at home. Agoraphobia without a history of panic disorder is rare in clinical studies (Kessler et al. 2006), but this may be because of the nature of the disorder e.g., strong fear of travel and widespread avoidance, would make clinic visits extremely difficult. In confirmation of this, it is more commonly found when researchers visit the home of the patient, as in community studies (Perugi et al. 2007). Agoraphobia also occurs as a ► comorbid condition with other Anxiety Disorders e.g., ► Social Anxiety Disorder, Generalized Anxiety Disorder, or with ► Depressive Disorders and it is also associated with Axis II personality disorders such as Avoidant or Dependent Personality Disorder. The risk of ► substance abuse, usually of alcohol or benzodiazepines, is increased in these patients when they need to travel or face situations they fear. The onset of agoraphobia is usually gradual and can easily become chronic if not recognized. Severe agoraphobic avoidance can be hidden for years and the disorder is therefore often inadequately treated.

A range of drugs is available to treat agoraphobia with and without panic disorder. However, after establishing the diagnosis, it is important to explain the nature and symptoms of anxiety to the patient clearly so that they do not present to numerous medical facilities searching for a physical rather than a psychological explanation for their somatic symptoms. Patients fear that panic symptoms signal imminent danger in terms of a heart attack, collapse, going mad, or death. Their understanding of bodily functions can be overestimated and simple explanations about ► hyperventilation and palpitations are extremely valuable. The value of regular exercise in understanding bodily symptoms and reducing tension and the frequency of panic attacks should also be explained. In addition, it is helpful to outline the negative impact of using both stimulant and sedative substances on symptoms. For example, large amounts of coffee (► caffeine) are likely to increase shakiness and heart rate and although ► Alcohol may lead to some temporary reduction in anxiety, its consumption is likely to lead to ► dependence, if used for this purpose.

Drugs used to Treat Agoraphobia With and Without Panic Disorder

Drug treatment and ► cognitive-behavioral therapy (CBT) have been shown to be equally effective in the acute treatment of agoraphobia with and without panic disorder (Mitte, 2005). However, it is essential to consider severity of agoraphobic avoidance, local service availability, and patient preference when selecting or combining treatments as some studies indicate that CBT is more acceptable to patients (Otto et al. 2001). The drug treatments which have been shown to be effective in the acute treatment of agoraphobia are shown in Table 1. Slightly higher doses than those recommended for depression may be necessary to control symptoms enough to promote behavior change.

Agoraphobia. Table 1. Therapies shown to be effective in the treatment of agoraphobia.

Drug	
SSRIs	Usual therapeutic dose (mg/day)
Paroxetine	20–40
Sertraline	100–200
Citalopram	20–30
Escitalopram	10–20
Fluvoxamine	100–200
Fluoxetine	20
TCA	
Clomimpramine	100–200
Imipramine	100–200
Benzodiazepines	
Alprazolam	4–6
Clonazepam	1–2
Diazepam	15–30
Lorazepam	1–4
Other antidepressants	
Venlafaxine	75–150
Reboxetine	8–10
Psychological	No of sessions
Cognitive behavior therapy	16–20
Behavior therapy – exposure	16–20

Although Tricyclic ► antidepressants (TCAs) and ► Selective Serotonin Reuptake Inhibitors (SSRIs) have been found to be equally effective in reducing both the severity and the number of panic attacks (Bakker et al. 2002), SSRIs are currently recommended as the first line of drug treatment. Initial side effects, to which anxious patients are especially sensitive, can be minimised by slowly increasing the dose. When first prescribing drug treatment, it is important to explain certain principles to the patient (Table 2).

If the patient has responded to the drug therapy by 12 weeks, treatment should be continued for a further 6 months. When stopping treatment, the dose should be reduced gradually over several weeks to avoid discontinuation and rebound symptoms. If longer term treatment is required, both ► paroxetine and ► sertraline have shown efficacy for long-term maintenance or for prophylactic use to prevent relapse (Perugi et al. 2007). However, CBT with exposure should be considered as there is evidence that this approach reduces relapse rates (Nathan and Gorman, 2002). If the patient has not responded to

Agoraphobia. Table 2. Principles of Drug Treatment for Agoraphobia.

1	The medication should be taken regularly.
2	The medication will not work immediately and may take several weeks.
3	The medication should not be stopped without discussion with the prescriber.
4	Any unwanted effects should be reported to the prescriber.
5	The dose of medication may need to be increased for it to be effective.
6	Additional behavioral treatment may be necessary to tackle avoidance, especially if it is longstanding.

treatment after 12 weeks, the prescriber should consider switching to a different treatment or combining drug and psychological approaches.

1. *Efficacy.* All the drug treatments shown in Table 1 have been shown to be more effective than placebo. SSRIs have been shown to be effective treatments for agoraphobia. They reduce panic severity, eliminate attacks, diminish agoraphobic avoidance, and improve overall quality of life. They are recommended as the first line of drug treatment. TCAs are also effective in reducing panic attack severity and the number of attacks and benzodiazepines have shown similar efficacy to antidepressants.
2. *Side effects and toxicity.* SSRIs can cause nausea and gastric side effects and decrease ► libido whereas ► benzodiazepines can cause sedation and impair some motor and memory functions. However, both SSRIs and benzodiazepines have relatively benign side effect profiles. TCAs can cause unpleasant ► anticholinergic side effects and weight gain and are dangerous in overdose.
3. Advantages and disadvantages of different agents. SSRIs are considered the first choice of treatment for agoraphobia because they combine therapeutic efficacy with safety and tolerability. However, they can increase activation levels leading to agitation and anxiety at the start of treatment and patients should therefore be started at low doses which are gradually increased. Tricyclic antidepressants (TCAs) are the second choice of treatment but their side effects can also lead to drop-outs or reduced ► adherence at the beginning of treatment. ► Benzodiazepines have been shown to be effective in the treatment of agoraphobia. They are also quicker acting and better tolerated than antidepressants. However, benzodiazepines

can cause tolerance, dependence, and withdrawal effects (► Sedative, Hypnotic, and Anxiolytic Dependence) and because of their palatability, they are also prone to misuse and ► diversion. These factors limit their usefulness and they should only be prescribed either when other drugs have not been effective or for short periods at the beginning of treatment, i.e., to counteract increased anxiety which can be caused by the antidepressant or until it takes effect. Some studies have examined the combination and found that patients who received combined treatment showed faster improvement than those receiving either drug alone but that the benefit was only apparent up to 6 weeks of treatment (Perugi et al. 2007). Benzodiazepines used as combined therapy in this way should therefore be tapered off after 6 weeks.

Other Medications

When no response occurs to the evidence-based drug treatments in Table 1, then, ► monoamine oxidase inhibitors (MAOIs) provide an alternative treatment. ► Phenelzine has been shown to help some patients but the dose has to be titrated on an individual patient basis as it can vary between 15 and 90 mg/day. ► Tranylcypromine has been used at doses of 10–60 mg/day. However, these drugs need careful supervision as they can cause toxicity if patients do not adhere to strict dietary and concomitant drug restrictions. The evidence for the efficacy of the reversible inhibitor of MAO, ► moclobemide, is mixed but it has proved effective at a dose of 450 mg/day in at least two studies.

Psychological Treatment

Behavior therapy comprises graded exposure in vivo to a personally constructed hierarchy of feared situations to target agoraphobic avoidance. ► Cognitive behavior therapy aims not only to change behavior but to challenge and modify beliefs focussed on the catastrophic misinterpretation of bodily symptoms. Both approaches have been shown to be effective but because CBT combines behavioral and cognitive approaches, it is more robust.

Combined Treatment

Several narrative or unsystematic reviews of combined psychological and drug treatment have been done but provided mixed results. However, a recent systematic review completed a ► meta-analysis of 23 studies which examined the effects of combining psychotherapy and antidepressant drug treatment for panic disorder with agoraphobia (Furukawa et al. 2006). The authors found that combined treatment was superior to antidepressant treatment alone. The combination decreased the global severity of the disorder and social dysfunction. The superiority was still evident at follow-up. In addition, combined treatment was more effective than psychotherapy alone at the end of acute phase treatment but this diminished at follow-up. A separate meta-analysis of 13 studies using patients with agoraphobia alone showed similar results. A systematic review of the combination of psychotherapy and benzodiazepines has been carried out (Watanabe et al. 2009). However only three trials were found and this was insufficient to show any advantage for combined therapy over either therapy alone.

Conclusion

Agoraphobia is often overlooked and undertreated. Early intervention is important as it can develop into a chronic, relapsing condition. Effective drug treatment is now widely available and access to psychological therapy has improved. The combination of antidepressant drug treatment and psychotherapy is especially effective in acute treatment and produces more improvement than drug treatment alone at follow up.

Cross-References

► Alcohol
► Antidepressants
► Benzodiazepines
► Caffeine
► Cognitive Behavior Therapy
► Depressive Disorders
► Meta-Analysis
► Monoamine Oxidase Inhibitors
► Panic
► Panic Disorder
► Sedative, Hypnotic, and Anxiolytic Dependence
► Social Anxiety Disorder
► SSRIs

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Agouti-Related Peptide

Definition
Orexigenic peptide produced by cells in the hypothalamic arcuate nucleus. This peptide is the natural antagonist to α-melanocyte-stimulating hormone, and as such, it has a potent orexigenic effect.

Cross-References
► α-Melanocyte-Stimulating Hormone

AIF

► Apoptosis-Inducing Factor

Akathisia

Definition
A syndrome of increased motor activity and/or subjective sense of desire for motor activity believed to be due to functional irregularities in the extrapyramidal motor system in the brain. Most blatantly, akathisia may involve fidgeting, inability to remain seated, shuffling gait, shortened stride, cogwheel rigidity, reduced accessory movements such as arm-swing while walking or gesturing, and pacing. It may include more subtle phenomena such as wandering (with attendant boundary issues) and excessive talking (which the patient may be aware of, but unable properly to control). Akinesia can also affect small muscle groups, such as those of the face and/or larynx, leading to a reduced amount and range of facial expression and/or monotonous voice tone. Subjectively, akathisia is frequently experienced as an unpleasant, dysphoric state.

Cross-References
► Depressive Disorder of Schizophrenia
► Medication-Induced Movement Disorders

Akinesia

Synonyms
Pseudo-parkinsonism

Definition
Reduced spontaneous movements.

Alarm Calls

► Distress Vocalization

Alcohol

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Synonyms
Ethanol; Ethyl-alcohol; EtOH

Definition
Alcohol (chemical formula C_2H_5OH or $CH_3–CH_2–OH$) is a volatile, flammable, and colorless liquid. Due to its psychoactive properties, it is the most widely used recreational drug, and the term "alcohol" generally refers to alcohol-containing beverages that vary in alcohol concentration, usually between 3 and 60%.

Pharmacological Properties

History
Alcohol is thought to be the earliest drug in common use, probably dating back to the paleolithic age (around 8,000 BC). Initially, alcoholic drinks were obtained through yeast-induced conversion of sugars (fermentation) from a variety of carbohydrate-based liquids, such as honey and grains steeped in water or fruit/vegetable juices. Fermentation-obtained beverages have a maximum alcohol content of about 12%, since alcohol concentration above that level causes the yeast to die, thus preventing further fermentation. Around 800 AD, Arabs discovered a process of distillation of fermented liquids, which produces beverages of much higher alcohol content, sometimes as high as 80%. The use of both types of alcoholic beverages – fermented

drinks such as beer, wine, or mead and distilled drinks ("spirits"), such as whiskey, vodka, or gin – is widely spread throughout the history as well as in modern times, and it plays a significant role in social and religious customs of many cultures.

Acute Effects

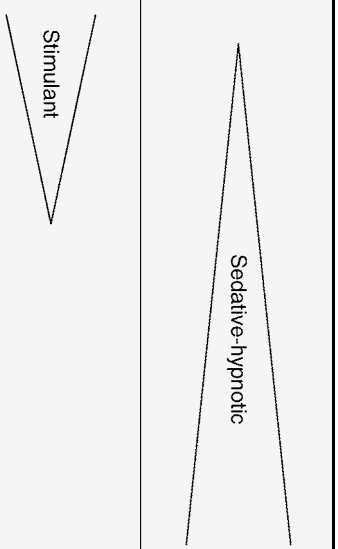
Alcohol exerts a number of effects, ranging from stimulant and pleasurable to sedative, anxiolytic, attention reduction, amnestic, anticonvulsant, muscle relaxant, hypnotic anesthetic, and can lead to death. The effects of alcohol are biphasic: at low blood alcohol concentrations (BAC) it is disinhibitory, thereby facilitating spontaneous behavior and having stimulant properties, while its effects at high BAC are sedative–hypnotic (Table 1). Acute alcohol poisoning (BAC $\geq$ 40%) may result in death due to the formation of edema (swelling) in the base of the brain (medulla), where centers of respiratory and cardiovascular regulation are located. Behavioral reaction to alcohol intake depends upon several factors, including the rate of alcohol absorption, alcohol metabolism, and ► tolerance.

Pharmacokinetics

Alcohol is a molecule soluble in water, which has low lipid solubility and which, like water, is easily absorbed into the bloodstream from the stomach and the duodenum (the top part of the small intestine). Since the majority of absorption occurs in the duodenum, the absorption rate tends to be slower for the stronger spirits than for the beverages of medium alcohol content, such as wine, because the high alcohol content of spirits inhibits the opening of the pyloric valve that allows for the stomach contents to pass into the duodenum.

The mode of alcohol transport in and out of the cells is passive diffusion, which is determined by the concentration gradient across the cell membranes. Thus, the absorption of alcohol into the body tissues depends on the level of vascularization (blood supply) of those tissues as well as the alcohol concentration of the beverage. In healthy adults, 80–90% of absorption occurs in the first 30–60 min following ingestion, although this is delayed and reduced if food is present in the stomach. Table 2 presents the number of standard drinks required to obtain a given BAC. The gender difference in the achieved BAC and, consequently, in the behavioral effects of the same dose of alcohol is thought to be due to the difference in the distribution of the body mass between men and women (Graham et al. 1998). Men have higher ratio of muscles to fat than women and thus proportionally more blood in the body (fat tissue lacks blood supply). Consequently, the same amount of alcohol is more diluted in the blood of men than women and less will be absorbed into the tissues due to the lower concentration gradient. Additionally, women have been suggested to metabolize alcohol more slowly, due to reduced levels of the metabolizing enzyme, ► alcohol dehydrogenase (► ADH),

Alcohol. Table 1. Progression of behavioral changes corresponding to increased BAC (modified from Koob and Le Moal 2006).

BAC	Behavioral changes	Biphasic alcohol effect
0.01–0.08%	Personality changes	
	Relief from anxiety	
	Social lubricant (more talkative, assertive, eloquent)	
	Disinhibition	
0.08–0.15%	Significant disinhibition ("life of the party")	
	Impaired judgments	
	Impaired cognition	
	Impaired motor function	
0.15–0.30%	Marked ataxia (staggering; slurred speech)	
	Major motor impairment	
	Impaired reaction time	
	Blackouts	
0.30–0.40%	Increased sedation/hypnosis (stuporous but conscious)	
	Approaching general anesthesia	
	Approaching coma	
$\geq$0.40%	Lethal dose for 50% of nondependent drinkers	

Alcohol. Table 2. Average BAC in men and women in relation to body weight and the number of drinks consumed.

Approximate BAC for men								
Number of drinks[a]	Body weight							
	45 kg (100 lb)	55 kg (120 lb)	64 kg (140 lb)	73 kg (160 lb)	82 kg (180 lb)	91 kg (200 lb)	100 kg (220 lb)	109 kg (240 lb)
1	0.04	0.03	0.03	0.02	0.02	0.02	0.02	0.02
2	0.08	0.06	0.05	0.05	0.04	0.04	0.03	0.03
3	0.11	0.09	0.08	0.07	0.06	0.06	0.05	0.05
4	0.15	0.12	0.11	0.09	0.08	0.08	0.07	0.06
5	0.19	0.16	0.13	0.12	0.11	0.09	0.09	0.08
6	0.23	0.19	0.16	0.14	0.13	0.11	0.10	0.09
7	0.26	0.22	0.19	0.16	0.15	0.13	0.12	0.11
8	0.30	0.25	0.21	0.19	0.17	0.15	0.14	0.13
9	0.34	0.28	0.24	0.21	0.19	0.17	0.15	0.14
10	0.38	0.31	0.27	0.23	0.21	0.19	0.17	0.16
Approximate BAC for women								
1	0.05	0.04	0.03	0.03	0.03	0.02	0.02	0.02
2	0.09	0.08	0.07	0.06	0.05	0.05	0.04	0.04
3	0.14	0.11	0.10	0.09	0.08	0.07	0.06	0.06
4	0.18	0.15	0.13	0.11	0.10	0.09	0.08	0.08
5	0.23	0.19	0.16	0.14	0.13	0.11	0.10	0.09
6	0.27	0.23	0.19	0.17	0.15	0.14	0.12	0.11
7	0.32	0.27	0.23	0.20	0.18	0.16	0.14	0.13
8	0.36	0.30	0.26	0.23	0.20	0.18	0.17	0.15
9	0.41	0.34	0.29	0.26	0.23	0.20	0.19	0.17
10	0.45	0.38	0.32	0.28	0.25	0.23	0.21	0.19

Subtract 0.01% for each 40 min of drinking. http://www.alcohol.vt.edu/Students/alcoholEffects/estimatingBAC/index.htm#educator

[a]1 drink=1 shot (40 ml/1.25 oz) of 40% spirit, 1 can (350 ml/12 oz) of 4.1% beer or 1 glass (150 ml/5 oz) of 12% wine

although this has not been demonstrated unequivocally (Graham et al. 1998).

The effects of alcohol consumption are determined not only by the rate of absorption but also by the rate of its metabolism and elimination. Less than 10% of alcohol is eliminated unchanged via lungs, urine, and perspiration. Most of the ingested alcohol (approximately 90%) is metabolized in the liver via several metabolic pathways. The main pathway of alcohol metabolism in the liver is the oxidative process involving the enzyme ADH. ADH is located in the cytoplasm of liver cells and utilizes the coenzyme ► nicotinamide adenine dinucleotide (NAD) to convert alcohol into ► acetaldehyde. Another metabolic mechanism in the liver which contributes to the conversion of alcohol into acetaldehyde is the ► microsomal ethanol-oxidizing system (MEOS) involving the enzyme CYP2E1. This process, however, only accounts for 10–15% of the total hepatic metabolism of alcohol, and its activity plays a more pronounced role only during heavy and sustained drinking (see below).

The first by-product of alcohol, acetaldehyde, is a highly toxic substance but its levels are usually very low as it is rapidly converted into acetic acid by the second oxidative process mediated by another cytoplasmic liver enzyme, aldehyde dehydrogenase (ALDH). Acetic acid is then released into the hepatic venous blood where it binds to coenzyme A forming acetyl CoA which is subsequently oxidized into carbon dioxide and water.

Some of the ingested alcohol is also metabolized in the stomach and the duodenum, prior to absorption into the bloodstream. However, since the gastric and intestinal levels of ADH are comparatively low, this "first-pass" metabolism is less efficient than the hepatic metabolism and may only exert a more significant effect on the BAC

when alcohol is ingested together with food, which tends to slow down the absorption of alcohol due to food-induced closure of the pyloric valve.

The average rate of alcohol metabolism is approximately 7–10 ml (6–8 g) of alcohol per hour and the rate-limiting factor is the ADH and the NAD availability. However, significant genetic differences exist in the efficiency of alcohol metabolism. Individuals with the allelic variations of the ADH genes-1B and -1C (ADH1B and ADH1C) show a reduced rate of conversion of alcohol into acetaldehyde, which results in an increased level of intoxication. Similarly, individuals with the allelic variation of the ALDH2 gene, which results in inactivity of the ALDH, experience accumulation of the toxic acetaldehyde in the blood and thus experience the "flush reaction" to alcohol. Flush reaction includes more intense feelings of intoxication, facial flushing, nausea, tachycardia, hypotension, and increased body sway. One of the drugs for the treatment of ► alcohol abuse and dependence, ► disulfiram ("Antabuse") is based on the same principle. Disulfiram pharmacologically blocks ALDH resulting in aversive reaction to alcohol which promotes abstinence.

Due to increased propensity of adverse reactions to alcohol, individuals with the ADH1B, ADH1C, and ALDH2 genotypes usually completely abstain from alcohol consumption. These genotypes are more common among the Asian population, where up to 80% of individuals in some subgroups posses at least one copy of one of these genes (Eng et al. 2007).

Tolerance

Tolerance to alcohol can be acute or chronic. ► Acute tolerance is observed during a single drinking session when some effects of alcohol are more pronounced during the ascending, compared to the descending, phase of the BAC curve. This so-called Mellanby effect has been suggested to occur due to the acute behavioral or cellular adaptations to the effects of alcohol (see below). It is also evident during the descending phase of the BAC curve, when subjective feelings of intoxication decline faster than the rate of decline of the BAC. Indeed, the subjective intoxication may entirely disappear during the descending phase of the BAC curve, even with BAC as high as 0.03–0.05% (Martin and Moss 1993). Chronic tolerance occurs as a result of repeated exposure to alcohol and is manifested by the reduced effectiveness of the same doses of alcohol, which were effective previously. This type of tolerance occurs as a result of metabolic (pharmacokinetic) or pharmacodynamic (cellular, molecular, functional) adaptations.

Metabolic tolerance is characterized by a diminished peak BAC obtained by a given dose of alcohol, resulting from increased absorption or clearance of alcohol from the bloodstream, which in turn result in a diminished alcohol effect. While repeated alcohol exposure may result in an increase in the ADH activity, this is unlikely to be the main mechanism underlying metabolic tolerance. This is because the degree of ADH activity is limited by the rate of the regeneration of the coenzyme NAD, which is insufficient to keep pace with the increased ADH production. Instead, it seems that the main mechanism underlying metabolic tolerance is the upregulation of the second major hepatic metabolic pathway involving the enzyme CYP2E1. This metabolic pathway is upregulated following chronic alcohol use, leading to as much as double the rate of alcohol breakdown in alcoholics when compared with moderate drinkers (Koob and Le Moal 2006). As a result of metabolic tolerance, peak BAC for the tolerant individual is much lower than for the nontolerant individual at the same dose of alcohol. Metabolic tolerance effect, however, is transient and is usually lost after as little as 3 weeks of abstinence.

► Pharmacodynamic tolerance occurs independently of the metabolic tolerance and is expressed as the shift to the right of the BAC dose-response curve. That is, a higher BAC is needed to produce the same degree of intoxication as previously obtained with a lower BAC, suggesting that the target central nervous system (CNS) tissues have become less responsive to alcohol. This is thought to be due to counteradaptive neuronal and molecular changes involving neurotransmitter release, receptors and secondary messenger systems including cAMP and G-proteins (Feldman et al. 1997; Pandey 1998). One proposed mechanism of pharmacodynamic tolerance involves latent hyperexcitability, resulting from alcohol-induced depression of neuronal activity. This depression of neuronal activity may result from desensitization or reduction of the number of existing receptors, making the postsynaptic targets less responsive to alcohol-induced neurotransmitter release. Another proposed mechanism involves reduction in neurotransmitter release, which may result from neurotransmitter depletion (e.g., not enough neurotransmitter synthesized to keep pace with the release) or end-product inhibition (stimulation of presynaptic autoreceptors inhibiting further release). Both these opponent mechanisms of pharmacodynamic tolerance are thought to contribute to the rebound phenomenon of acute alcohol ► withdrawal when effects opposite to those of alcohol are observed (e.g., sedation/anxiolysis during intoxication, ► hyperactivity/anxiety during withdrawal).

Pharmacodynamic tolerance and, to a lesser extent, metabolic (pharmacokinetic) tolerance are also revealed through the phenomenon of ► cross-tolerance, whereby heavy drinkers and alcoholics who display tolerance to alcohol are also tolerant to other drugs, particularly to pharmacologically related compounds. This has important clinical implications because the level of alcohol use needs to be taken into account when determining a therapeutic dose of a prescription drug.

Tolerance to alcohol as well as the rebound withdrawal symptoms are mediated not only by the adaptive processes occurring in response to the presence of the drug in the body but may also be ► conditioned drug effects, whereby environmental cues associated with alcohol use trigger the adaptive opponent process in anticipation of alcohol consumption. For an extensive review of different types of tolerance, see Fadda and Rossetti (1998).

Individual differences in sensitivity to the effects of alcohol are thought to be partly heritable and underlie differential susceptibility to ► alcohol abuse and dependence, with social drinkers who initially have low level of response to alcohol being more vulnerable (Schuckit et al. 2004).

Withdrawal

Withdrawal symptoms occur after abrupt cessation of prolonged heavy alcohol use, and in milder form withdrawal-like symptoms may also occur in social drinkers following alcohol binges ("hangover" effect). ► Alcohol withdrawal syndrome consists of two or more of the following symptoms and signs: autonomic hyperactivity (increased sweating and pulse rate), increased hand tremor, insomnia, nausea and vomiting, psychomotor agitation, anxiety, and irritability (Stage I). Following a longer history of alcohol dependence, Stage I symptoms become more severe and the following additional symptoms can be observed: transient visual, tactile or auditory hallucinations, grand mal seizures or even full-blown epileptic seizures (Stage II). A few days after the initial stage I and II withdrawal symptoms have diminished, between 1 and 15% of patients experience ► delirium tremens (Stage III). This is characterized by confusion, disorientation, and agitation, as well as terrifyingly vivid persecutory hallucinations, which are usually perceived as real by patients, even after the recovery. Between 1 and 15% of the patients who experience delirium tremens die due to cardiovascular collapse (Feldman et al. 1997).

Withdrawal symptoms result from acute and chronic neuroadaptive changes which also underlie tolerance to alcohol (Fadda and Rossetti 1998). Acute alcohol withdrawal produces long-lasting neurodegenerative changes, and there is evidence that previous repeated withdrawal episodes exacerbate these neurodegenerative processes, not only producing a worsening in withdrawal-associated hyperexcitability (the so-called "kindling of withdrawal") but also leading to neurotoxicity associated with cognitive impairment and emotional incompetence (Duka et al. 2004). Withdrawal-induced neurodegeneration may be one of the main factors contributing to brain damage observed in individuals suffering from alcoholism.

Chronic Effects

Chronic alcohol abuse and dependence lead to a number of morphological, neurophysiological, and biochemical changes in the CNS and the associated cognitive deficits (Fadda and Rossetti 1998). While some of these changes are due to direct effects of alcohol and alcohol withdrawal, others are more indirect, resulting from nutritional deficiencies common in this population. Postmortem studies of the brains of heavy drinkers and alcoholics as well as in vivo brain imaging studies reveal a number of morphological changes, including brain shrinkage, increased ventricle size, reduction in the volume of white matter in the cerebral hemispheres, and thinning of the corpus callosum (Fadda and Rossetti 1998; Feldman et al. 1997).

Approximately 10% of alcoholics develop alcohol amnestic disorder (► Korsakoff's syndrome) or alcoholic dementia. While the former is characterized by anterograde memory impairment with relative preservation of intelligence and other cognitive functions, the latter is characterized by global severe dementia and intellectual impairment. Some of the cognitive impairments and morphological changes observed after chronic alcohol use may be reversible by abstinence, while others, such as cerebellar atrophy seen after prolonged excessive alcohol use, appear to be irreversible (Feldman et al. 1997).

Mechanisms of Action

Alcohol has multiple mechanisms of action on the CNS.

Alcohol acutely facilitates γ-aminobutyric acid (GABA) transmission by potentiating GABA-stimulated Cl^- flux at the $GABA_A$-benzodiazepine (BDZ) receptor complex, inhibits glutamatergic transmission via its interaction with the *N*-methyl-D-aspartic acid (NMDA) receptors, increases serotonin (5-hydroxytryptamine; 5-HT) transmission by slowing its reuptake, and enhances 5-HT action at $5\text{-}HT_3$ receptors. Alcohol acutely increases the release of opioid β-endorphin and indirectly activates

mesolimbic dopamine (DA) system, via its actions on opioid system as well as the 5-HT_3 serotonin receptors. In addition to this, alcohol exerts a number of other effects, including enhancement of cholinergic function and increase on the levels of the corticosteroid hormones released from the adrenal glands. More recently, attention has been drawn to the effects of alcohol on ► neurosteroids which seem to contribute to neurophysiological and behavioral effects of alcohol. The most important of these actions are briefly discussed as follows:

$GABA_A$

The acute alcohol effects on ► GABAergic transmission contribute not only to the anxiolytic and sedative–hypnotic properties but also to its intoxication including motor incoordination. Alcohol induces allosteric changes in several ► $GABA_A$ Receptor subtypes, which is associated with increased function of these receptor subtypes. However, it is not clear yet which $GABA_A$ receptor subtypes are involved in the effects of alcohol. Alcohol is also found to increase the release of GABA in several brain areas, although the mechanism associated with the GABA presynaptic release is not yet clear.

Chronic effects of alcohol on $GABA_A$ receptor function and GABA release leads to functional adaptations of GABAergic system in several brain areas. Such neuronal adaptations contribute to the hyperexcitability like anxiety or even seizures seen during alcohol withdrawal (Pandey 1998). BZDs, which bind to $GABA_A$ receptors and facilitate GABAergic function are the treatment of choice for alcohol withdrawal symptoms.

Glutamate

Alcohol interacts with ► glutamate, the major excitatory neurotransmitter in the mammalian brain. Alcohol acutely inhibits glutamatergic synaptic transmission mediated by NMDA receptor that contributes to alcohol's anxiolytic effects. Neuronal plasticity mediated by ► NMDA receptors is also inhibited by alcohol; this alcohol effect on neural plasticity may contribute to its strong amnestic effects. NMDA receptor antagonists such as the drug ► ketamine have been reported to produce subjective effects resembling ethanol intoxication in healthy subjects as well as in detoxified alcoholics (Krystal et al. 2003).

Chronic alcohol exposure induces changes in NMDA receptor number and function as a result of compensatory mechanisms to counteract the inhibitory effects of acute alcohol. At withdrawal glutamatergic systems are disinhibited, leading to neuronal hyperexcitability and to neuronal damage induced by alcohol. ► Acamprosate, a drug that is thought to act by inhibiting neuronal activation probably due to an interaction with the glutamatergic neurotransmission is currently used as a treatment for alcohol addiction. Furthermore, a number of drugs that target glutamatergic transmission are currently being developed or tested for their efficacy in the prevention of relapse in alcoholism.

Dopamine

DA release in the mesolimbic system, from ventral tegmental area (VTA) into nucleus accumbens (NAcc), underlies motor stimulant and positive reinforcing effects of alcohol and other drugs of abuse. However, dopaminergic action of alcohol does not appear to be critical for maintaining alcohol reinforcement, since depletion of the mesolimbic DA did not significantly alter alcohol self-administration in animal studies.

Serotonin

Enhancement of 5-HT activity at the 5-HT_3 receptors contributes to alcohol's positive reinforcing and stimulant effects, since the densely distributed 5-HT_3 receptors in the mesolimbic DA-containing neuronal terminals enhance DA release. Consequently, 5-HT_3 receptor blockade was found to reduce alcohol-induced enhancement of DA release as well as alcohol consumption in humans. However, although the effects of alcohol on 5-HT and DA have been studied in the hope of developing new drugs for the treatment of alcoholism, the effectiveness of these drugs has been equivocal.

β-endorphin

The opioid system, particularly the β-endorphin, is thought to mediate positive hedonic effects of alcohol and to contribute to its reinforcing properties via indirect stimulation of DA release into NAcc (part of the reward pathway). Opioid receptor antagonists reduce alcohol-induced DA release, as well as alcohol consumption in animals and in humans. ► Naltrexone, an opioid antagonist, is commonly used as a treatment for alcoholism. Reduced consumption during naltrexone treatment may result either from reduction of the positive hedonic effects of alcohol ("liking") or by reduction of the positively reinforcing properties of alcohol ("wanting").

Due to its variety of actions in the CNS, alcohol produces a ► discriminative stimulus complex, or compound cue, composed of distinct components that are mediated by different receptor systems and which are not uniformly amplified as the ethanol dose is increased. This would account for the biphasic effects of alcohol described above. For instance, DA release into NAcc

underlies the stimulant effects of alcohol at lower doses, while at higher alcohol doses, despite further increase in DA release, the stimulant effects disappear due to increased sedative effects of ethanol, mediated by the GABAergic system; finally intoxication with even higher doses of alcohol may occur due to its interaction with the NMDA receptors.

Cross-References

- ► Acamprosate
- ► Alcoholism
- ► Alcohol Abuse and Dependence
- ► Conditioned Drug Effects
- ► Disulfiram
- ► Naltrexone
- ► Pharmacokinetics

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Alcohol Abuse and Dependence

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Synonyms

Alcohol addiction; Alcoholism; Alcohol use disorder; AUD

Definition

Pharmacological treatment of alcohol dependent subjects includes both treatment of the acute physical withdrawal syndrome and relapse prevention treatment (Anti-► craving).

Whereas today withdrawal treatment is highly standardized, on the basis of randomized controlled trials and clinical experience from several decades, relapse prevention treatment represents a fairly new intervention. The available compounds are not widely prescribed and proved evidence for differential pharmacotherapeutic strategies is lacking.

Role of Pharmacotherapy

Physical Withdrawal Treatment: General Pharmacological Withdrawal Strategies

In the majority of cases, treatment of patients suffering from alcoholism starts with the termination of alcohol use and treatment of withdrawal symptoms. The general consensus is that the complicated ► alcohol withdrawal syndrome (severe physical withdrawal or withdrawal with seizures, ► alcohol hallucinosis or ► delirium tremens) requires pharmacological treatment. It is also agreed that adequate hydration, electrolyte compensation, thiamine substitution and monitoring of the cardiovascular parameters are required during all phases of the withdrawal syndrome. In addition to curative therapy, avoidance of seizures and reduction of the risk for delirium tremens should be considered.

For the treatment of a moderate to severe withdrawal syndrome, administration of ► benzodiazepines such as ► chlordiazepoxide or ► clomethiazol, a sedative hypnotic, is preferred. Comparative studies did not show a difference in efficacy between benzodiazepines and clomethiazol. In cases of delirious and hallucinatory syndromes, additional medication with neuroleptics is often applied; ► butyrophenones are preferred due to a somewhat lower risk of seizure during withdrawal. In outpatient treatment, substances such as tiaprid, ► carbamazepine, and clonidine, which have no dependence potential, achieved good results.

Specific Pharmacologic Withdrawal Strategies

Benzodiazepines

Benzodiazepines are the first choice in the treatment of alcohol withdrawal syndrome, delirium tremens, and

seizures during withdrawal. This is based on a broad cross tolerance with alcohol, the large therapeutic window and the fast onset of effect. Benzodiazepines are sedative, hypnotic, anti-convulsive, anxiolytic, and muscle relaxing and thus appropriate for the reduction of withdrawal symptoms as well as the prevention of delirium, hallucinations and withdrawal seizures. Allergic reactions and pulmonary complications are rare. Different benzodiazepines in equivalent doses have a similar effect in the treatment of uncomplicated alcohol withdrawal syndrome. Substances such as ▶ diazepam and clordiazepoxide, which have a long half-life, are most frequently used in the treatment. Shorter acting benzodiazepines (▶ oxazepam, ▶ lorazepam), however, include benefits due to a lower accumulation (especially in terms of liver cell damage), a reduction of aversive effects, and better controllability.

Treatment with diazepam is presented as an example. Diazepam is nearly totally reabsorbed; the oral bioavailability amounts to 95%. The half-life period adds up to 20–40 h and is extended in cases of liver cirrhosis and at higher age. It is mainly eliminated through the liver by forming active metabolites (half-life period up to 100 h). Diazepam is not known to have hepatotoxicity.

A dose based on the clinical symptoms should be favored rather than a schematized administration, as the effect on the alcohol withdrawal syndrome cannot be predicted.

Sellers et al. (1983) recommend an oral diazepam "loading" with 20 mg initially and consecutive administrations after gaps of 1–2 h, until the withdrawal syndrome is significantly reduced or the patient is slightly sedated. The maximum dose per day is 150 mg. During the next couple of days, the dose should be reduced to 25–50% to avoid accumulation of active metabolites (e.g., N-desmethyldiazepam). The benefits of this therapy are fast saturation, rapid onset of effect and the "shielding" of patients during the course of the withdrawal syndrome due to the long half-life period of diazepam (20–40 h) and its metabolite (30–40 h).

Side Effects and Contra-Indications

During treatment with benzodiazepines, reduction of blood pressure, which increased during alcohol withdrawal syndrome, and sedation occur. Undesired side effects can be respiratory paralysis, tachycardia, intestinal atony and muscle relaxation. Myasthenia gravis and a known oversensitivity are absolute contra-indications. Special care should be taken in cases of sleep apnoea syndrome. Benzodiazepines initially improve sleep quality but after cessation, a rebound can occur, which can trigger a relapse.

In cases of overdosing of benzodiazepines, a benzodiazepine antagonist (anexate) can be administered. Dosage: initially 0.2 mg slowly i.v., later, medication of 0.1 mg up to a maximum of 1 mg at an interval of at least 1 min. An outpatient withdrawal treatment with benzodiazepines can be considered under continuous monitoring over a maximum period of 1 week, considering the dependence potential of the substance.

Clomethiazol

This medication is not used in Anglo-Saxon countries. However, it is widely prescribed in other parts of the world, such as central Europe. ▶ Clomethiazol is a synthetic derivate of the thiazole portion of vitamine B1 (thiamine). The exact mechanism of action is still unknown, but includes the potentiation of GABAergic inhibition, possibly via a direct effect on the chloride channel. Clinically, clomethiazole acts sedatively, hypnotically, anticonvulsively and anxiolytically. The risk of developing a delirium tremens is reduced.

Clomethiazol is metabolized via the liver by forming inactive metabolites with a half-life period of approximately 4–6 h and is excreted renally. In cases of impaired liver function, the half-life period is extended and increases the risk for accumulation, while the half-life period is abbreviated in alcohol-dependent individuals without liver damage. Clomethiazole is not hepatotoxic.

The dose titration should be adjusted according to clinical symptomatology rather than a merely schematized administration. A too careful up-dosing can often lead to the development of a delirium, whereas a too slow dose reduction does not consider the dependence potential of the substance.

In case of severe physical withdrawal syndromes and during pre-delirium, 2–4 capsules should be administered. If sedation is insufficient, 6–8 capsules can be administered additionally after approximately 30 minutes during the first 2 h. Later on, a maximum of 2 capsules/2 h, depending on the symptoms and the state of the cardiovascular system, should be administered.

The average dose in the clinical routine is about 10–15 capsules/day. A careful dose reduction of approximately 2–4 capsules/day can be considered the second day. In case of pronounced symptoms, a plateau phase of 3–5 days is recommended. Because of its addictive effect, clomethiazole should be tapered within 8–10 days.

Side Effects and Contra-Indications

Oral administration can cause a decrease in blood pressure, which increased during alcohol withdrawal and a reduction of tachycardia. However, cardiovascular

insufficiency requiring treatment is rare. The risk of a hypoventilation and unconsciousness is also very low when administration is done orally. Further undesirable side effects are rashes, irritations of the throat and sneezing, tears and stomach problems. Bronchial secretion is increased. If taken for a long period, medication carries the risk of developing a dependence.

Sleep apnoea syndrome and central respiratory problems are absolute contra-indications. Clomethiazole should not be administered in case of bronchial asthma or acute lung or bronchial diseases. A concomitant administration of other hypnotics, tranquilizers, neuroleptics or alcohol can have life-threatening effects due to effect intensification, which is difficult to assess.

Outpatient treatment with clomethiazole should not be considered because of a dependency potential, as well as possible serious side effects, especially in cases of overdosing and alcohol consumption.

Tiapride, Carbamazepine, Oxcarbazepine and Clonidine

A combination treatment with tiapride and carbamazepine, especially oxcarbazepine, offers a good alternative, especially for outpatient treatment and leads to good results in treating vegetative symptoms within the withdrawal syndrome and offers concomitant seizure prevention.

Tiapride is a selective D2-receptor antagonist and belongs to the group of benzamide derivates. The special field of application of the substance is the treatment of extrapyramidal motor diseases. However, long-term experiences in pharmacotherapy for alcohol withdrawal syndrome exist as well. Tiapride has psychomotor effects and is sedative and anxiolytic, but does not have an effect on the seizure threshold during alcohol withdrawal. The low rate of undesired effects, the lower sedative effect, and especially the non-dependence potential seem to be advantages, compared to clomethiazole or benzodiazepines. Undesired side effects are tiredness, vertigo, orthostatic dysregulation and, sometimes, extrapyramidal motor symptoms. As tiapride lacks anti-convulsive efficacy, a combination therapy with carbamazepine has been suggested. A major advantage of carbamazepine, besides its anti-convulsive effect and lack of interaction with alcohol, is the reduction of the kindling effect. The half-life period is 15 h, but is reduced by enzyme induction after prolonged intake. It is eliminated via hepatic oxidation and renal elimination. The active metabolite carbamazepine epoxy has a half-life of approximately 8 h. Because of this fact and the delayed onset, no retarded release preparation of carbamazepine should be administered during withdrawal treatment.

Patients with liver dysfunction can be treated with oxcarbazepine, a derivative of carbamazepine that does not have liver toxicity. It showed good effects, as its elimination requires no hepatic metabolisation.

Patients receiving outpatient treatment should be monitored daily; after 1 week, detoxification is usually concluded. A dose increase of tiapride up to 1,800 mg per day in cases of severe withdrawal symptoms has been suggested; for inpatients, the recommendation is upto 2,400 mg per day.

If arterial blood pressure increases, the administration of the imidazole derivate clonidine can be helpful. Clonidine acts sympathicolytically via stimulation of presynaptic inhibitory alpha-two receptors located in the locus coeruleus. It reduces cardiovascular stress during alcohol withdrawal and decreases agitation, anxiety, tremor, and tensions in the muscular system. The substance does not have anti-delirious or anti-convulsive effects. The oral bioavailability amounts to 75% and the half-life period is 20 h. When administered parenterally, the effect appears after 10 min. Elimination happens 60% renally and 40% via hepatic metabolisation.

In cases of slight to moderate alcohol withdrawal syndrome, clonidine should initially be administered at a dose of 75 µg orally; the max. daily dose is 600 µg. Typical side effects are drop in blood pressure (initially also rise in blood pressure!), bradycardia, tiredness, xerostomia, and muscle relaxation. Contra-indications are AV-block II and III grades, sick sinus syndrome, phaechromocytoma, pronounced hypotonia, and depression.

Therapy for Delirium Tremens

Only about 5% of alcohol-dependent individuals with a vegetative withdrawal syndrome develop delirium tremens. While hallucinations (mainly optical, rarely acoustic) can also be observed during severe vegetative withdrawal syndromes, the presence of disorientation is the critical differential-diagnostic criterion, recommending the diagnoses of delirium tremens. Additionally, visual, tactile and acoustic hallucinations can occur, and, rarely, grand mal seizures, as well as disorders of consciousness and cognitive abilities. Psychomotor hyperactivity is also a typical symptom.

The presence of delirium tremens is a life-threatening situation that always requires immediate referral to an intensive care unit. Pharmacotherapeutic treatment prefers ► benzodiazepines, usually in combination with neuroleptics (e.g., ► haloperidol 5 mg/4 h) which are injected i.v. for electrolyte and liquid compensation. Under this medication, a delirium tremens usually subsides in 2–4 days. In this case, a tapering dose of the medication is

important. The administration of thiamine (50 mg slowly i.v., 50 mg i.m.) is usually necessary for the prophylaxis of Wernicke's encephalopathy.

Pharmacological Relapse Prevention

About 40–60% of patients relapse within 1 or 2 years after treatment. This proves the necessity for additional medication to prevent a relapse. Recent studies show that "anti-craving" compounds, especially during the first months after discharge from an inpatient withdrawal treatment, reduce the relapse risk (O'Brien 2005). So far, substances with an effect on the cholinergic, glutamatergic, serotonergic, dopaminergic, gabaergic and opioidergic systems have been examined (Spanagel and Kiefer 2008).

Acamprosate

Acamprosate, a calcium-bis-acetyle-homotaurinate, has been approved for preventing relapse of alcohol dependence. In cases of chronic alcohol consumption, a higher activity of the glutamatergic system can be seen, caused by a counter regulation of the acute inhibiting effect of alcohol on the excitatory glutamatergic neurotransmission. ▶ Acamprosate binds on the NMDA receptor and thus inhibits the increased excitability. After confirmation of experimental results in animal models, the effect of acamprosate on alcohol dependence was also examined in numerous controlled clinical studies. Evidence-based reviews have confirmed the efficacy of acamprosate on abstinence rate and number of drinking days and recommend clinical application (Mann et al. 2009).

Acamprosate has an effect on alcohol dependence especially when given concomitantly with psycho-therapeutic or psychosocial measures. The COMBINE Study included 1,383 recently alcohol-abstinent patients (Anton et al. 2006) and showed no effect of acamprosate on abstinence proportion, in contrast to the majority of European studies on this topic. Patient characteristics suggest that subjects who had no physical withdrawal syndrome requiring withdrawal treatment were mainly included in the Combine study. As acamprosate's efficacy is associated with its ability to modulate withdrawal-induced hyperglutamatergic states inducing craving, the specific pharmacological target for acamprosate might have been missing in the patients included in this study.

Acamprosate does not cause any interaction to other medications, does not increase alcohol toxicity, and does not have any dependence potential or other psychotropic effects. Frequent but usually transient side effects are diarrhea, other gastrointestinal conditions, headaches, and pruritus. Contra-indications are pregnancy and lactation periods, serum creatinine $>120\,\mu$molg/L in patients with renal insufficiency and the presence of severe liver insufficiency. The medication should be administered after detoxification in patients motivated for abstinence. A treatment period of 12 months is recommended. Treatment should be maintained even after short term relapses. The combination with alcohol bears no safety risks.

The daily dose of acamprosate is 3×2 tablets (à 333 mg). According to the manufacturer, the medication should be started after achieving abstinence and continued for approximately 1 year. It has been suggested that acamprosate has also an anti-withdrawal and a neuroprotective effect. With respect to the kindling phenomenon, administration of acamprosate should be considered one week prior to withdrawal. This would include a period of 7 days until the brain is in a steady state.

Naltrexone

▶ Naltrexone acts antagonistically mainly at mu-opiate receptors, counteracting alcohol craving. It is assumed that the endorphin-mediated, subjectively pleasant and positive reinforcing effects of alcohol are inhibited (O'Brien 2005). In animal models, the alcohol-antagonistic effect of naltrexone was demonstrated. Various placebo-controlled studies verified this effect in humans as well. Naltrexone has proved especially effective in combination with psychotherapeutic treatments. Yet several large trials did not show a superiority of naltrexone over the placebo. A Cochrane meta-analysis, however, confirmed a reduction in alcohol consumption, even if the time to first alcohol consumption was not always extended (Johansson et al. 2007).

Nausea, gastrointestinal disorders, and headaches are the main side effects of the otherwise well- tolerated substance. Contra-indications are acute hepatitis or severe liver dysfunction. Prior to treatment it should be ensured that at least some days of abstinence were observed, to avoid a concurrence of possible gastrointestinal side effects and withdrawal syndrome. The opiate-antagonistic effect should be considered for the indication of the further course of treatment. An actual or recent opiate consumption, taken as addictive drug or as pain relief, is an exclusion criterion for the administration of naltrexone. An opiate analgesia, necessary under administration of naltrexone, requires special precautions, especially if discontinuation of the medication cannot be done in time. Treatment with naltrexone should be continued for more than 3 months and not interrupted or discontinued after a timely, limited relapse. Naltrexone does not increase the toxicity of alcohol and does not possess any

dependence potential. The recommended daily dose of nemexine® is 50 mg.

Disulfiram

► Disulfiram has caused more controversies than any other medical treatment for alcoholism . While in Scandinavia and Great Britain up to 50% of alcohol-dependent individuals have been treated with this substance during the last decades, no considerable prescriptions were given in Germany after an initial success during the last two decades of the twentieth century. Only the increasing discussion on the prescription of anti-craving substances for relapse prevention led to a reconsideration of the administration of disulfiram. A special treatment concept for severely alcohol-dependent individuals was also performed (Ehrenreich et al. 1997). It showed the efficacy of the substance under daily supervised intake. A prescription, however, implies detailed knowledge of the mode of action and especially of the possible life-threatening side effects. It should only be prescribed under strict supervision.

Disulfiram affects the metabolisation of alcohol. The acetaldehyde dehydrogenase is blocked, so that a further decomposition to acetic acid is interrupted, resulting in an accumulation of ► acetaldehyde. This leads to unpleasant symptoms such as flushes, headaches, nausea, vomiting, diarrhea, drop in blood pressure and potentially to syncopes. These symptoms can be ascribed to the toxicity of acetaldehyde. A genetically conditioned lack of an isoenzyme of the aldehyde-dehydrogenase can be found in 50% of the Asian population, though in only around 5% of Caucasians. Alcohol consumption leads to the clinical symptoms described above, especially in homozygous carriers of this variation.

According to specialty information the following dose is recommended: First day: 1.5 g disulfiram, equivalent to 3 antabus, 0.5 dispergettes. Second day: 2 dispergettes. Third day: 1 antabus, 0.5 dispergette, which should also be the maintenance dose.

Contra-indications are: Coronary heart disease, severe cardiac arrhythmia, clinically manifest cardiomyopathy, impaired cerebral blood flow, advanced arteriosclerosis, oesophageal varices, hypothyroidism. Disulfiram should not be administered in cases of non alcohol-related depressions and schizophrenic psychosis. The same holds true in cases of severe hypotonia, decompensated liver cirrhosis and asthma bronchiale.

A treatment with disulfiram and concomitant alcohol consumption leads to aversive symptoms as mentioned above. Some rare cases of death were reported when administration was not supervised. This means that today treatment with disulfiram should be regarded as the "therapy of last choice." On the other hand direct and indirect comparisons with other anti-craving substances suggest a possible superiority.

Two open randomized studies compared disulfiram with naltrexone and with acamprosate (de Sousa and de Sousa 2005). In both cases disulfiram showed a significant superiority. A further study with a concomitant comparison with naltrexone, acamprosate and disulfiram has been published. The superiority of disulfiram over naltrexone and acamprosate was also confirmed in some international meta-analyses (e.g., Berglund et al. 2003). These results confirm earlier indications, concluding that disulfiram requires a re-evaluation. Recent reviews agree with this view.

Differential and Combined Treatment

Pharmacological relapse prevention in alcoholics is currently based on three extensively tested medications: acamprosate, naltrexone, and disulfiram.

It is being discussed whether individuals respond differently to different drugs. Individualized treatment with the "right drug" could thus increase the effects of pharmacotherapy significantly. At least the effects of acamprosate and naltrexone appear to relate to different aspects of drinking behavior, with the former primarily stabilizing abstinence and the latter primarily decreasing alcohol consumption. However, due to large differences in baseline characteristics, it is unreliable to compare studies retrospectively.

A prospective study performed in Germany that compared and combined both drugs under RCT conditions showed that both prolonged the time to first drink and the time to first relapse into heavy drinking compared to the placebo. The combination of both drugs was more effective than both placebo and monotherapy with acamprosate (Kiefer et al. 2003). Feeney's open cohort study replicated these results (Feeney and Connor 2005). A larger comparative study addressing this issue and involving 1,383 recently alcohol-abstinent patients (Anton et al. 2006) showed no treatment effects of acamprosate on abstinence proportion and no additive effect of combining naltrexone with acamprosate. Only naltrexone showed a significant but modest treatment effect on one out of two predetermined endpoints (return to heavy drinking vs. percent days abstinent). Patient characteristics suggest that patients without a physical withdrawal syndrome requiring withdrawal treatment were mainly included in the Combine study.

Since acamprosate and naltrexone have an effect on different neurotransmitters, neurobiologically-based a

priori examinations could provide indications on specific predictors concerning the response to each of these medications. A prospective study targeting biologically based endophenotyes including fMRI, PET, and psychophysiology is currently under way (Mann et al. 2009).

Biological matching of patients with their specific treatment holds the potential of moving the field of pharmacotherapy of alcoholism forward.

Cross-References

- ► Acamprosate
- ► Alcohol
- ► Disulfiram
- ► Naltrexone

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Alcohol Addiction

► Alcohol Abuse and Dependence

Alcohol Dehydrogenase

Synonyms

ADH; ALDH

Definition

Alcohol dehydrogenase is an enzyme that is responsible for catalyzing the formation of alcohols into aldehydes or ketones. There are five classes of alcohol dehydrogenases in humans, and the hepatic form, which is used primarily, is alcohol dehydrogenase class 1. Class 1 dehydrogenase catalyzes the oxidation of ethanol to produce acetaldehyde.

Cross-References

- ► Acetaldehyde

Alcohol Dependence

Synonyms

Alcoholism

Definition

Alcohol dependence is characterized as a maladaptive pattern of drinking, leading to clinically significant impairment, as manifested by a compulsion to drink, a lack of control over the amount of alcohol consumed and continued drinking, despite a knowledge of the problems associated with it. DSM-IV defines alcohol dependence as current if any three or more of the following seven criteria are present in the past 12 months:

1. Tolerance – as defined by either of the following – a need for markedly increased amounts of alcohol to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount of alcohol.
2. Withdrawal.
3. Alcohol is often taken in larger amounts or over a longer period than was intended.
4. A persistent desire or unsuccessful efforts to cut down or control alcohol use.
5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.

7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Alcohol (Ethanol) Choice Tests

► Alcohol Preference Tests

Alcohol (Ethanol) Drinking Preference Tests

► Alcohol Preference Tests

Alcohol (Ethanol) Reinforcement Tests

► Alcohol Preference Tests

Alcohol (Ethanol) Reward Tests

► Alcohol Preference Tests

Alcohol Hallucinosis

Definition

Alcoholic hallucinosis represents a rare complication of the alcohol withdrawal syndrome. It includes mainly auditory hallucinations, often accusatory or threatening voices. Alcoholic hallucinosis develops and resolves rapidly, involves no disorientation nor physical symptoms.

Alcohol Preference Tests

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Synonyms

Alcohol (ethanol) choice tests; Alcohol (ethanol) drinking preference tests; Alcohol (ethanol) reinforcement tests; Alcohol (ethanol) reward tests

Definition

Alcohol preference tests generally include a set of experimental procedures that allow assessment of the intake of alcohol-containing solutions by laboratory animals when there is also an availability of one or more solutions at the same time that do not contain any alcohol. Alcohol preference is measured as the amounts of the alcohol solution(s) consumed, relative to those of the nonalcoholic solution(s). Although this is the most commonly used procedure for studying alcohol preference, several related behavioral procedures have also been used to draw inferences about preference for alcohol. These other procedures are briefly described in the next section.

Impact of Psychoactive Drugs

Description of Procedures

Many behavioral procedures have been used to assess the effect of psychoactive drugs on ethanol preference in nonhumans (Egli 2005). The most common approach is to assess ethanol intake relative to the intake of an alternative fluid (e.g., water) in a procedure that allows the animal to orally self-administer both fluids at the same time. For example, many studies have offered rats and mice a choice between drinking tubes containing 10% ethanol versus water in the home cage. Other studies have used operant self-administration procedures that require the animal to make a specific response to obtain each fluid, e.g., press lever A to obtain ethanol or press lever B to obtain water (Gonzales et al. 2004; Samson and Czachowski 2003). Regardless of the procedure used, the most informative data on treatment drug effects come from studies in which the pattern of self-administration is monitored continuously over time, or from studies in which the treatment drug is assessed during short sessions (e.g., 30–60 min) that normally yield high ethanol intakes (or high blood alcohol concentrations) in vehicle-treated control animals.

As the most commonly studied species (rats, mice) do not voluntarily consume sufficient alcohol to become dependent, most studies of psychoactive drugs have been conducted in nondependent animals. However, several recent studies have examined treatment drug effects on ethanol self-administration in animals that have been made dependent by chronic ethanol exposure (e.g., intragastric infusion or gavage, liquid diet or vapor inhalation

chamber). Importantly, these studies have shown that sensitivity to the effects of some psychoactive drugs is altered by a history of chronic ethanol exposure and dependence. Several examples of such findings are noted in later sections.

The development of stable ethanol self-administration in animals generally requires a prolonged period of training that may last several days, weeks, or months. In operant procedures, this training phase might also require a special "initiation" procedure (e.g., gradual reduction in the concentration of an added sweetener as ethanol concentration is increased). Thus, most studies of psychoactive drugs have examined treatment effects on a well-established baseline of ethanol self-administration. Over the last 10–15 years, however, there has been increasing interest in procedures that mimic relapse to ethanol self-administration after a period of abstinence (e.g., Alcohol Deprivation Effect, ADE), as well as procedures that produce reinstatement of responding after extinction of operant self-administration of ethanol (e.g., exposure to priming doses of ethanol, ethanol-associated cues or stressors). The primary purpose of such studies has often been to study the effects of treatment drugs on ethanol-seeking responses (i.e., responses that were previously paired with ethanol reinforcement), rather than direct effects on ethanol self-administration. Of interest, these studies have sometimes shown divergence in the effects of treatment drugs on ethanol seeking and ethanol self-administration.

The conditioned place preference (CPP) procedure offers another approach to evaluate treatment drug effects. In this procedure, the effect of a treatment drug on ethanol reward can be measured indirectly by drug-free testing of the animal's preference for contextual stimuli that have been previously associated with ethanol given alone (vehicle control group) or in combination with the treatment drug (experimental group). CPP can also be used to test the effect of a treatment drug on ethanol's conditioned rewarding effect by giving the drug just before a post-conditioning preference test in the absence of ethanol. Performance during a CPP test can be viewed as a form of ethanol seeking that is conceptually analogous to responding during the extinction or reinstatement of operant self-administration. One limitation on the use of CPP for studying treatment drug effects on ethanol reward is that although the phenomenon is robustly observed in mice, it has been much more difficult to demonstrate reliably across laboratories in rats.

Psychoactive Drug Testing

Ethanol is known to interact directly or indirectly with a wide range of neurochemical systems in brain (Koob and LeMoal 2006; Vengeliene et al. 2008). Effects of manipulating most of those systems have been studied using one or more types of alcohol preference test. Primary emphasis has been on systems implicated in ethanol's rewarding or conditioned rewarding effects and on systems thought to underlie the negative motivational effects of withdrawal (Koob and LeMoal 2008). Because space limitations preclude a detailed review of this literature, this essay focuses on psychoactive drugs currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol dependence, as well as several drugs that have been evaluated for their therapeutic potential or that are considered to be promising candidates (Heilig and Egli 2006; Tambour and Quertemont 2007; Vengeliene et al. 2008).

FDA-approved drugs: Currently, only four treatment drugs are approved for the treatment of alcoholism: oral or extended-release ► naltrexone, ► acamprosate, and ► disulfiram (Swift 2007). Disulfiram (Antabuse), which produces an aversive reaction when alcohol is ingested due to interference with ethanol metabolism, has rarely been studied in alcohol preference models and there is a mixed evidence for its efficacy in clinical trials (Heilig and Egli 2006; Swift 2007). In contrast, the more recently approved drugs (naltrexone, acamprosate), which yield more consistently positive results in clinical trials (Swift 2007), have also been effective in reducing ethanol intake and reinstatement in animals (Egli 2005; Vengeliene et al. 2008). In fact, the original naltrexone clinical trials were encouraged by animal studies that had shown a reduction in alcohol intake after injection of non-selective opioid antagonists. The mechanisms underlying the efficacy of naltrexone and acamprosate are not fully understood. Naltrexone is thought to modulate mesolimbic dopamine neurotransmission that may be involved in the direct and conditioned rewarding effects of ethanol, whereas acamprosate is hypothesized to act through its effects on ► glutamate neurotransmission (Tambour and Quertemont 2007).

Dopaminergic drugs: The mesolimbic dopamine system has long been implicated in the reinforcing and rewarding effects of most abused drugs, including ethanol. Animal studies have shown that both dopamine agonists and dopamine antagonists inhibit oral ethanol self-administration, a pattern of findings that has been difficult to reconcile (Gonzales et al. 2004). Some studies have suggested that dopamine antagonists have a greater impact on ethanol-seeking responses than on ethanol intake (Samson and Czachowski 2003). However, clinical studies with dopaminergic drugs have yielded mixed results, discouraging their use for alcoholism treatment in humans (Tambour and Quertemont 2007).

GABAergic drugs: Many of ethanol's physiological and behavioral effects have been linked to its interaction with the gamma-aminobutyric acid (► GABA) receptor system. Alcohol preference studies in animals have focused on drugs that target the ► $GABA_A$ receptor. These studies have generally shown an inhibitory effect of $GABA_A$ antagonists and benzodiazepine receptor ► inverse agonists and antagonists on ethanol self-administration. In contrast, results with $GABA_A$ agonists have been mixed, with reports of both increases and decreases in self-administration (Chester and Cunningham 2002). A few recent studies have indicated that the $GABA_B$ receptor agonist baclofen reduces ethanol self-administration, relapse after deprivation (ADE) and responding during extinction of self-administration (Heilig and Egli 2006), effects that may be mediated by suppression of mesolimbic dopamine signaling (Tambour and Quertemont 2007). Preliminary clinical studies have suggested that baclofen might also be effective in the treatment of alcoholism (Heilig and Egli 2006; Tambour and Quertemont 2007).

Recent clinical trials have also suggested that the antiepileptic ► topiramate has efficacy in the treatment of alcohol dependence (Heilig and Egli 2006; Tambour and Quertemont 2007). While topiramate is thought to alter GABA signaling, effects on glutamategic transmission and voltage dependent sodium channels have also been proposed. Topiramate's clinical efficacy has been attributed to putative indirect effects that alter mesolimbic dopamine transmission (Tambour and Quertemont 2007). The preclinical literature using alcohol preference tests is quite limited and it does not provide strong support for an inhibitory effect of topiramate on ethanol drinking (Heilig and Egli 2006).

Serotonergic drugs: Preclinical studies have shown that ► selective serotonin reuptake inhibitors (SSRIs) as well as agonists and antagonists at various ► serotonin receptors ($5\text{-}HT_1$, $5\text{-}HT_2$, $5\text{-}HT_3$) can reduce alcohol consumption (Vengeliene et al. 2008), although some of these findings may reflect non-specific effects on consummatory behaviors (Heilig and Egli 2006; Tambour and Quertemont 2007). Despite their efficacy in ethanol self-administration studies in animals, SSRIs and the partial $5\text{-}HT_{1A}$ agonist ► buspirone have not been effective in clinical trials (Egli 2005; Tambour and Quertemont 2007). However, the $5\text{-}HT_3$-receptor antagonist ondansetron appears to have relatively selective effects on ethanol self-administration in animals, an effect that some investigators attribute to a reduction in ethanol-induced dopamine release (Tambour and Quertemont 2007). Moreover, human trials have shown promising results for ondansetron in the treatment of early onset alcoholism (Heilig and Egli 2006; Tambour and Quertemont 2007).

Glutamatergic drugs: The observation that ethanol dose-dependently inhibits NMDA receptor activation has encouraged examination of glutamatergic drug effects on ethanol self-administration. However, animal studies have found few consistent effects of ► NMDA receptor antagonists on ethanol self-administration (Vengeliene et al. 2008). Thus far, the most promising preclinical studies have suggested that selective antagonists targeting the metabotropic mGluR5 glutamate receptor (e.g., 2-methyl-6-(phenylethynyl)-pyridine, MPEP) can reduce high levels of ethanol self-administration in selectively-bred alcohol preferring rats (Heilig and Egli 2006). MPEP also reduces cue-induced reinstatement of operant self-administration after extinction as well as relapse to self-administration after a period of abstinence (ADE) (Vengeliene et al. 2008). Although there have been no clinical trials with mGluR5 receptor antagonists, the preclinical and clinical efficacy of acamprosate might be related, at least in part, to antagonism of this receptor subtype (Tambour and Quertemont 2007).

Cannabinoid drugs: A potential role for the endocannabinoid system has been supported by studies showing that pharmacological blockade of the CB_1 receptor subtype reduces ethanol intake and cue-induced reinstatement of an extinguished operant self-administration response in animals (Tambour and Quertemont 2007; Vengeliene et al. 2008). The CB_1 receptor antagonist ► rimonabant is currently under investigation in a human study that is designed to test its effects on ethanol consumption in heavy drinkers (Heilig and Egli 2006).

