L

LAAM

► L-Alpha-Acetyl-Methadol

Labeled Ligand Binding

► Receptor Binding

Labeled Ligand Concentration Binding Isotherm

► Receptor Binding
► Saturation Binding Curve

Laboratory Animal Models of Minimal Brain Dysfunction

► Attention Deficit Hyperactivity Disorders: Animal Models

L-Alpha-Acetyl-Methadol

Synonyms

LAAM

Definition

LAAM is an opioid drug with limited usage in opioid agonist maintenance therapy. It is a derivative of and has a similar mode of action as ► methadone but has a longer half-life (two active metabolites) of up to 72 h. Because of a number of adverse events under LAAM, it has been withdrawn currently from the European and the American market.

Lamotrigine

Definition

Lamotrigine acts on ► GABA receptors to produce an anticonvulsant action. There are also some positive findings in the treatment of ► bipolar depression. The half-life is around 30 h and it is metabolized primarily by glucuronic acid conjugation. Serious, potentially life-threatening dermatological adverse events have been reported, albeit very rarely.

Lanreotide

Synonyms

BIM-23014; Somatuline

Definition

Lanreotide is a peptide analogue of SRIF, used to treat acromegaly and tumors in the gastroenteropancreatic tract. Lanreotide has high affinity for sst2 and sst5 receptors.

Laser Desorption Ionization

► Matrix-Assisted Laser Desorption Ionization

Late Luteal Phase Dysphoric Disorder

► Premenstrual Dysphoric Mood Disorder

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

Latent Inhibition

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Synonyms

Stimulus pre-exposure effect

Definition

Latent inhibition (LI) is the reduced efficacy of a previously exposed, inconsequential stimulus to generate a conditioned response when paired with reinforcement, compared with a novel stimulus. LI is extremely robust, appearing across many different learning paradigms and mammalian species, including humans.

While a variety of behavioral tasks are used to demonstrate LI in rodents, all of them share a basic procedure. In the first stage, pre-exposure, animals from each of two groups are placed in an environment that will later serve as the conditioning-test apparatus. Subjects in the "stimulus pre-exposed" (PE) group are repeatedly exposed to a stimulus (e.g., tone), which is not followed by a significant consequence. Subjects in the "nonpre-exposed" (NPE) group spend an equivalent amount of time in the apparatus without receiving the stimulus. Either immediately or a certain time after the pre-exposure time is completed, all subjects enter the conditioning stage of the procedure, in which the PE stimulus is paired with a reinforcer over a number of trials. Performance is assessed by examining some behavioral index of conditioned responding, either during the conditioning stage or in a third, test stage. LI is manifested in poorer performance of the PE when compared with the NPE group.

In terms of psychological processes underlying LI, it is believed that the pairing of stimulus–no event in the pre-exposure stage results in reduced attention to, or salience of, the stimulus, which subsequently interferes with the generation of the conditioned response resulting from the stimulus–reinforcement association in conditioning (Fig. 1).

LI is a phenomenon of ► selective attention in the sense that it reflects a modulating effect of past experience on the current performance. Specifically, it reflects the ability of organisms to ignore stimuli that had been irrelevant in the past, in spite of their current relationship with a reinforcer. Since selective attention deficit is a hallmark cognitive deficit of ► schizophrenia and a central target for treatment, research that examined the effects of psychoactive drugs on LI in rodents has focused primarily on the use of LI to develop animal models of deficient attention in schizophrenia and the identification of ► anti-psychotic activity. The link between LI and schizophrenia is supported by the presence of LI abnormalities in schizophrenia patients.

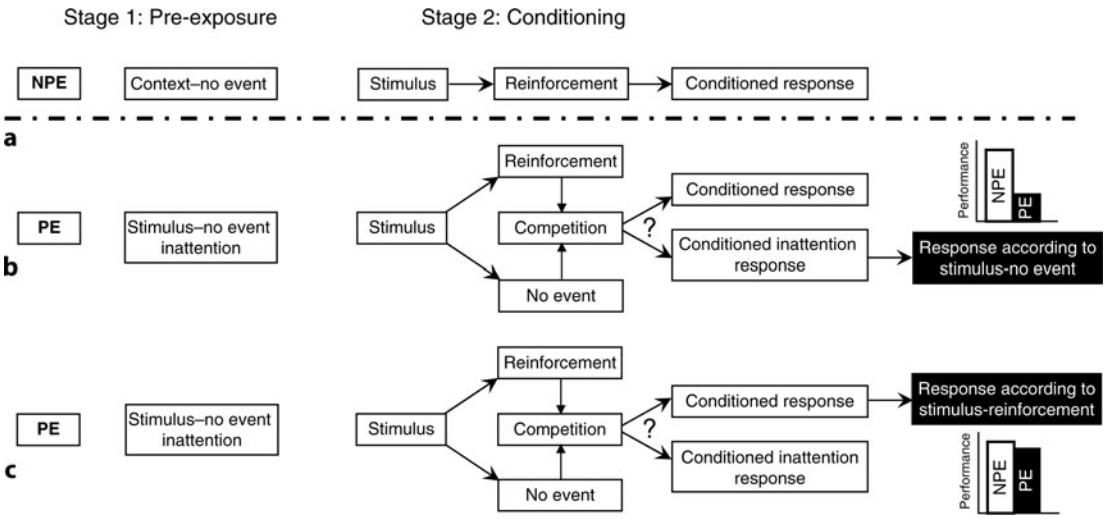
Impact of Psychoactive Drugs

Disrupted and Persistent LI

While drug effects are typically measured as a reduction or an abolition of the target behavior in comparison with its presence in drug nontreated controls, pharmacology of LI has taken a different path from its very inception, focusing on both the disruption and the *induction* of the phenomenon. The latter effect, termed interchangeably LI potentiation, enhancement, or persistence, is indexed by comparison with the *absence* of LI in drug nontreated controls. Thus, psychoactive drugs can produce two poles of LI abnormality, namely, disrupted LI under conditions that lead to LI in normal rats and abnormally persistent LI under conditions that disrupt LI in normal rats (Fig. 2). Both disruption and persistence of LI can stem from drug action in the pre-exposure stage or in the conditioning stage. In addition to unraveling the psychological mechanism by which a given drug affects LI (alterations in the acquisition or the expression of inattentional response), stage-specific action allows for a refined discrimination between the effects of different drugs on LI.

Models of LI Disruption and Persistence

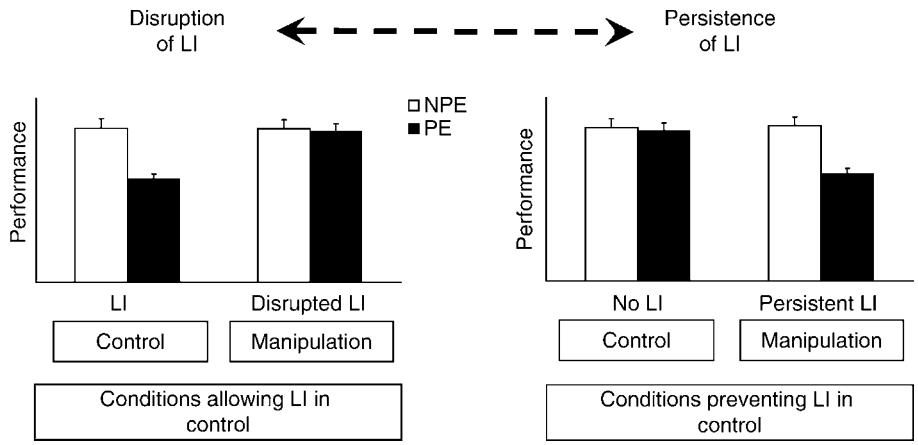
DA agonists. The notion of a hyperactive ► dopamine system in schizophrenia is supported by the capacity of the DA releaser, ► amphetamine, to induce psychosis in healthy humans and exacerbate symptoms, as well as enhance striatal dopamine release in schizophrenia patients. Because amphetamine produces only positive (psychotic) symptoms, amphetamine-induced behavioral abnormalities in animals are considered to model positive symptoms. Consistent with the expectation that the capacity to ignore irrelevant stimuli would be lost in a psychotic-like state, amphetamine disrupts LI in both rodents and humans. Amphetamine-induced LI disruption is due to the drug's action in conditioning stage rather than in pre-exposure stage, indicating that increased dopamine transmission does not produce a psychotic-like state by increasing stimulus salience but rather by weakening the inhibiting effect of reduced stimulus salience on behavior. LI is disrupted also after, as well as during withdrawal from, repeated amphetamine administration. Results with direct DA agonists are inconsistent.



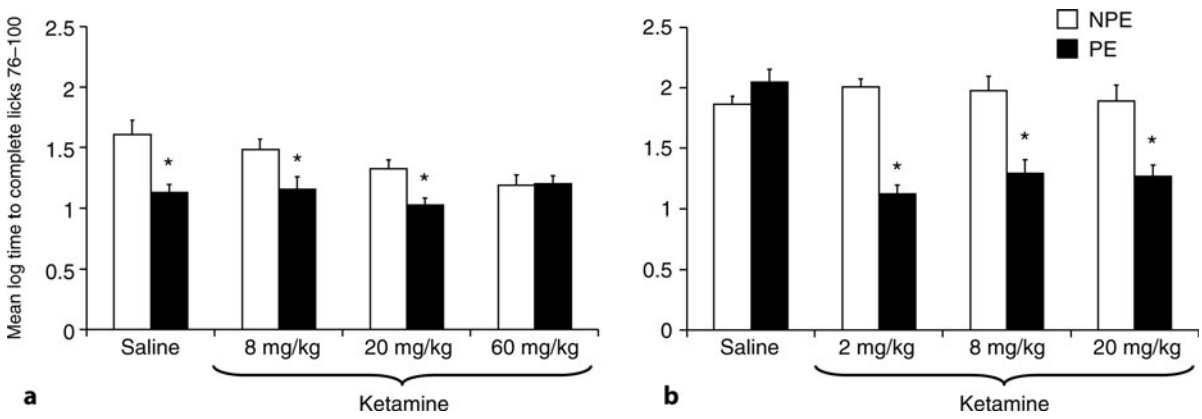
Latent Inhibition. Fig. 1. Latent inhibition as a response competition phenomenon. In the pre-exposure stage, stimulus pre-exposed (PE) animals acquire a stimulus–no event association, which results in a conditioned response of inattention to the PE stimulus. Following conditioned attention theory (Lubow et al. 1981), inattention is treated as a classically conditioned response, acquired when stimuli are consistently followed by the lack of a consequence and governed by the same rules that govern association formation during classical conditioning. In the conditioning stage, the stimulus signals conflicting outcomes, no-event vs. reinforcement, that compete for behavioral expression (conditioned inattention response vs. the conditioned response acquired in conditioning). Which of the two associations gains behavioral control depends on factors that determine their relative behavioral impact during conditioning. The three most conspicuous factors are strength of pre-exposure (usually manipulated by changing number of stimulus pre-exposures but can involve any manipulation known to affect classical conditioning such as stimulus intensity, ISI, etc.), strength of conditioning (usually manipulated by changing the number of conditioning trials or intensity of reinforcement), and context (manipulated by changing the context between pre-exposure and conditioning), but there are other factors as well, such as the time interval between pre-exposure and conditioning or the motivational state of the animal in the two stages. Pharmacological LI experiments typically manipulate number of pre-exposures and/or conditioning trials.

NMDA antagonists. The hypo-glutamatergic hypothesis of schizophrenia is derived from findings that noncompetitive NMDA antagonists such as ▶ phencyclidine (PCP) and ▶ ketamine provoke symptoms in human volunteers and exacerbate symptoms in schizophrenia patients, as well as abnormalities of glutamate neurotransmission in schizophrenia. Since NMDA antagonists also induce negative symptoms and ▶ cognitive impairments characteristic of endogenous schizophrenia, NMDA antagonist-induced behavioral effects in animals are considered to model negative/cognitive symptoms. Unlike amphetamine, low doses of noncompetitive NMDA antagonists, including PCP, ketamine, and MK-801, spare LI. While these results have led to the suggestion that NMDA antagonist-induced effects in LI cannot provide a valid model of the disorder, later studies have shown that NMDA antagonists affect LI in an opposite manner to that of amphetamine, namely, they induce persistent LI under conditions that prevent LI expression in controls (Fig. 3). Importantly, persistent LI is induced by doses of NMDA antagonists that do not produce the well-known deleterious effects of these drugs on associative learning. Higher doses that impair conditioning disrupt LI. NMDA antagonists produce LI persistence via effects in conditioning, indicating that ▶ NMDA blockade impairs rats' capacity to switch response based on changed relationships between stimuli and outcomes. The latter is consistent with numerous demonstrations of inflexible behavior following NMDA blockade in rats and humans and supports the relevance of NMDA antagonist-induced persistent LI to cognitive/negative symptoms of schizophrenia, which are characterized by inflexible and perseverative behaviors.

▶ Muscarinic antagonists. Muscarinic antagonists such as ▶ scopolamine and atropine induce a schizophrenia-like syndrome in humans, which includes positive



Latent Inhibition. Fig. 2. Two poles of LI abnormality. Based on the view of LI as a window phenomenon, namely, present under very specific and restricted conditions, two abnormalities can be produced in LI depending on the status of the phenomenon in control animals: disrupted LI under conditions producing LI in controls, and persistent LI under conditions preventing the expression of LI in controls. In psychological terms, the former reflects loss of normal ability to ignore irrelevant stimuli, whereas the latter reflects a failure to switch to respond to such stimuli when they become relevant.



Latent Inhibition. Fig. 3. Effects of ketamine on LI with weak and strong conditioning. LI was measured in a conditioned emotional response procedure in which rats were either PE to 40 tone presentations or not pre-exposed (NPE) prior to conditioning with 2 tone-shock trials (weak conditioning; Fig. 3**a**) or 5 tone-shock trials (strong conditioning; Fig. 3**b**). Time to complete 25 licks in the presence of the tone was used as a measure of fear conditioning to the tone. LI is manifested in faster times of the PE when compared with the NPE animals. The figures present mean times (logarithmically transformed) to complete 25 licks in the presence of the tone of PE and NPE rats treated with vehicle or ketamine. (**a**) Under conditions yielding LI in vehicle controls, ketamine spared LI at 8 or 20 mg/kg and disrupted LI at 60 mg/kg. (**b**) Under conditions preventing LI in vehicle controls, ketamine at doses of 2, 8, and 20 mg/kg led to persistent LI.

symptoms and cognitive impairments. Recent focus on cognitive impairments in schizophrenia has promoted attention to the cholinergic system because of its well-known role in cognition. Scopolamine can produce both LI disruption and persistence as a function of dose. Low doses of ► scopolamine disrupt LI, supporting the pro-psychotic quality of this agent. The mechanisms underlying this psychotic-like state differ however from those of amphetamine because scopolamine disrupts LI via effects at the pre-exposure stage. High doses of scopolamine spare LI under conditions yielding LI in controls, and induce persistent LI under conditions that prevent LI expression. The latter action is exerted in conditioning. Thus, scopolamine mimics both positive and negative/cognitive symptoms by

disrupting normal attentional processing, low doses preventing the development of inattention and high doses producing attentional perseveration.

Antipsychotics. In rodents, ▶ antipsychotics (APDs) are typically investigated for their ability to antagonize the effects of other drugs, but in research concerned with APD effects on LI, their direct influences on LI are also of central importance. Specifically, LI in nontreated rodents is used for indexing antipsychotic activity as well as for discriminating between typical and atypical APDs. The former is achieved under conditions of weak or absent LI in controls. Under these conditions, both typical and atypical APDs produce persistent LI. This effect, produced by a wide range of APDs differing in their in vivo and in vitro pharmacology, is also obtained in humans, and is the most widely used index of antipsychotic action in LI. The LI potentiating action of APDs is exerted at the conditioning stage, and is mediated by D2 blockade. Although APD-induced LI potentiation is very robust, it does not discriminate between typical and atypical APDs. Such discrimination is manifested under conditions that *produce* LI in controls. Whereas typical APDs do not affect LI, atypical APDs can, depending on dose and stage of administration, *disrupt* LI. The LI disruptive action of atypical APDs is exerted in the pre-exposure stage and is due to their $5HT_{2A}$ receptor antagonism. The pre-exposure-based $5HT_2$ antagonistic action competes with the conditioning-based D2 antagonistic action of these drugs. Since $5HT_2$ antagonism predominates at lower doses and D2 antagonism occurs at higher doses, depending on the dose, atypical APDs can potentiate, spare, or disrupt LI. The competition between the D2 and $5HT_2$ antagonism of atypical APDs has critical implications for interpreting the effects of these drugs on LI in animals and humans, as well as the clinical efficacy of these drugs.

In addition, since DA blockade is therapeutic against positive symptoms associated with abnormally increased DA function, but is ineffective for and may worsen negative symptoms associated with reduced DA function, recently it has been suggested that dopaminergic blockade-induced persistent LI, as exemplified by haloperidol-induced LI persistence, can model not only alleviation of positive symptoms but also induction of negative symptoms.

Reversal of Disrupted and Persistent LI

The four schizophrenia-relevant aberrations of LI, i.e., those induced by amphetamine, NMDA antagonists, and low and high-dose scopolamine, have been tested with typical and atypical antipsychotics to assess the predictive validity of these models for the identification of clinical treatments for schizophrenia. In recent years, new therapeutic strategies for schizophrenia, considered/hoped to improve negative symptoms and cognitive dysfunction, have emerged. These strategies include enhancement of NMDA transmission via the glycineB modulatory site on the NMDAR, either directly by agonists such as ▶ glycine transporter and D-serine, or indirectly by inhibiting the ▶ glycine transporter (GlyT1), and enhancement of cholinergic transmission using ▶ acetylcholinesterase inhibitors such as physostigmine, ▶ muscarinic agonists such as xanomeline, and alpha-7 nicotinic receptor agonists. Table 1 summarizes the distinct responses of five LI models (including haloperidol-induced persistence) to typical and atypical APDs, NMDA function enhancers, and cholinergic function enhancers.

Amphetamine- and low scopolamine-induced disrupted LI, although reflecting distinct psychological processes, are reversed by both typical and atypical APDs as well as by glycinergic enhancers. Scopolamine- but not

Latent Inhibition. Table 1. Summary of representative antipsychotic and other putative treatments tested against models of disrupted and persistent LI.

Drug \ Model	Disrupted LI		Persistent LI		
	Low amph	Low scop	Low MK801	High scop	Haloperidol
Haloperidol	+	+	–	–	
Clozapine	+	+	+	–	+
Glycine	+[a]	+	+	+	–
Physostigmine	–	+	+	+	–
α7 nicotinic agonist	+	?	+	?	?

