Antidepressant Treatment in Anxiety Disorders

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Contents

Abstract Antidepressant drug treatment is the clinical standard of care for all types of anxiety disorders. Broad efficacy of selective serotonin reuptake inhibitors suggests the importance of enhanced serotonergic function of the anxiolytic properties of current antidepressants. However, analysis of the preclinical evidence

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indicates that most conventional “anxiolytic” drug tests are not sensitive to antidepressants. Such dissociation is not surprising because of the traditional approach to validation of preclinical tests that is to a large extent based on establishing face validity as well as sensitivity to benzodiazepine anxiolytics. The present review argues for extending the cognitive model of antidepressant drug action to cover their anxiolytic properties as well. Such an approach is based on ambiguity or uncertainty in a broad sense as the hallmark of human stress that has different expressions ready for experimental modeling. These possibilities include schedule-induced behaviors that are directly based on intermittent reinforcement, conditioning to ambiguous stimuli, social stress where agonistic confrontations are possible but not predictable or controlled by the subject, and an even larger class of behaviors that are critically dependent on the inhibition of the prepotent responses in exchange for the ambiguous possibility of a later gain in reinforcement. Interestingly, in all these cases, antidepressant drug treatment is clearly effective in preclinical laboratory settings. One of the cognitive functions that appears to be affected by antidepressant drugs is inhibitory control. Inhibition of prepotent responding has beneficial effects in the “uncertainty” stress situations discussed above and therefore it is this cognitive function that may be critical for anxiolytic effects of antidepressants and novel anxiolytic drug development.

Keywords Antidepressant drugs · Anxiety · SSRI · Preclinical models

1 Introduction

In the last four decades of the last century, pharmacological therapy of anxiety disorders had been dominated by benzodiazepines. Due to their efficacy in acute and chronic treatment of a variety of anxiety states, they were classified as anxiolytic drugs, whereas the term “antidepressant drugs” was reserved for monoamine reuptake (e.g., tricyclics) and monoamine oxidase inhibitors (MAO-Is). As a consequence, GABAergic function was mainly linked to anxiety, whereas serotonergic and noradrenergic functions were linked to depression – in line with the respective monoamine theory. The development of animal models only responding to either anxiolytic or antidepressant drugs further contributed to this dichotomy. However, there is considerable overlap of symptoms in depression and anxiety disorders and high comorbidity, which is explained by shared genetic risk factors (Hettema 2008).

Benzodiazepines have proven efficacious in generalized anxiety disorder (GAD), panic disorder (PD) and social anxiety disorders (SADs). They are particularly appropriate in short-term treatment situations and thus still belong to the current therapeutic repertoire. However, their inability to treat comorbid depression, their adverse side-effect profile – including sedation, cognitive impairment and especially their liability to induce dependence and abuse – have limited their acceptance (Uhlenhuth et al. 1999a, b).

Early in the 1960s, before DSM-III or later DSM-IV criteria were established, first observations of anxiolytic effects of the prototypical tricyclic antidepressant imipramine and non-selective irreversible MAO-Is, like phenelzine, were published. This was followed later by similar reports on clomipramine. In contrast to benzodiazepines, the onset of anxiolytic action of these antidepressants was delayed as known for their antidepressant effect. While most tricyclic antidepressants inhibit neuronal reuptake of serotonin (5-hydroxytryptamine, 5-HT) as well as of noradrenaline (norepinephrine, NE), it is noticeable that anxiolytic efficacy was repeatedly demonstrated in controlled clinical studies only for non-selective NE/5-HT antidepressants and for clomipramine with its preference for the serotonin transporter. In contrast, antidepressants preferentially or selectively inhibiting NE uptake, like desipramine, nortriptyline, maprotiline, mianserin, and reboxetine, have not been shown to possess broad anxiolytic properties. This suggested that it is the serotonergic component that probably mediates the delayed anxiolytic response of tricyclic antidepressants and MAO-Is.

Despite the increasing evidence of efficacy in different anxiety disorders and the obvious lack of drug abuse liability, untoward effects like tyramine interaction for MAO-I, the many effects mediated by the autonomic nervous system, and antihistamine effects in tricyclic antidepressants clearly limited broader use in anxiety disorders. This situation changed with the introduction of selective serotonin reuptake inhibitors (SSRIs), which offered largely improved tolerability and efficacy proven in many controlled clinical studies. SSRIs are now recommended as the first-line medication for GAD, PD, SAD as well as for post-traumatic stress disorder (PTSD) and obsessive–compulsive disorder (OCD) in most recent European and US treatment guidelines (e.g., Bandelow et al. 2008).

The present review focuses on clinical and preclinical evidence, which suggests anxiolytic properties of antidepressant drugs and analyzes the mechanisms that are likely to be behind such properties.

2 Clinical Evidence on Anxiolytic Activity of Antidepressant Drugs

2.1 Generalized Anxiety Disorder

Antidepressants of different classes are in clinical use for the treatment of GAD (for review see Bandelow et al. 2008; Fricchione 2004; Hoffman and Mathew 2008). Due to the fact that major depression is the most common comorbid condition in GAD patients, tricyclic antidepressants like imipramine and amitriptyline drugs have long been used in this patient population, although initially it remained unclear to what extent antidepressant or genuine anxiolytic properties were responsible for treatment responses (Kahn et al. 1987).