Neuropeptides: Animal studies have suggested that ► neuropeptides implicated in stress and anxiety influence ethanol self-administration, especially those targeting the corticotropin-releasing factor (CRF) and neuropeptide-Y (NPY) systems. For example, non-selective CRF antagonists and selective CRF1 antagonists have been found to reduce ethanol self-administration, but only in alcohol-dependent animals (Heilig and Egli 2006; Vengeliene et al. 2008). CRF1 receptor antagonists have also been shown to interfere with cue- and stress-induced ► reinstatement of operant responding after extinction of ethanol self-administration (Vengeliene et al. 2008). NPY decreases ethanol self-administration in high-drinking animals, an effect that was enhanced by a period of alcohol deprivation. Blockade of NPY Y1, Y2 and Y5 receptors has also been reported to suppress ethanol drinking or operant responding for ethanol in non-dependent animals, though the effect of Y2 blockade is greater in ethanol dependent animals (Heilig and Egli 2006). Clinical

trials targeting the role of the CRF or NPY systems in alcohol dependence have not yet been reported.

Other Uses of Alcohol Preference Tests

Although this essay has focused on the use of alcohol preference tests to study effects of psychoactive drugs, it is important to note that these tests are widely used by basic scientists for many other purposes. For example, these procedures are used to study the basic behavioral processes involved in the learning, extinction, and recovery (e.g., reinstatement) of ethanol-related memories. These procedures are also commonly used to characterize the neurochemical systems, brain circuitry, and genes that underlie ethanol self-administration and excessive drinking. Finally, these procedures have been used to study the impact of addiction-related neuroadaptations on ethanol-reinforced behavior (e.g., tolerance, dependence, and withdrawal).

Cross-References

- ► Abuse Liability Evaluation
- ► Acamprosate
- ► Addictive Disorder: Animal Models
- ► Alcohol
- ► Alcohol Abuse and Dependence
- ► Conditioned Place Preference and Aversion
- ► Disulfiram
- ► Naltrexone
- ► Reinstatement of Drug Self-Administration
- ► Self-Administration of Drugs

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Alcohol Use Disorder

► Alcohol Abuse and Dependence

Alcohol Withdrawal

Definition

Alcohol withdrawal can occur after stopping alcohol use or following a reduction in use in individuals with a history of chronic use. Symptoms of alcohol withdrawal can include: autonomic hyperactivity, hand tremor, insomnia, nausea or vomiting, hallucinations, psychomotor agitation, anxiety, and seizures.

Alcohol Withdrawal Delirium

Definition

Alcohol withdrawal delirium, also known as delirium tremens, is the type of delirium that occurs during withdrawal from alcohol. It is commonly associated with tactile or visual hallucinations in addition to autonomic hyperactivity, disorientation, and agitation. It occurs in approximately 5–15% of patients in alcohol withdrawal typically within the first 72–96 h of withdrawal. Severe alcohol withdrawal delirium is a medical emergency and requires prompt treatment.

Alcohol Withdrawal-Related Anxiety

Synonyms

Alcohol withdrawal symptoms

Definition

Anxiety is an early withdrawal symptom that develops after cessation of ethanol drinking in alcoholics. Alcohol produces antianxiety effects and may be one of the factors responsible for the comorbidity of alcoholism and anxiety.

Cross-References

- ► Alcohol
- ► Alcohol Abuse and Dependence
- ► Generalized Anxiety Disorder

Alcohol Withdrawal Symptoms

► Alcohol Withdrawal-Related Anxiety

Alcohol Withdrawal Syndrome

Definition

A constellation of signs and symptoms that appears when a physically alcohol-dependent person stops drinking alcohol. The physiological basis is the alcohol tolerance: chronic alcohol intake causes reversible adaptations within the body that tend to compensate for the original alcohol effects over time. When alcohol intake is suddenly stopped or decreased, the adaptations do not immediately disappear. Unopposed by alcohol, the adaptations appear as withdrawal signs and symptoms that include tension, anxiety, sleep disturbance, increased blood-pressure and heart rate, tremor, sometimes seizures.

Alcoholism

► Alcohol Abuse and Dependence
► Alcohol Dependence

Alcohol-Related Neurodevelopmental Disorder

Synonyms

ARND

Definition

A developmental neuropsychiatric disorder with no characteristic facial dysmorphology resulting from prenatal exposure to alcohol.

Cross-References

► Foetal Alcohol Spectrum Disorders

ALDH

► Alcohol Dehydrogenase

Alexithymia

Definition

Difficulty in understanding other people's emotions and expressing one's own emotions.

Allocentric

Synonyms

Exocentric; Geocentric

Definition

Etymologically, allocentric means centred on another. In terms of spatial memory, allocentric is used to describe a frame of reference based on the spatial relations between objects in space.

Allodynia

Definition

Allodynia is a condition in which pain is produced by a stimulus that is not normally painful.

Cross-References

► Analgesics

Allosteric Modulators

Definition

In contrast to orthosteric molecules, which bind to the same receptor domain as the endogenous agonist, allosteric modulators bind to a site that is topographically different from the orthosteric binding site. Allosteric modulators produce an effect through a change in protein confirmation and can increase (positive allosteric modulator or PAM) or decrease (negative allosteric modulator or NAM) the affinity and/or efficacy of an orthosteric agonist.

Cross-References

► Agonist
► Antagonist
► Inverse Agonists
► Receptor Binding

Allosteric Potentiating Ligand

Definition

Allosteric antagonists or agonists produce unique effects by binding to a site on the receptor to produce a bias in

the receptor conformation. Allosteric modulators of nicotinergic receptors are compounds that interact with the receptor via binding sites that are distinct from those for acetylcholine and ► nicotinic agonists and antagonists. Consequently, modulators are not directly involved in the neurotransmission process they affect and hence usually do not induce compensatory processes, as direct agonists and antagonists may do (e.g., receptor ► desensitization, ► downregulation of expression).

Allosteric Site

Definition

A regulatory site of a receptor that is different from the orthosteric site in which the endogenous ligand binds to. Binding to the allosteric site can enhance or inhibit activity of the endogenous ligand to the orthosteric stie.

Allotropy

► Genetic Polymorphism

Allowable

► Legal Aspects of Psychopharmacology

(*RS*)-1-[2-(Allyloxy)Phenoxy]-3-(Isopropylamino)Propan-2-ol

► Oxprenolol

Alogia

Definition

Poverty of speech, as in schizophrenia.

S-Alpha-Hydrazino-3,4-Dihydroxy-α-Methyl-Bensemonopropanoic Acid Monohydrate

► Carbidopa

Alpha Waves

► Function of Slow and Fast Alpha

Alprazolam

Definition

Alprazolam is a high-potency, short-acting anxiolytic benzodiazepine medication used in the treatment of anxiety, panic, and phobic disorders. It has some antispasmodic and anticonvulsant effects. It is not antidepressant. It is sometimes used in conjunction with antipsychotic medication in acute psychotic episodes. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Long-term use may induce dependence with withdrawal reactions. Recreational use and abuse can occur: alprazolam is a scheduled substance.

Cross-References

► Benzodiazepines
► Minor Tranquilizers

Alternative Splicing

Synonyms

mRNA splice variants

Definition

Antisense technology has also been used to manipulate alternative splicing patterns altering the ratio of different splice variants of a gene and its function. Several diseases are linked to mutated alternative splicing of specific genes such as thalassemia, Duchenne muscular dystrophy, cystic fibrosis, and parkinsonism linked to chromosome 17. The therapeutic potential of this antisense approach, for example, to silence gene mutations responsible for defect pre-mRNA splicing is enormous.

► Antisense oligonucleotides that alter splicing should be different from those designed to downregulate gene expression and should be chemically modified such as to prevent activation of RNase H as this would destroy pre-mRNA before splicing, to have a higher nuclease resistance and affinity for the target sequence. According to ex vivo intracellular localization studies, the antisense oligonucleotides need to enter the nucleus for successful modulation of splicing. Aberrant splicing of pre-mRNA is

prevented or correct splicing is restored. In vivo confirmation of these mechanisms of action is missing.

Cross-References
► Antisense Oligonucleotides

Altricial

Definition
Offspring of certain mammalian species that are born at relatively immature stages, for example, with their eyes and ears closed, and without fur or the ability to thermoregulate.

Alzheimer's Disease

Definition
A type of dementia, neurodegenerative disease, that leads to progressive destruction of brain cells. The disease leads to severe memory loss, confusion, and often apathy. There is a progressive brain atrophy with multiple neurotransmitter changes. The degeneration of cholinergic neurons in the brain is one neurochemical loss that is commonly observed postmortem. In addition, the brains of Alzheimer's disease patients are marked by plaques (β-amyloid) and neurofibrillary tangles.

Cross-References
► Dementia

Amantadine

Synonyms
Tricyclo[3.3.1.1^{2,7}]decan-1-amine or 1-adamantanamine

Definition
Amantadine probably acts both as an anticholinergic and glutamate antagonist, releasing dopamine in the striatum/substantia nigra and possibly other central sites. Registered initially as an anti-influenza drug, amantadine is used alone or in combination with L-DOPA in idiopathic Parkinson's disease, other forms of Parkinsonism, related motor fluctuations, drug-induced extrapyramidal syndromes, and dyskinesias.

Cross-References
► Anti-Parkinson Drugs

Amenorrhea

Definition
Absence of at least three consecutive menstrual cycles in a woman of reproductive age.

Amentia

► Autism Spectrum Disorders and Mental Retardation

Amidation

Definition
The posttranslational modification at the C-terminal carboxylate group that substitutes a hydroxyl group with an amide. Since the C-terminal is responsible for a negative charge at neutral and basic pH, amidation neutralizes any negative charge by replacing the hydroxyl group.

Cross-References
► Gene Expression and Transcription

Amine Depletors

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Synonyms
Catecholamine depletion; Monoamine depletion; Tryptophan depletion

Definition
Amine depletion refers to a pharmacological or dietary manipulation that lowers levels of monoamine neurotransmitters in the brain for therapeutic or investigational purposes. An amine depletor is therefore an agent that diminishes levels of one or more monoamines in the brain.

Pharmacological Properties

Available Methodologies
The monoamines targeted by amine depletion are typically the catecholamine neurotransmitters, dopamine and

noradrenaline, and the indoleamine neurotransmitter, serotonin. Amine depletion in humans can be carried out in three principal ways:

1. Through pharmacological inhibition of vesicular storage of amines in the nerve terminal
2. Through pharmacological inhibition of neurotransmitter synthesis
3. Through dietary-induced brain depletion of amino acids required for neurotransmitter synthesis

Monoamine depletion may also occur as an adverse consequence of drug use, both licit and illicit; for example the substituted amphetamine, methylenedioxymethamphetamine (► MDMA), lowers brain serotonin levels. However, amine depletion occurring as an adverse effect will not be considered further in this article.

Inhibition of Vesicular Storage

A number of drugs including ► reserpine, ► tetrabenazine, and oxypertine bind to the vesicular monoamine transporter and thereby inhibit transport of synthesized monoamine from the cytoplasm to the vesicular storage granule. The monoamines in the cytoplasm are therefore exposed to metabolism by monoamine oxidase and monoamine levels at nerve terminals decline, lowering neurotransmission.

Reserpine has a long history in psychopharmacology and reserpine-induced depression formed the cornerstone of the monoamine theory of depression. Tetrabenazine and oxypertine have been used to treat ► tardive dyskinesia, presumably through their ability to deplete presynaptic ► dopamine levels. Tetrabenazine is still used for the treatment of abnormal movements, particularly those associated with Huntington's Chorea.

Pharmacological Inhibition of Neurotransmitter Synthesis

Under this heading, we can consider two pharmacological agents, para-chlorophenylanine (PCPA) and alpha-methyl-para-tyrosine (AMPT). PCPA irreversibly inhibits the enzyme tryptophan hydroxylase, which converts the amino acid ► tryptophan to 5-hydroxytryptophan and is the rate-limiting step in the synthesis of ► serotonin. PCPA administration therefore leads to depletion of brain serotonin. PCPA was previously used to treat carcinoid syndrome and has been employed in a limited way as an investigational tool in human psychopharmacology. For example, PCPA treatment of depressed patients who had responded to the monoamine oxidase inhibitor tranylcypromine resulted in clinical relapse showing the importance of intact serotonin function for the therapeutic action of this antidepressant. PCPA is still used extensively in animal experimental investigations as a pharmacological means of lesioning brain serotonin pathways.

AMPT is a competitive antagonist of the enzyme tyrosine hydroxylase, which converts the amino acid tyrosine to L-dopa. Administration of AMPT therefore decreases brain levels of ► noradrenaline and ► dopamine. In healthy volunteers, AMPT treatment results in sedation and can sometimes cause movement disorders such as Parkinsonism. Plasma prolactin is elevated and nocturnal melatonin secretion reduced, consistent with the known roles of dopamine and noradrenaline in the regulation of these two hormones. AMPT has been used clinically as an antihypertensive agent and in the treatment of pheochromocytoma.

AMPT has also been employed as an investigational tool in studies of the role of catecholamine pathways in depression and the mode of action of ► antidepressants. In healthy volunteers, AMPT does not reliably cause depression but in recovered depressed patients who have been withdrawn from antidepressant medication, AMPT causes a temporary clinical relapse. This suggests that in people vulnerable to depression, lowering catecholamine function is sufficient to produce clinical symptomatology. AMPT also reverses the therapeutic effect of antidepressant drugs such as desipramine which act primarily through noradrenergic mechanisms. This has been taken as evidence that intact noradrenaline neurotransmission is essential for the continued action of catecholamine-potentiating antidepressants in patients who have responded to this form of treatment (Booij et al. 2003; Ruhé et al. 2007).

Dietary-induced Brain Depletion of Amino Acids

As has been mentioned earlier, the synthesis of monoamine neurotransmitters depends on the availability of precursor amino acids to the brain. Dietary manipulations can take advantage of this fact to limit the availability of specific amino acids and thereby lower the synthesis in the brain of the corresponding neurotransmitter. The most studied manipulation is "tryptophan depletion" (TRD). In this procedure, participants are asked to ingest a balanced mixture of amino acids (traditionally about 80–100 g) from which tryptophan has been removed. This amino acid load drives protein synthesis in the liver and because tryptophan is an essential amino acid, the body has to use its own tryptophan supplies to manufacture protein. This leads to a sharp decline in plasma

tryptophan levels, which decreases the amount available for brain serotonin synthesis. In addition, amino acids compete with each other for active transport across the blood–brain barrier. The excess of other amino acids in plasma means that the small amount of tryptophan which remains available in plasma after TRD is inhibited by competition from transport into the brain. Thus, lowering levels of plasma tryptophan and decreasing its brain entry produces a substantial depletion of brain tryptophan and of serotonin synthesis. Because of the effects of the amino acid mixture on protein synthesis as well as subjective adverse effects (principally nausea), in investigational studies it is important to use a control mixture of amino acids containing a balanced amount of tryptophan.

Because of the interest in the role of serotonin pathways in psychiatric disorder and the effects of psychotropic drugs, TRD has been widely used as an investigational tool. The greatest volume of research has taken place in the field of mood disorders (Bell et al. 2005a,b). It seems fairly well established that TRD in healthy individuals with no risk factors for depression does not cause reliable effects on mood. Therefore, lowering serotonin function is not sufficient to cause depression in nonvulnerable individuals. However, TRD can cause acute depressive clinical symptomatology in some circumstances. For example, depressed patients who have responded successfully to serotonin-potentiating drugs such as ▶ selective serotonin reuptake inhibitors (SSRIs) may show a transient but striking relapse a few hours after TRD even though SSRI treatment is continued. This has been taken as evidence that the maintenance of the therapeutic response to SSRI treatment requires a sustained increase in the availability of serotonin. Interestingly, depressed patients successfully maintained on catecholamine-potentiating drugs such as desipramine do not relapse when administered TRD. This suggests that antidepressant drugs can produce therapeutic effects in depressed patients through distinct pharmacological mechanisms (Booij et al. 2003; Ruhé et al. 2007).

It is also noteworthy that patients with a history of depression, not currently on medication, can show transient clinical relapse following TRD (Smith et al. 1997). A mega-analysis revealed that female patients with a history of recurrent depression and suicide attempts were most likely to show this reaction (Booij et al. 2002). This finding suggests that in some vulnerable individuals, lowering serotonin function can be sufficient to cause clinical symptomatology. Theoretically, such individuals may have pre-existing deficits in serotonin pathways or perhaps abnormalities in the brain regions involved in mood regulation which are "revealed" in the low serotonin environment.

TRD is not particularly well tolerated since the amino acids load can cause nausea and retching. Attempts have therefore been made to use better-tolerated low-dose procedures with decreased total dose of amino acids (20–30 g). These mixtures reliably lower plasma tryptophan but their effect on mood is somewhat variable even in vulnerable individuals. However, changes in emotional processing that are congruent with depressed mood have been revealed (Hayward et al. 2005).

The success of TRD also led to dietary attempts to lower catecholamine neurotransmission by depleting plasma and brain tyrosine levels. In the body, tyrosine can be synthesized from phenylalanine, so dietary manipulations provide a mixture of amino acids lacking both phenylalanine and tyrosine. Ingestion of such a mixture produces a substantial lowering of plasma tyrosine. It also increases plasma prolactin indicative of a diminution in dopamine neurotransmission; however, nocturnal ▶ melatonin secretion is unaffected suggesting that noradrenaline function is not attenuated. This pattern of effect is consistent with experimental animal studies indicating that tyrosine depletion preferentially limits dopamine function, while apparently sparing noradrenaline neurotransmission. The reason for this is not clear but presumably relates to a greater dependency of dopamine neurons on tyrosine availability, perhaps because they have generally faster firing rate than noradrenaline neurons.

Tyrosine depletion has been less studied in experimental paradigms than TRD. Tyrosine depletion does not lower mood in healthy subjects and, in contrast to AMPT, fails to cause relapse in unmedicated recovered depressed patients. This suggests that the relapse seen in such subjects following AMPT is probably due to interruption of noradrenaline function or perhaps to a simultaneous decrease in noradrenaline and dopamine activity. Consistent with its ability to lower dopamine function, tyrosine depletion has been shown to attenuate the psychostimulant effects of ▶ methamphetamine in healthy volunteers and to diminish clinical ratings of mania in patients with ▶ bipolar disorder (McTavish et al. 2001). Tyrosine depletion does not attenuate the antidepressant effects of SSRIs arguing against theories that posit a key role for dopamine facilitation in antidepressant action.

Cross-References

▶ Acute Phenylalanine/Tyrosine Depletion
▶ Acute Tryptophan Depletion

► Aminergic Hypotheses for Depression
► Tryptophan

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Aminergic Hypotheses for Depression

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Synonyms

Catecholamine hypothesis; Indoleamine hypothesis; Monoamine hypotheses

Definition

The aminergic hypotheses of ► depression refer to theories of the role of abnormalities of aminergic neurotransmitters, or of physiologic perturbations in the functioning of neurons that contain aminergic neurotransmitters, in the cause and/or symptoms of a major depressive disorder.

Role of Pharmacotherapy

The aminergic hypotheses of ► depression were logical extensions of four landmark discoveries: that neurons communicate via the release of chemical substances called neurotransmitters; that aminergic neurotransmitters are found in high concentration in specific brain regions; that antidepressant drugs increase brain levels of aminergic neurotransmitters; and that drugs or procedures that reduce monoamine neurotransmitters induce depressive symptoms in some people. These discoveries provided the necessary scientific knowledge on which the aminergic hypotheses were based.

The theory that communication between neurons is mediated by chemical substances (neurotransmitters) rather than electrical impulses did not gain widespread acceptance until the mid-1900s. Prior to 1900, it was generally thought that neurons communicated with one another by electrical signals. The chemical theory of neurotransmission was initially based on the observation by J. N. Langley in 1901 that extracts from the adrenal gland had similar effects on end-organ targets as did stimulation of sympathetic nerves. He proposed that there could be "receptive substances" between a nerve cell ending and the target end organ that is activated when the nerve impulse reaches the nerve terminal. Elliot subsequently hypothesized in 1904 that an adrenalin-like substance might be secreted by sympathetic nerve terminals to chemically stimulate the target end organ. Many still doubted that this was relevant to communication between nerve cells, but the theory of chemical neurotransmission gained significant ground in 1921 when Otto Loewi conducted his now classic experiment showing that the liquid surrounding a heart that had had its nerves electrically stimulated to slow its rate could be transferred to a second un-stimulated heart to cause an identical slowing of the second heart's rate. Loewi proposed that the electrical stimulation of the nerves innervating the heart caused the release of a chemical substance that mediated the nerve's ability to reduce heart rate. In 1936, Loewi shared the Nobel Prize in medicine with Sir Henry Dale for their work on the discovery of chemical neurotransmission (see Tansey 1991 for a review). Subsequent research showed that other monoamine chemicals, such as ► dopamine (DA) and ► serotonin (5-HT), also served as neurotransmitters in the peripheral nervous system.

By the late 1950s, research had shown that the brain contained large amounts of several ► monoamines, including the ► catecholamine neurotransmitters ► norepinephrine (NE) and DA and the ► indoleamine 5-HT. These monoamines were localized to, and synthesized by, neurons within discrete brain nuclei. Two landmark observations,(1) that patients with Parkinson's disease showed a marked reduction in basal ganglia DA and (2) that oral administration of the metabolic precursor of DA, L-dihydroxy-phenylalanine (► L-DOPA), led to rapid improvements in the motor symptoms of

► Parkinson's disease Birkmayer and Hornykiewicz (1964), added considerable momentum to the investigation of the role of brain monoamines in behavior, and established a compelling theoretical model that greatly influenced the first aminergic hypotheses of depression (see Carlsson, 2001 for a review of the work of this time period).

The late 1950s and early 1960s saw the rapid clinical development of several drugs with potent effects on increasing or decreasing brain monoamines. This included drugs that were subsequently found to block reuptake, synthesis, metabolism, or receptors of one or more monoamines, as well as drugs and/or nutrients that served as synthetic precursors to monoamines. The drug ► reserpine (rauwolfia) had been shown in the 1950s to cause a long-lasting depletion of brain monoamines in laboratory animals, and this was associated with a profound depression-like state in laboratory animals and clinical depression in up to 18% of people receiving the drug for the treatment of hypertension. The catecholamine synthesis inhibitor alpha-methyl-para-tyrosine (AMPT) was also tested as a potential antihypertensive and a similar subset of patients developed clinical depression during the initial trials. Because reserpine caused profound sedation in humans, it was also used extensively as a sedative in agitated psychiatric patients, often in combination with other sedatives or the newly discovered antipsychotic drugs. Many other new drugs with central nervous system effects were introduced into clinical trials during the mid-late 1950s. ► Imipramine, a tricyclic compound, was being studied as a potential sedative, while isoniazid, a ► monoamine oxidase inhibitor (MAOI), was being used to potentiate antituberculosis treatments. Both drugs were noted by chance observation to cause resolution of depressive symptoms, stimulating an explosion of controlled clinical trials of these agents as potential treatments for depression. As evidence of the therapeutic effects in the depression of imipramine and its metabolites (such as desipramine) and MAOIs (such as iproniazid and tranylcypromine) accumulated, it became clear that understanding the pharmacology of these drugs might be relevant to the neurobiological underpinnings of major depression. Given that MAOIs were well known to increase brain levels of monoamines, this pharmacological property was suggested to underlie the therapeutic effects of such drugs in depression by the late 1950s (Carlsson 2001; Pare 1959).

The first fully developed aminergic hypotheses of depression finally emerged in the mid-1960s as investigators began to realize that these new antidepressant drugs potently increased brain levels of monoamines, while drugs that reduced monoamines could cause depression-like symptoms in some people. The catecholamine deficiency hypothesis of depression was based on the observation that many antidepressant drugs increased synaptic concentrations of NE, while the catecholamine-depleting drug reserpine seemed to cause depression-like symptoms (Schildkraut 1965). This hypothesis postulated that depression was due to a deficiency and mania, an excess of brain NE. The indoleamine hypothesis postulated that a deficit of brain 5-HT was responsible for depression, while drugs which increased synaptic 5-HT, such as MAOIs or 5-HT precursors such as 5-hydroxytryptophan (5-HTP) and ► L-tryptophan (TRP), relieved depression (Coppen 1967). These competing aminergic hypotheses led to an extensive body of research in the next few decades aiming to determine which of these two monoamine systems was most responsible for depression and the therapeutic effects of antidepressant drugs.

During the 1970s and 1980s, converging data made it seem as though mood disorders would turn out to be simple "chemical imbalances" of aminergic neurotransmitters. First, as the anatomy and physiology of monoamine systems began to emerge, it became clear that these systems play an important role in regulating the brain areas that are involved in core symptoms of depression, including mood, attention, sleep, sexual function, appetite, and pain perception. Monoamine systems are almost exclusively organized as large *systems* of single source divergent neurons, thereby able to simultaneously coordinate neural activity across many parts of the brain. Second, based on the theory that the antidepressants work by increasing NE and/or 5-HT, several new antidepressants that selectively inhibited the reuptake of one or two monoamines were developed. The ► selective serotonin reuptake inhibitors (SSRIs; e.g., ► fluoxetine), norepinephrine reuptake inhibitors (NARIs; e.g., ► reboxetine), and serotonin and norepinephrine reuptake inhibitors (SNRIs; e.g., ► venlafaxine) proved to be landmark drugs with comparable efficacy but greater tolerability and safety than the earlier line of drugs such as imipramine. Finally, human studies employing monoamine depletion showed that the depletion of catecholamines or 5-HT could induce a rapid return of depressive symptoms in some patients taking antidepressants. Depletion studies suggest that the 5-HT and NE effects of antidepressants may be independent of each other. For example, depleting 5-HT causes a rapid return of depression in depressed patients who have responded to fluoxetine, ► fluvoxamine, MAOIs, and imipramine, but not in those who have responded to desipramine, ► nortriptyline, or ► bupropion. Depleting NE and DA causes a rapid return of depression in those depressed patients who have

improved on desipramine, but not on fluoxetine. These results confirm that monoamines are necessary for maintaining antidepressant therapeutic response in most patients. This convergence of data on the anatomy and physiology of monoamine systems in the brain, pharmacological effects of antidepressants, and the depression-inducing effects of lowering monoamines generated considerable optimism in the field that the pathophysiology of these disorders was now close to being understood (Delgado et al. 1999; Delgado 2004).

However, there are inconsistencies and gaps in the aminergic theories. First, while antidepressants increase brain monoamine levels severalfold within minutes of their administration, the antidepressant response takes weeks to emerge. Attempts to speed up antidepressant responses by more rapidly increasing monoamine levels or using postsynaptic monoamine receptor agonists have largely failed. Further, deficiencies of NE or 5-HT or their metabolites in cerebrospinal fluid (CSF), blood, or urine have not been consistently demonstrated in depressed patients, despite extensive efforts to do so (Charney et al. 1981). When abnormalities have been found, they have tended to be nonspecific. Also, while a small subset of people with a history of prior psychiatric illness report depressive symptoms when exposed to monoamine depleting drugs or monoamine synthesis inhibitors, the majority of people exposed to these drugs or procedures do not experience clinical depression. For example, in an open treatment trial of AMPT in patients with essential hypertension, six of 20 hypertensive patients had a history of a previous depressive episode. Three of these six became agitated on AMPT, requiring drug discontinuation. In a trial of the 5-HT synthesis inhibitor para-chloro-phenylalanine (PCPA) in patients with carcinoid tumors, a subset of the patients experienced a variety of acute symptoms ranging from lethargy, irritability, anxiety, and depression to psychosis, although most subjects demonstrated little behavioral change. Neither 5-HT nor NE depletion has resulted in depressive symptoms in studies of volunteers without a personal or family history of depression (Delgado 2004).

Recent attempts to understand the slow onset of antidepressant action have focused on the "downstream" adaptive changes that temporally follow increases in synaptic levels of monoamines. This includes research on receptor adaptations, changes in second-messenger molecules, changes in ► gene expression, release of ► neurotrophic factors, and ► neurogenesis. This work has led some investigators to focus on the integrity and functioning of limbic brain areas modulated by monoamine systems as an alternative explanation for the pathophysiology of depression. Brain imaging and autopsy studies have noted marked differences in the structure and/or function of several limbic areas such as the ► prefrontal cortex, anterior cingulate gyrus, ► hippocampus, and ► amygdala that are believed to be involved in core brain functions that become abnormal in depression (Duman et al. 2004).

Current research suggests that depression is what geneticists define as a "complex" disorder, where illness results from the summation of numerous genetic and environmental factors, each of which have small effects and result in illness only when their combined effects surpass a certain threshold. If true, then the biochemical and genetic causes of major depression may differ markedly from one patient to another. This may explain the sometimes inconsistent results in research studies investigating specific biochemical abnormalities associated with depression. The results of monoamine depletion studies suggest that a simple deficiency of 5-HT or NE is not likely to be the sole cause of depression. Research pursuing causal pathways that directly cause injury to brain areas such as the frontal cortex, hippocampus/amygdala, and basal ganglia known to be modulated by monoamine systems is warranted.

Therefore, the available data suggests that the initial aminergic hypotheses were partially correct. While research supporting a causal role of monoamine dysfunction as the primary cause of depression is not sufficiently supported, the data supporting a primary role for an increase in monoamines in the initial step of antidepressant drug action is quite strong. Most or all drugs currently approved by the US Food and Drug Administration (FDA) for the treatment of depression directly or indirectly increase the synaptic availability of 5-HT and/or NE. Increasing brain NE and/or 5-HT appears to be the initial pharmacological step responsible for antidepressant efficacy in depression. This most likely includes a temporal sequence with increased monoamine levels causing alterations in presynaptic autoreceptor density and sensitivity that allow further increases in synaptic levels of the monoamines, culminating in postsynaptic receptor adaptations, and changes in neuronal plasticity and neurogenesis. The postsynaptic areas affected by the increased monoamine levels notably include most of the brain areas involved in emotion regulation, cognition, and sensory and pain perception. Increased monoamines observed as a result of treatment with 5-HT and NE reuptake inhibitors may serve to partially restore neuronal function in dysfunctional limbic circuits. The acute reappearance of depressive symptoms upon monoamine depletion in depressed patients in remission but not in

healthy people may underscore the possibility that depressed patients have greater fragility than healthy controls of the limbic networks modulated by monoamines.

Cross-References

- ▶ Acute Tryptophan Depletion
- ▶ Amine Depletors
- ▶ Antidepressants
- ▶ Antidepressants: Recent Developments
- ▶ Brain-Derived Neurotrophic Factor
- ▶ Depression: Animal Models
- ▶ Emotion and Mood
- ▶ Monoamine Oxidase Inhibitors
- ▶ NARI Antidepressants
- ▶ Serotonin
- ▶ SNRI Antidepressants
- ▶ SSRIs and Related Compounds

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Aminergic Hypothesis for Schizophrenia

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Definition

An explanation for the pathophysiology of schizophrenia and mechanism of action of antipsychotic drugs with a special focus on aminergic (dopamine, serotonin, and noradrenaline) neural systems.

Role of Pharmacotherapy

Schizophrenia is characterized by a variety of symptoms, including hallucination, delusion, and psychomotor excitement. A dopamine receptor antagonist, ▶ chlorpromazine, was introduced in the treatment of this illness in 1952 and has shown its effectiveness, which has made the dopaminergic system a primary target of research on the pathogenesis of schizophrenia as well as potential mechanisms of antipsychotic action of this type of drugs. This has led to the prototype of the dopaminergic hypothesis for schizophrenia where the increase and decrease in the dopaminergic neural transmission is attributed to its symptoms and treatment effects of ▶ antipsychotic drugs, respectively. Although this hypothesis has been revisited and further developed, the dopaminergic system cannot fully account for the mechanisms underlying this illness. Recently, other neural systems such as glutamatergic and cholinergic systems have also come to the front line of this line of research.

▶ Dopamine was the first target of research on schizophrenia, and is still considered to play a primary role in the pathogenesis of this illness and mechanisms of actions of antipsychotic drugs. The hypothesis that explains the involvement of the dopaminergic system in this illness (the dopamine hypothesis) has been supported by a vast amount of both animal and human studies and further occasionally updated with the accumulation of relevant new clinical and basic data. The first version of the dopamine hypothesis focused on the dopaminergic receptors where psychosis was considered to be due to excessive transmission at dopaminergic receptors and diminished by blocking these receptors. The most widely accepted support for this hypothesis is the fact that dopamine antagonist antipsychotic drugs can relieve psychotic symptoms. The first antipsychotic drug, chlorpromazine, was introduced in the treatment of schizophrenia in 1952. As this type of medication had been found to have a dopamine receptor blocking property, the dopaminergic system came to the forefront of scientific inquiry. While blockade of dopamine receptors had already been thought to be associated with therapeutic effects of antipsychotic medications in the 1960s and 1970s, Seeman et al. first systematically demonstrated that the degree of dopamine receptor antagonism by antipsychotics was closely associated with their antipsychotic efficacy in 1976 (Seeman

et al. 1976). This relationship is still valid after ► second-generation antipsychotics have become available, although ► clozapine seems exceptional, as we discuss next. Another frequently referred support for this hypothesis is the presence of psychotic symptoms associated with the administration of amphetamine. Both animal and human studies have demonstrated the increase of endogenous dopamine levels, following ► amphetamine administration, and shown that amphetamine-induced psychotic symptoms resemble schizophrenic symptoms. Furthermore, these amphetamine-induced psychotic symptoms are reversible with the use of dopamine antagonist antipsychotic drugs. In addition, psychotic symptoms caused by amphetamine administration in drug-free schizophrenia patients were found to be associated with exaggerated stimulation of dopaminergic transmission, compared to those who did not present those symptoms following its administration (Laruelle et al. 1996) – lending further support to this model.

In 1980, Crow proposed a hypothesis where schizophrenia could be grouped into two separate conditions: the type I syndrome characterized by positive symptoms, including delusion, hallucinations, and thought disorder, and type II syndrome characterized by negative symptoms, including affective flattering and poverty of speech (Crow 1980). In this theory, the type I syndrome was considered to be associated with high dopaminergic activity and reversible with antipsychotic treatment while negative schizophrenic symptoms were thought to be caused by deficiency in the dopaminergic function and involve a component of irreversibility. This hypothesis tried to comprehensively link potential pathogenesis and symptomatology of schizophrenia to the dopaminergic system. Although this proposal has often been criticized later due to its simple dichotomization and a lack of sufficient convincing biological support, its impacts on further investigations have still been tremendous. In 1991, Davis et al. published a landmark review and proposed the co-occurrence of high and low dopamine activities in schizophrenia to the concurrent presence of positive and negative symptoms (referred to as the dopamine hypothesis, Version II) (Davis et al. 1991). Evidence, particularly from intracellular recording studies in animals and plasma homovanillic acid (HVA) measurements, suggests that antipsychotics exert their effects by reducing dopamine activity in mesolimbic dopamine neurons. Postmortem studies have shown high dopamine and HVA concentrations in various subcortical brain regions and greater dopamine receptor densities in patients with schizophrenia, compared to healthy people. On the other hand, they attributed the negative/deficit symptom complex of schizophrenia to low dopamine activity in the prefrontal cortex, which is now known as "hypofrontality." Davis et al. hypothesized that abnormally low prefrontal dopamine activity caused deficit symptoms in schizophrenia, while excessive dopamine activity in mesolimbic dopamine neurons resulted in positive symptoms.

With further accumulation of basic and clinical data on the function of the dopaminergic system, psychopathology of schizophrenia, and potential mechanisms underlying treatment effects of antipsychotics, Kapur reviewed those findings (Kapur 2003) and linked the neurobiology (brain), the phenomenological experience (mind), and pharmacological aspects of psychosis in schizophrenia into a unitary framework. A central role of dopamine is to mediate the "salience" of environmental events and internal representations. It is proposed that a dysregulated, hyperdopaminergic state at a "brain" level of description and analysis leads to an aberrant assignment of salience to the elements of one's experience at a "mind" level. This would result in delusions as a clinical manifestation as patients make a cognitive effort to make sense of these aberrantly salient experiences. On the other hand, ► hallucinations reflect a direct experience of the aberrant salience of internal representations. Antipsychotic drugs are expected to dampen the salience of these abnormal experiences and by doing so permit the resolution of symptoms, where the antipsychotics are thought not to erase the symptoms but to provide the platform for a process of psychological resolution. Therefore, if antipsychotic treatment is stopped, the dysregulated neurochemistry returns, the dormant ideas and experiences become reinvested with aberrant salience, resulting in a relapse. Although this hypothesis does not explain the mechanisms of negative symptoms of schizophrenia, current ideas regarding the neurobiology and phenomenology of psychosis and schizophrenia, the role of dopamine, and the mechanism of action of antipsychotic medication are integrated.

In its latest iteration, Howes et al. proposed the updated version of the dopamine hypothesis (Version III), where multiple factors, including stress and trauma, drug use, pregnancy and obstetric complications, and genes, interact to result in the increased presynaptic striatal dopaminergic function in schizophrenia (Howes and Kapur 2009). This striatal dopaminergic dysregulation is considered the final common pathway of the pathogenesis of this illness, in this theory. This hypothesis suggests that current treatments act downstream of the critical neurotransmitter abnormality and emphasized the need of future drug development with a focus on the upstream factors that converge on the dopaminergic funnel point.

However, pathogenesis of schizophrenia and the resolution of its symptoms with antipsychotics are not expected to be solely related to the effects in the dopaminergic system. Superior clinical effects of clozapine despite its low dopamine D_2 receptor blocking propensity are one example of the limitations of the dopamine hypothesis. There are several others: many patients do not respond despite adequate dopamine blockade, some respond with rather low D_2 blockade, and many relapse despite adequate D_2 blockade. So, clearly the genesis of psychosis and its response depends on more than just dopamine. But, precisely what is beyond dopamine – has been harder to confirm. The involvement of other neural systems such as the glutamatergic, cholinergic, and serotonergic systems has been proposed.

Several lines of evidence suggest that the glutamatergic neural system is also involved in the pathogenesis of schizophrenia (Bubenikova-Valesova et al. 2008). ▶ Glutamate acts through several types of receptors, of which the ionotropic glutamate N-methyl-D-aspartate (▶ NMDA) receptor has been considered to be closely associated with schizophrenia (i.e. the glutamate hypothesis of schizophrenia). The most prominent support for this hypothesis is the acute psychomimetic effects of noncompetitive antagonists of glutamate NMDA receptors, such as ▶ phencyclidine and ▶ ketamine. These drugs have been shown to change both human and animal behavior and induce schizophrenia-like manifestations. For example, ketamine has been demonstrated to cause a variety of schizophrenia-like symptoms in healthy people, including positive symptoms (e.g., illusions, thought disorder, and ▶ delusions), negative symptoms (e.g., blunted emotional responses, emotional detachment, and psychomotor retardation), and cognitive symptoms, in particular impairments on tests of frontal cortical function (e.g., increased distractibility and reduced verbal fluency). In patients with schizophrenia, ketamine causes auditory or visual hallucinations while antipsychotics significantly reduce the ketamine-induced increase in positive symptoms. This hypothesis is also in line with the neurodevelopmental model of schizophrenia. Susceptibility to the psychotomimetic effects of ketamine is minimal or absent in children and becomes maximal in early adulthood, which is consistent with the fact that many schizophrenia patients experience their first episode until their 20s. Increased cellular destruction by ▶ apoptosis or changes in the function of NMDA receptors in the early development of the central nervous system are expected to be decisive for the subsequent development of ▶ psychosis, which in turn would be expected to finally manifest in their early adulthood. However, although pharmacological intervention to the NMDA receptors, using their antagonists, may lead to the development of novel therapeutic agents for schizophrenia in theory, no agent has been available until now.

The available evidence also suggests an important role for the muscarinic cholinergic system in the pathophysiology of schizophrenia (Raedler et al. 2007; Scarr and Dean 2008). ▶ Acetylcholine is synthesized in neurons from acetyl-CoA and choline in a reaction catalyzed by the enzyme ▶ choline acetyltransferase. There are two families of acetylcholine receptors: muscarinic receptors and nicotinic receptors. Muscarinic cholinergic neurotransmission has been shown to play a significant role in various cognitive functions, including learning and memory, which has lead to a hypothesis that these receptors are involved in cognitive impairment in schizophrenia (the cholinergic hypothesis of schizophrenia). Postmortem and in vivo brain imaging studies have consistently shown a significant decrease of muscarinic M1 receptor density, and this decrease is seen in patients with schizophrenia but not those with bipolar disorder or major depression. Thus, these changes are expected to be disease-specific and considered to be associated with deficits in the cognitive function in schizophrenia. Pharmacological studies of the muscarinic system in schizophrenia have indicated that targeting muscarinic M1 receptor might be an effective strategy to ameliorate the cognitive impairment in schizophrenia. Although stimulating cholinergic neurotransmission, using ▶ cholinesterase inhibitors, has not yielded promising therapeutic effects on cognitive function in schizophrenia, muscarinic M1 agonists have been shown to improve cognitive function. For example, N-desmethylclozapine, an active metabolite of ▶ clozapine, is a potent M1 agonist and has gathered attention as a new pharmacological agent for the treatment of schizophrenia although the data are still preliminary. Thus, the currently available evidence suggests that deficits in muscarinic M1 neurotransmission in brain are associated with cognitive impairments in schizophrenia. Although there is no clinically available muscarinic M1 agonist as a cognitive enhancer for the treatment of schizophrenia, the preliminary data indicate the potential benefits of targeting these receptors to improve cognitive function in patients with this illness.

The potential involvement of the serotonergic system in the pathogenesis of schizophrenia was first proposed earlier than the dopamine hypothesis. Based on a phenomenological similarity between psychosis-like effects of lysergic acid diethylamide (LSD) and symptoms of schizophrenia, it was proposed in the mid 1950s that the abnormal neural transmission in the serotonergic system

may be responsible for psychotic symptoms in schizophrenia (referred to as the serotonergic hypothesis of schizophrenia). A subsequent series of human and animal studies have confirmed that 5-HT_{2A}-receptor agonists such as LSD and psilocybin have effects that mimic schizophrenia-like symptoms (Geyer and Vollenweider 2008). These findings seem to support that psychopharmacological intervention in the serotonergic neural system may be promising for drug development, which is not the case in reality. Antipsychotic drugs such as clozapine and chlorpromazine had significantly higher affinity for 5-HT_2 than for D_2 receptors. However, as described earlier, the degree of dopamine receptor antagonism (rather than their 5-HT_2 antagonism) by these antipsychotics has been shown to be more closely associated with their antipsychotic efficacy, suggesting that 5-HT_2 blockade is not the principal mechanism of their antipsychotic action. Consistent with this contention, clinical trials have failed to provide robust antipsychotic effects of selective antagonists at 5-HT_{2A} receptors until now. Some atypical antipsychotics, including ► risperidone, have been suggested to have a safer side effect profile in motor function, which may be due to their 5-HT_{2A} antagonistic property. Although antagonism at 5-HT_{2A} when added to D_2 antagonism may contribute to the safe profile of those newer drugs, targeting solely serotonergic neural transmission is unlikely to provide antipsychotic effects for the treatment of schizophrenia.

In summary, while the current data suggest the involvement of several aminergic neural systems in the pathophysiology of schizophrenia and mechanisms of actions of antipsychotics drugs, the dopaminergic system is still considered to play a principal role. In fact, there is no effective antipsychotic that does not have an effect on the dopamine system. On the other hand, nonpsychotic symptoms, especially negative symptoms and cognitive impairment, may be reversed with the use of drugs working on nondopaminergic neural systems such as the glutamatergic and cholinergic system. Given that manipulating the dopaminergic system is effective, but not always perfect for the treatment of schizophrenia, further psychopharmacological research on other neural systems would also be needed.

Cross-References

► Amphetamine
► Animal Models for Psychiatric States
► Antipsychotic Drugs
► Atypical Antipsychotic Drugs
► Dopamine
► First-Generation Antipsychotics
► Glutamate
► Glutamate Receptors
► Hallucinations
► Monoamines
► Muscarinic Receptor Agonists and Antagonists
► Muscarinic Receptors
► Neurotransmitter
► NMDA Receptors
► Schizophrenia
► Schizophrenia: Animal Models
► Second and Third Generation Antipsychotics

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2-Amino-3-Hydroxy-N′-[(2,3,4-Trihydroxyphenyl) Methyl] Propanehydrazide

► Benserazide

(2R,3R,4R,5R)-2-(6-Aminopurin-9-yl)-5-(Hydroxymethyl)Oxolane-3,4-diol

► Adenosine

Amisulpride

Definition

Amisulpride is a benzamide derivative and is a second-generation antipsychotic with high affinity for D2 and D3 receptors. Its pharmacology is unusual in that at low doses, amisulpride preferentially blocks presynaptic D2 receptors, while at high dose it acts as an antagonist at postsynaptic D2 receptors. Amisulpride is used for the treatment of positive and negative symptoms of ► schizophrenia, as well as the management of dysthymia. Its therapeutic and safety profile is similar to that of the atypical antipsychotic ► risperidone, but amisulpride is associated with less weight gain and endocrine disturbance.

Cross-References

► Antipsychotic
► Second- and Third-Generation Antipsychotics

Amitriptyline

Definition

Amitriptyline is a ► tricyclic antidepressant with a tertiary amine chemical structure. One of the earlier tricyclics to be developed, it acts by inhibiting the reuptake of ► serotonin and ► norepinephrine, with roughly equal effects on each of these neurotransmitters. While its primary use is in the treatment of depression, it is also used in lower doses to treat migraine headache. It is metabolized to ► nortriptyline, which is itself marketed as an antidepressant. Usage of amitriptyline has declined in recent years due to its unfavorable side effect profile, including marked sedation, cardiovascular effects, and anticholinergic effects (e.g., constipation, dry mouth, blurred vision, urinary retention), and its high potential for lethality in overdose.

Cross-References

► Antidepressants
► Nortriptyline
► Tricyclics

Amnestic Compounds

► Inhibition of Memory

Amobarbital

Synonyms

Amylobarbitone

Definition

Amobarbital is a medium- to long-acting sedative ► barbiturate medication used in the treatment of severe and refractory anxiety and insomnia. It is sometimes used in conjunction with ► antipsychotic medication in acute psychotic episodes. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Interaction with ► alcohol can be hazardous. It depresses respiration and is highly toxic in overdose. It can induce liver microsomal enzymes. Long-term use induces dependence with severe withdrawal reactions. Recreational use and abuse can occur: amobarbital is a scheduled substance.

Cross-References

► Barbiturates

AMPA Receptor

Synonyms

AMPAR

Definition

The alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (or AMPA receptor) is a glutamate-activated ionotropic receptor (a ligand-gated cation channel) that mediates fast excitatory synaptic transmission and that has been linked to processes of synaptic plasticity that underlie learning and memory.

Ampakines

Definition

Ampakines are a new class of compounds that modulate ► glutamate in the brain. They work by allosterically binding to the AMPA subtype of ► glutamate receptors, which play a key role in memory formation and learning. Ampakines rapidly cross the ► blood–brain barrier and enhance the functioning of AMPA receptors to produce fast excitatory synaptic responses in the ► hippocampus. Thus, ampakines may produce cognitive benefits when

used as drugs. There is research interest in memory enhancement, stroke therapy, dementia treatment, sleep deprivation aid, and other therapeutic uses of ampakines.

Cross-References
► AMPA Receptors
► Blood–Brain Barrier
► Glutamate

AMPAR

► AMPA Receptor

Amperometry

► Electrochemical Techniques and Advances in Psychopharmacology

Amphetamine

Synonyms
Benzedrine

Definition
Amphetamine is a stimulant drug structurally related to the more potent and toxic stimulant ► methamphetamine. Amphetamine has two forms or isomers: (+)-amphetamine and (−)-amphetamine (otherwise called dextroamphetamine and levoamphetamine, respectively). The (−)-isomer has greater sympathomimetic properties; accordingly, the pure (+)-isomer is preferred for therapeutic use, although a mixture of 75% (+)-amphetamine salts and 25% (−)-amphetamine has become widely used for treating ADHD. Amphetamines were used to treat obesity due to their anorexic properties, but the tendency for tolerance reduced their effectiveness and increased the risk of dose escalation and abuse. Amphetamines are used for ► narcolepsy and chronic fatigue. Although they are also used as recreational drugs, with important neurotoxic consequences when abused, addiction is not a high risk when therapeutic doses are used as directed.

Cross-References
► Aminergic Hypotheses for Depression
► Aminergic Hypotheses for Schizophrenia
► Psychostimulants

Amphipathic

► Amphiphilic

Amphiphilic

Synonyms
Amphipathic

Definition
A molecule that is characterized by hydrophobic (nonpolar) and hydrophilic (polar) properties. When referring to peptides such as CRF, certain amino acid groups are hydrophobic or hydrophilic giving the peptide an amphiphilic surface.

Amygdala

Definition
Almond-shaped collection of nuclei in the anterior temporal lobe.

Amylobarbitone

► Amobarbital

Amyloid-Beta

Synonyms
Aβ; Abeta; Beta amyloid; β-Amyloid

Definition
A peptide derived from the amyloid precursor protein that accumulates extracellularly, regularly ordered in β-pleated sheets (which posses characteristic staining properties). The amyloid accumulation is usually surrounded by dystrophic axons as well as processes of astrocytes and microglias forming the amyloid or senile plaque, one of the hystopathological findings associated with Alzheimer's disease.

This low molecular protein is generated from amyloid precursor protein (APP) by β- and γ-secretase. β-amyloid

has neurotoxic properties and is suggested to be of causal relevance for the underlying pathology of Alzheimer's disease.

Anabolic Steroids

► Sex Hormones

Analgesia

Definition

Analgesia is a condition in which painful stimuli are perceived but not interpreted as painful. Analgesia involves a decrease in both the sensory component of pain as well as affective components such as discomfort or unpleasantness.

Cross-References

► Analgesics
► Opioids

Analgesia Tests

► Antinociception Test Methods

Analgesics

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Synonyms

Pain-relievers

Definition

Analgesics are drugs that are used to reduce pain.

Pharmacological Properties

Opioid Drugs

Opioid drugs have been the mainstay for the relief of mild to severe pain for centuries. It is worth noting that the first recorded use of ► morphine was in the third century BCE, and that it remains the first line analgesic in medical practice today. This reflects on both morphine's effectiveness in relieving pain and the inability of medical science to develop better drugs for the treatment of pain.

Opioid analgesics are defined as drugs that reduce pain by an action on opioid receptors. Before it was possible to define the protein structure of receptors, opioids were drugs whose effects could be prevented or reduced by administration of an ► opioid antagonist such as ► naloxone. Three opioid receptors, mu (named for the prototype drug that acts at this receptor, morphine), kappa, and delta receptors were defined by this method. Once the amino acid structure of receptor proteins could be determined, the definition of opioid receptor became a membrane protein with a structure that had considerable amino acid homology with the mu opioid receptor. Kappa and delta receptors continued to qualify, and a new receptor termed the Nociceptin/Orphanin FQ Peptide (NOP) receptor was discovered that met this definition as well.

Because of the effectiveness of ► mu opioid agonists in reducing pain, the capacity of agonists at each of the other opioid receptors to reduce pain has been thoroughly studied. Drugs that act on the kappa and delta receptors have analgesic effects, but have no clinical use for this indication because of adverse side effects (dysphoria in the case of kappa agonists and convulsions in the case of delta agonists) and because their pain-relieving potential seems not to be superior to that of morphine-like drugs. Drugs that act on these sites remain interesting and useful in experimental studies in animals and in vitro, and drugs with primarily kappa and delta activity have considerable promise in the treatment of itch and depression, respectively. The possibility that drugs that act on the NOP receptor may present a favorable profile of analgesic action is still under consideration in animal studies; this is described in more detail in the section Novel Approaches.

A great many analgesic drugs with mu opioid receptor ► affinity and ► efficacy have been developed over the past 50 years. Prior to that time, morphine and ► codeine, both naturally occurring opioids derived from the opium poppy, were almost the only strong analgesics that were available. Heroin, easily synthesized from morphine, was also in use as was ► methadone, the first totally synthetic opioid, which was identified in Germany in 1937. Between this time and 1977, when the most recent opioid analgesic (► tramadol) was introduced in Germany, the pharmaceutical industry expended gradually decreasing efforts to synthesize new opioid drugs in the hope that a drug could be identified that had morphine's ability to reduce pain but with fewer unwanted side effects.

The side effects of morphine that are most problematic include constipation, respiratory depression, sedation, and with some routes of administration, pruritus. In addition, when used daily for the treatment of chronic pain, morphine can produce physiological dependence and a resulting uncomfortable ► withdrawal syndrome if and when the drug is discontinued. The ► abuse liability of morphine is also of considerable concern, and has biased markedly some physicians against using opioid analgesics in cases of chronic, non-cancer pain. Over the years, drugs such as ► hydrocodone and hydromorphine, etorphine, ► fentanyl, and its derivatives (sufentanil, alfentanil, remifentanil), ► buprenorphine, ► pentazocine, nalbuphine, and tramadol were synthesized and marketed for analgesic use. Although these drugs differed widely in their pharmacokinetics, efficacies, and potencies, they all produced the majority of their analgesic actions through the mu opioid receptor. Pentazocine, with a confusing profile of action that may include some kappa receptor efficacy, and tramadol, which may act on serotonin as well as mu opioid receptors to reduce pain, are two opioid analgesics with additional sites of action. Unfortunately, the side effects that morphine produced were all found to be mediated through the mu receptor, and each of the newer opioid analgesics retained this same side-effect profile to a degree commensurate with their efficacies at the mu opioid receptor. These drugs are all currently available as analgesics in many countries, and are used because of their various pharmacokinetic advantages, but none has replaced morphine as the drug of choice in most situations that require relief of moderate to severe pain (Corbett et al. 2006). Most likely because of this determination, few pharmaceutical companies are currently attempting to develop improved opioid analgesics.

Two opioid analgesics, methadone and buprenorphine, because of their long-acting ► pharmacokinetic profile of action and because they can be taken by mouth, are currently used more frequently for the treatment of heroin abuse than they are used for the treatment of pain. The mechanism of methadone's ability to reduce heroin use is unknown, but variously attributed to methadone-induced cross-tolerance to heroin and to methadone-induced reduction in opioid cravings. The same mechanisms have been applied to buprenorphine, with the additional advantage that this partial mu opioid receptor agonist has some opioid antagonist effects as well. The pure opioid antagonist, ► naltrexone, is also effective in reducing heroin abuse by blocking the reinforcing effects of heroin. Compliance with opioid antagonist therapy for heroin abuse is a serious drawback, but may be soon overcome by the development of depot forms of antagonist administration (Comer et al. 2007).

When given frequently for the treatment of chronic pain, ► tolerance can develop to the analgesic effects of morphine. This means that the dose needs to be increased in order for the pain relief to be maintained. This has been demonstrated most readily in animal models of pain relief; there remains considerable debate about whether the requirement of increasing doses of morphine to treat chronic cancer pain, for example, is due to a reduced response to morphine or to an increase in the disease-related pain over time (Ballantyne and Shin 2008).

The mechanism of tolerance to morphine's analgesic effect is also a source of debate. There is no increased metabolic degradation of morphine with chronic administration, and no change in the number of mu opioid receptors or affinity of morphine for these receptors as a consequence of frequent administration. One of the more intriguing theories to account for opioid tolerance invokes a ► dual-process mechanism whereby the original actions of the drug (analgesia) are followed in time by the opposite action (► hyperalgesia). According to this theory, with chronic administration the hyperalgesic actions occur more rapidly and to a larger extent following each drug administration and attenuate the analgesic actions, resulting in a tolerance-like effect.

Morphine and most mu opioid analgesics are effective by oral or parenteral routes of administration, although variable gastric absorption of morphine makes intravenous or intramuscular administration more common in dealing with acute pain. Codeine is more consistently absorbed when given by mouth. Allowing patients to control their analgesic administration has become increasingly popular (► patient controlled analgesia or PCA). It has been found that providing patients in pain with a button to press that causes a brief intravenous injection of morphine produces better pain relief with less drug than the previous procedure of nurse-administered analgesia on a regular, every 4-h basis (Polomano et al. 2008). Certain limits are placed on the amount of morphine than can be infused over time, but there is rarely any tendency of patients to attempt to exceed these limits, and the amount of morphine infused typically decreases as the pain subsides.

Morphine and more lipophilic opioids such as remifentanil or sufentanil are also used frequently by the ► intrathecal or epidural route of administration for childbirth pain and postsurgical pain, and for patients who are resistant to or have unacceptable side effects from morphine given by other routes. For those in the latter group, it is possible to implant an intrathecal catheter and maintain

morphine analgesia by this route for dealing with chronic pain. Pain relief can be accomplished by much smaller doses of opioids when they are delivered around the spinal cord, which decreases the risk of adverse side effects. Nevertheless, respiratory depression remains the side effect of most concern with this route of administration, nausea and vomiting continue to occur, and pruritus may be more profound following intrathecal as compared with other routes of morphine administration (Schug et al. 2006).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are effective analgesics for mild to moderate acute pain such as minor trauma, dysmenorrhea, or headache, and for more chronic pain that is related to inflammatory responses, such as osteo- and rheumatoid arthritis. There are currently more than 25 members of this class, including the salicylic acid derivative, aspirin, the arylpropionic acids such as ibuprofen and naproxen, the COX-2 inhibitors such as celecoxib, rofecoxib, and parecoxib, and the heteroaryl acetic acids such as diclofenac and ketorolac. All but ketorolac and parecoxib are available only for oral administration. The mechanism of action of each of these drugs is inhibition of an enzyme (cyclo-oxygenase; COX) that normally produces prostaglandins and thromboxanes, some of which sensitize spinal neurons to pain, but others of which inhibit gastric acid secretion and protect gastric mucosa (Rang et al. 2007).

There are two primary cyclo-oxygenase isoforms, known as COX-1 and COX-2. COX-1 is a constitutive enzyme, active in most tissues, including red blood cells. The prostaglandins it catalyzes have a role in the protection of gastric tissues, and platelet aggregation. COX-2, on the other hand, is active when stimulated by inflammatory reactions, and the ► prostanoids that it catalyzes often mediate inflammation. Drugs such as aspirin, ibuprofen, and naproxen block both cyclo-oxygenase isoforms. It is generally thought that the ability of these drugs to reduce inflammatory pain is related to their block of COX-2, whereas the side effects of gastric irritation, and decreased clotting time were due to block of COX-1 enzyme. A concerted effort to develop drugs that blocked only the COX-2 enzyme and thereby yield NSAIDs that reduced pain but had fewer side effects resulted in the synthesis of the coxib drugs such as celecoxib and rofecoxib. In fact, these drugs do have a reduced ability to produce gastric irritation and bleeding while retaining considerable pain relieving effectiveness. Unfortunately, it appears as though some selective COX-2 inhibitors also increase the risk of adverse cardiovascular events, apparently because of the loss of a protective effect of COX-1 inhibition. A recent meta analysis of a series of NSAIDS and the risk they pose for adverse cardiovascular effects indicates that although the COX-2 selective inhibitors are more likely to produce dose-related myocardial infarction than NSAIDS that are less COX-2 selective, there is no close correspondence between the degree of COX-2 selectivity and risk of cardiovascular damage (Farkouh and Greenberg 2009).

The side effects of use of the nonselective COX-inhibitors are primarily gastric irritation and bleeding, which can be serious and life threatening, and decreases in platelet aggregation, which is a positive effect in individuals with coronary artery disease.

Other Drugs for Pain Relief

Acetaminophen is used to reduce mild to moderate pain, in much the same manner as aspirin. Acetoaminphen has less anti-inflammatory effects than NSAIDS, but it is very effective in reducing fever, which is done by blocking prostaglandin biosynthesis under conditions of fever. This analgesic is much less irritating to the GI tract than are NSAIDS, and does not alter blood coagulation as significantly as NSAIDS do. The primary risk factor of acetoaminophen is liver damage, which can occur if large doses are taken, or if an individual has a genetic polymorphism of liver enzymes that results in increased levels of a toxic acetoaminophen metabolite.

Calcium channel blockers. Although opioid drugs are recommended for moderate to severe pain, they are thought to be relatively ineffective in the treatment of neuropathic pain, or pain due to nerve damage or neuropathies. These conditions are usually chronic, making use of the large doses of opioids that are required to reduce this pain problematic. In 1994, a novel drug, gabapentin, was approved as an adjunct to the treatment of some types of seizures. It was fairly quickly discovered that ► gabapentin is also effective in reducing neuropathic pain, and it is currently widely prescribed for this purpose, although this is an off-label use. ► Pregabalin is a drug with a similar mechanism of action and spectrum of analgesic effects as gabapentin, and it is marketed for this use.

Both these drugs are structurally based on the inhibitory neurotransmitter ► GABA, but their effects are not related to the activity of this neurotransmitter. Rather, they may produce their analgesic effects through a blockade of a subunit of voltage-sensitive calcium channels in the brain and spinal cord. This blockade results in reduction in stimulated release of many neurotransmitters, including glutamate, GABA, ► substance P, and glycine, and this effect is currently thought to participate in the analgesic actions of these drugs (Taylor 2009). There are few side effects noted for these analgesic drugs.

Ketamine. This drug acts on the subtype of the ► glutamate receptor that is sensitive to *N*-methyl-D-aspartate (NMDA) application and produces both analgesia and anesthesia. ► Ketamine, the most widely used NMDA antagonist, is classified as a dissociative anesthetic because of the profound psychotomimetic effects of this drug that are apparent upon emergence. These effects are dysphoric in most individuals, limiting the use of ketamine as an anesthetic–analgesic primarily to patients with burn injuries, particularly children, who are less disturbed by the ► hallucinations produced by ketamine. Nevertheless, ketamine has a number of distinct advantages. It is rapidly effective by all routes of administration (intravenous, intramuscular, epidural, oral, rectal, and transnasal) and has analgesic, anesthetic, and amnestic effects. It does not depress respiration, and it stimulates the cardiovascular system in most patients (Aroni et al. 2009). The use of ketamine and other NMDA antagonists for the treatment of pain usually involves the use of relatively small doses in conjunction with opioid administration, frequently by means of PCA (Rang et al. 2007).

Antidepressants. The tricyclic ► antidepressants (► amitriptyline is the gold standard for analgesia) are recognized for their ability to reduce neuropathic pain. Other antidepressants, particularly the newer norepinephrine–serotonin reuptake inhibitors such as ► venlafaxine and ► duloxetine and the nonspecific reuptake inhibitors such as ► trazodone and nefazodone are inconsistently effective in this regard. The mechanism of action is likely complicated, but appears to be different from that mechanism involved in the antidepressant actions; not all antidepressants are effective analgesics. The side effects that accompany the treatment for depression remain when these drugs are used to treat pain, although the smaller doses used for analgesia tend to reduce these side effects. As with the calcium channel blockers, antidepressants have some efficacy in the treatment of neuropathic pain, and may be most useful when combined with opioid analgesics.

Novel Approaches

Although there is limited interest in opioid analgesic development currently by the pharmaceutical industry, basic science continues to search for drugs that reduce acute and chronic pain, with greater efficacy and/or fewer side effects than those currently available. Three such classes of compounds are sufficiently interesting to warrant mention. These drugs are not currently available for human use. Nevertheless, the promising profiles of these three agents, particularly given their divergent mechanisms, suggest that continued research on this topic may eventually yield more helpful pharmacotherapies for pain.

NOP receptor agonists. The Nociceptin/Orphanin FQ Peptide (NOP) receptor is the fourth type of opioid receptor (defined as a non-opioid branch of the opioid family), identified in a search for protein structures that were homologous with the mu opioid receptor. Drugs that bound to the NOP receptor were evaluated for their ability to produce analgesia. The vast majority of these tests were carried out in rats and mice, and it was found that agonists at the NOP receptor produced rather than reduced various types of experimental pain in rodents, especially when they were given centrally/supra-spinally (Lambert 2008). More recently, however, the analgesic properties of NOP agonists were evaluated in rhesus monkeys where they were found to be as effective as morphine by several routes of administration (e.g., Ko et al. 2009). More important, NOP agonists did not appear to have abuse liability in rhesus monkeys, and they did not produce pruritus, an important side effect of spinally administered morphine. Further testing in human and nonhuman primates may demonstrate the potential usefulness of these compounds as powerful analgesics devoid of the side effects associated with morphine.

Serotonin receptor agonists. Two aspects of mu opioid agonist-induced analgesia noted above, viz, the development of tolerance through a putative dual-action effect, and the relative ineffectiveness of these drugs in neuropathic pain, have prompted research into identifying a drug that produces pain initially as a "first-order" effect, but follows this with a longer lasting analgesia as a "second-order" effect. Because the dual process is likely to be neuronally mediated, this drug would be considered as potentially useful in treating chronic pain resulting from nerve damage.

Agonist actions at the serotonin 5-HT_{1A} receptor have recently been suggested as having this ability (Colpaert 2006). In contrast to morphine, which produces analgesia followed by hyperalgesia in rat models of mechanically induced pain, the 5-HT_{1A} agonist F-13640 produces hyperalgesia initially, but with further multiple injections, analgesia is obtained. Notably, following chronic administration of morphine, tolerance to its analgesic effects were observed, whereas, following chronic administration of F-13640, tolerance to its hyperalgesic effects and a resulting augmented analgesia was observed. Of particular interest was the finding that in rat models of tonic neuropathic pain, F-13640 was analgesic on initial administration, prompting the notion that the "first-order" effect of hyperalgesia may have been induced by the pain induced

by the intraplantar formalin injection, leaving the 5-HT_{1A} agonist to induce only the "second order" effect of reducing the pain sensation.