+ effective; – ineffective; ? unknown; [COND] acts via conditioning stage; [PREEX] acts via pre-exposure stage

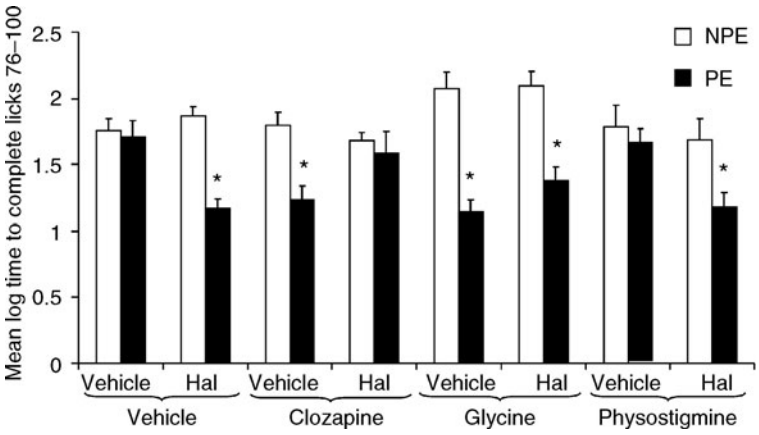
[a]The active compound is Glyt1 inhibitor SSR103800

amphetamine-induced LI disruption is reversed by ► physostigmine. *MK801-induced persistent LI* is reversed by atypical APDs (e.g., ► clozapine and ► risperidone) but not by typical APDs, as found with other NMDA antagonist-induced behavioral deficits, and in line with the differential efficacy of typical and atypical APDs in the clinic. MK801-induced persistent LI is also reversed by a wide range of compounds that potentiate NMDA transmission including glycine, D-serine, D-cycloserine (DCS), and GlyT1 inhibitors GDA, ALX5407, and the novel GlyT1 inhibitors SSR103800 and SSR504734. Importantly, MK801 is the only model that discriminates between atypical APDs and glycinergic compounds as the former reverse this abnormality via effects at pre-exposure and the latter via effects in conditioning. Finally, the novel alpha7-nAChR ► partial agonist SSR 180711 (4-bromophenyl-1,4-diazabicyclo(3.2.2)nonane-4-carboxylate-hydrochloride) is also effective in this model. *Scopolamine-induced persistent LI* is reversed by physostigmine and xanomeline, as well as glycinergic enhancers, but is resistant to both ► haloperidol and clozapine. While the inefficacy of haloperidol is expected based on its ineffectiveness in models of negative/cognitive symptoms including MK801-induced persistent LI, the inefficacy of clozapine is unexpected and sets this abnormality apart from MK801-induced as well as all other known instances of drug-induced LI persistence. *Haloperidol-induced persistent LI* is reversed by atypical APDs clozapine and risperidone but is resistant to glycine and physostigmine (Fig. 4). In addition, haloperidol-induced persistent LI is the only persistent LI that is alleviated by amphetamine, like negative symptoms in the clinic.

Using Pharmacology of Disrupted and Persistent LI to Model Domains of Pathology in Schizophrenia

Disrupted and persistent LI can be seen as two poles of dysfunctional attentional control, namely, a failure to inhibit attention to irrelevant stimuli and a failure to re-deploy attention when previously irrelevant stimuli become relevant. The former would likely give rise to the aberrantly increased salience perception and distractibility that are associated with psychotic symptoms, whereas the latter would result in the cognitive inflexibility and impaired attentional shifting that are associated with negative/cognitive symptoms. Indeed, both disrupted and excessively strong LI are found in schizophrenia patients, the former associated with acute psychosis and the latter associated with predominance of negative symptoms.

Based on their distinct pharmacological profiles, LI abnormalities produced by amphetamine, haloperidol, NMDA antagonists, and scopolamine have been suggested to represent four domains of pathology in schizophrenia (Table 2). *Amphetamine- and scopolamine-induced disrupted LI* represents the domain of positive symptoms, the only domain responsive to both typical and atypical APDs. Notably, disrupted LI is responsive to APDs irrespective of the mechanisms underlying the disruption. *NMDA antagonist-induced persistent LI* represents a (hypoglutamatergia-driven) domain of negative/cognitive



Latent Inhibition. Fig. 4. Effects of clozapine, glycine, or physostigmine on haloperidol-induced persistent LI. Mean times (logarithmically transformed) to complete 25 licks in the presence of the tone of PE and NPE rats treated with vehicle or haloperidol (hal) and pre-treated with clozapine (5 mg/kg), glycine (800 mg/kg), or physostigmine (0.15 mg/kg). No LI was evident in the vehicle control but there was LI in rats treated with haloperidol. Haloperidol-induced persistent LI was antagonized only by clozapine. Clozapine and glycine but not physostigmine led to LI persistence in vehicle-treated rats.

Latent Inhibition. Table 2. Five pharmacological LI models proposed to model five domains of pathology of schizophrenia.

Model / Pharmacological response	Disrupted LI		Persistent LI		
	Amphetamine	Scopolamine	Scopolamine	MK801	Haloperidol
Reversed by	Typical and atypical APDs and some cognitive enhancers	Typical and atypical APDs; cognitive enhancers	Cognitive enhancers	Atypical APDs; cognitive enhancers	Atypical APDs
Resistant to	Some cognitive enhancers		Typical and atypical APDs	Typical APDs	Cognitive enhancers
Symptom domain	**Positive**		**Cognitive**	**Negative/ Cognitive**	**Negative**

symptoms that respond to atypical APDs and cognitive enhancers but not to typical APDs. *Scopolamine-induced persistent LI* represents a domain of cognitive impairments that are resistant to APDs. This model may have utility in identifying effective treatments for APD-resistant cognitive impairments in schizophrenia. However, given its insensitivity to APDs, the model is likely to represent a class of behavioral inflexibility that is common to a variety of neuropsychiatric disorders, including Parkinson's disease (PD), and obsessive compulsive disorder (OCD). Indeed, both PD and OCD patients display abnormally enhanced LI. Finally, *haloperidol-induced persistent LI* represents a domain of (hypodopaminergia-driven) negative symptoms that are treatable by atypical antipsychotics but are resistant to cognitive enhancers. This abnormality may represent a class of cognitive/behavioral inflexibility that is selective to schizophrenia. The domain-specific LI model fits the future directions of drug development for treatment of schizophrenia, which will use polypharmacy strategies, with independent therapeutic agents for each domain of pathology.

Cross-References

- ▶ Acetylcholinesterase Inhibitors as Cognitive Enhancers
- ▶ Antipsychotic Drugs (APDs)
- ▶ Attention
- ▶ Cognitive Enhancers
- ▶ Excitatory Amino Acids (NMDA)
- ▶ Muscarinic Agonists and Antagonists
- ▶ Nicotinic Agonists and Antagonists
- ▶ Psychomotor Stimulants (Amphetamine)
- ▶ Schizophrenia
- ▶ Schizophrenia: Animal Models

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Latin Square Design

Definition

A systematic way of controlling the order of administration of treatments within a test session and of balancing treatments between repeated test sessions. The design enables the uncontrollable effects of unexpected events to be distributed evenly between the treatment conditions.

Lawful

► Legal Aspects of Psychopharmacology

Laxatives

Definition

Drugs taken to induce bowel movements or to loosen the stool, most often taken to treat constipation.

L-Deprenyl

► Antidepressants
► Selegiline

L-Dopa

Definition

Levo-di-ortho-phenylalanine.

Cross-References

► Anti-Parkinson Drugs
► Levodopa

Leaden Paralysis

Definition

A feature of atypical depression, leaden paralysis refers to severe fatigue creating a sensation of extreme heaviness of the arms or legs.

Learned Helplessness

Definition

First described by Seligman and colleagues in the 1970s, learned helplessness describes the impairment of learning that follows exposure to uncontrollable stress. The term "learned helplessness" implies that animals learn that they are helpless to control their environment. A variety of simpler explanations have also been proposed, and most "learned helplessness" experiments are not conducted in a manner that allows a clear interpretation.

Cross-References

► Animal Models of Psychiatric States

Learning

Definition

In its broadest sense: the fact or process of change that occurs in the relationship between a stimulus and a response as a result of experience. Also referred to as acquisition. The "black box" that relates the stimulus to the response usually refers to a whole organism but may also refer to part thereof or to an isolated biological system. Learning concerns cognitive, but also sensory, motor, emotional, and mood-related life events or items.

Learning & Memory: Molecular Mechanisms

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Definition

Alterations in gene expression have been proposed to underlie key aspects of learning and memory in diverse systems. The mechanisms by which behavioral experience, via alterations in synaptic transmission, induce changes in gene expression in specific brain regions are reviewed. Such mechanisms include alterations at the level of chromatin structure, which might be expected to mediate particularly long-lasting adaptations. There are many examples of psychotropic drugs that regulate learning and memory via their effects on gene expression.

Impact of Psychoactive Drugs

The ability of an organism to learn and remember, sometimes for extended periods of time, indicates that environmental experience can induce long-lasting changes in the brain. The nature of these changes, at the molecular and cellular levels, has accordingly been intensively studied for several decades. This work has provided an impressive appreciation of the types of adaptations that

occur in the brain in association with many types of learning and memory. It also has been possible to directly demonstrate the importance of a given molecular or cellular mechanism in mediating a particular aspect of learning and memory. However, despite these important gains, we still know relatively little about how these molecular and cellular adaptations actually summate to create a behavioral memory or enable its long-term storage and retrieval. This latter level of understanding, which represents perhaps the greatest remaining challenge in the neurosciences, requires a neural circuit level of analysis that is not yet available.

This chapter provides a brief overview of the types of molecular and cellular adaptations in the brain that have been implicated in learning and memory, and focuses on changes achieved at the level of ▶ gene expression, or gene transcription, which have been thought for over a decade to provide the long-lasting mechanisms underlying stable behavioral change.

From Synapse to Nucleus

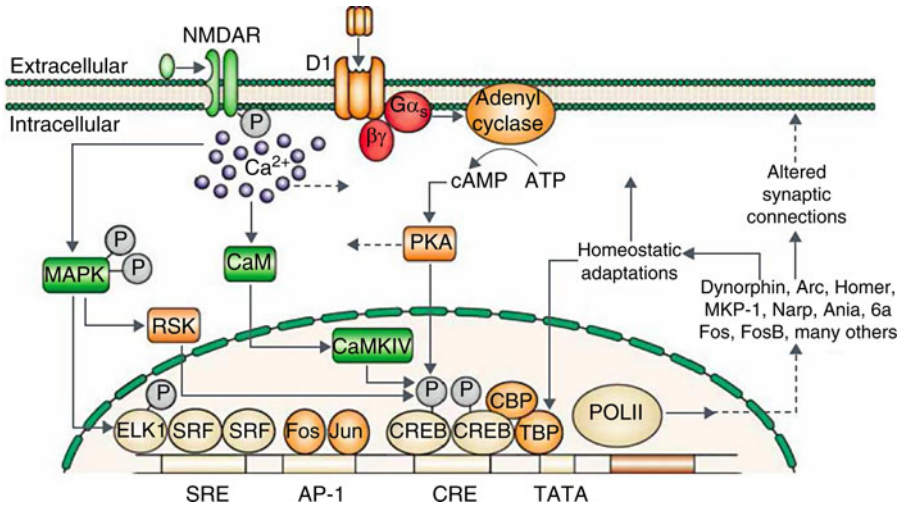
Synaptic transmission is best understood as the effects that a neurotransmitter, released by one nerve cell, exerts on a second nerve cell by virtue of its binding to a specific receptor. The activation of a receptor by its neurotransmitter triggers chemical changes inside the second nerve cell that alter its electrical activity. This occurs on the time scale of milliseconds to seconds. Operating on a much slower time scale, on the order of minutes to hours, are more complex chemical changes triggered by that very same neurotransmitter–receptor interaction. Thus, in addition to regulating ion channels, such interactions initiate cascades of chemical changes that eventually signal to the nerve cell's nucleus, where changes in gene expression – alterations in the amounts and types of proteins expressed by that cell – are induced. For example, synaptic transmission can alter the levels of ion channels or receptors expressed by a nerve cell. Consequently, at some later time point, when the first nerve cell again releases neurotransmitter onto that second nerve cell, the second nerve cell shows an altered response due to these changes in gene expression. This represents a unit of "molecular memory." Somehow, by summating these changes across the trillions of synapses in the brain, and integrating them over time, an organism learns and remembers and thereby adapts and responds to its environment.

We now know a great deal about the mechanisms by which synaptic transmission alters gene expression. The most important mechanism involves the activation of a class of proteins termed transcription factors (TFs), which bind to regulatory regions (called promoters) of specific genes and thereby increase or decrease the rate by which those genes are expressed. Hundreds of TFs are known, which exhibit three general mechanisms for their activation by synaptic transmission. Some TFs, expressed in nerve cells under basal conditions, are activated by cascades of ▶ second messenger and protein phosphorylation pathways that are stimulated (or inhibited) when neurotransmitters bind to their receptors. A prototypical example is CREB (cAMP response element binding protein), which can be phosphorylated and activated by a wide range of second messenger cascades illustrated in Fig. 1. For example, in striatum, ▶ dopamine (via activation of the cAMP pathway) and ▶ glutamate (via activation of Ca^{2+} pathways) activate several different protein kinases, each of which phosphorylates CREB on the same serine residue, resulting in the activation of its transcriptional properties. The TFs Elk1 and SRF (serum response factor) are regulated via similar mechanisms (Fig. 1). A related mechanism exists for another TF, termed NFκB (nuclear factor κB). At baseline, NFκB is bound to an inhibitor protein, IκB (inhibitor of κB), which sequesters NFκB in the cytoplasm. Upon activation of certain second messenger cascades, IκB is phosphorylated, leading to its degradation and the freeing up of NFκB to enter the nucleus where it exerts its transcriptional effects.

Other TFs are expressed at very low levels under normal conditions but are induced in nerve cells in response to neurotransmitter–receptor interactions. Examples include Fos (e.g., c-Fos, FosB) and Egr (early growth response) families of TFs. These TFs are induced because their promoter regions contain target sites for preexisting TFs such as CREB and SRF (see Fig. 1).

The third paradigm of TF activation operates for the steroid hormone receptor family of proteins, which are activated upon binding their respective hormone (e.g., glucocorticoids, gonadal steroids, etc.) and can therefore be viewed as ligand-activated TFs. Under basal conditions, steroid hormone receptors are bound by chaperone proteins which keep them in the cytoplasm. Steroid hormones, which readily permeate cell membranes, bind to the receptors and trigger their release from the chaperones and their movement to the nucleus. Once in the nucleus, the steroid receptors bind directly to responsive genes or bind to and inhibit other TFs (e.g., CREB, c-Fos).

An important principle of TF action is that most bind to DNA as dimers. Some bind as homodimers (e.g., CREB), whereas others must complex with distinct families of TFs: Elk1 dimerizes with SRF, Fos family proteins dimerize with Jun family proteins (to form an



Learning & Memory: Molecular Mechanisms. Fig. 1. Regulation of CREB activity in striatum. Stimulation of D1 dopamine receptors and glutamate receptors on striatal neurons activates several second messenger cascades. Not shown is the ability of several growth factor-associated receptors to stimulate some of the same cascades, for example, MAPK. Depicted in the cell nucleus is a model of binding sites from the *cFos* promoter including a serum response element (SRE), activator protein-1 element (AP-1), and a cyclic AMP (cAMP) response element (CRE). CBP, CREB binding protein; CREB, cAMP response element binding protein; MAPK, MAP kinase; NMDAR, NMDA receptor; PKA, protein kinase A; TBP, TATA binding protein. (From McClung CA, Nestler EJ (2008) Neuroplasticity mediated by altered gene expression. Neuropsychopharmacology 33:3–17.)

AP1 (activator protein 1) complex), and so on. Together, this results in an incredibly complex array of transcriptional regulation during the normal process of synaptic transmission.

Implicating TFs in Learning and Memory

An important role for all of the aforementioned TFs, and many others, in diverse types of learning and memory has been established over the past decade. Investigators have demonstrated the activation of specific TFs in a given brain region in response to an environmental challenge in tight temporal correlation with a form of behavioral plasticity. Examples include the phosphorylation and activation of CREB, and the induction of c-Fos and Egr, in hippocampus and amygdala in parallel to aversive learning, in some cases in parallel to a specific facet of aversive learning such as acquisition, consolidation, or extinction, among others. Likewise, exposure to a drug of abuse activates each of these TFs in drug-responsive regions (e.g., striatum, ► amygdala, ► prefrontal cortex) and such activation has been correlated with different aspects of drug-induced plasticity, such as locomotor sensitization, reward tolerance, or sensitization, etc. An interesting variation in this theme is the induction of ΔFosB, a truncated splice variant of the *fosB* gene, uniquely by chronic drug exposure. ΔFosB, normally present at very low levels in nerve cells, is induced to a small extent via CREB and SRF, but unlike all other Fos family members (which are highly unstable and therefore degrade to low basal levels shortly after the stimulus), ΔFosB is highly stable which enables it to accumulate to high levels in response to chronic stimuli. In this way, ΔFosB could mediate some of the longer-lasting effects of drug exposure on behavior.

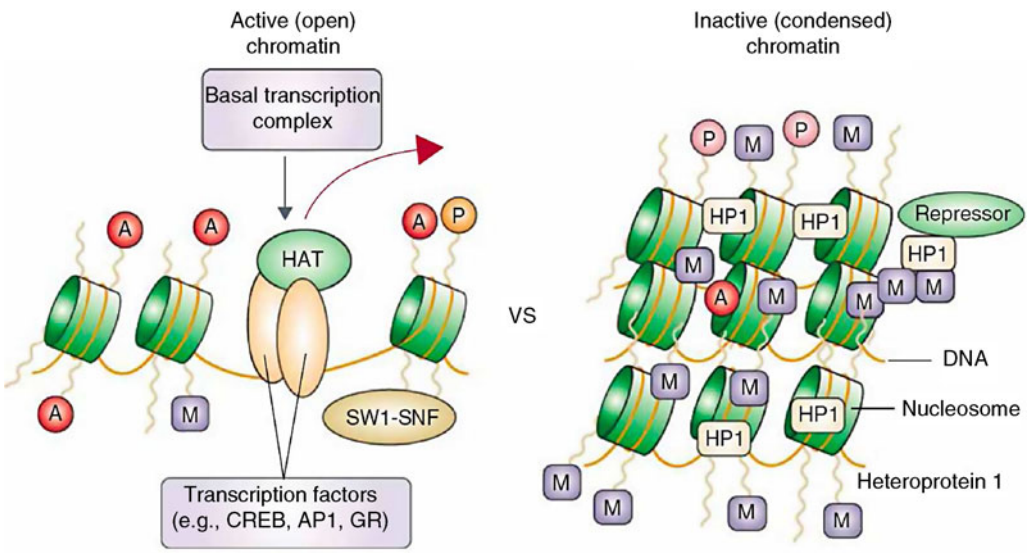
The second key step in implicating a TF in learning and memory is to manipulate that TF and demonstrate an effect on behavior. This causal information came initially from gene knockout studies, where deletion of CREB or another TF of interest was shown to obliterate an aspect of learning and memory. However, the interpretability of these early experiments was limited by the fact that the TF was knocked out from all brain regions (indeed all tissues) from the earliest stages of development, making it difficult to conclude that the TF was required in a given brain region of an adult. Such limitations have been overcome in recent years with the advent of an awesome array of powerful genetic tools, where a TF of interest – or an inhibitor (sometimes referred to as a dominant negative antagonist) – can be overexpressed in a given brain region of an adult animal or can be knocked out

selectively from that region of an adult animal. Such methods have greatly strengthened the level of proof for a TF's role in learning in memory. Overexpression of CREB specifically in ▶ hippocampus or amygdala promotes aversive learning, while overexpression of a CREB antagonist has the opposite effects. Likewise, CREB overexpression in striatum dampens an animal's sensitivity to the rewarding effects of a ▶ drug of abuse, with a CREB antagonist having the opposite effect. These latter data support the hypothesis that CREB induction by drugs of abuse represents a homeostatic mechanism mediating ▶ tolerance and ▶ dependence. Conversely, ΔFosB overexpression in striatum increases the rewarding effects of a drug of abuse, while its antagonist reduces drug reward, supporting the notion that ΔFosB induction represents a mechanism of sensitization.

From TF to Chromatin

In recent years, our level of analyzing transcriptional mechanisms in the brain has been extended to ▶ chromatin structure, where the covalent modification (e.g., acetylation or methylation) of ▶ histone proteins, around which DNA is wound in the cell nucleus, and methylation of the DNA itself, have profound effects on the ability of genes to be expressed. ▶ Chromatin exists in a continuum from a permanently inhibited (closed) state to a constitutively active (open) state (Fig. 2). Genes in closed chromatin are not expressed because they are not accessible to the cell's transcriptional machinery, whereas other genes exist in permissive chromatin where the genes are accessible to transcriptional machinery. This explains, for example, why CREB cannot induce neural gene targets in peripheral tissues where the genes exist in silenced chromatin, but can in nerve cells where the genes exist in permissive chromatin. TFs induce genes in permissive chromatin by recruiting to those genes many types of co-activator proteins. TFs recruit ▶ histone acetyltransferases, enzymes that acetylate histones; such acetylation further opens the chromatin. TFs also recruit so-called SWI-SNF factors, proteins that provide the molecular motor for histones to move across a strand of DNA as it is being actively transcribed.