In patients without major depression, Rickels et al. (1993) found that diazepam showed the most improvement in anxiety ratings during the first 2 weeks of treatment; in contrast, antidepressant drugs achieved comparable (trazodone) or even somewhat better efficacy (imipramine) after 3–8 weeks of treatment. Among completers, the most discernible improvements were seen with imipramine. Imipramine also significantly facilitates benzodiazepine discontinuation in patients with GAD (Rickels et al. 2000). Systematic clinical investigations in controlled and sufficiently powered clinical studies of other tricyclic antidepressants, selective or non-selective NE reuptake inhibitors, and selective or non-selective MAO-I are missing for GAD. The same is true for non-tricyclic agents with different pharmacologic profiles: bupropione (a mixed NE and dopamine reuptake inhibitor), mianserin and mirtazapine (α_2-adrenoceptor antagonists enhancing NE and 5-HT release and blocking 5-HT_{2A} and 5-HT_{2C} receptors), and nefazodone (a 5-HT_2 and histamine H_1 antagonist).

For many SSRIs, efficacy similar to that of imipramine was found in several randomized placebo-controlled studies in GAD (for review see Hoffman and Mathew 2008). For instance, it was shown that SSRIs led to reduction in clinical anxiety ratings after 8 weeks of treatment (Davidson et al. 2004; Rickels et al. 2003) and prevented relapse when treatment continued for 6 months (Allgulander et al. 2005; Stocchi et al. 2003). From existing clinical trials it remains unclear whether the therapeutic effect of paroxetine and escitalopram is a class effect and can be generalized to all other SSRIs. However, from available evidence, SSRIs like sertraline seem to exert a similar therapeutic effect in GAD (Allgulander et al. 2004; Dahl et al. 2005).

Venlafaxine and duloxetine are classified as selective serotonin and noradrenaline reuptake inhibitors (SNRIs). Due to the serotonergic component of their pharmacological profile it could be expected that their clinical profile would replicate that of SSRIs. Indeed, both medications were equally effective in placebo-controlled studies (e.g., Hartford et al. 2007) and are approved for the treatment of GAD. Like in depression, there is an impression that the onset of efficacy of SNRIs may be faster than that for other antidepressants. However, the extent to which NE reuptake inhibition contributes to the therapeutic effect remains unknown. In vitro, both SNRIs have more than tenfold higher affinity for the human 5-HT transporter compared to the human NE transporter (Bymaster et al. 2001). Blockade of the 5-HT transporter alone would be sufficient to explain anxiolytic effects and there are no clinical studies unequivocally demonstrating superior efficacy of SNRIs in comparison to SSRIs. Like in other anxiety disorders, treatment of GAD with SSRIs or SNRIs should usually be continued for 6–12 months, although objective clinical data are sparse (Fricchione 2004).

2.2 Panic Disorder

Up to 80% of patients with PD have experienced major stress events (Manfro et al. 1996) and 90% have at least one comorbid psychiatric disorder in their lives – often

depressive episodes (Kessler et al. 2005). These facts may explain why all classes of antidepressants have been investigated in patients with this disease. It is currently believed that tricyclic antidepressants and SSRIs are at least equivalent in their efficacy to benzodiazepines (for review see Bandelow et al. 2008; Hoffman and Mathew 2008; Katon 2006).

Among tricyclic antidepressants, imipramine and clomipramine were effective in placebo and comparator-controlled studies, reducing the number of panic attacks and the severity of anxiety. In comparison to benzodiazepines, their effect is delayed for about 4 weeks, with maximal efficacy taking up to 12 weeks. Although it has been suggested that all tricyclics may be similarly effective, both imipramine and clomipramine are potent 5-HT reuptake inhibitors, whereas desipramine, a preferential NE reuptake inhibitor, was not convincingly superior to placebo (Lydiard et al. 1993). Similarly, in a small non-placebo-controlled study, the non-tricyclic NE reuptake inhibitor maprotiline failed to reduce the frequency of panic attacks (den Boer and Westenberg 1988).

Non-selective irreversible MAO-I like phenelzine and tranylcypromine with their unfavorable side-effect profile are considered to have therapeutic potential for PD with or without agoraphobia, at least as second-line medication. However, only one phenelzine study showed superiority over placebo and equal efficacy to imipramine in the treatment of "phobic neurosis" (Sheehan et al. 1980). The impression that MAO-Is are more potent antipanic agents than tricyclics has never been proven in clinical studies. The efficacy of moclobemide, a reversible and MAO-A-selective inhibitor has never been unequivocally established in sufficiently large placebo-controlled trials.