Transient receptor potential, vanilloid subfamily member 1 (TRPV1) is one of a family of cation channel receptors, and is activated by changes in temperature, acid pH, capsaicin, and some animal venoms. The receptor is located in the dorsal root gangion neurons and the trigeminal ganglion neurons as well as on a subset of primary sensory neurons (Aδ fibers) in the presence of inflammation.

Activity at TRPV1 receptors appears to sensitize the channel to other stimuli. Antagonists of TRPV1 have been targeted as analgesic agents because they seem to block the ability of the neurons to release a number of pro-inflammatory neuropeptides. Interestingly, TRPV1 agonists such as capsaicin, although they produce pain initially, also have considerable subsequent analgesic actions, probably by desensitizing sensory fibers. There is considerable ongoing experimental work targeting TRPV1 and other members of this family, searching for a profile of specificity and agonists/antagonist actions that result in the treatment of inflammatory, thermal, and other pain (Cortright and Szallasi 2009).

Cross-References

- ► Antidepressants
- ► Antinociception Test Methods
- ► Classification of Psychoactive Drugs
- ► Ethical Issues in Animal Psychopharmacology
- ► Opioid Dependence and Its treatment
- ► Opioids
- ► Pharmacodynamic Tolerance
- ► Receptors: Functional Assays

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Analytical Column

Definition

The analytical column is where the chromatographic separation takes place. It is a narrow tube, typically less than 5 mm in diameter, and 10–50 cm in length, filled with the stationary phase. The exact dimensions of the column and the characteristics of the stationary phase will depend on the application.

Anandamide

- ► N-arachidonylethanolamine
- ► Cannabinoids and Endocannabinoids

Androgens

Synonyms

Sex hormones

Definition

Androgens are a class of hormones with testosterone being the primary product of the testes. Dihydrotestosterone is an androgen metabolite of testosterone produced in target tissues due to the actions of the 5α-reductase enzyme. Dihydrotestosterone is more potent at androgen receptors than is testosterone.

Anesthesia

► General Anesthesia

Animal Model

Definition

The use of experimental intervention (e.g., drugs and lesions) in the laboratory animal in order selectively to induce defined behavioral or physiological changes. These changes show the validity of an animal model to the extent that they reproduce some aspect of a recognized human disease state.

Cross-References

► Construct Validity
► Face Validity
► Predictive Validity
► Screening Models
► Simulation Models

Animal Model with Construct Validity

► Simulation Models

Animal Models for Psychiatric States

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Synonyms

Animal models of psychopathology; Behavioral models of psychopathology; Simulations of psychopathology

Definition

Animal models of psychiatric states are procedures applied to laboratory animals that engender behavioral changes which are intended to be homologous to aspects of psychiatric disorders, and can therefore be used as experimental tools to further the understanding of human psychopathology.

Principles and Role in Psychopharmacology

Basic Concepts

The concept of modeling psychopathology in animals is as old as the use of animals in psychological investigations: its roots may be found in the work of Pavlov, Watson, and even earlier. However, for many years, practical attempts to devise animal models were sporadic, ad hoc, and unconvincing. As a result, animal models of psychiatric states were until recently viewed with justified suspicion. Over the last 20–30 years, this situation has changed, with the recognition that animal models can provide a means of investigating the neurobiological mechanisms underlying psychopathology. Indeed, given the limitations of the investigational techniques currently available for use in human subjects, animal models represent the only means of asking many important questions. Animal models can also be of great value in the process of psychotropic drug development, and again, frequently represent the only viable method of predicting novel therapeutic actions. The recent development and acceptance of animal models may thus be seen as an adjunct to the concurrent growth and maturation of psychopharmacology and biological psychiatry, where they serve as indispensable tools for ► translational research.

The definition of animal models of psychiatric states presented above includes a number of features:

1. The *procedures* used to generate models are many and varied. Broadly, they involve environmental manipulations (e.g., exposure to social or physical stressors, or training regimes), and/or alteration of the internal environment (e.g., by brain lesions or administration of psychotropic drugs), and/or identification of vulnerable individuals (by selective breeding or genomic methods). Some examples of each of these procedures are shown in Table 1.
2. While in principle any animal species could be used, in practice the scope of modeling is restricted to *laboratory animals*. The most extensively used species has traditionally been the rat, but mouse models are being increasingly developed in order to capitalize on the availability of genetically modified strains. (► Genetically modified animals) Other species used occasionally include guinea pigs, marmosets, and chicks.
3. Some earlier definitions of animal models described them as analogous to psychiatric disorders. The present definition emphasizes that models aim to be *homologous*: that is, to simulate essentially the same process across species. This issue is discussed further below.

Animal Models for Psychiatric States. Table 1. Some examples of the procedures used to construct animal models of psychiatric states.

General procedure	Specific example	Primary behavioral end point	Condition modeled
Manipulation of the external environment			
► Social stress	Social conflict	Loser in competition for food source	Anxiety[a]
	Isolation rearing	Impairment of ► prepulse inhibition	Schizophrenia[b]
Physical stress	Uncontrollable footshock	Impairment of avoidance learning ("► learned helplessness")	Depression[c]
	► Chronic mild stress	Decreased response to rewards	Depression[c]
Training[i]	Operant responding for intravenous drug administration[k]	Drug self-administration[k]	Drug addiction[d]
	Punished operant responding	Suppression of responding by a signal paired with punishment[j]	Anxiety[a]
Manipulation of the internal environment			
Drug administration	► Phencyclidine	Stereotyped behavior and decreased social contact[m]	Schizophrenia[b]
	► Scopolamine	Impairment of ability to remember information across short time delays[l]	Dementia[e]
Brain lesion	Olfactory bulbectomy	Locomotor hyperactivity	Depression[c]
	Neonatal hippocampal lesion	Locomotor hyperactivity and hyper-responsiveness to stress	Schizophrenia[b]
Identification of vulnerable individuals			
Selective breeding	Flinders sensitive line (FSL) rat	Increased immobility in the forced swim test[f]	Depression[c]
	High saccharin–consuming (HiS) rat	Self-administration of cocaine and heroin[k]	Drug addiction[d]
Genomic manipulations[h]	Transgenic rat over-expressing amyloid precursor protein	Impairment of spatial learning[n]	Dementia[e]
	5HT 1A receptor knockout mouse	Avoidance of open spaces[g]	Anxiety[a]

The models listed in this table are chosen in order to illustrate the breadth of animal models in current use. There is no implication that these are the "best" or most valid models available

[a] ► Anxiety: Animal Models
[b] ► Schizophrenia: Animal Models
[c] ► Depression: Animal Models
[d] ► Addictive Disorder: Animal Models
[e] ► Rodent Models of Cognition
[f] ► Behavioral Despair
[g] ► Elevated Plus-Maze; ► Open Field Test
[h] ► Genetically Modified Animals
[i] ► Operant Behavior in Animals
[j] ► Pavlovian Fear Conditioning; ► Punishment Procedures
[k] ► Self-Administration of Drugs
[l] ► Short-Term and Working Memory in Animals
[m] ► Social Recognition and Social Learning
[n] ► Spatial Learning in Animals

4. An animal model of a psychiatric disorder includes a behavioral end point, which represents a model of a process that is thought to be important in the disorder. The scope of models is typically limited: they aim to simulate specific *aspects* rather than the entirety of the disorder, though it may be found subsequently that further aspects of the disorder are also present. Table 1 lists the primary behavioral end points that

were the focus of the original publications on each model, but in almost every case, a variety of other behavioral changes have also been described.

5. The definition also emphasizes the purpose of animal models of psychopathology: to provide a means of studying aspects of mental disorders. Animal models are *experimental tools*, and they are developed for specific investigational purposes. Initially, the primary aim was to elucidate psychological processes, but models are now used largely to address neurobiological issues. The specific issues most commonly addressed include: mechanisms of action of psychotherapeutic drugs, the neurotransmitter, neuroreceptor, and intracellular changes underlying psychiatric states, the neuroanatomical basis of psychiatric states, and increasingly, questions about the role of specific genes.

This article discusses some general issues concerning animal models of psychiatric states; models of specific psychiatric states are discussed elsewhere. ► Animal models; ► Anxiety: Animal Models; ► Autism: Animal Models; ► Dementias: Animal Models; ► Depression: Animal Models; ► Eating Disorder: Animal Models; ► Primate Models of Cognition; ► Rodent Models of Cognition; ► Schizophrenia: Animal Models. The references at the end of this article provide further reviews of this general area, from a variety of different perspectives.

Fitness for Purpose

Because models are built to be used, they have to be viewed in relation to the broader objectives of a research program. Behavioral models are used in psychopharmacology for two distinct purposes: as simulations within which to study aspects of psychiatric states, and as screening tests for the development of new treatments. Screening tests are subject to logistical considerations: for example, the test should be completed in the shortest possible time, and ideally will respond to acute drug treatment. However, in a model of a psychiatric state, these same features may be counter-indicated. For example, antidepressant drugs are clinically ineffective if administered acutely and largely inert if administered to nondepressed people: therefore, a model of clinical antidepressant action should involve chronic drug treatment, administered within a context of abnormal behavior rather than to "normal" animals. (► Antidepressants) Thus, a particular time course of antidepressant action and a particular level of behavioral sophistication may be desirable or undesirable features, depending upon the purpose for which a procedure is being used.

Conclusions arising from the use of a model are essentially hypotheses, which must eventually be tested against the clinical condition being modeled. The more valid a model, the more likely it is that insights derived from it will hold true for the clinical condition. Therefore, an assessment of the validity of a model provides an indication of the degree of confidence that we can place in the hypotheses arising from its use. Assessment of validity is not a yes/no judgment, but rather an evaluation of strengths and weaknesses and areas of uncertainty.

The systematic validation of an animal model is no different in principle from that of any other psychological device, such as a psychometric test or a psychiatric diagnosis, and the same general approaches to validation are applicable. Several systems of evaluation have been proposed, which have the common feature that models are assessed on two or more independent dimensions. One widely used method, described below in more detail, employs the three dimensions of predictive, face, and construct validity: ► predictive validity means that performance in the test predicts performance in the condition being modeled (and vice versa); ► face validity means that there are phenomenological similarities between the two; and ► construct validity means that the model has a sound theoretical rationale.

Some reviewers have advocated the primacy of one of these three dimensions, and each has its advocates. In principle, construct validity should be considered as the most fundamental dimension. In practice, however, the construct validity of animal models of psychopathology is difficult to determine, and therefore a balanced approach is needed, in which a view of the validity of a model is formed only after considering all three sources of evidence. In all three areas, discriminant validity is a further consideration: that is, the extent to which the evidence points to a particular disorder, as distinct from a different or a nonspecific psychiatric disorder. The three sets of validation criteria provide a convenient framework for organizing large volumes of data and ensuring that when different models are compared, like is compared with like. The major issues described below are summarized in Table 2.

Assessment of Predictive Validity

The concept of predictive validity implies that manipulations known to influence the pathological state should have similar effects in the model: thus, manipulations known to precipitate or exacerbate the disorder should precipitate or exacerbate the abnormalities displayed in the model, while manipulations known to relieve the disorder should normalize behavior in the model. In

Animal Models for Psychiatric States. Table 2. Issues to consider in assessing the validity of animal models.

Predictive validity	Specificity: No false positives
	Sensitivity: No false negatives
	Relative potencies and appropriate dose ranges
	How firmly established are the clinical data on effective and ineffective treatments?
Face validity	Extent of correspondence vis-à-vis symptoms and neurobiological features
	Specificity of symptoms/features modeled
	Centrality of symptoms/features modeled
	Coherence of symptoms/features modeled: Do they co-occur clinically?
	How robust is the psychiatric diagnosis?
Construct validity	How well do we understand the model: Does it measure what it claims to measure?
	How well do we understand the disorder: Would clinicians agree with how it is being characterized?
	If there is a parallel human experimental model, how well has that model been validated?
	Do similar theoretical structures apply: Can homology be demonstrated in relation to psychological processes, anatomical localization, neurochemical mechanisms, or gene expression?

practice, the predictive validity of the animal models used in psychopharmacology is determined largely by their response to therapeutic drugs.

In this context, the primary requirements for predictive validity are that a valid test should be sensitive and specific: sensitivity means that the test should respond to effective therapeutic agents and specificity means that it should fail to respond to ineffective agents. Positive responses should occur at sensible doses, and should be demonstrable with a range of structurally diverse compounds, and where applicable, to nonpharmacological treatment modalities. Negative responses should be demonstrable with agents that cause behavioral changes similar to the therapeutic effect but achieve these effects by nonspecific actions (e.g., by changing locomotor activity). However, while sensitivity and specificity are crucial to an assessment of predictive validity, results may sometimes be distorted by species differences in drug kinetics or metabolism, which can lead to apparent discrepancies of drug action in animal models versus human patients.

In some circumstances, it may be possible to demonstrate that the relative potencies of different agents in a model correlate positively with their potencies in clinical use. This is potentially a powerful test, provided that there is sufficient variation among the chosen drugs in their clinical potencies. However, it can generate trivial data if the analysis fails to sample a range of chemically distinct compounds. For example, the positive correlation between the clinical potency of ▶ benzodiazepines and their performance in several animal models of anxiety (▶ Anxiety, animal models) serves only to confirm that these drugs act at the same receptor.

There will always be a group of drugs for which, through a shortage of research, there is uncertainty over their status as clinically effective or ineffective. Moreover, the clinical classification of drugs as active or inactive may sometimes be incorrect. Drugs thought to be active on the basis of early open trials are frequently found to be inactive in later well-controlled tests; conversely, a drug may appear to be inactive because the emergence of side effects prevents its administration at adequate dosages, a problem that is less likely to arise in an animal model. It follows that the failure of an animal model to predict accurately will tend to weigh against the model, but may sometimes call instead for a reevaluation of the clinical wisdom. This illustrates an important principle: that the validity of a model is absolutely limited by the quality of the clinical information available to describe the condition modeled.

Assessment of Face Validity

Face validity refers to a phenomenological similarity between the model and the disorder modeled. On the one hand, the model should resemble the disorder; on the other, there should be no major dissimilarities. The checklist approach to psychiatric diagnosis adopted by the Diagnostic and Statistical Manuals of the American Psychiatric Association (▶ DSM) provides a useful starting point for enumerating areas of potential comparison. In DSM, psychiatric diagnoses are established by reference to a checklist of core symptoms and a further checklist of subsidiary symptoms, with a requirement to demonstrate the appropriate number of symptoms from each list. If several points of similarity are demonstrable between a model and the disorder, then it is necessary to ask whether the cluster of symptoms identified forms a coherent grouping that might realistically be seen in a single patient, or whether they are drawn from a variety of diagnostic subgroups. Frequently, animal models focus on a single behavioral endpoint. In that case, it is important to

assess whether this models a core symptom or a subsidiary symptom. For example, if the behavior in the model consists simply of a change in locomotor activity, this is likely to be of peripheral relevance to most psychiatric disorders. Similarly, the face validity of the model is less strongly supported if the symptom modeled is common to a several different psychiatric disorders (discriminant validity).

While a comparison with DSM provides an extremely useful starting point for assessment of face validity, other relevant comparisons should also be considered. For example, if the clinical condition only responds to chronic drug treatment (e.g., depression), then the model should also respond only to chronic drug treatment. Any neurobiological parallels between the model and the disorder also contribute to face validity.

Similarity between behavior in the model and the clinical symptom modeled should be demonstrated, rather than assumed. The demonstration of similarity requires a thorough experimental analysis, which, sadly, is often lacking. This can result in specious claims for face validity being advanced on the basis of unsupportable interpretations of behaviorally unsophisticated models. For example, many animal models of depression are based on a decrease in locomotor activity. (► Depression: animal models) It is certainly possible that a decrease in locomotor activity might simulate symptoms of depression such as psychomotor retardation or loss of motivation, but without further behavioral analysis, these remain unsupported analogies. As a general rule, the less sophisticated the behavior (in the sense that its interpretation is less open to experimental investigation and analysis), the lower is the possibility of making a judgment of face validity.

A fundamental consideration in assessing face validity is that the comparison of symptoms between a model and the clinical condition can only proceed in respect of symptoms that are expressed behaviorally. Many symptoms of psychiatric disorders are only known from patients' verbal reports, and these symptoms, in principle, cannot be modeled. An example is suicidal ideation in depression. However hard we worked, we could never know if a rat was feeling suicidal (or to take an actual research example, if it was feeling a state of "despair"), (► Behavioral despair) and therefore, this question falls outside the realm of scientific discourse: we simply cannot ask it. Nevertheless, it may sometimes be possible to express subjective symptomatology in behavioral terms. ► Hallucinations are subjective phenomena that should be out of bounds for modeling in animals, but from careful observation of patients who are hallucinating, a set of operational criteria was developed to define associated behavioral phenomena (such as staring intently at an invisible object), thus enabling the inclusion of hallucinations as symptoms that in principle could be simulated in animal models of schizophrenia. (► Schizophrenia: animal models) The rule, then, is that if a symptom can be expressed behaviorally and defined operationally, we can attempt to model it, but if it can only be expressed verbally, we cannot.

It is also important to remember that most DSM diagnoses are poorly established hypothetical constructs that can change radically between successive revisions of the manual. Again, the assessment of the validity of animal models is limited by the quality of the clinical data.

Assessment of Construct Validity

In order to evaluate the theoretical rationale of an animal model (construct validity), we require a theoretical account of the disordered behavior in the model, a theoretical account of the disorder itself, and a means of bringing the two theories into alignment. This can only be done if the clinical theory occupies an appropriate framework, which uses terms and concepts applicable also to subhuman species. Clearly, the subjective dimension of psychopathology cannot be central to such a theory, since subjective phenomena in animals are for most practical purposes outside the realm of scientific discourse. However, at the level of the cognitive processes underlying psychopathology, and the neurobiological mechanisms that underlie those cognitive processes, the possibility exists of constructing parallel theories. It follows from this analysis that the assessment of construct validity involves a number of relatively independent steps.

First, the theoretical account of behavior in the animal model requires evaluation. Just how well do we understand the model? Does it measure what it claims to measure? For example, if an animal model of depression is conceptualized as a decreased ability to respond to rewards, then at the very least, it must be convincingly demonstrated that the decrease in rewarded behavior cannot be explained by, for example, sedative effects or a nonspecific decrease in consummatory behavior (► Depression: animal models). Similarly, an animal model of dementia must demonstrate that performance failures result from a disorder of learning or memory, rather than from nonspecific causes, and further work should seek to characterize the specific memory processes involved. (► Rodent models of cognition; ► Primate models of cognition)

In some areas, human experimental procedures have been developed that are based on procedures used in animal studies. However, demonstrating that a similar

psychological process occurs in humans and animals is of limited value, since its role in the disorder also needs to be demonstrated. For example, some groups of schizophrenic patients show sensorimotor gating deficits that are very similar to those seen in animal models of schizophrenia: however, the contribution of sensorimotor gating deficits to schizophrenia remains uncertain (► Prepulse inhibition, ► Latent inhibition). It will be clear that a detailed consideration of the human disorder forms an essential step in the evaluation of animal models, and that the relatively poor state of theoretical understanding of most psychopathologies places an upper limit on construct validity.

Recent developments in neuroimaging and psychiatric genetics may help to decrease the difficulty of establishing homology between animal models and psychiatric states. A major focus of work with animal models has been to establish the brain areas responsible for the behavioral changes, and neuroimaging methods can now provide similar information for psychiatric states, making it possible to evaluate in a much more precise manner whether common mechanisms are involved. (► Magnetic resonance imaging: functional) Similarly, the identification of susceptibility genes and ► endophenotypes can now be translated directly into genetically modified animal models. (► Genetically modified animals) This is a rapidly developing area of research, and it is likely that it will be used increasingly to develop animal models of psychopathology that by definition will have a degree of construct validity.

Cross-References

► Addictive Disorder: Animal Models
► ADHD: Animal Models
► Antidepressants
► Anxiety: Animal Models
► Autism: Animal Models
► Behavioral Despair
► Benzodiazepines
► Chronic Mild Stress
► Construct Validity
► Dementias: Animal Models
► Depression: Animal Models
► Eating Disorder: Animal Models
► Elevated Plus-Maze
► Endophenotypes
► Face Validity
► Genetically Modified Animals
► Hallucinations
► Latent Inhibition
► Learned Helplessness
► Magnetic Resonance Imaging: Functional
► Open Field Test
► Operant Behavior in Animals
► Pavlovian Fear Conditioning
► Phencyclidine
► Predictive Validity
► Prepulse Inhibition
► Primate Models of Cognition
► Punishment Procedures
► Rodent Models of Cognition
► Schizophrenia: Animal Models
► Self-Administration of Drugs
► Short-Term and Working Memory in Animals
► Social Recognition and Social Learning
► Social Stress
► Spatial Learning in Animals
► Translational Research

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Animal Models of Acute Stroke

Definition

A model of acute stroke produced in a laboratory animal, generally a rodent but sometimes a higher species such as

a primate. A cerebral blood vessel (commonly the middle cerebral artery, since this is the vessel most often affected in human stroke) is occluded by clipping, electrocoagulation, or a thread. If the occlusion is not removed, this is referred to as permanent focal ischemia; if the occlusion is removed, it is called transient focal ischemia. Injection of small clots into the cerebral arteries is called a thromboembolic stroke model.

Animal Models of Psychopathology

► Animal Models for Psychiatric States

Animal Tests of Anxiety

► Anxiety: Animal Models

Animal Welfare Act

Definition

The Animal Welfare Act of 1966 (latest amendment 2006) authorizes the U.S. Secretary of Agriculture to regulate transport, sale, and handling of dogs, cats, nonhuman primates, guinea pigs, hamsters, and rabbits intended to be used in research or "for other purposes."

Anisomycin

Definition

An antibiotic isolated from *Streptomyces griseolus* that binds to 60S ribosomal subunits preventing elongation and hence inhibiting protein synthesis.

Anorectics

► Appetite Suppressants

Anorexia

► Eating Disorder: Anorexia Nervosa

Anorexia Nervosa

Synonyms

Eating disorders: animal models

Definition

Eating disorder that primarily affects women and that is characterized by an obsession with losing weight, and distorted body image. Patients suffering from anorexia nervosa will restrict their diet to levels that lead to severe malnutrition, and if left untreated, could lead to death.

Anorexigenic

Definition

Systems or endogenous factors that prevent or foreshorten eating events.

Antagonist

Synonyms

Receptor inhibitor

Definition

An antagonist binds to a receptor but causes no change in receptor activity itself. Rather, an antagonist maintains the receptor in the same state as exists when it is not bound by a stimulatory (agonist) or inhibitory (inverse agonist) substance. Thus, an antagonist has no impact on receptor activity in the absence of an agonist or inverse agonist, but prevents or reverses the effects of such substances when they are present by blocking their binding to the receptors. An antagonist may be competitive (or surmountable), that is, it binds to a region of the receptor common with the endogenous agonist. The effects of a competitive antagonist may be overcome by increasing the concentration of agonist. Alternatively, antagonists may be insurmountable, where no amount of agonist is capable of completely overcoming the inhibition. Insurmountable antagonists may bind covalently to the agonist binding site, or act allosterically at a different site on the receptor.

Cross-References

► Agonist
► Allosteric Modulator
► Inverse Agonist

Anti-anxiety agents

► Punishment Procedures

Antianxiety Drugs

► Anxiolytics

Antianxiety Medication

► Anxiolytics
► Minor Tranquilizer

Anticholinergic Side Effects

Definition

The inhibition of acetylcholine receptors can cause various side effects, including dryness of mucous membranes, diaphoresis, constipation, urinary retention, dizziness, and confusion. Tolerance occurs over time to some of these effects, while others will persist for the duration of drug use.

Anti-Cholinesterases

► Acetylcholinesterase and Cognitive Enhancement

Anticipatory Food Seeking

► Goal Tracking

Anticipatory Goal Seeking

► Goal Tracking

Anticonvulsants

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Synonyms

Antiepileptics; Mood stabilizers

Definition

Anticonvulsants are drugs defined by their efficacy in the treatment of epilepsy. They are also widely used to treat nonepileptic conditions such as neuropathic pain, migraine, and ► bipolar disorder.

Pharmacological Properties

History

Anticonvulsants were first studied and approved for the treatment of epilepsy, while their therapeutic activity in other disorders was identified later. Anticonvulsants are traditionally divided into two groups, according to the year of marketing (before and after 1990) (Beghi 2004): ► first-generation anticonvulsants (or "older"), including ► phenobarbital, ► phenytoin, primidone, ► carbamazepine, ► valproic acid, and ethosuximide, and ► second-generation anticonvulsants (or "newer"), such as ► lamotrigine, ► gabapentin, ► topiramate, ► oxcarbazepine, levetiracetam, ► pregabalin, ► tiagabine, and ► zonisamide.

In addition to their use for the management of epilepsy, anticonvulsants are also commonly used to treat a variety of nonepileptic neurological conditions, such as neuropathic pain, migraine, and essential tremor, and psychiatric disorders, such as bipolar disorder and anxiety. This presumably reflects their complex mechanisms of action involving a wide range of pharmacological effects on different neurotransmitter systems and ion channels.

Concerning their use as ► mood stabilizers, anticonvulsants began to be studied in the late 1970s, when a logical parallel was drawn between affective and seizure disorders, based on the theory that mania may "kindle" further episodes of mania (Post et al. 2007). Since the first compounds tested, namely carbamazepine and valproate, proved effective in treating the manic phase of bipolar disorder, this has led to the idea that many anticonvulsants could be mood stabilizers, especially for mania. In recent years, a number of anticonvulsants have been more rigorously investigated for their potential mood-stabilizing properties. Anticonvulsants are heterogeneous in their mechanisms of action, ► pharmacokinetics, and ► efficacy in the various mood states in bipolar illness, as well as in their safety/tolerability profiles.

Mechanisms of Action

The exact mechanism of action of anticonvulsants remains largely unknown. However, anticonvulsants have various

targets of action in the synapse and may affect pathophysiological processes regulating neuronal excitability. The main pharmacological mechanisms responsible for the clinical efficacy of anticonvulsants in epilepsy and in the various nonepileptic neurological and psychiatric disorders are likely to include increased GABAergic inhibitory neurotransmission, decreased glutamatergic excitatory neurotransmission, blockade, or inhibition of voltage-dependent sodium or calcium channels, and interference with intracellular signaling pathways (Johannessen Landmark 2008). In addition, indirect mechanisms may be involved, such as the modulation of other neurotransmitters, including the ► monoamines. Current knowledge indicates that most anticonvulsants have more than one mechanism of action, each of which may contribute to its therapeutic efficacy to a variable extent.

Anticonvulsants differ in their effects on neurotransmission and on ion channels, both of which may be related to the pathophysiology of epilepsy and nonepileptic disorders. Valproate inhibits voltage-gated sodium channels and potentiates the inhibitory action of gamma-aminobutyric acid (► GABA), by either increasing its release, decreasing its reuptake, or slowing its metabolic inactivation. Valproate may also interact with other ion channels, such as voltage-gated calcium channels, and also indirectly block ► glutamate action. Carbamazepine and structurally related oxcarbazepine may act by blocking the alpha subunit of voltage-gated sodium channels, and may also interfere with calcium and potassium channels. As with carbamazepine, the mood-stabilizing effect of lamotrigine is probably related to the inhibition of sodium and calcium channels in presynaptic neurons and the subsequent stabilization of neuronal membranes. In addition, lamotrigine may reduce the release of the excitatory neurotransmitter glutamate. Topiramate has been demonstrated to possess many molecular effects, including enhanced GABAergic activity, reduced glutamatergic neurotransmission, and inhibition of voltage-gated calcium channels. Gabapentin and pregabalin possess a selective inhibitory effect on the $\alpha_2\delta$ subunit of the voltage-gated calcium channels and may also facilitate GABAergic function. Levetiracetam binds to the synaptic vesicle protein 2A (SV2A), thereby reducing glutamate release. Tiagabine inhibits GABA reuptake, thereby increasing its postsynaptic availability.

Interference with intracellular mediators and signaling pathways is an important postulated mechanism in the pathophysiology of bipolar disorder (Rogawski and Loscher 2004). In addition, recent evidence from brain imaging and postmortem histopathology indicates that atrophy and glial death in specific brain regions, especially prefrontal cortex and hippocampus, are involved in mood disorders (Zarate et al. 2006). It has been hypothesized that mood-stabilizing agents may exert long-term beneficial effects by activating intracellular signaling pathways that promote neuroplasticity, ► neurogenesis or cell survival. Common actions on cell signaling of anticonvulsants and ► lithium, the gold standard in the treatment and prophylaxis of bipolar disorder, have been identified in recent years. As with lithium, the mood-stabilizing action of valproate and, possibly, carbamazepine has been linked to inositol depletion. Lithium and valproate block inositol monophosphatase (IMPase), preventing the conversion of inositol-1-phosphate (IP_1) to *myo*-inositol. This effect is considered to result in the stabilization of the structural integrity of neurons and the enhancement of synaptic plasticity. Valproate shares with lithium other effects on downstream signal transduction cascades, such as the inhibition of protein kinase C (PKC) and myristolated alanine rich C kinase substrate (MARKCS). The mood-stabilizing properties of lithium have also been attributed to the inhibition of glycogen synthase kinase 3β (GSK3β), an enzyme that contributes to many cellular functions, including apoptosis. Valproate and lamotrigine have similar effects on GSK3β, whereas carbamazepine does not. Other common effects of lithium and valproate are to increase the activity of the extracellular signal-regulated kinase (ERK) pathway, resulting in the enhanced transcription of neurogenesis and cell survival factors, such as antiapoptotic protein Bcl-2 and ► brain-derived neurotrophic factor (BDNF). Valproate may also regulate ► gene expression and transcription by acting as a ► histone deacetylase inhibitor.

In summary, anticonvulsants may be effective in many non-epileptic disorders. With regard to their use as mood stabilizers, anticonvulsants such as valproate, carbamazepine, and lamotrigine appear to have a clear role based on their effect on intracellular pathways. Anticonvulsants with effects on voltage-gated sodium or calcium channels, such as gabapentin, pregabalin, carbamazepine, lamotrigine, and valproate, may be particularly useful in neuropathic pain. Some agents, namely valproate and topiramate, have demonstrated efficacy in the prevention of migraine, possibly by increasing GABAergic and decreasing glutamatergic neurotransmission, thereby reducing neuronal hyperexcitability. The enhancement of GABAergic function may explain the beneficial effect of gabapentin, pregabalin, valproate, and tiagabine in anxiety disorders and essential tremor.

Animal Models

There is a limited number of fully validated and appropriate animal models of bipolar disorder for in-depth

behavioral, biochemical, histological, and pharmacological analysis (Gould and Einat 2007). The paucity of suitable animal models and difficulty in assessing the prophylactic effects of mood stabilizers is a rate-limiting step in the process of understanding the neurobiology of the disorder, as well as in the development of novel medications. Modeling bipolar disorder in animals is problematic for a number of reasons, including limited knowledge about underlying pathophysiology, susceptibility genes, and mode of action of the available mood stabilizers. In addition, in humans, the disease is cyclical and clinically heterogeneous, and there are no established biomarkers for the disease state or the effects of treatment.

The existing animal behavioral tests and models may be classified into a number of general areas, such as whether they focus on particular symptoms, bipolar endophenotypes, and pathophysiology, or response to existing medications (Gould and Einat 2007). Symptom-based models of bipolar disorder are attempts to represent aspects of either the manic or the depressive phase of the illness. Symptoms of mania that can be modeled in mania include increased activity, irritability, aggressive behavior, sexual drive, and reduced need for sleep. Models of the depressive phase are based on models previously validated in the context of depression research, and are available for symptoms such as anhedonia, fatigue, changes in sleep patterns, and changes in appetite or weight. Models based upon ► endophenotypes and pathophysiology can be neurophysiological, biochemical, endocrine, neuroanatomical, genetic, cognitive, or neuropsychological. In particular, the identification of susceptibility genes for bipolar disorder might help to define specific neurobiological processes and associated behaviors. Consequently, animal models studying the relevance of changes in the levels of proteins, circuits and synapses, and brain function, without regard to modeling of symptoms, may be particularly useful. A number of models have been developed based upon response to existing medications. They have considerable value both in understanding the mechanism of action of available drugs and in developing new treatments for bipolar disorder. In this respect, given the evidence for some overlapping signal transduction properties of lithium and valproate, it is reasonable for newly developed drugs that have effects on neuronal intracellular signaling and ion channel-mediated actions to be considered in preclinical and clinical testing for their potential effects on bipolar disorder, irrespective of whether such drugs are called anticonvulsants.

A model based on the phenomenon of "kindling," which is an animal model of epileptogenesis, was proposed as relevant to bipolar disorder pathophysiology and the mechanism of action of anticonvulsants used for treatment (Post 2007). The kindling model predicts temporal variation in the function of neural circuits and associated episodes, evolution of the illness and episode cyclicity, and might explain how events trigger affective episodes. Many anticonvulsants have demonstrated antikindling effects in vitro and this may account for their efficacy in both epilepsy and bipolar disorder.

► Pharmacokinetics

Anticonvulsants are generally well absorbed. They are lipophilic compounds that easily cross the ► blood–brain barrier and accumulate in fatty tissues. All commonly used anticonvulsants, except gabapentin, pregabalin, and levetiracetam are metabolized in the liver by cytochrome P450 isoenzymes (CYPs) or uridine diphosphate glucuronosyltransferases (UGTs). The elimination half-lives of anticonvulsants differ among the various agents, ranging between a few hours (valproate) and days (phenobarbital). Time to reach steady-state levels differs accordingly, but once- or twice-daily dosing is possible for all compounds. In this respect, extended-release formulations of valproate and carbamazepine have recently become available. As most anticonvulsants are extensively metabolized via hepatic enzymes, they may be involved in ► drug interactions. Their biotransformation can be affected by the concomitant administration of other drugs, including other anticonvulsants with inhibiting or inducing properties toward these enzymes. In addition, some anticonvulsants have prominent inhibitory or inducing effects on the activity of the hepatic enzymes that metabolize the majority of existing medications. In this respect, valproic acid is considered a broad-spectrum inhibitor of various drug-metabolizing enzymes. The first-generation anticonvulsants carbamazepine, phenytoin, and phenobarbital are broad-spectrum inducers of a variety of CYP enzymes, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4, as well as UGTs and microsomal epoxide hydrolase. Compared with older agents, new anticonvulsants appear to have clear advantages in terms of a lower potential for such interactions. As the mode of action of anticonvulsants involves different effects on various neurotransmitter systems and ion channels, these compounds may be involved in potentially adverse pharmacodynamic interactions with other drugs, in particular other central nervous system (CNS) agents.

Efficacy

Although traditionally used to treat epilepsy, anticonvulsants have proven to be effective in a variety of disease

states (Spina and Perugi 2004). With regard to their ► efficacy in psychiatric conditions, three anticonvulsants, namely valproate, carbamazepine, and lamotrigine, are currently approved for the treatment of various aspects of bipolar disorder in most countries (Weisler et al. 2006). Large-scale, randomized, double-blind, well-controlled studies have documented that valproate and carbamazepine are highly effective in the treatment of acute mania. On the other hand, neither valproate nor carbamazepine has robust evidence supporting their efficacy in the treatment of acute bipolar depression. Valproate and, to a lesser extent, carbamazepine appear to be effective in the prophylactic treatment of many bipolar patients, including those refractory to or intolerant of lithium, but they are not approved for long-term maintenance therapy. While some studies have suggested that lamotrigine may be effective for the acute treatment of bipolar depression, there is strong evidence of its efficacy in preventing the recurrence of depressive episodes without the associated risks of cycle acceleration or manic/hypomanic switches (Weisler et al. 2008). Lamotrigine is currently approved only for the prophylaxis of bipolar I disorder. Concerning other newer anticonvulsants, oxcarbazepine has limited data suggesting efficacy in acute mania, while gabapentin and topiramate are ineffective as primary antimanic treatments, although they may be useful adjuncts for the treatment of comorbid conditions such as anxiety, pain, migraine, or weight problems. No controlled trial data are available for levetiracetam, tiagabine, or zonisamide.

Some anticonvulsant medications are widely used in the treatment of a number of chronic pain syndromes. Carbamazepine is commonly prescribed as first-line therapy for patients with trigeminal neuralgia. Gabapentin and pregabalin have been approved for the treatment of neuropathic pain associated with diabetic polyneuropathy and postherpetic neuralgia. Topiramate and valproate, in the form of divalproex sodium, are indicated for the prophylactic treatment of migraine.

Safety/Tolerability

Treatment with valproate is commonly associated with CNS side effects (tremor, somnolence, dizziness, ataxia, and asthenia) and gastrointestinal distress (nausea, vomiting, abdominal pain, and dyspepsia). Other important adverse events include weight gain, hair loss, and hyperammonemic encephalopathy in patients with urea cycle disorders. Hepatotoxicity and pancreatitis are rare but serious adverse effects associated with valproate therapy. The most common side effects reported during carbamazepine treatment include dizziness, somnolence, ataxia, nausea, and diplopia. Other important events less frequently observed include benign skin rashes, mild leucopenia, and thrombocytopenia, and hyponatremia, which is more common in the elderly population. Rare, but serious adverse events associated with carbamazepine therapy include severe dermatologic reactions, namely, Lyell syndrome (toxic epidermal necrolysis) and Stevens–Johnson syndrome (erythema multiforme major). The use of both valproic acid and carbamazepine during the first trimester of pregnancy is associated with an increased risk of congenital malformations, in particular spina bifida.

Lamotrigine is generally well tolerated, except for its propensity to cause rashes, including rarely the life-threatening Stevens–Johnson syndrome. Rashes by lamotrigine are in most cases reversible and can be minimized by very slow titration of the drug during the initiation of therapy and by avoiding or managing drug interactions, such as those with valproate, that raise lamotrigine levels. Further and rare side effects are vertigo, somnolence, diplopia, and gastrointestinal symptoms.

Other newer anticonvulsants occasionally used to treat bipolar disorders, such as oxcarbazepine, topiramate, gabapentin, or levetiracetam, have a relatively favorable tolerability profile. Oxcarbazepine is less sedating and has less bone marrow toxicity than its congener carbamazepine. Moreover, differently from carbamazepine, oxcarbazepine seems to possess only a modest inducing effect on hepatic drug-metabolizing enzymes and, therefore, has a lower potential for pharmacokinetic drug interactions. Topiramate is associated with weight loss and is sometimes given as an adjunct to mood stabilizers that cause weight gain.

Conclusion

In summary, anticonvulsants represent a heterogeneous group of drugs that, in addition to having proven efficacy for the management of epilepsy, are increasingly used to treat a variety of other neurological and psychiatric conditions. In particular, some anticonvulsants, namely valproate, carbamazepine, and lamotrigine, have become an integral part of the pharmacological treatment of bipolar disorder. Other newer anticonvulsants appear to have more favorable tolerability and drug interaction profiles as compared to older compounds, thus improving compliance with treatment. However, evidence for their efficacy in treating the various phases of bipolar disorder is still inadequate. Therefore, there is an ongoing need for controlled studies with a large number of patients and greater homogeneity of diagnosis in order to establish the efficacy of individual anticonvulsants in the management of psychiatric disorders.

Cross-References

- ▶ Bipolar Disorder
- ▶ Blood–Brain Barrier
- ▶ Brain-Derived Neurotrophic Factor
- ▶ Drug Interactions
- ▶ First-Generation Antiepileptics
- ▶ Gene Expression
- ▶ Gene Transcription
- ▶ Histone Deacetylase Inhibitors
- ▶ Lithium
- ▶ Mood Stabilizers
- ▶ Neurogenesis
- ▶ Second-Generation Antiepileptics

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Anti-Dementia Drugs

Definition

Drugs that give symptomatic relief to cognitive and memory dysfunction in the early stages of ▶ dementia (Alzheimer's disease). The drugs currently available enhance cholinergic and/or glutamatergic function.

Antidepressants

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Synonyms

Classification of psychoactive drugs; Thymoleptics

Definition

Antidepressants are compounds used to treat depression. Specifically, they reduce symptoms of depression. They do not elevate mood. The agents approved for the treatment of depression, however, are also useful in an array of other disorders, including anxiety disorders, pain syndromes, attention deficit hyperactivity disorder (ADHD), smoking cessation, and premenstrual dysphonic disorder. In most cases, the term "antidepressant" is still retained to refer to the class of drugs.

Pharmacological Properties

History

The first agents approved for use in depression by the US Food and Drug Administration (FDA) were discovered in the late 1950s. Roland Kuhn, a Swiss psychiatrist, was exploring compounds that might have value in depression. He observed that G 22355, a J. R. Geigy company compound, appeared to be of value in patients with endogenous depression. This compound, also known as ▶ imipramine (*Tofranil*), possessed a three-ring structure somewhat similar to ▶ chlorpromazine, an antipsychotic. This finding had enormous consequences not only for the treatment of depression, but also in providing a conceptual basis for a psychopharmacologic theory of depression (Schildkraut 1965). In subsequent years, several other tricyclic (TCA) and related heterocyclic compounds were introduced for treating depression (Nelson 2009). These agents would be the first-line agents for the treatment of depression for the next 3 decades.

Also during the late 1950s, a drug used in treating tuberculosis, iproniazid (a ▶ monoamine oxidase inhibitor [MAOI]) was observed to improve symptoms of depression. Further testing confirmed antidepressant effects and it was widely used for a short period of time. Because of concerns that iproniazid caused jaundice, its successors, isoniazid (*Marplan*), ▶ tranylcypromine (*Parnate*), and ▶ phenelzine (*Nardil*) became the MAOI agents used for the treatment of depression. Because of safety issues involving interactions with tyramine in the diet, and

interactions with sympathomimetic and other medications, the MAOI drugs were not widely used.

During the 1980s, several new antidepressants were developed. Unlike the tricyclics, which had similar chemical structures, the newer agents differed in structure but were grouped according to their function. The first of these to be marketed was ▶ trazodone (*Desyrel*). Trazodone is an antagonist at the postsynaptic serotonin 2 (5-HT_2) receptor and has antihistaminic properties. It was widely used in the 1980s but its use in depression declined with the introduction of the selective serotonin reuptake inhibitors (SSRIs). ▶ Bupropion was also introduced in the 1980s. As it was coming to market, a few patients in a bulimia study experienced seizures and its marketing was delayed while this safety issue was explored. It was reintroduced with the recommendation not to exceed 450 mg/day.

In the late 1980s, ▶ fluoxetine (*Prozac*) was approved for use in depression. It was followed later by ▶ paroxetine (*Paxil*), ▶ sertraline (*Zoloft*), and ▶ citalopram (*Celexa*). The greater tolerability of these agents led to rapid acceptance; by 1994, this class of antidepressants surpassed the tricyclics as the most widely used antidepressants. The active marketing of the SSRIs in depression coupled with new indications for ▶ panic disorder, ▶ obsessive–compulsive disorder, ▶ social anxiety disorder, ▶ posttraumatic stress disorder, ▶ premenstrual dysphoric disorder, bulimia, and ▶ generalized anxiety disorder, led to a substantial growth, in the 1990s, of the market for antidepressants in general and the SSRIs in particular. ▶ Fluvoxamine (*Luvox*), another SSRI, was approved by the FDA for use in OCD, but not in depression. ▶ Escitalopram (*Lexapro*), the s-isomer of citalopram, was the last SSRI developed for use in depression.

For a period of time in the 1980s and into the 1990s, drug development focused on these "selective" agents. While their improved tolerability and safety offered advantages, their efficacy was no better than the tricyclics, and some questioned if they were less effective. In an attempt to improve efficacy, new agents were introduced that had actions on both ▶ serotonin (5-HT) and ▶ norepinephrine (NE). These dual action agents were known as the SNRIs and included ▶ venlafaxine (*Effexor*) and ▶ duloxetine (*Cymbalta*). Recently, the desmethyl metabolite of venlafaxine (▶ desvenlafaxine [*Pristiq*]) was introduced. Each of these compounds is relatively more potent in blocking 5-HT uptake than NE uptake, but as the dose increases, NE uptake blockade increases. These compounds are relatively free of the antihistaminic, anticholinergic, and sodium channel effects of the TCAs that contributed to side effects. Venlafaxine and duloxetine were also approved for use in generalized anxiety disorder, and additionally appeared to have the beneficial effects in chronic pain syndromes shown by amitriptyline and other tricyclics. Duloxetine is now approved for use in diabetic neuropathic pain and fibromyalgia.

Two other second-generation antidepressants were marketed in the USA – nefazodone (*Serzone*) and ▶ mirtazapine (*Remeron*). Nefazodone is somewhat similar to trazodone but less antihistaminic. Its principle effect is postsynaptic at the 5-HT_2 receptor and in theory, this should have reduced side effects. While it had little effect on weight or sexual function, cases of fatal hepatic failure led to decreased use of the drug. Mirtazapine has a different mechanism of action. As the result of antagonism of $alpha_2$ adrenergic receptors, levels of serotonin and norepinephrine increase. The agent also antagonizes 5-HT_2 receptors and 5-HT_3 receptors, and is antihistaminic.

Mechanism of Action

The principal mechanism of action of most antidepressants involves the blockade of serotonin and norepinephrine at the presynaptic neuron in the brain (Charney et al. 1991). This increases the availability of these neurotransmitters at the synapse, the junction at which one neuron communicates with another. In response to the increase in these neurotransmitters, autoreceptors on the presynaptic neuron turn down the firing rate of those cells and less neurotransmitter is released. During a few weeks of treatment, these autoreceptors are desensitized and the firing rate returns to its tonic rate. At this point, neurotransmission is increased. While the feedback mechanisms in the norepinephrine system are less well understood, the net effects are similar. These delayed effects that occur over time are thought to be more consistent with the timing of symptomatic change during the treatment of depression. The confirmation of a central role for serotonin and norepinephrine in the mechanism of action of several agents came from studies depleting serotonin or norepinephrine (Delgado et al. 1993). In depressed patients who had responded to a serotonin antidepressant, the blockade of serotonin synthesis with ▶ tryptophan depletion resulted in relapse. Similar effects were noted in patients taking a norepinephrine antidepressant if NE was blocked with AMPT (alpha-methyl-para-tyrosine). ▶ Clomipramine, amitriptyline, imipramine, doxepin, venlafaxine, desmethylvenlafaxine, and duloxetine all block the uptake of serotonin and norepinephrine with varying potency. In some cases (clomipramine, amitriptyline, imipramine), the parent compound has a greater effect on serotonin uptake and the metabolite on norepinephrine. Mirtazapine also increases 5-HT and NE

concentrations, but through a different mechanism – the blockade of alpha$_2$ adrenergic receptors. Trazodone, nefazodone, mirtazapine, and some tricyclic antidepressants (amitriptyline and nortriptyline) are also 5-HT$_2$ receptor antagonists. This receptor acts in opposition to the primary serotonin receptor (5-HT$_1$), so that antagonism at the 5-HT$_2$ receptor enhances the effects of serotonin. Clinically this appears to benefit sleep and may help reduce anxiety. Bupropion appears to have a different mechanism, blocking the uptake of dopamine and norepinephrine. Both the parent drug and its metabolite, hydroxybupropion, participate in these effects.

The antidepressants also have other effects that have been thought to contribute to side effects. The tricyclics have ► anticholinergic side effects, which can contribute to dry mouth, blurred vision, constipation, and urinary hesitancy. These effects can also impair cognition and in older patients can cause delirium. Amitriptyline is the most anticholinergic of the antidepressants. The tricyclics, trazodone, and mirtazapine are antihistaminic. These effects can contribute to sedation and weight gain. Mirtazapine is the most antihistaminic antidepressant followed, by doxepin. Alpha$_1$ adrenergic effects contribute to orthostatic hypotension, the most common side effect of the tricyclic antidepressants that limits treatment. The tricyclic antidepressants also have effects on sodium channels, which prolong cardiac conduction. In most patients, this is not a problem. However, in patients who already have delayed conduction, this effect can result in heart block. This effect increases at the high plasma concentrations that are frequently achieved with overdose and is the primary reason for death with overdose.

Recently, interest in the neuroprotective effects of antidepressants has emerged (Schmidt and Duman 2007). A number of converging lines of evidence suggest this mechanism may be involved in the treatment of depression. It has been demonstrated in animals that repeated or chronic exposure to cortisol damages the hippocampus. Cortisol levels are elevated in some depressed patients. Brain imaging studies in depressed human subjects show evidence of smaller hippocampal volumes, and one study found the duration of untreated depression was correlated with smaller hippocampal volumes. A particularly intriguing finding is that antidepressants increase neuroprotective factors, such as ► brain derived neurotrophic factor (BDNF), and that antidepressant treatment regenerates nerve cell growth in the dentate gryus of the ► hippocampus. These findings suggest a role for ► neuroprotection in the action of antidepressants. It is unclear currently if these effects are involved in acute treatment response or if these effects become more important during chronic treatment. All antidepressants share this effect, so it would not explain differences among them. Some agents that are not antidepressants have these effects. This theoretical model does not appear as useful for predicting some of the synergistic effects of medication combinations as have the older synaptic transmission models.

Animal Models

There are no adequate animal models for depression. None of the animal models adequately account for all of the symptoms seen in human subjects, especially the psychological symptoms. As a result, it is not possible to use animal models to develop a comprehensive understanding of the neurobiology of depression. There are animal assay models that test certain properties of antidepressant drugs. There are also "homologous" models in which animals display behaviors that are somewhat similar to those observed in depressed subjects. These models include the reduction in motor activity induced by ► reserpine, the swim test immobility model, the syndrome in monkeys induced by isolation and separation, and the uncontrolled foot shock model (also known as the ► learned helplessness model). The chronic stress models may come closest to mimicking the physiology of depression. Recently gene "knock-out" models, usually in mice, have been used to explore the effects of specific genes on behaviors seen in depression and then test the effects of drugs on these behaviors. Selective breeding has been used to develop strains of animals with specific behaviors. While these models have aided drug development, insofar as they provide a model of what existing antidepressants do, ironically they may lead to development of drugs with profiles similar to older agents rather than to truly novel agents.

► Pharmacokinetics

All of the antidepressants described here are cleared from the body by hepatic metabolism. Various enzymes in the cytochrome P450 system in the liver participate in this process. Polymorphisms (genetic variants) of certain genes that control these enzymes can result in widely variable plasma concentrations of drugs given at the same dose. Individuals deficient in certain enzymes can develop dangerously high plasma concentrations of the drug. Alternatively, a few individuals may be "ultra fast" metabolizers and have very low, ineffective plasma levels at usual doses. Because side effects were common and limited dosing of the tricyclics, blood level monitoring was sometimes employed to achieve adequate levels without exceeding safe concentrations. With the second-generation agents, improved tolerability allowed these agents to be given at

doses high enough to be effective in most individuals and blood level monitoring is seldom employed.

► Cytochrome P450 enzymes are important for understanding drug interactions (Nemeroff et al. 1996). Drug that block the enzymes are known as inhibitors. Drugs that speed up the enzymes are inducers. Enzyme induction results from the production of more enzymes and takes 2–3 weeks. The 1A2 pathway is induced by nicotine. The 3A4 pathway is induced by ► carbamazepine, ► barbiturates, ► phenytoin, and St. John's Wort. Enzyme inhibition occurs within days and is more common. Some antidepressants are potent enzyme inhibitors. Fluvoxamine inhibits the 1A2 pathway as well as 2C9 and 2C19, fluoxetine inhibits 2D6 and the 2C family, and paroxetine inhibits 2D6, as does bupropion and duloxetine. Nefazodone inhibits the 3A4 pathway.

During metabolism, active metabolites may be produced. Their effects may differ from the parent compound. The tertiary tricyclic agents are metabolized to secondary amines (e.g., desipramine, nortriptyline, and desmethylclomipramine). The secondary amines tend to be more potent NE uptake blockers, while their parent compounds have greater effects on 5-HT. The hydroxy-metabolite of bupropion is selective for NE uptake blockade, while bupropion itself has greater effects on dopamine. The net effect of the drug, then, depends on the relative concentrations of the parent and metabolites. Among the SSRIs, fluoxetine is noteworthy for its active metabolite norfluoxetine. This metabolite has activity similar to the parent but a much longer half-life of 5–7 days. The metabolite of venlafaxine has a longer half-life than the parent and extends the action of the compound. Nefazodone has perhaps the most complicated array of three active metabolites with different effects and different half-lives.

The antidepressants are widely distributed in the body. In order to cross the ► blood–brain barrier, they are lipophilic (fat soluble). This property makes them less soluble in plasma and they are carried in the blood stream attached to plasma proteins. In most cases, they are highly bound to these proteins. Venlafaxine is an exception and protein binding is lower. As the result of hepatic metabolism, most of these compounds are conjugated to inactive substances and excreted by the kidney.

The hepatic clearance of the antidepressants is variable. Ideally, drugs with a half-life of about 24 h can easily be given once a day. Some agents such as bupropion, which has a half-life of 16 h, were initially given several times a day. Extended-release preparations allowed for less frequent dosing. As mentioned earlier, the half-lives of fluoxetine and its metabolite were considerably longer than those of the other SSRIs. This helped to reduce the effect of occasional missed doses, and at one point, the manufacturer marketed a once weekly formulation of the drug. The long half-life also resulted in a gradual decline in the plasma level, which helped to minimize discontinuation symptoms. On the other hand, the long half-life required a longer washout period – about 5 weeks – before most of the drug was out of the body.

The MAOI agents have a different pharmacology. The older compounds had irreversible effects, inactivating monoamine oxidase enzymes. As a result, the duration of their effects was unrelated to the duration of their plasma concentrations; instead, effects persisted until new MAO enzyme was produced. Usually it would take 2 weeks after stopping an MAOI for enzyme levels to return to normal. ► Moclobemide, an MAOI not marketed in the USA, is a reversible MAOI. The advantage of this compound is that foods containing tyramine do not need to be restricted in the diet. The recent ► selegiline transdermal system allows for cutaneous absorption. As a result, the drug has less effect on MAO enzymes in the gut, so at lower doses dietary restrictions are not required.

Efficacy

Antidepressants are effective in the treatment of depression, several pain syndromes, anxiety disorders, ADHD, and smoking cessation. One of the largest recent reviews of antidepressants in major depressive disorder found 182 controlled trials conducted in over 36,000 individuals (Papakostas and Fava 2009). The mean pooled response rate was 54% with drug treatment and 37% with placebo, and the difference was highly significant. This translates into an estimated number need to treat of about six, which is considered clinically meaningful. Recently it has been suggested that the published literature may overestimate efficacy because negative studies are less likely to be published; however, there is little question that these drugs are effective, and analyses of all trials reported to the FDA, published or not, have been preformed. The difference between drug and placebo is greater in more severely depressed individuals and greater if the likelihood of receiving placebo is higher. There also appears to be recent a trend toward higher placebo response rates and smaller drug-placebo differences.

Antidepressants are also effective in chronic major depressive disorder and dysthymia. Their efficacy as monotherapy in psychotic depression appears to be reduced, but they are often given with ► antipsychotics. In bipolar I disorder, antidepressants can induce mania and may aggravate rapid cycling; most guidelines recommend avoiding their use or giving them only with mood stabilizers.

In addition to being effective for the acute treatment of depression, antidepressants reduce relapse and recurrence in depression. This is particularly important because depression is usually a recurrent illness. A meta-analysis of 31 randomized controlled trials in major depressive disorder found that drug treatment reduced relapse and recurrence rates by 70% (Geddes et al. 2003). In fact, this appears to be the most potent and well replicated effect of antidepressant agents, although it is noted that this effect is demonstrated in individuals who have had an acute response to the same agent.

An area of considerable interest is whether one antidepressant or a class of antidepressants is more effective than another. A specific question raised by the widespread use of SSRI agents is whether they were as effective as the tricyclics. A review of over 100 comparison trials found comparable efficacy except for a small number of studies in inpatients (Anderson 2000). Two studies by the Danish University Group found the tricyclic clomipramine more effective than the SSRIs citalopram and paroxetine. Clomipramine has effects on both NE and 5-HT. Recently, it has been suggested that other dual action ► SNRIs (serotonin-norepinephrine reuptake inhibitors) might also be more effective. Reviews of venlafaxine and duloxetine studies found some evidence to support this; however, the largest meta-analysis of 93 trials of dual action drugs found that while the difference was statistically significant, it was sufficiently small to be of doubtful clinical importance. Another question of great interest is whether there are predictors of response to one agent or another. In the pre-SSRI era, the MAOIs were found to be superior to tricyclics in ► atypical depression, a syndrome in which mood is reactive to current events and sleep and appetite are increased. However, the second-generation antidepressants do not appear to differ in efficacy in this syndrome. Few prospective trials of symptom predictors have been performed and there is no well-established pattern of symptoms that predicts response to a particular drug class. Investigators have also examined if there are biological differences that might predict response in depression to a particular drug class. Recently, this exploration has shifted to looking for genetic predictors. To date, no reliable biologic predictor has been identified.

Uses in Other Disorders

Antidepressants, tricyclics in particular, have been extensively studied in chronic pain syndromes. Evidence suggests the magnitude of the effect (effect size) may be larger in pain than depression. It appears that dual action NE – 5-HT drugs are most effective, followed by NE uptake inhibitors, with SSRIs least effective for chronic pain. Duloxetine is the first antidepressant approved by the FDA for use in diabetic neuropathic pain and fibromyalgia.

Although imipramine was the first antidepressant shown to be effective for panic disorder and generalized anxiety disorder, it was never approved for use in these conditions. Clomipramine was shown to be effective in OCD and has that indication in the USA. The SSRIs are the first class with FDA approval in a variety of anxiety disorders including panic disorder, OCD, PTSD, social anxiety disorder, and generalized anxiety disorder. Not all SSRIs are approved for use in each disorder but it appears likely this is a class effect. Sertraline and paroxetine are approved for panic disorder, PTSD, and SAD. Paroxetine and escitalopram are approved for generalized anxiety disorder. Four of the SSRIs are approved for use in OCD and this is the only indication for use in the USA for fluvoxamine. Fluoxetine is approved for use in bulimia. Fluoxetine and sertraline are approved for use in premenstrual dysphoric disorder. Venlafaxine and duloxetine are both approved for use in generalized anxiety disorder. It appears that agents that block 5-HT uptake, whether they are SSRIs or SNRIs, have efficacy across a spectrum of anxiety disorders. Among these serotonergic agents, differences in the indications that are approved appear to reflect marketing decisions more than real differences in efficacy; however, without controlled trials this supposition is unconfirmed.

Bupropion is approved for use in smoking cessation under the brand name Zyban. The tricyclic norepinephrine reuptake inhibitor desipramine was previously commonly used in treating childhood ADHD but cases of sudden death in children under 12 years led to a rapid decline in use. ► Atomoxetine, a more selective NE uptake inhibitor, is approved for use in ADHD. Bupropion in controlled studies appeared to be effective in adult ADHD but does not have FDA approval for that indication.

Safety and Tolerability

The tricyclic antidepressants have a variety of tolerability issues related to their anticholinergic, antihistaminic, and alpha-1 blocking properties (Richelson and Nelson 1984). Patients often experienced dry mouth, increased heart rate, and light-headedness on standing, and sometimes sedation, urinary hesitancy, and constipation. It was uncommon for a patient on a tricyclic not to notice at least one side effect. The tricyclics delayed ventricular conduction (Glassman et al. 1993). In vulnerable individuals, at high plasma levels or after overdose, this could cause heart block. Seizures also occurred with the tricyclics, and risk was higher in vulnerable individuals, at high plasma levels, or after overdose. The tricyclics could be fatal in

overdose with as little as a 10-day supply of the drug. For many years, amitriptyline was the second leading cause of death by overdose with a single agent in the USA, after acetaminophen.

The MAOIs could also cause hypotension at therapeutic doses. The main concern with this class was the possibility of a hypertensive crisis or ▶ serotonin syndrome. A hypertensive crisis could occur when a patient on an MAOI ingested foods rich in tyramine or other drugs with sympathomimetic properties. The hypertensive crisis could result in a stroke. As a result, patients taking a MAOI needed to follow a diet low in tyramine and avoid certain drugs. These risks appeared reduced with the reversible MAOI meclobemide. The selegiline transdermal system (patch), because it is absorbed through the skin, has less effect on MAO enzyme in the gut, and at a dose of 6 mg/24 h does not require a tyramine restricted diet. Serotonin syndrome can occur in patients on an MAOI who ingest an SSRI or meperidine. Serotonin syndrome is characterized by confusion, fever, restlessness, myoclonus, hyperreflexia, diaphoresis, hypomania, shivering, and tremor, and can be fatal. It is thought to be caused by the excessive activation of 5-HT_{1A} receptors. The severity of these risks and the need to restrict diet and other drugs limited the use of the MAOIs.

The second-generation agents are substantially safer than the TCAs and MAOIs. They are less likely to be fatal in overdose. They do not prolong the electrocardiographic QTc interval. With the exception of bupropion, the risk of seizures is low. Perhaps the biggest difference, however, is tolerability. While few studies have assessed overall side effect burden, relatively more patients on a second-generation agent can take the drug without experiencing disruptive side effects during chronic dosing. When starting an SSRI, patients can experience nausea and some patients experience restlessness. Both are dose-related and usually transient. With long-term treatment, some patients experience sexual dysfunction or weight gain. The acute and long-term side effects of the SSRIs were shared by venlafaxine and duloxetine. Venlafaxine is associated with hypertension at high doses, e.g., 300 mg/day. This had also been observed in younger patients on desipramine and may be related to norepinephrine effects. Other uncommon events can occur. SSRIs block the uptake of serotonin into the platelet and affect platelet function. This can increase the risk of bleeding, with a risk similar to that of taking one aspirin a day. SSRIs have also recently been reported to increase bone demineralization and increase the risk of nontraumatic fractures. Although not well studied, the SNRIs, having similar effects on 5-HT uptake, would be expected to have similar risks.

Bupropion has a different side-effect profile. The most common side effects are agitation, insomnia, sweating, dry mouth, constipation, and tremor. Of the antidepressants, it is least likely to cause sedation or sexual dysfunction and is either weight-neutral or associated with weight loss. The most serious safety issue is seizures. The risk is dose related and similar to the tricyclics. This risk led to the recommendation not to exceed 450 mg/day. Seizure risk is reduced with delayed-release formulations that are associated with lower peak levels.

Mirtazapine, because of its antihistaminic properties, is the antidepressant most likely to cause sedation during initial treatment. Tolerance usually develops. Because the antihistaminic effect occurs at low doses and the alpha-2 adrenergic antagonism (which may be alerting or activating) occurs at higher doses, it was suggested that paradoxically the drug might become less sedating at higher doses. The antihistaminic effect also contributes to increased appetite and weight gain in some patients. This tends to limit the use of the agent in younger patients, but can be an advantage in older depressed patients.

Cross-References

- ▶ Aminergic Hypotheses for Depression
- ▶ Analgesics
- ▶ Animal Models for Psychiatric States
- ▶ Antidepressants: Recent Developments
- ▶ Brain-Derived Neurotrophic Factor
- ▶ Depression: Animal Models
- ▶ Drug Interactions
- ▶ Emotion and Mood
- ▶ Major & Minor & Mixed Anxiety-Depressive Disorders
- ▶ Monoamine Oxidase Inhibitors
- ▶ NARI Antidepressants
- ▶ Neuroprotection
- ▶ SNRI Antidepressants
- ▶ SSRIs and Related Compounds
- ▶ Tryptophan Depletion

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Antidepressants: Recent Developments

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Synonyms

Depression medications

Definition

Antidepressants are drugs used to treat depression, although many have been studied in and are used to treat a wide variety of conditions, including anxiety disorders, pain disorders, and others.

Pharmacological Properties

History

Since the serendipitous discovery of the ▶ antidepressant effects of tricyclics in the 1950s, depression has generally been treated by agents that boost the synaptic actions of one or more of the three ▶ monoamines (serotonin (5HT), ▶ norepinephrine (NE), and ▶ dopamine (DA)). Acutely enhanced synaptic levels of monoamines could lead to adaptive downregulation and desensitization of postsynaptic receptors over time, a pharmacological action consistent with current ▶ aminergic hypotheses of depression, which posit that the disorder may be due to the pathological upregulation of neurotransmitter receptors (Stahl 2008a). Thus, antidepressants theoretically reverse this pathological upregulation of receptors over time. Adaptive changes in receptor number or sensitivity are likely the result of alterations in ▶ gene expression and transcription. This may include not only turning off the synthesis of neurotransmitter receptors but also increasing the synthesis of various ▶ neurotrophic factors such as ▶ brain-derived neurotrophic factor (BDNF). In fact, preclinical studies demonstrate that antidepressants increase BDNF expression (Duman et al. 2001). Such prototrophic actions may apply broadly to all effective antidepressants and may provide a final common pathway for the action of antidepressants.