This knowledge of chromatin biology has now begun to inform our understanding of gene expression regulation in the brain and, in particular, its role in learning and memory. First, changes in histone acetylation and DNA



Learning & Memory: Molecular Mechanisms. Fig. 2. Differential states of chromatin. Chromatin exists in a continuum of states from being open (i.e., active, allowing gene expression) to condensed (i.e., inactive, repressing gene expression). Changes across this continuum are mediated in part by modifications to core histone proteins. Histone acetylation (A) is associated with chromatin relaxation and the binding of TFs and coactivators, such as HATs (histone acetyl transferases) and SWI-SNF proteins that mediate the movement of histone complexes along a strand of DNA. Histone methylation (M) results in condensed chromatin and transcriptional repression (REP). Methylation of the DNA itself also results in condensed, repressed chromatin. (From McClung CA, Nestler EJ (2008) Neuroplasticity mediated by altered gene expression. Neuropsychopharmacology 33:3–17.)

methylation have been shown to occur in hippocampus in parallel to aversive learning. These findings are striking because they emphasize the degree to which fundamental mechanisms of gene regulation are affected during the course of normal synaptic transmission – on a time scale of hours. Similar changes in chromatin have been demonstrated in striatum in response to drugs of abuse. Second, it has been possible to directly implicate mechanisms of chromatin regulation in aversive learning and drug addiction by demonstrating that direct manipulations of histone or DNA modifications has profound effects on behavior. Inhibitors of ► histone deacetylases (enzymes that remove acetyl groups from histones and thereby inhibit gene expression) or of DNA methyltransferases (enzymes that add methyl groups to DNA and thereby inhibit gene expression) promote hippocampal-dependent memory as well as the rewarding effects of drugs of abuse. In contrast, overexpression of these inhibitory enzymes in specific brain regions exerts the opposite effects.

The Future

One of the major challenges of current research is to identify the target genes through which a given TF exerts its particular effects on behavioral plasticity. Small numbers of target genes have been identified for all of the TFs mentioned above; however, some TFs may regulate hundreds of targets. This has been demonstrated by use of gene expression arrays (which measure levels of all mRNAs in a tissue) and ChIP (chromatin immunprecipitation)-chip or ChIP-Seq (sequence) methods (which measure levels of chromatin modifications across the entire genome). Understanding how the coordinated regulation of such large numbers of genes summate to produce the net functional effects of a TF, and how the effects of multiple TFs are summated, remains a great technical challenge.

Ultimately, it is essential to define the many ways in which brain function is altered by transcriptional and chromatin regulation to mediate the behavioral plasticity associated with learning and memory. In addition to altering levels of ion channels and neurotransmitter receptors, and many related second messenger proteins, as stated at the outset, there is increasing evidence that environmental experience produces more profound changes in nerve cells, including alterations in their overall size and shape, and the extent of their dendritic arborizations and synaptic inputs. Work is beginning to define the changes in gene expression, and the specific TFs and chromatin modifying enzymes that underlie this long-lasting reordering of nerve cells. As we build this increasingly complete view of molecular and cellular changes that occur in concert with behavioral plasticity, it is essential to then understand at a circuit level how such changes mediate behavioral memory.

Cross-References

► Addictive Disorder: Animal Models
► Chromatin Remodeling
► Gene Expression and Transcription
► Reference Memory and Consolidation
► Spatial Learning in Animals
► Synaptic Plasticity

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Learning Set

Definition

Learning set (and the closely related concept, task set), is when a learned rule is generalized so that there is facilitation of learning a new discrimination or task when a previously learned rule or principle applies to the new situation (see Harlow, 1949). There is a corresponding impairment of new learning when a previously learned rule or principal does not apply, as exemplified by the "Einstellung effect" (Luchins, 1942).

Legal Aspects of Psychopharmacology

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Synonyms

Allowable; Constitutional; Lawful; Legitimate (aspects of psychopharmacology)

Definition

"Legal" as a topic means falling within the province of the law and its study. It also has the more specific connotation of such as is required by the law and not falling outside what is permitted.

Current Concepts and State of Knowledge

Introduction

Human societies are governed by social rules that moderate our basic biological instincts. Moreover, such social rules reflect moral and ethical principles (Harris 2002). These social institutions and conventions are governed by the rules of law. These can be complex with codes of law extending to numerous densely written tomes. In a complex society, it is almost impossible to find any human activity that is not touched on in some way by the law. Psychopharmacology, a branch of science that involves the activities of the most complex human organ – the brain – is particularly affected by rules, regulations, and the panoply of the law. Both criminal and civil laws contain swathes of material directly relevant to psychopharmacology. Rules of law may forbid certain activities or specify certain conditions that must be carried out. Rules are normative – what ought to happen, rather than factual – what actually does happen. They lay down rules of behaviour to which we are expected to conform. If we do not, the law can apply sanctions, from a fine, or restriction of liberty, right through to the death penalty, still imposed in a minority of countries.

Durkheim (1964) regarded society as ranging from a relatively simple, technologically undeveloped society to an advanced, mobile, sophisticated social structure. The purpose of laws was to maintain social cohesion by striving for balance between competing ideas and interests. If a group perceives a law as failing to recognize a strongly held belief, they may adopt extralegal measures, for example, some animal rights activists.

Legislation of Morality

This raises the question of the relationship between the law and morality. A society's code of morality is the set of beliefs, values, principles, and standards of behaviour adhered to by most members of the society. In a homogeneous society, the set of morals tends to be fairly consensual. In a multicultural society, moral values may differ greatly. To accommodate these disparate views, the law which formalizes such moral principles may have to introduce special cases, exemptions, and exceptions. Even so, some members of the society may feel unable to abide by the law, for example, human embryo research may clash with imperatives from established religions.

One cardinal example in psychopharmacology concerns the complex laws relating to the use of the oldest of psychotropic substances, ▶ alcohol. Laws outlawing alcohol in the USA ("Prohibition") were in response to pressures from those in society who took the moral high ground. These groups were organised into religious and temperance organisations that emphasised both the moral shortcomings of heavy drinking and its medical and social toll. The moral disadvantages and legal injustice of penalising moderate and occasional social drinkers were submerged under the waves of moral temperance rectitude. The Prohibition Laws failed because they were too draconian and large numbers of US citizens flouted them. But, in many countries, achieving a just balance in the licensing of alcohol still remains a distant objective, viz. ▶ binge drinking in the United Kingdom.

Legal Instruments

It is an impossible task to even outline different forms of jurisdiction. Most European countries rely on systems of law based on the Roman model and codified by Napoleon. The United States and England (but not Scotland) use a common law system, in which judges interpret and modify legislation. Some countries maintain tight central control; others devolve to the periphery. Some have both, such as Federal and State laws in the United States, the relationship between which is being constantly adjusted. In some countries, religious law such as sharia is paramount; in others it exists in parallel and may be resorted to by the religious groups. In the European community, national laws have yielded precedence to EC laws, regulations, and directives. International courts such as those in The Hague have become increasingly recognised.

Research

Legal systems, under pressure from animal rights activists, have long introduced measures to regulate the treatment of animals. As these activists vary in their attitudes from

country to country, so do the regulations. Many countries have a set of rules rather than guidelines. In some, registration of laboratories, projects, and individual experimenters is required. Particular stringency is often applied to studies on primates. Research on Great Apes may be prohibited altogether, as may that on species deemed at risk of extinction even if they are not primates (► ethical issues in animal psychopharmacology).

In the human sphere, a series of declarations followed the abhorrent practices of the Nazis. The Declaration of Helsinki (1964) states that, "It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject." Ethical committees were set up, first in the USA, and then in other countries, to regulate human research, first voluntarily but increasingly under statute (► ethical issues in human psychopharmacology). On basis of a detailed protocol, a properly constituted ethical committee containing both professional and lay members should consider the proposal, modify it if necessary, and ensure that it is adhered to. Such committees have a special (fiduciary) duty to act properly and responsibly. Any researcher failing to submit an appropriate protocol would, depending on the jurisdiction, find himself subject to the criminal code for inflicting bodily harm, or to redress under the civil code for causing a personal injury ("tort"), or expulsion from the relevant professional body. With psychotropic drugs, psychological harm could be the basis for a court action (Carson and Bull 2003).

► Informed consent is typically a sine qua non for the recruitment of experimental subjects. This entails that each potential participant be adequately informed of the purpose of the study, its methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the expected risks and potential benefits of the study, and the anticipated discomfort. The presence of a neutral witness is a useful safeguard. The volunteer should be informed of the right to withdraw from the study at any time without explanation. The investigator must be sure that the potential subject has understood the information and has been encouraged to ask questions. Consent should be in writing wherever possible. Special rules generally pertain to subjects who suffer from a severe psychiatric disorder, or lack mental capacity to give informed consent, and to children. Recently, the question of genetic privacy has been raising concern.

Two European Directives, Clinical Trials Directive (2001) and Good Clinical Practice (2005) initiated change in medical research procedures across Europe to varying extents (Brazier and Cave 2007). A Directive sets out the broad goals of the legislation but allows each EU country to determine the form and precise content of that legislation (► randomized clinical trials).

Therapeutics

It is a truism that every administration of a therapeutic substance is essentially an experiment. If that usage in a patient is grossly negligent, criminal proceedings may follow. If it falls short of that, then the injured party generally has to show that the drug administration was below acceptable clinical standards, that it caused an injury that can be quantified, at least in financial terms. Standard rates are applied to gross physical injuries such as an amputation, but psychological or psychiatric damage is difficult to quantify. Often the functional impairments are evaluated, as well as symptomatic complaints.

Psychotropic drugs have some special aspects. First, on occasion a treatment may be administered compulsorily and stringent safeguards are essential. Second, some medications have a low therapeutic index and must be monitored according to the specified protocols (e.g., ► lithium salts, ► clozapine).

No consensus exists between various jurisdictions with respect to topics such as ► withdrawal syndromes, ► neuroleptic malignant syndrome, and ► tardive dyskinesia. Currently, much concern is being expressed with regard to suicidal phenomena with ► SSRIs, especially in adolescents where evidence for efficacy is often exiguous.

In most jurisdictions, the development of an ► adverse effect, ipso facto, does not constitute grounds for action as long as the drug was administered in accord with accepted clinical standards. These can change over time, and regulatory bodies may suggest different practices. Prescribers must be aware of the latest developments and even trends.

Regulatory Affairs

How medicines are developed and licensed is dealt with elsewhere ("► Licensing and Regulation of Drugs"). Randomised Clinical Trials raise particular concerns.

Consumer Protection

Various jurisdictions (including the EU) have brought in legislation to protect consumers from defective products – those that are unfit for purpose, or those that are not of a quality that a reasonable consumer has a right to expect. Medicinal products are usually subject to such control. A group of consumers who believe that a product is defective and that they have suffered from using the product may bring an action and may subsequently recover damages. The manufacturer's usual defence is to try and prove that

the produce is not defective or that scientific knowledge at the relevant time was not sufficient for a reasonable manufacturer to detect the defect.

Misuse of Drugs

One area where psychopharmacology is closely involved with the law is in the area of drug misuse. This can relate to drugs which have no recognised therapeutic properties, such as ▶ LSD, and therefore whose use can only be a misuse, or to products that have a licit indication, such as ▶ morphine, but can be misused (Glaser and Warren 1999). A controversy attends the use of ▶ cannabis products, where some products have been licensed in some countries to establish a legitimate therapeutic usage in pain and nausea.

Jurisdictions differ widely in both the form and content of the illicit drug "scheduling" legislation. The classification of drugs of dependence is usually into several categories, and maximum penalties for use, possession, and supply vary according to the category. For example, sanctions, often swingeing, are imposed with respect to heroin and ▶ cocaine; at the other end of the spectrum, penalties are minimal with ▶ benzodiazepines, which may not even be scheduled in some countries. Cannabis is controversial and debates continue as to where it should be classified. Chemical precursors and intermediates can be scheduled.

The penalties cover a range of unlawful activities – producing a Controlled/Scheduled Drug, supplying or offering to supply one to another person, possessing a Controlled/Scheduled Drug, and in some countries, cultivating any plant of the opium or cannabis type. Exemption is available for legitimate purposes, for example, the manufacturers of morphine, the pharmacists who store and supply it, and the medical, dental, and veterinary practitioners who prescribe and administer it. Special dispensations for research purposes can be applied for but are often notoriously difficult to facilitate. Most jurisdictions lay down strict rules for safe custody.

The misuse of Controlled Drugs is further regulated in various ways. In professional circles, the prescription of a Controlled Drug usually has to follow a strictly applied proforma, and careful records are mandatory. Addicts may have to be reported to a government department or agency. Some Controlled Drugs such as heroin can only be prescribed by specially recognised doctors. Irresponsible prescribing is penalised.

Various crimes are established under legislation and involve the criminal law system, police, judges, the prison system, and customs and excise departments. Much of this is governed by the Single Convention on Narcotic Drugs signed in New York on March 30, 1961 and by the 1971 convention covering drugs more widely. Searches of individuals, possessions, and premises can usually be authorised.

Sales Outlets

Jurisdictions generally reorganise various ways in which medicinal products can be provided (Appelbe and Wingfield 2005). The most restricted is a Prescription-Only Medicine, prescribed by a recognised medical, dental, or veterinary practitioner. The least restricted is a General Sale Medicine which can be sold in shops and supermarkets. Some countries have an intermediate category of drugs which are available without prescription under the supervision of a pharmacist.

Many remedies are "alternative"; the most widely used being herbal and homeopathic "medicines." Countries vary enormously with respect to whether or how these are regulated. Finally, concoctions that are used as folk remedies are rarely encountered in legal systems unless poisonous effects are produced. Alternative medicines may also raise problems with toxic constituents (▶ herbal remedies).

Alcohol is also subject to regulation. The Scandinavian countries are typically the most stringent. Some states in the United States are also quite restrictive. The minimum age for purchasing and drinking alcoholic beverages may be 21, and the bottles containing the same cannot be openly displayed.

Cross-References

▶ Ethical Issues in Animal Psychopharmacology
▶ Ethical Issues in Human Psychopharmacology
▶ Herbal Remedies
▶ Randomized Clinical Trials

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Legitimate

▶ Legal Aspects of Psychopharmacology

Lep^{db}/Lep^{db} mouse

► db/db Mouse

Lep^{ob}/Lep^{ob} mouse

► ob/ob Mouse

Leptin

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Synonyms

OB protein

Definition

A hormone produced in and secreted primarily by adipose tissue that regulates appetite, body weight, and neuroendocrine functions.

Pharmacological Properties

History

The hormone leptin was discovered in 1994; its name is derived from the Greek word for thin, *leptos*. Like other hormones, leptin is secreted in a pulsatile manner and shows a diurnal variation with a peak during the night. Lack of leptin signaling due to a mutation of *leptin* (e.g., ► ob/ob mouse) or the leptin receptor (*lepr*) (e.g., ► db/db mouse) in rodents and humans results in increased food intake, reduced energy expenditure, and severe obesity. Leptin replacement reverses many of the phenotypes of leptin-deficient mice. However, it was quickly apparent that an absolute leptin deficiency is an extremely rare cause of human obesity. Plasma leptin levels are elevated, rather than reduced, in the majority of obese subjects and plasma leptin levels are highly correlated with total fat mass. Thus, resistance to leptin action appears to be a more likely cause of human obesity.

Leptin also plays a role in the regulation of neuroendocrine function. Mutations in the leptin gene are associated with not only obesity but also neuroendocrine impairments, including impaired reproduction and low ► sex hormones, low thyroid hormone, low growth hormone, and elevated glucocorticoids. In 1996, it was first proposed that the physiological role of leptin is the regulation of the neuroendocrine system during starvation. Fasting reduces leptin gene expression and plasma leptin levels. Leptin treatment to prevent fasting-induced fall in endogenous leptin, blunts the fasting-induced changes in the neuroendocrine system. Thus, circulating leptin serves to communicate the state of body energy stores to the central nervous system (CNS) in order to maintain normal metabolic and neuroendocrine functions. A tremendous amount of research has since then focused on the role of leptin in the regulation of metabolism and neuroendocrine function as well as CNS signaling pathways that mediate leptin action.

Mechanisms of Action

Substantial evidence shows that the leptin pathway plays a significant role in body weight regulation by communicating the status of the energy stores to the brain. Leptin has been implicated in activating a variety of intracellular signaling cascade primarily through the long-form leptin receptor, LepRb.

Leptin Receptors (LepR or ObR)

The LepR contains a single transmembrane domain and is structurally similar to the class 1 ► cytokine receptor family. There are multiple LepR isoforms, all of which are products of a single *lepr* gene containing 17 common exons and several alternatively spliced 3′-exons. In mice, the six distinct LepR isoforms that have been identified are designated LepRa–LepRf. LepR isoforms can be divided into three classes: secreted, short, and long forms. The secreted form (LepRe) contains only extracellular domains that bind circulating leptin, perhaps regulating the concentration of free leptin. Short forms (LepRa, LepRc, LepRd, and LepRf) and the long form LepR (LepRb in mice) have identical extracellular and transmembrane domains as well as the same first 29 intracellular amino acids, but diverge in sequence thereafter due to the alternative splicing of exons. Unlike the other LepR isoforms, the long form LepRb contains a 302-amino acid cytoplasmic domain that includes motifs for binding of intracellular signaling molecules, and therefore LepRb is crucial for leptin action. The *db/db* mice are deficient in LepRb, but not other LepR isoforms, as a consequence of a mutation that causes mis-splicing of the LepRb mRNA. These mice display a ► phenotype that is indistinguishable from that of mice, which are deficient in all LepR isoforms (db^{3J}/db^{3J} mice) and of leptin-deficient *ob/ob* mice. The function of short form

LepRs is less clear, although proposed roles include the transport of leptin across the ► blood-brain barrier (BBB).

CNS Leptin Action

It is currently accepted that a leptin receptor-bearing neurons within the ► hypothalamus are responsible for mediating a concerted response to fluctuations of body energy stores. Before leptin reacts with its target cells in the hypothalamus, leptin must first cross the BBB. This step is facilitated by a transporter that is an alternatively spliced product (LepRe) of the leptin receptor gene present in brain endothelial cells. Long form leptin receptors, LepRb, are expressed in the CNS and leptin injection induces neuronal activation as evidenced by c-Fos induction. Substantial evidence suggests that the brain mediates the majority of leptin's action on energy homeostasis. Intracerebroventricular injection of leptin decreases food intake and body weight. Mice with a specific deletion of LepRb in the brain are obese, but the deletion of peripheral leptin receptors does not change the normal phenotype of the animal. Expression of LepRb in neurons of LepRb-deficient mice leads to an amelioration of their obesity.

Among the various brain areas that express LepRb, the basomedial hypothalamus is implicated as playing an especially important role. There are two primary populations of neurons that express LepRb and exert potent, opposing effects on food intake and body weight in the arcuate nucleus (ARC) of the ► hypothalamus. Leptin stimulates the production of proopiomelanocortin (POMC) and its derived products including ► α-melanocyte stimulating hormone (α-MSH), which act on melanocortin 4 receptor (MC4R). Leptin also stimulates the production of cocaine amphetamine-regulated transcript (CART). Both α-MSH and CART inhibit feeding as ► appetite suppressants. In another type of ARC neuron, leptin inhibits the production of ► agouti-related peptide (AGRP), an endogenous antagonist that acts on MC4R, and ► neuropeptide Y (NPY). AGRP and NPY are potent stimulators of feeding as ► appetite stimulants. Thus, leptin decreases food intake and increases energy expenditure by simultaneously stimulating the production of α-MSH and CART and inhibiting the production of NPY and AGRP in the ARC. These ► neuropeptides are transmitted to and interact with receptors in neurons of the paraventricular nucleus (PVN) of the ► hypothalamus. These PVN neurons, in turn, generate outputs that coordinate feeding behavior and energy expenditure and send these outputs to the hindbrain. Expression of LepRb is sufficient to reduce food intake and body weight gain when directed to the ARC, but not other hypothalamic regions of leptin receptor-deficient animals. Consistently, deletion of LepR only in POMC neurons leads to a mild obesity and restoration of ARC LepRb signaling attenuates obesity and ► hyperphagia in LepRb-deficient mice. These findings constitute direct evidence that LepRb signaling in the ARC is required for normal energy homeostasis.