SSRIs are by far the most prescribed class of antidepressants in PD. They are significantly more effective than placebo in reducing the number of panic attacks as well as in reducing global anxiety and a significant percentage of treated patients become panic-free (for review see Hoffman et al. 2008). Efficacy has been shown for all clinically used SSRIs (citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline) as well as for the SNRI venlafaxine. Its efficacy in placebo-controlled trials was equivalent to that of paroxetine; it reduced the frequency of attacks and prevented relapse (e.g., Pollack et al. 2007). As for GAD (see above), there is a doubt whether the noradrenergic component contributes significantly to venlafaxine's efficacy and superiority of venlafaxine over SSRIs is not established. For the selective NE reuptake inhibitor reboxetine, there are some hints of efficacy in PD (Versiani et al. 2002), but rigorous data in placebo-controlled sufficiently powered clinical studies are still missing for reboxetine just as for a number of other interesting drugs such as duloxetine, buproprion, nefazodone, and mirtazapine.

2.3 Social Anxiety Disorder

SAD, also known as social phobia, has a high lifetime prevalence of 12%, and comorbid psychiatric diseases, especially major depression, other anxiety disorders

and alcohol abuse are frequent (Kessler et al. 2005; Stein and Stein 2008). Benzodiazepines and beta-adrenoceptor antagonists, such as propranolol, are often used for non-generalized symptoms and in predictive situations, like public speaking, although evidence of efficacy is more limited than in other anxiety diseases (Schneier 2006). SSRIs and SNRIs are now commonly used as first-line pharmacological therapy (Bandelow et al. 2008; Hoffman and Mathew 2008; Schneier 2006; Stein and Stein 2008).

In contrast to GAD and PD, efficacy of tricyclic antidepressants has never been established. A small double-blind study comparing clomipramine with diazepam suggested efficacy of this preferential 5-HT reuptake inhibitor (Allsopp et al. 1984), but this has not been confirmed in a larger trial. An open trial with imipramine did not support its use in social anxiety (Simpson et al. 1998). In contrast, there is evidence from several studies that the irreversible MAO-Is such as phenelzine and tranylcypromine are efficacious in social anxiety (e.g., Stein et al. 2004; Versiani et al. 1988). The reversible MAO-A inhibitor moclobemide has been reported initially to be superior to placebo and comparable to phenelzine – a finding that has not been consistently confirmed in later studies (Stein et al. 2004).

The largest database concerning efficacy of pharmacological treatment of SAD exists for many SSRIs and venlafaxine as an SNRI. Many large studies proved higher response rates of 50–80% for citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, and venlafaxine (for review see Hoffman and Mathew 2008; Schneier 2006; Stein and Stein 2008). Most studies investigated efficacy within 12 weeks of treatment, but relapse prevention trials with escitalopram, paroxetine, and sertraline proved their superiority over placebo also in an extended time frame of 24 weeks (e.g., Montgomery et al. 2005). Although several head-to-head comparison studies have been carried out among SSRIs and with venlafaxine, there is little reason to assume clear superiority of one compound over the other within this pharmacologic class (Stein and Stein 2008). The fact that venlafaxine shows comparable efficacy at lower doses, which preferentially inhibit 5-HT reuptake, and at higher doses, which in addition may block NE uptake, suggests that the influence on the serotonergic system is more relevant for efficacy than an effect on the noradrenergic system (Stein et al. 2005). This is in line with the fact that no studies reporting efficacy of preferential or selective NE reuptake inhibitors in SAD have been published.

2.4 Post-Traumatic Stress Disorder

Among all anxiety disorders, PTSD is the least studied and is characterized by the smallest effect sizes for currently available antidepressants. Only paroxetine and sertraline are approved for this indication, but Expert Consensus Guidelines on the treatment of PTSD consider switching to nefazodone or venlafaxine, when these medications fail (Foa et al. 1999). The general finding is that paroxetine and sertraline are superior over placebo and patients improve in all three symptom

Table 1 Recommended use of antidepressant drugs for the treatment of anxiety disorders (based on Bandelow et al. 2008)

Anxiety disorder	TCA	MAOI	SSRI	SNRI	NRI
GAD	++		++	++	
Panic attacks	++	+	++	+	+
Social phobia		+	++		
PTSD	+		++		
OCD	++		++		

++ first-line treatment; + second-line or supportive treatment

clusters (hyperarousal, re-experiencing, avoidance/numbing) (e.g., Marshall et al. 2001). Among older antidepressants, imipramine and phenelzine were reported to be superior over placebo; therapeutic potential of other drugs such as mirtazapine needs to be confirmed (for review see Hoffman and Mathew 2008).

2.5 Obsessive–Compulsive Disorder

Although OCD is phenotypically different from other anxiety disorders and is primarily characterized by the presence of costly obsessions and compulsions causing marked distress, pharmacological treatment options include clomipramine and various SSRIs (see Schruers et al. 2005 for review). While non-serotonergic agents are not considered as first-line therapy and may not be effective as a stand-alone treatment, dopaminergic and norepinephrinergic drugs often contribute to augmentation strategies in 40–60% of patients with OCD who do not respond to SSRIs.