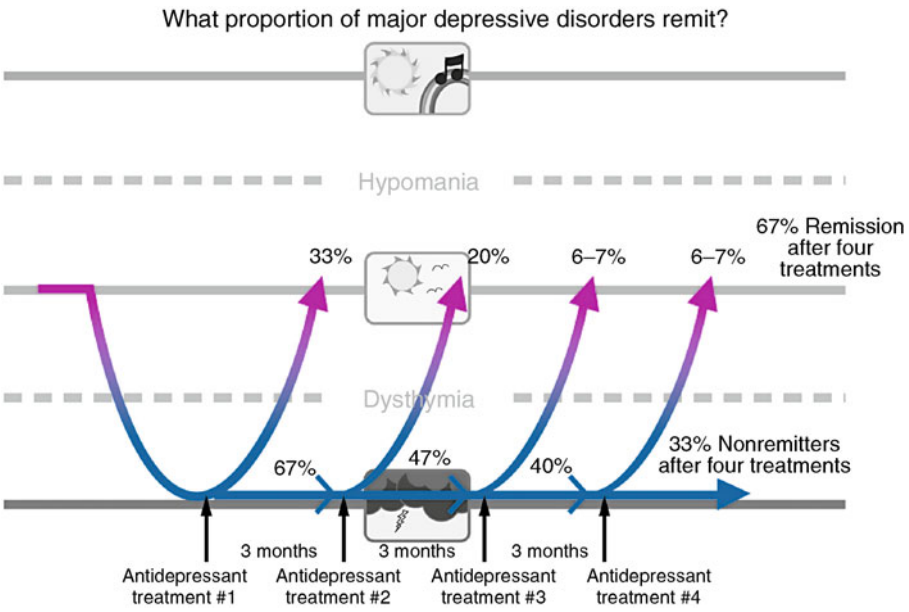
Although treatment with currently available antidepressants is effective for many patients, a large proportion experience residual symptoms, treatment resistance, and relapse. In the recent STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study (Warden et al. 2007), only one-third of the patients on monotherapy with ▶ citalopram remitted initially. For those who failed to remit, the likelihood of ▶ remission with another antidepressant monotherapy decreased with each successive trial. Thus, after a year of treatment with four sequential antidepressants taken for 12 weeks each, only two-thirds of patients achieved remission (Fig. 1). Of additional concern is the fact that the likelihood of relapse increased with the number of treatments it took to get the patient to remit.

These results highlight the need for the continued exploration of more effective methods to treat major depression. A plethora of treatments are either under investigation or newly available for major depressive disorder, including new formulations of current antidepressants, new and existing agents that exploit the monoaminergic link to depression, and experimental agents with novel mechanisms of action.

New Twists on Old Drugs

One developmental focus for antidepressants is to improve the tolerability of existing agents. A recently approved hydrobromide salt formulation of ▶ bupropion allows the administration of single-pill doses up to 450 mg equivalency to bupropion hydrochloride salt, unlike bupropion hydrochloride controlled release formulations for which the biggest dose in a single pill is 300 mg. This could facilitate dosing for difficult-to-treat patients.

In addition, approval is pending for a once-daily controlled release formulation of ▶ trazodone that allows



Antidepressants: Recent Developments. Fig. 1. Remission rates in major depressive disorder with sequential monotherapies.

much more tolerable administration of high antidepressant doses (e.g., 300–450 mg). This may increase the utility of trazodone in depression, as the immediate release formulation is often not tolerated at high antidepressant doses due to its propensity to cause severe next-day sedation, and is used instead at low doses as a hypnotic.

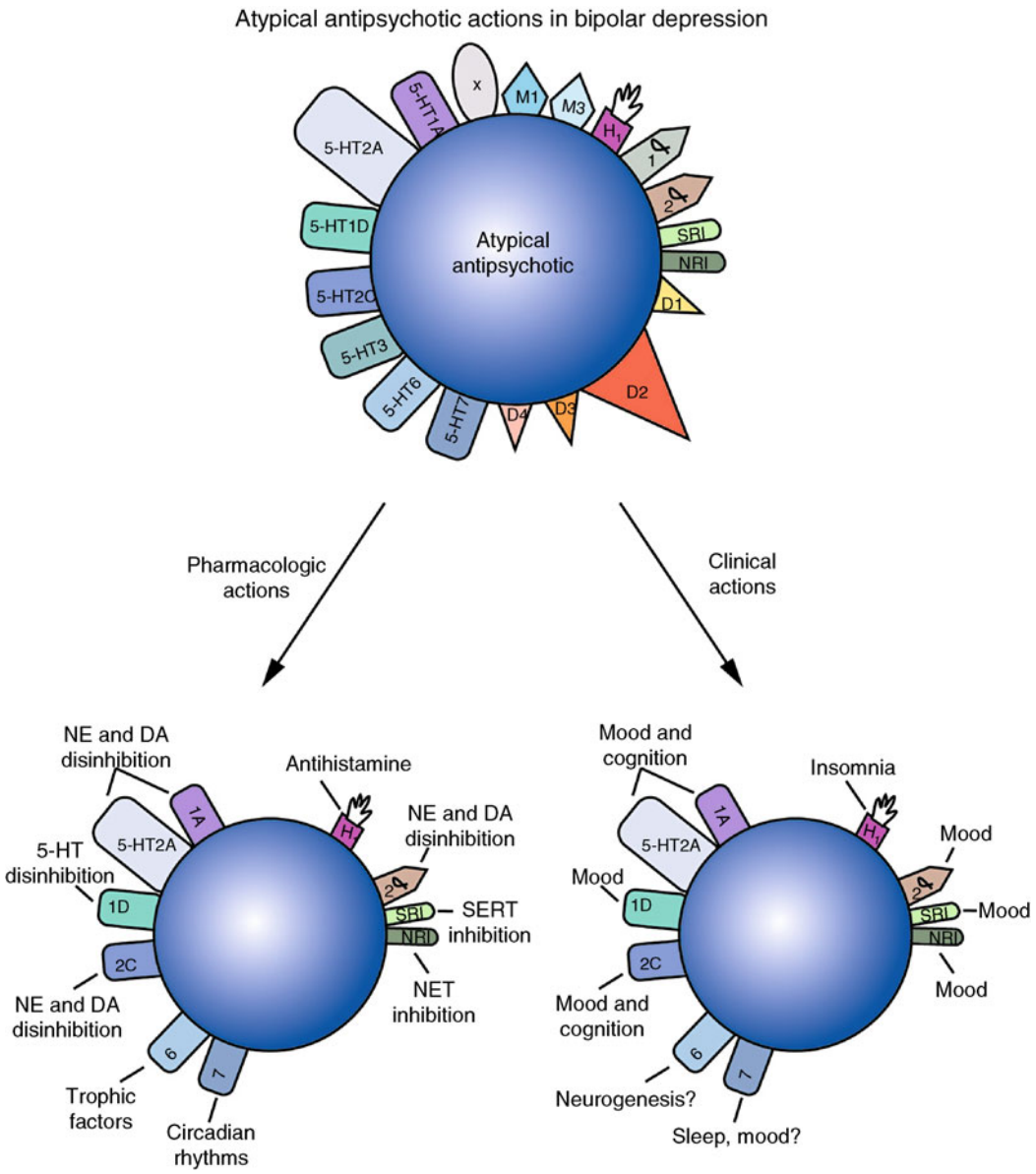
Another twist on an old drug is the availability of ► desvenlafaxine, the active metabolite of ► venlafaxine, as a unique antidepressant agent. Desvenlafaxine is formed as the result of CYP450 2D6 and thus itself bypasses this metabolic step, potentially giving it more consistent plasma levels than venlafaxine (Stahl 2009). In addition, although desvenlafaxine, like venlafaxine, is more potent at the 5HT ► transporter (SERT) than the NE transporter (NET), it has relatively greater actions on NET versus SERT than venlafaxine does at comparable doses. This greater potency for NET may make it a preferable agent for symptoms theoretically associated with NE actions, such as pain symptoms and vasomotor symptoms. In fact, desvenlafaxine was shown to be efficacious for hot flushes in perimenopausal women (Stahl 2008a; Wise et al. 2008), although it was not approved for this use due to cardiovascular safety concerns.

New Means of Monoaminergic Modulation

Atypical Antipsychotic Drugs

Currently, atypical ► antipsychotic drugs are used to treat ► bipolar disorder, with similar efficacy to each other in the manic phase but varying efficacy in treating the depressed phase. Several mechanisms are feasible explanations for how certain atypical antipsychotic drugs may work to improve symptoms in the depressed phase of bipolar disorder (Stahl 2008a). Actions at numerous receptors by different atypical antipsychotic drugs can increase the availability of 5HT, DA, and NE, which, as discussed earlier, are critical in the action of current antidepressants in unipolar depression (Fig. 2). Specifically, actions at $5HT_{2A}$, $5HT_{2C}$, and $5HT_{1A}$ receptors indirectly lead to NE and DA disinhibition, which may improve mood and cognition. Mood may also be improved by increasing NE and 5HT via actions at alpha 2 adrenergic receptors, by increasing NE via the blockade of the NE transporter, and by increasing 5HT via actions at $5HT_{1D}$ receptors and the blockade of the 5HT transporter. Antihistamine actions could improve insomnia associated with depression. Actions at other 5HT receptors may also play a role in treating depression.

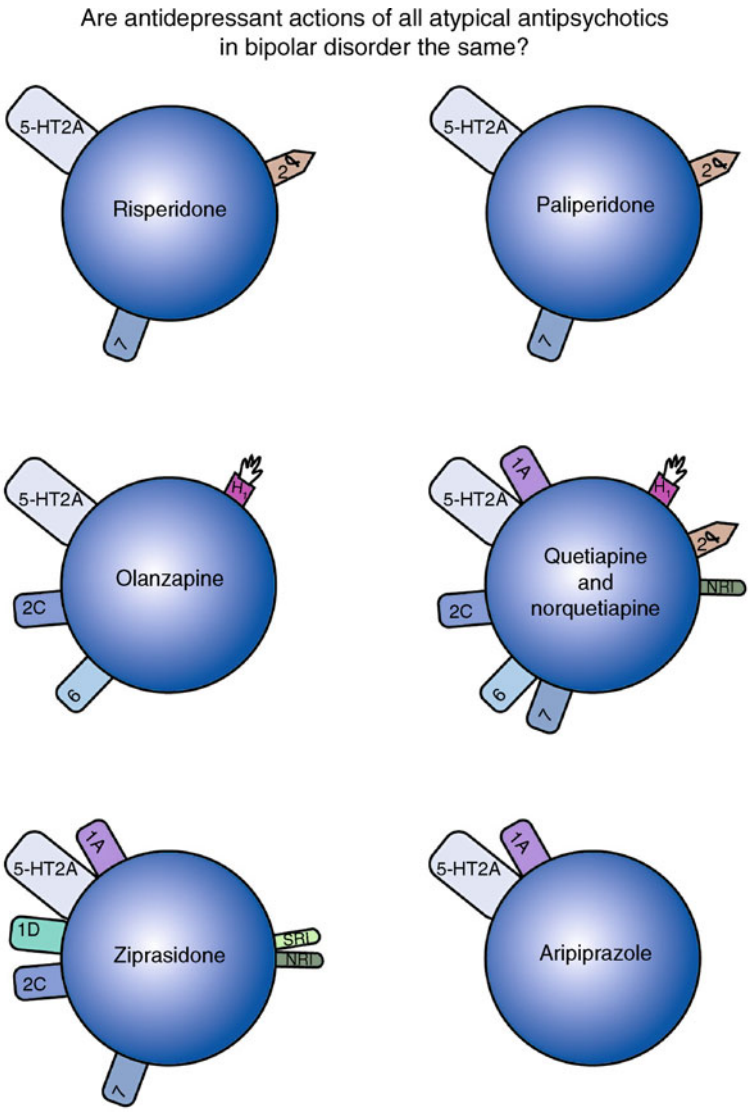
Each atypical antipsychotic has a unique portfolio of pharmacological actions that may contribute to its antidepressant actions (Fig. 3). This may explain why these agents differ in their ability to treat the depressed phase of ► bipolar disorder and also why some patients respond to one of these drugs and not to another. The agent with the most evidence of efficacy as a monotherapy for bipolar depression is ► quetiapine, which was recently approved for this indication. The effective dose of quetiapine in bipolar depression is 300–600 mg/day, lower than



Antidepressants: Recent Developments. Fig. 2. Pharmacologic properties of atypical ► antipsychotic drugs and their links to symptoms of depression.

that needed for the saturation of the D2 receptor but sufficient to cause $5HT_{2C}$ antagonism, $5HT_{1A}$ agonism, and norepinephrine reuptake inhibition, especially through the newly discovered pharmacologic actions of its active metabolite norquetiapine (Stahl, 2008a, 2009). This lends further weight to the speculative mechanisms described earlier for antidepressant action of atypical antipsychotic drugs.

Whether atypical antipsychotic drugs will be proven effective with a sufficiently favorable side effect and cost profile for unipolar depression is still under intense investigation (Papakostas et al. 2007). ► Aripiprazole was recently approved as an adjunct treatment for resistant depression (defined as failing one SSRI/SNRI trial). At its effective dose in depression – 2–10 mg/day, lower than that used for ► schizophrenia – aripiprazole is



Antidepressants: Recent Developments. Fig. 3. Atypical antipsychotic drugs: differing portfolios of pharmacologic action for bipolar depression.

primarily a D2 and D3 ► partial agonist with only weak $5HT_{2A}$ ► antagonist and $5HT_{1A}$ partial agonist properties (Stahl 2008b).

Triple Reuptake Inhibitors (TRIs)

These drugs are testing the idea that if one mechanism is good (i.e., selective serotonin reuptake inhibitors or SSRIs [► SSRIs and related compounds]) and two mechanisms are better (i.e., serotonin and norepinephrine reuptake inhibitors or ► SNRI antidepressants), then maybe targeting all three mechanisms of the trimonoamine neurotransmitter system would be the best in terms of efficacy. Several different triple reuptake inhibitors (or serotonin–norepinephrine–dopamine reuptake inhibitors) are listed in Table 1 (Stahl 2008a). Some of these agents have additional pharmacological properties as well. In particular, LuAA 24530, currently in clinical trials, is not only a TRI but also binds 5HT2C, 5HT2A, 5HT3, and alpha 1A adrenergic receptors. The question regarding TRIs is how much blockade of each monoamine transporter is desired, especially for the dopamine transporter or DAT. Too much dopamine activity can lead to a drug

Antidepressants: Recent Developments. Table 1. Antidepressants in development: triple reuptake inhibitors.

Triple reuptake inhibitor	Additional receptor targets	Development stage
DOV 216303		Phase II depression (terminated)
DOV 21947		Phase II depression
GW 372475 (NS2359)		No ongoing clinical trials in depression; Phase II for attention deficit hyperactivity disorder
Boehringer/NS2330		No ongoing clinical trials in depression; Phase II for Alzheimer dementia and for Parkinson's disease discontinued
NS2360		Preclinical
Sepracor SEP 225289		Phase II depression
Lu AA24530	5HT2C, 5HT3, 5HT2A, alpha 1A	Phase II depression
Lu AA37096	5HT6	Phase I
Lu AA34893	5HT2A, alpha 1A, and 5HT6	Phase II depression (terminated)

Antidepressants: Recent Developments. Table 2. Antidepressants in development: novel serotonin-linked mechanisms.

Novel serotonergic targets	Agent	Additional receptor targets	Development stage
$5HT_{2C}$ antagonism	Agomelatine	Melatonin 1,2	Approved EMEA with liver monitoring, Phase III depression in the USA
SSRI/$5HT_3$ antagonism	Lu AA21004	$5HT_{1A}$	Phase III depression
SSRI/$5HT_{1A}$ partial agonism	Vilazodone (SB 659746A)		Phase III depression
$5HT_{1A}$ partial agonism	Gepirone ER		Late-stage development for depression
$5HT_{1A}$ partial agonism	PRX 00023		Phase II depression, phase III for generalized anxiety disorder
$5HT_{1A}$ partial agonism	MN 305		No clinical trials in depression; Phase II/III for generalized anxiety disorder
Sigma 1/$5HT_{1A}$ partial agonism	VPI 013 (OPC 14523)	Serotonin transporter	Phase II depression
$5HT_{1A}$ agonism/$5HT_{2A}$ antagonism	TGW-00-AD/AA		Phase II depression
SRI/$5HT_2$/$5HT_{1A}$/$5HT_{1D}$	TGBA-01-AD		Phase II depression
$5HT_{1B/D}$ antagonism	Elzasonan		Phase II depression

of abuse, while not enough means that the agent is essentially an SNRI. Perhaps the desirable profile is the robust inhibition of SERT and the substantial inhibition of NET, like the known SNRIs, plus the addition of 10–25% inhibition of DAT. Some testing suggests that dopamine reuptake inhibition also increases acetylcholine release, so TRIs may modulate a fourth neurotransmitter system and act as multitransmitter modulators (Stahl 2008a). Further testing will determine whether TRIs will represent an advance over SSRIs or SNRIs in the treatment of depression.

Novel Serotonin Targets (Serotonin Agonists and Antagonists)

A large number of novel serotonin targets are in testing and are listed in Table 2 (Stahl 2008a). One particularly interesting novel serotonin target is the $5HT_{2C}$ receptor. Blockade of $5HT_{2C}$ receptors causes the release of both norepinephrine and dopamine, which is why these agents can be called norepinephrine dopamine disinhibitors (NDDIs). The novel antidepressant ► agomelatine combines this property of $5HT_{2C}$ antagonism with additional agonist actions at ► melatonin receptors (MT1 and

Antidepressants: Recent Developments. Table 3. Antidepressants in development: novel sites of action.

Novel mechanism	Agent	Development stage
Beta 3 agonism	Amibegron	Phase III discontinued
Neurokinin (NK) 2 antagonism	Saredutant (SR48968)	Phase III discontinued
NK2 antagonism	SAR 1022279	Preclinical
NK2 antagonism	SSR 241586 (NK2 and NK3)	Preclinical
NK2 antagonism	SR 144190	Phase I
NK2 antagonism	GR 159897	Preclinical
NK3 antagonism	Osanetant (SR142801)	No current clinical trials in depression; preliminary trials in schizophrenia
NK3 antagonism	Talnetant (SB223412)	No current clinical trials in depression; Phase II for schizophrenia and for irritable bowel syndrome
NK3 antagonism	SR 146977	Preclinical
Substance P antagonism	Aprepitant [MK869; L-754030 (Emend)]	Phase III for nausea/vomiting
Substance P antagonism	L-758,298; L-829,165; L-733,060	No clinical trials in depression; Phase III for nausea/vomiting
Substance P antagonism	CP122721; CP99994; CP96345	Phase II depression
Substance P antagonism	Casopitant (GW679769)	No clinical trials in depression; Phase III for nausea/vomiting
Substance P antagonism	Vestipitant (GW 597599) +/− paroxetine	No clinical trials in depression; Phase II for social anxiety disorder
Substance P antagonism	LY 686017	No clinical trials in depression; Phase II for social anxiety disorder and for alcohol dependence/craving
Substance P antagonism	GW823296	Phase II
Substance P antagonism	(Nolpitantium) SR140333	No clinical trials in depression; Phase II for ulcerative colitis
Substance P antagonism	SSR240600; R-673	No clinical trials in depression; Phase II for overactive bladder
Substance P antagonism	NKP-608; AV608	No clinical trials in depression; Phase II for social anxiety disorder
Substance P antagonism	CGP49823	Preclinical
Substance P antagonism	SDZ NKT 34311	Preclinical
Substance P antagonism	SB679769	Preclinical
Substance P antagonism	GW597599	Phase II depression
Substance P antagonism	Vafopitant (GR205171)	No clinical trials in depression; Phase II for insomnia and for posttraumatic stress disorder
MIF-1 pentapeptide analog	Nemifitide (INN 00835)	Phase II depression
MIF-1 pentapeptide analog	5-hydroxy-nemifitide (INN 01134)	Preclinical
Glucocorticoid antagonism	Mifepristone (Corlux)	Phase III depression
Glucocorticoid antagonism	Org 34517; Org 34850 (glucocorticoid receptor II antagonists)	Phase III depression
► Corticotropin releasing factor (CRF) 1 antagonism	R121919	Phase I

Antidepressants: Recent Developments. Table 3. (continued)

Novel mechanism	Agent	Development stage
CRF1 antagonism	CP316,311	Phase II (trial terminated)
CRF1 antagonism	BMS 562086	Phase II
CRF1 antagonism	GW876008	No clinical trials in depression; Phase II for social anxiety disorder and for irritable bowel syndrome
CRF1 antagonism	ONO-233M	Preclinical
CRF1 antagonism	JNJ19567470; TS041	Preclinical
CRF1 antagonism	SSR125543	Phase I
CRF1 antagonism	SSR126374	Preclinical
Vasopressin 1B antagonism	SSR149415	Phase II

MT2). Agomelatine also has $5HT_{2B}$ antagonist properties. This portfolio of pharmacological actions predicts not only antidepressant actions due to the NDDI mechanism of 5HT2C antagonism but also sleep-enhancing properties due to MT1 and MT2 agonist actions. Positive trials of agomelatine have been completed in the USA, and it is now approved in Europe with liver function monitoring required.

Another novel serotonergic agent is LuAA21004, currently in clinical trials. This agent is a serotonin reuptake inhibitor and also an antagonist at $5HT_3$ receptors, with additional actions at $5HT_{1A}$ receptors.

Novel Targets and Mechanisms

An interesting development is the potential utility of L-5-methyl-tetrahydrofolate (MTHF) as an adjunct treatment for depression. MTHF is a key derivative of ▶ folate and plays a critical role in monoamine synthesis; thus, the administration of MTHF could theoretically boost trimonoamines (Stahl 2008a). Current research specifically suggests that MTHF may be indicated for depressed patients with low folate levels and who have not responded adequately to antidepressants (Fava 2007). Available as a "medical food," MTHF appears to be safe with few side effects, but further research is necessary to determine its ultimate role in depression treatment.

Nonpharmacological developments in the treatment of depression include the approval of ▶ transcranial magnetic stimulation, in which a rapidly alternating current passes through a small coil placed over the scalp to generate a magnetic field that induces an electrical current in the underlying areas of the brain (Avery et al. 2006), and research into ▶ deep brain stimulation, in which a battery-powered pulse generator is implanted in the chest wall with one or two leads tunneled directly into the brain, especially within the subgenual area of the ventromedial prefrontal cortex, to send brief repeated pulses there (Mayberg et al. 2005).

Finally, a large number of agents that act at several other novel targets are in preclinical or early clinical development, and are listed in Table 3 (Stahl 2008a). Many of these agents are low-molecular-weight drugs that target stress hormone release from the hypothalamic–pituitary–adrenal (HPA) axis, while many others are antagonists at neurokinin receptors.

Conclusion

In summary, there are many avenues of pursuit for increasing the effectiveness of antidepressant treatment, including not only building on existing agents and/or existing mechanisms but also exploring new and unique mechanisms and techniques. It remains to be seen which of these will ultimately represent major advances in the treatment of depression.

Cross-References

▶ Aminergic Hypotheses for Depression
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Bipolar Disorder
▶ Brain-Derived Neurotrophic Factor
▶ Corticotropin Releasing Factor
▶ Gene Expression
▶ Gene Transcription
▶ SNRI Antidepressants
▶ SSRIs and Related Compounds

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Antidiuretic Hormone

► Arginine-Vasopressin

Antiepileptics

► Anticonvulsants

Antihistamines

► Histaminic Agonists and Antagonists

Antimuscarinic/Anticholinergic Agent

Definition

An anticholinergic drug is one that blocks the physiological action of the neurotransmitter ► acetylcholine in the central and the peripheral nervous system. These drugs are classified according to the receptors that are affected. Most anticholinergics are muscarinic receptor antagonists, that is, agents that reduce the activity of the muscarinic acetylcholine receptor. Others are antinicotinic agents operating on the ► nicotinic receptors. The antimuscarinic drugs are used in the treatment of a variety of medical conditions including Parkinson's disease and antipsychotic-induced parkinsonism.

Antinociception

Definition

Antinociception refers to the reversal or alteration of the sensory aspects of pain intensity. Most models for examining antinociception were developed for use in animals in order to explore alterations in sensitivity to a painful stimulus following the administration of a drug with potential analgesic (pain-relieving) properties. The term is usually used to avoid the anthropomorphic connotation of the term analgesia, which strictly means reversal of the subjective sensation of pain, the presence of which can only be inferred in animals.

Cross-References

► Analgesics
► Opioids

Antinociception Test Methods

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Synonyms

Analgesia tests

Definition

Antinociceptive tests encompass a large group of experimental procedures specifically developed for examining sensitivity to painful stimuli and the alteration of pain sensitivity following drug administration. Since most antinociceptive tests have been designed for examining pain sensitivity in animals, they provide limited

information about the affective aspects of pain perception such as discomfort or unpleasantness. These characteristics are more likely to be examined in studies with human subjects.

Principles and Role in Psychopharmacology

A number of procedures have been developed for examining the pain-relieving (i.e., ► analgesic) properties of drugs in laboratory animals. Each of these procedures involves the presentation of a potentially painful (or ► nociceptive) stimulus, followed by the measurement of a clearly observable response. Typically, data are based on the time it takes the organism to respond to or withdraw from a nociceptive stimulus. Once baseline levels of responding in response to the nocicepetive stimulus are determined and considered reliable, a drug is administered, and response latencies are then redetermined in the presence of the drug. If the time it takes the organism to respond to the stimulus is longer following drug administration, and importantly, if this change is not because the animal is unable to make the response due to the sedative or motor effects of the drug, then the drug is said to produce antinociceptive effects.

Although this experimental paradigm appears relatively simple and straightforward, it becomes far more complex when one considers the multiple variables that influence the data that can be obtained with these procedures. For example, the type of nociceptive stimulus (e.g., thermal, mechanical, electrical, or chemical), its intensity, and the duration and outcome of its effect determine the drug-induced alterations in response latency, and therefore, these must be quantified very precisely. Similarly, the nature of the response itself – whether it involves an elementary reflex response or a more integrated escape or ► avoidance response – can influence the interpretation of a drug's effect. Antinociceptive tests also attempt to differentiate nonspecific response alterations from those that are specific to the nociceptive stimulus. This is particularly important in the assessment of drug-induced alterations in response to the nociceptive stimulus since a drug may produce motor effects that interfere with the ability of the organism to execute a particular response. A more extensive discussion of these issues can be found in a classic review by Beecher (1957) and a recent review by Le Bars et al. (2001). For the discussion of parallel issues related to pain assessment in humans, see Turk and Melzack (2001).

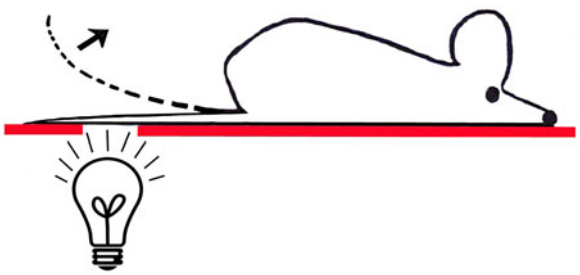
Although antinociceptive procedures vary in many ways, it is convenient to place them in one of two larger groups – those that involve acute pain and those that involve more persistent pain as might occur with tissue injury or nerve damage.

Models of Acute (or Phasic) Pain in Animals

In general, antinociceptive tests for examining acute pain involve the presentation of a brief thermal, mechanical, or electrical stimulus that is delivered to the skin, paws, or tail of an animal. One of the most common procedures in this category is the *tail-flick procedure,* originally developed by D'Amour and Smith (1941). In this procedure, a high intensity light is focused on an area close to the tip of the tail as shown for a mouse in Fig. 1, and the time (response latency) taken by the mouse to remove (i.e., flick) its tail from the light source is determined. The light intensity can be adjusted to yield baseline response latencies that are relatively short (i.e., between 3 and 5 s) or long (i.e., between 8 and 10 s).

Typically, the time taken by the mouse to remove its tail from the heat source is measured prior to the drug administration to determine baselines response latencies. After baseline latencies have been determined, drug administration takes place, and tail flick latencies are determined either once or multiple times over a set time period. However, caution has to be taken with repeated measurements, as the tail-flick response is prone to ► habituation. The tail flick response is easy to observe, and it is considered to involve simple spinal reflexes. It can be measured either with a stopwatch or through a system that uses photocells to determine when the tail has been removed from the light source. ► Opioid analgesics such as ► morphine are very active in this procedure, though their effects depend on the intensity of the thermal stimulus. For example, if the light intensity is very high and elicits short tail flick latencies, a higher dose of morphine is usually required to alter the tail flick latency than when the light is set at a lower intensity.

One very important characteristic of the tail flick procedure, and almost all other acute antinociceptive procedures, is the use of a cutoff time to prevent tissue damage. The *cutoff time* is defined as the maximal time



Antinociception Test Methods. Fig. 1. This figure provides a simple schematic of the tail-flick procedure, showing the position of the mouse's tail over a light source.

that an animal is exposed to the nociceptive stimulus. For example, if a high intensity light is used in the tail flick procedure and the animal (e.g., a mouse) does not remove its tail from the light source within 10 s (cutoff time), the mouse is removed from the apparatus by the experimenter. The cutoff time also influences certain aspects of the data analysis since it is one of the variables in the formula commonly used to quantify antinociceptive drug effects.

A drug's effect in the tail flick procedure is usually quantified by determining the difference between the response latency obtained under baseline conditions and response latency obtained after drug administration. This difference is then divided by the difference between the cutoff time and the baseline latency and a *percent maximal effect (%MPE)* is derived from these measures.

$$\%\text{MPE} = \frac{\text{latency (s) following drug administration} - \text{latency (s) under baseline conditions}}{\text{cutoff time(s)} - \text{latency (s) under baseline conditions}}$$

Since baseline latencies vary between animals, this formula accommodates individual differences in response to the nociceptive stimulus.

The *tail-withdrawal test* (Janssen et al. 1963) is a modification of the tail-flick test. In this procedure, mice or rats are gently restrained, and their tail is placed into a water bath maintained at temperatures between 48° and 56°C. Some investigators have also used cold water as the painful stimulus, although this is less common. Latency to remove the tail from the water is measured, much in the same way as in the tail flick procedure, and data are usually described with the percent maximal effect formula described for the tail flick procedure.

The *tail-withdrawal test* has also been used in primates and the procedure parallels those used in rodents. In this procedure, a monkey is placed in a restraint chair and the lower portion of their tail is immersed in water maintained at a specific temperature (40, 50, or 55°C). The latency to remove the tail from the water is then determined. Typically, monkeys do not remove their tails from 40°C water; however, response latencies might average 10 s when the water is 50°C and 5 s or less when the water is 54°C (Dykstra and Woods 1986). If the monkey does not remove its tail from the water within the predetermined cutoff time (e.g., 20 s), the tail is removed by the experimenter and the latency assigned a value of 20 s (cutoff time). Investigators have shown that reliable data can be obtained with this procedure and tail withdrawal responses can be measured every 15–30 min for periods as long as 3 h.

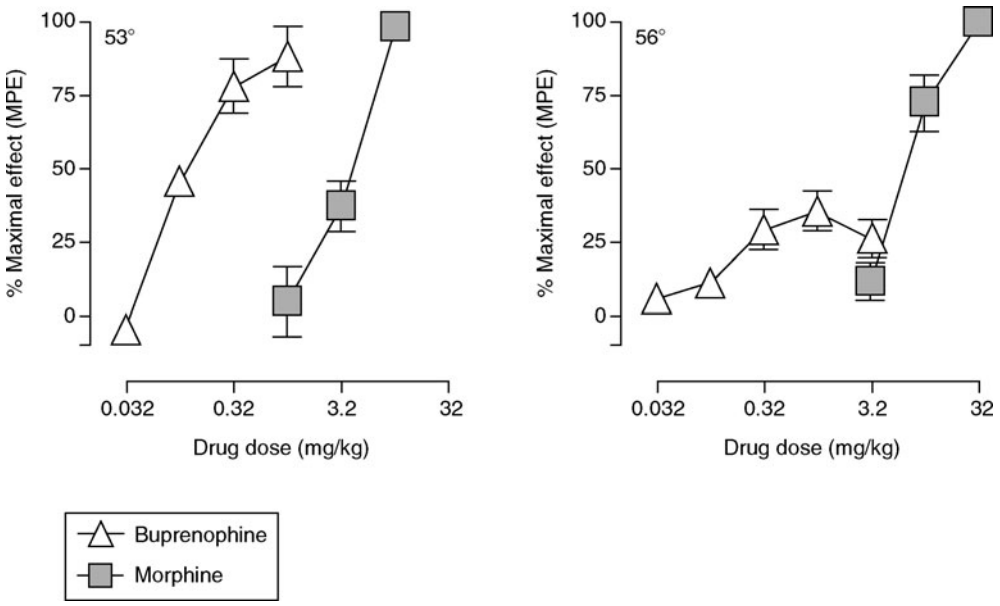
The *hot plate procedure* is another acute antinociceptive test that is commonly used to assess drug effects. In this procedure, an animal (usually a rodent) is placed on a flat surface maintained at a set temperature (e.g., 52–56°C). The baseline nociceptive response to the hot plate is evaluated by recording the latency to lick or shuffle the hind paw(s), or jump from the hotplate surface. Following the determination of baseline response latencies, drug administration is initiated. Figure 2 illustrates data obtained with this procedure. Responses are measured using a stopwatch and a predetermined cutoff time is established to prevent tissue damage. If an animal does not exhibit a nociceptive response after this cutoff period, they are manually removed from the hot plate and assigned a response value equal to the cutoff time.

Figure 2 shows data obtained at two different hot plate temperatures following the administration of two different opioid analgesics, a high efficacy opioid, morphine, and a lower efficacy opioid, ▶ buprenorphine. The left portion of Fig. 2 shows data obtained when the hot plate temperature was 53°C. Under these conditions, both morphine and buprenorphine produced dose-dependent increases in the percent maximal possible effect (%MPE), with morphine producing 100% maximal effect at 10 mg/kg. The right portion of Fig. 2 shows data obtained when the hot plate temperature was 56°C. Under these conditions, a higher dose of morphine was required to produce 100% maximal effect (32 mg/kg), and buprenorphine's effects were markedly attenuated at the higher temperature. (Adapted from Fischer et al. 2008.)

In contrast to the procedures described above, which usually involve assessment of an unlearned response following presentation of an acute stimulus, a few procedures, especially those conducted in primates, involve a period of training. In the titration procedure, monkeys are trained on an avoidance task in which a stimulus such as an electric shock is presented to the monkey's tail (or foot) in increasing intensities. If the monkey makes one or more responses on a lever, the shock is turned off (avoided) for a period of time and the intensity is reduced when the shock resumes again. The intensity at which each monkey maintains the shock is then used as a measure of sensitivity to the potentially painful stimulus. One advantage of this procedure is that the animal, rather than the experimenter determines the level at which the stimulus is maintained. Moreover, responding can be maintained for relatively long periods of time with this procedure, which provides a convenient way to examine onset and termination of a drug effect (Allen and Dykstra 2001).

Models of Persistent (Tonic) or Neuropathic Pain

Antinociceptive test methods that involve persistent or long duration pain typically administer an irritant, which



Antinociception Test Methods. Fig. 2. Antinociceptive effects of several doses of morphine or buprenorphine on a hot plate set either at 53°C (left) or 56°C (right).

produces inflammation, or they induce injury, often by ligation of a nerve such as the sciatic nerve. These procedures often examine multiple aspects of pain sensitivity, including heightened sensitivity to pain (► hyperalgesia) or ► allodynia, a condition in which stimuli that are not normally painful are perceived as painful.

The *abdominal constriction (or writhing)* test is one example of a persistent pain model. In the abdominal constriction test, an irritant is injected directly into the peritoneal cavity of a mouse, resulting in a characteristic writhing response. Although a number of compounds have been used in this assay (acetic acid, acetylcholine, bradykinin, hypertonic saline, phenylquinone, etc.), a solution of 0.6% acetic acid is one of the most commonly used. The onset of inflammation following acetic acid occurs about 5 min after the injection and lasts for approximately 30 min, but has been reported to last for longer periods, depending on the concentration of acetic acid. In order for this assay to produce consistent data, the writhing response must be clearly defined. For example, writhes are often defined as "lengthwise stretches of the torso with a concomitant concave arching of the back" often in combination with a reduction in motor activity and some loss of coordination. Scoring is done by experimenter observations, usually of videotaped experimental sessions. One of the advantages of this procedure is the fact that it is sensitive to weak analgesics such as aspirin and other ► nonsteroidal anti-inflammatory drugs (NSAIDs); however, the lack of specificity in response to drugs without analgesic activity (false positives) sometimes makes interpretation more difficult.

The Formalin test (Dubuisson and Dennis 1977) is one of the most commonly used tests for examining persistent pain. With this test, responses are measured following a subcutaneous injection of a formalin solution into the hind paw. Two spontaneous responses are typically measured with the formalin test, an acute, early phase response and a tonic, inflammatory phase response that occurs somewhat later. These responses are usually scored on a four-level scale, from normal posture to licking, nibbling, and/or shaking of the injected paw. Given the two types of responses elicited by the formalin injection, it is possible to examine both acute pain and tonic pain in the same animal, in response to a single injection of formalin.

Carrageenan, a substance derived from Irish sea moss, is another compound that has been used in persistent pain models as it produces inflammation and consequent hypersensitivity in rodents. In a typical procedure, a 2% suspension of carrageenan is injected subcutaneously into one of the hind paws of a mouse; the opposite hind paw is not injected. This two-paw protocol in which comparisons are made between an inflamed paw and healthy paw was first introduced by Randall and Selitto

(1957) and is now the standard protocol for tests of this nature. Several hours after the carrageenan injection, mice are tested for pain sensitivity and the *Hargreaves' test* is often used for this assessment. To conduct the Hargreaves' test, mice are placed in individual, transparent chambers with a glass floor. After adaptation to the chamber, a high-intensity beam such as a projector bulb is directed at the plantar surface of the mouse's hind paw. Time to withdraw the paw is then measured.

The *von Frey test* of mechanical sensitivity provides another way to examine pain sensitivity in animals that have been treated with irritants or have experienced nerve damage. In this procedure, animals are placed in a transparent box which rests on a metal mesh floor. Von Frey monofilaments (or hairs) are then applied to the foot with a single, steady application. Since each monofilament has a different bending force, experimenters can determine the monofilament that elicits foot withdrawal 50% of the time under baseline conditions, and then following drug administration.

Another procedure that has been used to examine pain sensitivity as well as hyperalgesia and/or allodynia is capsaicin, the pungent ingredient in hot chili peppers. Exposure to capsaicin produces inflammation and allodynia, which is defined as pain that is produced by a stimulus that is not normally painful. A modification of the primate tail withdrawal procedure, using warm water rather than hot water, has been used to examine allodynia following exposure to capsaicin. The monkey is restrained and the distal part of its tail is immersed in water maintained at a comfortable temperature such as 46°C. At this temperature, monkeys usually leave their tails in the water for at least 20 s, which is used as the cutoff time. After baseline latencies are determined, capsaicin is injected above the tip of the tail. Following administration of capsaicin, allodynia develops as revealed by a decrease in tail-withdrawal latencies from 20 s to approximately 2 s. Local administration of an opioid analgesic has been shown to inhibit the allodynia induced by capsaicin under these conditions (Ko et al. 1998).

Advantages and Limitations of Antinociceptive Tests

One clear advantage of most of the antinociceptive procedures described here is that they are relatively easy to perform in animals. As a group, they require very little training time and produce reliable, repeatable, and easily quantified measures of nociception across a range of stimuli. The acute antinociceptive procedures, such as the tail flick and hot plate, are predictive of the effects of morphine-like opioid analgesics, but do not reveal activity for a number of other drugs, including the nonsteroidal anti-inflammatory drugs (NSAIDS). In contract, persistent pain procedures such as the abdominal constriction test, and formalin test, are predictive of the antinociceptive effects of nonsteroidal anti-inflammatory drugs (NSAIDS) as well as morphine-like analgesics. The fact that these procedures can predict the analgesic activity of drugs in humans, certainly verifies their usefulness as animal models. Beyond being predictive of analgesia in humans, investigations using these procedures have also advanced understanding of the multiple variables that influence the processing of nociceptive stimuli as well as the alteration in nociception following administration of different classes of drugs.

Cross-References

- ▶ Active Avoidance
- ▶ Analgesics
- ▶ Ethical Issues in Animal Psychopharmacology
- ▶ Habituation
- ▶ Opioids

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Anti-Parkinson Drugs

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Definition

► Parkinson's disease (PD): a syndrome defined in life by clinical criteria involving tremor at rest, rigidity, slowness and paucity of movement, altered posture, gait and balance with the absence of "atypical" features (Lang and Lozano 1998a,b). It is defined at autopsy by strict pathological criteria including the loss of neurons in the pars compacta of the substantia nigra, locus ceruleus and dorsal motor nucleus of the vagal nerve, and the presence of Lewy bodies.

Pharmacological Properties

Although Parkinson's disease (PD) is classified as a "movement disorder," it should also be considered as a "neurobehavioral" disorder. The diagnosis of PD is based on the presence of clinical criteria having to do purely with movements and the absence of exclusionary or atypical features, laboratory tests being of little or no value. Nevertheless, the most devastating aspects of PD are more often behavioral. Other nonmotor problems, such as sympathetic dysfunction and sleep disorders have only attracted clinical and research attention in the last few years. For perspective two studies, one a large retrospective review in Australia, and the other, a county wide prospective study with formal testing in Norway, both concluded that by the time of death, 80% of PD patients are demented. In addition, at any point in time, somewhere between 30 and 50% are depressed; 40% suffer from anxiety; 40% with apathy; 30% of drug treated patients with visual hallucinations; 5–10% of drug treated patients with delusions; and over 30% of newly diagnosed patients, untreated, suffer from fatigue unrelated to depression or the severity of their motor dysfunction.

PD in simplistic terms is often understood as a dopamine deficiency disease. While it is this, there are also abnormalities in multiple neurotransmitter systems. The dopamine motor system is the best understood and deficiencies here do cause many of the major motor problems in PD, including bradykinesia, rigidity, tremor, and gait dysfunction. Improving dopamine transmission has been the focus of modern drug therapy, starting with the introduction of the first rational designed treatment for a neurological disorder, L-Dopa.

► L-Dopa, combined with an aromatic amine decarboxylase inhibitor (AADI), ► carbidopa, has been the mainstay of the treatment of PD since it was introduced in the late 1960s (Cotzias et al. 1967). The AADI reduces the amount of L-Dopa converted in the bloodstream to ► dopamine, dramatically reducing the problem of nausea which was frequent when L-Dopa was used alone. L-Dopa is the precursor to dopamine, and in the chemical path that converts tyrosine to dopamine, L-Dopa occurs after tyrosine hydroxylase, the rate-limiting enzyme. L-Dopa is taken up by the remaining nigral cells and converted to dopamine. L-Dopa improves slowness, rigidity, akinesia, and gait, but does not usually improve speech, freezing, balance, and its effect on tremor are unpredictable. In addition to the existence of symptoms not responsive, and therefore presumably not of dopamine deficiency origin, the disease progresses and drug manipulations are unable to keep up. As more dopamine secreting cells die, the drug becomes less effective.

Long-term use of L-Dopa often leads to motor complications, which are not seen when other drugs are used in PD patients who have never been exposed to L-Dopa (Fox and Lang 2008). These include ► dyskinesias induced by the drug, as well as markedly variable responses to the drug with "on" periods, when patients have a good response to the drug, and either predictable or unpredictable "off" periods when the medicine stops producing benefit.

Other ways of enhancing dopamine transmission involve reducing dopamine breakdown or altering L-Dopa ► pharmacokinetics. The monoamine oxidase-b inhibitors (MAOb-I), ► selegiline and ► rasagaline, are both used as adjunctive agents to enhance the activity of dopamine. These drugs work both peripherally, in the bloodstream to block the degradation of L-Dopa and centrally, in the brain to reduce degradation of dopamine. In the brain, dopamine is primarily resorbed by the presynaptic neuron though the dopamine transporter, but about 10% is broken down in the synaptic cleft by monoamine oxidase b and catechol-o-methyltransferase. Blocking the degradation of dopamine in the synapse allows more dopamine to activate the dopamine receptors, thereby increasing the potency of the dopamine stimulation as well as its duration of action. Both drugs are therefore approved for the purpose of increasing "on" time in patients who suffer from clinical motor fluctuations in reponse to L-Dopa. Rasagaline is also used as a monotherapeutic drug, presumably acting in the same fashion, enhancing dopamine stimulation. Its benefits are less than those typically seen with dopamine agonist monotherapy, but its side effect profile in these patients is not much different than that of placebo.

The greatest interest in the MAO-b inhibitors lies in their possible disease "modifying" effect that is, slowing of

disease progression. There is suggestive data supporting this contention for rasagaline. The first large study to slow PD progression used selegiline, and while initially deemed a positive study, was reinterpreted in light of its mild, but statistically significant symptomatic effects. The rasagaline studies used a different research paradigm to avoid this confound (Olanow et al. 2009).

Although nonspecific MAO inhibitors hold the potential for a large number of drug and food interactions, all of these are due to MAO-a inhibition. At the doses approved for PD, the MAO-b inhibitors are free of MAO-a inhibition and are quite safe, free of tyramine interactions, and of interactions with selective serotonin reuptake inhibition (SSRI) antidepressants. However, there is a concern about an unexplained, potentially fatal interaction with meperidine.

In monotherapy, rasagaline has no significant behavioral effects. When used adjunctively with L-Dopa, all L-Dopa side effects are enhanced.

The catechol-o-methyltransferase inhibitors (► COMT-i) block the enzyme, catechol-o-methyltranserfase that, along with MAO-b, breaks down dopamine. There are two such drugs used in USA, ► tolcapone and ► entacapone, neither of which crosses the blood-brain barrier to an appreciable degree. These drugs therefore exert their effect on the pharmacokinetics of L-Dopa. By themselves, these drugs do not have any known effect on PD. Tolcapone may cause severe liver damage in a very small percentage of users. Entacopone is less effective, but is free of liver toxicity.

Since dopamine does not cross the blood-brain barrier, dopamine agonists have been used to compensate. These medications, ► bromocriptine, ► pramipexole, ropinerole, lisuride, ► rotigotine, ► cabergoline, and ► apomorphine, all directly stimulate D2 receptors (along with variable potencies at other dopamine receptors), and produce motor benefits comparable to L-Dopa at the early stages of the disease, but are less effective for the long-term. Unlike L-Dopa, these medications do not cause long-term motor side effects such as "wearing off," in which the benefit of L-Dopa declines before the next dose, unpredictable fluctuations, in which the L-Dopa doses last highly variable periods of time, or dyskinesias, which are involuntary movements, usually choreic in nature (Constantinescu et al. 2007; Jankovic and Stacy 2007). Unfortunately, these drugs produce more short-term side effects including hypotension, ► hallucinations, nausea, and generally need to be supplemented with L-Dopa within a few years. The ► dopamine agonists are often used as initial therapy to postpone the long-term side effects of L-Dopa, or may be added to L-Dopa as its benefits decline.

Anticholinergic drugs were the mainstay of drug therapy of PD until the development of L-Dopa. These drugs are helpful in reducing tremor and rigidity, but are thought to provide little benefit in slowness, or gait, two of the most functionally debilitating symptoms in PD. Additionally, these drugs have profound side effects that make them difficult to use, particularly in older people. These side effects are very common, and include dry mouth (which may be useful to reduce drooling), constipation, memory dysfunction, urinary retention, blurred vision, hallucinations. These drugs are primarily used in younger patients, who tolerate them better, particularly where tremors and drooling are problems.

► Amantadine was first reported in 1972 to ameliorate the motor symptoms of PD as a serendipitous observation when used to treat influenza in people with PD. The drug had been thought to work by increasing dopamine secretion or by blocking acetylcholine, but it is currently believed to work as an NMDA glutamate antagonist. It is helpful for all aspects of PD, including tremor, but is not as effective as dopamine agonists or L-Dopa. It has been increasingly used in recent years after it was shown to reduce L-Dopa induced dyskinesias in PD patients, without a reduction in the other drugs used to treat PD motor symptoms. Amantadine may induce psychotic symptoms, delirium, and mild anticholinergic side effects, as well as livedo reticularis (which has no negative consequences other than appearance) and pedal edema (Pahwa et al. 2006).

Although ► dementia is a common problem in PD, only one drug has been approved for its treatment (Burn et al. 2006). Most authorities believe that the three cholinesterase inhibitors probably work about equally well, but this is not based on clinical data. Since Parkinson's disease dementia (PDD) patients have a greater cholinergic deficit than Alzheimer's patients, it was assumed that the cholinesterase inhibitors might therefore work better than in Alzheimer's disease (AD). This has not been borne out by clinical observation. The mechanism of action of these drugs is presumed to be the same in PDD as in AD, blocking the degradation of acetylcholine. However, the benefits of ► rivastigmine in PDD are extremely limited, and most patients do not sustain sufficient benefits to justify the cost of the drug. ► Memantine, which is the only noncholinesterase inhibiting drug approved for treating dementia in AD, shares NMDA glutamate antagonism with amantadine, but it has not been shown to produce any motor benefit in PD. Rivastigmine is more helpful for concentration, apathy, and hallucinations than it for cognitive and memory problems (Burn et al. 2006).

No antipsychotic is approved for treating hallucinations and delusions in PD in USA, but ► clozapine, at extraordinarily low doses, is approved for this use in other countries based on two multi-center double blind placebo controlled trials (Parkinson study group 1999). In USA, ► quetiapine has been recommended as the drug of first choice by an American Academy of Neurology task force, despite the fact that no double blind trials, support its efficacy (Miyasaki et al. 2006). Clozapine is the task force's second line recommended drug.

No antidepressant has been approved for treatment of depression in PD, and none has been adequately tested to confirm benefit. Some high quality data published in 2009 indicates that depression in PD may be medication responsive, and that tricyclics may be more effective than ► selective serotonin reuptake inhibibitors (SSRI) (Menza et al. 2009). Although the SSRI's may produce tremor or parkinsonism, they have been well tolerated in PD.

Conflict of interests: JHF has received remuneration from the following companies in the past 12 months either for consultation, lectures, or research: Acadia Pharmaceuticals, Astra-Zeneca, Novartis, Glaxo, Ingelheim-Boehringer, Teva, Valeant, Cephalon, EMDSerono, Schwartz.

Novartis makes clozaril (clozapine)

Astra-Zeneca makes Seroquel (quetiapine)

Acadia is testing pimavanserin as an antipsychotic for PD

Cross-References

► Antipsychotic Drugs
► COMT Inhibitor
► Disease Modification
► Hallucinations
► Hallucinogens
► Medication-Induced Movement Disorders
► Neuroprotection

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Antipsychotic

Synonyms

Major tranquilizer; Neuroleptic

Definition

Drug that is effective against psychotic symptoms (e.g., treating schizophrenia).

Antipsychotic Drugs

► Classification of Psychoactive Drugs

Antipsychotic-Induced Movement Disorders

► Movement Disorders Induced by Medications

Antipsychotic Medication

Synonyms

Major tranquillizers; Neuroleptics

Definition

Antipsychotic medication refers to the use of a group of psychoactive drugs that is mainly used to treat patients

suffering from psychoses, most often ► schizophrenia but also mania and other delusional disorders. A wide range of antipsychotics has been developed. The first generation of antipsychotics was discovered in the 1950s. Most of the drugs in the second generation (often called atypical antipsychotics) have been developed more recently, although the first atypical antipsychotic, ► clozapine, was discovered in the 1950s. Both classes of medication block dopamine receptors in the brain and in many cases, they also act at a much wider range of receptor targets. Side effects vary greatly between different antipsychotics and include weight gain, movement disorders, and agranulocytosis (a loss of the white blood cells that help a person fight infection). The development of new antipsychotic medication and the relative efficacy of different ones is an important ongoing field of research. The most appropriate drug for an individual patient requires careful consideration.

Cross-References

► First-Generation Antipsychotics
► Schizophrenia
► Second-Generation Antipsychotics

Antipsychotic Medication: Future Prospects

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Synonyms

Ongoing and future development of antipsychotics (neuroleptics)

Definition

Antipsychotic medications are a group of psychoactive drugs used to treat psychosis, which is typified by ► schizophrenia. The currently available antipsychotic medications show some benefit to patients, but have considerable limitations in terms of efficacy and side effects. The development of new antipsychotic compounds with novel mechanisms of action is being pursued based on specific strategies and guided by various pathophysiologic hypotheses. This article focuses on novel goals and targets for therapeutic intervention and potential strategies for future development of antipsychotic medication.

Pharmacological Properties

Limitations of Currently Available Antipsychotic Medications

The introduction of newer ► second-generation antipsychotics (SGAs) represents an important advance in the pharmacologic treatment of schizophrenia since the advent of ► chlorpromazine, the prototypical ► first-generation antipsychotics (FGAs). However, current evidence suggests that the clinical benefits of SGAs in terms of efficacy are modest at best (Leucht et al. 2009), and the effect sizes on ► cognitive impairment are small. In the largest and longest effectiveness trial, the ► clinical antipsychotic trials of intervention effectiveness (► CATIE) study, no substantial advantage for the SGAs was demonstrated over the FGA for the treatment of negative and cognitive symptoms (Lieberman et al. 2005). Negative and cognitive symptom domains are recognized as a core feature of schizophrenia and play a greater role in poor functional outcome. Thus, it is obvious that there is a distinct need to identify and validate novel molecules that possess pharmacological profiles that better treat these symptom domains.

To date, the prototypical SGA ► clozapine remains the "gold standard" antipsychotic drug because of a lower liability for ► extrapyramidal motor side effects (EPS) and because it has proved superior to all other ► antipsychotic drugs in efficacy (Leucht et al. 2009), particularly in treatment-resistant schizophrenia. However, even with clozapine, a significant number of patients are unresponsive to treatment and it carries a risk of serious side effects such as agranulocytosis, weight gain, and metabolic abnormalities. Because individuals with schizophrenia have many risk factors that may predispose them to poor health and excess mortality, safety and tolerability of antipsychotic medications are an essential treatment concern. Furthermore, remission and recovery rates for schizophrenia by the treatment with current antipsychotic medications are discouragingly low. Thus, it is important to pursue the development of more tolerable and more effective antipsychotics than clozapine. To expedite the clinical development of such drugs, biological or surrogate markers of the illness and treatment effects using chemical technologies (e.g., ► PET imaging) must be identified and validated to enable more efficient and reliable proof of efficacy of novel compounds.

Challenges of Future Drug Discovery

A number of mechanisms of action of antipsychotics have been explored during the past 30 years. However, it is still unclear as to what pharmacological profile of

antipsychotic medication is necessary to show the highest efficacy and effectiveness without serious adverse effects in the treatment of schizophrenia and other psychosis. Moreover, there is still an ongoing debate as to whether drugs selective for single molecular target (i.e., "magic bullets") or drugs selectively nonselective for several molecular targets (i.e., "magic shotguns") will lead to new and more effective medications for psychosis (Agid et al. 2008; Roth et al. 2004).

All currently available antipsychotic medications target dopamine D_2 receptors, but one example of new multitarget strategies is the utility of combined dopamine D_2-like receptor antagonism and ▶ serotonin 5-HT_{1A} receptor agonism (Jones and McCreary 2008). It is suggested that the balance between D_2 antagonism and 5-HT_{1A} agonism may be critical in determining the efficacy of these compounds. In addition, further serotonergic strategies may be a key area of schizophrenia research such that combined activity at the D_2 receptor with ▶ selective serotonin reuptake inhibitor, and the use of 5-HT_{2C} receptor agonists, 5-HT_6 receptor antagonists, or 5-HT_7 receptor agonists may be of great interest in expanding treatment options (Jones and McCreary 2008).

Recent antipsychotic research has examined agents that have no direct effect on the dopamine system, although most of them have indirect effects on dopaminergic pathways. For example, with the emerging evidence for glutamatergic dysregulation in schizophrenia, a number of agents with direct or indirect activity on the ▶ glutamate system are being investigated, especially for their potential impact on cognitive and negative symptom domains (Miyamoto et al. 2005). Glutamate-based agents in various stages of development include agonists at the glycine allosteric site of the ▶ N-methyl-D-aspartate (NMDA) receptor, ▶ glycine transporter 1 inhibitors, ▶ Group II metabotropic glutamate receptor agonists, α-amino-3-hydroxy-5-methy-isoxazole-4-propionic acid (AMPA)/kainate receptor antagonists, and higher-potency ▶ ampakines. The putative antipsychotic action of these drugs has been studied as monotherapy and/or add-on treatment (Gray and Roth 2007).

It has also been suggested that the central cholinergic system is involved in the cognitive deficits observed in schizophrenia, and enhanced cholinergic activity may improve these deficits (Miyamoto et al. 2005). Currently available treatments which are potentially suitable for this purpose include ▶ acetylcholinesterase inhibitors (e.g., galantamine), partial ▶ muscarinic agonists (e.g., xanomeline), ▶ nicotinic agonists, and allosteric potentiators of nicotinic receptor function (Gray and Roth 2007). These potential ▶ cognitive enhancers may be better suited to particular stages of schizophrenia, perhaps showing efficacy in early or later stages.

In recent years, significant progress has been made on elucidating various susceptibility genes in schizophrenia, including ▶ dysbindin, neuregulin 1, catechol-O-methyltransferase (COMT), disrupted in schizophrenia 1 (DISC1), and others (Gray and Roth 2007). Many of these genes appear to be associated with the control of ▶ synaptic plasticity and glutamate transmission, especially NMDA receptor function. Research on these molecules will allow for rational drug development in which drugs are developed on the basis of targets derived from theories of pathogenesis of the disease. However, the conundrum of single-target versus multitarget agents will remain at the forefront of drug development until the etiology of the illness is fully elucidated. In the near future, optimal treatment will probably include different therapeutic agents, each uniquely targeting a specific dimension of schizophrenia (Agid et al. 2008). In other words, single-target agents will augment multitarget agents, and there is a possibility that novel biological agents will also be investigated (Nikam and Awasthi 2008).

Recently, a growing body of evidence has demonstrated that some SGAs may increase or preserve neurotrophic factor levels, ▶ neurogenesis, neuronal plasticity, mitochondrial biogenesis, cell energetic, and antioxidant defense enzymes (Lieberman et al. 2008). Moreover, specific SGAs can ameliorate the loss of gray matter in schizophrenic patients in the early stages. These neuroprotective properties of some SGAs have become more relevant in the light of the increasing acceptance by the field of a progressive pathophysiological process and possibly neurodegenerative process coincident with the onset of schizophrenia that may underlie the clinical deterioration. Ongoing research on the neuroprotective effects of antipsychotics may reflect another mechanism of action that antipsychotics can act through that is clinically relevant and should stimulate the search for new agents for psychosis with novel mechanisms beyond the monoaminergic systems (Lieberman et al. 2008).

New Preparations of Antipsychotic Medications

At present, antipsychotic medications are available as tablets, liquid concentrates, orally dissolving formulations, short-acting intramuscular (I.M.) preparations, or long-acting injection (LAI) preparations. Among them, several SGA LAI preparations have been and are being developed. By increasing the available treatment choices for clinicians and patients alike, new preparations such as drug-in adhesive transdermal patches and nasal spray are

a welcome development. Researchers must study these preparations beyond the usual registration package.

Moving Toward the Future Individualized Treatment

There is a great need for the development of novel methods to identify optimum individualized treatment plans. In particular, the efficacy and tolerability of antipsychotics could be directly influenced by genetic variations in ► cytochrome P450 (CYP) enzymes. Their activity may also be influenced by genetic alterations affecting the drug target molecule, such as monoaminergic receptors, neurotransmitter transporters, and enzymes. In the future, genetic tests for the pretreatment prediction of drug metabolic status, antipsychotic response, and drug-induced side effects such as EPS and weight gain are expected to bring enormous clinical benefits by helping to chose the medication, adjust therapeutic doses, and reduce adverse reactions (Arranz and de Leon 2007). Further development of genetic tests and ► pharmacogenetic research into genetically determined drug metabolic polymorphisms as well as ► pharmacogenomic strategies to the identification of novel factors influencing response would lead to a better understanding of the rational basis for the personalization of antipsychotic treatment. In addition, antipsychotic drugs may also be targeted to specific patient subgroups based on profiling and the identification of endophenotypes of schizophrenia. Clinical implementation of this practice may have a strong impact in reducing adverse effects and improving treatment adherence and efficacy (Arranz and de Leon 2007).

Conclusion

Future drug discovery approaches will have to be truly revolutionary, but there is a hope that we could obtain novel antipsychotic drugs with greater efficacy and improved safety profiles. These drugs, however, alone may not produce a complete cure. It is essential that all of the pharmacologic tools should always be used in combination with psychosocial and psychotherapeutic intervention to optimize overall ► quality of life and return patients to the best level of functioning.

Cross-References

► Ampakines
► Chlorpromazine
► Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study
► Cognitive Impairment
► Dysbindin
► Glycine Transporter 1
► Group II Metabotropic Glutamate Receptor
► NMDA Receptor

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Antipsychotic Drugs

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Synonyms

Neuroleptics; Major tranquilizer

Definition

Antipsychotics are drugs used to treat all kinds of psychoses, although the best evidence for their clinical effects stems from studies in the treatment of schizophrenia.

Pharmacological Properties

History

Antipsychotics, as we use the term now, were introduced into clinical psychiatry in the 1950s. They were originally

called neuroleptics, a term still broadly used in medical jargon which is derived from Greek and loosely translated as "grasping the nerve." This reflects the fact that originally the sedative effects of these drugs were in the foreground of clinical interest. This was also the origin of the American term "major tranquilizers."

Over the last two decades antipsychotics has become the preferred term for this class of drugs based on their main indications and clinical effect. While it was originally felt that antipsychotic efficacy was inextricably linked to ▶ extrapyramidal motor side-effects (EPS), the introduction of ▶ clozapine in the early 1970s demonstrated that this was not the case, as this drug proved to be an excellent antipsychotic with only a minimal risk to induce EPS. This also triggered a new classification of antipsychotics, which had so far been differentiated either by their chemical structure (e.g., ▶ phenothiazines, ▶ thioxanthenes, and ▶ butyrophenones) or their affinity to the dopamine D2 receptor (high and low potency neuroleptics). The fact that clozapine was found to be an effective antipsychotic without inducing motor side-effects was considered an "anomaly," and the term "atypical" was coined to describe clozapine and to differentiate it from the older "typical" drugs with their considerable potential for such adverse events. Consequently, antipsychotics which were developed following clozapine's introduction and which shared at least some of its characteristics were also subsumed under the category "▶ atypical antipsychotics." It soon became clear that "atypical antipsychotics" represent a rather inhomogeneous group, both from preclinical and clinical pharmacological perspectives. As the receptor pharmacology of these drugs is complex and provides no solid basis for differentiation, the field agreed upon classifying these drugs based upon a less contentious base, namely a more historical dimension. Thereby, all drugs developed until the advent of clozapine were called ▶ first-generation antipsychotics (or sometimes "classical" or "traditional") while the drugs that were introduced after clozapine and shared its low risk for EPS are now called ▶ second-generation antipsychotics. We are now on the threshold of a ▶ third-generation of antipsychotics, initiated with the registration of ▶ aripiprazole, the first licensed antipsychotic which is not a D2 antagonist.

Mechanisms of Action

It took about 10 years after the clinical efficacy of these drugs had been established until it was realized that antipsychotics block ▶ dopamine receptors. This finding can be seen as the cornerstone of the dopamine hypothesis of schizophrenia. More than adecade later, Seeman et al. (1976) published their classic paper on the correlation between D2 dopamine receptor affinity and clinically effective doses of antipsychotics, demonstrating that drugs with high receptor affinity required lower doses than drugs with lower affinities. All currently licensed antipsychotics with the exception of aripiprazole, a partial D2 agonist, block postsynaptic dopamine D2 receptors. The fact that most of these drugs also influence other receptor systems has given rise to a number of alternative attempts to achieve antipsychotic effects. The most prominent targets were various subtypes of the serotonin receptor (e.g., $5HT_{2A}$, $5HT_{1A}$) and lately the glutamatergic system, including both ionotropic and ▶ metabotropic receptors (Miyamoto et al. 2003).