Leptin Signaling

The hypothalamus is a major CNS site of leptin's action. It has been proposed that several signaling pathways are involved in mediating the diverse functions ascribed to leptin.

Jak-STAT3

Leptin has been postulated to signal through the Jak kinase family (JAK)-signal transducer and activator of transcription (STAT) signal transduction pathway (Villanueva and Myers 2008). Like other cytokine receptors, LepRb does not contain intrinsic enzymatic activity, but instead signals via a noncovalently associated tyrosine kinase of the JAK family, specifically Jak2. LepRb exists as a preformed homodimer before leptin binding. Leptin binding alters the conformation of the LepRb dimer, enabling transphosphorylation and activation of the intracellular LepRb-associated Jak2 molecules. The activated Jak2 molecule then phosphorylates other tyrosine residues within the LepRb/Jak2 complex to mediate downstream signaling.

Several lines of evidence strongly support a major role of STAT3 in mediating leptin signaling in the hypothalamus. Upon leptin binding, activated Jak2 phosphorylates itself and residues Tyr985, Tyr1077, and Tyr1138 within the intracellular tail of LepRb. Tyr1138 recruits and phosphorylates STAT3 proteins, which then dimerize and translocate to the nucleus and activate a specific program of gene transcription. Leptin activates STAT3 in the hypothalamus, and neuron-specific STAT3 knockout mice develop obesity recapitulating phenotypes of leptin-deficient *ob/ob* and leptin-resistant *db/db* mice. A knockout mouse that leaves the leptin receptor intact but specifically disrupt the LepRb-STAT3 signal are hyperphagic and obese. In these animals, the cytoplasmic tyrosine residue (Tyr1138) in LepRb was replaced with a serine residue, causing a disruption of the LepRb-STAT3 signaling. These findings indicate that the cytoplasmic tyrosine residue (Tyr1138) is necessary for proper LepRb-STAT3 signaling in the hypothalamus after leptin stimulation.

STAT3 mediates the transcription of the suppressor of cytokine signaling 3 (SOCS3) which then binds to Tyr985 of LepRb to inhibit LepRb-STAT3 signaling. Deletion of SOCS3 in the brain results in prolonged leptin-induced STAT3 activation in the hypothalamus and increased leptin sensitivity. More specifically, mice with a mutation

of Tyr985 show reduced food intake and body weight. Hypothalamic STAT3 phosphorylation and anorectic and weight-reducing effect of leptin are also increased in these mice. Thus, Tyr985-dependent attenuation of LepRb signaling represents a leptin-stimulated autoinhibitory signal and SOCS3 functions as a negative regulator of leptin signaling in the hypothalamus.

The mechanisms controlling and terminating the leptin signal transduction also include the dephosphorylation and inactivation of signaling proteins, mediated by protein-tyrosine phosphatase (PTP). PTP1B dephosphorylates activated Jak2 and STAT3. Ablation of PTP1B in *ob/ob* mice attenuates obese phenotype caused by leptin deficiency. PTP1B-deficient mice show an enhanced response toward leptin-mediated weight loss and suppression of feeding. Hypothalami from these mice also display markedly increased leptin-induced STAT3 phosphorylation. Consistent with the inhibition of Jak-STAT signaling, PTP1B overexpression attenuates leptin-induced, STAT-dependent gene activation. Thus, PTP1B is another negative regulator of leptin signaling.

Shp2

Src homology-containing tyrosine phosphatase 2 (Shp2) is a widely expressed cytoplasmic tyrosine phosphatase with two Src homology 2 domains. Phosphorylation of Tyr985 recruits Shp2, which then downregulates Jak2/STAT3 activation by leptin. Thus, it is assumed that the deletion of Shp2 in the CNS enhances leptin-induced Jak2/STAT3 activation and thereby shifts to negative energy balance. However, neuron-specific Shp2 knockout mice develop obesity in the presence of enhanced leptin-induced tyrosine phosphorylation levels of Jak2 and STAT3. Leptin also induces phosphorylation of extracellular signal-regulated kinase (ERK) in the hypothalamus and leptin-induced ERK activation is attenuated in neuron-specific Shp2 knockout mice compared to wild-type mice. However, mice with a mutation of Tyr985 show increased leptin sensitivity, possibly by inhibiting Tyr985-SOCS3-mediated inhibition of LepRb signaling (Villanueva and Myers 2008). Thus, although Shp2 enhances leptin signaling by enhancing ERK signaling, the physiologic role for Shp2 in leptin action remains unclear.

MAPK

ERK, a member of the mitogen-activated protein kinase (MAPK) family, is a key enzyme for many intracellular signaling processes. Leptin induces phosphorylation of ERK1/2 in a receptor-mediated manner that involves Jak2. Leptin-induced ERK1/2 activation was restricted to the ARC POMC neurons. Activation of ERK by leptin is mediated by both Shp2 and direct interaction with Jak2. Pharmacological blockade of hypothalamic ERK1/2 reverses the anorectic and weight-reducing effects of leptin (Rahmouni et al. 2009). Thus, hypothalamic ERK plays a key role in the control of food intake and body weight by leptin.

IRS-PI3K

The phosphatidylinositol-3-kinase (PI3K)/Akt pathway in hypothalamic neurons has been implicated in the regulation of food intake and energy homeostasis. Insulin receptor substrates (IRS) proteins are members of a class of intracellular signaling molecules termed docking proteins that are phosphorylated on multiple tyrosine residues to mediate SH2-protein recruitment and downstream signaling. Although IRS proteins contain tyrosine phosphorylation sites, most of them lie in motifs that bind and activate PI3K.

LepRb signaling is also coupled to the intracellular IRS-PI3K pathway (Villanueva and Myers 2008). IRS-2-deficient mice display increased adiposity and food intake and decreased metabolic rate. Plasma leptin levels are elevated in IRS-2-deficient mice, suggesting that these mice are resistant to the metabolic effect of leptin. Deletion of any of other three IRS proteins does not cause such obese phenotype. Thus, IRS-2 plays a specific role in mediating the effect of leptin on energy homeostasis. Leptin stimulates IRS-2-associated PI3K activity in the hypothalamus, and the pharmacological blockade of hypothalamic PI3K activity blocks the anorectic effect of leptin. Although the cellular mechanisms by which LepRb couples to the regulation of PI3K remain unclear, these findings indicate that PI3K is downstream of leptin signaling. Leptin and insulin act in parallel to stimulate PI3K in POMC neurons, suggesting that the effects of leptin and insulin are integrated by these anorexigenic neurons in the hypothalamus. Thus, IRS-2-PI3K is likely to lie downstream of leptin signaling and participates in mediating the metabolic action of leptin.

AMPK

AMP-activated protein kinase (AMPK) is a heterotrimer consisting of catalytic α-subunits and regulatory β- and γ-subunits. AMPK is regulated by the cellular AMP/ATP ratio and by upstream kinase. AMPK is activated by stress and regulates cellular metabolism by inhibiting energy-consuming pathways and inducing pathways that generate ATP. Once activated, AMPK phosphorylates acetyl-CoA carboxylase (ACC) and switches on energy-producing pathways at the expense of energy depleting processes. Leptin decreases α2AMPK activity in the hypothalamus and decreases food intake by reducing the expression of ► orexigenic AGRP and NPY in the ARC. In contrast to

leptin-induced STAT3 phosphorylation in many hypothalamic regions, leptin-induced decrease in α2AMPK activity is restricted in the PVN and ARC of the hypothalamus (Minokoshi et al. 2004). Thus, AMPK signaling specifically in the PVN and ARC plays a role in mediating anorectic effect of leptin. Insulin-induced inhibition of hypothalamic AMPK activity is blocked by the PI3K inhibitor. Because the effects of leptin and insulin are integrated by hypothalamic neurons via the PI3K/Akt signaling pathway, the leptin-induced inhibition of hypothalamic AMPK activity may be mediated through the PI3K/Akt pathway.

mTORC1

The mammalian target of ▶ rapamycin complex 1 (mTORC1) protein is a serine–threonine kinase that regulates cell-cycle progression and growth by sensing changes in energy status. A number of hormones and cytokines mediate their cellular effects through the mTORC1 signaling pathway. Leptin treatment increases the phosphorylation of both S6 kinase 1 (S6K1) and S6 ribosomal protein (S6), downstream targets of mTORC1 action, in the hypothalamus. Rapamycin, an mTOR inhibitor, attenuates the anorectic and weight-reducing effects of leptin, indicating that increased mTORC1 activity is required for the leptin-induced anorexia (Villanueva and Myers 2008). Mutation of Tyr985 in *leprb* blocks S6 phosphorylation, suggesting a potential role for the Shp2-ERK signaling cascade in leptin-induced mTORC1 activation. While mTORC1 was presumed to serve as the direct cellular sensor for ATP levels, mounting evidence has implicated AMPK in the regulation of mTORC1 activity. Most neurons expressing AMPK in the ARC and PVN possess mTORC1, and leptin-induced anorexia and the AMPK activator blocks hypothalamic mTORC1 activation. Thus, AMPK and mTORC1 interact in the hypothalamus to mediate the metabolic effect of leptin.

FoxO1

The forkhead transcriptional factor subfamily forkhead box O1 (FoxO1 or Fkhr) is a downstream target of Akt. Activation of Akt phosphorylates FoxO1, leading to its nuclear exclusion and proteosomal degradation, and thereby inhibiting its action. The anorectic effect of leptin is inhibited when hypothalamic FoxO1 is activated. Moreover, rats receiving constitutively nuclear mutant FoxO1 in the ARC showed impaired satiety in response to leptin treatment. The anorectic effect of leptin was almost doubled in FoxO1 heterozygous knockout mice compared to wild-type littermate controls, indicating that the loss of FoxO1 function is associated with increased sensitivity to the anorectic effect of leptin. Conversely, the anorectic effect of leptin was greatly reduced in mice expressing FoxO1-3A, indicating that hypothalamic FoxO1 activation can attenuate the effects of leptin on food intake. Furthermore, leptin decreases the hypothalamic expression of FoxO1, a downstream target of Akt and the i.c.v. administration of the PI3K inhibitor attenuates the effect of leptin on hypothalamic FoxO1 expression, suggesting that leptin decreases hypothalamic FoxO1 expression through PI3K activation and that FoxO1 is downstream of the PI3K/Akt signaling pathway in hypothalamic neurons. FoxO1 binds to *Agrp* and *Pomc* promoters and leptin inhibits FoxO1 binding to these promoters through STAT3-mediated competition (Kitamura et al. 2006). Thus, the hypothalamic PI3K-Akt-FoxO1 signaling pathway mediates the effect of leptin on the transcriptional regulation of *Agrp* and *Pomc* and thereby mediates the effect of leptin on energy homeostasis.

Leptin Resistance and Obesity

Leptin resistance, rather than leptin deficiency, appears to be a major cause of human obesity. Although the identity of the crucial mediator(s) of leptin resistance remains unclear, there are some possibilities including the failure of circulating leptin to reach its targets in the brain and inhibition of the intracellular LepRb signaling cascade.

One possible mechanism for leptin resistance is a defective leptin transport across the BBB. The transportation of leptin into the brain is mediated via a specific transport mechanism across the BBB and/or via the ▶ circumventricular organs. Leptin is transported across the BBB by a saturable transport system that may be in part mediated by the short form of leptin receptor, LepRe. In rats, lacking all leptin receptor isoforms, there is a marked decrease in leptin transport rate from the circulation into the brain. Normal transport rate of leptin is maintained in *db/db* mice in which only LepRb is missing, but other isoforms are intact. Leptin transport rate is also reduced in high-fat diet-induced obese (DIO) rats, an animal model of leptin resistance, and DIO mice do not respond to peripherally administered leptin (Levin et al. 2004). Similar impairments are also observed in aged animals, another model of leptin resistance (Scarpace et al. 2001). Systemic administration of leptin inhibited glucose-stimulated insulin secretion in young rats, but this effect was abolished in aged rats. These findings indicate that impairments in leptin transport rates across the BBB cause leptin resistance in the CNS.

Another possible mechanism for leptin resistance is impairments in intracellular LepRb signaling system.

Leptin-resistant DIO mice and aged rats do not respond to peripherally administered leptin, but they partially respond to central injection of leptin, suggesting that the downstream signaling pathways are partially capable of mediating leptin action. This also indicates that the ability of leptin to activate hypothalamic signaling is impaired in leptin-resistant animals. For example, leptin-induced phosphorylation of STAT3 is reduced in the hypothalamus of DIO animals and aged rats. Leptin-induced activation of PI3K and mTORC1 and the inhibition of AMPK are reduced in DIO animals (Cota et al. 2008; Martin et al. 2006; Metlakunta et al. 2008). These data indicate that impairments in these LepRb signaling contribute to the development of leptin resistance. SOCS3 and PTP1B are known to be negative regulators of leptin signaling in the hypothalamus. Overexpression of each of these proteins attenuates signaling through LepRb. Thus, PTP1B and SOCS3 are important physiologic determinants of leptin signaling strength, and PTP1B or SOCS3 contribute to the development of leptin resistance and obesity by inhibiting signaling through LepRb. The LepRb-STAT3 pathway stimulates SOCS3 expression and SOCS3 expression levels correlate with the attenuation of LepRb signaling. Thus, high levels of leptin may induce SOCS3 expression and thereby attenuates leptin signaling in obesity. Theoretically, this increase in SOCS3 should inhibit LepRb signaling, which in turn reduces SOCS3 expression. However, SOCS3 levels are elevated in obese animals with elevated leptin levels. It is possible that chronically elevated leptin levels induce its own feedback inhibition through the induction of SOCS3, effectively limiting the efficacy of chronic exposure of high levels of leptin.

Conclusion

Leptin serves to communicate the state of body energy stores to the CNS in order to maintain normal metabolic and neuroendocrine functions. These actions of leptin require its transportation to the CNS across the BBB via the short form LepRe and its binding to the long form LepRb, followed by the activation of diverse intracellular signaling pathways. Resistance to the metabolic effect of leptin is a major cause of human obesity. Interventions that can enhance the rate of leptin transport across the BBB and intracellular signaling through LepRb are expected to be therapeutically effective in the treatment of obesity.

Cross-References

- ▶ Agouti related peptide
- ▶ Alpha melanocyte stimulating hormone
- ▶ Appetite stimulants
- ▶ Appetite suppressants
- ▶ Blood-brain barrier
- ▶ Body mass index
- ▶ Circumventricular organs
- ▶ db/db mouse
- ▶ Eating and appetite
- ▶ Eating Disorders: Animal Models
- ▶ Energy metabolism
- ▶ Hyperphagia
- ▶ Hypophagia
- ▶ Hypothalamus
- ▶ Neuropeptide Y
- ▶ ob/ob mouse
- ▶ Rapamycin
- ▶ Satiety

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Leucoplakia

Definition

A white-coloured thickened patch in the mucosa of the oral cavity. This lesion is primarily caused by chronic

irritative stimuli such as tobacco use or friction and may potentially evolve in cancer.

Levodopa

Synonyms
l-DOPA; l-3,4-dihydroxyphenylalanine; 3-hydroxy-l-tyrosine

Definition
Levodopa is used in the treatment of Parkinson's disease, since it is a precursor of dopamine. l-DOPA can cross the ▶ blood–brain barrier, but tends to be metabolized peripherally by both aromatic l-amino acid decarboxylase or DOPA decarboxylase (DDC) and catechol-O-methyl transferase (COMT). Therefore, l-DOPA is often associated with a DDC inhibitor (e.g., ▶ carbidopa) or a ▶ COMT inhibitor (▶ entacapone) as double combinations, or even with both a DDC inhibitor (e.g., carbidopa) and a COMT inhibitor (entacapone), as a triple combination. The combinations are used to prolong the plasma half-life of l-DOPA, but also to avoid its conversion into ▶ dopamine in the periphery, thus avoiding peripheral dopaminergic side effects. Once in the brain, l-DOPA is converted to dopamine, since the DDC inhibitors do not cross the brain barrier, and dopamine will then activate dopamine receptors; this is the basis for the treatment of ▶ Parkinson's disease or dopamine responsive dystonias. Unfortunately, l-DOPA treatment response diminishes over the years, at which point various combination therapies must be started. Also, long-term treatment with l-DOPA may be accompanied by the "on-off" phenomenon, patients oscillating between symptom improvement and abrupt onsets of ▶ akinesia.

Cross-References
▶ Anti-Parkinson Drugs

Levodopa-L-Di Ortho Phenylalanine

▶ Anti-Parkinson Drugs

Levo-Duboisine

▶ Scopolamine

Levomepromazine

Synonyms
Methotrimeprazine

Definition
Levomepromazine is a ▶ phenothiazine antipsychotic with a plasma half-life of 16–78 h. It is mainly metabolized by 1A2 and 2D6 CYP450 isoenzymes. It is said to have strong sedative properties, probably due to strong histamine H1 receptor blockade.

Cross-References
▶ First-Generation Antipsychotics

Lewy Bodies

Definition
Globular protein-rich inclusions in cell soma, characteristic of a number of diseases, in particular ▶ Parkinson's disease (PD) and certain ▶ dementias. Although dopamine depletion can occur in a number of disorders, the presence of Lewy bodies in the dopaminergic neurons of the ventral midbrain are considered as defining of idiopathic PD. The principle molecular component of the Lewy body is α-synuclein, and several of the mutations associated with familial PD involve disturbance in the α-synuclein gene or in the genes encoding-related interacting proteins.

Lewy Body Dementia

Synonyms
Dementia with Lewy bodies; DLB

Definition
Lewy body dementia is characterized by distinct ▶ cognitive impairment with fluctuating confusion, disturbance of consciousness, visual ▶ hallucinations, ▶ delusions, falls, and significant parkinsonism. The hallmark feature is the widespread ▶ Lewy bodies throughout the cortex with the presence of Lewy body and cell loss in the subcortical nuclei.

Lexington Narcotics Farm

▶ Narcotics Prison Farm

Liberation

Definition
Liberation is the process of releasing the drug from its formulation.

Cross-References
- ► Absorption
- ► Distribution
- ► Excretion
- ► Metabolism
- ► Pharmacokinetics

Libido

Definition
Libido is the capacity for sexual desire.

Cross-References
- ► Agoraphobia
- ► Sexual Disorders
- ► SSRIs
- ► SSRIs and Related Compounds

Licensing and Regulation of Medicines in the UK

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Synonyms
Drug licensing; Medicines control; Medicines regulation

Definition
The licensing and regulation of ► medicines in the United Kingdom is the statutory responsibility of their Medicines and Healthcare Products Regulatory Agency (MHRA), based in London. Before any medicine can be prescribed or sold in the UK it must have a marketing authorization (previously known as a product license). The marketing authorization specifies precisely the ► summary of product characteristics (SPC), along with the labeling and package leaflet for the product. The regulation of medicines, and the overall responsibilities of the MHRA, involves considerably more than a "once only" marketing authorization. Regulation also entails post-licensing surveillance of safety and scrutiny of any proposed variation to the clinical indications for the medicine, any changes in availability, the on-going quality of the production process, and the enforcement of regulations when required, all in respect of the Agency's principal aim, which is to safeguard the public health. Marketing authorization is given or refused on the grounds of safety, quality, and efficacy. Financial cost plays no part in regulatory decisions.