As summarized in Table 1, anxiety disorders respond to different classes of antidepressant drugs. Most of these drugs have shown superiority over placebo, but there are only few clinical studies that clearly differentiate efficacies of compounds within one class of drugs. A clear dominance of SSRIs has developed over the last 10–15 years. They are indeed effective in all forms of anxiety, but they are not necessarily more efficacious than older antidepressants. Their extensive clinical use is mainly based on their favorable tolerability. It is to be noted that all these antidepressants share similar mode(s) of pharmacodynamic action: direct or indirect influence on serotonergic and/or noradrenergic neurotransmission. The broad efficacy of SSRIs clearly demonstrates that enhanced serotonergic function – but not necessarily enhanced noradrenergic function – is crucial for the anxiolytic properties of current antidepressants. It remains to be established, if new antidepressant principles in development, like agomelatine, a melatonin MT_1 and MT_2 receptor agonist with additional 5-HT_{2C} antagonism[1] (Olié and Kasper 2007), or drugs affecting the hypothalamus–pituitary–adrenal gland axis, like antagonists of

[1]First clinical reports suggested efficacy in the treatment of GAD but this evidence needs to be further extended by additional studies, with active comparisons as well as over longer periods of time (Stein et al. 2008).

the corticotropin releasing factor (CRF) receptor 1[2] or the vasopressin V1b receptor, will be effective in anxiety disorders.

3 Preclinical Evidence

3.1 Is Anxiolytic Activity Predicted by Efficacy in Classical Antidepressant Tests?

The most used high-throughput screening models employed to detect antidepressant-like activity are the forced swim test and the closely related "dry" version, tail suspension test. These tests are based on the observations of Porsolt et al. (1977) that rats, when forced to swim in a restricted space from which they cannot escape, will eventually cease apparent attempts to escape and become immobile apart from the small movements necessary to keep their heads above the water. Several hypotheses have been suggested to explain why animals stop struggling – e.g., behavioral despair, fatigue or saving energy for survival. None of these hypotheses make it easy to relate the immobility response to the clinical symptoms of depression or anxiety disorders, and therefore such tests conducted in standard healthy laboratory animals clearly lack face and construct validity. At the time these tests were developed, knowledge of the anxiolytic effects of antidepressants was still rather limited. Therefore, the tests were labeled as being able to detect antidepressant-like properties of drugs, and this is indeed supported by most antidepressants showing efficacy in these tests. Thus, despite several false positives described (e.g., Nagatani et al. 1987; Wieland and Lucki 1990), these tests are usually said to have certain predictive validity.

The question remains, however, whether efficacy in these tests predicts antidepressant activity, anxiolytic activity, or just (sub)acute effects on release of neurotransmitters such as noradrenaline and/or serotonin. Given that clinical efficacy of antidepressants is seen typically after at least 2–3 weeks of treatment, the latter seems to be the more likely.

Similar to what is said above about the "behavioral despair" tests, other commonly used tests to detect antidepressant-like activity do not seem to provide information on potential anxiolytic activity. First, there are drugs that lack meaningful anxiolytic properties in the clinic but nevertheless are found to be fully efficacious in preclinical studies evaluating antidepressant-like activities. Second, benzodiazepine anxiolytic drugs that are effective in the treatment of anxiety disorders usually produce no appreciable effects in the antidepressant tests.

[2]First clinical studies indicated lack of clinical efficacy of CRF1 antagonists in the treatment of GAD (Coric et al. 2008; see also Steckler*** 2009). However, it may be too early to interpret this evidence because, even successful drug classes like SSRIs took several clinical trials to firmly establish their clinical usefulness.

Thus, taking all available evidence together, one comes to the conclusion that commonly used antidepressant tests are not suited for detecting anxiolytic drug activity.

3.2 Efficacy of Antidepressant Drugs in Classical "Anxiolytic" Tests

A great variety of preclinical models that allow assessment of anxiolytic drug potential are thought to exist. While they can hardly be grouped based on the potential relevance to clinical anxiety categories (however, see Sects. 3.3–3.5 for comments on animal models of PD, PTSD and social anxiety), they are easily grouped into a small number of categories based on the operating behavioral mechanisms (e.g., Griebel 1995).

3.2.1 Ethological Models: Exploratory Activity

This category includes several very popular and frequently used tests such as elevated plus maze, zero maze, open field, and light-dark box. The members of this category have a common trait in that they represent easy to administer, single-trial short tests that are based on the exploration of a novel territory that consists of non-aversive and aversive parts (e.g., dark versus light compartments in the light-dark box; closed versus open arms in the elevated plus maze, etc.). Overall, no consistent effects of antidepressant drug treatment were found in these tests. For example, in the elevated plus maze – one of the most widely used models to study effects of antidepressants on anxiety-related behavior – the majority of the studies reported no effects of antidepressant on anxiety-related behavior both after acute or chronic application (see Borsini et al. 2002 for review). In fact, some studies even reported anxiogenic-like responses to antidepressant drug administration.

3.2.2 Ethological Models: Social Behavior

This group consists of models based on social contacts and communication such as social interaction, social competition, or ultrasonic calling. Social interaction under bright light conditions is one of the most popular representatives of this category and is reported to reliably detect effects of benzodiazepine anxiolytics; antidepressants of different classes, however, produce mixed effects. One chronic study with paroxetine resulted in anxiolytic-like effects after 3 weeks of treatment (Lightowler et al. 1994), but studies with chronic administration of other antidepressants (including more members of the SSRI class) did not reveal any meaningful effects (e.g., File et al. 1999).