Countless clinical and preclinical experiments link the effects of antipsychotics to the dopaminergic system. In very general terms, the acute administration of antipsychotics leads to an increased firing rate and neurotransmitter turnover in dopaminergic neurons while these effects are reversed after chronic administration (Grace 1992). In this respect older drugs, such as ▶ haloperidol, are different from newer ones such as clozapine insofar as haloperidol demonstrates these characteristics both in neurons originating in the substantia nigra (A9 dopaminergic neurons) as well as in those which project from the ventral tegmentum (A10 neurons) while clozapine only blocks A10 neurons. This has been replicated many times using different electrophysiological, neurochemical, and imaging techniques and is considered the reason why clozapine exerts antipsychotic effects without affecting the motor system (Miyamoto et al. 2003).

Clinically, the introduction of single photon emission tomography (▶ SPECT) and positron emission tomography (▶ PET) have provided the most relevant neurobiological leads into the effects of antipsychotics in humans. All available antipsychotics bind to striatal (and possibly extrastriatal) dopamine receptors in varying degrees. A dose–response relationship between human D2 receptor affinity and clinical profile is very likely, albeit it is challenged by the findings that the highly effective antipsychotic clozapine and also ▶ quetiapine only loosely bind to this receptor (Stone et al. 2009).

In summary, all evidence taken together clearly points to a disruption of dopaminergic function in schizophrenia patients and strongly suggests that a restoration of balance in this system contributes to the therapeutic efficacy of antipsychotics.

As outlined earlier, other receptor systems have also been investigated in this context. As clozapine has high affinity to a number of other neurotransmitter receptors (including ▶ serotonin, histamine, and ▶ noradrenaline),

these systems have been explored regarding their potential contribution to the drug's benefit–risk profile. The hypothesis most vigorously explored was the one that linked its serotonin ($5HT_2$) antagonist properties to the clinical profile. In conjunction with previous preclinical research which had found that serotonin antagonists can counteract extrapyramidal motor side-effects of neuroleptics, Meltzer et al. (1989) formulated the hypothesis that $5HT_2$ antagonism which is proportionally larger than D2 antagonism is responsible for the advantages that clozapine and all other drugs sharing this profile have over the older drugs in terms of lower EPS risk. In addition, they and other authors feel that these pharmacological characteristics also contribute to enhanced clinical efficacy, especially with regard to negative symptoms and cognitive impairment. Although an intriguing and well thought through hypothesis, it is somewhat challenged by the pure dopamine antagonist ► amisulpride which has no direct effects on the serotonergic systems, yet shares a lot of the clinical effects with $5HT_2$/D2 antagonists (McKeage and Plosker 2004).

The glutamate system is intricately linked with dopaminergic neurotransmission throughout the central nervous system (CNS), a topic reviewed by Carlsson et al. (2001). It functions as a modulator of dopaminergic neurotransmission. This has led to a number of clinical experiments aiming at investigating drugs that do not directly act via the dopaminergic systems. Both the glycine sites of ► NMDA receptors and ► metabotropic glutamatergic receptors have been the targets of such investigations. Clinical studies are encouraging but have not yet led to licensed medications (Miyamoto et al. 2005).

Other neurotransmitter systems have mostly been considered in the context of drug safety. Many antipsychotics which block noradrenergic α_1 receptors have been found to affect blood pressure. Antihistamine effects have been related to sedation and weight gain, just to provide a few examples.

Animal Models

There is no reliable and valid animal model for schizophrenia. All available models are either derived from the dopamine hypothesis of schizophrenia or from the actions that effective antipsychotics induce in laboratory animals. Many of them are related to non-therapeutic effects of antipsychotics such as those which affect the motor system. At the most, we may optimistically assume that these models are in some approximation to the clinical syndrome of the disorder. Nevertheless, animal models, imperfect as they may be, are still a cornerstone of antipsychotic drug development (Lipska and Weinberger 2003). Conditioned ► active avoidance is a classic among these models. All antipsychotics block conditioned avoidance and this test is therefore one of the early screening experiments in the development of potential antipsychotics.

Another set of experiments involve the various motor effects of this class of drugs. Spontaneous locomotor activity as well as pharmacologically enhanced psychomotor activity is usually decreased after the administration of antipsychotic drugs. First- and second-generation antipsychotics are nicely differentiated by the dose needed to induce catalepsy, which is a good indicator for clinical EPS risk.

More recent models which can also be performed in humans include various variants of sensory motor gating studies. One example for these is ► prepulse inhibition (PPI), which is based on the finding that a weak prepulse reduces the startle reflex to a given, usually acoustic, stimulus. It is seen as part of the information processing capabilities of the CNS. PPI can be disrupted by both dopamine agonists and NMDA antagonists, thereby providing a model within the dopamine/glutamate hypothesis of schizophrenia. As antipsychotics restore PPI in animals in which it has been disrupted, such sensory motor gating models are also seen as indicative of potential antipsychotic effects.

► Pharmacokinetics

Antipsychotics are generally well absorbed and most of them are metabolized by hepatic ► cytochrome P450 isoenzymes. They are generally highly lipophilic and therefore cross the ► blood-brain barrier well and accumulate in fatty tissues. The benzamides ► sulpiride and ► amisulpride are an exception to these rules.

The elimination half-lives of antipsychotics are distributed over a wide range between a few hours (► quetiapine) and days (aripiprazole). Steady-state levels differ accordingly, but as a rule of thumb once-daily dosing is possible. It is important to note that elimination from the brain and the drugs' target organs has been shown to be much slower than from plasma (Gruender 2007).

Given that all drugs with the exception of the benzamides are metabolized via cytochrome isoenzymes in the liver, the potential for interactions with other drugs which compete for these enzymes needs to be considered. Pharmacodynamic interactions are to be expected when antipsychotics are coadministered with drugs that target the same receptor systems, either centrally or peripherally. These include drugs with antihistamine and antiadrenergic effects which can lead to a potentiation of sedation, weight gain, or hypotensive adverse events.

Efficacy

Next to antipsychotic effects, i.e., reducing ▶ delusions and ▶ hallucinations, most antipsychotics also have sedative properties. Furthermore, they have been shown to reduce negative symptoms, enhance cognitive functions, ameliorate affective symptoms (both manic and depressive) in patients suffering from schizophrenia and, most likely as a secondary effect, improve the quality of life and psychosocial reintegration (Miyamoto et al. 2003). Although most research with antipsychotics has been performed in schizophrenia patients, the therapeutic actions of these drugs extend beyond this diagnosis. Indications include mania, psychotic depression, ▶ schizoaffective disorder, ▶ bipolar depression, psychotic symptoms in the context of organic disorders from delirium to ▶ dementia, personality disorders, and treatment-resistant obsessive compulsive disorder, just to list the better researched disorders. As most of these are be covered in other entries, only general treatment principles in schizophrenia patients are briefly reviewed.

Recent evidence indicates that the onset of antipsychotic action in schizophrenia can be seen within days of commencing treatment (Agid et al. 2006), although it may take up to 6 months to achieve full remission of symptoms. Close to two thirds of first-episode schizophrenia patients reach symptom remission within this time if the duration of previously untreated psychosis is not too long. Response patterns become less favorable with increasing chronicity of the disorder. Next to acute symptom control and stabilization, antipsychotics also have powerful relapse-preventing properties (Kane 2007). Regularly taking medication over long periods of time protects about 80% of patients from a psychotic relapse. Having said that, compliance is one of the major challenges of the long-term management of schizophrenia (Fleischhacker et al. 2003). To aid uninterrupted dosing, depot antipsychotics that are injected at regular, long intervals have been developed. So far ▶ risperidone and ▶ olanzapine are the only second-generation antipsychotics available for this method of administration (Fleischhacker 2009).

Clozapine plays a special role in the management of schizophrenia. On the one hand, it is the drug of choice in patients with a treatment-resistant course of the disorder; on the other hand, it has a 1% risk to induce agranulocytosis which makes it a third line drug despite its excellent efficacy (Tandon et al. 2008).

Safety/Tolerability

For first-generation antipsychotics, sedation as well as acute and tardive extrapyramidal motor side effects represented the biggest safety obstacles that also translated into tolerability and compliance problems. Next to that, these drugs, depending on their receptor profiles, induced a number of other adverse events including anticholinergic side effects, orthostatic hypotension, weight gain, hormonal aberrations including sexual disturbances, dermatologic problems including acne-like manifestations and photosensitivity, disturbances of gastrointestinal motility, hematological side effects, cardiac arrhythmias, seizures, and the ▶ neuroleptic malignant syndrome, just to name the clinically most relevant. Apart from potentially life-threatening adverse events such as clozapine-induced agranulocytosis, tachyarrhythmia, and the neuroleptic malignant syndrome, many of these side effects constitute problems affecting subjective tolerability rather than objective health risks. Prevalence rates differ considerably between drugs, and the incidence of these side effects is difficult to predict on an individual level. Therefore, patients treated with antipsychotics have to be well informed and monitored regularly.

Second-generation antipsychotics as a group have a considerably lesser risk to induce EPS than the older drugs. This applies to both frequency and severity of acute and chronic motor side effects. Some of these drugs, most notably clozapine and olanzapine, have a substantial propensity to induce weight gain and metabolic disturbances such as hyperlipidemia and reduced insulin sensitivity. Apart from these concerns the newer drugs appear to be tolerated appreciably better than traditional neuroleptics. Clearly, despite this, the same recommendations regarding patient information and monitoring must be followed (Miyamoto et al. 2003).

Conclusion

In summary, antipsychotics represent a crucial component of the pharmacotherapeutic options in psychiatry. A large array of effective drugs is available. Antipsychotics are employed over a broad range of indications with a very favorable benefit–risk profile. It is hoped that their main therapeutic limitations, namely efficacy beyond psychotic symptoms, will be overcome with the exploration of pharmacologic mechanisms which extend beyond the dopamine system.

Cross-References

▶ Butyrophenones
▶ Clozapine
▶ Extrapyramidal Motor Side Effects
▶ First-Generation Antipsychotics
▶ Neuroleptic Malignant Syndrome (NMS)
▶ Phenothiazines

► Second-Generation Antipsychotics
► Third-Generation Antipsychotics
► Thioxanthenes

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Antisaccade Task

Definition

An important variant of the prosaccade task, in which participants are required to saccade to the mirror image location of a sudden onset target. Healthy participants typically make errors (prosaccades toward the target) on around 20% of trials. This figure is increased in patients with lesions to the dorsolateral prefrontal cortex and patients with schizophrenia. The task indexes cognitive processes associated with goal activation and inhibitory control.

Antisense DNA

► Antisense Oligodesoxynucleotides
► Antisense Oligonucleotides

Antisense Oligodesoxynucleotides

Synonyms

Antisense DNA; Antisense oligonucleotides

Definition

Antisense oligodesoxynucleotides are relatively short, single-stranded synthetic DNA molecules (between 13 and 25 nucleotides) that are complementary to a chosen mRNA causing translational arrest. Chemical modifications improve their cellular uptake and intracellular stability. Functionally, they are antisense oligonucleotides.

Also, ribozymes and DNA enzymes have antisense properties (Fig. 1D). Ribozymes are RNA enzymes that are catalytically active oligonucleotides that bind to and cleave their target mRNA. These RNA processing capabilities are of potential interest for their use as antisense agents. A number of ribozymes have been characterized, including the most widely studied form called the hammerhead ribozyme.

Cross-References

► Chemical Modifications
► Ribozymes

Antisense Oligonucleotides

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Synonyms

Antisense DNA; Antisense oligodesoxynucleotides; Antisense RNA; Ribozymes; RNA interference; siRNA; Short interfering RNA

Definition

► Antisense oligonucleotides are relatively short, single-stranded DNA (► antisense oligodesoxynucleotides) or single- (► antisense RNA) or double-stranded (► short interfering RNA, ► siRNA) RNA molecules (between 13 and 25 nucleotides or *mer* from Greek *meros*, "part") which are complementary to a chosen (coding or non-coding) mRNA. The potential of oligonucleotides to act as antisense agents that inhibit viral replication in vitro was discovered by Zamecnik and Stephenson (1978). Both in vitro and in vivo, their common mechanism of action is the complementary binding to a specific target mRNA via Watson–Crick base-pair hybridization; thus inhibiting translation of mRNA and blocking the transfer of the genetic information from DNA to protein; thereby reducing the availability of the gene product within a given tissue. Synthetic, antisense oligonucleotides can be potentially used as therapeutic agents for selective gene silencing, and are currently used as tools to study gene functions in preclinical research including psychopharmacology (antisense technology).

Principles and Role in Psychopharmacology

Modes of Action of Antisense Oligonucleotides

There are several main intracellular mechanisms of actions of antisense oligonucleotides to prevent the expression and translation of the target protein (Dias and Stein 2002, Fig. 1a–e). The first mechanism is based on the disruption of protein translation of target mRNA by base-pairing of single-stranded antisense oligodesoxynucleotides (► antisense DNA) to the respective complementary mRNA strand and physically/sterically obstructing the translation machinery, prevention of ribosomal complex formation, and translation of mRNA into the gene product (translational arrest) (Fig. 1b). The second main mechanism is also based on the complementary binding between the antisense oligodesoxynucleotides (antisense DNA) and the target mRNA. This DNA/RNA hybrid can then be degraded by the enzyme RNase H, a mechanism which significantly enhances the efficacy of antisense potency (Fig. 1c). The RNase endonuclease specifically cleaves RNA in DNA/RNA heteroduplexes. Short-term effects of antisense oligodesoxynucleotides inhibiting neuronal responsiveness without altering gene protein content and availability have been described in neuroendocrine cells (Fig. 1d) (Neumann and Pittman 1998).

Also, ► ribozymes have antisense-like properties (Fig. 1d); those RNA molecules bind to and cleave their target mRNA.

A revolutionary development in antisense research is the finding that 20–25 nucleotide double-stranded RNAs, called siRNA, can efficiently block gene expression (Figs. 1e and 2) via the ► RNA interference (► RNAi) pathways. Any gene of interest with known sequence can be targeted by siRNAs that match the mRNA sequence.

Cellular Uptake of Antisense Oligonucleotides

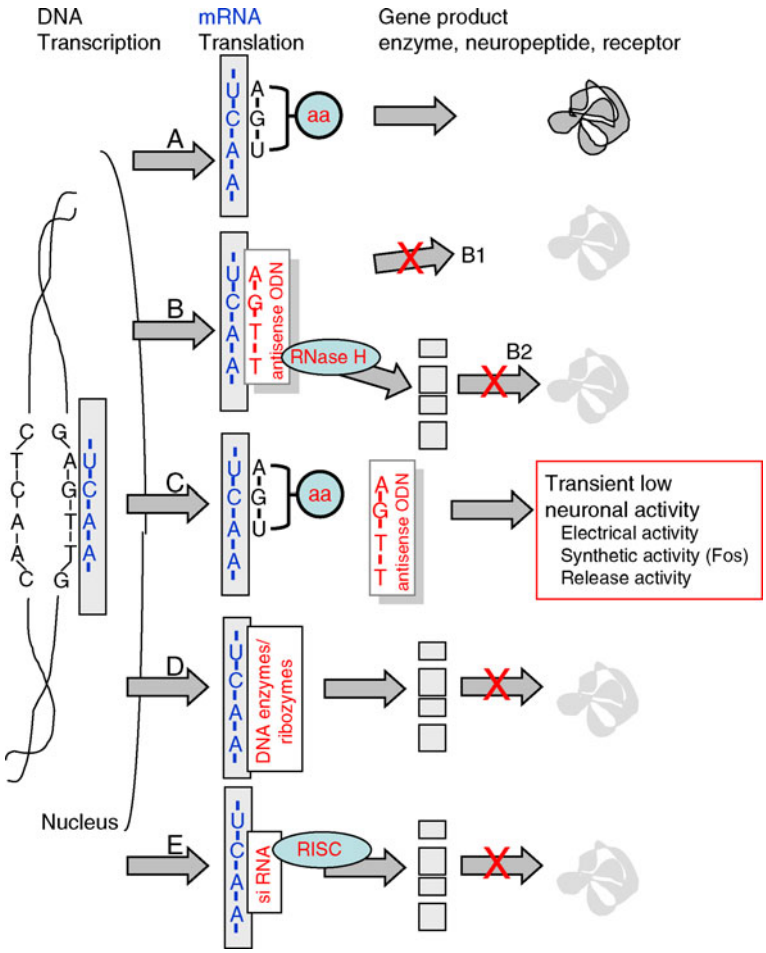
A main problem for antisense technologies is the limitation of cellular uptake of these nucleic acids due to their hydrophilic nature. This is true for negatively-charged siRNA, or chemically modified antisense oligodesoxynucleotides with uncharged backbones such as methylphosphonates, phosphorothioates, or morpholino-derivatives.

For improved efficacy of antisense uptake, agents that enhance transmembrane permeation, i.e., cell-penetrating peptides (CPP) and drugs that target specific receptors, i.e., cell-targeting ligands (CTL) are discussed (Juliano et al. 2008). Also, antisense oligonucleotides tend to localize in lysosomes and endosomes where their antisense properties are poor. The use of vectors (liposomes, i.e., vesicular colloid vesicles) increases stability and cellular internalization. There are commercially available vectors (so-called eufectins), which are used in basic research.

In vivo, the cellular uptake of antisense oligonucleotides into the target tissue is further impaired by several biological barriers (capillary endothelium, extracellular matrix), degradation by serum and tissue nucleases (liver, spleen), and rapid excretion via the kidney; but if oligonucleotides are bound to plasma proteins, ultrafiltration is retarded (Juliano et al. 2008). In order to target the brain tissue, the blood–brain barrier prevents their uptake as polyanionic molecules, and antisense targeting the central nervous system (CNS) requires direct infusion.

In vivo Delivery of Antisense Oligonucleotides

If brain tissue is targeted, antisense oligonucleotides need to be directly infused either into the ventricular system or the target region to circumvent the ► blood–brain barrier; and they are relatively easily taken up by neurons. Prolonged action and slow delivery within the target region can be achieved by use of biotechnical modifications or polymer microparticle encapsulation with high biocompatibility (Choleris et al. 2007).

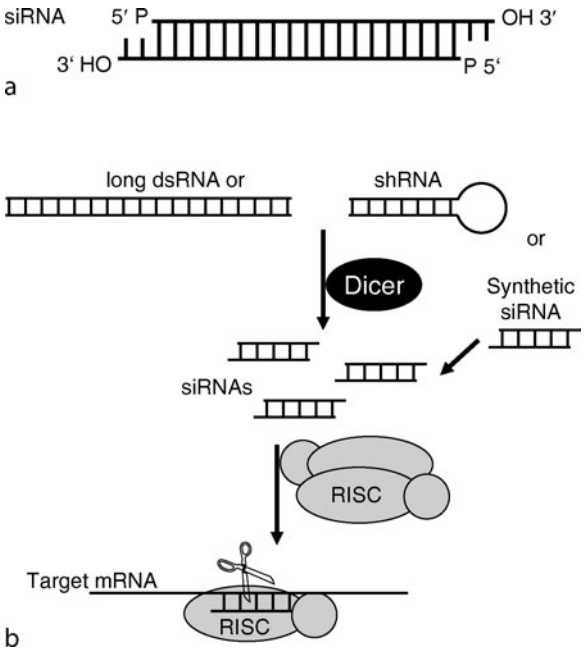


Antisense Oligonucleotides. Fig. 1. Mechanisms of action of antisense oligonucleotides. (**A**) Regular transcription of a gene and translation of mRNA into the gene product. (**B**) Antisense oligonucleotides bind to the complementary strand of gene target mRNA and (B1), sterically block the translation process or (B2), the mRNA/oligonucleotide complex activates an RNase H cleaving the mRNA and preventing translation. (**C**) Short-term effects of antisense oligonucleotides on neuronal responsiveness via unknown mechanisms. (**D**) DNA and RNA enzymes (ribozymes) result in cleavage of mRNA. (**E**) siRNA activate intracellular mechanisms resulting in mRNA cleavage and translational arrest via the RNA interference (RNAi) pathway (see Fig. 2).

The most common strategy for siRNA in vivo delivery is to construct expression vectors driven by a constitutively active RNA polymerase III (Pol III) promoter (e.g., the U6 promoter), to drive transcription of small hairpin RNA (shRNA). shRNA are sequences of RNA that make tight hairpin turns upon intramolecular Watson–Crick base-pairing (Fig. 2b), with perfect duplex RNA of 18–25 nucleotides in length. Cellular enzymes, most likely involving Dicer, process shRNA into siRNA molecules that are capable of performing gene silencing via the RNAi pathway. Although plasmid vectors are effective at delivering shRNA and consequently, siRNA to cultured cells and for the generation of transgenic plants or mice, there are limitations for their use, e.g., in somatic cells of adult brain tissue. To overcome these limitations, viral vectors for the delivery of siRNA have been developed, including lentiviral vectors derived from human immunodeficiency virus-1 (HIV-1) and adenoviral and adeno-associated viral vectors that are used to deliver siRNA into selected brain regions of rodents (Kühn et al. 2007).

Chemical Modifications of Antisense Oligonucleotides

Antisense oligonucleotides are rapidly degenerated by intracellular enzymatic activity. In order to increase efficiency, the cellular uptake and intracellular stability can be



Antisense Oligonucleotides. Fig. 2. Specific knockdown of a target mRNA by siRNA via the RNAi pathway. (**a**) Molecular hallmarks of an siRNA molecule are 18- to 23-nucleotide duplexed RNA region with 2-nt unphosphorylated 3′ overhangs and 5′ phosphorylated ends. (**b**) Mechanism of inhibition of gene expression by siRNA. Long siRNA or shRNA are cleaved by the RNase III family member Dicer to produce siRNA molecules. Alternatively, siRNA can be chemically synthesized and transfected into cells. These siRNAs are then unwound by RISC and incorporated as single-stranded antisense RNA to guide RISC to mRNA transcripts of complementary sequence. This leads to selective endonucleolytic cleavage of the matching target mRNA with subsequent elimination by further cellular RNases.

improved by ► chemical modifications of antisense oligonucleotides (Dias and Stein 2002). The most common chemical modifications employed are replacing an oxygen group of the phosphate-diester backbone with either a methyl group (methyl phosphonate oligonucleotide) or a sulfur group (phosphorothioate oligonucleotide) which have been introduced into clinical therapeutic trials. Increased specificity and efficacy of phosphorothioates are achieved with chimeric oligonucleotides in which the RNase H-competent segment (the phosphorothioate moiety) is bounded on both termini by a high-affinity region of modified RNA. Other chemical modifications include 2′-OH modifications, locked nucleic acids, peptide nucleic acids, and morpholino compounds or hexitol nucleic acids. Although high RNA affinity and high stability have been reported, they do not support RNase H activation. Nevertheless, they can exert their antisense activity via translational arrest or modulation of ► alternative splicing.

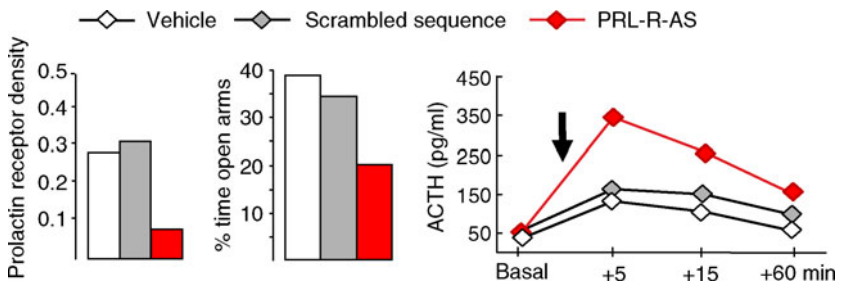
Antisense Oligonucleotides in Psychopharmacology

Antisense oligonucleotide technologies including oligodeoxynucleotides and siRNA are used in psychopharmacology to sequence-specifically, transiently, and locally downregulate the expression of target genes (neuropeptides and their receptors, neurotransmitter receptor subtypes and subunits, steroid receptors, neuronal enzymes, transcription factors), identified by microarray and proteomic approaches or by human genetic studies in vivo in addition or alternatively to established pharmacological means (selective ► agonists and ► antagonists, generation of knockout mice) (Hoyer et al. 2006; Landgraf et al. 1997; McCarthy 1998) for detailed methodological description (Fendt et al. 2008).

Functional consequences of antisense-induced downregulation of neuronal gene products in the brain can be monitored in a behavioral, neuroendocrine, or neuronal context. Antisense oligonucleotides need to be directly infused into the brain ventricles or into a selected brain target region over several days using an osmotic minipump or repeated infusions. They are relatively easily taken up by neurons, have a relatively high stability in neurons and in CSF – likely due to negligible cell proliferation within the brain and lack of exo- and endonucleases within the CSF (McCarthy 1998). Nevertheless, in order to increase central efficiency, mainly phosphodiester and phosphorothioated antisense oligonucleotides are used in psychopharmacology, but unspecific effects were repeatedly described making respective controls essential.

Both acute effects on neuronal functions after single infusion as well as long-term effects after repeated or chronic administration have been described. Often, short-term, antisense-induced blockade of neuronal activation without altering the availability of the gene product (Figs. 1 and 2) is likely to contribute to the observed behavioral, neuroendocrine, and neuronal effects of antisense oligonucleotides, especially if neuropeptides are targeted and stored in rather large amounts (Neumann and Pittman 1998).

Various neuropeptides and their receptors have been targeted using antisense oligonucleotides in the absence of highly selective receptor antagonists (Hoyer et al. 2006; Landgraf et al. 1997; McCarthy 1998), including the receptors for neuropeptide Y_1, corticotropin-releasing hormone (CRH), oxytocin and its receptor, vasopressin



Antisense Oligonucleotides. Fig. 3. Antisense oligodesoxynucleotides targeting the brain prolactin receptor (PRL-R-AS, icv, 6 days) reduced PRL-R density in the choroid plexus, increased anxiety-related behavior on the plus-maze, and elevated the acute stress-induced rise in plasma ACTH in virgin rats. (Data from Torner et al. 2001.)

and its V1a receptor, or the long form of prolactin receptors (Fig. 3).

Antisense oligonucleotides have also been used to target the expression of other neurotransmitter and steroid receptors including the receptors for 5-HT_{2A}, dopamine (D_2), progesterone, as well as NMDA receptor subunits and metabotropic glutamate receptor subtypes. Also, immediate early genes (c-fos, c-jun) and enzymes essential for neurotransmitter synthesis (GABA, 5-HT) have been successfully targeted in order to reveal local effects and behavioral and other functional consequences.

Essential Controls for Antisense Oligonucleotides

To exclude sequence-independent, unspecific effects of mostly chemically modified antisense oligonucleotides in vivo and in vitro, appropriate control groups are essential, i.e., the use of oligonucleotides with identical chemical modification and length which do not match a particular gene. Possible controls include a sense-strand sequence from the same site of mRNA, a scrambled sequence of the nucleotides used in the antisense oligonucleotides in random order, a nonsense oligonucleotide of same length but consisting of a different nucleotide composition without complementarity to any known mRNA sequence.

siRNA in Psychopharmacology

Among the earliest studies of siRNA in the brain were the attempts to perform icv infusion of synthetic siRNA using osmotic minipumps in rodents and concomitant behavioral analysis (Hoyer et al. 2006). To establish this strategy, enhanced green fluorescent protein overexpressed in a transgenic mouse line was successfully targeted in several brain regions. Also, targeting the dopamine transporter (DAT) resulted in reduced DAT mRNA and protein levels in substantia nigra, ventral tegmental areas (VTAs), and nucleus accumbens (Hoyer et al. 2006) accompanied by behavioral changes. Additional proof of concept for siRNA in rodent models of neuropsychiatric disease was provided by siRNA-induced reduction in serotonin transporter (SERT) mRNA in the raphe nucleus after 2 weeks of icv siRNA infusion with antidepressant-like behavioral consequences.

In addition, targeting the ► metabotropic glutamate receptor subtype 7 (mGluR7) by selective siRNA resulted in robust emotional and stress-related changes despite limited local mRNA knockdown (25%) (Fendt et al. 2008).

The use of viral vectors for RNAi in the mammalian brain is particularly suited for local gene knockdown even in small brain nuclei (Hoyer et al. 2006).

Advantages and Limitations of siRNA Procedures

The major advantages of siRNA over classical antisense oligonucleotides and ribozymes appear to be threefold (Zamecnik and Stephenson 1978): siRNA is generally more potent, efficient, and selective because it utilizes natural and efficient cellular machinery, i.e., the RNAi pathway providing assistance at multiple steps for the actions of siRNA, while antisense oligonucleotides and ribozymes hybridize to their targets without any assistance (Dias and Stein 2002). siRNA approaches always result in efficient endonucleolytic cleavage and subsequent elimination of the target mRNA, whereas antisense oligonucleotides not recognized by RNase H result in translational block only via steric hindrance (Neumann and Pittman 1998). Antisense oligonucleotides require relatively high concentrations to target their matching mRNA because at least one oligonucleotide per target RNA is required for

translational blockade or RNase H degradation resulting in toxic side effects. In contrast, one guide strand of siRNA incorporated in RISC (RNA-induced silencing complex) can sequentially bind to and eliminate several mRNA transcripts (multiple turnover).

Limitations of siRNA approaches include (Zamecnik and Stephenson 1978) their capacity to induce cellular virus defense mechanisms, mainly interferon gene induction and cellular arrest and (Dias and Stein 2002) possible unspecific off-target effects on closely related sequences making careful design of the siRNA sequence and use of different siRNA molecules targeting the same mRNA transcript essential.

Cross-References

► Agonist
► Antagonist

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Antisense RNA

Definition

Antisense RNA is naturally occurring single-stranded RNA with properties of antisense oligonucleotides that is complementary to an mRNA strand regulating gene expression machinery of the cell as found, for example, in bacterial plasmids. Transcription of longer noncoding antisense RNAs is a common phenomenon in the mammalian transcriptome including within the brain. No general function of these noncoding antisense RNAs has been elucidated. In contrast to antisense oligodesoxynucleotides, antisense RNA still lacks effective design, biological activity, and efficient route of administration. The effects and mechanisms of antisense RNA should be well separated from those of small interfering RNA (siRNA) and RNA interference (RNAi).

Cross-References

► Antisense Oligonucleotides
► RNA Interference (RNAi)
► Small Interfering RNA (siRNA)

Anxiety

Definition

Anxiety is an emotion shared by all mammals when challenged with dangerous threatening situations at risk for their physical or intellectual integrity. In this case, anxiety is an adaptive response and therefore shaped along the ages by the evolution. Anxiety disorders occurs as a pathological condition, involving unwanted reactions (behavioral and neurovegetative) that are either extreme or occur to inappropriate eliciting stimuli or situations.

Cross-References

► Defensive Behavior: Fear
► Emotional State

Anxiety: Animal Models

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Synonyms

Animal tests of anxiety; Experimental models of anxiety

Definition

Animal models of anxiety refer to experimental preparations developed for one species, generally rodents, with the purpose of studying different facets (e.g., etiology, symptomatology, physiopathological basis, and treatment) of human anxiety. In most of the existing models, anxiety is inferred from defensive responses to artificial (e.g., electric shocks) or ecological (e.g., loud noises and predators) threatening stimuli. Both normal subjects and selected animals (e.g., strain lines resulting from selective breeding, transgenic, knockout animals, and animals with brain lesions) have been used for this purpose.

Current Concepts and State of Knowledge

Anxiety has been defined as an emotional state aroused by the perception of threat, which is subjectively experienced as unpleasant. In its full expression, behavioral, autonomic/endocrine, affective, and cognitive/perceptual changes are manifested. Although usually adaptive, leading to harm avoidance, anxiety may turn out to be disruptive, giving rise to different pathologies. In modern psychiatric classifications, such as the Diagnostic and Statistical Manual, 4th edition, revised (DSM-IV-RT) of the American Psychiatric Association, anxiety is considered pathological when excessive, disproportional to the eliciting event, causing significant distress, disrupting interpersonal relationships, and impairing social and occupational functioning. According to the symptomatology and time course of development, anxiety disorders are classified into different nosological categories, such as ► generalized anxiety disorder (GAD) and ► panic disorder (PD).

The first question one should face while using animal models is that none of the existing models is capable of modeling all aspects of human anxiety. Accordingly, while behavioral and neurovegetative features of this emotion can be successfully assessed in animals, its cognitive/perceptual aspect is invariably left apart, given the vast differences in cognitive abilities between humans and laboratory animals.

After acknowledging this limitation, a subsequent question should be formulated: what makes possible to relate animal defensive behavior to human anxiety? The most accepted answer is phylogenetic continuity as advocated in the theory of evolution.

Charles Darwin himself laid the ground for this line of thought in his book "The Expression of Emotions in Man and Animals" by proposing that behavioral characteristics, no less than physical, would be acquired as a result of natural selection. This view justifies the use of experimental animals to study the neurobiology of psychological functions. Since several environmental constraints are similar across species, many adaptations are species-general, among which stand the basic emotions. Although emotional expression varies from one species to another, functional behavioral classes, such as escape and avoidance from danger or approach to sources of food, remain the same and constitute the basis for the classification of basic emotions (Panksepp 1998). No wonder that the neural substrate of such emotions is conserved along biological evolution. On this basis, Panksepp has proposed that basic emotions are represented by inborn neural networks that coordinate behavioral strategies allowing animals to deal with enduring environmental (including social) challenges.

In this context, anxiety and the related emotional states of fear and panic are rooted in defensive reactions displayed in situations of threat to the physical integrity or survival of the organism. Consequently, anxiety disorders may be viewed as pathologies of defense.

Defensive Reactions in Animal Models of Anxiety

Existing animal models of anxiety may differ in many aspects. For instance, sources of danger that evoke defensive reactions may be manifold, including predators, environmental stimuli or situations, such as height, illumination, painful stimuli, novel places or objects, and confrontation or competition with animals from the same species. To deal with these challenges, animals use defensive strategies such as escape, immobilization, defensive attack, and submission (Blanchard et al. 2008). In the experimental setting, the expression of one particular strategy will be driven by several factors, such as the characteristics of the environment, distance from the threatening stimulus and previous experience with the stimulus and/or environment.

To evaluate to which extent a given response in the animal model is related to the aspect of human anxiety intended to be modeled (generally symptoms of anxiety), three criteria of validation (► Animal Models for Psychiatric States) have been commonly used: analogy or ► face validity, predictability of drug response, and homology or theoretical ► construct validity. As pointed out by Joel (2006), "Face validity refers to a phenomenological similarity between the model and the disorder it simulates. Ideally, the model should resemble the condition it models in its etiology, symptomatology, treatment and physiological basis. ► Predictive validity means that performance in the test predicts performance in the modeled condition. In principle, predictive validity can rely on etiology, physiology and response to treatment, but in practice, predictive validity is usually based in the latter. Construct validity means that the model has a sound theoretical rationale, and depends on the degree of homology between the behavior that is being modeled and the behavior in the model (two behaviors are considered homologous if they share a similar physiological basis), and on the significance of the modeled behavior in the clinical picture."

Earlier attempts to validate animal models of human psychopathologies, including anxiety disorders, have tended to be concentrated largely on the assessment of face validity. It was soon realized that this criterion could be misleading, since in different species similar behaviors often serve different adaptive functions and, conversely, distinct behaviors may lead to the same goal. For instance, rat probe-burying behavior is attenuated by anxiolytics, although it does not resemble any symptom of GAD. However, this model has good correlation with the latter disorder (De Boer and Koolhaas 2003).

With the consolidation of the role of drug therapy in modern psychiatry, the pharmacological investigation of a given model turned out to be the gold standard in the validation process. However, although important, the predictive criterion alone is insufficient to grant a given test the status of an animal model of anxiety, since correlation between the drug response in the model and in the clinics may happen, despite differences in brain mechanisms of pathophysiology and drug effect. For instance, a behavioral index may detect classical anti-anxiety drugs, such as the ► benzodiazepines, and predict their therapeutic outcome only because it involves γ-aminobutyric acid type A ($GABA_A$) receptor mechanisms. However the mechanisms unpinning the behavior may be entirely different from those implicated in the pathophysiology of anxiety and, as a consequence, the model will fail to detect non-GABAergic anxiolytics.

It may be concluded that only homology fully qualifies an animal model as representative of a given psychopathology. Although this goal is being currently pursued, it is hampered by limitation of the available knowledge on the etiology and pathophysiology of anxiety disorders.

Yet, in this respect, animal models of anxiety fare rather well, when compared to other psychiatric disorders, such as schizophrenia or even depression.

Animal Models of Anxiety: Past and Present

Early animal models of anxiety were developed within the conceptual framework of experimental psychology, before classifications of psychiatric disorders split pathological anxiety into distinct nosological entities. These animal models of anxiety rely on either inhibition of ongoing behavior elicited by conditioned stimuli that predict unavoidable electric shock (conditioned suppression) or on the inhibition of rewarded responding by response-contingent electric-shock (► punishment). The latter relates to clinically-derived constructs that emphasize the role of inner conflict in pathological anxiety, and this may be the reason why these tests became known as conflict models. Early pharmacological analysis has shown that conflict tests have a higher predictive value than conditioned suppression and, as a result, punishment tests have become paradigmatic for assaying anxiolytic drugs.

However, classical conflict tests failed to consistently detect the anxiolytic action of drugs that act primarily on serotonin (5-HT)-mediated neurotransmission, such as ► buspirone and ritanserin (Serotonin Agonists and Antagonists). Such false-negative results undermined the general confidence in conflict models, although many arguments may be summoned to their defense, as for instance the time course of drug action. Unlike benzodiazepine anxiolytics, newer drugs need several weeks of continuous administration to become clinically effective, initial doses being sometimes anxiogenic. Therefore, single administration of these agents should not be expected to have anxiolytic effects in animal models. In spite of this, it became generally accepted that conflict tests were good only for anxiolytics that acted primarily on the neurotransmission mediated by ► GABA, such as ► barbiturates and ► benzodiazepines.

A theoretical shift from the experimental analysis of behavior to the systematic observation of animals in their natural environment (Ethology) has also contributed to the discredit of conflict models, which have been

criticized because of their artificiality and the confounding influence of appetitive drives, such as hunger and thirst, and of pain (Graeff and Zangrossi 2002). As a result, a search for ethologically-based animal models of anxiety has occurred. The most widely used animal model of anxiety resulting from this trend has been the ▶ elevated plus maze, which is based on the natural aversion that rats have for the open arms of the apparatus. Yet, this model has also failed to consistently detect non-benzodiazepine anxiolytics, unless behavioral items shown by the rodents while exploring the elevated plus-maze are measured.

As this development was taking place in basic research, the split of anxiety disorders into distinct diagnostic categories, a trend initiated by the DSM III classification, became accepted world-wide. As a consequence, the search for models that represent specific anxiety disorders has started.

The trend towards theoretically-based models that represent specific anxiety disorders has been strongly influenced by the work carried out by Robert and Caroline Blanchard on predatory defense in rats and mice (Blanchard et al. 2008). As a result of this investigation, the Blanchards have established that the type of defense strategy is mainly determined by the presence or absence of the predator, by the distance between the predator and the prey, and by the availability of an escape route. The first pattern of defense occurs when the predator is absent, but had already been met by the prey in the same environment; it also occurs when the context is new, thus containing both potential reward and harm. These instances generate approach-avoidance conflict, and the resulting defense strategy consists of cautious exploration aimed at risk-assessment. The second defense pattern occurs when the predator is present, but is placed at a safe distance from the prey, thus characterizing distal threat. If an exit is available, the animal rapidly escapes, but if not, the animal remains in tense immobility, a posture known as "▶ freezing" behavior that impairs detection by the predator. Finally, when the predator is close or makes actual contact with the prey (proximal threat), the animal reacts with flight or defensive fight.

Although different species show quite distinct behavioral responses to the above types of threat, (e.g., birds fly, while rats run away from danger), antipredator defense is generally organized in the same way, ranging from risk assessment to tense immobility, escape, defensive threat and defensive attack as the danger grows nearer. The same strategies are used in conspecific agonistic interactions, except for submission, an additional defense pattern with the function of establishing social rank, thus minimizing injury and, sometimes, avoiding death of the contenders. Bridging the gap between these defense strategies and animal models of anxiety disorders, the above strategies of antipredator defense have been related to normal and pathological emotions: potential threat with anxiety and GAD, distal threat with fear and phobias (▶ agoraphobia), and proximal threat with dread and PD, respectively. In addition, submission has been related to shyness and ▶ social anxiety disorder.

In terms of neural organization, animal research has indicated that potential and distal threat engage mainly forebrain brain structures, such as the ▶ prefrontal cortex, the ▶ hippocampus and the ▶ amygdala, while proximal defense is chiefly organized in the ▶ hypothalamus and the midbrain periaqueductal gray matter (PAG). Functional neuroimaging results in humans have accordingly shown that brain activation shifts from the prefrontal cortex to the PAG as a virtual threat approaches a virtual prey, and the intensity of punishment increases (Mobbs et al. 2007).

This knowledge underpins theoretical constructs that implicate forebrain structures in the pathophysiology of GAD and the PAG, in PD. Therefore, animal models with theoretical validity can be derived from the same perspective. One clear example of this trend is the elevated T-maze (ETM), which is derived from the elevated plus-maze by shutting off one of its enclosed arms. In this apparatus, the same rat performs two tasks in succession: inhibitory avoidance of the open arm, when placed for three successive times at the end of the enclosed arm, and one-way escape, when placed for three times at the end of one of the open arms. Pharmacological validation studies have shown that not surprisingly, the inhibitory avoidance has predictive value for GAD, since it is another version of a conflict test. More interesting are the findings that chronic, but not acute treatment with antidepressants impairs one-way escape, whereas the panicogenic agent CCK enhances its performance, both changes correlating with drug effects that have been observed in panic patients (Pinheiro et al. 2007). Moreover, the ETM has been successfully used to test hypotheses on the role of serotonin (5-HT) in anxiety and panic, and is being used to screen potentially antianxiety and/or antipanic agents in extracts from plants.

Based on the same rationale, other models of GAD and/or PD have been developed (e.g. the mouse defense test battery and the electrical/chemical stimulation of panic related brain areas such as the dorsal aspect of the PAG and medial hypothalamus). A detailed description of these models as well as a comparative analysis of their

validity and feasibility can be found in Graeff and Zangrossi (2002)

Finally, animal models for social anxiety disorder, ► obsessive compulsive anxiety disorder and ► traumatic stress disorder have also been developed following the present trend towards theoretically-based models addressed to specific anxiety disorders. Nevertheless, their pharmacological validation is still under way.

Cross-References

► Agoraphobia
► Animal Models for Psychiatric States
► Benzodiazepines
► Elevated Plus Maze
► Generalized Anxiety Disorder
► Obsessive Compulsive Anxiety Disorder
► Panic
► Social Anxiety Disorder
► Traumatic Stress (Anxiety) Disorder

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Anxiety Neurosis

► Generalized Anxiety Disorder

Anxiety or Mixed States

► Adjustment Disorders

Anxiety-Reducing Drugs

► Anxiolytics

Anxiogenic

Definition

An anxiogenic substance is one that causes anxiety. Anxiogenic effects can be measured by, for example, the hole-board or elevated plus maze in rats and mice. A number of agents are used to provoke anxiety (anxiogenes) or panic (panicogenes) in experimental models.

Anxiolytic Dependence

► Sedative, Hypnotic, and Anxiolytic Dependence

Anxiolytics

Synonyms

Antianxiety drugs; Anxiety-reducing drugs; Minor tranquillizers

Definition

Anxiolytics are drugs that are prescribed for the treatment of symptoms of anxiety. ► Benzodiazepines are the most widely used class of drugs for treating anxiety states. Recently, drugs that act on 5-HT_{1A} receptors in the brain have been introduced as anxiolytics because they cause little sedation. β-adrenoceptor antagonists such as ► propranolol reduce physical symptoms of anxiety (e.g., tremor, palpitation, etc.) but have no effect on the affective component.

Cross-References

► β-Adrenoceptor Antagonists
► Barbiturates
► Benzodiazepines

APOE

► Apolipoprotein E

Apolipoprotein E

Synonyms

APOE

Definition

APOE is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. APOE was initially recognized for its importance in lipoprotein metabolism and cardiovascular disease. More recently, it has been studied for its role in several biological processes not directly related to lipoprotein transport, including Alzheimer's disease (AD), immunoregulation, and cognition.

The APOE gene is polymorphic with three major alleles: ApoE2, ApoE3, and ApoE4, which translate into three isoforms of the protein:

E2 is associated with the genetic disorder type III hyperlipoproteinemia and with both increased and decreased risk for atherosclerosis.

E3 is found in approximately 64% of the population. It is considered the "neutral" Apo E genotype.

E4 has been implicated in atherosclerosis and Alzheimer's disease, impaired cognitive function, and reduced neurite outgrowth.

Apomorphine

Definition

Apomorphine is a drug used to treat impairments in motor function (tremor, slow movement, and difficulty walking and speaking) in Parkinson's patients. It is sometimes used for erectile dysfunction. In larger doses, it has emetic effects and was used in aversion therapies. It is a nonspecific dopamine agonist with actions at several subtypes of dopamine receptors, both presynaptic and postsynaptic. As a pharmacological tool for probing the function of dopamine receptors, it has been largely replaced by more selective substances. It does not have morphine-like effects and does not interact with opioid receptors.

Cross-References

► Anti-Parkinsonism Drugs
► Sexual Disorders

Apoptosis

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Synonyms

Physiological cell death; programmed cell death

Definition

Apoptosis is a form of regulated physiological cell death that is important during ontogenesis but which may also contribute to tissue homeostasis as well as pathology.

Current Concepts and State of Knowledge

Characteristics of Apoptosis

Apoptosis may be triggered by signals from within the cell or proximal and distal cells, as well as exogenous agents; apoptotic cell death may also result from the withdrawal of trophic factors (► nerve growth factors). All of these triggers initiate a cascade of events that results in the elimination of cells without releasing harmful substances into the surrounding areas. Apoptosis is not associated with an inflammatory response; in situ, apoptotic cells are phagocytosed by macrophages or neighboring epithelial cells, whereas the fragments of cells that have undergone apoptosis in vitro are eventually lysed.

In its original sense, the term apoptosis was used to refer to a form of "programmed cell death" that depends on the activation and/or repression of ► gene transcription to delete biologically redundant or dysfunctional cells. Growing knowledge of how cell death is triggered and of the processes that lead up to it indicate a degree of overlapping mechanisms in different forms of cell death; this has resulted in a blurring of how apoptosis should be defined. However, the consensus is that apoptosis can only be ascertained through the morphological observation of chromatin condensation with evidence of DNA cleavage, nuclear fragmentation, cell shrinkage, blebbing of the nuclear and plasma membranes, and formation of membrane-bound apoptotic bodies in cells that otherwise have an integral plasma membrane. At the biochemical level, apoptotic cells show signs of mitochondrial dysfunction. Specifically, the mitochondrial membrane

potential is perturbed and results in a leakage of mitochondrial proteins, such as cytochrome *c*, into the cytoplasm; cytochrome *c* is a soluble protein whose ability to transfer electrons plays a key role in energy generation.

Apoptosis Versus Necrosis

In contrast to apoptosis, cell death through necrosis may be considered to occur "accidentally" following direct disruption of cellular homeostasis of cellular functions by a toxin or noxious stimulus (e.g., hypoxia, hypothermia), resulting in an influx of water and extracellular ions. Morphologically, this form of cell death, which differs from apoptosis, is characterized by swelling of the cytoplasm and mitochondria and the ultimate disintegration of the plasma membrane, leading to the leakage of lysosomal enzymes that lyse a group of contiguous cells (typically apoptosis affects only individual cells), usually followed by an inflammatory response. Other important features that distinguish apoptosis and necrosis are (1) DNA fragmentation in apoptosis occurs through the actions of specific DNA-cleaving enzymes (endonucleases) while the cell is still intact, whereas DNA breakdown in necrotic cells occurs only after cell lysis and the DNA fragments are of random size; (2) apoptosis is an energy (ATP)-dependent process, whereas necrosis is a passive process; and (3) whereas necrosis results from a massive influx of calcium in the cell, apoptosis is triggered by moderate increases in calcium influx. Various assays that are based on the above-mentioned morphological and cytological descriptions serve to discriminate between apoptotic and necrotic cells both in vivo and in vitro; in addition, researchers increasingly rely on other biochemical and molecular markers to detect early- and late-stage apoptosis.

Apoptotic Mechanisms

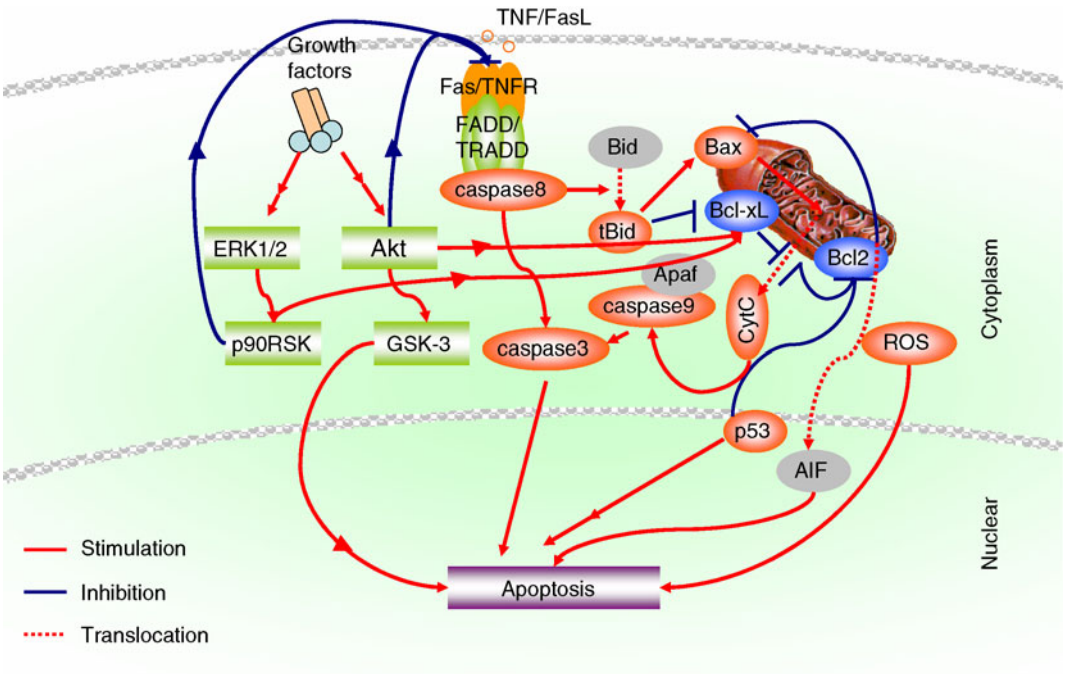
An understanding of the molecular and cellular basis of apoptosis has grown immensely in the last decade. While the molecular processes that lead to apoptosis are initiated in the cytoplasm or the membranes of organelles, the final execution of the apoptotic process takes place in the nucleus where irreversible, Ca^{2+}/Mg^{2+}-dependent internucleosomal DNA fragmentation occurs in a sequential fashion, mediated by endonucleases.

In general, apoptosis results through one of two cellular pathways, the intrinsic and extrinsic pathways; however, growing evidence points to the possibility that these pathways may converge under certain circumstances. The sequential activation of caspases is central to both pathways; the activation of caspase 3, a so-called executor caspase serves as a good biochemical marker of apoptosis. In addition, apoptosis may occur independently of caspase activation. Several stimuli, including DNA damage, and oxidative and excitotoxic stress, cause the translocation of apoptosis-inducing factor (AIF) from the mitochondrial intermembranous space to the nucleus where AIF binds to DNA and initiates apoptosis by promoting chromatin condensation (Fig. 1).

The intrinsic pathway is initiated by the perturbation of the mitochondrial transmembrane potential, which is rheostatically regulated by the availability of pro- (e.g., Bax, Bid) and anti-apoptotic (e.g., Bcl-2, Bcl-X_L) members of the Bcl-2 family of proteins. A shift in the ratio of these proteins in favor of the pro-apoptotic members leads to the release of mitochondrial cytochrome *c* (a heme-containing protein involved in electron transfer) which, in turn, binds to apoptosis protease activator factor-1 (Apaf-1), forming an apoptosome that subsequently cleaves and activates pro-caspase 3. In the extrinsic pathway, the binding of either Fas ligand, tumor necrosis factor (TNF) α, or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to their corresponding membrane receptors results in the formation of a complex between liganded and pro-caspase 8. When cleaved, caspase 8 can activate caspase 3 directly, or indirectly by cleaving the pro-apoptotic protein Bid in the cytoplasm; truncated Bid (tBid) translocates to the mitochondrion where it disrupts that organelle's permeability transition pore, resulting in cytochrome *c* release and the ultimate activation of caspase 3.

Neuronal apoptosis may be triggered by both, pro-apoptotic signals as well as limited availability of (neuro) trophic molecules (nerve growth factors); the latter mechanism is important in both physiological and pathological contexts and led to the discovery of pro-survival signaling pathways that act to suppress the cell death machinery. Among the best-characterized survival pathways are the Ras-MAPK (mitogen-activated protein kinase) and the PI3K (phosphatidylinositide-3′-OH kinase)-Akt pathways.

It is estimated that neurons undergo apoptotic death within 6-12 h from first being exposed to a pro-apoptotic stimulus. Under normal circumstances, apoptosis occurs widely in the developing brain; it also occurs throughout postnatal life, albeit at a much reduced rate. It is estimated that apoptosis results in the elimination of up to 70% of neurons during early brain development; accordingly, it is thought to serve a physiological role, serving to ensure appropriate structure and function of the brain and the



Apoptosis. Fig. 1. The pathways to apoptotic cell death. Two pathways, the so-called intrinsic and extrinsic pathways, regulate apoptosis. In both pathways, caspases, a family of cysteine proteases, play a central role. The arrival of apoptotic signals leads to the activation of initiator caspases (e.g., caspase-8, -9) and sequential cleavage/activation of downstream effector caspases; caspase-3 is the last caspase in this cascade and is known as the "executor caspase" since the process cannot be reversed once this caspase is activated. The extrinsic pathway is triggered after the binding of FasL or TNF to their respective cognate receptors (Fas and TNFR), followed by the activation of caspase-8 through the adaptor protein FADD/TRADD. Activated caspase-8 can stimulate apoptosis through one of two cascades: direct activation of caspase-3 or cleavage of Bid. Truncated Bid (tBid) translocates to the mitochondrion where the extrinsic pathway converges with the intrinsic pathway in which the formation of pores in the outer mitochondrial membrane and the leakage of cytochrome *c* is a central event. Cytochrome *c* binds Apaf1 to form an activation complex with caspase-9, an event critical to the activation of the intrinsic pathway. Members of the BCl-2 family of proteins, including the anti-apoptotic proteins Bcl-2 and Bcl-xL and pro-apoptotic protein Bax, rheostatically control apoptosis by determining the integrity and permeability of mitochondrial membranes and thus, cytochrome *c* release. The tumor suppressor protein p53, which is activated following DNA damage, induces the transcription of Bax, which, in turn, disrupts the mitochondrial potential. More recently, another apoptotic mechanism involving mitochondrial release of apoptosis inducing factor (AIF) was identified. AIF translocates to the nucleus and directly triggers the internucleosomal degradation of DNA. Reactive oxygen species (ROS) can also directly induce apoptosis by damaging DNA strands. On the other hand, anti-apoptotic signals, including growth factors and cytokines, act by inducing the phosphorylation of signaling molecules such as Erk1/2 and Akt. Erk1/2 activates p90RSK, which upregulates the expression of the anti-apoptotic proteins Bcl-xL and BCl2 and inhibits the Fas pathway; similarly, activated Akt regulates the expression of members of the Bcl2 family and of Fas while inhibiting GSK-3 signaling.

ability of the brain to adapt to changing demands. As neuronal apoptosis is essential to normal brain development and function, it is conceivable that it may contribute to brain pathology and pathophysiology if it arises at an inappropriate time or location, or in excess or an insufficient extent.

Neuronal Birth, Death, and Plasticity

Ensuring the correct number of functional neurons in a given brain area depends on the coordinated birth and death of neurons. Extensive neuronal birth (► neurogenesis) in the mammalian brain ceases during postnatal life; two areas, the ► hippocampus and

olfactory bulb however continue to show neurogenesis throughout life although the rate of cell birth tapers off with age.

The mechanisms that regulate neurogenesis are common to other forms of cell proliferation, and include the expression of cyclin-dependent kinases that drive the dividing cells through the various stages of the cell cycle in a temporally coordinated fashion. The end of cell proliferation (mitosis) is marked by the expression of proteins that induce cell cycle arrest; however, whereas most other cell types can go through repeated mitotic cycles, differentiated neurons are considered to be in a permanent postmitotic state. While differentiated neurons are sensitive apoptotic stimuli, undifferentiated or migrating young neurons appear to be particularly sensitive and their elimination through apoptosis (probably through the programmed withdrawal of neurotrophic support nerve growth factors) is responsible for giving the brain its final structure. Importantly, a growing body of evidence shows that some mature neurons may reenter the cell cycle, namely by reactivating several of the molecular components that typify mitosis; however, this reentry into the cell cycle is abortive and ends in apoptosis, a mechanism now thought to be of importance during brain development and neurodegenerative disease such as Alzheimer's disease (► dementias and other amnesic disorders).

Brain structure and function undergoe dynamic – plastic – changes from early development through to old age. Neurogenesis and neuroapoptosis are essential parts of this process insofar as they determine communication between individual neurons (adjacent or at a distance), and whole pathways or networks and even whole systems, as well as interactions with supporting glial and vascular tissues. Additionally, the balanced relationship between neurogenesis and apoptosis can be expected to be important to histogenetic constancy (stability) as well as flexibility (► synaptic plasticity); computational models suggest neuronal turnover to play a facilitative role in learning and information recall (memory) by, respectively, filtering relevant information from irrelevant information and reducing interference from other information (► long-term potentiation and memory).

Why IS Apoptosis of Interest to Neuropsychiatry?

In the mature brain, apoptosis occurs at a low rate but that may, nevertheless, be sufficiently significant to contribute to the reorganization of neuronal circuits. Neuropsychiatric diseases are thought to be neurodegenerative or neurodevelopmental in origin. Neuronal death, including that occurring through apoptosis, is a defining pathological feature of neurodegenerative diseases (► neurodegeneration and its prevention) such as ► Parkinson's disease, ► Alzheimer's disease, ► Huntington's disease, amyloid lateral sclerosis (or Lou Gehrig's disease), and human immunodeficiency virus (HIV)-associated dementia. Aberrant neuronal apoptosis may also underlie neurodevelopmental disorders such as ► schizophrenia, ► autism, and ► fragile X syndrome. Some of the known effects of various classes of psychoactive drugs on neuronal survival are summarized in Table 1.

Loss of neurons through apoptosis appears to underlie ► fetal alcohol syndrome, a neurodevelopmental disorder

Apoptosis. Table 1. Influence of various psychoactive drugs on neuronal survival.

Agent	Examples	Properties/Uses	Neuronal survival
Stimulants and addictive drugs ► psychomotor stimulants and abuse, ► abuse liability evaluation		Inhibit serotonin (5HT) and norepinephrine (NE) reuptake, increase glutamatergic activity, and stimulate dopamine (DA) release to produce "reward"	Associated with cerebral atrophy; increase cellular oxidative stress (due to increased DA catabolism) and activate apoptotic signaling pathways
	Amphetamine, metamphetamine, "ecstasy" (3,4-methylenedioxy-N-methylamphetamine, MDMA), ► cocaine, ► psychostimulant abuse	Enhance locomotion and repetitive behavior; tolerance and dependence develop after chronic use, addictive/used recreationally for feelings of euphoria, energy, increase sensory perception, sense of well being, alertness, mental acuity, and creative thinking	Induce apoptosis (intrinsic pathway)

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
	► Methylphenidate (cognitive enhancers)	Inhibits DA reuptake; enhances cognition, may cause anxiety and general nervousness, emotional lability, aggression and paranoia; treatment of attention-deficit hyperactivity disorder, narcolepsy, and chronic fatigue syndrome; likely to be abused	Reportedly protective against excitotoxicity but also pro-apoptotic
	Ampakines (cognitive enhancers)	Alkaloid analgesic; tolerance and dependence may develop after chronic use; addictive/clinical management of pain	Neuroprotective (increase neurotrophin production)
	Morphine (prototypic opiate) (► opioids)	Alkaloid analgesic; tolerance and dependence may develop after chronic use; addictive/clinical management of pain	Pro-apoptotic
	Heroin (opioids)	3,6-diacetyl ester of morphine recreational to obtain a "rush"	Pro-apoptotic (intrinsic and extrinsic pathways)
	► Caffeine	Xanthine alkaloid, antagonizes adenosine receptors; may produce tolerance, physical dependence, and craving, irritability, nervousness, anxiety, insomnia, and headache/most common nonprescription psychostimulant ("energizer") in food and beverages	Regulates cell cycle checkpoint proteins and DNA repair and may protect against Parkinson's disease
	► Nicotine	Affects cholinergic, DA-, NE-, and 5HT-ergic, and neuropeptidergic transmission; highly addictive/in cigarettes, to produce euphoria/pleasure, relaxation, increased arousal/alertness and memory (low doses), reduced appetite and induce sedation and pain (high doses); treatment of nicotine addiction (only medical use)	No consensus; suggested reduced risk of Parkinson's and (possibly) Alzheimer's disease; may be risk factor for schizophrenia

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
Sedatives and anxiolytics		Suppress neuronal activity by acting as GABA mimetics, and modulating activity of NMDA, opioid and cannabinoid receptors; highly addictive; reduce attention and slow reflexes; are not addictive but ''discontinuity symptoms'' arise upon abrupt withdrawal	
	Opiates, general anesthetics (► analgesics, ► opioids)	Some, such as phencyclidine (''angel dust'') may cause hallucinations, delirium, mania and disorientation/in anesthesia (phencyclidine now replaced in anesthesia by ketamine, another NMDAR antagonist)/analgesia and anesthesia; opiates are subject to abuse	Phencyclidine and ketamine are pro-apoptotic; opiates also induce apoptosis
	► Barbiturates, ► benzodiazepines and other ► anticonvulsants	Block Na+ channels and bind to GABA receptors; anti-convulsant, anxiolytic, hypnotic/have high-abuse potential/treatment of epilepsy and ► bipolar disorder (barbiturates now rarely used); also used as recreational drugs	Barbiturates and benzodiazepines are pro-apoptotic, especially in developing brain
	Ethanol/(alcohol abuse and dependence)	Impairs problem solving, abstract thinking, concept shifting, psychomotor performance, and performance in memory tasks (severe amnesia in extreme cases), and may cause dementia; causes attention-deficit hyperactivity disorder and learning difficulties in childhood and high incidence of major depression and psychosis in later life/in pharmaceutical preparations; widely used for recreational purposes	Pro-apoptotic; acute doses cause dendritic re-arrangements; fetal exposure results in apoptosis of developing neurons and causes diminished brain size (causes fetal alcohol syndrome by increasing reactive oxygen species production, while reducing defenses against them; and hyperactivation of GABAergic transmission and increase of glutamate excitotoxicity)
	5HT 1a receptor agonists (e.g., buspirone)	Lower anxiolytic potency than benzodiazepines, but do not cause sedation and have less-severe effects on cognition; have no abuse potential	Anti-apoptotic, currently being tested in models of stroke, brain trauma, and ethanol-induced apoptosis

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
► Anti-psychotic drugs (neuroleptics)	*Typical:* haloperidol, chlorpromazine; *atypical or second-generation*: olanzapine, risperidone, quetiapine	Activate DA D2 receptors and inhibit DA release; may cause one or more of the following: tardive dyskinesia, acute dystonia, akathisia, parkinsonianism (rigidity and tremor), lethargy, seizures, psychosis, intense dreams, or nightmares/treatment of schizophrenia	Possibly induce neuronal apoptosis through excitotoxic mechanisms, disruption of the mitochondrial respiratory chain, or reduced neurotrophic support
► Anti-depressants			Generally, increase neurotrophic support and promote neuroplasticity, although cell culture studies indicate that many have the potential to trigger oxidative stress and activate apoptotic pathways
	► Monoamine oxidase inhibitors (MAO)	MAO-A inhibitors reduce breakdown of 5HT, and NE/treatment of depression, bipolar disorder, and agoraphobia (social anxiety); MAO-B inhibitors reduce catabolism of DA/treatment of Parkinson's disease	Appear not to cause apoptosis in neural cell cultures
	Tricyclic compounds	Inhibit presynaptic reuptake of 5HT and NE; some tricyclics interfere with memory performance, many reduce histamine actions (H1 receptor), producing sedation/treatment of major depression, and insomnia, migraine, anxiety, attention-deficit hyperactivity disorder, chronic pain, (sometimes) schizophrenia	Induce neurogenesis and neuroplasticity
	Selective serotonin- or NE-reuptake inhibitors (► SSRIs and related compounds, ► SNRI antidepressants)	Increase 5HT and NE levels in synaptic cleft by inhibiting their presynaptic reuptake/treatment of major depression and anxiety disorders, as well as eating disorders and chronic pain	Induce neurogenesis and neuroplasticity
	Neuropeptide receptor antagonists	Block pituitary receptors for hypothalamic peptides that stimulate adrenal activity/in trials for use as antidepressants and anxiolytics	► Corticotropin-releasing hormone (CRH), implicated in depression and anxiety, appears to be neuroprotective

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
► Mood stabilizers and ► anti-convulsants	► Benzodiazepines, barbiturates, GABA analogs, and inhibitors of GABA breakdown (e.g., vigabatrin), hydantoins (e.g., phenytoin), carbamates, carboxamides	Anti-convulsant actions result from blockade of Na+ channels and enhancement of GABAergic-mediated inhibition of neuronal firing or block glutamatergic transmission/treatment of acute and recurrent seizures	Reduce neurotrophic molecules, leading to neuronal apoptosis (may account for microcephaly and impaired neurodevelopment and cognitive functions); some drugs disrupt neuronal migration in the developing brain
	► Valproic acid	Inhibits GABA transaminase, increasing GABA production; affects long-term gene expression by inhibiting ► histone deacetylase (HDAC)/treatment of epilepsy and manic phase of bipolar disorder	Interferes with neuronal migration and induces neuronal apoptosis in developing brain; is neuroprotective in postnatal neurons (via insulin-dependent activation of PI3-K/Akt
	► lithium	Respectively, decreases and increases NE and 5HT release; inhibits glycogen synthase 3β (GSK-3β)/treatment of manic phase of bipolar disorder	Promotes neuronal survival by inhibiting GSK-3β, activating the PI3-K/ Akt pathway, increasing neurotrophin production factors, heat shock proteins (hsp 70) and anti-apoptotic proteins (e.g., Bcl-2)
Hormones	Sex hormones (estrogens, androgens, progestins)	Act through nuclear receptors (transcription factors), but may also rapidly alter membrane properties and neuronal firing rates; cognition, reward processes, mood and emotion are positively influenced by estrogens and androgens; progestins induce anxiolysis, sedation and somnogenesis by allosteric modulation of $GABA_A$ receptors; all are involved in aggressive and affiliative behaviors/naturally produced by the gonads, may be prescribed for a variety of endocrine dysfunctions and during aging; androgens may be used as anabolics	Anti-apoptotic actions resulting from phospho-activation of the MAP and Akt pathways, stimulation of neurotrophin production and altered anti- and pro-apoptotic protein ratios; estrogens can scavenge oxygen free radicals

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
	Glucocorticoids (natural hormones include cortisol and corticosterone; synthetic glucocorticoids include prednisolone and dexamethasone)	Bind to nuclear receptors – mineralocorticoid (MR) and/or glucocorticoid receptors (GR) – in an amplitude-dependent fashion to induce or repress gene transcription; have anxiogenic and depressogenic properties, interfere with learning and memory/naturally produced by the adrenal cortex, glucocorticoids may be prescribed as anti-inflammatory agents and for shock and certain cancers; also used in endocrine diagnostics	Activation of GR by high glucocorticoid levels leads to neuronal apoptosis, low glucocorticoid levels that selectively occupy MR are neuroprotective; glucocorticoids also inhibit neurogenesis and neurotrophin synthesis, and induce dendritic retraction

that is associated with hyperactivity, learning disabilities and depression during childhood, and psychoses in adulthood. Convincing data demonstrate that ethanol (► alcohol abuse and dependence) stimulates neuronal apoptosis in a variety of cortical regions by interfering with GABAergic and glutamatergic neurotransmission during developmental stages characterized by a high rate of synaptogenesis. Similar mechanisms are also thought to be responsible for the apoptotic actions of a number of drugs that have medical applications (anesthesia, epilepsy) but which are also subject to abuse.