Current Concepts and State of Knowledge

Status and Function of the MHRA
The legal context within which MHRA operates is described in the Medicines Act of 1968, which became operational in 1971. The Act designated the Secretary of State for Health in England (and equivalents in Scotland, Wales, and Northern Ireland), the Licensing Authority for Human Medicines in the UK. This is a retained authority within the UK. In 2003, the then Medicines Control Agency was re-established as the MHRA, which became responsible not only for the regulation of medicines, but also medical devices and, more recently, blood and blood products. Many of the provisions of the 1968 Act have now been superseded by regulations implementing European legislation on medicines. A diminishing number of medicines are licensed on a national basis by MHRA, solely for use in the UK. Most medicines are now authorized through European procedures to ensure that they are available to, and used in the same way across, all the member states of the European Union (EU). This is either through agreement of identical national authorizations in all member states, based on the assessment of a lead member state (a mutual recognition or decentralized authorization) or through a single EU authorization issued by the European Medicines Evaluation Agency (EMEA) (centralized authorization). Under the "mutual recognition or decentralized" procedures, all EU countries in which marketing permission is sought receive the full marketing authorization application and any objections are considered and resolved through the EMEA's scientific advisory committee, the Committee for Medicinal Products for Human use (CHMP). The centralized approval system is compulsory for biotechnology products and has expanded in scope to cover drugs for AIDS, cancer, neurodegenerative diseases, and diabetes. Often the MHRA will be asked to take the

lead on the licensing process in Europe, particularly for biological and biotechnology treatments, such as a gene therapy.

The Marketing Authorization Process

Authorization to market a medicine is based on detailed requirements and elaborate processes, the scope of which is constantly changing. However, the core elements of medicines control remain essentially unchanged, the primary focus being on the evaluation of pre-licensing data (from nonclinical tests and phases 1 to 3 clinical trials) on safety, quality, and efficacy generated or commissioned by companies and submitted for approval in a Marketing Authorization Application. A medicine progresses "from bench to bedside" over a period of many years, and innovation usually involves the discovery, development, and bringing to market of a new molecular entity (NME). Often the NME is original, such as the first SSRI or atypical antipsychotic, but it may also be a relatively minor molecular modification of an existing drug. The preclinical and nonclinical assessment involves necessary animal and bench testing before administration to humans. ► Phase 1 clinical trials are also known as "first time in man" studies and are conducted usually with healthy volunteers. ► Phase 2 clinical trials are for "proof of concept"; evidence of efficacy, and safety in patients with the target condition. ► Phase 3 clinical trials represent the main clinical reference point upon which marketing authorization may be granted. These are usually large trials (involving many thousands of patients suffering from the target condition), they usually involve comparison of clinical benefits and risk between randomized samples of the target population given either the active drug or a ► placebo and/or active comparator and the results inform the labeling and patient information for the medicine when it is marketed. The benefits recorded in phase 3 clinical trials represent the main database on "► efficacy." Phase 4 trials are conducted post-marketing, the principal aim being to provide ongoing, structured safety information. Benefits recorded in Phase 4 trials are usually more appropriately termed the medicine's "► effectiveness" and more faithfully reflect every day clinical practice in that they derive from patients who have not been so strictly selected or supervised as those involved in Phase 3 studies.

Clinical Trial Authorization

Clinical trials are conducted according to Guidelines on Good Clinical Practice (GCP) as described in EU Directive 2001/20/EC, Article 1, Clause 2, which deal with ethical and scientific issues relating to the design, conduct, recording, and reporting of clinical trials that involve human subjects. The principles of GCP are outlined in Articles 2–5 in the EU Directive 2005/28/EC. The serious side effects experienced by volunteers taking part in a trial of TGN1412 in March 2006 at Northwick Park Hospital are extremely rare but indicate the importance of thoroughly testing a treatment before widespread use. Another regulatory responsibility of MHRA is to authorize any clinical trial of a medicinal product in the UK. Information on the quality of the product and its nonclinical safety will have been obtained before Clinical Trial Authorization can be obtained and any clinical trial programme commencing.

Judging the Balance of Risks and Benefits

Evidence in pursuit of authorization is submitted by the applicant (normally a pharmaceutical company) either in paper form or electronically. Thorough assessment of all of the clinical and preclinical data is conducted in-house by MHRA assessors and a recommendation is then made to one or more elements of the Agency's expert advisory structure. The main independent, expert, group advising the Agency is the Commission on Human Medicines (CHM), which came into being in October 2005. The Commission has three statutory, standing, Expert Advisory Groups – in (1) pharmacovigilance, (2) chemistry, pharmacy, and standards, and (3) biologicals and vaccines. The Chairs of the Expert Advisory Groups are members of the Commission. In addition, there are a number of established Expert Advisory Groups covering a range of specific therapeutic areas such as Psychiatry and Old Age Psychiatry. The Commission is charged with the responsibility to advise Ministers, through the MHRA, on matters relating to human medicinal products.

The Life Cycle of a Medicine

Marketing Authorizations are granted for periods of up to 5 years, when they then have to be renewed. On renewal each marketing authorization must reflect all current knowledge about the product, including any necessary action from the most recent periodic safety update report (PSUR) submitted by the applicant. Once renewed, the marketing authorization will be valid for an unlimited period unless there are justified grounds relating to pharmacovigilance, when it may become necessary to proceed with one additional 5-year renewal. Variations to marketing authorizations must be approved before introducing any changes. They take account of technical and scientific progress, introduce additional safeguards, or reflect

evolving therapeutic indications. It is common practice for new products to be varied many times, particularly in the first 2 years after marketing. Once licensed, a medicine is normally under patent protection for 10 years. Once that period has expired, the originating pharmaceutical company is deemed to have been rewarded for the costs and risks of innovation, and generic versions of the medicine may then enter the market. Such generic medicines contain the same active ingredients as the original product, and the regulatory standards for safety, quality, and efficacy, are the same as for branded products, and marketing authorization must be obtained before the generic medicine is allowed on to the market.

Safety Monitoring

No medicine is completely free of risk but sound evidence underpins all of the MHRA's decisions to ensure that an acceptable balance exists between risks and benefits. Companies applying for a marketing authorization are required to submit a risk management plan which states what is known about the medicine, identifies any gaps in knowledge about safety, and outlines plans to collect data in the post-marketing period to fill those gaps. The MHRA monitors safety and quality standards by a number of means. It conducts regular inspections of good and safe practice including medicines manufacture and supply, carries out routine sampling of marketed medicines at manufacturers' premises, considers on-going reports from health professionals, patients, and manufacturers (such as the Yellow Card scheme, see below), reviews important new evidence on products (such as the SSRIs), and assesses misleading or incorrect information contained in advertisements, product labeling, or product information leaflets (PILs).

Pharmacovigilance is the process of detection, assessment, understanding, and prevention of adverse effects of medicines, against which benefits must be weighed in coming to any decision about the need to modify, restrict, or withdraw marketing authorization. By law, manufacturers must report to the MHRA any important defects in the quality (chemical identity and purity) or clinical safety of a medicine. Any action taken by MHRA is determined by the scale of the threat posed to the public health. If a new side effect is identified, MHRA can seek advice from its external experts and/or commission further research to illuminate the issues. A number of options are available to the Agency short of requiring withdrawal of the product, and any modifications to clinical usage are reflected in the SPC. Health professionals are informed of important new information and advice in relation to medicines via a letter sent by the manufacturer, or via a direct communication from the MHRA through the Department of Health Central Alerting System. The MHRA also issues a monthly bulletin "Drug Safety Update" which includes the latest advice for users of medicines and is available on the Agency's website; www.mhra.gov.uk/mhra/drugsafetyupdate The MHRA operates a "Black Triangle Scheme" under which all new medicines, and established medicines newly authorized for a different patient population, are intensively monitored for the first few years of marketing. Products monitored under this scheme are denoted by an inverted black triangle which appears on any advertising material and in the British National Formulary (BNF). For medicines denoted by a black triangle, it is advised that *all* suspected reactions (including any considered not to be serious) should be reported. The "Yellow Card" scheme is run by the MHRA and the CHM and is used to collect information submitted spontaneously from health professionals and the general public on suspected side effects or adverse drug reactions (ADRs). For established drugs and herbal remedies, all serious adverse reactions in adults and all serious and minor adverse reactions in children under the age of 18 should be reported. Prescribers and users need not be certain about causality, and the golden rule is "if in doubt, report." Reports can be made through the MHRA website; www.yellowcard.gov.uk and paper copies of yellow cards are attached at the end of the BNF. A rich source of data on marketed medicines comes from the general practice research database (GPRD), the management of which is entrusted to the MHRA. The GPRD is the World's largest computerized database of longitudinal medical records from Primary Care. Currently, data are collected on over 3.6 million active patients from around 450 Primary Care practices throughout the UK. It is used worldwide for research by the pharmaceutical industry, clinical research organizations, regulators, Government departments, and leading academic institutions, and is an internationally recognized source of information on the safety and effectiveness of licensed medicines.

The potential for ► selective serotonin reuptake inhibitors (SSRIs) to cause withdrawal reactions, dependence, and suicidal thoughts and behavior has been the subject of controversy and public concern since the late 1980s. The safety of SSRIs was closely monitored leading to updates to the SPC and patient information as evidence accumulated. An Expert Working Group of the Committee on Safety of Medicines (predecessor of CHM) established in 2003 conducted a detailed investigation of clinical trial data, data from the Yellow Card Scheme, and from GPRD.

Their recommendations were published in 2004 and fed into the NICE clinical guideline on depression. In 2005 analyses of 17 placebo-controlled studies found that ▶ atypical antipsychotics were associated with an increased risk of death in elderly people with ▶ dementia. The product information for these medicines was updated to include warnings about this risk. There is increasing awareness of psychiatric adverse effects of non-psychiatric medicines. ▶ Rimonanbant (Acomplia) was withdrawn from the market in the EU in 2008 because the risk of psychiatric disorders, particularly depressive reactions, was considered to outweigh its benefits in the management of obesity.

Herbal Medicines

The regulation of ▶ herbal medicinal products also falls within the remit of MHRA. There are three possible regulatory routes by which a herbal remedy can reach a consumer as an unlicensed, registered, or licensed herbal medicine. By April 2011 all manufactured herbal medicines will be required to have either a traditional herbal registration or a product license. The simplified registration scheme (the Traditional Herbal Medicines Registration Scheme) began in October 2005. Registered products are required to meet specific standards of safety and quality and to be accompanied by agreed indications based on traditional usage. To be licensed a herbal medicine requires to demonstrate safety, quality, and efficacy (or effectiveness) and to be accompanied by the necessary information for safe usage. As with conventional medicines, herbal remedies may be the subject of Yellow Card reports.

Counterfeit Medicines

The detection and confiscation of counterfeit medicines represents a growing activity for MHRA. The World Health Organisation (WHO) estimates that up to 1% of medicines available in the developed world are likely to be counterfeit, and this figure rises to 10% globally. Therapeutic psychoactive drugs are no exception – counterfeit Zyprexa (▶ olanzapine) was detected and recalled in the UK by the MHRA in 2007. Counterfeit medicine is commonly available to consumers via internet online pharmacies, WHO estimating that 50% of medicines available from such sites which conceal their physical address are counterfeit. Counterfeits discovered in the UK typically contain a reduced amount of the active pharmaceutical ingredient, although the wrong ingredient or no ingredient at all have been found less frequently; therefore all counterfeit medicines are potentially dangerous.

Medicines Availability

Marketing authorization of a medicine may specify whether it can be made available either on prescription (prescription only medicines (POM)), available in a pharmacy without prescription under the supervision of Pharmacist (P), or on general sale (GSL). Prescriptions can be issued by doctors, dentists, nurse independent prescribers, pharmacist independent prescribers and supplementary prescribers. Before restrictions on the supply of a medicine can be downgraded from POM, Ministers, advised by MHRA, must be satisfied that it would be safe to allow it to be supplied without prescription. Similarly, switching from P to GSL requires demonstration of acceptable safety if sold or supplied otherwise than by or under the supervision of a pharmacist.

Orphan Drugs

The pharmaceutical industry has little interest, under normal market conditions, in developing and marketing medicines intended for small numbers of patients ("orphan drugs"), and the EU offers a range of incentives to encourage the development of these medicines, including reduced licensing fees. In that case the company applies to the EMEA requesting "orphan designation" for their product.

Powers

When regulations have been breached, the MHRA has the power to prosecute. Courts can impose fines or prison sentences when the law has been broken and the Agency has the power to require unlicensed/illegal products to be withdrawn from the market.

Cross-References

▶ Herbal Remedies
▶ Legal Aspects of Adverse Drug Effects
▶ SSRI's and Related Compounds
▶ Suicide
▶ Withdrawal Syndromes

Ligand Binding

▶ Receptor Binding

Ligand-Directed Trafficking

▶ Functional Selectivity

Ligands

Definition

Substances that bind to receptors and alter the three-dimensional shape of selected receptor proteins. The shape of a receptor protein determines the functional state of a receptor. Ligands include substrates, inhibitors, activators, and neurotransmitters.

Liking and Wanting

Definition

Liking is the hedonic quality of food and the pleasing experience of consumption, while wanting is the desire to consume food and its motivational salience. The two are distinct as we can like a food without wanting it and vice versa; however, both are probably intrinsic components of palatability. In terms of animal behavior, the strength of initial feeding response is held to indicate liking, while later feeding behavior, including returning to food source, indicates the desire to consume.

Cross-References

► Palatability

Lipid Soluble

► Lipohilic

Lipohilic

Synonyms

Fat soluble; Lipid soluble

Definition

A chemical compound that dissolves in fats, oils, lipids, and nonpolar solvents (i.e., accumulate in lipid stores in the body).

Cross-References

► Blood Brain Barrier
► Sex Differences in Drug Effects

Liquid Diet for Administering Alcohol

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Definition

This is a technique of feeding ► alcohol (ethanol) as part of a liquid diet. The technique helps to mimic in experimental animals the effects of chronic alcohol intake in man and is used in research on alcohol effects in experimental animals, especially rodents. It has been used for more than forty years in many experimental studies that investigate and evaluate the effects of ► alcohol abuse and dependence in animals.

Proper controls and dietary adequacy pose significant challenges in studies on chronic exposure to ► alcohol in rodents. Thus, a suitable ► animal model that mimics the effects of chronic alcohol intake in man has long been sought. The technique of feeding ethanol as part of a totally liquid diet was first reported in 1963 (Lieber et al. 1963). Then the liquid diet technique became the most preferred and practical method to induce alcohol physical dependence experimentally since aversions to alcohol can be overcome and the intake is sufficient to sustain high daily alcohol consumption.

The route of drug delivery is an important consideration when evaluating the long-term biobehavioral adaptations occurring in response to chronic drug administration. Before the development of liquid diet technique of alcohol feeding, alcohol was commonly given to rats as part of their drinking water. Alcohol administration in water is associated with insufficient consumption and heavy weight loss. Insufficient intake of alcohol results in low levels in blood; on the other hand, if the intake of alcohol is sufficient, there is significant liver damage due to an inadequate intake of dietary nutrients rather than to effects of alcohol (Lieber and DeCarli 1989). Esophageal and gastric ulceration may also frequently appear. Administering alcohol to experimental animals as part of a liquid diet provides an efficient model allowing investigation of chronic effects of alcohol without irrelevant harmful effects. It is also closer to chronic intake of alcohol in man. In addition to achieving a significant alcohol intake, this technique has also the advantage of following minimization of alcohol-induced liver injury.

There are several liquid diet formulae available containing a mixture of mainly carbohydrates, oils, proteins, vitamins, and mineral (Lieber and DeCarli 1989). Milk is known to be an essential nutrient for growth of mammals. Cow's milk contains the major ingredients of an ideal liquid diet. It has also been reported that cow's milk may be used as a liquid diet in rats after addition of 1% (w/v) sugar (Parale and Kulkarni 1986) or a synthetic sweetener and vitamin A (Uzbay et al. 1995). A modified liquid diet of chronic alcohol administration to rats has also been defined and used (Uzbay and Kayaalp 1995).

Principles and Role in Psychopharmacology

Some Critical Points in Liquid Diet Practice

Liquid diet mixtures with or without alcohol provide 1,000 kcal/L. The liquid diet method for administration of alcohol involves pair-feeding of control and treated animals with identical amounts of the same diet to control exposure to putative nutritional deficits. Control rats are pair-fed with an isocaloric liquid diet containing a carbohydrate such as sucrose or dextrin maltose as a caloric substitute for ethanol. It is highly recommend to have a second control group with continuous access to standard laboratory diet and water. If the alcohol-treated group differs from both control groups and the control groups do not differ from each other, effects seen will not be due to limitations in dietary intake or the liquid diet but rather to alcohol *per se* (Driscoll et al. 1990).

To prevent decrease in diet intake and weight loss, ethanol (96.5%, v/v) should be gradually presented in progressively increasing concentrations during a habituation phase. After almost a week's feeding with liquid diet without ethanol, ethanol (about 2.5% v/v) can be added to the liquid diet for 3–4 days. Then the ethanol concentration can be increased to approximately 5% for 3 days and finally to 7.0–7.5%. When ethanol concentration is increased, a carbohydrate ingredient such as sucrose or dextrin maltose is reduced to maintain isocaloricity of the diet. Then, exposure to ethanol contained in liquid diet (approximately 7%, v/v) is carried on (Uzbay and Kayaalp 1995). A simple formula is shown in Table 1.

Although the liquid diet is meant to be the sole source of fluid and food, decreases in diet consumption can be avoided by giving access to water. Animals which receive water *ad libitum* lose less weight than groups that do not receive water *ad libitum* and keep consuming the same amount of liquid diet (Piano et al. 2001).

Daily alcohol consumption and blood ethanol levels are the most critical parameters for testing the validity of a liquid diet as a vehicle for alcohol administration. Above 10 g/kg/day alcohol consumption for a couple of week and more than 150 mg/dl blood ethanol concentrations may be adequate for development of ► physical dependence on alcohol in rats (Uzbay and Kayaalp 1995). It has been recommended that in an acceptable liquid diet 36–50% of total energy should be acquired by ethanol (Lieber and DeCarli 1989; Uzbay and Kayaalp 1995). Lieber and DeCarli (1989) found that the alcohol obtained from a liquid diet containing 35% ethanol provided about 36% of the daily energy intake, with average ethanol intakes in the range of 10–14 g/kg/day. The associated blood-alcohol levels were over 100 mg/dl when pregnant rats consume the majority of their daily intake. These 100 mg/kg levels were similar to those estimated after human consumption of three drinks in 1 h, and produced most major neurobehavioral effects of ► prenatal exposure to alcohol in their offspring (Driscoll et al. 1990).

Liquid Diet for Administering Alcohol. Table 1. A simple liquid diet formula for studies on alcohol dependence.[a]

Ingredients	Liter
Cow milk	925 ml
Ethanol (%96.5)	75 ml
Vitamin A	5000 IU
Sucrose	17 g

[a]Uzbay and Kayaalp 1995; 1000.7 kcal/L

Utilization of Liquid Diet Technique in Experimental Practice

► Alcohol abuse and dependence remain among the greatest substance abuse problems worldwide. The mechanisms underlying physical dependence to alcohol are poorly understood. Generally accepted criteria for animal models of alcoholism include physical dependence upon and ► tolerance to alcohol. Tolerance is often inferred when large doses of alcohol have minimal effects on behavioral performance after chronic alcohol exposure. Physical dependence is defined by the appearance of withdrawal signs upon removal of alcohol after a period of intoxication.

The technique for the administration of ethanol as part of a liquid diet is preferable in the animal models for the development of alcohol tolerance and dependence. Alcohol ► withdrawal syndrome induced by discontinuing chronic ethanol intake is the most important evidence indicating the presence of physical dependence on alcohol (O'Brien 1996). A severe alcohol withdrawal syndrome is produced by the liquid diet technique in rats. Also, this

method can be used to assess the pharmacological profile of drugs on the alcohol withdrawal syndrome in rodents (Uzbay and Kayaalp 1995).

The liquid diet technique has been adapted to a number of animal species other than rodents. One of the most successful applications has been the baboon liquid diet. The composition of the liquid diet is adjusted to meet the primate's needs. Thus, the ethanol content of the baboon liquid diet is significantly higher than that in the rat because of a lesser aversion to ethanol in the former species (Lieber and DeCarli 1989).

Advantages of Liquid Diet Techniques

The liquid diet technique is a relevant model for alcohol consumption in humans. It provides high daily alcohol intake and sufficient blood alcohol concentrations. It does not cause severe body weight loss. Even body weight increases have been reported in rats consuming ethanol-containing liquid diet (Lieber and DeCarli 1989; Uzbay and Erden 2003).