3.2.3 Unconditioned Stress-Induced Responses

A third subcategory consists of models in which stress-induced alteration of behavior or physiological responses are studied. While stress does seem to be a common denominator, this group is clearly very heterogeneous. Most of these stress-based procedures such as stress-induced hypothermia fail to detect anxiolytic-like potential of antidepressant drugs. However, all classes of antidepressants demonstrate efficacy against isolation-induced vocalizations in guinea pig pups (see Borsini et al. 2002 for review). In rat pups though, acute application of drugs that affect the serotonergic system appear to be effective, whereas compounds that affect the noradrenergic system exert opposite or no effects (e.g., Hodgson et al. 2008). One potential drawback of this model is that the blood brain barrier is not fully developed in pups, which makes it less suitable for screening purposes. An alternative model in adult animals is based on the vocalizations induced by mild electroshock. Such vocalizations are sensitive to acute treatment with SSRIs, clomipramine, imipramine, but not desipramine or maprotiline (see Borsini et al. 2002 for review). Similar readout (vocalizations) and sensitivity to antidepressant treatment make isolation distress calls and electroshock-induced vocalizations look similar. However, one should keep in mind that drugs may suppress vocalizations via various mechanisms including non-specific ones (e.g., sedation, analgesia) and the value of these methods in detecting novel anxiolytics is not firmly established.

3.2.4 Conditioned Fear Tests

Conditioned fear tests include models such as fear-potentiated startle but may also be extended to cover shock rod burying, active/passive avoidance, etc. Overall, no single model is found to convincingly detect antidepressant drugs with anxiolytic-like activity. However, certain members of this category do show significant promise in this regard. In the shock-conditioned freezing paradigm, SSRIs have been reported to exert lasting anxiolytic-like effects while NE reuptake inhibition is not expected to share these effects (e.g., Hashimoto et al. 2009; Inoue et al. 2006). Certain modifications of the fear conditioning protocol can make it even more attractive. For example, one may manipulate the contingency between shocks and to-be-conditioned stimuli in such a way that the latter become only partially predictive of shocks and therefore are less effective in eliciting freezing during the test. Tsetsenis et al. (2007) demonstrated that stimulation of 5-HT1A receptors in hippocampus reverses enhanced fear conditioning to such ambiguous stimuli – a hallmark of human anxiety – in 5-HT1A knockout mice. Because of the expected up-regulation of 5-HT neurotransmission, repeated administration of antidepressant drugs is expected to have an opposite effect – i.e., reduced conditioned responding to ambiguous cues.

3.2.5 Conflict Tests

In tests such as the Geller-Seifter's or Vogel conflict test, positive reinforcement contingency (food or water) is concurrent with a mild shock delivery schedule representing a punishment contingency. Overall, while classical benzodiazepine anxiolytics are very effective in these tests, antidepressant drugs are generally not active (see Borsini et al. 2002 for review). Lack of efficacy of antidepressants in these tests is quite noteworthy given the above mentioned effects of these agents on shock-induced vocalizations. Thus, it appears that while antidepressant drugs attenuate expression of behaviors directly elicited by the aversive events (i.e., vocalizations), they do not affect the behavioral significance of these events (i.e., as assessed by the response rates on the concurrent positive reinforcement schedule).

3.3 Animal Models of Panic Attacks

There are several approaches to preclinical modeling of panic attacks. The most straightforward approach is based on the views of panic attacks being simply extreme cases of anxiety. For example, a classical elevated plus maze can be modified by making it unstable and to elicit unconditioned flight/escape behaviors in rats. This new quality was associated with the gain of sensitivity to chronic, but not acute, treatment with fluoxetine (Jones et al. 2002). Alternatively, extreme anxiety in mice is readily evoked by exposure to a natural threat (a rat). Defensive and avoidance behaviors displayed by mice under conditions of the so-called mouse defense test battery are attenuated by chronic treatment with antidepressant drugs, illustrating once again the efficacy of these drugs against extreme anxiety states (see Blanchard et al. 2003 for review).

Elevated anxiety levels may also be produced by acute treatment with anxiogenic drugs such as pentylenetetrazole or electrical stimulation of brain areas implicated in the regulation of fear and escape behaviors such as dorsal periaqueductal grey. Due to its robustness and reliability, the latter becomes increasingly popular for modeling panic attacks in preclinical settings. Pharmacological studies indicate that both SSRIs such as citalopram, fluoxetine, or paroxetine, and the benzodiazepines like alprazolam reduce the flight-like escape behaviors produced by electrical stimulation of the dorsal periaqueductal grey in the rat (Hogg et al. 2006). Efficacy of SSRIs does not seem to require subchronic administration that somewhat alleviated the validity arguments for this method.

3.4 Animal Models of Social Anxiety

Reviews of the clinical signs and symptoms of social anxiety tend to suggest that this disorder can hardly be modeled in laboratory animals. Indeed, it seems difficult to imagine animal models of socially determined dysphoric ruminations, one of the

distress types found in patients with social phobia. Social nature of this disorder dictates the use of social hierarchy-derived stressors in preclinical models. Several research groups observed that (sub)chronic treatment with antidepressants enhances aggressive behavior of subdominant and subordinant rats and mice, indicative of elevated social position (Malatynska et al. 2005; Mitchell 2005).