An etiologic role for enhanced apoptosis has also been proposed in major depression, although post mortem examinations have led some authors to challenge its importance. Although increased levels of apoptosis are observed in some animal models of depression (► depression: animal models) based on chronic stress paradigms that elevate glucocorticoid secretion and despite strong evidence that glucocorticoids are potent pro-apoptotic (and anti-neurogenic) hormones, a causal link between neuroapoptosis and depression remains to be firmly established. Studies showing that stress and glucocorticoids induce dendritic reorganization and synaptic connections suggest a rather more important role for these mechanisms in the etiology of depression. While a number of ► antidepressants have been shown to induce apoptosis in neuronal cultures, the majority of studies in animals indicate that antidepressants might exert their therapeutic actions by stimulating neurotrophin (► nerve growth factors) production and therefore, neuroplasticity. The known inhibition of neurotrophin expression by glucocorticoids may be the link between stress and psychiatric diseases such as depression and anxiety (► emotion and mood). In addition, elevated glucocorticoids have been clearly shown to impair cognition; besides their ability to modulate neuronal firing patterns and synaptic plasticity, ► glucocorticoids have been recently shown to promote the aberrant processing and posttranslational modification of proteins implicated in mild and severe forms of dementia (► dementias and other amnesic disorders).

In addition to glucocorticoids, several endogenous peptidergic and steroid hormones have emerged as being potentially important in neuropsychiatry. ► Corticotropin-releasing hormone and ► arginine vasopressin are examples of neuropeptides that have gained considerable attention; both peptides act on the pituitary and ultimately stimulate glucocorticoid secretion and because they have marked influences on ► emotion and mood and cognition in animals, they have been implicated in ► major and minor and mixed anxiety-depressive disorders. Progestins and their derivatives (► neurosteroids) are well known for their sedative and anxiolytic effects that are mediated by $GABA_A$ receptors, and estrogens (► sex hormones) appear to have mood- and cognition-enhancing (► cognitive enhancers) effects that are attributed to their neurotrophic and anti-apoptotic actions.

Conclusion

Many psychoactive drugs have been studied for their possible apoptotic effects on neurons. Studies of such

effects during brain development raise concerns that drug-induced apoptosis can have a major impact on the development of neuropsychiatric conditions in childhood and later life. Demonstrations of psychoactive drug-induced apoptosis in the mature brain are important in that they may account for some of the undesired side effects of therapeutic agents, the ▶ antipsychotic drugs being a good case in point (see Table 1). However, caution is called for in the interpretation of results since many of them derive from experiments in artificial cell culture settings that may differ in terms of kinetics and which lack the normal drug metabolism mechanisms that operate in the whole organism; also, to be considered is the fact that the disposition and action of a drug varies according to the context in which it is administered (▶ pharmacokinetics, ▶ sex differences in drug effects). Physicians' prescribing decisions are guided by evidence of therapeutic efficacy and immediacy, and careful risk-benefit analysis on a case-by-case basis.

Cross-References

▶ Abuse Liability Evaluation
▶ Alcohol Abuse and Dependence
▶ Analgesics
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Arginine Vasopressin
▶ Barbiturates
▶ Benzodiazepines
▶ Bipolar Disorder
▶ Caffeine
▶ Cocaine
▶ Cognitive Enhancers
▶ Corticotropin Releasing Hormone
▶ Dementias and Other Amnesic Disorders
▶ Depression: Animal Models
▶ Dysthymic Mood Disorder
▶ Emotion and Mood
▶ Histone Deacetylase Inhibitors
▶ Lithium
▶ Long-Term Potentiation and Memory
▶ Major and Minor and Mixed Anxiety-Depressive Disorders
▶ Nerve Growth Factors
▶ Neurodegeneration and Its Prevention
▶ Neurogenesis
▶ Neurosteroids
▶ Nicotine
▶ Opioids
▶ Pharmacokinetics
▶ Psychostimulant Abuse
▶ Schizophrenia
▶ Sex Differences in Drug Effects
▶ Sex Hormones
▶ SNRI Antidepressants
▶ SSRIs and Related Compounds
▶ Synaptic Plasticity

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Apoptosis-Inducing Factor

Synonyms

AIF

Definition

It is a protein found on the inner leaflet of mitochondrial membranes. Upon the arrival of an apoptotic stimulus, AIF contributes to the increased permeability of mitochondrial membranes, resulting in its own entry into the cytosol and nucleus.

Apoptosome

Definition

It is the term used to describe the multimeric cytoplasmic complex that forms when cytochrome *c* is released from

mitochondria into the cytosol and binds to apoptosis protein-activating factor 1 (Apaf1), dATP, and initiator caspases such as caspase 9. The apoptosome plays a key role in the activation of ► apoptosis.

Apparent Volume of Distribution

► Volume of Distribution

Appetite

Definition

The desire to eat. A willingness to consume food that can be indexed by the tendency to engage in activities that will procure food, and by the rate, duration, and quantity of food consumed. Appetite can be aroused by external food stimuli (such as the sight or smell of food) and enhanced or diminished by the oral sensory qualities of the taste, flavor, and texture of foods as they are eaten. Specific appetites (or cravings) may occur in relation to specific physiological imbalance, illness, or external food cues.

Cross-References

► Hunger
► Palatability
► Satiety

Appetite Stimulants

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Synonyms

Hunger-mimetics; Hyperphagics; Orexigens

Definition

Appetite stimulants are agents that promote the motivation to eat through actions on psychological, neurochemical, metabolic, or endocrine processes. Their actions may increase ► hunger and the desire to eat, promote the anticipation of, or craving for food, and/or enhance hedonic responses to the sensory properties of foods. These psychological effects may cause over consumption by increasing the salience of, and attention to, food stimuli and so advance the initiation of eating, or by increasing meal frequency, meal size, or meal duration. Drugs that increase ► appetite and/or food intake, and that may be used for the amelioration of loss of appetite and body weight associated with illness or radical medical treatments of disease.

Pharmacological Properties

History

Unlike the substantial commercial and academic research efforts that have been devoted to the development of appetite suppressant treatments, relatively few resources have been expended on the rational design of appetite stimulants. Several classes of drug possess the ability to increase appetite and food intake, but these effects are often poorly characterized side effects of treatments that were primarily intended for other clinical purposes. Multiple neurochemical and endocrine systems have been implicated in the stimulation of appetite through the hyperphagic actions of endogenous or synthetic receptor ligands. These include gamma-aminobutyric acid (► GABA), agouti-related peptide (AgRP), neuropeptide Y (► NPY), melanin-concentrating hormone (MCH), ghrelin, the endogenous ► opioids, and the ► endocannabinoids. With recent progress in the characterization of the systems involved in appetite control and body weight regulation, a wide range of experimental compounds that act as agonists or antagonists at specific receptors have been shown to have orexigenic effects in animal models. However, for most of these agents, their use is restricted to experimental probes for the study of neural appetite-control pathways.

Mechanisms of Action

Some drugs have hyperphagic effects that are widely acknowledged in clinical populations, but for which clear mechanisms have yet to be identified – despite considerable knowledge about their principal pharmacological actions being available. Appetite stimulation and the development of overweight or obesity are not uncommon side effects of drugs used to treat psychiatric disorders (Schwartz et al. 2004). Intriguingly, of the more classical drug groups, agents with anxiolytic-sedative properties are most likely to exert hyperphagic actions – at least under laboratory conditions. These agents include ► benzodiazepines, some antihistamines, ► barbiturates, ► opiates, and ► cannabinoids.

The majority of experimental agents that have exhibited orexigenic efficacy in animal models have not been assessed

in relation to that activity in humans: the few that have, rarely – if ever – progress beyond the preclinical stages of development. Similarly, clinical exploitation of the hyperphagic side effects of psychotropic drugs and other medicines are often poorly studied, with a dearth of controlled clinical trials. In the long term, continuing research into the central and peripheral processes that mediate appetite control and energy balance will ultimately clarify specific processes through which the orexigenic properties of drugs come to be expressed. Currently, however, precise mechanisms of action are defined for only relatively few of these drugs. Therefore, the main emphasis here will be on a largely phenomenological description of those drugs which have demonstrable hyperphagic actions in humans and for which clinical applications for the treatment of appetite and weight loss have been actively pursued.

Clinical Application of Appetite Stimulants

An often-overlooked area in a world obsessed by obesity is the treatment of clinical conditions in which the progress of a disease is associated with involuntary weight loss. For example, wasting, or cachexia, is a common feature of the later stages of diseases such as AIDS and metastatic cancer, and is a significant factor in their morbidity. Cachexia is characterized by the loss of fat and lean mass resulting from abnormalities in protein synthesis/degradation, lipid and glucose metabolism, and energy utilization. Additionally, sufferers typically fail to exhibit any compensatory increase in eating motivation to counter these changes – as would be the case with weight loss caused by fasting. Disease-related wasting may be further exaggerated by the effects of radical drug or radiation therapies, which frequently lead to loss of appetite and malnutrition, sometimes as a consequence of treatment-induced nausea, vomiting, and taste aversions. Wasting and loss of appetite are also clinically important features of aging, particularly in relation to the dementias.

Cannabinoids

Of all the drugs that might be discussed here, alkaloids (► cannabinoids) derived from Cannabis *sativa* (marijuana) have the most widely recognized and well-documented hyperphagic actions. Cannabis, or pharmacologically active preparations derived from the plant, has been ascribed appetite stimulant effects for centuries, and this medicinal application is evident in the pharmacopeia of many cultures throughout history. With the identification of the psychoactive molecules in cannabis in the 1970s, such as Δ^9-tetrahydrocannabinol, it became possible to standardize cannabinoid-dosing regimen for both clinical and research purposes - although the extent of research, and clinical use, of THC is relatively limited.

Using animal models, the underlying mechanisms responsible for cannabinoid ► hyperphagia have been established to involve the stimulation of cannabinoid CB_1 receptors within the central nervous system. Exogenous CB_1 agonists, such as THC, and the natural ligands for these receptors (the endocannabinoids; e.g., anandamide, 2-arachidonoylglycerol, noladin ether) all exert orexigenic actions in animal models. Conversely, CB_1 blockade by antagonist drugs such as ► rimonabant will not only prevent agonist-induced eating, but also suppress food intake in its own right. Additionally, brain levels of endocannabinoids have been shown to increase in response to fasting, and increased brain endocannabinoid activity has been associated with overeating of palatable foods and diet-induced obesity.

Overall, current evidence indicates that cannabinoid hyperphagia reflects alterations to the incentive and reward aspects of eating motivation (Kirkham 2005). Cannabinoid receptor agonists can energize food-seeking behavior independently of need or energetic status: advancing the onset of feeding even in satiated animals, and increasing the effort an animal will expend to obtain food. Additionally, there are data that support specific modulation by endocannabinoids of the hedonic aspects of eating, with CB_1 agonists specifically enhancing the liking for foods.

These findings are in line with anecdotal evidence from cannabis users and laboratory experiments in healthy human volunteers with cannabis cigarettes, and oral THC. Thus, it is frequently reported that cannabis can promote the anticipation and enjoyment of food, while it has been demonstrated empirically that THC will amplify the normal pre-meal rise in hunger and promote the overconsumption of palatable foods.

There are indications that cannabinoids produce their effects on appetite in part by the modulation of other neurotransmitters that have been implicated in the control of food intake. For example, cannabinoid receptor antagonists can block the hyperphagic effects of the putative peptide "hunger" signal ghrelin, and of the potent orexigenic peptides NPY and MCH. Of particular interest, is the apparent relationship between endocannabinoids and the endogenous opioid peptides (e.g., beta-► endorphin).

Overall, current evidence supports an important role for endocannabinoids in the instigation of hunger and food seeking, the anticipation of food, and eating pleasure. Within the brain, these different processes are linked to pathways that center upon the ► nucleus accumbens, a region that is intimately associated with incentive and reward processes. Mesolimbic dopaminergic neurons,

originating in the ▶ ventral tegmental area (VTA) and projecting to the nucleus accumbens are linked to incentive motivation, and the generation of emotional arousal and behavioral activation in response to stimuli that predict reward. Food stimuli cause dopamine release in the nucleus accumbens, and this effect is mimicked by both THC and anandamide. By contrast, accumbens dopamine release provoked by palatable foods is blocked by rimonabant, suggesting that endocannabinoids normally facilitate the mesolimbic dopamine signaling that gives rise to appetite. Endocannabinoids may thus be essential for the orientation to food stimuli, the attribution of incentive salience and reward anticipation, and the elicitation of hunger, food seeking, and eating initiation.

Mesolimbic dopamine neurons synapse with accumbens opioid neurons that are critical to the experience of pleasure. The opioid peptides have an established role in the hedonic evaluation of foods, with opioid receptor agonists and antagonists respectively increasing or reducing the liking of foods. The hyperphagic effects of THC and anandamide are both blocked by the opioid receptor antagonist ▶ naloxone; while a simultaneous blockade of cannabinoid and opioid receptors produces a very dramatic suppression of appetite. Such findings provide evidence of an important functional relationship between endocannabinoids and opioids in appetite, particularly in relation to food ▶ palatability and the enjoyment that is derived from eating. THC has been shown to stimulate beta-endorphin release in the accumbens – a phenomenon also associated with the consumption of palatable foods and the associated pleasure response. Importantly, both anandamide and the opiate ▶ morphine increase the liking of sweet solutions when injected into the same sites within the nucleus accumbens.

The ability of cannabinoids such as THC to promote appetite through combined effects on specific neural mechanisms that promote eating and mediate eating pleasure thus provides clear medical opportunities. Given the low toxicity of cannabis or THC, combined with their established ability to elevate mood, prevent nausea and vomiting, and to impede the acquisition of conditioned taste aversions (such as might be associated with the symptoms of disease, or the consequences of chemo- or radiotherapy), cannabinoids could provide effective therapies for appetite loss and wasting. Largely misguided political interference has prevented a comprehensive investigation of medicinal uses of cannabinoids. However, clinical studies in cancer and AIDS patients have shown positive benefits of a pharmaceutical form of THC (▶ dronabinol), leading to approval for the clinical use of the drug in the treatment of AIDS-associated anorexia and weight loss.

Steroids

Although the underlying mechanisms are largely unknown, steroids have been administered for their appetite-stimulating and weight-enhancing properties. The best example is megasterol acetate (a synthetic form of the hormone progesterone), which is reported to improve appetite and promote weight gain in patients with cystic fibrosis, AIDS, and cancer, as well as in the frail elderly (Chinuck et al. 2007). Treatment often involves very high doses (up to 800 mg per day) and is associated with a wide range of, often serious, side effects, with the consequent risks to the patient potentially overriding any desired clinical benefits. In addition, the weight gain that accompanies improved appetite with megasterol may result primarily from an increase in adipose mass rather than of lean tissues, the loss of which is a critical factor in the wasting associated with disease and aging. Growth hormone and testosterone have been shown in some trials to promote increases in lean body mass. However, the extent to which such improvements are related to changes in appetite is unknown, and side effects associated with chronic administration again restrict the use of these agents. Overall, the specific benefits of growth hormone and testosterone in relation to appetite remain to be assessed in properly controlled studies and their likely modes of action are currently little understood.

Antihistamines, Antipsychotics, and Antidepressants

One of the older pharmaceutical orexigenic treatments involves the antihistamine cyproheptadine. This drug, which also has anticholinergic properties and acts as a ▶ serotonin antagonist, has been shown to have beneficial effects in some clinical trials of disorders involving weight loss or wasting, including asthma, tuberculosis, and HIV–AIDS (but is seemingly less effective in relation to cancer cachexia). Additionally, there are some tentative findings that the drug may have positive consequences in relation to the treatment of anorexia nervosa (Powers and Santana 2004). The precise mechanism of cyproheptadine action is unknown, which is perhaps unsurprising given the broad pharmacological profile of the drug. However, animal experiments have implicated histamine in appetite control processes, and specifically the inhibition of eating. Thus, the blockade of hypothalamic histamine H_1 receptors by antagonist drugs stimulates eating, while agonists suppress food intake.

Actions on histamine systems may also partly underlie the well-known weight increasing effects of ► antipsychotic drugs (coincidentally, the first widely prescribed neuroleptic drug, ► chlorpromazine, was initially developed as an antihistamine). Both older neuroleptics and the newer atypical antipsychotics (e.g., ► olanzapine and ► clozapine) can stimulate appetite and promote significant weight gain in patients (Casey and Zorn 2001; Kluge et al. 2007; Wirshing 2004). Some studies have demonstrated significant increases in food craving, and even binge eating, in patients treated with atypical antipsychotics. Obviously, these phenomena can both impair general health (by causing or exacerbating comorbidities such as diabetes and cardiovascular disease) and reduce patient compliance with continuing treatments. Although a variety of possible mechanisms may explain these effects (including changes to the peripheral regulation of glucose utilization and fat storage), preclinical data suggest that antipsychotics that are antagonists with high affinity for H_1 are more likely to promote eating and weight gain. Additionally, antipsychotic-induced weight gain has also been linked with antagonistic actions at dopamine D_2, muscarinic ► acetylcholine M_1 and serotonin 5-HT_{2C} receptors, and agonist actions at 5-HT_{1A} receptors. Weight gain in patients taking atypical neuroleptics has also been linked to increased levels of ghrelin.

Weight gain is also a common feature of ► antidepressant treatment. The older tricyclic and monoamine oxidase inhibitors, and some of the selective serotonin reuptake inhibitors (SSRI) can produce significant weight gain, particularly with longer treatments at higher doses. Of the new atypical antidepressants, ► mirtazapine (a noradrenergic and specific serotonergic antidepressant), has pronounced appetite stimulant– and weight gain–inducing properties that have been explored clinically. Mirtazapine hyperphagia has again been attributed to actions on histamine systems, although other mechanisms cannot be precluded.

Benzodiazepines

The ► benzodiazepines have been widely exploited as anxiolytics, ► anticonvulsants, and hypnotics. But, in addition to these effects (and often in conjunction with them), benzodiazepines can exert extremely potent hyperphagic actions. These agents act via specific high affinity benzodiazepine receptors to enhance the inhibitory effects of GABA neurotransmission. In animal models, the hyperphagic actions of benzodiazepines are among the most profound of any class of orexigen, and involve the specific enhancement of the palatability or rewarding properties of food. These effects on appetite appear dissociable from the other psychological effects of benzodiazepines. Surprisingly, although appetite stimulation and substantial increases in food intake have been shown in humans under laboratory conditions, little is known about benzodiazepine effects on food intake or body weight in clinical populations. Despite their potent hyperphagic actions, and adoption by veterinarians to encourage eating in domestic animals, there is little or no recognition within the human clinical literature of these effects of benzodiazepines. However, it is evident from anecdotal reports on various user-oriented Web sites that increased appetite and overconsumption are recognized by patients themselves.

► Mood Stabilizers

A final group of drugs that may stimulate appetite comprises agents with anticonvulsant and/or mood-stabilizing properties used to treat epilepsy and ► bipolar disorder (Ben-Menachem 2007; Martin et al. 2009; Torrent et al. 2008). Within this group (which may also include the benzodiazepines and atypical neuroleptics), ► valproate and ► lithium in particular are associated with significant, unwanted weight gain. Again, the precise mechanisms have yet to be determined. However, valproate (► valproic acid) has been linked to an increase in the motivation to eat, as well as changes in appetite-related neuroendocrine factors – including an increase in levels of the orexigens ghrelin and NPY. Hyperphagic- and weight-increasing tendencies of valproate treatment are of particular concern in relation to childhood epilepsy and the risk for the development of obesity with lifetime treatment. It should be noted however that other anticonvulsants, such as topiramate, are associated with weight loss.

Specificity of Drug Action

Although there are tentative neuroendocrine mechanisms to account for overeating and increased body weight following the administration of different psychotropic drugs, what is missing in relation to most of the agents we have discussed is a clear description of more fundamental psychological/behavioral factors that might contribute to weight gain. For example, it is likely that (in addition to any specific action on appetite control processes or energy balance), sedative effects of neuroleptics, antidepressants, or other agents compound a patient's already diminished ability to maintain a good diet, or to engage in an active, non-sedentary lifestyle. Even if a drug does exert a specific action on appetite, it is unlikely that these effects have been studied in great detail in people (as

opposed to laboratory species). In the absence of detailed behavioral measurements, there is often the implicit assumption that weight gain results from specific motivational adjustments and increased food intake, but this may not be the case. Similarly, it is common to read statements that are largely unsupported by empirical data – such as that a particular drug causes craving for foods high in carbohydrate. Until these issues are properly addressed, appetite stimulant actions of many drugs are likely to remain as little more than an interesting footnote in clinical pharmacology texts, or a side effect listed in the pharmacopeia. A concerted research effort with properly controlled studies is required to identify the most useful and effective drugs that can be used for the specific purpose of increasing appetite, and to understand the mechanisms by which hyperphagia/weight gain may accompany the principal actions of psychiatric drugs.

Conclusion

Overeating and increased body weight are common side effects of many different psychiatric drugs and other medications. However, these phenomena are generally unwanted consequences of treatments: considerable effort is directed toward ameliorating such effects, rather than exploiting them in clinical situations where facilitating appetite and increasing body mass are the desired outcomes. The majority of drugs discussed here provide uncertain benefits in terms of clinically significant appetite stimulation or weight gain, produce their effects through unknown mechanisms, and their administration may entail a broad spectrum of unwanted and potentially health-threatening side effects. By contrast, cannabinoid receptor agonists have established hyperphagic actions, which can be understood in terms of specific neurochemical pathways that mediate appetite control and eating motivation. That these effects may be obtained in the absence of toxic side effects, and at doses below those that induce unwanted psychotropic actions, indicates that this class of drugs is a suitable target for the development of clinically useful appetite stimulants.

Cross-References

- ▶ Acetylcholine
- ▶ Anandamide
- ▶ Anticonvulsants
- ▶ Antidepressants
- ▶ Antihistamine
- ▶ Antipsychotics
- ▶ Benzodiazepines
- ▶ Cannabinoids
- ▶ Endocannabinoids
- ▶ Endorphin
- ▶ GABA
- ▶ Lithium
- ▶ Mirtazapine
- ▶ Naloxone
- ▶ Neuroleptics
- ▶ Neuropeptide Y
- ▶ Opioids
- ▶ Rimonabant
- ▶ Serotonin
- ▶ Steroids
- ▶ Valproate

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Appetite Suppressants

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Synonyms

Anorectics; Hypophagics; Weight control drugs; Weight loss; Weight management drugs

Definition

Any drug that alters ► energy balance by changing eating behavior to reduce caloric intake, thereby producing an energy deficit. These drugs are most often used for the treatment of obesity (excessive body mass) and the cardiometabolic risk factors associated with adiposity (excessive body fat). This contrasts with other pharmacological approaches to weight control which (1) inhibit nutrient digestion or absorption, or (2) prevent the storage or increase the utilization of energy within the body.

Pharmacological Properties

History

Appetite suppressants have traditionally been used to distract patients from feelings of severe ► hunger and for weight control. However, appetite suppressants provide only an option for weight management and historically numerous devices, diets, and other pharmacological treatments have been employed to control body weight. The commercialization of weight control products dates from the start of the mass production of these products and a plethora of "dieting" products have since been marketed. These include diuretics and preparations containing metabolic stimulants such as thyroid hormones.

The first modern appetite suppressant was ► amphetamine. Amphetamine (marketed as Benzedrine) became popular for weight control in the 1930s, and the treatment of obesity became one of its many legitimate medical uses. Amphetamine (dexamphetamine, not metamphetamine) remained available in some countries for weight control until quite recently, despite its psychological effects, effects of blood pressure, and abuse potential. However, after the Second World War amphetamine alternatives were sought. Some of these monoaminergic acting agents were the beta-phenethylamine derivatives, which had lower abuse potential. ► Phentermine became available in 1959 and is still used (under a multiplicity of names including Duromine, Fastin, Adipex, and Lonamin) to treat obesity in many countries despite its amphetamine-like nature. Other amphetamine-like drugs used for weight control, often "off label," include Diethylcathinone (Diethylpropion, Tenuate, Tenuate Dospan, Amfepramone), Mazindol (Mazanor or Sanorex), and ► Phenylpropanolamine (Acutrim and Dexatrim). Along with cardiovascular stimulation, side effects such as insomnia, anxiety, and irritability remain an issue with many of these drugs (Haddock et al. 2002).

From the late 1960s and 1970s the beneficial effects of the amphetamine-related compound ► fenfluramine on body weight were noted. Fenfluramine differed from the other amphetamine alternatives as it primarily acted on serotonergic rather than catecholaminergic systems. It was as effective as amphetamine but lacked the side effect profile and abuse potential (Blundell 1977). Fenfluramine (Pondimin) became available for medical use in the early 1970s and was eventually used in combination with phentermine as "Fen-Phen." The more serotonin (5-HT) selective isomer of fenfluramine, D-fenfluramine (Redux, Adifax), was approved in 1996 in the US for the treatment of obesity, although the drug was widely available outside the US prior to this date. However, in 1997, all forms of fenfluramine were withdrawn from the global market due to serious side effect issues (see side effect section later).

The withdrawal of fenfluramine-based treatments coincided with a growing awareness of the treatment of obesity and obesity-related disease by national health care systems, and the launch of two new antiobesity drugs, the gastrointestinal lipase inhibitor, Orlistat (Xenical, Alli) and the appetite suppressant, ► Sibutramine (Merida, Reductil). Sibutramine is a noradrenergic and serotonergic reuptake inhibitor originally developed in the late 1980s and early 1990s for the treatment of depression. However, it was soon apparent during clinical testing that the drug produced significant weight loss. Further research confirmed that this was primarily due to its selective effects on human appetite. The drug was approved for obesity treatment in the US and other markets in 1997 and despite periodic concerns over safety the drug has remained in use. Despite the growing obesity problems, prescription use of sibutramine and orlistat remained fairly constant and it was not until 2006 that another appetite suppressant successfully came to market.

The endocannabinoid CB_1 receptor antagonist ► Rimonabant (Acomplia) was approved in Europe in 2006 as pharmacotherapy for obesity and resulting comorbidities. However, the drug failed to gain similar approval in the US in 2007 because of persistent concerns over safety data (see later). Due to incidents of adverse psychiatric events, it was later recommended that the drug not be given to those with a history of suicide or related psychiatric problems. In 2009 the drug was withdrawn from all markets. Despite an inability to successfully develop new appetite-suppressing drugs for the treatment of obesity over the last decade, many drugs licensed for other indications produce changes in appetite and body weight. A few of these drugs may eventually become legitimate antiobesity drugs. For instance the glucagon-like peptide (GLP)-1 analog Exenatide (Byetta), approved in the US for the management of type 2 diabetes, has been shown to produce changes in appetite and persistent weight loss in obese diabetics.

Appetite Regulation

Signals that serve to terminate eating behavior and act as powerful inhibitors of further intake are generated from the start of consumption. There is an important distinction between the short-term satiety signals produced by the physiological consequences of meal intake (episodic), and the longer-term signals created by the body's constant metabolic need for energy (tonic). Episodic signals such as GLP-1 are a crucial factor in the meal-by-meal regulation of energy intake, and are critical to both the appetite fluctuations and patterns of eating behavior we undertake throughout the day (Halford and Blundell 2000). Tonic inhibitory signals, by contrast are generated by the storage and metabolism of energy. Whilst episodic and tonic factors comprise separate aspects of appetite regulation, generated by markedly distinct processes, both ultimately act to inhibit food intake via common hypothalamic circuitry (Halford and Blundell 2000).

It is not only the peripheral targets which provide opportunities for drug development. Within the central nervous system (CNS), a complex array of chemicals and structures regulate the expression of appetite, particularly the brain stem and the hypothalamus. The arcuate nucleus (ARC) of the hypothalamus is considered to play a key integrative role between the these afferent signals from the periphery such as glucose, ▶ leptin, insulin, and ghrelin and other CNS changes such as serotonin function. The ARC has neuronal subpopulations that produce ▶ orexigenic (▶ neuropeptide Y (NPY) and ▶ agouti-related peptide (AgRP)) as well as ▶ anorexigenic peptides (α-melanocyte-stimulating hormone (α-MSH)), galanin-like peptide (GALP), and cocaine-and-amphetamine-regulated transcript (CART)). The ARC neurons project to "second-order" neurons implicated in the control of feeding, such as the paraventricular nucleus of the hypothalamus (PVN), the dorsomedial hypothalamic nucleus (DMN), and the lateral hypothalamic area. However, appetite expression is not exclusively a process of homeostatic energy regulation. Our motives for eating are also based in pleasure and other systems, such as the endogenous opioids and endocannabinoids implicated in liking and dopamine implicated in wanting. These are critical in stimulating appetite and sustaining eating behavior (see ▶ Appetite Stimulants). These also provide pharmacological targets for potential antiobesity treatments.

Mechanisms of Action of Past and Present Drugs

With regard to past appetite-suppressing antiobesity drugs, amphetamine and amphetamine-like drugs generally stimulate central noradrenaline and dopamine release and these effects may be mediated by a number of receptors such as α1 and β2 adrenoceptors, and dopamine D_1 and D_2 receptors found in the hypothalamus and other areas of the limbic system. These receptors are probably involved in both, the satiating and rewarding (i.e., "wanting") aspects of food intake. However, any selective effects of amphetamine on the motivation to feed tend be masked by other behavior changes which disrupt feeding (e.g., hyperactivity). Of all the monoamine neurotransmitters, it is ▶ serotonin (5-HT) that has been most closely linked with the process of ▶ satiation and the state of ▶ satiety. Both fenfluramine and D-fenfluramine are 5-HT releasing agents and have been shown to induce satiety in both rodent and animal models. These effects appear to be mediated by the 5-HT_{1B} and the 5-HT_{2C} receptors on neurons projecting from the ARC into the hypothalamus. Unfortunately, activation of other serotoninergic receptors, particularly 5-HT_{2B} receptors in the periphery, led to the withdrawal of these drugs. This has driven research into far more selective 5-HT based antiobesity drugs.

Sibutramine is a selective noradrenergic and serotonergic reuptake inhibitor. Upon administration sibutramine is rapidly broken down into its first (BTS 54354) and then second (BTS 54505) metabolites. The metabolites are both far more potent reuptake inhibitors in vivo and it is to these metabolites that sibutramine predominately owes its action. Selective antagonism of sibutramine ▶ hypophagia has demonstrated that α1 adrenoceptors are critically involved in sibutramine's effect on food intake, with some role also for β2 adrenoceptors and serotoninergic $5\text{-HT}_{2A/2C}$ receptors. Sibutramine produces changes to feeding behavior in rodents and appetite in humans similar to those produced by D-fenfluramine and other 5-HT drugs, suggesting changes in feeding behavior may be mediated by central serotonin mechanisms (Halford et al. 1998; Heal et al. 1998).

With regard to rimonabant, the drug is an ▶ inverse agonist of the CB_1 receptor, which is widely distributed throughout the CNS and periphery. The role of endocannabinoid receptors in the natural operation of appetite has yet to be fully determined (see ▶ Appetite Stimulants) and surprisingly little published data on the effects of CB_1 drugs on human appetite expression are available. However, evidence suggests that the endocannabinoid system may be more involved in hedonic rather than homeostatic aspects of appetite control (Tucci et al. 2006).

Animal Models

Feeding is an essential part of an animal's behavior and, in this respect, need not be artificially modeled. Rodents,

like humans, show a tendency to gain weight when exposed to a highly palatable energy dense diet and during this period they demonstrate marked ▶ hyperphagia. Animal models of obesity provide important indices for the assessment of potential therapeutic effects such as changes in adiposity and body fat distribution, and in key endocrine and metabolic factors. Behavioral indices such as hyperphagia are necessary for assessing the potential efficacy of appetite-suppressing, antiobesity drugs. The nature of drug-induced hypophagia is critical in determining if a potential appetite-suppressing antiobesity drug can progress into clinical trials. Drugs can reduce food intake in rodents and humans in a variety of ways, through the induction of nausea or malaise, or through CNS-related effects such as hyperactivity or sedation. Such effects, even if secondary to drug action on mechanisms of satiety or food preference, prevent the compound being of any clinical value. One of the most detailed behavioral assays of drug action on appetite expression is the behavioral satiety sequence (BSS) (Halford et al. 1998 for review). The BSS examines the microstructure of rodent behavior, and the sequence consists of a stochastic progression of behavior from an initial phase of eating, through peaks of active and grooming behavior, to an eventual phase of predominately resting behavior. The BSS appears robustly related to the processes of satiation (meal termination) and the development of satiety (post-ingestive inhibition of eating).

Assessing the Effects of Drugs on Human Feeding Behavior

A variety of approaches to measuring the effects of antiobesity drugs on human food intake can be employed. Laboratory-based observation studies provide more precision and reliability at the expense of "naturalness" (Hill et al. 1995). In human studies, researchers are able to assess the effects of drugs on subjective experiences of appetite to confirm any satiety-enhancing effect. Self-report scales have been used to determine the nature of a drug's effect on food intake in some of the earliest human studies (Hill et al. 1995). The measures come in a variety of forms but the most widely accepted format is the Visual Analog Scale (VAS). It is interesting to note that ratings of appetite sensations are not only predictors of energy intake but also of body weight loss (Drapeau et al. 2007). The effects of drugs on parameters within a meal have also been studied for nearly 30 years. Rogers and Blundell (1979) clearly demonstrated that whilst amphetamine and fenfluramine both reduced food intake, the increase in eating rate produced by amphetamine represents the activating effects of the drug, whilst the reduction in eating behavior produced by fenfluramine represents enhanced satiety. Sibutramine appears to produce similar effects to fenfluramine on eating rate (Halford et al. 2008).

Efficacy

Many drugs produce changes in appetite expression and reduce food intake in humans. In fact, serotonergic drugs such fenfluramine, D-fenfluramine, the selective serotonin reuptake inhibitors fluoxetine and sibutramine have all been shown to reduce caloric intake, premeal hunger and enhance postmeal satiation in humans. In contrast, other centrally acting agents such as ▶ opioid antagonists have been shown to decrease the liking for pleasant or preferred foods demonstrating the distinct role of the endogenous opioid system in hedonic aspects of appetite control. Endocannabinoid CB_1 receptor antagonists/inverse agonists such as rimonabant and taranabant have been show to reduce caloric intake in humans also. The nature of this drug-induced reduction in food intake remains unclear with little strong evidence to suggest how they alter human appetite expression. A number of peripheral factors have been shown to reduce food intake and enhance satiety. These include CCK, GLP-1 and Peptide YY (PYY). GLP-1 and PYY remain the basis for a number of potential antiobesity drugs under development (Halford 2006).

The ultimate test/indication of efficacy of any antiobesity drug is sustained and clinically meaningful weight loss (usually accepted as 5–10% reduction from baseline) rather than short-term reductions in intake. In addition, regulatory authorities also demand reductions in risk factors for cardiovascular and metabolic diseases. These include high fasting and postprandial blood glucose, HbA_{1c} (glycosylated hemoglobin), insulin, total plasma cholesterol, low density lipoproteins (LDL), triglycerides, uric acid, and blood pressure. Very little reliable data are available regarding the efficacy effects of amphetamine or other early appetite suppressants. Similarly, the published data for fenfluramine and fen-phen are limited. Meta-analysis suggests that fenfluramine could produce placebo-subtracted weight loss of 2.4 kg in trials over an average of 10 weeks. D-fenfluramine produces average placebo-subtracted weight loss of 3.8 kg over an average of 33 weeks. Sibutramine produces averaged placebo-subtracted weight loss in the region of 4.3 kg over 1 year (seen in the first 6 months of treatment), which compares to 2.7 kg over 1 year produced by orlistat (a non-appetite suppressant antiobesity drug) and 4.8 kg produced by the recently withdrawn rimonabant. These changes are accompanied by significant improvements in

aforementioned cardio-metabolic risk factors (Haddock et al. 2002; Padwal et al. 2003).

Safety/Tolerability

Because of their diverse mechanisms of action, the safety and tolerability of appetite suppressants vary greatly between drugs. Amphetamines are now virtually withdrawn across the globe and are not recommended because of significant cardiovascular and CNS side effects and a potential for dependence. However, phentermine and diethylpropion are still used in some countries but are not recommended for routine or prolonged use. Side effects with phentermine include increased heart rate and blood pressure, nervousness, restlessness, and insomnia. Diethylpropion possesses a similar side effect profile including dizziness, headache, sleeplessness, nervousness, and the possible risk of pulmonary hypertension. The side effects associated with fenfluramine-based treatments include diarrhea, dry mouth, and drowsiness. These drugs were withdrawn due to valvular heart disease and pulmonary hypertension.

The side effects associated with sibutramine include cardiovascular effects (such as an increase in systolic and diastolic blood pressure, an increase in heart rate, tachycardia, palpitations, and vasodilatation), and gastrointestinal effects (including constipation and nausea). Other effects include dry mouth, insomnia, light-headedness, paraesthesia, and aesthesia. Most side effects occur within the first 4 weeks of treatment and decrease in severity and frequency with time. With rimonabant, the most commonly reported side effects were nausea, dizziness, diarrhea, and anxiety. FDA approval for rimonabant was withheld over concerns over suicidality, depression, and other related side effects associated with use of the drug. Reports of severe depression were frequent. This led to the recent withdrawal of the drug. With regard to the GLP-analog exenatide (Byetta), the most commonly recorded side effects are gastrointestinal and warnings have been issued by regulatory authorities over acute pancreatitis.

Cross-References

- ► Appetite Stimulants
- ► Cannabinoids
- ► Cholecystokinins
- ► Hypocretins/Orexins
- ► Leptin
- ► Liking and Wanting
- ► Palatability
- ► Somatostatin

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Appetitive Conditioning

► Conditioned Taste Preferences

Appetitive Responses

Synonyms

Approach response; Preparatory behavior

Definition

These are responses evoked when an organism is exposed to stimuli previously associated with a reinforcer, such as the application of a natural goal object or a self-administered drug. The responses are ones that bring

the organism into contact with the actual reinforcer. They serve a searching or preparatory function.

Cross-References

► Conditioned Place Preference and Aversion
► Conditoned Reinforcer
► Conditioned Taste Preferences

Approach-Avoidance

► Punishment Procedures

Approach Response

► Appetitive Responses

Approval and Marketing of Psychotropic Drugs

► Ethical Issues in Human Psychopharmacology

2-Arachidonoylglycerol

Definition

An endocannabinoid, abbreviated 2-AG.

N-Arachidonylethanolamine

Synonyms

AEA; Anandamide

Definition

An endocannabinoid; also called anandamide.

ARC

► Addiction Research Center

ARCI

► Addiction Research Center Inventory

Area Under the Curve

Synonyms

AUC

Definition

The area under curve, AUC, corresponds to the integral of the plasma concentration versus an interval of definite time. In practice, the approximation is used: AUC = $\int$ ([C] $\times$ Dt), where [C] is measured concentration and Dt is interval of time between two measurements. The precision of the AUC grows with the number of measurements of concentration taken. The AUC is expressed in mass (mg, g) $\times$ L^{-1} $\times$ h.

Cross-References

► Bioavailability
► Elimination Half-Life or Biological Half-Life
► Pharmacokinetics

Arginine-Vasopressin

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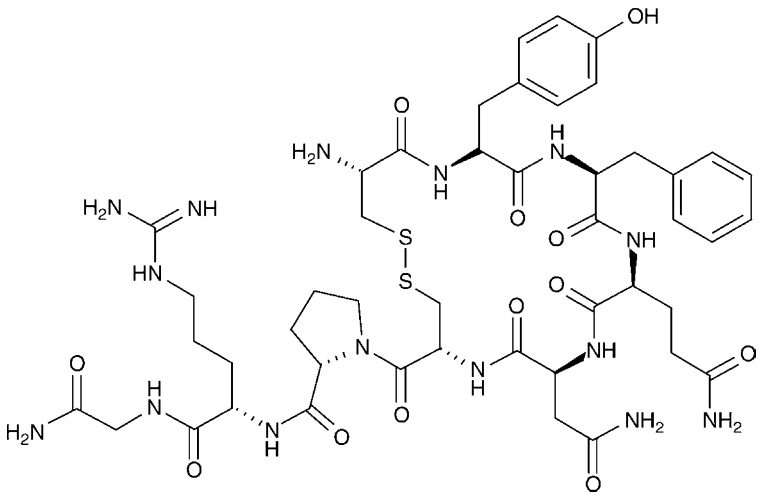
Synonyms

ADH; Antidiuretic hormone; AVP; Vasopressin

Definition

Arginine-vasopressin (AVP) is a nine-amino acid peptide, which is synthesized and released from nerve terminals in the central nervous system (CNS) (Fig. 1). In the brain, AVP acts as a modulator of neuronal function and is involved in the control of stress, anxiety, cognitive behaviors, ► circadian rhythms, and autonomic function. AVP is also released from nerve terminals into the blood stream where it regulates water absorption and urine production



Arginine-Vasopressin. Fig. 1. Arginine-vasopressin (AVP).

in the kidney, and glucose and fatty acid metabolism in the liver, and it increases arterial blood pressure and heart rate.

Pharmacological Properties

The Neuroanatomy of the Central AVP System

AVP is synthesized in neurons of the hypothalamus (Ring 2005). AVP-containing neurons are located in three hypothalamic structures: the supraoptic nucleus (SON), the paraventricular nucleus (PVN), and the suprachiasmatic nucleus (SCN). AVP produced in the SON is transported to nerve terminals of the posterior pituitary and is released in response to changes in plasma osmolality and decreased blood pressure. AVP from the PVN is released into the hypothalamic–hypophyseal portal blood, which supplies the anterior pituitary. The AVP-containing neurons of the PVN also project to the regions of the hindbrain and spinal cord, which are involved in control of the autonomic function. The AVP neurons of the SCN are involved in the control of circadian rhythms. AVP synthesis occurs also in the bed nucleus of the stria terminalis (BST) and the medial amygdaloid nucleus (MeA). The vasopressin neurons in the BST project to the lateral septum, amygdaloid areas, the locus coeruleus, and the dorsal raphe, while MeA neurons project to the ▶ hippocampus and lateral septum. These neuronal pathways are likely to underlie the effects of AVP on stress, anxiety, fear, and social cognitive behavior (▶ Social Recognition and Social Learning). The degree of AVP expression in the brain is gender specific, with males having denser AVP levels than females (Frank and Landgraff 2008) due to an effect of ▶ sex hormones on AVP expression. Sex hormones may exert some of their effects on social cognitive behaviors, such as pair-bonding and parent-offspring relationships, through influencing AVP expression in the CNS.

Arginine-Vasopressin Receptors in the CNS

The biological effects of AVP are mediated via interaction with a family of ▶ G-protein-coupled receptors (▶ GPCRs) (Ring 2005). There are four known vasopressin receptor subtypes (V_{1a}, V_{1b} (V_3), V_2, and oxytocin (OT)) defined on the basis of differences in pharmacology and tissue distribution. Activation of the V_{1a}, V_{1b}, and OT receptors stimulates a number of signal transduction pathways via Gq G-protein coupling to phospholipase C, while activation of the V_2 receptor by AVP stimulates adenylyl cyclase via Gs coupling (▶ Receptors; Functional Assays).

The V_{1a} receptor is the predominant AVP receptor found in the brain, localized in the cortex, hippocampus, ▶ amygdala, septum, ▶ hypothalamus, and thalamus. The V_{1a} receptor plays a dominant role in the behavioral effects of AVP. In the periphery, V_{1a} receptors are expressed in vascular smooth muscle cells, hepatocytes, ▶ platelets, adrenal cortex, uterus cells, kidney, spleen, and testis. The V_{1b} receptor is expressed in corticotrophs of the anterior pituitary and throughout the brain, especially in the pyramidal neurons of the hippocampal CA2 field, although at lower levels than the V_{1a} receptor. In the anterior pituitary, the V_{1b} receptor modulates adrenocorticotrophin (ACTH) secretion. The V_{1b} receptor is also expressed in kidney, pancreas, and adrenal medulla, although the functional significance of expression in these tissues is unclear. Vasopressin V_2 receptors are primarily

expressed in the kidney, where their primary function is to respond to AVP by stimulating mechanisms that concentrate the urine and maintain water homeostasis. The V_2 receptor is understood to have a limited expression in the CNS. The OT receptor is expressed in the CNS in the amygdala and hippocampus and brain regions involved in the regulation of stress (► Social Stress) responses and social behavior (► Social Recognition and Social Learning). The OT receptor is also expressed in uterus and mammary gland, where its primary function is to induce uterine contractions and milk ejection.

The Effect of AVP on CNS Function

Effects on Neuronal Excitability: AVP directly controls neuronal excitability and hence, is described as a modulator of synaptic transmission (Raggenbass 2008). In general, AVP exerts an excitatory effect on neuronal activity (e.g., in hippocampus, amygdala, spinal cord), although an inhibitory influence of AVP has also been described (e.g., in the lateral septum). AVP alters neuronal excitability, and hence synaptic transmission, through modulation of ion-channel activity, leading to activation of a cationic inward current and/or reducing potassium conductance. In the rat hippocampus, for example, AVP enhances excitatory post-synaptic currents and long-term potentiation (LTP) (► Long Term Potentiation and Memory; ► Synaptic Plasticity). Hippocampal LTP is the long-lasting improvement in synaptic communication which is postulated as one of the cellular mechanisms underlying learning and memory. Thus, the benefits of AVP on cognitive function may be exerted by virtue of its influence on LTP.

Control of cardiovascular function: Brain AVP is suggested to play a role in the regulation of blood pressure under both normal and pathophysiological conditions (Toba et al. 1998). Central AVP influences the cardiovascular system via modulation of both sympathetic and parasympathetic function (Raggenbass 2008). Administration of AVP into the CNS results in an increase in blood pressure and heart rate which is most likely to be mediated via enhancement of sympathetic nervous system outflow from the CNS to the heart and vasculature.

Temperature regulation: Administration of AVP directly into the CNS of rats causes a reduction in body temperature, although there is little evidence to suggest that AVP plays a role in normal thermoregulation. However, AVP arising from BST has been described as an antipyretic, in that it can reduce increases in temperature during fever (Pittman et al. 1998).

Water homeostasis: AVP derived from the neurons of the PVN and SON of the hypothalamus is released into the circulation following osmotic challenge, for example, dehydration and high sodium levels. Under these conditions, plasma AVP, via activation of V_2 receptors, induces increased reabsorption of water in the kidney. Inadequate secretion of AVP from the posterior pituitary and/or abnormal kidney responsiveness to AVP results in diabetes insipidus, which is characterized by excessive urination and thirst.

Circadian rhythms. The SCN of the hypothalamus is the site of the master circadian clock which generates 24-h circadian rhythms in mammals. AVP is one of the dominant neuropeptides expressed within the SCN and exhibits a diurnal pattern of synthesis and release, with increased levels of AVP secretion occurring during the day in both rats and humans (Ingram et al. 1998). Brattleboro rats, which lack vasopressin peptide due to a mutation in the AVP gene, still express circadian rhythms, although of reduced amplitude. Thus, AVP is not critical to circadian clock function but plays a role in amplifying clock rhythmicity. The AVP-containing neurons of the SCN transmit a circadian signal to the other parts of the brain by which they may regulate behavioral, neuroendocrine, and autonomic nervous system processes in a circadian fashion, for example, controlling the rhythmic release of cortisol and the circadian pattern of motor behavior and appetite.

Social recognition and social learning: Social relationships are a key feature of many species. Although the underlying neurobiology of social behavior/cognition is not well understood, there is an emerging hypothesis that AVP may play a role (Donaldson and Young 2008). Rats and mice are an excellent model species for studies of the involvement of AVP on social behavior given their natural tendency to explore unfamiliar individuals. In rats and mice, direct administration of AVP into the brain prolongs the duration of social memory. By contrast, vasopressin receptor antagonists impair social memory, probably due to disruption of the acquisition, storage, and/or recall of social olfactory cues (Frank and Landgraff 2008). Studies in which vasopressin receptor antagonists or V_{1a} receptor ► Antisense Oligonucleotides are applied directly into specific brain regions implicate a role for the V_{1a} receptor in the lateral septum in the regulation of social recognition. Furthermore, mice which lack the V_{1a} receptor exhibit deficits in social recognition behaviors which can be restored upon reexpression of the V_{1a} receptor in the lateral septum. Deficits in social recognition behaviors have also been described in V_{1b} receptor knock-out mice. A possible role for AVP in the regulation of parental behavior has also been described. Paternal behavior in the male prairie vole is enhanced following

AVP administration into the CNS, whereas vasopressin receptor antagonists disrupt this behavior. AVP is also implicated in maternal care, with increased brain AVP levels being described during the late stages of pregnancy, parturition, and lactation in the rat. Thus, enhanced parental behavior is correlated with increased AVP function.

The exact effects of AVP on social behaviors can vary from one species to the next, most likely due to differences in the pattern of brain V_{1a} receptor expression between species. For example, the differences in pair bonding observed between the monogamous prairie vole and the polygamous montane vole are regulated by the pattern of V_{1a} receptor expression in the brain (Donaldson and Young 2008). Male prairie voles exhibit mating-induced partner preferences, care for their offspring, and exhibit ► aggressive behavior to other males within the same species, unlike the polygamous montane vole. Analysis of V_{1a} receptor distribution shows that the polygamous montane vole exhibits a lower level of receptor expression in the ventral forebrain/ventral pallidum in comparison with the monogamous prairie vole. Expression of the prairie vole V_{1a} receptor gene in the ventral pallidum of the meadow vole resulted in increased pair bond formation, in a manner similar to the prairie vole. Genetic studies have identified an insertion of approximately 500 base pairs of a repetitive sequence (microsatellite) upstream of the prairie vole V_{1a} receptor gene. By contrast, the same region upstream of the montane vole V_{1a} gene is only around 50 base pairs long. This microsatellite region may influence the expression pattern of the V_{1a} receptor, leading to differences in mating behavior between these two species.

It is a challenge to extrapolate the data obtained from the rodent studies described above, where social behaviors are heavily reliant on olfactory cues, to humans, where social behaviors are more dependent upon auditory and visual cues. To date, the modulatory effect of AVP on social behavior in humans has not been extensively studied. Even so, in humans, there is an emerging hypothesis that genetic variations in the V_{1a} receptor locus may also influence behaviors such as partner bonding and parental care (Donaldson and Young 2008). Variations in the V_{1a} receptor gene have also been associated with the social behavioral deficits underlying autism (► Autism Spectrum Disorders and Mental Retardation). Deficits in social behavior are a key feature of other psychiatric diseases such as ► schizophrenia, social phobia (► Social Anxiety Disorder), and depression. As such, gaining a better understanding of the role of AVP in the regulation of social behavior may lead to the development of treatments that are able to address the social deficits of these disorders.

The involvement of AVP in nonsocial cognitive function is unclear. The majority of studies in rodents point toward a facilitatory effect of AVP on nonsocial memory, mainly via an effect on memory retrieval (► Cognitive Enhancers). Loss of vasopressin receptor function, either via genetic knock-out or through antagonist administration, can alter performance in some but not all tests of nonsocial cognitive behavior. Clinical data also indicate that AVP enhances ► attention and arousal but does not have a direct effect on memory per se. Indeed, AVP does not improve cognitive function in individuals suffering from age-related memory impairment.

Regulation of stress and emotional behaviors. The hypothalamic pituitary adrenal (HPA) axis is the main neuroendocrine system involved in regulation of the "flight, fight, fright" response to a stressful stimulus. Exposure to stress (social stress) results in the release of AVP and ► corticotrophin releasing factor (CRF) from the hypothalamus into the portal vessel system. Both AVP and CRF act on receptors on the anterior pituitary (V_{1b} and CRF1, respectively) to stimulate ACTH release. In turn, ACTH stimulates the release of glucocorticoids such as cortisol (in humans) or corticosterone (in rodents). Glucocorticoids trigger physiological changes (e.g., glucose mobilization, suppression of the immune response, increased cardiovascular tone) required to enable the organism to respond appropriately to a stressor. Studies suggest that CRF plays a critical role in both basal and acute-stress-induced ACTH release whereas AVP, which has weaker secretory activity, may have a lesser role (Aguilera and Rabadan-Diehl 2000). However, when co-released, AVP can act synergistically with CRF to amplify the ACTH release response.

There is mounting evidence suggesting that abnormalities in HPA axis responsiveness may underlie psychiatric disorders that are associated with impaired stress-coping (e.g., depression, anxiety) and a shift toward AVP drive of HPA axis function underlies these abnormalities. Exposure to repeated or chronic stress causes an upregulation of AVP levels, increased V_{1b} receptor expression, and downstream signaling. Through this mechanism, AVP may contribute to the sensitization of the ACTH/cortisol response that occurs following chronic stress. Both clinical and animal studies show a correlation between increased anxiety behavior and elevated AVP levels. In studies where the cholecystokinin B receptor agonist, pentagastrin, (► Cholecystokinins) is used to stimulate anxiety in healthy volunteers, a correlation between the severity of symptoms and AVP levels has been observed. Vasopressin-deficient Brattleboro rats exhibit less anxiety-related behaviors in comparison with normal rats. Rats and mice that have been selectively bred

for high anxiety-related behaviors in the ► elevated plus-maze anxiety model (► Anxiety: animal models) exhibit increased brain AVP expression in comparison with low-anxiety behavior counterparts (Frank and Landgraff 2008). Application of V_{1a} receptor antagonists to "high anxiety" rats reduces anxiety-related behaviors. In addition, over-expression of the V_{1a} receptor gene in the lateral septum significantly increases anxiety-related behavior, implicating the V_{1a} receptor in the anxiety response.

► Aggression: There are strong data from animal studies suggesting that AVP promotes aggressive behavior (Ferris 2005). Administration of AVP directly into the brain facilitates attack behavior in rats and hamsters. The effects of AVP on aggressive behavior probably occur through an interaction with the serotonin system (Serotonin agonists and antagonists); serotonin being associated with a reduction in aggressive behavior. Studies with knock-out mice or vasopressin receptor antagonists indicate that the effects of AVP on aggressive behavior are mediated through both the V_{1a} and V_{1b} receptors. In patients with personality disorders, increased cerebrospinal fluid (CSF) levels of AVP are correlated with a life history of aggressive behavior. Furthermore, intranasal AVP administration in men causes an enhanced emotional response to neutral stimuli, consistent with an increased perception of threat. From a clinical perspective, interpersonal violence can be a feature of antisocial behavior which can exist alongside psychiatric illnesses, such as ► bipolar disorder, ► attention-deficit hyperactivity disorder (ADHD) (► Attention Deficit and Disruptive Behavior Disorders), post-traumatic stress disorder (► Traumatic Stress (Anxiety) Disorder), and autism (► Autism Spectrum Disorders and Mental Retardation). However, the involvement of AVP in regulation of aggressive behavior associated with psychiatric disorders in humans has not yet been established.

Involvement of AVP/Vasopressin Receptors in Psychiatric Disorders

Anxiety: Anxiety disorders (► Generalized Anxiety Disorder) are associated with feelings of apprehension, tension or uneasiness. The ► amygdala is the region of the brain which is proposed to play a pivotal role in anxiety and fear. This brain structure contains high levels of vasopressin receptors and AVP causes excitation of amygdala neurons. Furthermore, animal studies have demonstrated a clear correlation between AVP levels and anxiety behavior (► Anxiety: animal models), and data are emerging to suggest that this correlation may also exist in humans. Unfortunately, the data linking alterations in the AVP system to clinical anxiety disorders are sparse, and more research in this area is warranted. Nevertheless, the preclinical data indicate that vasopressin receptors are a suitable target for the development of drugs for the treatment of anxiety-related disorders.

Depression: Major depressive disorder is characterized by depressed mood and lack of pleasure or interest and may include symptoms such as appetite disturbances, sleep abnormalities, concentration difficulties, and suicidal thoughts. Clinical studies have shown that the central AVP system is altered in depressed individuals (Ring 2005). Elevated AVP concentrations in the brain and CSF, and alterations in V_{1a} receptor density in post-mortem analysis of brain tissue from depressed individuals have also been described. Elevated AVP levels in the plasma of depressed patients have also been observed, and the neuroendocrine response to vasopressin agonists is increased in depressed subjects in comparison with healthy volunteers. These data have led to the suggestion that AVP receptor antagonists may prove useful for the treatment of the symptoms of depression (► Antidepressants: Recent Developments).

Schizophrenia: A feature of ► schizophrenia is a deficit in the ability to filter out unnecessary information. These deficits are exhibited in measures such as ► prepulse inhibition (PPI) in which a weaker prestimulus inhibits the reaction of an organism to a subsequent strong startling stimulus. Deficits in PPI have been described in V_{1b}-receptor knock-out mice, indicating that loss of vasopressin receptor function can cause sensorygating abnormalities. Abnormalities in levels of plasma, CSF, and brain AVP in schizophrenic patients have been described, but not consistently across all studies. Given that AVP has been implicated in regulation of social cognitive behaviors and dysfunction of these behaviors are a core symptom of schizophrenia, it is possible that abnormalities in the central AVP system may underlie these symptoms. However, the data supporting this hypothesis should be considered as being preliminary.

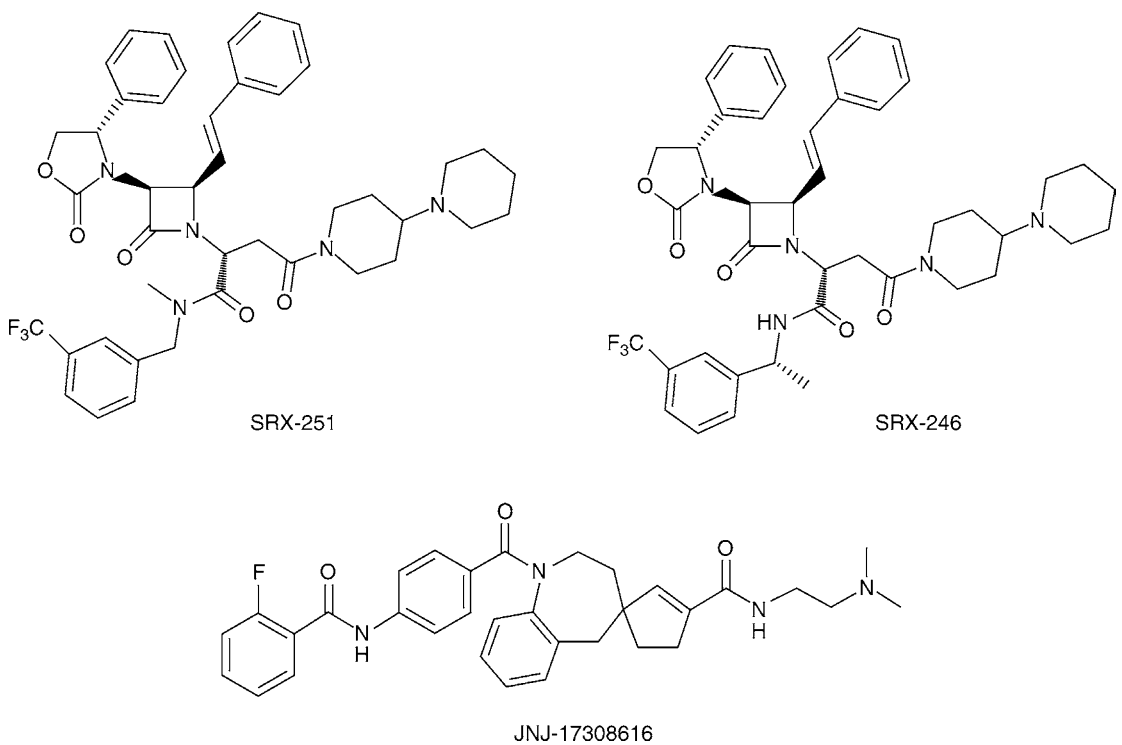
Autism: Individuals diagnosed with autistic disorder (► Autism Spectrum Disorders and Mental Retardation) generally appear to be uninterested in social contact, exhibit impaired communication, and display patterns of repetitive behavior. Autistic disorder is believed to result from a complex interaction between several genetic and environmental factors, although the exact mechanisms involved are poorly understood. Considering that a role for AVP in modulation of social behavior has been established, it is plausible to suggest that alterations in the AVP system may underlie at least some of the behavioral abnormalities that are associated with autism (Frank and Landgraff 2008). Genetic analysis of the regulatory region

upstream of the V_{1a} receptor gene has identified a polymorphic microsatellite which is associated with autism. However, little is known about the functional impact of these genetic variations on V_{1a} gene expression, and whether they contribute to the behavioral changes associated with autism is open to debate. Further studies are therefore required to establish whether alterations in the AVP system contribute to the symptoms of autism.

Vasopressin Receptor Antagonists in Psychiatric Drug Development

Vasopressin V_{1a} and V_{1b} receptor antagonists are widely recognized to represent a novel approach for the treatment of depression and anxiety. The identification and development of high-affinity, nonpeptidic ligands with the desired drug-like properties for oral bioavailability (and CNS penetration), however, is proving challenging.