One of the major advantages of this technique is facilitation of the pair-feeding process. Usually the alcohol-fed animals are allowed dietary consumption *ad libitum,* with amounts consumed being self-limited. Their dietary intake is monitored by determining the amount of liquid consumed (Lieber and DeCarli 1989).

The liquid diet technique has also the advantage of allowing for an accurate recording of the nutrients consumed and for an easy change of the nutritional components according to specific experimental needs. This technique has been useful in characterizing the metabolism of alcohol, in assessing the interactions between ethanol and nutrition, other drugs that are also hepatotoxic agents and carcinogens, as well as in elucidating the mechanisms of alcoholic liver injury, endocrine abnormalities, withdrawal states, developmental problems and other central nervous system changes, including some degenerative and harmful complications (Lieber and DeCarli 1989).

Another use for the liquid diet technique is investigation of prenatal exposure to alcohol in animals. When prenatal exposure to alcohol is required, pregnant rats should receive a liquid diet as their sole source of nutrition and thus a proportion of their caloric intake will consist of ethanol or an isocaloric carbohydrate such as sucrose. A commercially available liquid diet with high protein content meets the requirements during pregnancy and lactation. This technique facilitates comparisons with controls by simplifying pair-feeding procedures (Lieber and DeCarli 1989); this method also avoids effects due to inadequate maternal diets that can exacerbate the effects of ethanol (Lieber 1991).

In contrast to administering ethanol by gastric intubation, not allowing the development of physical dependence to alcohol in rats within a short time may be the main disadvantage of the liquid diet technique. More exposure time is necessary for a satisfactory model of physical dependence in animals.

Cross-References

- ▶ Abuse
- ▶ Alcohol
- ▶ Alcohol Abuse and Dependence
- ▶ Animal Model
- ▶ Physical Dependence
- ▶ Prenatal Exposure to Alcohol
- ▶ Tolerance
- ▶ Withdrawal Syndrome

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Lisdexamfetamine

Definition

Lisdexamfetamine (L-lysine-D-amphetamine) belongs to the phenethylamine and ▶ amphetamine chemical classes, and is a drug specifically developed as an alternative to

D-amphetamine for the treatment of ADHD. Lisdexamfetamine has been tailored to have a more prolonged effect than D-amphetamine, yet with a reduced abuse potential. Despite these advantages, the use of lisdexamfetamine has been associated with several side effects including dry mouth, decreased appetite, insomnia, and heart attack or stroke in individuals with preexisting cardiovascular disorders.

Cross-References

- ► Adolescence and Response to Drugs
- ► Amphetamine
- ► Attention Deficit Hyperactivity Disorder
- ► Hyperactivity
- ► Impulsivity
- ► Psychomotor Stimulants

Listening Span Test

Definition

In this test, subjects listen to sets of two to seven sentences and complete a written factual verification question for the content of each sentence. After the last sentence of each set, subjects recall the final word of each sentence in the order in which they were presented. The span (working memory capacity) represents the maximum number of sentences performed correctly on at least two out of three trials.

Lithium

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Synonyms

Lithium salts

Definition

Lithium is an alkali metal. Its salts, lithium salts, are used as a psychopharmacological drug for recurrence prevention of manic-depressive illness, in the treatment of acute mania, in augmenting the effects of antidepressants, and in cluster headache. The pharmacologically active compound is the lithium ion (Li^+).

Pharmacological Properties

History

Lithium was first used in psychiatric patients in 1871, based on a wrong pathophysiological hypothesis but abandoned shortly afterwards. In 1949, the Australian psychiatrist John Cade showed first antimanic effects of lithium in psychotic patients. Starting an intensive research in the 1950s, his Danish colleagues Mogens Schou and Poul Christian Baastrup proved the efficacy of lithium in the treatment of acute ► mania and in the prevention of affective episodes in controlled studies.

Mechanism of Action

The initial direct target of Li^+ is the competition with Mg^{2+} at circumscribed metal ion-binding sites of proteins that need the binding of this ion as a cofactor in order to function. The enzymes thus inhibited by Li^+ comprise quite a heterogeneous group of enzymes such as inositolmonophosphatase (IMPase), phosphoglucomutase (FGM), biphosphate-3′-nucleotidase (BNP1), adenylylcyclase (AC), and glycogen synthase kinase 3 (GSK-3). AC, IMPase, and GSK-3 play a critical role in cellular signal transduction mechanisms, which are believed to be the main targets in the mechanism of action of Li^+ ions. Signal transduction mechanisms transmit the information impinging at receptors on the surface of the cell into the interior of the cell. Particularly important components are the "G-proteins," a family of heterotrimeric proteins located at the inner plasma membrane consisting of an α-subunit and the tightly associated βγ-subunits. The α-subunit binds guanyl nucleotides. Interaction with an activated receptor induces exchange of the bound GDP with GTP and dissociation into free α- and βγ-subunits which can activate various effector proteins. Activation is terminated by hydrolysis of GTP to GDP by the intrinsic GTPase activity of the α-subunit and reassociation of the heterotrimeric αβγ-complex. Effector proteins encompass enzymes like AC and phospholipases (C, D, A_2), which synthesize ► second messenger-molecules such as cyclic AMP, inositoltrisphosphate (IP_3), or diacylglycerol (DAG). "Second messengers" often act via activation of protein kinases, which phosphorylate various target proteins such as ion channels or transcription factors. Given the crucial role of signal transduction in cellular regulation, it is not surprising that these systems in the brain are also critically

involved in ► neural plasticity and resilience, and are therefore candidates as potential targets in the mechanism of action of ► mood stabilizers such as lithium. Effects of lithium ions on signal transduction mechanisms have therefore been a major focus of research during the last two decades (for review, see van Calker 2006).

Effects of Lithium on the Adenylylcyclase System

The inhibition by Li^+ ions of AC is known for 30 years. It appears to be due to a competition with Mg^{2+} ions at the catalytic unit of AC. In contrast, the chronic inhibitory effects of lithium on AC are not influenced by Mg^{2+} ions, but reversed by GTP, and therefore believed to be due to actions of lithium on G-proteins (discussed below). More recent research has also confirmed an inhibitory effect of lithium on the inhibitory interaction of receptors with AC and revealed its mediation by an action of lithium on the G_i-protein. In summary, lithium ions appear to balance signal transduction via the AC system. This could dampen the excessive pathological fluctuations of signaling that might be causative related to the mood swings in bipolar disorder.

Effects of Lithium on Phosphatidylinositol (PI) Signaling

Phosphatidylinositolphosphates (PIP), minor components of the lipids in the cell membrane, play an important role in the process of receptor-activated signal transduction. Hormones and neurotransmitters stimulate via activation of particular receptor subtypes the hydrolysis of PIP_3 to two second-messenger molecules, DAG and IP_3, which activate, respectively, protein kinase C (PKC) and the intracellular release of Ca^{2+}-ions. IP_3 is metabolized to myo-inositol, which is used together with DAG for the resynthesis of PIs. The last step in the metabolism of IP_3, the hydrolysis of inositolmonophosphate to myo-inositol by IMPase, is inhibited by lithium ions in the therapeutic concentration range (K_i = 0.8 mM). The "inositol depletion hypothesis" postulates that the lithium-induced inhibition of IMPase leads to a depletion of the brain of myo-inositol and, subsequently, due to a compromised synthesis of PIs to a reduction of receptor-stimulated formation of PI-dependent second-messenger molecules. It is, however, now clear that even a 90% reduction of myo-inositol content in the brain as observed in mice with targeted deletion of the Na^+/myo-inositol-cotransporter (SMIT, discussed in detail below) does not result in functionally relevant reduction of PI synthesis (Buccafusca et al. 2008) although these mice show behavioral abnormalities reminiscent of mice treated with lithium salts (Bersudsky et al. 2008). Thus, while myo-inositol appears to play a role in the behavioral effects of lithium, effects beyond PI-formation seem to be responsible.

Measurements of the effects of lithium treatment on myo-inositol levels in the human brain are partly consistent with the inositol depletion hypothesis. Proton magnetic resonance spectroscopy (MRS) scans of bipolar patients show a significant reduction of myo-inositol content in the frontal cortex already after 5 days of lithium administration, at a time when the patient's clinical state was completely unchanged. Thus, while lithium indeed lowers the myo-inositol in the brain this action alone cannot explain the therapeutic effect but may be the initial trigger for a cascade of subsequent alterations that ultimately account for the therapeutic effect.

In addition to hydrolysis of PIs, brain cells also acquire myo-inositol from the extracellular space by virtue of the sodium/myo-inositol cotransporter (SMIT), a high-affinity myo-inositol transport system that transports myo-inositol into the cells against a steep concentration gradient. Both the activity of SMIT and the expression of its mRNA in astrocytes are downregulated after chronic treatment with therapeutical concentrations of lithium salts. Two other mood stabilizers, ► valproate and ► carbamazepine, elicit the same effect, indicating that it might represent a common mechanism of action of ► mood stabilizers.

Similar to rat astrocytes, downregulation of SMIT mRNA expression also occurs in vivo in bipolar patients chronically treated with lithium or valproate as measured in neutrophils (Willmroth et al. 2007). SMIT expression in neutrophils was increased in bipolar-1 patients. On the one hand, IP_3 and Ca^{2+} signaling were found to be compromised in peripheral blood cells of patients chronically treated with lithium salts. On the other hand, peripheral blood cells of depressive or manic patients showed an increased sensitivity of the PI-system when compared with controls. These results provide evidence for an increased sensitivity of the PI system in peripheral cells of manic-depressive patients that is compensated or even overcompensated by treatment with lithium and, perhaps, other mood stabilizers (see van Calker 2006 for review).

Effects of Lithium on the Arachidonic Acid Cascade in the Brain

Membrane phospholipids can serve as a substrate for phospholipase A_2 (PLA_2), which is also activated by receptor/G-protein coupling. The released arachidonic acid (AA) and its bioactive eicosanoid metabolites can influence many physiological processes, including membrane excitability, gene transcription, ► apoptosis, sleep, and behavior. All three mood stabilizers, lithium, carbamazepine, and valproate downregulate the ► gene expression,

protein level, and activity of the AA-specific PLA_2, and also reduce the protein level and activity of cyclooxygenase 2 (COX-2) and prostaglandin E_2. Thus, AA metabolism might be another common target of mood stabilizers (see Rao et al. 2008 for review).

Effects of Lithium on Glycogensynthase-Kinase-3 (GSK-3)

GSK-3 is recognized as an important regulator of many vital cellular functions such as apoptosis, ► synaptic plasticity, cytoskeletal rearrangement, and ► circadian rhythm. Lithium inhibits GSK-3 directly by virtue of competition with Mg^{2+}-ions and indirectly by virtue of Akt-mediated phosphorylation on the n-terminal serine (for review see Beaulieu et al. 2009). The inhibition by lithium of GSK-3 likely contributes to its antiapoptotic and neuroprotective effects.

Effects of Lithium on Protein Kinase Activities and Protein Phosphorylation

As discussed above, lithium ions modulate the basal and agonist-stimulated concentrations of the second-messenger molecules cyclic AMP, IP_3, Ca^{2+}, and DAG, and should therefore also influence the activity of the protein kinases A, C, and others that are regulated by these second messengers. Several studies have reported that lithium can modulate protein kinase A-mediated protein phosphorylation. Alterations of PKC activity by lithium have been conjectured earlier after the formulation of the inositol depletion hypothesis, since a depletion of inositol should result in a decreased consumption for PI-resynthesis and, thus increased accumulation of DAG, the activator of PKC. PKC regulates many pre- and postsynaptic aspects of neurotransmission including long-term alterations in gene expression and neuronal plasticity. Persistent activation of PKC is often followed by its rapid proteolytic degradation and downregulation of enzyme activity. This could explain why lithium after acute or subchronic treatment induces an increase, while chronic treatment results in a decrease of PKC or PKC-mediated processes. The alterations in gene expression observed after chronic lithium treatment (see below) could at least in part be mediated by effects on PKC.

Effects of Lithium on G-Proteins

As discussed above, the effects of lithium on AC and its actions on PI signaling suggest the involvement of mechanisms beyond alterations of the catalytic subunit of AC or depletion of myo-inositol, respectively. One additional mechanism by which lithium could modify the activity of these signal transduction systems is the alteration of activity of G-proteins. An influence of lithium on G-protein function can be assessed by cholera toxin and pertussis toxin, which via ADP-ribosylation directly activate or inhibit, respectively, the G_s-protein, which stimulates and the G_i-protein, which inhibits adenylylcyclase. Using this approach, it was shown by in-vivo experiments with microdialysis technique that chronic lithium treatment inhibits the function of G_i thereby increasing the basal level of cyclic AMP in the brain of rats. On the other hand, chronic lithium treatment apparently also inhibits the function of G_s, since the inhibition by chronic lithium of the receptor-mediated activation of adenylylcyclase is counteracted by GTP. The inhibition of G_i may be due to a lithium-induced stabilization of the undissociated, inactive heterotrimeric $\alpha\beta\gamma$ state of the G_i-protein. Only this form is subject to ADP-ribosylation (for review, see Manji and Lenox 2000).

Effects of Lithium on Gene Expression

As already mentioned the activation by second messengers of protein kinases can lead to phosphorylation of nuclear transcription factors that regulate gene expression. Accordingly, treatment with Li^+ ions affects the expression of a number of genes, most likely at least in part secondary to modulation of PKC and/or GSK-3 (for review, see Wang and Young 2006). Of particular interest are the actions of lithium on so-called "immediate early genes," members of the c-fos and c-jun families, which encode proteins that form the constituents of a family of transcription factors called AP-1 (activator protein 1). These genes are of pivotal importance for long-term changes in neuronal function. Genes regulated by AP-1 include neurotrophins, ► neuropeptides, neurotransmitter synthesizing enzymes, and other transcription factors. It is now well established that lithium regulates AP-1-binding activity and function. The regulation by lithium of transcription factors is obviously not restricted to AP-1, since it also modulates two other such factors, cyclic AMP-responsive element-binding protein (CREB) and nuclear factor κB (NF-κB).

Effects of Lithium on Cellular Resilience

The neuroprotective effects of lithium were only recently fully appreciated. They are at least partly explained by the finding that lithium upregulates the neuroprotective and antiapoptotic protein Bcl-2. Very recently, it has been shown that mood stabilizer also increases BAG-1, an antiapoptotic, glucocorticoid receptor co-chaperone protein. Many of these effects may be in part mediated via inhibition of GSK-3β. That neuroprotection could also be an important mechanism in vivo is suggested by the

findings that lithium induces ▶ neurogenesis in adult rodent brain and increases the total gray matter in human brain. These results are particularly important in view of the recent evidence from brain imaging and post-mortem studies that mood disorders are associated with morphometric changes suggestive of cell loss and/or atrophy.

Pharmacokinetics

After oral application lithium salts are almost completely resorbed from the intestine. Maximal plasma concentrations are reached after 1–3 h. Elimination occurs exclusively through the kidneys. Steady-state concentrations are achieved after 4–5 days of treatment.

Dosage

The dosage of lithium should be slowly escalated if possible to minimize initially more pronounced adverse effects. At steady state, i.e., 5 days after the last dose escalation, plasma levels should be determined (12 h after last intake). When determining the dose of lithium, it is important to consider that different lithium salts have quite different molecular weights. Lithium tablets must therefore be dosed according to their content of Li^+ given in mmol. When switching from one lithium salt to another, this must be accounted for to avoid, for example, severe intoxication. Thus, for example, while lithium aspartate tablets of 500 mg contain 3,2 mmol Li^+, lithium carbonate tablets of 450 mg contain 12,2 mmol Li^+. When changing 1:1 from lithium aspartate to lithium carbonate this would slightly reduce the dose measured in milligram, but, in fact, increase the dose of the active compound (Li^+) by a factor of almost 4, given the narrow therapeutic range of Li^+ – perhaps, already a toxic dose! While ordinary daily doses amount to 20–30 mmol, older patients with reduced lithium clearance often need much smaller doses.

Efficacy

Lithium salts have been proven efficacious as a monotherapy of acute mania of the euphoric type. Lithium is only a second-line treatment in mixed or dysphoric mania where valproate, ▶ atypical antipsychotics, and carbamazepine are considered first-line choices.

The second indication for lithium is the treatment of acute ▶ bipolar disorder. Lithium can be used as monotherapy as well as in combination with an ▶ antidepressant agent. The latter strategy of primarily combining lithium with an AD should not be mistaken as lithium augmentation (see below). The combination of lithium and the antidepressant should prevent the patient from switching into mania.

There is convincing evidence that lithium is the drug of first choice in the long-term treatment and prophylaxis of bipolar disorder. However, with the expansion of the bipolar spectrum, data on the effectiveness of lithium in routine care have been controversial.

Current guidelines specify that long-term lithium treatment is indicated in patients

(a) who experienced at least one single-manic episode of disruptive severity and have a positive family history;
(b) who experienced two episodes, one of them manic, and have a positive family history;
(c) who experienced three episodes.

In addition, lithium has the greatest evidence supporting an antisuicidal and mortality-reducing effect in bipolar disorder. Clinicians should thus strongly consider initiating lithium treatment in patients with mood disorders accompanied by a high risk of suicide.

Lithium augmentation of an antidepressant has been recommended as the strategy of first choice in patients with therapy-resistant unipolar depression in many of the current guidelines. The addition of lithium to a preceding antidepressant serves as a net-enhancing effect on serotonin function.

Lithium may as well be used for the long-term treatment of recurrent unipolar depression, first of all as the antisuicidal effect has been proven for this diagnostic group too, but in addition due to lithium's episode-preventing effect. However, evidence is not as solid as for bipolar illness.

Other indications for lithium treatment are

- conduct disorder including severe aggression and explosive affect in children and mentally retarded patients, based on lithium's serotonin-enhancing effects;
- cluster headache, with a minor role of lithium behind various first-choice drugs;
- prophylaxis of herpes virus infections, based on lithium's antiviral activity.

Recent research covers the immunoregulatory effects of lithium, possibly relevant in AIDS and cancer as well as neuroprotective effects that are potentially useful in the prevention of dementia and neurological diseases.

Safety/Tolerability

Long-term side effects of lithium are infrequent and serious side effects are rare, if the patients and the dosage are properly selected and monitored. Because lithium ions influence a large number of important biochemical

processes (see above), lithium has a potential to induce a relatively wide spectrum of adverse reactions in a variety of organ systems. With regard to safety and tolerability, acute and prophylactic lithium therapies follow similar basic principles. When considering side effects, it is important to distinguish between acute and long-term changes, the relatively common symptoms that can appear during the normal course of lithium prophylaxis, and the rare, intense symptoms indicative of lithium intoxication.

Table 1 shows the relative and absolute contraindications of lithium therapy.

Table 2 shows adverse effects of lithium therapy and comments on frequency and therapeutic options.

The most important laboratory tests before starting long-term lithium treatment are

- serum creatinine and creatinine clearance (estimate using the Cockcroft equation);
- T3, T4, TSH levels;
- complete blood count;
- ECG;
- fasting glucose levels.

The serum lithium level should be measured 12 ± 1 h after the last dose has been taken. The dose requirement can then be estimated proportionally. Following the initiation of lithium prophylaxis, serum lithium levels must be checked on a weekly basis. Later, monitoring should be performed approximately once per month during the first year of treatment and, subsequently, every 6–12 weeks.

In general, for most patients, a serum lithium level in the range of 0.6–0.8 mmol/l is recommended for lithium prophylaxis. In older patients, in most women, and in patients who are particularly sensitive to side effects, it may be advisable to reduce lithium levels to 0.6 mmol/l.

Serum creatinine should be monitored at least every 6–12 months. Serum calcium should be monitored every 6–12 months due to the risk of hyperparathyroidism during lithium treatment. The patient's thyroid hormone status should be checked by measuring serum T3, T4, and basal TSH once a year. Regular ultrasound examination of the thyroid is also recommended.

A complete blood count (or at least a leukocyte count) should be performed every 6–12 months.

Medical diseases occurring during lithium treatment should be carefully monitored. Serum lithium should be assessed more frequently and the dosage adjusted so that serum lithium levels remain as low as possible.