An alternative approach relies on identification of the core operating mechanisms that underlie development and expression of social anxiety. For example, anticipatory anxiety, another distress type associated with social phobia, may have mechanisms based on classical conditioning and could therefore be amenable to preclinical modeling. The phobic symptoms associated with social phobia overlap greatly with those of other anxiety disorders (e.g., specific phobias), while patients with social phobia may have characteristics conventionally associated with other anxiety disorders (e.g., enhanced anxiety reactions to high concentrations of CO2, caffeine, or cholecystokinin; Nutt et al. 1998). Collectively, this evidence suggests that preclinical models do not necessarily have to involve social stressors.

Further, conditioned fear has long been acknowledged as an important etiological mechanism in social anxiety and clinical evidence indeed supports enhanced conditionability of aversive socially specific stimuli (Lissek et al. 2008). While the preclinical models for such social fear conditioning are still to be developed (e.g., based on the use of distress-specific ultrasound vocalizations), there are no reasons to believe that drugs that reduce conditioned fear in the conventional paradigms will not affect socially specific conditioned fear. This expectation relies at least in part on the available evidence indicating that clinically effective drugs (SSRIs, MAO inhibitors) attenuate the expression of conditioned fear responses in laboratory animals (see above). On the other hand, there are a number of various investigational drugs that effectively reduce expression of conditioned fear, but clinical data will be needed to establish predictive validity of such approach to identification of novel treatments of social anxiety.

3.5 Animal Models of Post-Traumatic Stress Disorder

PTSD develops following extreme stressful experiences and therefore animal models are based on exposures to brief sessions of intense physical or social stressors. Generally speaking, animal models that are characterized by long-lasting conditioned fear responses as well as generalized behavioral sensitization to novel stimuli following short-lasting but intense stress have a phenomenology that resembles that of PTSD in humans (see Stam 2007 for review). Animals that were subjected to brief, but intense, electrical foot- or tail-shocks or strong social stressors (predators or aggressive conspecifics) displayed gradually increasing and long-lasting hyper-responsiveness to novel stressful stimuli (e.g., exposure to the novel environment, open or lit spaces, etc.), and reduced response to appetitive stimuli (e.g., preference for sweet solution or appetitive anticipatory behaviors).

PTSD is characterized by hyperarousal, re-experiencing of the traumatic event, withdrawal or avoidance behavior, and emotional numbing; however, not every aspect of PTSD can obviously be modeled in laboratory animals and, therefore, it is rather difficult to correlate effects in the animal models with clinical efficacy. Indeed, preclinical evidence generated using stress-sensitization models suggested that benzodiazepine anxiolytics are as effective if not more effective than SSRIs in reducing behavioral hyper-reactivity induced by shock pre-exposure (van Dijken et al. 1992).

Another serious limitation of the currently available evidence is that there is not much data on efficacy of drug treatment during the early stages of post-traumatic stress (i.e., prophylactic treatment). Therefore, predictive validity of animal models can only be judged on therapeutic properties (i.e., treatment of the fully developed disorder) while preclinical data suggest that prophylactic treatment could be very effective.

3.6 Animal Models of Obsessive–Compulsive Disorder

Spontaneous behaviors resembling clinical symptoms of OCD are hardly seen in laboratory animals (see, however, Garner et al. 2004 for discussion on barbering behavior in mice) and therefore current models of OCD focus on perseverations and compulsive checking, induced either genetically or pharmacologically (e.g., quinpirole-induced checking behavior or reduction in spontaneous alternation in T-maze). There is only a limited degree of validation of these models (see Joel 2006 for review).

Other animal models where significant efforts were invested into pharmacological validation require further evaluation because of the limited experience outside the lab that originally developed the model (e.g., signal attenuation; Joel 2006) or the large number of false positives that attenuate marble burying via mechanisms varying from motor stimulation to sedation (Van Gaalen, Bespalov, Wicke, unpublished results).

3.7 "Benzodiazepine" Versus "Anxiolytic Activity" Tests

Over the last 15–20 years there were several reviews of the published evidence on the effects of antidepressant drugs in classical anxiolytic-like activity tests (e.g., Borsini et al. 2002). The overall evidence, briefly summarized above, is rather disappointing. Of course, a number of factors contributed to the lack of consistency in the study outcomes – e.g., administration routes, dose ranges tested (Soderpalm et al. 1989), species differences (Barrett and Gleeson 1991), gender effects (Rosenzweig-Lipson et al. 2007), environmental effects (Wettstein 1992), etc. However, all these discussions do not hide the main fact – classical anxiolytic

drug tests are not very sensitive to antidepressant drugs clinically effective in the treatment of anxiety disorders.