V_{1a} Antagonists: A number of pharmaceutical companies have developed potent-selective V_{1a} antagonists for peripheral indications such as cardiovascular/circulatory indications and dysmenorrhoea (pelvic pain associated with menstruation). Few V_{1a} antagonists, however, have been identified with good brain penetration, a prerequisite for psychiatric drug development given the localization of the V_{1a} receptor. Azevan Pharmaceuticals describe two CNS penetrant compounds: SRX-246 (4-(bipiperidin-1′-yl)-4-oxo-2(R)-[2-oxo-3(S)-[2-oxo-4(S)-phenyloxazolidin-3-yl]-4(R)-(2-phenylvinyl)azetidin-1-yl]-*N*-[1(R)-phenylethyl]butyramide) and SRX-251 (4-(bipiperidin-1′-yl)-*N*-methyl-oxo-2(R)-[2-oxo-3(S)-[2-oxo-4(S)-phenyloxazolidin-3-yl]-4(R)-(2-phenylvinyl) azetidin-1-yl]-*N*-[3-(trifluoromethyl)benzyl]butyramide), achieving brain levels of compound ~100 times in vitro receptor affinities following oral dosing. SRX-251 is being evaluated in the clinic for the treatment of pain associated with primary dysmenorrhoea and preclinically for the management of agitation and violence. SRX-251 reduces aggression in a hamster model of offensive aggression with no effect on olfactory communication, motor activity, or sexual motivation (Ferris 2006). SRX-246 is currently in preclinical development for the treatment of anxiety/depression. Johnson and Johnson have described JNJ-17308616 (*N*-(2-(dimethylamino)ethyl)-1-(4-(2-fluorobenzamido)benzoyl)-1,2,3,5-tetrahydrospiro[benzo[b]azepine-4,1′-cyclopent[2]ene]-3′-carboxamide), a potent and selective V_{1a} antagonist both in vitro and in vivo. The anxiolytic activity of JNJ-17308616 has been demonstrated by a number of groups in a variety of

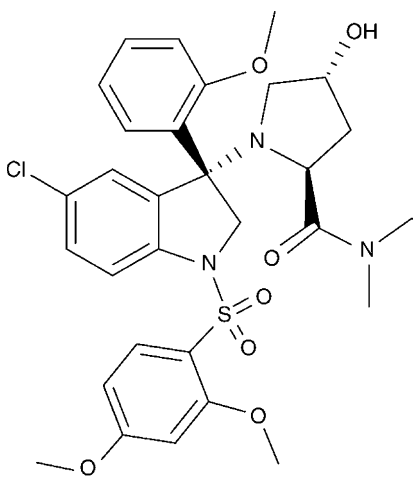


Arginine-Vasopressin. Fig. 2. V_{1a} Antagonists in psychiatric drug development.

animal models of anxiety behavior (► Anxiety: animal models), including the rat-elevated plus-maze, rat-elevated zero-maze, rat-conditioned lick suppression, rat- and guinea pig-pup separation-induced ultrasonic vocalization and mouse marble burying. JNJ-17308616 was also shown to reduce isolation-induced aggression in mice. JNJ-17308616 neither impaired social recognition, induced sedation nor reduced locomotor activity (Fig. 2).

V_{1b} Antagonists: Given the localization of the V_{1b} receptor in the anterior pituitary, and the role of this receptor in driving the neuroendocrine stress response, CNS penetration may not be a requirement for a V_{1b} antagonist aimed at treating psychiatric disorders. To date, only two pharmaceutical companies, Sanofi-Aventis and Abbott Laboratories, have progressed selective V_{1b} antagonists into clinical development. Nelivaptan (SSR-149415) was being evaluated by Sanofi-Aventis in clinical trials for the treatment of anxiety and depression, but was discontinued for both indications in 2008. Preclinical data reported by Sanofi-Aventis have shown that nelivaptan (SSR-149415) (Fig. 3) reduces CRF- and AVP-induced increases in plasma ACTH in male rats (Frank and Landgraff 2008). Nevilaptan (SSR-149415) is reported to strongly reverse stress-induced behavior as measured in the rat-elevated plus-maze, mouse defense test battery, rat- and guinea pig-pup separation-induced ultrasonic vocalization models (► Anxiety: animal models), supporting the rationale for a V_{1b} antagonist in the treatment of stress-induced anxiety. Anti-depressant-like activity was also demonstrated in the forced swim test model of depression (► Depression: Animal Models) and in the differential reinforcement of low rate 72s (DRL-72s) model (► Operant Behavior in Animals). Abbott Laboratories are investigating a series of selective V_{1b} antagonists in the clinic for the potential treatment of depression and anxiety. In preclinical studies, two compounds ABT-436 and ABT-558 (structures not reported) were shown to inhibit vasopressin- and stress-induced increases of stress hormones in mice, a preclinical model of the HPA axis dysregulation implicated in depression and anxiety. ABT-436 and ABT-558 were shown by Abbott to have comparable antidepressant and anxiolytic effect to nelivaptan (SSR-149415) in preclinical behavioral models (Fig. 2).

The identification and development of vasopressin antagonists targeting CNS receptor subtypes represents a promising new therapeutic class for the treatment of anxiety and depression. As such, selective V_{1a} and V_{1b} and mixed V_{1a}/V_{1b} antagonist programs remain a focus for many pharmaceuticals with increasing numbers of novel chemical series appearing in the patent literature.



Nevilpatan (SSR-149415)

Arginine-Vasopressin. Fig. 3. V_{1b} Antagonists in psychiatric drug development.

Cross-References

► Excitatory postsynaptic currents
► G-protein-coupled receptor
► Glucocorticoid

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ARND

► Alcohol-Related Neurodevelopmental Disorder
► Foetal Alcohol Spectrum Disorders

Aripiprazole

Definition

Antipsychotic drug of the second generation, atypical category with partial agonist properties at dopamine D2 receptors, as well as at serotonin$_{1A}$ receptors, and in addition antagonist properties at serotonin$_2$ receptors.

Aropax

► Paroxetine

Arousal Disorders

► Parasomnias

Arylalkylamines

► Trace Amines

Asperger's Disorder

Definition

Asperger's disorder exhibits a qualitative impairment in social interaction and repetitive and stereotyped patterns of interests, behavior, and activities. There is no delay in language ability, cognitive development, or adaptive behavior.

Cross-References

► Autism Spectrum Disorders and Mental Retardation

Assessing Brain Function

► Magnetic Resonance Imaging (Structural)

Assessments

► Rating Scales and Diagnostic Schemata

Associated Depression in Schizophrenia

► Postpsychotic Depressive Disorder of Schizophrenia

Associative Learning

► Classical (Pavlovian) Conditioning
► Verbal and Non-Verbal Learning in Humans

At-Risk Mental State

► Pre-psychotic States and Prodromal Symptoms

Ataxia

Definition

Unsteady gait resulting from impaired motor coordination or balance.

Ataxin-3 Transgenic Mice

Definition

A transgenic method that expresses a mutant form of ataxin-3, which accumulates inside the cells and leads to progressive neuronal degeneration.

Atomoxetine

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Synonyms

(3R)-*N*-methyl-3-(2-methylphenoxy)-3-phenyl-propan-1-amine; Tomoxetine; Atomoxetine hydrochloride;

LY139603; Methylphenoxy-benzene propanamine; Strattera™

Definition

Atomoxetine is a highly selective centrally acting norepinephrine reuptake inhibitor (SNRI), licensed for the treatment of attention-deficit hyperactivity disorder (ADHD) in USA, United Kingdom, and elsewhere. Atomoxetine is a white solid intended for oral administration.

Pharmacological Properties

► Pharmacokinetics

Following oral ingestion with or without food, atomoxetine is rapidly absorbed with peak plasma levels occurring at approximately 1–1.5 h (Sauer et al. 2005). With regular dosing, steady-state concentrations are obtained by day 10, with trough plasma concentrations of ~30–40°ng/mL. The metabolism of atomoxetine is dependent primarily on the hepatic ► cytochrome P450 (CP450) system, which is highly polymorphic such that individuals can be classified into extensive metabolizers (EMs) or poor metabolizers (PMs) (Trzepacz et al. 2008). The majority of people (>90%) are EMs, while rarer PM individuals or individuals taking enzyme inhibitor medications, show fivefold greater peak plasma concentration and slower ► half-life elimination. Following a single oral dose, EMs exhibit an atomoxetine half-life of ~5.2 h with plasma clearance of ~0.35 L/h/kg, while PMs exhibit half-life of ~21.6 h and clearance of ~0.3 L/h/kg.

Neurochemical Mechanisms

Atomoxetine selectively inhibits human ► norepinephrine transporters in vitro with high potency, and has relatively low affinity for ► serotonin and ► dopamine transporters (Bymaster et al. 2002). In vivo, atomoxetine rapidly penetrates the rat ► blood–brain barrier via mainly passive mechanisms; and increases levels of noradrenaline and dopamine (but not serotonin) approximately threefold in the rat ► prefrontal cortex, a region critically implicated in cognition (Bymaster et al. 2002). In contrast to ► psychostimulants, atomoxetine does not increase dopamine levels in the accumbens and striatum, thereby limiting its abuse potential as compared to this other class of agent (Wee and Woolverton 2004). Thus, atomoxetine may offer benefits over psychostimulants in terms of lower addictive potential due to its more selective neurobiological effects.

Cognitive Effects

Noradrenaline and dopamine have been strongly implicated as neurochemical substrates of cognition. Consequentially, and in light of the above findings, it is important to question whether atomoxetine can enhance cognition and ameliorate cognitive deficits in the context of neuropsychiatric disorders. Most translational studies to date have focused on measuring the effects of short-term atomoxetine treatment on laboratory-based measures of impulsivity, assessed in terms of inappropriate and/or premature motor responses on cognitive tasks. This focus on impulsivity stems from the utility of atomoxetine in the treatment of ADHD (discussed in the following section).

On the ► five-choice serial reaction time task (5-CSRT), atomoxetine reduced premature impulsive responses in rats across three studies (Robinson et al. 2008). In humans, atomoxetine was found to improve impulse control on the ► stop signal reaction time task (SSRT) in healthy volunteers, and in adult patients with ADHD (Chamberlain et al. 2006, 2007). By combining the SSRT with ► functional magnetic resonance imaging (fMRI), it was subsequentially found that atomoxetine augmented activation in the right inferior frontal gyrus during inhibitory control in healthy volunteers, with this region being critically implicated in impulse control and in the neuropathology of ADHD (Chamberlain et al. 2009).

The effects of longer-term treatment with atomoxetine on cognition have received scant attention. In work by Spencer and colleagues, 3-week treatment with atomoxetine was associated with improvements on a measure of inhibition from the Stroop task in adult ADHD patients, particularly in those patients with poor baseline performance (Spencer et al. 1998).

Treatment of Neuropsychiatric Disorders

Atomoxetine was first explored as a potential antidepressant, but then the focus shifted to its potential utility in the treatment of ADHD. Atomoxetine is licensed for the treatment of ADHD in children and adults in USA and UK. Meta-analysis of data from nine randomized placebo-controlled trials indicated that atomoxetine was superior to placebo in the treatment of childhood and adolescent ADHD (number needed to treat, NNT, 3.43) (Cheng et al. 2007). Adverse events occurring significantly, more commonly than under placebo, were reduced appetite, somnolence, abdominal pain, vomiting, dyspepsia, dizziness, fatigue, infection, and pruritis (listed in decreasing frequency of occurrence; number needed to harm, NNH, range 9–120). No evidence of liver injury was detected in initial clinical trials. Two reported cases of elevated hepatic enzymes and bilirubin linked with treatment have been detected in >2 million patients during the first two years after initial marketing (www.fda.gov/medwatch). As with other medications used in the

treatment of childhood psychiatric disorders, there has been some concern regarding atomoxetine and suicidality. In one analysis, six suicide related events were identified in 1,357 pediatric ADHD patients taking atomoxetine compared to zero events in 851 patients taking placebo (Virani 2005), leading to the FDA instructing that increased risk of suicidal thinking be added to the box-warning for this product. Although rare, these findings indicate the importance of monitoring for the emergence of adverse events relating to hepatic function, and suicidality in patients.

Atomoxetine appears similarly effective versus ► methylphenidate in the treatment of childhood ADHD albeit with evidence of significantly higher rates of mild to moderate adverse events. In UK, guidance from the National Institute for Health and Clinical Excellence (NICE), published in 2008, posits either methylphenidate or atomoxetine as first-line drug treatment in children with severe ADHD, as part of a comprehensive treatment program (www.nice.org). In terms of cost-effectiveness, a UK economic modeling study indicated that the cost of atomoxetine compared favorably with immediate release methylphenidate per Quality Adjusted Life Year gained in the treatment of childhood ADHD (Cottrell et al. 2008).

It is established that 40–60% of children with ADHD continue to exhibit clinically impairing symptoms into adulthood. However, in comparison to the child literature, few adult treatment studies using atomoxetine exist to date. The available data suggest similar efficacy and side-effects profiles to those identified in the treatment of children and adolescents (Faraone et al. 2005).

Summary

The SNRI atomoxetine is playing a growing role in the treatment of ADHD. Translational studies indicate that this agent modulates prefrontal noradrenaline (and dopamine), and is capable of improving response inhibition, a cognitive function dependent on the right inferior frontal gyrus and under likely noradrenergic control. Further clinical trials are required to explore the efficacy and safety of atomoxetine into the longer term in the treatment of ADHD, in children and in adults, and to evaluate the efficacy of this agent in the treatment of other disorders. For example, registered ongoing trials are exploring the utility of atomoxetine in the treatment of alcohol/substance abuse, Parkinson's disease, and Binge Eating disorder (www.clinicaltrials.gov). In addition to further clinical trials, it will also be important to explore the role of different components of the brain noradrenaline system in cognition (i.e., sub-receptors) in translational research; and to evaluate the effects of atomoxetine on the spectrum of cognitive deficits exhibited across neuropsychiatric disorders.

Cross-References

► Attention Deficit and Disruptive Behavior Disorders
► Impulse Control Disorders
► Impulsivity
► Methylphenidate and Related Compounds
► Rodent Models of Cognition

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Atomoxetine Hydrochloride

► Atomoxetine

A

Attention

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Synonyms

Vigilance

Definition

Attention describes a range of cognitive processes and capacities that support the ability to detect stimuli that occur rarely, unpredictably, and over longer periods of time (sustained attention), to discriminate such stimuli from non-target stimuli (or "noise"; selective attention), and to perform in situations requiring attention to multiple stimuli, multiple sources of stimuli, stimuli presented in multiple modalities, and/or the processing of multiple and competing stimulus–response rules (divided attention).

Impact of Psychoactive Drugs

Psychopharmacological research on attentional functions has intensified during recent years, fostered in part by an increasing understanding of the fundamental relevance of attentional capacities for learning and memory (Sarter and Lustig 2008), the identification of neuronal mechanisms and brain systems mediating attention (Raz and Buhle 2006), and the development and validation of tasks for the measurement of attentional processes and capacities in laboratory animals and humans. Psychopharmacological research in rodents has enormously progressed as a result of the introduction of translational tasks for the measurement of attentional capacities, particularly the ▶ five-choice serial reaction time task (Robbins 2002) and operant sustained and divided attention tasks (Arnold et al. 2003). Research in humans likewise has evolved, due in part to advances in cognitive theories of attention and the development of new test paradigms and their successful use in neuroimaging studies (Awh and Jonides 2001). The assessment of effects of psychoactive drugs on attentional performance-associated brain activity patterns ("pharmaco-fMRI") represents a particularly informative new approach as effects on attention can be attributed to modulation of activity in the distributed neuronal circuits known to mediate attention. The literature on psychotropic drug effects on attention is extensive and diverse; below, selected major research themes on the psychopharmacology of attention are briefly discussed.

Do the ▶ amphetamines facilitate attention and benefit the attentional symptoms of ADHD? Amphetamine and related stimulants, including ▶ methylphenidate, produce a wide range of effects in laboratory animals, including effects on response output and response speed that are a function of baseline response rates and the type of response required. Furthermore, these drugs affect complex motivational processes, often in interaction with the requirements for responding, the testing environment, and the animals' motivational state. Attentional performance can be affected indirectly as a result of such effects on response output or motivational processes. However, the available evidence does not conclusively indicate that psychostimulants generally and selectively enhance attentional processes or capacities. Evidence from healthy humans likewise does not indicate robust support for psychostimulant-induced enhancement of attention (Koelega 1993).

Psychostimulant treatment benefits the behavior and academic performance of patients with ADHD. However, similar to effects of these drugs in laboratory animals, the behavioral and cognitive mechanisms underlying the beneficial treatment effects in ADHD patients have remained unsettled. Furthermore, psychostimulants may act primarily by attenuating the high levels of cognitive and behavioral impulsivity of ADHD patients. Studies show that the benefits of psychostimulants on overall behavior and academic performance, indicated typically by ratings from parents and teachers, in fact were not associated with normalization of cognitive deficits. Thus, collectively, psychostimulants produce a wide range of effects that may, depending on the testing conditions, produce limited beneficial effects on attentional performance. However, it seems less likely that these compounds specifically enhance the attentional capacity of healthy subjects and/or that they specifically attenuate the attentional impairments associated with ADHD.

Do wake-promoting drugs such as modafinil enhance attention? ▶ Modafinil is a well-tolerated and relatively safe drug, and has therefore become a widely and increasingly recreationally used treatment to combat sleepiness and the cognitive components of sleepiness, including attentional impairments (Minzenberg and Carter 2008). However, numerous studies also suggested that administration of modafinil enhances cognitive performance per se, independent of its main wake-promoting properties. Similar to the psychostimulants, modafinil appears to act via stimulation of dopaminergic neurotransmission, requiring functional ▶ dopamine D1 and D2 receptors to induce wakefulness. Likewise, modafinil was not found to produce selective effects on attention in animals that were

not sleep-deprived. Furthermore, and also similar to the effects of psychostimulants, modafinil was demonstrated to enhance inhibitory response control in laboratory animals and to improve the symptoms of ADHD.

Modafinil was found to benefit the impaired attentional set-shifting capacities of schizophrenic patients, suggesting that this drug may have significant clinical usefulness as a co-treatment for this disorder. As the treatment of schizophrenic patients with amphetamine was also reported to benefit their cognitive abilities, it is intriguing to hypothesize that modafinil produces effects on attentional set-shifting by stimulating the down-regulated dopamine D1 receptors observed in the prefrontal cortex of these patients. Collectively, new wake-promoting compounds such as modafinil may produce relatively specific attentional enhancement in disorders associated with dopaminergic abnormalities in prefrontal regions.

Noradrenergic agents. Hypotheses concerning the contributions of forebrain noradrenergic afferents to the mediation of attention have originated from observations demonstrating increases in cortical "signal-to-noise" ratios following local administration of noradrenaline and the increased distractibility of animals with noradrenergic depletions. Neurophysiological recordings of the locus coeruleus, the main source of noradrenergic projections to the cortex, indicated multiple and complex contributions of phasic and tonic changes in noradrenergic activity to attention. However, the determination of specific attentional functions of the noradrenergic system in behavioral experiments, and their dissociation from more general effects on "arousal" or "alertness," continues to represent a challenging subject. These problems generalize to psychopharmacological studies on the effects of noradrenergic compounds on attention. The studies have focused overwhelmingly on the effects of alpha-2 adrenergic receptor agonists (clonidine, guanfacine, dexmedetomidine) and, more recently, the noradrenaline-reuptake inhibitor ► atomoxetine.

The evidence concerning the attentional effects of alpha-2 agonists in animals and humans is conflicting and remains inconclusive. In animals and humans, beneficial as well as detrimental effects on attention following the treatment of clonidine and guanfacine were reported. The presence and direction of the attentional effects of these drugs appear to depend on specific task parameters, testing conditions, and the subjects' level of "alertness" at baseline. The interpretation of these conflicting findings is further complicated by results indicating that alpha-2 *anta*gonists such as idaxozan and atipamezole likewise enhance aspects of attentional performance in healthy volunteers and patients. A definition of the experimental conditions that foster the demonstration of beneficial versus detrimental attentional effects of alpha-2 agonists is clearly needed. Treatment with drugs such as guanfacine may benefit the attentional impairments of particular disorders, based perhaps on an "optimization" of noradrenergic neurotransmission (Arnsten et al. 2007).

This latter statement may also hold true for the attentional effects of the noradrenaline uptake inhibitor atomoxetine. Beneficial attentional effects of this drug were demonstrated in animals with reduced levels of noradrenergic neurotransmission, but not consistently in intact animals. While recent clinical studies suggested efficacy in patients with ADHD, the precise cognitive mechanisms that are enhanced by atomoxetine is not known. Extensive psychopharmacological research, involving controlled studies and the test of hypotheses predicting specific attentional mechanisms that are modulated by noradrenergic drugs, are required in order to render conclusions about the general pro-attentional efficacy of noradrenergic drugs.

Attentional enhancement by agonists at ► nicotinic acetylcholine receptors (nAChRs). The cortical cholinergic input system represents a key branch of the forebrain circuits that mediate attentional functions and capacities (Sarter et al. 2005). Recent evidence indicated that prefrontal cholinergic activity mediates a switch from intrinsic or associational processing to the processing of external stimuli, and thereby the detection and selection of stimuli in attention-demanding situations. Neuroimaging studies suggested that administration of nicotine enhances the processing of attentional information by attenuating the activity of the brain during resting periods.

Therefore, it would be expected that drugs that block or stimulate the fast and reversible component of post-synaptic cholinergic neurotransmission, the nAChR, robustly impair or benefit, respectively, attentional performance. While robust impairments in attentional performance following nAChR blockade with ► mecamylamine can be readily shown in humans and animals, the demonstration of nicotine-evoked attentional enhancement in healthy (nonsmoking) humans and drug-naive animals has been less straightforward. Several experiments in humans and animals clarified that in interaction with increased demands on attentional performance, including the demands for top-down processing (e.g., by requiring performance during the presence of distractors), ► nicotine reliably enhances attentional performance. Collectively, these findings indicate the importance of integrating variations of the demands on attention as a secondary independent variable into experiments testing the effects of nicotine on attentional performance (Hahn et al. 2003).

Compared to the effects of nicotine, drugs that act at subtypes of the nAChR, particularly at alpha4/

beta2*nAChRs, were found to produce more robust effects on attentional capacities in humans and animal experiments. Ligands that selectively stimulate alpha4/beta2*-nAChRs and have been under investigation for treating cognitive disorders include ABT-089, ABT-418, ispronicline, and SIB1765F. Furthermore, promising effects of such drugs in tests of their therapeutic efficacy in patients with ADHD, schizophrenia, and dementia were reported. The attentional benefits of compounds acting at other nAChR subtypes, such as alpha7 nAChRs, remain less clear, largely because little evidence on the effects of these drugs has accumulated.

The neuropsychopharmacological reasons why agonists at alpha4/beta2*nAChRs may exhibit greater attentional enhancement than nonspecific agonists such as nicotine are largely unknown. However, evidence from experiments determining the effects of nAChR agonists on the transient increases in prefrontal cholinergic activity that mediate the detection of cues begins to form the basis for hypotheses. This evidence indicated that selective agonists at alpha4/beta2*nAChRs augment these transient increased without altering the "shape" (rise and clearance rates) of these transients. In contrast, nicotine, via stimulation of additional receptors and mechanisms, not only is less potent in augmenting the amplitude of these transients but drastically prolongs the duration of cholinergic activity. It is intriguing to speculate that such "blunting" of a critical neuronal signal interferes with, or at least limits, the enhancement of the detection process that is key to improving attentional performance.

Collectively, drugs that directly stimulate subtypes of nAChRs or modulate the stimulation of these subtypes by acetylcholine appear to produce specific and efficacious effects on attentional functions and thus are promising candidates for clinical use. Moreover, the accumulating evidence on the attentional effects of these drugs informs theories concerning the general neurobiological mediation of attention.

Conclusion

Although research on the modulation of attentional processes and capacities by psychotropic drugs, primarily by drugs acting at ascending modulator systems, has rapidly expanded during recent years, much of the evidence remains rather preliminary and inconclusive. The attentional effects of drugs acting at nAChRs, particularly those that bind selectively to subtypes of this receptor family, form a more consistent set of evidence than the effects of psychostimulants or noradrenergic drugs, or drugs not discussed herein, including drugs acting at serotonergic receptors. Furthermore, the interpretation of the psychopharmacological effects of nAChR agonists is supported by converging neurobiological evidence on the mediation of attentional functions by cholinergic systems. Ongoing research will demonstrate the clinical usefulness and also the psychopharmacological limitations of these treatments, in part by addressing the important question about the degree to which treatments that focus primarily on the improvement of attentional capacities benefit the overall cognitive abilities of patients. Finally, and similar to the presently increasing use of modafinil by nonclinical populations, drugs that enhance attentional abilities, particularly if associated with limited side effects, are likely to be used in the near future by non-patient groups as general cognition enhancers.

Cross-References

- ▶ Acetylcholinesterase Inhibitors as Cognitive Enhancers
- ▶ Atomoxetine
- ▶ Attention Deficit and Disruptive Behavior Disorders
- ▶ Attention Deficit Hyperactivity Disorders: Animal Models
- ▶ Cognitive Enhancers
- ▶ Nicotine
- ▶ Nicotinic Agonists and Antagonists

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Attention Deficit and Disruptive Behavior Disorders

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Synonyms

Hyperkinetic child syndrome; Minimal brain damage; Minimal cerebral dysfunction; Minor cerebral dysfunction.

Definition

► Attention-deficit/hyperactivity disorder (ADHD) affects about 8–12% of school age children, being more common in boys than in girls by a ratio of approximately 3:1. This condition is characterized by excessive inattention and impulsivity/hyperactivity for a given developmental level. In at least 50% of cases, this condition produces enduring impairment in adulthood. ADHD has deleterious impact on several areas of social development such as educational attainment, family life, and occupational stability. ADHD has a strong hereditary basis, with genetic factors accounting for about 80% of the phenotypic variance. Weak associations with ADHD have been reported for the 7-repeat polymorphism of the D4 dopaminergic receptor gene, the 10-repeat allele of the dopamine transporter (DAT1), alleles of the D2 and D5 dopaminergic receptors, the gene coding for catechol-O-methyl-transferase, and genes related to the noradrenergic and serotonergic systems.

The estimated rate of comorbidity (co-occurrence) between ADHD and other psychiatric and learning disorders is between 50% and 90%. The most common comorbidities are with disruptive behavior disorders, which includes oppositional defiant disorder, present in some 40% of patients; conduct disorder, present in ~14% of children with ADHD; anxiety disorder (~34%); tic disorders (~11%), and others such as depression, bipolar disorder, substance use disorders, and learning disabilities (Kunwar et al. 2007). ADHD is a risk factor for the appearance of disruptive behaviors, as the onset of these symptoms occurs earlier in ADHD subjects than in non-ADHD patients. Children with ADHD and conduct disorder are at a higher risk of antisocial behavior and substance abuse as adolescents and adults. This motivates attempts to provide early treatment with the hope of preventing malignant behavioral outcomes, although such has not been demonstrated.

Role of Pharmacotherapy

Currently, ADHD is subdivided into three diagnostic subtypes, defined by predominance in inattention, hyperactivity, and impulsivity, or as the combined type that includes both inattention and hyperactivity/impulsivity.

Pharmacological treatments for ADHD enhance catecholaminergic neurotransmission. This repeated observation, combined with neuroimaging evidence strongly implicate fronto-striatal and fronto-cerebellar circuits in deficits affecting behavioral organization and the ability to predict events and behavioral outcomes; a further deficit in the fronto-amygdalar loop that assigns emotional significance to predicted and detected events is also hypothesized (Swanson et al. 2007). However, no differences in medication response have been reported among the three subtypes.

Treatment: Stimulants

The first-line pharmacological treatment for all types of ADHD consists of the psychostimulants ► methylphenidate (MPH) or ► amphetamines (Table 1). The overall short-term efficacy and tolerability of these compounds have been conclusively demonstrated in both children and adults (Findling 2008; Stein 2008). About 70–80% of the patients showed improved attention when treated with a stimulant (Rappley 2005). Owing to its lower cost, the generic amphetamine, dextroamphetamine, is most frequently used in developing countries. However, between 30% and 50% of patients discontinue pharmacotherapy due to adverse effects or inadequate response. In most such cases, the next step should include changing to the other type of stimulant. Also widely approved for the treatment of ADHD is the nonstimulant, noradrenergic reuptake inhibitor ► atomoxetine (ATX). Guanfacine is an alpha2A adrenoceptor agonist indicated for the treatment of essential hypertension that also appears to be efficacious as monotherapy, but may also be particularly useful as an adjunctive agent.

Mechanism of Action of Stimulants

Amphetamines are considered to exert their effects partly by promoting the liberation of ► dopamine from vesicular transporters and inhibiting the degradative enzyme

Attention Deficit and Disruptive Behavior Disorders. Table 1. Recommended dosages for first-line medications for ADHD (data from Pelham et al. 1999; Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement 2001; Swanson and Volkow 2002, 2003; Swanson et al. 2004).

Drug	Approximate daily dose per weight (mg/kg)	Usual dose (mg)	Requires dose titration	Peak efficacy level (h) (equivalent to the onset of peak of serum concentration and brain level)	Daily dosage schedule	Duration (h)	Adverse effects and contraindications
Methylphenidate IR (Ritalin®, Methylin®)	0.3–1	5–20	No	0.75–1.5	1, 2 or 3	3–4	Loss of appetite, trouble sleeping, headaches, stomachaches, "zombie effect," sadness, motor tics, nail-biting/picking, irritability, deceleration in rate of growth, mild increase in blood pressure and heart rate. Abuse risk (more for amphetamine). Contraindicated in glaucoma and psychosis. Caution but not contraindicated in Tourette disorder and epilepsy
Methylphenidate ER-OROS[a] (Concerta®)	0.3–1	18, 27, 36, 54, 63, 72	No	2 (see OROS system below)	1	12	
Methylphenidate ER-Diffucaps[b] (Metadate CD®, Ritalin LA®)	0.3–1	20, 30, 40	No	1–2 (see diffucaps below)	1	8	
D,L-amphetamine (Adderall®)	0.2–0.8	5–30 (5–15 BID)	No	1.5–3	1 or 2	6–8	
D-amphetamine (Dexedrine®)	0.1–0.8	2,5–15	No	1.5–3	1 or 2	4–6	
Atomoxetine (Strattera®)	1.2–1.8	36, 40, 50 or 60	Yes, in 2–4 weeks (initial dose 0.5 mg/kg)	2–3	1	12–24	Decreased appetite, somnolence and fatigue. Dyspepsia, nausea, vomiting, weight loss, dry mouth, insomnia, constipation, urinary retention, erectile disturbance, decreased libido. Heart rate increase and EKG PR interval decrease. Caution in patients who have significant cardiovascular disorder. May produce liver failure, reversible with discontinuation of medication

[a]OROS® = Osmotic Release Oral System. Initial bolus of IR-MPH on capsule overcoat, and a reservoir consisting of polymer and MPH layers surrounded by a semipermeable membrane to deliver MPH at a smoothly increasing rate from 2 to 10 h after dosing

[b] Diffucaps® = Coated bead system. A capsule containing 30% of the total dose of MPH in uncoated beads to deliver the initial bolus, and 70% in beads coated with a polymer that degrades over time to deliver MPH at a smoothly increasing rate from 2 to 6 h after dosing

monoamine oxidase. These effects dramatically increase intracellular concentrations of dopamine in the presynaptic terminal, which results in massive efflux of neurotransmitter into the extracellular synaptic space. Additionally, amphetamine reversibly blockades the dopamine transporter (DAT) and enhances the internalization of DAT. These actions inhibit reuptake and prolong the increased concentration of catecholamines in the presynaptic terminal. Methylphenidate (MPH) is a pure reuptake blocker, with potent affinity for DAT and for the ▶ norepinephrine transporter (NET). The extrasynaptic dopamine increasing effect of MPH through DAT blockade has been documented in the human ▶ striatum and nucleus accumbens, and found to be qualitatively similar to ▶ cocaine effects (Volkow et al. 1998). However, pharmacodynamic kinetics differentiates MPH from cocaine in important ways that appear to account for the lower addictive potential of MPH.

Although most of the researches focus on the mechanism of action of the stimulants on the striatum, recent work in the ▶ prefrontal cortex suggests that MPH improves cognitive function (particularly the maintenance of items in working memory) by increasing endogenous stimulation of both alpha2A adrenoreceptors and dopamine D1 receptors. MPH also robustly blocks the NET, which is expressed in high concentrations throughout the cerebral cortex and cerebellum. The NET is reported to have an even higher affinity for dopamine than for norepinephrine. This finding is of interest in light of the demonstrated albeit less robust efficacy of atomoxetine and may also be related to the less thoroughly demonstrated efficacy of alpha-2 agonists like clonidine and guanfacine, which are also used to treat ADHD.

Adverse Effects

Immediate adverse effects of stimulants tend to be mild, dose-dependent, and usually diminish with continued use. The most common include loss of appetite and difficulty going to sleep; headache and stomachache are also reported but occur with almost equal frequency on double-blind placebo. More worrisome concerns have been raised regarding delayed or suppressed growth, appearance of motor and vocal tics, and possible sensitization leading to ▶ substance abuse (Biederman and Faraone 2005). Since stimulants nearly always reduce appetite to some extent, the concern over growth rates and possible enduring loss of height cannot be discarded. Nevertheless, existing albeit flawed evidence suggests that growth deficits from MPH are generally reversible. However, the much longer excretion half-lives of amphetamines would suggest that possible growth suppression effects may also be stronger than for MPH. With regard to the emergence of ▶ tics, early anecdotal evidence suggesting a causal link has been disconfirmed by systematic studies, which have highlighted familial factors. In the United States, MPH remains contraindicated for use in patients with a personal or family history of tics, although amphetamines are not so labeled, for historical reasons. Several controlled studies have shown that many children with pre-existing tic disorders can benefit from stimulants, although some do experience exacerbations that exceed the benefits derived. Nonstimulant medications are considered as a second line option in cases of risk of substance abuse, tics, and when weight loss is a significant concern.

Perhaps the most sensitive issue is the long-term risk of substance addiction. Long-term studies and meta-analyses have mostly not detected the increased risks following early stimulant treatment, and some studies have suggested that such early use may proffer a protective effect. Furthermore, despite similar mechanisms of action, the abuse potential of methylphenidate seems to be much lower than cocaine owing to the latter's more abrupt pharmacokinetic profile. This difference is especially marked for oral administration of MPH. Nevertheless, considering that ADHD subjects represent a population at risk of substance abuse, and the advantages of single daily dosing, many extended release stimulant formulas have been developed in the recent years. Comparing immediate release with extended release formulations of methylphenidate, similar peak DAT blockade levels are reached, but at different times (1.7 and 5 h, respectively), with mild reinforcing effects noted for the immediate release formula (Swanson et al. 2007). Thus, it has been proposed that kinetic factors, rather than absolute plasma concentrations may be the most relevant factor in producing subjective responses to MPH (and by extension to other stimulants). Along this line, a 10-year longitudinal study determined that misuse of stimulants only occurred with immediate-release forms; epidemiological reports indicate that users of immediate-release formulas are at a greater risk of substance abuse than users of extended release formulations (Findling 2008).

Recommended Medications for ADHD

There are three critical parameters in determining the appropriate pharmacological treatment in ADHD:

1. The duration of the effect, as multiple daily dosing increases the risk of discontinuation
2. An acceptable risk profile
3. The concern of abuse potential, especially in a population such as ADHD that may already have an elevated risk.

Methylphenidate

MPH is available in immediate release formulation (IR-MPH), in different extended release forms (ER-MPH), and as dexmethylphenidate (DMPH, the active D-isomer of MPH), which is also marketed in both immediate and extended release forms. The short-term efficacy of MPH for treating ADHD has been conclusively demonstrated by showing significant improvements on standardized rating scales, such as the Conners Global Index, the Conners Inattention/Hyperactivity with Aggression subscale, or the Clinical Global Impressions Improvements Scale (CGI-I). The landmark study, The MTA Cooperative Group report (1999), established that carefully adjusted stimulant medication (predominantly immediate release MPH, given three times per day, 7 days per week), either in combination with behavioral therapy or alone, produced a significantly greater improvement during the 14-month trial than behavioral management alone or standard community care in reducing core ADHD symptoms. In the intent-to-treat analyses, groups assigned to medication alone or medication combined with behavioral treatment did not differ, suggesting that MPH alone provides the best ratio of cost to benefit. Likewise, adverse effects were generally mild, the most common being appetite suppression, stomachache, and headache.

While the first generation "slow-release" MPH formulation left much room for improvement, formulations using an osmotic controlled release system (OROS MPH) and formulations combining rapid delivery and extended delivery elements in various proportions have been embraced by clinicians and patients. Efficacy is reported to be comparable with that of IR-MPH, with robustly significant improvements over placebo (Findling 2008). Mild adverse effects are comparable, e.g., headache (2–14% vs. 3–10% for placebo), abdominal pain (6–7% vs. 1% for placebo), emotional lability, anorexia (3–10% vs. 0–3%), and insomnia (3–7% vs. 0–5%). A new formulation consists of a MPH transdermal delivery system (MTS), which has been reported in a study sponsored by the manufacturer to show good efficacy and tolerability, with minimal adverse effects (headache was reported by 4% in both treatment and placebo groups), but a subsequent study found somewhat higher rates of adverse effects with MTS treatment than with OROS-MPH treatment (reduced appetite 26% MTS, 19% OROS, 5% placebo; insomnia 13%, 8%, and 5%, respectively; and nausea 12%, 8%, and 2%, respectively). Dexmethylphenidate (the active D-isomer of MPH) has been reported to be efficacious and well tolerated in children, and there is an extended release formulation.

Amphetamines

The first stimulant used for hyperactivity was Benzedrine, which contains equal proportions of dextro- and levo-amphetamine isomers. Because of weaker sympathomimetic effects with the dextro-amphetamine isomer, it was preferred for behavioral effects over the levo-isomer. However, the manufacturer of branded dextroamphetamine generally eschewed advertising and marketing despite substantial evidence of efficacy and nearly comparable tolerability to MPH. An alternative formulation that combines 4 amphetamine salts (75% dextro-isomer, 25% levo-isomer) has been extensively marketed in immediate release tablets and extended release capsules (mixed amphetamine salts, MAS). Whereas studies sponsored by the manufacturer have generally reported that MAS produced significantly greater improvement than MPH or placebo in aggression, defiance, and inattention/hyperactivity, children treated with MAS evidenced higher incidence of sadness and stomachache than those receiving MPH (Faraone et al. 2002; Rappley 2005). Where available, MAS is marketed in a wide range of doses, which facilitates tailoring of dose and improves compliance. Extended release MAS (XR-MAS) formulations are also efficacious and relatively well tolerated, although the duration of adverse effects can greatly exceed the duration of direct benefits. The substantial intersubject variation in pharmacokinetic parameters highlights the need for personalized treatment.

► Pemoline is a stimulant with an distinct pharmacokinetic profile that may have accounted for its greatly diminished abuse liability. Despite having been shown to be efficacious for ADHD, it is no longer recommended owing to confirmed reports of fatal liver damage (Rappley 2005) and the availability of nonstimulant alternatives.

Nonstimulants

Nonstimulant medications that modulate noradrenergic neurotransmission have also been found to be efficacious for ADHD. The first class of such medications are the tricyclic ► antidepressants, which have comparable efficacy with MPH. However, purely noradrenergic compounds such as desipramine may be more cardiotoxic than mixed noradrenergic/serotonergic drugs, although all tricyclics also produce prominent anticholinergic side effects (Biederman and Faraone 2005). The use of tricyclics, in general, and desipramine, in particular, has diminished sharply following reports of deaths of four children who were treated with recommended doses of desipramine.

In clinical trials, atomoxetine (ATX) separates from placebo in symptom improvement at all ages, with efficacy being

the strongest at the highest doses tested (1.2–1.8 mg/kg per day; Table 1). Trials sponsored by the manufacturer found no significant differences in efficacy between ATX and IR-MPH, but other trials, also commercially sponsored, have found XR-MAS and OROS-MPH to be somewhat more efficacious than ATX. In clinical practice, ATX is rarely considered a first-line medication, except for patients with ADHD and a history of substance abuse, comorbid anxiety, tics, or history of nonresponse to stimulants. Despite the generally benign effect on tics, some patients have been reported to develop tics after ATX use. Higher doses of ATX are associated with anorexia (12%) and somnolence (7–11%). ATX may produce delayed growth, which is reported to be reversible after discontinuation. Overdoses of ATX may result in seizures, which requires patients with seizure histories to take caution. Unlike tricyclic antidepressants, ATX does not have anticholinergic or cardiovascular side effects. However, a rare risk of liver injury (two cases in two million), which recovers after interruption of treatment has been reported. Therefore, ATX is not recommended in patients with jaundice or evidence of liver injury; treatment should be discontinued if patients develop pruritis, dark urine, or other symptoms of liver damage (Biederman and Faraone 2005).

The antidepressant ► bupropion has shown modest efficacy in ADHD treatment, but has been proposed to control cigarette smoking in ADHD patients, and for patients with comorbid depression, ► bipolar disorder, or substance abuse. In general, bupropion is well tolerated but is less efficacious than MPH and has a substantial risk of inducing seizures at higher doses (Biederman and Faraone 2005; Findling 2008). ► Modafinil has also some efficacy in ADHD and some studies suggest it is well tolerated, with insomnia, abdominal pain, anorexia, cough, fever, and rhinitis being the most common adverse events. However, more clinical studies are needed to determine the utility of this drug as an alternative treatment (Rappley 2005).

The alpha adrenergic agonist clonidine has been evaluated in ADHD treatment, with relatively poor results. Although it provides some benefit to patients and is well tolerated (main adverse effect is drowsiness), it is significantly less efficacious than MPH (Rappley 2005). Guanfacine is a more specific alpha agonist (alpha2A) whose effectiveness has been assessed recently in ADHD in an extended release formulation providing 1–4 mg/day (Strange 2008). Although initial studies have had confounding design flaws, improved trials have confirmed a decrease in hyperactivity/impulsivity scores and in tic frequency, even in subjects who had not responded to MPH. As with clonidine, the major adverse effects of guanfacine are sedation (16–35%) and fatigue (12–60%). Depression, headache, and upper abdominal pain have been also reported as possible adverse effects. Not surprisingly, given its primary indication, a tendency to lower blood pressure has been found compared with placebo, but the drug was well tolerated, and there was no relation between blood pressure changes and headaches or dizziness.

Prodrug Stimulants

A prodrug is a substance that needs to be transformed within the organism before it can produce its effects (Findling 2008). ► Lisdexamphetamine dimesylate (LDX) is converted into L-lysine and D-amphetamine, and its absorbance is independent of gastrointestinal processes. At least two studies reported a significant improvement in ADHD symptoms when compared with placebo, which was comparable with the benefit of XR-MAS. This finding is of interest given that, contrary to extended release formulas, the variability in absorption kinetics is much lower. Furthermore, LDX has similar tolerance levels than current stimulants. The hedonic impact of LDX was found to be much lower than that of D-amphetamine in subjects with a history of stimulant abuse, who were rated with the Drug Rating Questionnaire-Subject (DRQS), which suggests that this may be an alternative for patients with histories of substance abuse, although this indication has not yet been evaluated systematically.

Comorbidities

The NIMH Multimodal Treatment Study of ADHD found that children with ADHD and disruptive behavior disorders benefit from stimulant treatment, showing a significant decrease in aggressive behaviors (Kunwar et al. 2007). Nevertheless, behavioral intervention is recommended to promote social integration and academic performance. Though stimulants may be an effective treatment for aggressive or antisocial behavior in ADHD, ► mood stabilizers or atypical ► antipsychotics have become widely used with the intent of treating manic symptoms or aggression. Concerns are being raised regarding the serious potential for metabolic derangements with such treatments, especially with certain atypical antipsychotics. Stimulants exacerbate psychotic symptoms in a sizeable proportion of such patients. While stimulants may be modestly helpful for children with learning disabilities without prominent hyperactivity/impulsivity, they are never sufficient. Such children require additional educational support. Coexisting anxiety appears to attenuate impulsivity in ADHD. Contradictory results regarding stimulant response in ADHD children with comorbid

anxiety have been reported by well designed studies, with both poorer and equivalent response being found. Systematic studies have not examined the extent to which children with ADHD/depression or with ADHD/bipolar disorder can benefit from stimulants, although stimulants in conjunction with antidepressants have been recommended in cases of ADHD/major depressive disorder. Finally, anti-tic agents in combination with stimulants can be useful for children with ADHD and tic disorders.

Conclusions

Methylphenidate and amphetamines, preferably in extended release formulations, are the recommended first choice in children, adolescents, and adults with ADHD, including those with comorbid disruptive behavior. In cases of history of substance abuse, the use of nonstimulants or LDX may be preferred. Medications for ADHD are chronically administered over years, and require sometimes subtle adjustments in dosing, timing, and adjuncts. Establishing and maintaining a therapeutic alliance with adolescents remains one of the greatest challenges of providing psychopharmacological care for ADHD.

Cross-References

- ► Adolescence and Responses to Drugs
- ► Alcohol Abuse and Dependence
- ► Amphetamine
- ► Atomoxetine
- ► Attention
- ► Attention Deficit Hyperactivity Disorders: Animal Models
- ► Dopamine
- ► Dopamine Transporter
- ► Methylphenidate and Related Compounds
- ► Methylphenydate
- ► Norepinephrine
- ► Stimulant

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Attention Deficit Hyperactivity Disorder

Synonyms

ADHD

Definition

An axis-I neuropsychiatric disorder listed in the Diagnostic and Statistical Manual (DSM-IV, American Psychiatric Association). ADHD is characterized by inattentive, hyperactive, and/or impulsive symptoms that interfere with everyday functioning. Although initially presenting in childhood, ADHD symptoms often persist into adulthood where they can impede social relationships, contribute to criminality, and have a negative impact on the ability to work effectively.

Cross-References

- ► Attention Deficit and Disruptive Behavior Disorders

Attention Deficit Hyperactivity Disorders: Animal Models

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Synonyms

Experimental animal models of attention deficit/hyperactivity disorder; Laboratory animal models of minimal brain dysfunction; Model organisms of hyperkinetic syndrome

Definition

Nonhuman animals, because of their specific characteristics that resemble human attention deficit/hyperactivity disorder (ADHD), were selected for use in ADHD experimental research, testing, or teaching. They provide an invaluable tool for investigating ADHD etiology, its diagnosis, and treatment.

Animal models of ADHD can be induced by genetic manipulation, physical or chemical means, or selected from the normal population on the basis of their behavioral characteristics.

Current Concepts and State of Knowledge

ADHD research has long employed animal models in the study of the neural basis of this multifactorial and heterogeneous pathology. The core clinical symptoms of ADHD – namely, inattentiveness, ► hyperactivity and ► impulsivity – have been used as constructs in animal research for a long time. Following early attempts to model these symptoms in animals such as dogs and cats, laboratory models of ADHD have been developed mostly in rodents, partly because more is known about their biology and genetics. Several authors have put forward some essential characteristics of a good animal model of ADHD. They can be summarized as follows: (1) behavioral symptoms should be evident only in particular environments and stage of development, according to the specific characteristics of ADHD symptom manifestation; (2) biochemical and morphological abnormalities – as well as their etiology – should be similar to those shown by ADHD sufferers; (3) the model should respond to the same drugs used for the treatment of ADHD with a measurable improvement of the main symptoms and be able to predict the efficacy of new treatments. Thus, in preclinical ADHD research, a particular emphasis should be put on the techniques used to assess the behavioral symptoms and on the peculiar response of the model to drugs used in ADHD pharmacotherapy on those behavioral measures.

Animal models of ADHD can be divided into genetic, chemical intoxication/physical trauma, behavioral, and brain lesion models. These models are of great value because their use can help in defining the causal relations between the symptoms and the applied experimental manipulation. Moreover, they allow us to test the efficacy of new pharmacological and behavioral interventions for the treatment of ADHD, and to understand the mechanisms underlying currently used therapies.

Assessing Impulsivity and Attention Deficits in Rodents

The diagnosis of ADHD is based on behavioral criteria. Many behavioral tests commonly used in human neuropsychology have been modeled in animals. Though relatively simple tasks have been extensively used to measure locomotor activity (e.g., ► open field test), anxiety (e.g., ► elevated plus-maze), and learning and memory (e.g., ► radial-arm maze) in animal models of ADHD, more sophisticated tasks have been developed to specifically measure impulsivity and ► sustained attention.

Tasks assessing impulsivity can be broadly divided into those measuring impulsive decision-making and those measuring ► behavioral inhibition (Winstanley et al. 2006). Both subtypes of impulsivity are highly relevant to ADHD research, given the fact that affected individuals react differently to reinforcers when compared with normal subjects and that one of the core deficits in ADHD is response inhibition.

The most widely used tests of behavioral inhibition are the ► go/no-go task and the ► stop-signal reaction time task (SSRTT) (Eagle et al. 2008). These tasks have been successfully adapted to be used in animals and have shown good face and predictive validity. In the go/no-go paradigm, subjects have to respond to a cue – the "go" signal – and not to respond to a different infrequent stimulus – the "no-go" signal – to be rewarded. Children with ADHD showed impaired ability to succeed in this task when compared with control subjects.

The SSRTT is a sophisticated variant of the go/no-go task, in which the subject is required to cancel an already initiated motor response on receiving an unexpected stop signal. By varying the timing of the stop signal presentation, it is possible to measure the speed of the inhibitory process (the SSRT) (Logan 1994), which has been shown to be consistently longer and more variable in ADHD individuals. The SSRT in animals is speeded by drugs

commonly used for the treatment of ADHD, although for some drugs, the effect depends on baseline performance (Eagle et al. 2008).

Both stopping and no-go types of behavioral inhibition in humans are under the control of fronto-striatal circuits, which are differently modulated by psychostimulants in ADHD and control subjects. When putative homologous areas are lesioned in rodents by microinfusion of neurotoxins, they show inhibitory deficits qualitatively similar to those seen in ADHD patients. Eagle and colleagues showed that lesions of the orbitofrontal cortex (OFC) impair stopping performance in the rat. Moreover, SSRT is slower in rats with medial striatal lesions, a region homologous to the caudate nucleus in humans, which has been shown to be smaller or dysfunctional in ADHD patients.

Impulsive decision-making in animals is commonly assessed by means of the ► delay-discounting (DD) paradigm. In this task, impulsive choice is defined as the preference for a smaller immediate reward over a larger but delayed one. ADHD patients show faster switches of preference toward the smaller but more immediate reward when the delay to the bigger reward is gradually increased. In rodents, ► atomoxetine, ► amphetamine (AMPH), and ► methylphenidate (MPH) – drugs commonly used in ADHD pharmacotherapy – reduce impulsive choice in the DD paradigm, and some animal models of ADHD show intolerance to delay in this task (see Table 1). Cardinal and colleagues showed that lesion of the NAc core renders animals less tolerant to delays, leaving intact the preference for the large reward when no delays are interposed. In the same task, OFC lesions had less consistent effects.

Intermediate between tasks measuring impulsive decision-making and motor disinhibition are the behavioral tasks, in which the rat has to perform an action for a predetermined number of times – or to withhold from responding for a predetermined amount of time – before emitting the response that will be rewarded. Any premature interruption of these chains of actions is considered as an impulsive response. Examples of this kind of tasks are the differential reinforcement of low rates of responding (DRL) schedule, the lever-holding task (LHT), and the fixed consecutive number (FCN) schedules. In DRL schedules, a response is rewarded only if made after the predetermined amount of time has elapsed since the last response. Available studies on DRL yielded contrasting results in ADHD sufferers as well as in rodent models of ADHD. In the LHT, the subject is required not to release a lever or a button for a predetermined amount of time to be rewarded. FCN schedules require a certain number of responses in one location, before producing a single response in a different one, to receive the reward; premature interruption of these chains of responses is usually punished with a short time-out.

One of the most used tests of sustained ► attention in rodents is the ► 5-choice serial reaction time task (5-CSRTT), which was developed partly with the aim of investigating and better understanding the deficits underlying ADHD (Bari et al. 2008). The basic task is modeled on the continuous performance task used to study human attentional processes. The rat version of the task requires animals to detect brief flashes of light presented pseudorandomly in one of the five holes and to make a nose-poke response in the correct spatial location to receive a food reward. The rat is required to monitor a horizontal array of apertures and to withhold from responding until the onset of the stimulus. Generally, the accuracy of stimulus discrimination provides an index of attentional capacity, while premature responses – made before the presentation of the stimulus – are regarded as a form of impulsive behavior and hence a failure in impulse control.

Performance on the 5-CSRTT has been evaluated after lesions of discrete areas of the rat brain. Anterior cingulate (ACg) cortex lesions impair selective attention, whereas infralimbic (IL) and postgenual ACg lesions increase impulsivity, and damage to the OFC results in perseverative responding. Lesion to the medial striatum impairs response accuracy and increases both premature and perseverative responses, whereas NAc core lesions increase impulsivity without affecting response accuracy.

Depleting brain 5-HT by intracerebroventricular infusion of 5,7-dihydroxytryptamine (5,7-DHT) during adulthood produces long-lasting hyperactivity and impulsivity in the 5-CSRTT, but no attentional impairments. Finally, attentional deficits with no increase in impulsivity have been obtained by globally interfering with cholinergic neurotransmission and, under certain conditions, with the noradrenergic system (Robbins 2002).

Genetic Models

One of the most investigated animal models of ADHD is the spontaneously hypertensive rat (SHR), an inbred genetic model derived from the Wistar Kyoto (WKY) rat. Hyperactivity and impulsivity in the SHR develop over repeated testing and are particularly evident in settings with a low rate of reinforcement (Sagvolden 2000). These traits are present before the SHR develops hypertension and remain stable during adulthood. Compared with Sprague–Dawley (SD) rats, SHR show a neurochemical profile characterized by subcortical hyperdopaminergic tone and reduced ► noradrenaline (NE) function in the

Attention Deficit Hyperactivity Disorders: Animal Models. Table 1. Summary of selected models of ADHD, their behavioral characteristics, and tasks used to assess them.

Model	Impulsivity	Hyperactivity	Attention deficits
Genetic			
SHR	Yes (FI/Ext)[9] Yes (DRL, LHT) Yes/No (DD)[19] Yes (SVD)[1,15] Yes (FCN)	Yes (FI/Ext) Yes (EPM)[4] Yes (OF)[1,2] Yes (SVD)[1,15]	Yes (FI/Ext) No (5-CSRTT) Yes (Y maze)[2,8] Yes (SVD)[1,15]
TRβ-1 mouse	Yes (DD)	Yes (LA)[2] Yes (OF)	Yes (RT)
DAT-KO mouse	Yes (radial maze)	Yes (OF/LA)[1–4, 7,10,11]	Yes (radial maze)
NHE rat	?	Yes (Làt maze)[12,13]	Yes (SC)[12,13]
Coloboma mouse	Yes (DD)	Yes (OF/LA)[1, 5,14]	Yes (LI)[14]
Pharmacological			
6-OHDA lesion	Yes (EPM)	Yes (radial maze) Yes (OF/LA)[1–4, 6,18]	Yes (radial maze)
Lead exposed	?	Yes (LA)[1,2] No (OF)	?
Physical trauma			
Anoxia/Hypoxia	?	Yes (OF)[1,16]	?
X-ray exposed	?	Yes (T maze)	Yes (T maze)
Behavioral			
Poor 5-CSRTT performers	Yes (5-CSRTT)[2,18] Yes (DD) No (SSRTT)	Yes (OF) Yes/No (LA)[a] No (CC, RW)	Yes (5-CSRTT)[2]
Poor SSRTT performers	Yes (SSRTT)[1,2, 17,18]	?	?

Abbreviations: *CC* circular corridor; *DD* delay discounting; *EPM* elevated plus-maze; *FI/Ext* fixed interval/extinction schedule; *FCN* fixed consecutive number schedule; *LA* locomotor activity; *LHT* lever holding task; *LI* latent inhibition; *OF* open field; *RT* reaction time procedure; *RW* running wheel; *SC* scanning activity; *SSRTT* stop-signal reaction time task; *SVD* simultaneous visual discrimination task; *5-CSRTT* five-choice serial reaction time task.

[a]Depending on selection criteria. Numbers refer to drugs that acutely improved the specific deficit as measured by the task indicated between brackets: 1, AMPH; 2, MPH; 3, NET inhibitors; 4, SERT inhibitors; 5, alpha-2c adrenergic receptor antagonists; 6, DA D4 receptor antagonists; 7, 5-HT (2a) receptor antagonists; 8, nicotine; 9, MAO-B inhibitors; 10, 5-HT enhancing agents; 11, AMPAkines; 12, galactosylated form of DA; 13, D1 agonists; 14, NA depletion by DSP-4; 15, guanfacine; 16, acetyl-L-carnitine; 17, modafinil; 18, atomoxetine; 19, CB1 cannabinoid receptor agonists

► prefrontal cortex (PFC) (Heal et al. 2008). In theory, such catecholaminergic imbalance would predict the increased locomotor activity of SHR and the beneficial effect of drugs that regulate noradrenergic transmission on impaired ► executive functions. Conversely, there is also evidence from *in vitro* experiments for the opposite biochemical profile in SHR. NE concentrations and tyrosine hydroxylase ► gene expression have been found to be higher, whereas dopamine (DA) efflux was reduced in the striatum of SHR compared with WKY rats. These results led researchers to hypothesize that ADHD is characterized by hypofunctional dopaminergic system and hyperfunctional NE transmission in the PFC, with the latter being congruent with poor PFC regulation of NE levels by noradrenergic receptors found in the SHR. Moreover, the SHR brain displays anatomical abnormalities similar to ADHD patients as well as a decreased expression of the ► dopamine transporter (DAT) gene, which could explain the reduced responsiveness to psychostimulants (Russell 2007). Serotonin (5-HT) transmission also seems

to be abnormal in the SHR and administration of the 5-HT transporter (SERT) inhibitor ► citalopram decreases hyperactivity in the ► elevated Plus-Maze. Despite its high face validity, the SHR does not show cognitive deficits across all behavioral tasks of impulsivity and sustained attention. Moreover, the ability of drugs used in the treatment of ADHD to improve performance in this animal model have also been inconsistent, probably depending on the behavioral test employed and on the rat strain used as a control.

Mice lacking the dopamine transporter (DAT-KO) are hyperactive in new environments, have learning and memory deficits as well as impaired inhibition of ongoing behavior. DAT-KO mice are characterized by high levels of extracellular DA in the striatum and reduced phasic DA release. Hyperactivity in this model is reduced by psychostimulants and serotonergic manipulation, but not by NE transporter (NET) inhibitors. This would suggest that in this model, psychostimulants do not decrease hyperlocomotion by increasing catecholamine levels via DAT or NET blockade, but probably by modulating the serotonergic system (Gainetdinov et al. 1999). A 5-HT(2A) receptor gene ► polymorphism has been associated with human ADHD and antagonists of this receptor ameliorated DAT-KO mice deficits. However, drugs targeting the 5-HT system are of limited use in the treatment of human ADHD and it is not clear yet whether this pathology is characterized by increased or decreased DAT function.

Naples high-excitability (NHE) rats are selected for high levels of activity in the Làt maze. This model exhibits decreased DA D1 receptor availability and increased DAT and tyrosine hydroxylase activity within the PFC. It has been suggested that impaired attention and hyperactivity in NHE rats may be caused by a hyperfunctional mesocorticolimbic DA system.

The Coloboma mutant mouse bears a mutation of the synaptosomal-associated protein 25 (SNAP-25) gene and has been proposed as a model of ADHD. SNAP-25 is an important protein required for neurotransmitter release and protein translocation. Coloboma mice display impulsivity in the delayed reinforcement task and their hyperactivity is decreased by AMPH but not by MPH. It has been suggested that the hyperactive phenotype of this model is caused by an imbalance between noradrenergic hyperfunction and dopaminergic hypofunction.

Recently, a genetic mouse model based on the deletion of the β2-subunit of the nicotinic receptor has been described as having ADHD-like behavioral inflexibility and inhibitory deficits. Considering a reported association between polymorphisms of the nicotinic receptor subunit and ADHD, a high incidence of cigarette smoking in individuals with ADHD and the beneficial effects of ► nicotine administration on attentional functions, further investigation of this model is warranted.

Male transgenic mice expressing a mutant form of the human thyroid hormone receptor (TRβ-1) display increasing hyperactivity over time, impulsivity, and inattention. Thyroid hormone controls the development of brain areas involved in the regulation of executive functions. This genetic model shows increased striatal dopamine turnover and its hyperactivity is reduced by MPH administration.

Chemical Intoxication and Physical Trauma Models

Despite its high heritability, some forms of ADHD are thought to be caused by heavy metal exposure, drug intoxication, or physical traumas, at pre-, peri- or post-natal developmental stage. Some environmental factors may in fact have ► teratogenic effects on the fetus during pregnancy, which will cause ADHD symptoms in the offspring. Although exposure to chemicals and complications during pregnancy and/or delivery represent independent risk factors for the development of ADHD, it is useful to create animal models that mimic such conditions.

Heavy metal exposure in early ► ontogeny causes hyperactivity, which improves after acute AMPH or MPH administration. In animals exposed to lead, 5-HT and DA turnover is decreased in the PFC and striatum, respectively. Other heavy metals, such as manganese and cadmium, are believed to cause similar effects as lead exposure in producing hyperactive rats.

Other chemical-induced animal models are created by pre- or post-natal administration of polychlorinated biphenyls (PCBs), methylazoxymethanol, and transretinoic acid. However, these conditions have had only limited success as models of ADHD.

Prenatal ethanol and nicotine exposure can cause ADHD-like symptoms in humans and other animals. Accordingly, rats prenatally exposed to ethanol display dysregulation of dopaminergic neurons in the VTA, which is normalized by AMPH or MPH administration. However, this condition is probably better suited to model ► fetal alcohol syndrome rather than ADHD.

Physical trauma models of ADHD include, amongst others, neonatal anoxia and X-ray exposure. Neonatal anoxia is a risk factor for human ADHD and causes long-lasting behavioral impairment and monoaminergic dysregulation in the rat brain. Exposure to X-radiation during development damages the ► hippocampus and causes hyperactivity and learning deficits in rats. These models both possess predictive validity since they respond to acute AMPH administration, but are created by means

of physical insults, which are unlikely to be the cause of the majority of ADHD cases in humans.

Chemical Lesion and Behavioral Models

Animal models relevant for ADHD research can be created by lesioning of selective brain areas or interfering with neuromodulatory systems. These lesions are mainly created by microinfusion of neurotoxins during animal adulthood or at early postnatal days, to mimic abnormal neurodevelopmental processes.

The most widely used neurodevelopmental model of ADHD is the neonatal ▶ 6-hydroxydopamine (6-OHDA) lesioned rat. Shaywitz and colleagues, in 1976, showed that rats lesioned 5 days after birth by intracerebroventricular infusion of 6-OHDA display marked hyperactivity and other cognitive deficits that were claimed to be attenuated by acute administration of AMPH. Further research demonstrated that the behavioral phenotype of this model also improves after MPH administration, and that these animals (rats or mice) have decreased striatal DAT density, increased dopamine D4 receptor expression, and alterations in central 5-HT neurotransmission. These rats show patterns of hyperactivity similar to those of childhood ADHD in that their hyperlocomotion is less evident in novel environments, but then increases with repeated exposures to the testing apparatus. Thus, the 6-OHDA model presents good face and predictive validity, but lacks construct validity, as it is very unlikely that the almost complete destruction of the dopaminergic system caused by the neurotoxin mirrors the ADHD condition (Kostrzewa et al. 2008). Nevertheless, this model could provide important insights on the relationship between monoaminergic alterations in ADHD and the mechanisms underlying hyperactivity.

Rats achieving poor levels of attentional performance on the 5-CSRTT have been proposed as a model of the inattentive subtype of ADHD. These rats are hyperactive, show impulsivity – as measured by the number of premature responses – in addition to low levels of attentional accuracy. In cortical areas, 5-HT turnover of these animals is inversely related to choice accuracy, while DA and 5-HT turnover correlate positively with attentional performance and premature responses, respectively. On the other hand, rats specifically selected for high levels of premature responses in the 5-CSRTT (high-impulsive rats) have lower DA D2 receptor density in the ventral, but not in the dorsal striatum, compared with nonimpulsive rats (Dalley et al. 2007). Moreover, dopamine release and metabolism are unchanged in the nucleus accumbens (NAc) of high-impulsive rats. These behavioral phenotypes have been validated in part by their capacity to predict susceptibility to drug use (Belin et al. 2009) – for which ADHD is known to be a risk factor – and by their sensitivity to drugs used for the treatment of ADHD.

Rats that show slow inhibitory processes, as measured by the SSRTT, display differential responses to drugs used in ADHD pharmacotherapy when compared with fast stoppers in the same task. Thus, AMPH and modafinil speed stop processes only on slow stoppers and have limited effect on fast-stopping animals; MPH improves action inhibition in slow stoppers, but impairs it in fast stoppers and, finally, atomoxetine speeds SSRT in all animals independent of baseline performance (Eagle et al. 2008).