In patients with arterial hypertension, low salt diets should not be used, and diuretics should only be

Lithium. Table 1. (Absolute and relative) Contraindications to lithium.

	Absolute	Relative	Special caution with
Renal	Acute renal failure	Disorders with decreased glomerular filtration rate, tubular disorders	
Cardiovascular	Acute myocardial infarction	Cardiac rhythm disorders ("sick sinus" syndrome)	Arterial hypertension
Neurological		Cerebellar disorders Myasthenia gravis	Cerebral sclerosis Dementia; epilepsy Parkinson's disease
Dermatological		Psoriasis	
Endocrine		Hypothyroidism Addison's disease	
Gynecological		Pregnancy, 1st trimester	Pregnancy, 2nd and 3rd trimesters; childbirth; breastfeeding
Hematological		Myeloid leukemia	
General		Low sodium diet Anesthesia/surgery	Diarrhea, vomiting, fever
Medication		Diuretics	Antiphlogistics Muscle relaxants; anesthesia Anticonvulsants Tetracyclines; spectinomycin ACE inhibitors Methyldopa; neuroleptics

Lithium. Table 2. Adverse effects of lithium salts.

Organ system	Symptoms	Remarks/Therapy
Neurological/Psychiatric	Fine tremor of the fingers	Frequent side effect. Therapeutic options: dose reduction, change of dose regimen, beta-receptor blockers
	Muscle weakness	More likely at start of therapy
	Memory impairment	
Gastrointestinal	Nausea	Often at start of therapy
	Vomiting	Diarrhea and vomiting can be signs of lithium intoxication!
	Abdominal pain	
	Diarrhea	
Cardiovascular	Changes in ECG; flattening/ inversion of T wave	Reversible. Nonspecific changes are not dangerous
	Arrhythmias	Very rare. Result from initiation or conduction defects
	First-degree atrioventricular block	Regular ECG monitoring
	Sick-sinus syndrome, ventricular extrasystoles	Discontinuation of lithium
	Second- and third-degree AV block, bundle-branch block	
Renal	Polyuria, polydipsia, reduced concentration capacity	Reversible on discontinuation. Management options: dose reduction, amiloride
	Reduced glomerular filtration rate	Rare, prevent or avoid transient lithium subintoxications
	Nephrotic syndrome	Rare, reversible on discontinuation
Metabolism, electrolytes, and water balance	Weight gain	Frequent. Consider low caloric diet with normal sodium intake
	Edema	Rare. Caution when administering diuretics
Endocrine	Euthyroid goiter	Common. Suppressive therapy with L-thyroxin
	Rise of TSH, hypothyroidism	Common in long-term treatment, substitution necessary
	Hyperparathyroidism with hypocalcemia	Infrequent. Check serum calcium
Hematological	Moderate leukocytosis	Common. Reversible
Dermatological	Acne	Treat as usual
	Hair loss	Rare (check for hypothyroidism)
	Psoriasis	Can be exacerbated; maybe a relative contraindication

administered cautiously. Furthermore, in renal hypertension and diabetes mellitus, the late renal sequelae of each disease must be taken into account.

In cases of cerebral sclerosis, dementia, and other psychoorganic disorders, lithium – even at therapeutic levels – can lead to disorientation and other neurotoxic symptoms.

Pregnancy, breastfeeding

The risk of abnormal fetal development under lithium therapy has been overestimated for a long time. Based on case-control studies, the risk can be estimated as only slightly higher than normal during lithium therapy in pregnant women (at standard serum lithium concentrations). If the course of affective illness does not allow for interrupting long-term treatment, a continuation of lithium treatment during the first 3 months of pregnancy may be considered (Cohen et al. 1994). The side effects of lithium therapy apply both to the pregnant mother and the fetus. However, the toxicity threshold for the fetus is lower. A mother may nurse her child when on lithium therapy. However, the child's development must be properly monitored and the advantages of breastfeeding over formula-feeding need to be weighed against the risks.

Cross-References

► Bipolar Disorder
► Gene Expression
► Gene Transcription
► Mania
► Mood Stabilizers
► Neuroprotection

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Lithium Salts

► Lithium

Liver Toxicity

► Hepatotoxicity

Local Field Potentials

Synonyms

Field potentials

Definition

The electrophysiological recorded local field potential (LFP) is thought to represent the synchronized input (sum of somato-dendritic potentials) into a neuronal ensemble, as opposed to output neuronal spiking activity. This signal is typically recorded using a low impedance extracellular microelectrode that is subsequently band-pass filtered to remove slower (<10 Hz) and faster signal fluctuations (>300 Hz) indicative of sleep-related slow oscillations and neuronal spiking (action potential) activity, respectively.

Cross-References

► Magnetic Resonance Imaging (Functional)

Locomotor Activity

► Motor Activity and Stereotypy

Lofepramine

► Antidepressants
► Tricyclic Antidepressants

Lofexidine

Definition

Lofexidine is as an agonist at α2 adrenoceptors and acts presynaptically to decrease adrenergic neurotransmission in the central nervous system, notably activity of the locus coeruleus. Through this mechanism, it decreases many of the autonomic symptoms of opioid withdrawal in humans and in animal models. It is under investigation for managing withdrawal from heroin or ► methadone and has been found more effective than placebo. Its efficacy appears similar to that of clonidine, another α2 agonist, but it has lesser adverse effects.

Cross-References

► Opioid Dependence and Its Treatment

Long QT Syndrome

Synonyms
LQTS

Definition
A cardiac arrhythmia where the QT interval on the ECG is prolonged; it can be inherited or acquired. The acquired form is due to disturbances in blood electrolytes or to various drugs. It is a condition with delayed repolarization following depolarization (excitation) of the heart, associated with syncope (fainting) due to ventricular arrhythmias, which can deteriorate into ventricular fibrillation and ultimately sudden death.

Cross-References
► Opioid Dependence and Its Treatment
► Sex Differences in Drug Effects

Long-Delay Learning

Definition
Long-delay learning refers to the phenomenon whereby an association of two temporally related stimuli can be made when there is an extended period of time between their presentations. Traditional learning theory suggests that as the temporal delay between the presentations of two stimuli increases, there is a graded reduction in the strength of the association between the two. When long-delay learning occurs, the association of the two stimuli occurs over longer intervals than seen under traditional learning conditions. Such learning is usually suggested to be evolutionarily important.

Cross-References
► Conditioned Taste Aversions

Longitudinal Aspect

Definition
Concerning the long-term course of a disorder with its specific patterns and characteristics.

Long-Lasting Synaptic Depression

► Long-Term Depression and Memory

Long-Term Depression

► Long-Term Depression and Memory
► Synaptic Plasticity

Long-Term Depression and Memory

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Definition

Memory
► Memory describes the storage of information acquired during learning in a form that can be accessed and retrieved. It encompasses the conscious memory of factual information as well as the unconscious use of procedural information.

The acquisition, storage, and retrieval of information are arguably the most complex and fascinating functions of the nervous system, and undoubtedly involve many brain regions. Following pioneering studies in the twentieth century, a convenient working model of learning and memory emerged whereby different brain regions are deemed responsible for storing different types of learned information (Table 1). The famous case of patient H.M. who suffered specific memory deficits following bilateral removal of the medial temporal lobe (reviewed by Squire and Zola-Morgan 1988) was pivotal in highlighting the separation of brain systems concerned with ► declarative memory (conscious recollection of episodic or semantic information) vs. nondeclarative memory (unconscious use of learned information). Whether or not the different forms of memory stored in different brain regions involve common mechanisms, such as alterations in synaptic strength (e.g., long-term depression), remains controversial.

Long-Term Depression
Long-term depression (LTD) is the weakening of neuronal synaptic connections, typically following a specific pattern of neuronal activity. The reduction in synaptic strength (a form of ► synaptic plasticity) lasts from hours to days. It can be ► homosynaptic (specific to the synapses

Long-Term Depression and Memory. Table 1. Classification of memory. (Reviewed by Squire and Zola-Morgan 1988.)

	Declarative	Nondeclarative
Synonyms	Explicit	Implicit
Definition	Conscious recollection of specific information	Unconscious use of learned information
Brain regions	Hippocampus	Basal ganglia
	Perirhinal cortex	Amygdala
	Prefrontal cortex	Cerebellum
Examples	Episodic memory – the features of an event, e.g., *what, where, who*	Procedural learning of skills and habits
	Semantic memory of factual information	Operant conditioning
	Recognition memory	Classical Pavlovian conditioning, e.g., emotional conditioning; motor conditioning (e.g., eye-blink)
	Working (short-term) memory	

that are subject to the inducing pattern of activity) or ► heterosynaptic (spreading to nonstimulated synapses).

LTD is widely expressed throughout the central nervous system (CNS) and is elicited at excitatory and inhibitory synapses via a diverse number of mechanisms (Table 2). Evidence suggests that mechanisms of LTD contribute to experience-dependent development and forms of learning and memory, as well as being implicated in neurological disorders, including mental retardation, ► Alzheimer's disease, and drug addiction. For the purpose of simplicity, we have chosen to focus on LTD at excitatory synapses in two brain regions: the hippocampal CA1 area, where the classical form of LTD is expressed, best understood mechanistically, and a potential target site for cognition-enhancing drugs (► cognitive enhancers), and the ► ventral tegmental area (VTA) of the midbrain, where LTD is targeted by ► drugs of abuse and is therefore of particular psychopharmacological interest.

LTD and Memory in the Hippocampal CA1 Region

The ► hippocampus forms part of the temporal lobe learning and memory system concerned with declarative memory of episodic and semantic information (Table 1). Three forms of ► glutamate receptor-dependent LTD have been described in the hippocampal CA1 region (reviewed by Malenka and Bear 2004); each form is summarized in Table 3. The first description of LTD in the hippocampus was Homosynaptic NMDAR-Dependent LTD at Schaffer collateral synapses onto pyramidal cell dendrites in the CA1 region of hippocampal slices (Fig. 1). Postsynaptic NMDA glutamate receptors permit Ca^{2+} entry into the neuron and it is generally well accepted that this Ca^{2+} influx triggers activation of ► postsynaptic proteins including the protein phosphatases, calcineurin, and protein phosphatase 1 (PP1). Expression of NMDA receptor-dependent LTD depends on modification of AMPA glutamate receptor phosphorylation states in addition to physical loss of ► AMPA receptors from the synapse (► receptor trafficking). ► Protein synthesis and degradation of postsynaptic density 95 (PSD-95) are required for the expression of this form of LTD.

Hippocampal mGluR-dependent LTD was first described in the CA1 region of hippocampal slices (reviewed by Malenka and Bear 2004) and requires mGluR5 receptor activation for its induction. This form of LTD can be induced chemically, via application of the selective group I mGluR agonists, or electrically via synaptic stimulation (Table 3). mGluR-dependent LTD, like NMDA receptor-dependent LTD, is expressed via mechanisms involving protein synthesis and the loss of postsynaptic AMPARs.

A distinct form of mGluR-dependent LTD exists in young rats that is induced by the group 1 mGluR agonist, DHPG, and synaptic stimulation but is expressed presynaptically. A retrograde messenger released from the postsynaptic cell is required, and likely candidates include ► endocannabinoids and 12-lipoxygenase metabolites of arachidonic acid, including 12-(S)-HPETE, recently shown to be the endogenous mediator of mGluR-dependent LTD at excitatory synapses onto CA1 stratum radiatum interneurons (Gibson et al. 2008). This heterosynaptic form of LTD (*TRPV1-dependent LTD*) occurs in response to high-frequency stimulation and release of

Long-Term Depression and Memory. Table 2. Examples of LTD in different brain regions.

Brain region	LTD expressing synapses	Drugs affecting LTD	Implications in memory
Hippocampus	*SC–CA1* pyramidal neurons	*NMDAR* and Ca^{2+} channel antagonists	Declarative learning and memory
	SC and *AC* input to *CA1* and *CA3* pyramidal neurons	mGluR antagonists	e.g., semantic and spatial memory, novelty and learned recognition of environment, stress-induced memory recall
	PP to dentate gyrus interneurons	mGluR antagonists	
	SC–CA1 interneurons	Rimonabant (SR141716A), *CB*1 and TRPV1 receptor antagonists, mGluR antagonists	Clinical relevance: amnesia and cognitive impairment
	Interneuron to *CA1* pyramidal neurons	Δ^9-THC	
Ventral tegmental area	*EPSC*s onto dopamine neurons *IPSC*s onto dopamine neurons	Amphetamine, D2 receptor agonists, Opioids	Nondeclarative forms of learning and memory
Caudate/ putamen	Cortical inputs to medium spiny neurons	NOS and soluble guanylyl cyclase inhibitors, mGluR, D2 and *CB1* receptor antagonists	Adaptive learning of motivated actions in response to salient stimuli; development of habits
Nucleus accumbens	Cortical inputs to medium spiny neurons	Δ^9-THC, *CB1* and TRPV1 receptor antagonists, mGluR antagonists	Clinical relevance: development of "unhealthy" habits, e.g., drug addiction
Perirhinal cortex	Cortical inputs from entorhinal cortex to layer II/III pyramidal neurons	Quinpirole, NMDA, and kainate receptor antagonists	Recognition memory
Prefrontal cortex	Layer II/III fibers to layer V/VI pyramidal neurons	5-HT2A/C antagonists, Group I mGluR antagonists, *CB1*R antagonists, MAPK inhibitors	Executive memory functions e.g., working memory, organization of voluntary movements, emotion
Visual cortex	Thalamocortical input to layer V pyramidal neurons	Group II mGluR antagonists, *NMDAR* antagonists, cocaine	Development of visual circuitry
	White matter to layer II–IV neurons	mGluR antagonists	
Cerebellum	Parallel fiber input to Purkinje neurons	NOS and soluble guanylyl cyclase inhibitors, mGluR, D2 and *CB1* receptor antagonists	Procedural (motor) learning

CB1 cannabinoid type 1 receptor; *EPSC* excitatory postsynaptic currents; 5-HT, serotonin; *IPSC* inhibitory postsynaptic currents; *MAPK* mitogen-activated protein kinase; *mGluR* metabotropic glutamate receptor; *NMDAR* ▶ *N*-methyl-D-aspartate glutamate receptor; *NOS* nitric oxide synthase; Δ^9-THC, delta 9-tetrahydrocannabinol; *TRPV1* transient receptor potential vanilloid 1; *SC* Schaffer collateral; *AC* associational commissural; *PP* perforant path.

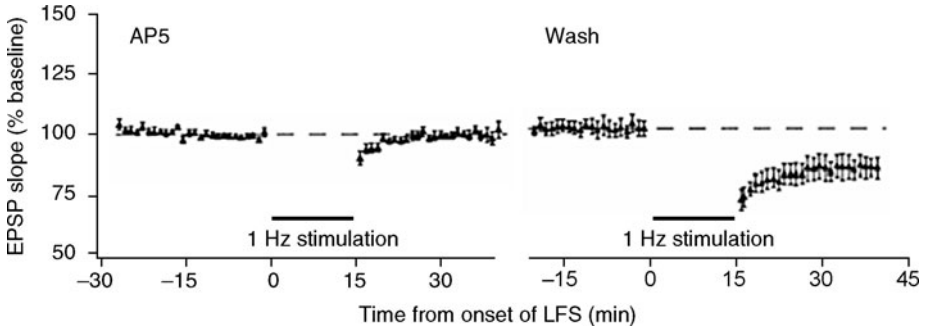
endocannabinoid-like molecules known as endovanilloids that act on presynaptic TRPV1 (transient receptor potential vanilloid 1) receptors.

The question of whether or not experimental models and mechanisms of LTD in the hippocampus underlie memory (reviewed by Massey and Bashir 2007) remains controversial. In principle, one would determine whether or not LTD is induced in the hippocampus coincidentally with learning and memory and then block LTD, producing correlating impairments in memory acquisition and storage. In practice, the difficulties of "measuring" learning and memory make definitive, conclusive experiments of this kind challenging. CA1-restricted *NMDAR1* gene knockout mice lack NMDA receptor-dependent LTD at CA1 synapses and exhibit impaired spatial memory during a hippocampal-dependent task, while learned

Long-Term Depression and Memory. Table 3. Different forms of LTD in the hippocampal CA1 region.

	NMDAR-dependent LTD	mGluR-dependent LTD	Endocannabinoid/Endovanilloid-mediated LTD
Synapses expressing	*SC–CA1* pyramidal neuron	*SC–CA1* pyramidal neuron, *SC–CA1* s. radiatum interneuron	*SC–CA1* pyramidal neuron, *SC–CA1* s.radiatum interneuron
Induction protocol	Low-frequency stimulation (*LFS*), 0.5–3.0 Hz, typically 1 Hz for 15 mins	Paired-pulse low-frequency stimulation (*PP–LFS*), typically 1 Hz for 15 min; Application of *DHPG*	*PP–LFS*, typically 1 Hz for 15 mins; application of *DHPG;* high-frequency stimulation (*HFS*); e.g., 100 Hz (× 2, 20 s inter-train interval)
Mechanism of induction	*Postsynaptic:* NMDAR activation; Ca^{2+} influx and release from intracellular stores	*Postsynaptic*: Group 1 mGluR activation; Ca^{2+} influx	*Postsynaptic:* Group 1 mGluR activation; Ca^{2+} influx; phosphoinositide hydrolysis; release of retrograde messengers
Mechanism of expression	*Postsynaptic*: Activation of protein phosphatase, calcineurin, *PP1*; *PSD-95* degradation; modification and internalization of *AMPARs*; protein synthesis	*Postsynaptic*: Activation of protein tyrosine phosphatase, p38 mitogen activated protein kinase cascade, *PI3K* and Ras-activated *ERK*; *AMPAR* internalization; protein synthesis	*Presynaptic*: Activation of presynaptic receptors e.g., *CB1* and *TRPV1* by retrograde messengers; decreased presynaptic neurotransmitter release

AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate acid glutamate receptor; *CB1* cannabinoid type 1 receptor; *DHPG* Dihydroxyphenylglycine; *HFS* high-frequency stimulation; *hertz* (Hz); *mGluR* metabotropic glutamate receptor; *NMDAR* N-methyl-D-aspartate glutamate receptor; *PI3K* phosphoinositide-3 kinase; *PP1* protein phosphatase; *PP-LFS* paired-pulse low-frequency stimulation *PSD-95* postsynaptic density-95;*TRPV1* transient receptor potential vanilloid 1;*SC* Schaffer collateral



Long-Term Depression and Memory. Fig. 1. Original experimental data of Dudek and Bear (1992) showing NMDA receptor-dependent LTD in the hippocampus. In the presence of the NMDA receptor antagonist AP5, low-frequency synaptic stimulation (1 Hz for 15 min) produces no change in the synaptic response. When AP5 is washed off, the same low-frequency synaptic stimulation now produces a decrease in synaptic responses: LTD. (Reproduced from Dudek S, Bear M (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of *N*-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci USA 89: 4363–4367 with permission.)

recognition of a novel environment in rats correlates well with the facilitation of homosynaptic NMDAR-dependent CA1 LTD. Hippocampal LTD is also enhanced by stress, which may be significant in stress-induced cognitive impairment. Overall, evidence suggests that LTD in the hippocampus is associated with at least certain forms of learning and memory (Massey and Bashir 2007).

LTD in the Ventral Tegmental Area (VTA)

The VTA is a midbrain nucleus containing dopaminergic neurons that project to the ventral striatum and the prefrontal cortex, along with nondopaminergic projection and local circuit neurons, some of which are GABAergic. Ascending mesocorticolimbic dopaminergic pathways along with nigrostriatal pathways play a role in internally

generated movements, motivation and reward processing, learning, and cognitive functions, including nondeclarative forms of learning and memory. From a psychopharmacological perspective, these pathways are interesting because they are targets for drugs of abuse and are likely target sites for ▶ anti-psychotic drugs.