Indeed, most of these classical tests are pharmacologically validated using benzodiazepine anxiolytics and are therefore "benzodiazepine tests" rather than "anxiolytic drug tests." An elegant illustration of this difference was provided by the study by Thiebot and colleagues (1985) who suggested that at least some of the effects of benzodiazepine drugs in "anxiolytic" tests may be explained by their ability to stimulate impulsive choice. Benzodiazepines are known to reduce tolerance to delay of reward resulting in the enhanced preference for smaller but immediate rewards over delayed larger rewards. Thiebot and colleagues (1985) illustrated how these pro-impulsive properties of benzodiazepines may help understanding their effects in the conventional conflict tests. Similar arguments can be applied to tests where conflicts are less explicit but nevertheless significant (e.g., conflict between exploratory and safety drives in the plus maze and social interaction). Interestingly, antidepressants like SSRIs do not stimulate impulsive choice like benzodiazepines and after chronic administration are actually found to enhance tolerance to delay of reward (Wolff and Leander 2002). Thus, despite clinical anxiolytic potential, antidepressant drugs do not necessarily reproduce the preclinical psychopharmacology of benzodiazepines and it is not well established that effects of benzodiazepines in classical "anxiolytic" tests reflect their therapeutic effects.

3.8 Need for New "Anxiolytic" Tests Sensitive to Antidepressant Drug Treatment

There are a number of novel therapeutic candidates for treatment of anxiety and depression and a greater number of emerging targets for developing such therapies. As the discussion above suggests, one can hardly count on the classical anxiolytic tests when it comes to testing drugs with non-benzodiazepine-like mechanism of action. What are the features that the new tests should have?

First, clinical experience clearly indicates that a preclinical model should be sensitive to treatment with serotonergic antidepressants. Further, clinical efficacy has a rather delayed onset and therefore preclinical models that require subchronic drug administration are potentially of higher value. While there is no animal model that unequivocally meets all the requirements, one should mention again anxiolytic-like effects of SSRIs in the conditioned freezing paradigm as well as in the four-plate and novelty-suppressed feeding tests (see also Borsini et al. 2002 for review). Independent confirmations of these results in a larger number of studies could make these tests a valuable tool in novel anxiolytic drug development.

Second, evidence on clinical efficacy of antidepressants is obtained in patients who have been diagnosed with anxiety disorders. In contrast, most preclinical research is conducted using normal laboratory animals. The following example illustrates the significance of this discrepancy. Mice overproducing CRF exhibit

various alterations including increased anxiety-related behaviors and hypothalamus-pituitary-adrenocortical activity (Stenzel-Poore et al. 1994). Chronic treatment with citalopram decreased anxiety-related behavior in CRF overproducing animals in conditioned fear test, whereas it had opposite effects in controls (Fig. 1, left panel). Importantly, there was no such genotype dependence when effects of citalopram were studied in relation to 5-HT1A receptor autoreceptor function. 5-HT1A receptors serve both somatodendritic autoreceptor and post-synaptic heteroreceptor function. In mice, 8-OH-DPAT-induced hypothermia has been attributed to activation of somatodendritic 5-HT1A autoreceptors (Bill et al. 1991). Chronic treatment with citalopram or other antidepressants of various classes as well as repeated electroconvulsive shock therapy attenuate 8-OH-DPAT-induced hypothermia (Bill et al. 1991; Goodwin 1989). Chronic treatment of wild type and CRF overexpressing mice with citalopram results in desensitization of 5-HT1A autoreceptors, as indicated by the attenuated hypothermic response to 8-OH-DPAT administration in both wild types and transgenics (Fig. 1, right panel). This demonstrates that chronic treatment with antidepressants can lead to similar cellular changes in neurotransmitter systems under normal and pathological conditions, but that such changes may lead to opposite effects on anxiety-related behavior.

3.8.1 Social Stress

Repeated and/or prolonged exposures to stress have long been argued to present a path towards a disease model that would allow preclinical evaluation of novel antidepressant principles with anxiolytic properties. For example, Keeney and Hogg (1999) investigated the effect of the SSRI citalopram in normal mice and mice that were exposed to repeated social defeat, coupled with the stress of continuously living in proximity to the dominant mice. Mice were repeatedly tested in the dark-light transition box. As expected, control animals initially avoided the illuminated part of the apparatus but, with repeated testing, this avoidance behavior was greatly diminished. Interestingly, no such changes were seen in stressed animals which showed even greater avoidance of the illuminated part. When treated with citalopram, stressed animals spent more time in the illuminated section, but not earlier than after 2 weeks of daily injections.

More recently, a similar stressor was applied by Berton and Nestler (2006). In this study, mice were subjected to daily bouts of social defeat, followed by continuous protected sensory contact with their aggressor for 10 days and were then screened for social behavior by measuring social approach toward an unfamiliar mouse enclosed in a wire mesh. Control mice spent most of their time interacting socially with the unfamiliar mouse, while the defeated mice displayed intense aversive responses and spent less time close to the target mouse. Chronic, but not acute, treatment with fluoxetine or imipramine improved social interaction in the defeated animals. Importantly, this effect was not seen after acute or chronic