Summary

This chapter reviewed the main behavioral and neurochemical characteristics of some of the most investigated rodent models of ADHD. The collection of animal models of ADHD described here is far from complete, but is illustrative of the different approaches. Table 1 summarizes some of the behavioral tasks used to characterize ADHD-like symptoms – namely, impulsivity, hyperactivity, and attention deficits – in selected animal models and the drugs that were efficacious in ameliorating the performance of the models when compared with control animals. Some of these behavioral tasks – borrowed from clinical neuropsychological research – have highlighted the translational value of ADHD research in animals. They not only prove useful in the definition of the behavioral phenotype under investigation, but also have the potential to investigate the mechanisms of action of drugs used in ADHD. Their use, in conjunction with appropriate animal models of ADHD, can help in discovering new treatments with fewer side effects and enhanced therapeutic value.

Cross-References

▶ Animal Models for Psychiatric States
▶ Atomoxetine
▶ Attention Deficit and Disruptive Behavior Disorders
▶ Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal
▶ Delay Discounting Paradigm
▶ Genetically Modified Animals
▶ Impulse Control Disorders
▶ Impulsivity
▶ Methylphenidate and Related Compounds
▶ Phasic Neurotransmission
▶ Phenotyping of Behavioral Characteristics
▶ Polymorphism
▶ Psychostimulants
▶ Rodent Models of Cognition
▶ SSRIs and Related Compounds

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Attentional Bias to Drug Cues

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Synonyms

Addiction Stroop test; Incentive properties of drug cues

Definition

Attentional bias refers to the observation that motivationally relevant cues can "grab" or "hold" selective attention, and this is related to individual differences in appetitive and aversive motivation. For example, individuals with eating disorders tend to get readily distracted by cues related to food, whereas individuals with anxiety disorders are hypervigilant for threat-related cues. In the context of psychopharmacology, the term is usually used to refer to attentional processes among individuals with drug problems. As predicted by numerous theoretical models, drug dependent individuals have an attentional bias for drug cues, such as drug-related pictures or words.

Current Concepts and State of Knowledge

Measurement

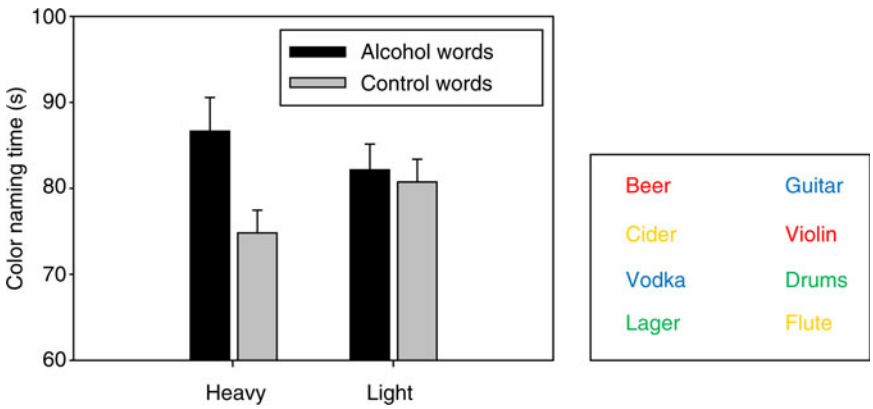
The last two decades have seen a large body of research devoted to the study of attentional biases in addiction and other disorders. A variety of experimental tasks, derived from those used in mainstream experimental psychology, have been used to assess attentional bias. For example, MacLeod et al. (1986) adapted the visual probe task, which is described below, to demonstrate that clinically anxious patients but not nonanxious controls tend to direct their attention toward threat-related words. Since this seminal study, a large volume of research has been devoted to the characterization of such attentional biases in a variety of emotional disorders (for a recent review, see Bishop 2007). More recently, researchers have used these tasks to study attentional biases for drug-related cues in addiction. With few exceptions, these tasks do not provide a direct readout of attentional processes; instead, the allocation of ▶ attention must be inferred based on a secondary measure, such as response time.

Perhaps the most commonly used task is a modified version of the classic "Stroop" task. In the classic Stroop task, participants are required to name the color in which different words are printed. A highly robust observation is that when color-related words are presented in an incongruent color (e.g., the word GREEN printed in red ink), participants are relatively slow to specify the ink color, compared to a control condition (e.g., the word TABLE printed in red ink). The interpretation of this "Stroop interference" is that people automatically process the semantic content (meaning) of words that they encounter; when the semantic content of a word (e.g., the word GREEN) conflicts with the required response (to say "red"), this leads to a slowing down of color-naming, or errors in color-naming. In the modified version of this task (the addiction Stroop), participants are required to

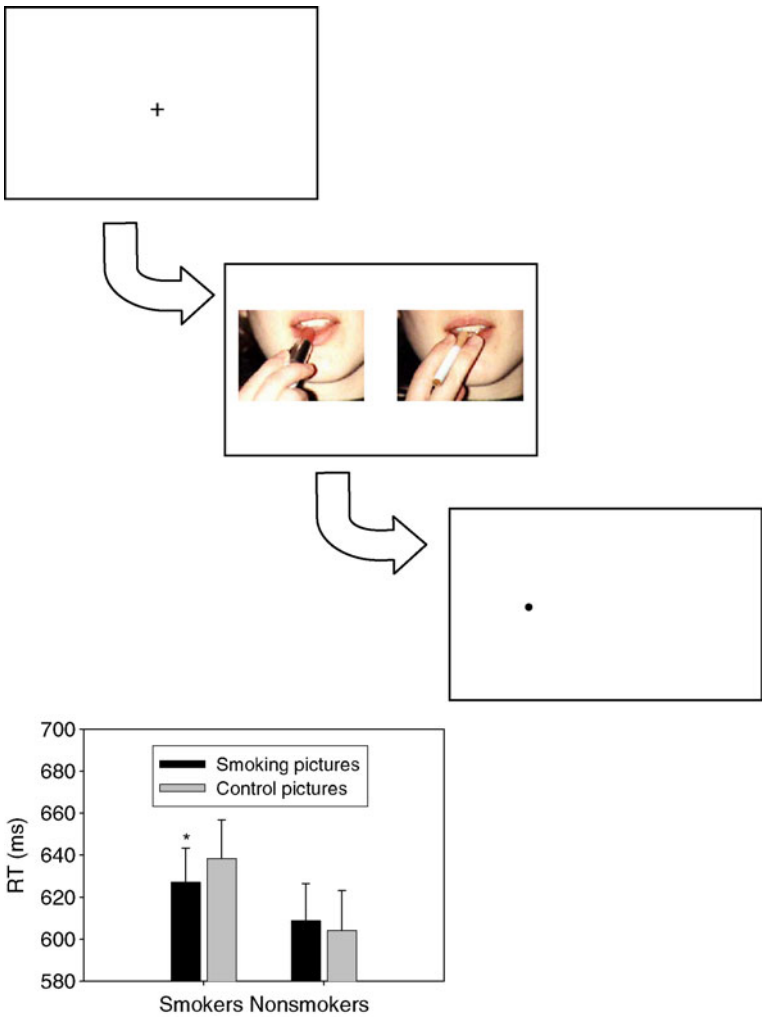
name the color in which drug-related words are printed, and their color-naming times for these drug-related words are compared to those for a control category (e.g., words related to musical instruments). See Fig. 1 for an example of the procedure and some illustrative findings. As reviewed by Cox et al. (2006), a highly robust finding in the literature is that drug users are slower to name the color in which drug-related words are presented, compared to words from a control category, but control participants do not exhibit this pattern of Stroop interference. Such Stroop interference has been demonstrated in users of a variety of different drugs, including alcohol, cannabis, cocaine, heroin, and tobacco (reviewed by Cox et al. 2006). This suggests that, compared to nonusers, drug users engage in excessive semantic processing of drug-related words, i.e., those words can "grab their attention." However, it is important to note that other explanations for this Stroop interference have been put forward, including delayed color-naming as a consequence of attempts to suppress the processing of drug-related words, or a generic slowdown in cognitive processing induced by the drug-related words, perhaps independently of any bias in selective attention (see Field and Cox 2008). Indeed, any Stroop interference that is observed may reflect the combined influence of all of these factors, and the specific influence of selective attention to drug-related words may be minimal; these issues mean that results from this task must be interpreted with some caution.

The visual probe task is an alternative measure of attentional bias that has been extensively used in psychopharmacology research, particularly over the past 5 years. In this task (see Fig. 2), a pair of pictures are presented on the left and right of a computer screen. One of the pictures is drug-related (e.g., an image of a person smoking a cigarette), and the other picture contains no drug-related content. The pictures are shown for a short period (typically between 50 and 2,000 milliseconds (ms)), and after pictures have been removed from the computer screen, a visual probe stimulus (for example, a small dot) is presented on either the left or right of the screen, in the spatial position that had been occupied by either the drug-related or the control picture. Participants are instructed to respond to the probe as quickly as possible. As reviewed by Field and Cox (2008), a robust observation is that drug users are faster to respond to probes that replace drug-related pictures, than to probes that replace control pictures. Control participants are equally fast to respond to probes that replace drug-related and control pictures. This has been demonstrated not only with tobacco smokers in several studies, but also with cannabis users, heroin users, and heavy drinkers.

Given that people are faster to detect and respond to a stimulus if it appears in a location of the visual field that they were attending to, this finding (faster reaction times to probes that replace drug-related pictures, rather than control pictures) is usually interpreted as indicating that drug users were directing their attention toward drug-related pictures. Indeed, when participants' eye movements are monitored while they complete the task (as detailed below), there is usually a large positive correlation between the index of "attentional bias" (derived from reaction times to probes) and the amount of time that



Attentional Bias to Drug Cues. Fig. 1. The addiction Stroop test. Participants are required to quickly identify the color in which words are printed. One list of words is drug-related; the other is neutral. In this study, adolescent heavy drinkers were slower to name the color of alcohol-related words, than to name the color of neutral words, but light drinkers took a similar amount of time to name the color of words in the two word lists. (Reprinted with permission from Field M, Christiansen P, Cole J, Goudie A (2007) Delay discounting and the alcohol Stroop in heavy drinking adolescents. Addiction 102:579–586.)



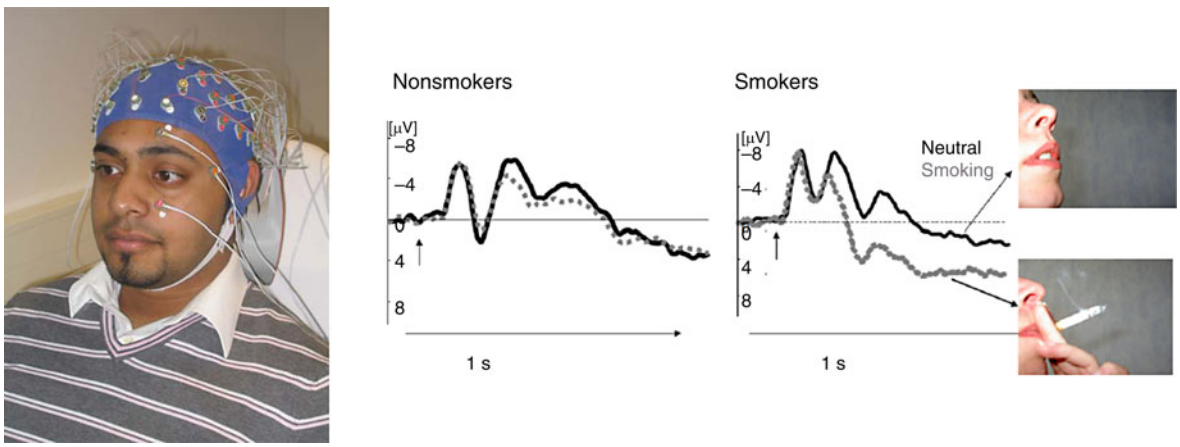
Attentional Bias to Drug Cues. Fig. 2. The visual probe task. Following a centrally presented fixation cross, a drug-related picture and a neutral picture are presented side by side on a computer screen for a brief period. After the pictures disappear, a visual probe is presented, and participants are required to rapidly respond to the probe. In this study, tobacco smokers were faster to respond to probes that replaced smoking-related pictures, than to probes that replaced neutral pictures, but nonsmokers did not show this difference. (Reprinted with permission from Mogg K, Bradley BP, Field M, De Houwer J (2003) Eye movements to smoking-related pictures in smokers: relationship between attentional biases and implicit and explicit measures of stimulus valence. Addiction 98:825–836.)

people maintain their gaze on the drug-related cues. So, it appears valid to use reaction times to visual probes to infer the allocation of attention to drug-related cues that precede those visual probes. A further issue with the visual probe task is that researchers have experimentally manipulated the amount of time that picture pairs are presented on the screen before they are removed and replaced by the visual probe. By varying the stimulus onset asynchrony (SOA), in this way, for example, using very short exposure durations (e.g., 50–200 ms) or longer durations (e.g., 2,000 ms), it is assumed that reaction time can capture the extent to which cues "grab" the attention (with very short SOAs) or "hold" the attention (with longer SOAs). Some studies suggest within-subject and between-group differences in attentional bias when short and long SOAs are used, which is consistent with the notion that these different SOAs can be used to measure different aspects of cognitive processing of drug cues. However, there is currently some controversy over whether reaction times obtained from the visual probe task can ever be used to

index orienting of attention, regardless of how brief the SOA is (Field and Cox 2008).

Given these issues with interpreting results from the visual probe and addiction Stroop tasks, there is a need to use measures of attentional bias that provide more direct readouts of selective attention. Eye movement monitoring is one such measure, because people are usually attending to whatever is currently the focus of gaze. Some researchers have monitored participants' eye movements while they complete a visual probe task in which drug-related and control pictures are presented. It is possible to then look at the orienting of attention to drug-related cues, by measuring which picture (drug-related or control) participants initially direct their gaze toward on each trial of the task. It is also possible to measure the maintenance of attention on, or latency to disengage attention from, drug-related cues, by comparing the amount of time that participants direct their gaze toward drug-related pictures with the amount of time that they direct their gaze toward control pictures. Tobacco smokers, ► cocaine users, and cannabis users (but not control participants) tend to preferentially maintain their gaze on drug-related pictures; however, the evidence for a bias in the initial orienting of attention toward drug-related pictures is currently equivocal (Field and Cox 2008).

Additional laboratory measures have been used in recent years to investigate attentional bias for drug-related cues. These include tasks such as the flicker induced change blindness task and the attentional blink task (see Field and Cox 2008). However, these are not discussed in detail in this section as they are not currently widely used, although both methods may have advantages over existing measures. The final measure that we consider here is ► electroencephalography (EEG), particularly the study of event-related potentials (ERPs) elicited by drug-related cues. EEG recording involves attaching electrodes to various sites on the scalp of participants (see Fig. 3) that measure the electrical activity produced by the brain. Participants are then shown drug-related (or control) pictures, and activity in the cortex can be measured in the form of electrical activity on the scalp in response to presentation of the pictures (ERPs). Although there are many different forms of ERPs, which differ in their latency, magnitude, and brain region of origin (see separate entry), researchers have focused on ERP components such as the P300 (a slow positive wave that typically occurs about 300 ms after stimulus presentation). This particular ERP component has been implicated in selective attention, such that its magnitude (in response to a visually presented stimulus) seems to correlate highly with the degree to which participants attend to that stimulus. This has particularly been observed for motivationally relevant stimuli. In several studies, it has been demonstrated that P300 magnitude in response to drug-related



Attentional Bias to Drug Cues. Fig. 3. Measuring event-related potentials (ERPs) in response to smoking-related cues. Smoking-related and neutral pictures were presented for 2 s, and participants were asked to watch the pictures attentively. The ERP results indicate that both the P300 and the subsequent slow wave amplitudes in response to smoking-related pictures are significantly enhanced in smokers compared to nonsmokers at frontal and central sites, whereas the magnitude of the P300 and SPW amplitudes in response to neutral pictures does not differ between the groups. Accordingly, it can be concluded that smokers show more bias for smoking-related pictures than smokers. (Data published in Littel M, Franken IHA (2007) The effects of prolonged abstinence on the processing of smoking cues: an ERP study among smokers, ex-smokers and never-smokers. J Psychopharmacol 21:873–882.)

cues is significantly larger in drug-users than in control participants (see Fig. 3 for an example). This has been demonstrated in heroin, cocaine, alcohol, and tobacco users (e.g., Franken et al. 2008).

Theoretical Relevance

Arguably, interest in attentional bias in humans originated from animal models of incentive learning processes. It has been known for decades that after ► classical (Pavlovian) conditioning, laboratory animals will direct approach behaviors to conditioned stimuli that are reliable predictors of appetitive rewards, such as food or addictive drugs. This conditioned approach behavior is known as autoshaping. Interestingly, animals show increased interest in conditioned stimuli that predict appetitive rewards, and they orient their attention to them ("sign-tracking") before those cues elicit an overt behavioral approach response. In an influential theory, Robinson and Berridge (1993, cited in Field and Cox 2008) argued that these incentive learning processes are mediated by dopaminergic activity in the ► nucleus accumbens and related structures within the mesolimbic dopamine system. According to the theory, chronic exposure to drugs of abuse leads to sensitization of dopamine activity in this ► dopamine circuit. As a consequence, these incentive learning processes are exaggerated, and drug-related cues acquire very powerful incentive properties, meaning that their capacity to grab the attention and elicit approach behaviors is enhanced. As reviewed by Hogarth and Duka (2006), an emerging body of evidence suggests that a classical conditioning process may be responsible for the development of attentional bias in humans: people tend to direct their attention toward a cue that was previously paired with the availability of ► alcohol or ► nicotine in the laboratory.

Alternative theoretical models are more explicitly grounded in clinical and experimental psychology, yet their predictions are not inconsistent with the aforementioned learning processes. For example, the theory of current concerns (see Cox et al. 2006) suggests that drug users have a dysfunctional motivational structure, such that their goal to use drugs takes precedence over all other goals, leading to a general cognitive hypersensitivity to goal-related (i.e., drug-related) environmental cues. Ryan 2002; cited in Field and Cox 2008) emphasized the need to consider cognitive processes when trying to understand why drug users react to drug-related cues with physiological and subjective changes. In essence, Ryan argued that drug users find it difficult to ignore drug-related cues in their environment, which exacerbates subjective craving in response to those cues; this in turn leads to drug-seeking behavior. Finally, Franken (2003) integrated predictions made by Robinson and Berridge (1993) with some observations of human patients. Franken's (2003) model suggests that attentional bias for drug cues occurs as a consequence of a dysfunctional, dopamine mediated incentive learning process, as discussed above. This causes drug users to be more likely to detect drug-related cues in their environment. Once drug cues have been detected, the drug user experiences subjective ► craving, which leads to a further increase in the salience of drug-related cues (i.e., drug-related cues become even more difficult to ignore). In addition, attentional bias and subjective craving mean that the cognitive resources required for coping strategies (e.g., attempts to resist craving) are further diminished, and the combined effect is that drug-seeking behavior is more likely to occur. All of these theoretical models converge on the common prediction that attentional bias should be positively correlated with subjective craving, and we discuss relevant evidence in the following paragraphs.

Clinical Relevance

The theoretical models discussed above suggest that attentional bias is likely to develop as a consequence of chronic exposure to drugs of abuse, perhaps through a conditioning process. Once established, attentional bias may be long-lasting and difficult to reverse, and this is consistent with results from one study that demonstrated no difference in attentional bias between current tobacco smokers and individuals who had been abstinent from smoking for 6.5 years, on average. These theoretical models also suggest that attentional bias can contribute to the maintenance or escalation of drug-seeking behavior, perhaps because it increases the magnitude of subjective drug craving, or even triggers drug-seeking behavior directly. As such, attentional bias may be clinically relevant, and therefore it could be a viable target for clinical intervention. Two primary clinical applications of attentional bias research can be described. First, if attentional bias causes (or at least indexes the underlying processes that cause) drug-seeking behavior, then individual differences in attentional bias might indicate vulnerability to relapse among drug users who are currently abstinent, possibly in ways that cannot be captured by self-report measures. Consistent with this notion, a number of recent studies demonstrated that individual differences in attentional bias (among tobacco smokers, alcohol abusers, and heroin users) predicted subsequent clinical outcome (either treatment dropout, or time to relapse to drug-seeking after treatment completion; see review by Field and Cox 2008). However, all of these studies used the addiction Stroop task to measure attentional bias; given the problems with interpreting results from this task,

there is a need to replicate these findings with more direct measures of selective attention, such as eye movement measures. The second clinical implication is that attentional bias itself might be a suitable target for treatment intervention: if individuals can be "trained" to reduce the extent to which they get distracted by drug-related cues, they might be less likely to relapse to drug-seeking behavior in the future. There is currently a great deal of enthusiasm for this type of intervention, although it should be noted that the early results are not promising. That is, when attentional bias is experimentally reduced, it does not consistently lead to a reduction in drug-seeking behavior (see Field and Cox 2008).

The association and causal relationship between attentional bias and subjective craving (rather than drug-seeking behavior) is currently more compelling. Among drug users, all measures of attentional bias are positively correlated with subjective drug craving (Field and Cox 2008; Franken 2003), and the association is particularly robust for more "direct" measures of attention, such as eye movement monitoring or the P300 component of ERPs (see Field et al. 2009). As predicted by some of the theoretical models discussed earlier (e.g., Franken 2003; Ryan 2002), there appears to be a reciprocal causal relationship between attentional bias and subjective craving. That is, when subjective craving is experimentally manipulated (e.g., through stress, enforced abstinence), attentional bias seems to increase in line with subjective craving; on the other hand, when attentional bias is experimentally increased, this leads to a small but significant increase in subjective craving (all reviewed by Field and Cox 2008).

So attentional bias may be related to drug-seeking behavior, although the evidence for this is limited at present. The evidence for an association, and mutual causal relationship, between attentional bias and subjective craving is much more compelling. Given that some investigators (e.g., Tiffany 1990; cited in Field and Cox 2008) believe subjective craving to be of little relevance to drug-seeking behavior itself, it remains to be seen whether attentional bias could have a clinically meaningful role in the prediction of treatment outcome in drug abusers, or whether it is a suitable target for treatment.

Pharmacological Modulation

The effects of a variety of pharmacological challenges on attentional bias have been studied. Firstly, administration of small to moderate doses of alcohol seems to increase attentional bias for alcohol- and smoking-related cues in heavy drinkers and tobacco smokers, respectively (see Field and Cox 2008). Alcohol affects a variety of neurotransmitter systems, but its direct effects are to increase ▶ GABA activity and reduce ▶ glutamate activity, which then has knock-on effects on other neurotransmitter systems, such as ▶ dopamine and ▶ serotonin. The precise mechanism of action through which alcohol increases attentional bias is unclear, but it may be related to some of the other effects of alcohol priming doses, such as increased craving or a decreased ability to regulate attention. Investigators have also increased or decreased dopamine and serotonin function before examining the effects on attentional bias (reviewed in Munafo and Albery 2006). In one study, ▶ Haloperidol, a dopamine antagonist, was seen to eliminate Stroop interference produced by heroin-related words in heroin addicts. In another study, researchers depleted dopamine levels by administering an amino acid mixture which was devoid of the amino acids tyrosine and phenylalanine, which are required for dopamine synthesis. Compared to a control manipulation (consumption of an amino acid mixture that did not deplete tyrosine and phenylalanine), this led to reduced Stroop interference for smoking-related words in tobacco smokers. However, these effects were not particularly robust, as they were only seen in female participants, but not in males. In a further study, researchers replicated this effect of tyrosine depletion on Stroop interference, but again the effects were not robust: in this study, effects were moderated by the sequence in which participants consumed the two different amino acid mixtures.

So, there is emerging evidence that a dopaminergic mechanism is involved in attentional bias, with manipulations that reduce dopamine function leading to a reduction or abolition of attentional bias in tobacco smokers and heroin users. This is very important theoretically because it is consistent with the dopamine sensitization theory of addiction, which was discussed previously (Robinson and Berridge 1993; see Field and Cox 2008). To briefly recap, according to the theory, chronic drug use leads to sensitization of dopamine function in the nucleus accumbens and interconnected structures, which leads to an increase in the "salience" of drug-related cues. As predicted by the model, pharmacological manipulations that reduce dopamine function seem to reduce the salience of drug-related cues, i.e., they reduce attentional bias. However, dopamine is unlikely to be the only neurotransmitter involved. One group of investigators were able to increase Stroop interference for smoking-related words in tobacco smokers by depleting levels of ▶ typtophan, an amino acid required for the synthesis of serotonin (5-HT). So, although the evidence is limited, different neurotransmitter systems may have conflicting roles in attentional bias, with some (e.g., dopamine) increasing it and others (e.g., serotonin) reducing it. Finally, we note

that these pharmacological challenge studies used the addiction Stroop task to measure attentional bias. Given that it is difficult to accurately characterize the roles of selective attention versus other cognitive processes (e.g., generic slowdown, thought suppression) in the production of Stroop interference, future researchers should explore the effects of pharmacological challenges on other, more direct measures of attentional bias, such as eye movement monitoring or ERPs.

Cross-References

► Attention
► Classical (Pavlovian) Conditioning
► Event-Related Potentials

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Attentional Effect

Definition

Attentional effect refers to the immediate effect of a drug on the allocation of cognitive resources required for timing. These effects are reflected, for example, in the alteration of the delay in responding that follows a retention interval. Should subjects pay more attention to timing, they would be able to stop timing during the delay and resume timing afterward with little or no loss of accumulated time prior to the interruption. Should subjects pay less attention to timing, they would not be able to stop timing during the delay, and they will restart (reset) timing afterward. In the PI procedure with gaps, an attentional effect is observed by an immediate shift in the response function in trials with gaps (retention intervals), indicative of more or less attention paid to the timing task (see Buhusi 2003).

Attentional Learning

► Blocking, Overshadowing and Related Concepts

Attentional Retraining Intervention

Definition

Attentional retraining interventions involve procedures that are designed to assist individuals in maintaining, focusing, redirecting, and dividing attention. Extrapolated from neuropsychological testing and interventions, attentional retraining utilizes auditory and/or visual stimuli to isolate different areas of attention. Through repeated completion of specific tasks, attentional retraining can lead to increased overall attention, reduced distractibility, and increased ability to shift attention. In relation to drug effects, attentional retraining interventions are designed to redirect automatic attentional bias in order to lessen the impact of drug-related cues. By redirecting attention, these interventions decrease distractibility from drug cues and subsequently disrupt the activation of drug-seeking behavior.

Cross-References

► Attentional Bias to Drug Cues
► Expectancies and Their Influence on Drug Effects

Attentional Set

Definition

Attentional set refers to the bias to attend to restricted perceptual aspects of the environment. Organisms learn to attend to the sensory features and responses that are relevant to performing a task and ignore the features and responses that are irrelevant. When certain features and responses retain their relevance across tasks, an

"attentional set" may develop that bias perception and responses and increases the speed of learning new tasks as long as those features and responses remain relevant.

Atypical Antipsychotic Drugs

Synonyms
Second- and third-generation antipsychotics

Definition
All conventional antipsychotics (also called first-generation antipsychotics) share the central property of dopamine 2 receptor antagonism and, in association with this property, can cause extrapyramidal side effects (EPS). Atypical antipsychotics are so-called because they generally have a lower propensity to cause EPS than the older agents; the exact reason for this is unknown but is believed to be due to the fact that these agents have the additional property of 5HT2A antagonism and/or dopamine 2 partial agonism (as opposed to antagonism).

Cross-References
- ▶ Antipsychotic Drugs
- ▶ Bipolar Disorder in Children
- ▶ Schizophrenia

Atypical Autism

- ▶ Pervasive Developmental Disorder Not Otherwise Specified

Atypical Depression

Definition
A form of depression that is characterized by the presence of mood reactivity (responsiveness to positive events) and two or more of the following: significant weight gain or an increase in appetite, hypersomnia (oversleeping), leaden paralysis, and significant social/occupational impairment resulting from a long-term pattern of sensitivity to interpersonal rejection. Exclusionary criteria include depression with melancholic or catatonic features. Patients with atypical depression are often responsive to MAOIs.

Cross-References
- ▶ Antidepressants
- ▶ Monoamine Oxidase Inhibitors

AUC

- ▶ Area Under the Curve
- ▶ Distribution
- ▶ Pharmacokinetics

AUD

- ▶ Alcohol Abuse and Dependence

Augmentation

Definition
Pharmacological strategy to enhance a therapeutic effect.

Aurorix

- ▶ Moclobemide

Autism

Synonyms
Autistic disorder

Definition
Autism is defined by impairment in social interactions and communication, along with restricted repetitive and stereotyped patterns of behavior, interests, and activities. Delays in social interaction, language, or imaginative play must be noted before the age of 3 years.

Cross-References
- ▶ Autism Spectrum Disorders and Mental Retardation

Autism: Animal Models

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Synonyms
Rodent models of autism

Definition

Autism is a neurodevelopmental disorder characterized by impairments in social interaction, verbal and nonverbal communication, and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities appearing before the age of three (American Psychiatric Association 1994). Its clinical manifestations and severity of impairments vary from mild to severe. The core symptoms are frequently accompanied by a spectrum of neurobehavioral derangements, including: hyperactivity, aberrant sensitivity to sensory stimulation, anxiety, mental retardation, seizures, self injury, sleep disturbances, and upset to change in routine. The etiology of autism is thought to involve an interaction between genetic susceptibility, mediated by multiple genes, and environmental factors. Epidemiological studies find a four times higher incidence of autism in boys than in girls. Because the primary diagnostic criteria of autism are abnormal behaviors, rather than biochemical or neuroanatomical factors, the use of animal models in the study of autism is unavoidable, as this is the only way to study behavioral defects in context of a whole organism.

Current Concepts and State of Knowledge

Concepts for In Vivo Modeling

There is an ongoing discussion about the criteria to be used in the evaluation of animal models. It has been suggested that the only meaningful initial evaluating criterion for an animal model is its ability to lead to accurate predictions (predictive validity). Other authors stressed that the demonstration of construct validity (similarity to the underlying causes of the disease) represents the most important and necessary component in validation of an animal model. Others claim that the modeling of symptoms (face validity) must remain the primary goal of animal models of psychiatric disorders. The resolution of this puzzling controversy depends on the desired purpose of the model that one wishes to validate. Although, regarding complex psychiatric disorders such as autism, a multidimensional approach should be used as an optimal strategy.

Challenges for Animal Models of Autism

In recent years, several rodent models of autism have been developed that reflect some behavioral, genetic, and neuroanatomical alterations associated with this disorder. One of the main problems for the development of a relevant model is to define markers of autism, addressing its complexity and diversity. An ideal rodent model of autism should display symptoms of aberrant social interaction and communication, as well as repetitive behaviors. Tasks that could examine these behavioral symptoms in rodents have been already developed and are summarized in Table 1. However, an animal model of autism based solely on behavioral assays would be incomplete. Animal model should also address a combination of the neuropathological, biochemical and genetic factors implicated in autism. Another challenge lies in the fact that many clinical hallmarks of autism are difficult or almost impossible to replicate in rodents, e.g., theory of mind (ability to intuit the feelings and intentions of others) or speech deficits. It is also important to realize that assumed "core" psychopathological phenomena observed in autism are present as common clinical features in schizophrenia, depression, obsessive-compulsive disorder and other medical and psychiatric illnesses. What is specific for autism is a pattern of socio-behavioral aberrations and their appearance before the age of three, and animal models should try to address this fact.

Behavioral Tests for Autistic-Like Aberrations in Rodents

As an important prerequisite, it is necessary to use appropriate behavioral test batteries for the validation of an animal model of autism. The three core symptoms of autism should be targeted first:

1. Impairment in social interaction is a critical component for such models. Rodents are highly social animals displaying a plethora of different social behaviors. The propensity of animals to spend time with conspecific rather than non-social novel objects shall be used as one of the measures. This can be best done in an automated three-chambered apparatus in which social interactions, social recognition, and social memory can also be scored (Crawley 2007). Measures of the level of social approach should be accompanied by more specific analyses of reciprocal social interactions, including, nose-to-nose contacts, anogenital inspections, aggression, escape behavior, nesting patterns, juvenile rough and tumble play, etc.
2. Impairments in social communication may be meaured in rodents using olfactory and auditory communication tasks. Different kinds of ► ultrasonic vocalizations can be elicited in rodents, starting from separation calls in pups isolated from their mothers, to frequency modulated vocalizations in social situations in adult animals, treated, at least in rats, as indicators of positive and negative affective states (Portfors 2007). Both frequency and time structures of ultrasonic vocalizations should be analyzed. Olfactory social signals, including deposition of ► pheromones,

Autism: Animal Models. Table 1. Rodent behavioral tasks relevant to autism (for references see Crawley 2007).

Tests analogous to core autistic symptoms	Tests analogous to associated symptoms
1. Impairment in social interactions • Reciprocal social interactions (partner grooming, nose-to-nose contacts, anogenital inspections, aggression, escape behavior, juvenile rough and tumble play etc.) • Propensity to spend time with conspecific vs. novel objects • Conditioned place preference to conspecifics • Preference for social novelty • Aggression (resident-intruder test) • Social recognition • Nesting patterns in the home cage 2. Impairments in social communication • Behavioral responses to social olfactory cues from conspecifics • Deposition of social olfactory pheromones • Vocalizations emitted during social interactions • Responses to vocalizations from conspecifics • Parental retrieval of separated pups • Ultrasonic vocalizations by separated pups 3. Repetitive, stereotyped patterns of behavior, interests, and activities • Motor stereotypies • Extinction of a learned response in an operant chamber • Reversal of a position habit in an appetitive T-maze task, aversive Y-maze task or the Morris water maze • Spontaneous responses to errors during reversal tasks	1. Anxiety: elevated plus maze; light-dark box exploration; Vogel conflict licking test; marble burying 2. Theory of Mind deficits: location of buried food following observation of conspecifics; social transmission of food preference; avoidance of aggressive encounters 3. Cognitive aberrations: acquisition of different maze tasks; operant learning tasks; attentional measures in the five choice serial reaction time task; contextual and cued fear conditioning; discriminative eyeblink conditioning and reversal 4. Seizure susceptibility: spontaneous seizure activity; sensitivity to audiogenic and drug-induced seizures 5. Motor clumsiness: balance beam foot slips; rotarod motor coordination and balance; gait analysis 6. Sleep disturbances: circadian running wheels; home cage sleep and activity patterns 7. Responses to sensory stimuli: acoustic startle; tactile startle; hot plate; Von Frey filaments; unresponsiveness to sensory attentional cues (failure to disengage attention) 8. Developmental progression: maturational and developmental milestones; brain weight and volume; size of structures

are another form of rodent communication (Arakawa et al. 2008). Rodents' chemical signals play a particularly important role in determining social dominance and intersexual relationships.

3. Finally, repetitive behavior encompasses both motor stereotypy and self-injury, can be scored using standardized scales, and behaviors reflecting general cognitive rigidity, such as ability to change, resistance to change, and responses to the change in routine can be investigated by exploratory choices and reversal tasks using spatially contingent reinforcers, e.g., reversal learning in T-maze or water maze.

Because autism is accompanied by a plethora of neurobehavioral aberrations, it is important to include a range of additional behavioral tasks assessing, e.g., anxiety, seizure susceptibility, sleep patterns, sensitivity to sensory stimuli, learning and memory, and maturation and development. Finally, both pathological features of autism (e.g., decreased number of Purkinje cells) and biological findings (e.g., increased serotonin levels) should be addressed.

Current Animal Models of Autism

More than a dozen of different rodent models of autism are currently used. They can be classified into three categories: (1) models created by neonatal lesions of brain areas shown to be abnormal in autism, e.g., cerebellum, the ► amygdala, ► hippocampus, or the medial ► prefrontal cortex; (2) models mimicking environmental factors that increase the risk for autism in humans, e.g., prenatal exposure to ► valproic acid (VPA) or pre- and neonatal immunological challenges; and (3) ► genetically modified animals, e.g., targeted mutations in genes associated with autism or localized in chromosomal regions identified by linkage analyses.

Lesion Induced Models

The exact locus of brain dysfunction in autism remains a point of debate (Bauman and Kemper 2005). Many brain regions, ranging from brainstem and cerebellum to association areas of the neocortex, have been suggested as potential candidates. Nevertheless, converging lines of evidence suggest that dysfunctions and morphological abnormalities in the medial temporal lobe, especially

amygdala, and the prefrontal cortex (PFC) might underlie social deficits in autism. On that basis several models of autism have been proposed (Tordjman et al. 2007). For example, neonatal ibotenic acid lesion of the amygdala on PND 7 in rat produces a spectrum of behavioral abnormalities resembling those described in autism: decreased social interaction, increased stereotypic-like activity and decreased exploratory behavior. Similarly, neonatal ventral hippocampus lesion in rats leads to impaired social behaviors, motor hyperresponsiveness to stress, enhanced stereotypies, deficits in pre-pulse and latent inhibitions, and working memory problems. Rats with neonatal PFC lesions display reduced social play and non-play behavior in early adolescence, and reduced amount of self-grooming in adulthood. However, as these injuries destroy entire brain regions they have little relationship to the mild neuroanatomical pathologies observed in autism. Furthermore, abilities to investigate genetic or developmental mechanism in such models are very limited.

Models Created by Environmental and Immune Factors

An exposure during embryogenesis to at least three teratogens appears to be a risk factor for autism: ► thalidomide, VPA, and ► misoprostol (Arndt et al. 2005). Accordingly, one of the best validated animal models of autism is induced by prenatal exposure to VPA on the twelfth day of gestation (reviewed in Markram et al. 2007). VPA rats show several brainstem and cerebellar abnormalities resembling those found in autistic patients. At the behavioral level, VPA rats exhibit decreased social interactions, increased repetitive behaviors, enhanced anxiety, locomotor hyperactivity combined with lower exploratory activity, lower sensitivity to pain, higher sensitivity to non-painful sensory stimulation, impaired pre-pulse inhibition, and faster acquisition of eye-blink conditioning. Interestingly, behavioral aberrations described in VPA rats are observed mostly in males and can be reversed by ► environmental enrichment procedure. These might resemble both disproportion in boys to girls ratio in autism and efficacy of early behavioral-cognitive intervention in some patients with autism. VPA rats express also molecular and immunological aberrations resembling those observed in autism, e.g., increased serotonin level in several brain structures and ► hyperserotoninemia, increased frontal cortex dopamine level, enhanced excitatory transmission, and decreased cellular immune response.

Another factor implicated in the pathogenesis of autism is disturbed functioning of the immune system, especially pre- and/or neonatal immunological challenge. The best characterized model of autism utilizing this approach is induced by neonatal Borna disease virus (BDV) infection in rat (Pletnikov et al. 2005). Infected animals have injured cerebellum, progressive loss of Purkinje cells and dentate gyrus neurons, and cortical shrinkage. Neonatal BDV infection induce abnormal social interaction and communication, increased emotional reactivity, reduced cognitive abilities in spatial memory and learning, hyperactivity, stereotypies, and decreased startle responsiveness. These abnormalities mimic the impaired social interaction and atypical responses to sensory and emotional stimuli characteristic in autism. Similarly, mouse prenatally exposed to maternal infection or inflammation also displays autistic-like phenotype, including deficiencies in social interaction, exploration and sensorimotor gating. The disadvantage of infection models is that they lead to a persistent infection of the brain precluding more precise characterization of the time course and structural specificity of the created neuronal aberrations.

Genetically Induced Models

To date, several genetically induced mouse models of autism have been proposed (Moy and Nadler 2008). They were created using three general approaches. One approach is to induce mutations in genes regulating social behavior. For example, oxytocin gene knockout pups display reduced exploration, less separation distress calls, and later on a diminished social recognition. Reduced social interaction and decreased exploration were also observed in serotonin transporter-null mice.

A second approach uses monogenic aberrations, such as loss of Fmr1 or methyl-CpG-binding protein-2 (Mecp2) function, that underlie syndromes associated with autistic-like behavior. The Fmr1-null mice display increased levels of social anxiety, reduced social interaction, hyperactivity, and deficits in spatial and reversal learning. Interestingly, exposure to an enriched environment can reverse some behavioral deficits in this model. The Mecp2-null mice show deficits in social behavior, hypoactivity, impaired learning and memory, and increased anxiety.

A third approach uses gene mutations relevant to loci for autism susceptibility, identified by association or linkage studies. For example, $Reln^{rl/+}$ mice show lower rates of separation distress calls, impairments in reversal learning, increased anxiety, decreased pre-pulse inhibition, and a progressive loss of Purkinje cells. Similarly, Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules. Another example, mutants of genes regulating synaptic function may show highly specific deficits in social interaction, like mouse with a loss-of-function mutation in X-linked Nlgn4, or a

combination of symptoms, including social deficits, hyperactivity, reduced spatial learning, impaired motor coordination, smaller cerebellum and reduced numbers of Purkinje neurons, like En2-null mice. An important drawback of a targeted gene disruption in animal models of autism is that the null allele is not what is normally observed in humans, and that autism, as a polygenic disorder, is probably a result of an interaction of several dozens of genes.

Conclusions

The advantage of animal models of autism is to study developmental and behavioral deficits in context of a whole organism. We can use such models to clarify complex relationships between genetic, behavioral and environmental variables to better understand and potentially cure autism. What we need now is to combine these different approaches into multidisciplinary studies determining the consequences of environmental factors (e.g., stress, teratogenic substances, enriched environment) on the development of autistic-like behavioral changes in genetically modified animals, and *vice versa*, to determine the genetic basis of negative and positive effects of environmental factors in animal models. It is also critical to facilitate the process of identifying reliable measures of the human phenomenon, as better understanding of the neuropathology of autism will be essential to continue to build and improve animal models in the future.

Cross-References

- ▶ Animal Models for Psychiatric States
- ▶ Antinociception Test Methods
- ▶ Anxiety: Animal Models
- ▶ Autism Spectrum Disorders and Mental Retardation
- ▶ Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal
- ▶ Construct Validity
- ▶ Distress Vocalizations
- ▶ Elevated Plus-Maze
- ▶ Face Validity
- ▶ Genetically Modified Animals
- ▶ Open Field Test
- ▶ Operant Behavior in Animals
- ▶ Phenotyping of Behavioral Characteristics
- ▶ Prepulse Inhibition
- ▶ Rodent Models of Cognition
- ▶ Schizophrenia: Animal Models
- ▶ Short-Term and Working Memory in Animals
- ▶ Social Interaction Test
- ▶ Social Recognition and Social Learning
- ▶ Social Stress
- ▶ Spatial Learning in Animals
- ▶ Thalidomide
- ▶ Valproic Acid

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Autism Spectrum Disorders and Mental Retardation

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Synonyms

Amentia; Autism spectrum disorders; Intellectual disability; Mental deficiency; Mental retardation; Oligophrenia; Pervasive developmental disorders

Definition

Autism Spectrum Disorders

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders that involve qualitative

impairments in social interaction and communication, and restricted repetitive and stereotyped patterns of behavior (► stereotypical and repetitive behavior), interests and activities. The ASDs include ► autism or autistic disorder, ► Asperger's disorder, and ► pervasive developmental disorder not otherwise specified (PDD NOS). The category of ► Pervasive Developmental Disorders (PDDs) is broader and also includes ► Rett's disorder and ► childhood disintegrative disorder. All these disorders cause significant impairment in functioning.

Mental Retardation

Mental retardation (MR) is described as an IQ of 70 or below, age of onset less than 18 years, and deficits in at least two of the following areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety. The severity of MR is based on intellectual impairment. Mild MR is described as an IQ of 50–55 to 70, moderate MR 35–40 to 50–55, severe MR 20–25 to 35–40, and profound MR below 20–25 (American Psychiatric Association 2000).

Role of Pharmacotherapy

Autism Spectrum Disorders

In ASDs, there are several symptom domains, some core and some associated, that are common targets of pharmacological therapy. These domains are frequently seen in individuals with ASDs and may interfere with their ability to adapt and function. Among others, these symptom domains include motor hyperactivity and inattention, interfering stereotypical and repetitive behavior, aggression and self-injurious behavior (SIB), and core ► social impairment. We will not discuss all possible pharmacotherapies for ASDs in this entry. For example, mood, anxiety, and sleep disorders are often treated with drugs in individuals with ASDs. However, due to a paucity of randomized controlled trials (RCTs) in these areas, they will not be reviewed.

Although the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition – Text Revision (DSM-IV-TR) precludes individuals with ASDs from being diagnosed with attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association 2000), symptoms of hyperactivity, distractibility, and motor restlessness are common in this population. Stimulants such as the norepinephrine reuptake inhibitor ► atomoxetine, and alpha2 adrenergic agonists have all been used to treat these symptoms in individuals with ASDs. Stimulants are the treatment of choice for typical developing children with ADHD. Early trials of stimulants in ASDs concluded they were not effective in this population. Several newer RCTs have suggested that stimulants may in fact be helpful, to some extent, for this group of symptoms in ASDs. A recent RCT sponsored by the National Institute of Mental Health (NIMH) on children with ASDs found that 49% of the subjects responded to ► methylphenidate; 18%, however, discontinued the drug due to adverse events. It was concluded that children with ASDs, compared with typically developing children diagnosed with ADHD, have a decreased response rate and an increased likelihood of side effects when prescribed methylphenidate (McDougle et al. 2006).

Clonidine and guanfacine are two alpha-2 adrenergic agonists that have been studied to treat ADHD symptoms in ASDs (Stigler et al. 2008). Clonidine was investigated in two small, controlled trials in individuals with autism. The results of one study yielded improvement on both a teacher and parent rating scale, but not a clinician rating scale. The other study of transdermal clonidine noted significant improvement in hyperactivity and anxiety. Side effects included sedation, hypotension, irritability, and fatigue.

Guanfacine requires less frequent dosing, may be less sedating and decreases the chance of rebound hypertension due to a longer half-life than clonidine (McDougle et al. 2006). RCTs of guanfacine have not yet been performed in ASDs. However, a systematic review of 80 patients with these disorders found improvement in hyperactivity, inattention, and impulsivity, with a response rate of 24%. Overall, participants tolerated guanfacine well and no significant changes in vital signs were noted (Stigler et al. 2008).

Repetitive thoughts and behaviors (stereotypical and repetitive behavior) are a core component of the ASDs (McDougle et al. 2006). These repetitive phenomena can be intrusive and interfere with day-to-day functioning. Due to the success of treating the repetitive thoughts and behaviors of obsessive–compulsive disorder with serotonin reuptake inhibitors (SRIs), studies have been performed with these agents in ASDs. Controlled trials of ► clomipramine, ► fluvoxamine, and ► fluoxetine have been published. Treatment effects on this symptom domain have also been assessed in controlled trials of the antipsychotics ► haloperidol and ► risperidone in individuals with ASDs.

Clomipramine has been evaluated in individuals with PDDs in multiple open-label and two controlled studies (Stigler et al. 2008). Both of the controlled trials found the drug to be superior to placebo. However, side effects were a significant problem and included the prolongation of the

cardiac QTc interval, tachycardia, grand mal seizure, sedation, and tremor.

Results of three double-blind, placebo-controlled studies of fluvoxamine have yielded mixed results (Stigler et al. 2008). It appears that adults with ASDs are better able to tolerate this drug than young children. Side effects included sedation, nausea, hyperactivity, insomnia, aggression, agitation, and behavioral activation.

There have been multiple open-label and two controlled trials published with fluoxetine (Stigler et al. 2008). The drug was generally found to be effective in the majority of open-label trials and superior to placebo in the two placebo-controlled trials. Side effects included aggression, hyperactivity, and decreased appetite.

RCTs of haloperidol and risperidone have both shown efficacy in decreasing stereotypic behavior (► stereotypical and repetitive behavior) in subjects with ASDs (McDougle et al. 2006).

The overall findings of these studies concluded that prepubertal children with ASDs may not respond to or tolerate SRIs as well as postpubertal adolescents or adults with these disorders (McDougle et al. 2006). There are several factors that could contribute to this. It may be that changes in the serotonin system over the course of development in individuals with ASDs could influence their ability to tolerate and respond to SRIs.

Irritability that can be manifested as aggression, SIB, or severe tantrums is another target symptom domain associated with ASDs that can be amenable to pharmacological management (Stigler and McDougle 2008). The ► atypical antipsychotics are emerging as first-line agents for this purpose. Other classes of drugs that have been studied include typical ► antipsychotics, ► anticonvulsants, and ► mood stabilizers.

Early studies found haloperidol effective for treating maladaptive symptoms in children with ASDs (Stigler and McDougle 2008). However, significant side effects were noted with this drug, including dystonic reactions and dyskinesias (especially on withdrawal of the drug). Due to its side effect profile, haloperidol is normally limited to treatment-refractory patients.

The atypical antipsychotics have replaced the typical antipsychotics as the first-line treatment for irritability in ASDs due to their decreased propensity for dyskinesias and extrapyramidal symptoms (EPS) (Stigler and McDougle 2008). ► Clozapine, ► risperidone, ► olanzapine, ► quetiapine, ► ziprasidone, and ► aripiprazole all have published reports of their use in the ASDs.

There are only three published reports of clozapine in the ASD population describing a total of five patients (Stigler and McDougle 2008). All showed significant improvement with clozapine. The paucity of reports is likely due to clozapine's potential to cause agranulocytosis, its ability to lower the seizure threshold, and the need for weekly to biweekly venipuncture.

Risperidone is a well-studied drug for the treatment of irritability in ASDs (Stigler and McDougle 2008). Multiple case series, open-label trials and double-blind placebo-controlled studies have found risperidone to be effective for treating irritability in individuals with ASDs. Due in part to the results of two RCTs demonstrating the efficacy and tolerability of risperidone for the treatment of irritability in children and adolescents with autism aged 5–16 years, it was approved by the US Food and Drug Administration (FDA).

Olanzapine has been studied in several open-label trials and one small placebo-controlled trial (Stigler and McDougle 2008). It has been shown to be effective for irritability and behavioral symptoms of autism. Side effects noted in the studies included increased appetite and often significant weight gain.

Four open-label reports of quetiapine have been published involving the treatment of ASDs (Stigler and McDougle 2008). The results have been mixed. Side effects reported included increased appetite, weight gain, sedation, agitation, aggression, and sialorrhea.

Two different open-label trials with ziprasidone reported it to be effective in treating irritability and aggression in individuals with ASDs (Stigler and McDougle 2008). Side effects included transient sedation, a clinically insignificant increase in the QTc interval and dystonic reactions. There is an FDA warning regarding the use of ziprasidone in relation to its potential to increase the cardiac QTc interval. It should not be given without consultation with a cardiologist to individuals with a known cardiac history, a long QT syndrome or in those taking other medications that can prolong the QTc interval.

Two open-label studies and one retrospective chart review found aripiprazole to be effective for treating irritability in individuals with ASDs (Stigler and McDougle 2008). Adverse events included transient sedation and weight gain (greater in individuals less than 12 years of age).

Mood stabilizers and anticonvulsants have also been used to treat irritability in ASDs (Stigler and McDougle 2008). Reports have been published for the use of ► lithium, divalproex sodium, ► lamotrigine, ► topiramate, and levetiracetam. However, RCTs supporting the use of mood stabilizers and anticonvulsants for the treatment of irritability in ASDs have not been published. The current literature suggests that atypical antipsychotics are more effective for the treatment of this symptom domain in

ASDs than mood stabilizers or anticonvulsants. Only one report has appeared demonstrating the effective use of lithium in one individual with autism that had significant irritability.

One open-label and one double-blind, placebo-controlled study have been published with divalproex sodium (Stigler and McDougle 2008). The open-label study determined divalproex to be effective. However, the double-blind, placebo-controlled trial found no significant difference between the two groups in irritability after 8 weeks. Adverse events included sedation, weight gain, behavioral activation, hair loss, elevated liver enzymes, increased appetite, skin rash, and hyperammonemia.

A double-blind, placebo-controlled study of lamotrigine did not find a significant difference between drug and placebo on several standardized outcome measures (Stigler and McDougle 2008).

One published report on the use of topiramate in five youths with autism and treatment-refractory severe behavioral problems found most children able to tolerate the drug but did not show notable improvement (Stigler and McDougle 2008).

One double-blind, placebo-controlled study of levetiracetam has been performed in 20 children and adolescents with autism to assess its efficacy in treating aggression and affective instability (Stigler and McDougle 2008). No difference was found between the drug and placebo groups. Adverse events included agitation and aggression.

One fundamental core deficit in ASDs is social impairment that is severe and persistent (McDougle et al. 2006). Social impairment can be seen through deficits in nonverbal behavior, for example, eye contact, facial expression, and body gestures. These children often fail to develop age appropriate relationships. They also may not seek to share achievements or enjoyment with others. Initially, preliminary reports of fenfluramine and naltrexone to treat social impairment were encouraging. However, subsequent placebo-controlled studies of these drugs failed to show any difference between groups for this core symptom deficit.

There has been consideration that ▶ glutamate may have a role in the pathophysiology and treatment of autism (McDougle et al. 2006). Thus, several drugs that affect the glutamate system have been studied for treating the social impairment seen in ASDs.

Two case reports described an improvement in autistic patients' social impairment after being prescribed lamotrigine, an anticonvulsant that slows glutamate release (McDougle et al. 2006). However, a double-blind, placebo-controlled study of lamotrigine in 28 children with autism failed to show a difference between drug and placebo.

▶ Amantadine, an antagonist at the *N*-methyl-D-asparate (▶ NMDA) subtype of glutamate receptor, has also been studied in autism (McDougle et al. 2006). An initial open-label study showed improvement in half the children given the drug. However, a double-blind, placebo-controlled trial failed to show a difference based on a parent rating scale. A clinician rating scale showed significant improvement in hyperactivity and inappropriate speech.

D-cycloserine is an antibiotic used to treat tuberculosis (McDougle et al. 2006). It is a ▶ partial agonist at the NMDA receptor. A small pilot study showed a statistically significant improvement on the Aberrant Behavior Checklist (ABC) Social Withdrawal subscale. Adverse events included transient motor tics and increased echolalia.

Research in the pharmacotherapy of ASDs will continue to pursue treatment for the core and associated symptoms related to this condition. Many individuals with ASDs have interfering symptoms in multiple domains. Thus, coactive pharmacological treatment strategies, involving concomitant treatment with more than one drug at a time, will be a future area of research (Stigler et al. 2008).

Mental Retardation

In the past, there was a belief that individuals with MR could not have co-occurring mental illness. It is now widely accepted that these patients develop such comorbidity at a higher rate than the normal population. Most studies estimate the prevalence of mental illness in the MR population at between 30 and 70% (Szymanski and King 1999). Approximately 20–45% of individuals with MR are prescribed psychotropic medications (Deb et al. 2007). All DSM-IV-TR diagnostic categories are potentially represented in these patients. However, the evaluation and diagnostic determination can be difficult due to inherent limitations, including communication deficits, physical limitations (Szymanski and King 1999), and lack of collateral information regarding the patient and their environment (Madrid et al. 2000). Additionally, due to a lack of capacity to give informed consent, there are relatively few RCTs in individuals with MR (Deb et al. 2007). This leads clinicians to base treatment decisions on a few well-designed investigations or to use studies in individuals without MR to guide treatment (Madrid et al. 2000).

Common reasons for pharmacologic referrals of patients with MR include SIB, aggressive behavior, impulsiveness, and hyperactivity. These symptoms are nonspecific and can be the result of anything from a medical illness to a mood, anxiety, psychotic or impulse control disorder. The context surrounding the onset of symptoms,

associated symptoms, and environmental changes can all be clues to the diagnosis. If there are associated sleep and appetite changes, a mood disorder may be considered. If the symptoms occur only in certain environments, then a psychotic or mood disorder is less likely. If the symptoms are of sudden onset, a medical illness may be contributing to the presentation (Madrid et al. 2000).

The MR population is two times more likely to suffer from a medical disorder than other mental health populations. One study showed 75% of the referrals for psychiatric assessment had undertreated or undiagnosed medical illnesses. In addition, psychiatric symptoms can be caused by several medical illnesses (Szymanski and King 1999). Thus, it is always important to consider a medical illness as a cause of psychiatric symptoms in the differential diagnosis of individuals with MR.

Screening assessments can be used to identify individuals with MR who need psychiatric referral. Some of these instruments can also be used for determining and evaluating symptoms over the course of treatment. The more commonly used scales in the MR population include the Reiss Screen for Maladaptive Behavior, the Reiss Scales, the Psychopathology Inventory for Mentally Retarded Adults (PIMRA), the ABC, and the Diagnostic Assessment for Dual Diagnosis (Madrid et al. 2000; Szymanski and King 1999).

Anxiety disorders can be difficult to diagnosis in MR individuals because of the necessity of subjective complaints. However, by observing patients, symptoms such as avoidance, autonomic arousal, psychomotor agitation, or irritability can help to clarify the diagnosis (Madrid et al. 2000). Specifically, posttraumatic stress disorder should be considered in the differential diagnosis. Individuals with MR are an inherently vulnerable population; they have difficulty reporting events and often want to please their caretaker (Szymanski and King 1999).

Psychotic disorders should be considered in individuals with MR that present with observable hallucinations such as yelling or hitting at empty space, catatonic posturing that appears psychotic in nature, negative symptoms or grossly disorganized behavior. Imaginary friends should not be confused with psychosis (Madrid et al. 2000; Szymanski and King 1999).

Mood disorders are common in individuals with MR. They can be diagnosed when there is a significant change in the baseline affective state. Observations of change in sleep, activity level, and appetite can be obtained from caretakers to help to confirm the diagnosis. Mood disorders can also present atypically in this population. Sometimes aggressive behavior can be a symptom of depression. This is sometimes termed "► behavioral equivalent" in the literature. A recent change in the environment, death of a family member, rejection, or abuse can also cause depression in the MR population (Hurley 2006; Madrid et al. 2000; Stigler et al. 2005).

► Disorders of impulse control may be considered one of the most common justifiable indications for psychotropic use in the MR community. The three most common behaviors include SIB, stereotyped behavior (stereotypical and repetitive behavior), and aggressive behaviors (Szymanski and King 1999). Studies indicate that 14–30% of the MR population receiving psychotropics are prescribed them for these types of behavior problems (Deb et al. 2007).

Pharmacotherapy in the MR population should only be a part of the overall treatment plan. The lowest possible dose of drug that is effective for the patient should be used and should not adversely affect the individual's ability to function. Drug treatment should follow the adage "start low, go slow." Certain drugs are more likely to cause side effects in MR individuals. Some of these patients seem to be more sensitive to the disinhibiting effects of ► benzodiazepines. There has been some evidence to suggest that the combination of stereotypy (stereotypical and repetitive behavior) and SIB may be a significant risk factor for benzodiazepine-induced disinhibition. There is also the potential for benzodiazepines to cause hyperactivity, SIB, or withdrawal-induced manic symptoms in the MR population. Individuals with compromised central nervous system function may be more sensitive to drugs with anticholinergic side effects, as well (Madrid et al. 2000; Szymanski and King 1999).

Antipsychotics are often used in the MR population to target aggressive or stereotyped behavior (stereotypical or repetitive behavior) and SIB, but can also be given for psychotic symptoms. Careful attention to side effects of these drugs should be paid. Patients with MR are more susceptible to tardive dyskinesia, withdrawal irritability, and EPS than other mental health populations. This is one of the reasons for the increasing trend of using atypical antipsychotics over typical antipsychotics (Madrid et al. 2000; Szymanski and King 1999). The RCTs that do exist have demonstrated the efficacy of risperidone for aggressive behavior in individuals with MR. However, most studies found side effects of weight gain and somnolence. To date, studies have not systematically reviewed adverse metabolic issues arising from risperidone. Evidence for the use of the other atypical antipsychotics in the adult MR population is mostly based on case studies. Short follow-up periods were used in these trials, making it difficult to know if the drugs would provide sustained

behavioral effects. In addition, several studies used the antipsychotics as add-on therapy (Deb et al. 2007).

► Antidepressants are used to treat depressive symptoms in individuals with MR as in the general population (Madrid et al. 2000; Stigler et al. 2005). ► Selective serotonin reuptake inhibitors (SSRIs) are frequently the first-line pharmacotherapy for individuals with MR due to their tendency to cause fewer side effects. Tricyclics are not used as often due to their side-effect profile of potentially lowering the seizure threshold, cardiac arrhythmias, and cognitive dulling. However, to date, there have been no published RCTs of antidepressants supporting their use for the treatment of depression in patients with MR (Stigler et al. 2005). One retrospective chart review of treatment with an SSRI or clomipramine for aggression, SIB, destructive/disruptive behavior, and depression/dysphoria showed a significant decline in these symptoms. This study gives support to "behavioral equivalents" being used as signs/symptoms of depression in the MR population (Hurley 2006). Other open-label studies of SSRIs have been conducted for behavioral problems in MR individuals with mixed results. Due to these findings, it is difficult to come to a clear conclusion regarding the use of antidepressants for treating behavioral problems in individuals with MR. The noted favorable outcomes were mostly for SIB and perseverative/compulsive behaviors. In addition, many of the studies used antidepressants as an add-on drug to an existing psychotropic regimen (Madrid et al. 2000; Stigler et al. 2005).

Mood stabilizers and anticonvulsants are often used to treat cyclical mood disorders in the general population. To date, there have been no published RCTs for the treatment of comorbid bipolar disorder in patients with MR (Stigler et al. 2005). Based on open-label reports, first-line options for this purpose in patients with MR include ► carbamazepine and ► valproic acid. Although lithium may be effective, it can cause a magnified cognitive dulling in this population that would make it a less attractive choice. Individuals with MR may also be more likely to develop lithium toxicity due to a change in their fluid intake (Szymanski and King 1999). Some studies have been performed regarding the use of mood stabilizers and anticonvulsants for the management of behavior problems in the MR population. The conclusion from three trials of lithium indicated an improvement in behavioral problems in a large portion of the individuals studied. Lithium toxicity was mostly absent in these studies. Two studies with valproate add-on therapy indicated improvement in SIB and aggression. One retrospective study with topiramate as an add-on therapy also indicated improvement in SIB and aggression. One double-blind, controlled, crossover study with carbamazepine indicated no difference between drug and placebo in decreasing overactivity. Although most of these studies indicate improvement in behavioral problems with these medications, methodological problems compromised many of them (Deb et al. 2007). Side effects that may be more common with carbamazepine in the MR population compared with the general population include the elevation of carbamazepine–epoxide levels during polypharmacy (resulting in seizure exacerbation), hyponatremia, hypovitaminosis D, folic acid and riboflavin deficiency, and irritability. Side effects of concern for valproate include pancreatitis, hepatotoxicity, and myelodysplasia (Szymanski and King 1999).

Even though between 20 and 45% of people with MR are receiving psychotropic drugs, there are very few published RCTs to guide practitioners. Much more research is needed to determine the efficacy and tolerability of psychotropics in individuals with MR for treating the majority of comorbid DSM-IV-TR diagnoses that commonly co-occur with the core intellectual disability.

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Cross-References

► Anticonvulsants
► Antidepressants
► Antipsychotic Drugs
► Atomoxetine
► Attention Deficit and Disruptive Behavior Disorders
► Benzodiazepines
► Bipolar Disorder
► Impulse Control Disorders
► Lithium
► Major and Minor and Mixed Anxiety-Depressive Disorders
► Methylphenidate and Related Compounds
► Mood Stabilizers
► Movement Disorders Induced by Medications
► Muscarinic Agonists and Antagonists

- ▶ Rating Scales and Diagnostic Schemata
- ▶ SSRIs and Related Compounds
- ▶ Traumatic Stress (Anxiety) Disorder
- ▶ Withdrawal Syndromes

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Autistic Disorder

- ▶ Autism

Autoinhibition

Definition

Inhibition of DA release from a neuron mediated by the activation of D_2 receptors on the neuron by endogenous DA or D_2 agonists.

Autonomous

- ▶ Independents

Autoreceptors

Definition

Receptors located on presynaptic nerve terminals sensitive to the neurotransmitter that is released by the same neurons in whose membrane the autoreceptor sits. Somatodendritic autoreceptors, such as serotonin-5-HT_{1A}, dopamine-D_2, and a_2-adrenoceptors, exert an inhibitory effect on the firing activity of the cell. Autoreceptors present on presynaptic nerve terminals usually regulate the synthesis and release of the neurotransmitter without affecting the firing activity of the cell.

Aversive Drug Effects

- ▶ Conditioned Taste Aversions

Aversive Stimuli

Definition

Unpleasant or noxious stimuli or events.

Avoidance

Definition

A conditioning procedure in which the instrumental response, for example, absence of a transfer response, prevents exposure to the context associated with an aversive stimulus.

Avoidance of Feared Places and Situations: Anticipatory Anxiety

- ▶ Agoraphobia

Avoidant Personality Disorder

► Social Anxiety Disorder

Avolition

Definition

Inability to initiate or persist in goal-directed behavior.

AVP

► Arginine-Vasopressin

Aβ

► Amyloid-Beta