A substantial body of literature suggests that glutamatergic synaptic plasticity in dopaminergic pathways may contribute to reward-related learning and the neuronal plasticity mechanisms underlying drug ▶ addiction (reviewed by Kauer and Malenka 2007; Wolf et al. 2004). Persistent forms of synaptic plasticity have been described in dopaminergic pathways (reviewed by Kauer 2004; Kauer and Malenka 2007; Wolf et al. 2004). A form of LTD at glutamatergic synapses was first described in VTA dopaminergic neurons in 2000. This form of VTA LTD was not dependent on either NMDARs or mGluRs, but did require an increase in intracellular Ca^{2+}, most likely via influx through voltage-gated Ca^{2+} channels, subsequent activation of a novel signaling mechanism utilizing protein kinase A, and downregulation of AMPARs. A second form of mGluR-dependent LTD is also expressed in VTA (Bellone and Lüscher 2006).

VTA LTD has been proposed as a potential "brake" on dopaminergic neuron excitability (Kauer 2004), as weakening excitatory synaptic strength would limit the tonic and phasic excitatory drive to these neurons from cortical and brainstem regions, potentially minimizing opportunities for synaptic strengthening such as ▶ long-term potentiation. Removal of this "braking" mechanism is a plausible route for psychoactive drugs to manipulate synaptic plasticity in dopaminergic pathways and drive forms of learning that may be dysfunctional, such as habit learning in drug addiction.

Impact of Psychoactive Drugs

Hippocampal LTD, Cognitive Dysfunction, and Cognition-Enhancing Drugs

Evidence supports the idea that LTD may contribute to cognitive dysfunction. For example, soluble ▶ amyloid-beta protein (Aβ) extracted from the brains of ▶ Alzheimer's disease patients enhances hippocampal mGluR-dependent LTD and disrupts the memory of learned behavior in rats (Shankar et al. 2008). Mouse models of ▶ Huntington's disease, a neurological disorder involving cognitive dysfunction, exhibit impairments in CA1 hippocampal LTD as well as behavioral deficits in hippocampal ▶ spatial learning tasks (e.g., Murphy et al. 2000). NMDAR-dependent hippocampal LTD is both necessary and sufficient to cause an acute ▶ stress-induced impairment of ▶ spatial memory retrieval and may be involved in mediating some of the cognitive deficits that occur in disorders whose symptoms are aggravated by stress (reviewed by Massey and Bashir 2007). Taken together, these data suggest an underlying role for the mechanisms of hippocampal LTD in some aspects of cognitive dysfunction associated with specific neurological disorders.

Mechanisms underlying hippocampal LTD serve as possible drug targets for the treatment of cognitive dysfunction. For example, 17beta-estradiol ameliorates cognitive and memory dysfunction in postmenopausal women in addition to minimally suppressing hippocampal LTD in adult rats, suggesting that estrogen may act to improve memory by suppressing forgetfulness via a synaptic mechanism such as LTD (Vouimba et al. 2000). The NMDAR co-agonist D-serine enhances ▶ NR2B-dependent hippocampal LTD and reversal learning in the ▶ Morris water maze, supporting a role for NMDAR-dependent LTD in spatial learning, and highlighting molecular components of the LTD mechanism as targets for cognition-enhancing drugs.

VTA LTD and Psychoactive Drugs

VTA LTD is blocked by dopamine D2 (but not D1) receptor agonists (reviewed by Wolf et al. 2004), and therefore may be targeted by drugs of abuse that cause an increase in extracellular dopamine levels in the VTA. This has been shown for ▶ amphetamine, which blocks and reverses the somatodendritic ▶ dopamine transporter, thus causing release of dopamine within the VTA. One might expect that D2 receptor antagonists, such as many of the anti-psychotic drugs used to treat ▶ schizophrenia, could potentially enhance VTA LTD. However, comprehensive testing of the antipsychotic drugs used in clinical practice against VTA LTD has not been carried out.

If VTA LTD acts as a "brake" on the excitability of dopaminergic neurons (Kauer 2004), inhibiting LTD may provide a window of opportunity for synaptic strengthening. This ▶ synaptic plasticity would be associated with the salient event that caused elevated levels of extracellular dopamine in the VTA – for example, acquisition of novel reward information, or the presence of a drug of abuse. Such associations may contribute to the learning of procedural information with respect to drug-seeking and drug-taking behaviors that are, one might argue, maladaptive forms of memory. Conversely, induction of VTA mGluR-LTD reverses the ▶ cocaine-induced

strengthening of glutamatergic synapses in dopaminergic neurons, and is a putative mechanism for reversing the neuronal plasticity induced by cocaine (Bellone and Lüscher 2006).

Cross-References

- ► Addictive Disorders
- ► Antipsychotic Drugs
- ► Classical Pavlovian Conditioning
- ► Cocaine
- ► Cognitive Enhancers
- ► Declarative Memory
- ► Endogenous Cannabinoids
- ► Excitatory Amino Acid
- ► Long-Term Potentiation
- ► Memory
- ► Operant (Behavior)
- ► Spatial Memory
- ► Stress
- ► Synaptic Plasticity
- ► Working (Short-Term) Memory

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Long-Term Memory

Definition

A protein synthesis-dependent type of memory in charge of maintaining acquired information in a long-lasting manner.

Cross-References

- ► Protein Synthesis as a Mechanism of Memory

Long-Term Potentiation

Synonyms

LTP

Definition

The process by which simultaneous stimulation of two or more neurons induces a long-lasting improvement in the efficacy of the communication between them. A brief and rapid series of stimulation of axons can lead to a long-lasting potentiation of the response of the postsynaptic neurons to a new input. The duration of the potentiation varies from minutes or hours in brain slices and (more rarely) up to weeks in intact animals. It is especially associated with glutamatergic synapses that lasts many hours.

Cross-References

- ► Long-Term Potentiation and Memory
- ► Synaptic Plasticity

Long-Term Potentiation and Memory

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Definition

Memory is central to our understanding about ourselves with a personal history, and consequently memory loss has a devastating impact on both the individual concerned and their carers. Thus, one of the major goals in neuroscience is to understand the neural mechanisms that underlie the formation of memory within different brain

regions. ►Long-term potentiation (LTP), which is the long-lasting increase in synaptic strength produced by trains of stimuli, has been proposed to provide a suitable cellular model of information storage in the brain. This argument is based on the defining characteristics of LTP (i.e., specificity, associativity, and persistence) and the demonstration that psychoactive drugs that block LTP have been shown to impair memory. This chapter presents the evidence that the mechanisms that underlie LTP may be the same as those that are responsible for the formation of memory, with a focus on the impact of specific pharmacological manipulations. Memory formation clearly relies on fast, long-lasting changes in the connections between neurons; however, whether LTP, as per current studies, underlies learning and memory is still unproven and consequently a matter for ongoing debate.

Impact of Psychoactive Drugs

Any neural mechanism underlying learning and memory must involve processes that enable rapid but lasting changes in the efficacy of synaptic connections in the brain. Hebb (1949) famously proposed that memories may be stored in the brain through changes in the strength of communication between neurons. He postulated that "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." In 1973, Bliss and Lømo showed that the repeated application of high-frequency stimulation (a tetanus) to the perforant pathway in the ►hippocampus produced a long-lasting increase in the synaptic response to a subsequent single-pulse stimulus. This long-lasting increase in synaptic strength is termed long-term potentiation (LTP).

The Induction of LTP

LTP has been most extensively studied in the CA1 region of the hippocampus, a region significant because damage here results in severe memory impairments in both humans (specifically, impairments in episodic memory) and in animals (spatial and associative memory). At excitatory synapses in this region, there are two subtypes of ionotropic ►glutamate receptor, the ►AMPA and ►NMDA receptor. LTP is known to depend on the activation of ►NMDA receptors, which are not involved in normal synaptic transmission owing to the presence of magnesium in the ion channel pore of the receptor. However, sustained release of glutamate, which occurs during high-frequency stimulation, causes the post-synaptic cell to depolarize, which removes the magnesium ions from the pore of the NMDA receptor, thus enabling the NMDA receptor to become activated. The NMDA receptor is therefore in a position to detect the co-activation of the presynaptic and postsynaptic cells and can act as what has been described as a "coincidence detector" (Collingridge 2004). Following activation of the NMDA receptor, there is an influx of calcium into the postsynaptic cell, which triggers a range of intracellular second messenger systems, the effect of which is to produce an increase in synaptic strength (LTP). Thus, in most synapses that show LTP, the increase in calcium and thus the induction of LTP depend on the activation of NMDA receptors, but note that there are other forms of LTP, for example in the mossy-fiber-CA3 synapses, that do not depend on NMDA receptors (described as NMDA receptor-independent LTP).

LTP, A Cellular Basis for Memory

It has been argued that LTP displays properties that are consistent with the premise that it is a cellular mechanism underlying memory storage (see Collingridge 2004). These properties include the demonstration that LTP is (1) input-specific, (2) associative or cooperative, and (3) persistent. Input specificity refers to the demonstration that only the afferents that have received stimulation show potentiation. Associativity or cooperative refers to the demonstration that if stimulation of one pathway is insufficient for the induction of LTP, simultaneous strong stimulation of another pathway will induce LTP at both pathways. If LTP is to be considered as a model mechanism for the storage of information, it needs to fulfil other criteria; for example, it must be relatively long lasting, although how long it is required to last is still unclear. Further, LTP must be demonstrated in regions of the brain other than the hippocampus, and indeed there is now accumulated evidence that LTP may be induced in brain areas associated with memory including cortex, striatum, thalamus, cerebellum, and amygdala (see Lynch 2004).

One strategy to investigate the link between memory and LTP has been to investigate whether learning produces LTP-like changes. A number of studies have reported that exposure to stimulus-enriched environment or training on learning tasks such as eye-blink conditioning or radial arm maze can result in increases in synaptic strength within the hippocampal formation (see Martin and Morris 2002). In addition, there is increasing interest in the relationship between LTP in the amygdala and a specific form of learning and memory process known as ►fear conditioning. Fear conditioning is a simple Pavlovian conditioning paradigm, which involves pairing a neutral stimulus, for example a tone (the conditioned stimulus, CS) with an aversive stimulus, for example a mild footshock (the

unconditioned stimulus, US). This form of memory is rapidly acquired, the memory is long-lasting, and the paradigm presents an attractive model for investigation of the neural basis of memory as it is relatively simple when compared with the memory paradigms associated with the hippocampus.

There are several lines of evidence to suggest that LTP in the amygdala underlies the formation of fear conditioning memory. For example, first, LTP may be induced in the same sensory afferents to the amygdala, which show enhanced synaptic transmission during fear conditioning, and second, pharmacological and molecular manipulations that block LTP have also been shown to block the acquisition of fear conditioning (see below). It has also been demonstrated that both LTP and fear conditioning are dependent on the reliability of the CS to predict the US (known as CS–US contingency). Thus, in fear conditioning paradigms, it is well reported that if the CS does not accurately predict the US, or if there is a better predictor, for example other environmental cues, then the memory will be weaker. Similarly, in electrophysiological experiments, it has been shown that when a train of high-frequency stimuli applied to the afferents of the amygdala, were paired with a series of depolarizing current pulses to the postsynaptic cell in the lateral amygdala, robust LTP was produced. However, if a further, unpaired, depolarization was added 10 s after the pairing, no LTP occurred (see Martin and Morris 2002).

Different Forms of LTP may Subserve Different Memory Processes

Further evidence to support the link between LTP and memory is provided by the demonstration that neither LTP nor indeed the formation of a memory is a single process. Different forms of LTP have been described, depending on how long the increase in synaptic efficacy lasts and the degree to which each form of LTP is sensitive to receptor antagonism, dependent on protein synthesis and/or ▶ gene transcription. Broadly, LTP has been divided into two sub-categories: early LTP (E-LTP) and late LTP (L-LTP), where L-LTP lasts for hours in vitro and weeks in vivo. E-LTP (also described as LTP1) decays rapidly, is insensitive to protein synthesis inhibitors, and therefore does not depend on the formation of new proteins in the cell. L-LTP has been further subdivided into LTP2 and LTP3. LTP2 last for an intermediate length of time and depends on new protein synthesis, but not on gene transcription, LTP3 is the long-lasting and most stable component of LTP, which depends on both new protein synthesis and gene transcription (Raymond 2007).

In light of this dissociation between different forms of LTP, mediated by distinct cellular processes, it has been suggested that each may subserve different mnemonic processes. Thus, LTP1 may underlie short-term memory, LTP2 intermediate memory, i.e., memory that lasts up to 3 h, and LTP3 may underlie long-term memory, i.e. memory retained for longer than 3 h (see Blockland and Boess 2008).

The Effects of Pharmacological Agents on LTP and Memory

There is now a vast body of experimental evidence, which has identified pharmacological agents that block both LTP and memory or indeed enhance LTP and memory; hence, a comprehensive review of all such treatments is beyond the scope of this chapter and the reader is referred to the references provided.

Glutamate

NMDA Receptors

One of the first pieces of evidence to suggest that LTP might be required for memory formation in vivo was provided by the demonstration that blockade of ▶ NMDA receptors, by the NMDA receptor antagonist AP5, in the hippocampus, blocks both the induction of LTP and produces an impairment in ▶ spatial learning but not in visual discrimination learning in the rat (see Martin and Morris 2002). Since that initial demonstration, NMDA receptor blockade has been shown to impair a range of hippocampal-dependent memory tasks including T-maze alternation, ▶ contextual fear conditioning, and non-hippocampal-dependent tasks such as fear conditioning. Interestingly, while blockade of NMDAR have been shown to impair both the ▶ encoding and early ▶ consolidation of memory information, and the induction of LTP, blockade of these receptors, has been shown to have no effect on memory ▶ retrieval or on pre-established LTP (Collingridge 2004; Martin and Morris 2002).

▶ Metabotropic Glutamate Receptors

There has been disagreement over the role that metabotropic glutamate receptors (mGluRs) play in LTP. LY341495, an mGluR antagonist, which at certain concentrations antagonizes all known mGlu receptors, has been shown to have no effect on LTP at hippocampal CA1 synapses. In contrast, antagonism of group 1 MGlu receptors has been shown in some studies to block the induction of LTP and blockade of group 1 mGLURs has also been shown to impair a range of behaviors including spatial learning, contextual fear conditioning, and inhibitory avoidance learning (see Lynch 2004).

AMPA Receptors

► Ampakines are a class of compounds, which bind to AMPA receptors but do not show either agonist or antagonist effects. These compounds act to keep the channel open once glutamate has bound, thus prolonging current flow through the receptor. Ampakines have been shown to lower the threshold for the induction of LTP and increase the magnitude of LTP. Behavioral studies have revealed that these compounds improve retention in the ► radial arm maze and improve ► short-term memory (Lynch and Gall 2006).

► Acetylcholine

► Muscarinic Receptors

Acetylcholine muscarinic receptors (mAChRs) are ► G-protein coupled receptors of which there are five subtypes (M_1–M_5). mAChRs have long been implicated in a variety of memory functions, for example ► scopolamine a non-selective mAChR antagonist has been shown to produce significant behavioral impairments in tasks including the water maze, fear conditioning, and ► object recognition. Consequently, the roles of the mAChRs in LTP at many areas of the central nervous system have been extensively studied. Activation of mAChRs has been shown to facilitate the induction of LTP and application of the muscarinic agonist carbacol has been shown to enhance LTP and to improve memory performance (see Blockland and Boess 2008; Shinoe et al. 2005). However, in contrast to such reports, administration of the nonselective mAChR antagonist atropine was found to have no effect on the induction of LTP, although it did significantly reduce the magnitude of the LTP, and scopolamine has been shown to have no effect on the induction of LTP in the perirhinal cortex.

► Nicotinic Receptors

Neuronal acetylcholine nicotinic receptors (nAChRs) are ligand-gated ion channels comprising either α subunits or a combination of α and β subunits, with α7 and α4 β2 being the two main subtypes in the central nervous system. Studies have shown that application of ► nicotine can both induce LTP and enhance LTP produced by sub-threshold levels of stimulation, an effect dependent on both α7 and non- α7 nAChRs. In memory tasks, acute intrahippocampal administration of nicotine after training has been shown to enhance hippocampal-dependent memory, and chronic administration of nicotine has been shown to improve spatial working memory in the radial arm maze however other studies using different doses, dosing methods, and regimes have found conflicting results (see Kenney and Gould 2008).

► Dopamine and Noradrenaline

The neuromodulators dopamine and noradrenaline have been implicated in both LTP and memory. Thus, pharmacological blockade of dopamine D1/D5 receptors has been shown to impair L-LTP in the CA1 region of the hippocampus and to impair long-term but not short-term spatial memory in the water maze while blockade of beta-adrenergic receptors modulates E-LTP (see Martin and Clark 2007). LTP has been produced in the mesolimbic dopamine system, which comprises the ► ventral tegmental area and ► nucleus accumbens and in view of the key role this neural system plays in the behavioral effects of drugs of abuse, there is increasing research into the role of LTP, and other forms of ► synaptic plasticity in the development of addiction (see Saal and Malenka 2005).

Conclusions

There is now a huge body of research attempting to evaluate the hypothesis that LTP is a cellular substrate for learning and memory, and clearly much of this evidence has been obtained from pharmacological studies like those described above. However, such evidence is correlative, and although both LTP and memory may be disrupted by the same interventions, this does not prove that both processes are mediated by the same underlying mechanisms. For example, it has been argued by some investigators that the observed impairments in the water maze following NMDA or muscarinic receptor blockade might be accounted for by impairments in sensorimotor processes, or that LTP might play a role in cognitive processes other than memory, for example attention, that contribute to performance in behavioral tasks (see Martin and Morris 2002). Further, LTP is often studied in vitro, using highly artificial stimulation protocols; so, while the processes that produce LTP in the laboratory may provide valuable insights into synaptic physiology, it must be remembered that they do not represent the actual mechanism for the storage of information in vivo.

Thus, while the acquisition and consolidation of memory must require quick and long-lasting changes in neural circuitry, a definitive link between LTP and the engram has not yet been provided.

Cross-References

► Excitatory Amino Acids and Their Antagonists
► Muscarinic Agonists and Antagonists
► Nicotinic Agonists and Antagonists

► Spatial Learning in Animals
► Synaptic Plasticity

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Long-Term Treatments for Bipolar Disorder

► Mood Stabilizers

Loprazolam

Definition

Loprazolam is a high-potency medium-acting benzodiazepine medication used in the treatment of sleep disorders. It has some antispasmodic and anticonvulsant effects. It is not antidepressant. 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: loprazolam is a scheduled substance.

Cross-References

► Benzodiazepines
► Insomnias
► Minor Tranquilizers

Lorazepam

Definition

Lorazepam is a ► benzodiazepine that has anxiolytic, sedative, and anticonvulsant properties. Its duration of action is of intermediate length relative to other benzodiazepines (i.e., its ► elimination half-life is 10–18 h) and it does not have active (i.e., benzodiazepine) metabolites. Lorazepam is used primarily to treat anxiety, including panic. Like most similar compounds, it is subject to tolerance, dependence, and abuse.

Cross-References

► Anxiolytics
► Benzodiazepines

Lormetazepam

Synonyms

Methyl-lorazepam

Definition

Lormetazepam is a benzodiazepine medication that has anxiolytic, sedative, and anticonvulsant properties. Its duration of action is of intermediate length relative to other benzodiazepines (i.e., ► elimination half-life 10–12 h) and it does not have active (i.e., benzodiazepine) metabolites. It has been used clinically as a hypnotic. Like most similar compounds, lormetazepam is subject to tolerance, dependence, and abuse.

Cross-References

► Anxiolytics
► Benzodiazepines
► Hypnotics

Love Drug

► Methylenedioxymethamphetamine (MDMA)
► Oxytocin

Love Hormone

- ▶ Methylenedioxymethamphetamine (MDMA)
- ▶ Oxytocin

LQTS

- ▶ Long QT Syndrome

LSD

- ▶ Hallucinogen Abuse and Dependence
- ▶ Hallucinogens

LTD

- ▶ Long-Term Depression and Memory

LTP

- ▶ Long-Term Potentiation

LY127809

- ▶ Pergolide

LY139603

- ▶ Atomoxetine

Lysergic and Diethylamide

- ▶ Hallucinogen Abuse and Dependence
- ▶ Hallucinogens