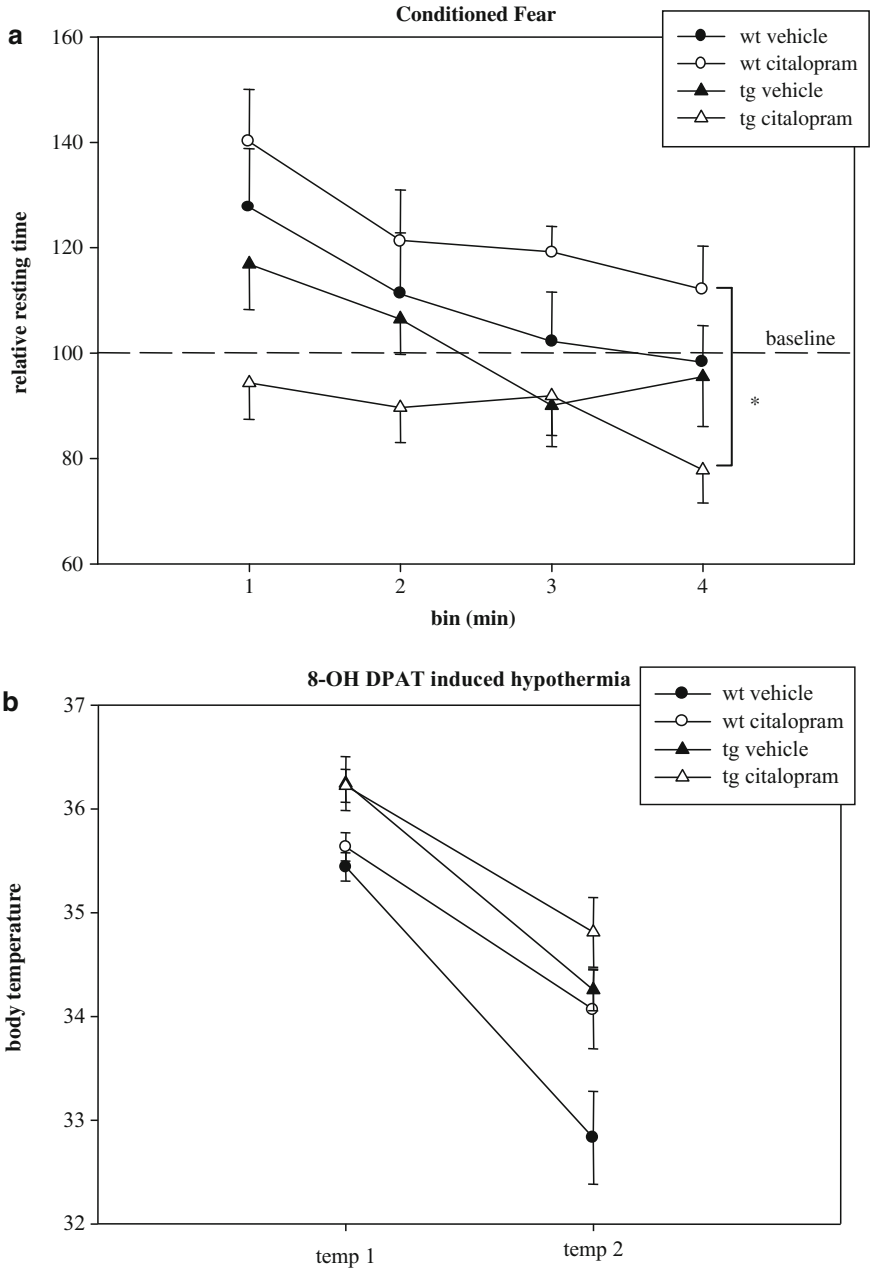

Fig. 1 Effects of chronic citalopram treatment in CRF overproducing and wild type mice on conditioned fear and body temperature. *Left panel*, change in the relative time not moving during re-exposure to the light relative to baseline (*dotted line*) 24 h after conditioning is shown. wt: wildtype; tg: transgenic. *$P<0.05$ (wt citalopram compared to tg citalopram). *Right panel*, body temperature measured under basal conditions (temp 1) and 20 min after treatment with 8-OH DPAT (temp 2). Citalopram attenuated the 8-OH DPAT induced hypothermia ($P<0.05$). From: Van Gaalen (2001)

treatment with chlordiazepoxide, suggesting that this disease model may be selectively sensitive to anxiolytic effects of antidepressant drugs.

Social stress mechanisms are also key to suggested value of the mouse defense test battery mentioned above. In this test, anxiogenic effects of fluoxetine and imipramine have been reported after acute treatment, while anxiolytic effects were shown after chronic drug application (e.g., Griebel et al. 1995).

3.8.2 Non-Social Stress

In most preclinical studies, stress is associated with exposures to aversive, painful stimulation such as electrical footshocks. In contrast, in humans, exposure to such noxious stimulation is often difficult to reveal and document. Meanwhile, both in animals and humans, stress stimuli have specific characteristics imposed by intermittent reinforcement contingencies. In other words, stressful experiences may be associated with positive or negative reinforcers delivered in a manner, which is not controlled by the subjects. Previous research suggested that compared with the ratio schedules of reinforcement, interval schedule (fixed or variable) might have aversive properties and are less preferred by the subjects (e.g., Nevin et al. 2001). Accordingly, such stressful intermittent schedules of reinforcement generate concurrent, excessive behaviors such as polydipsia (Cook et al. 1983; Falk 1971) and may even lead to adverse physiological consequences including cardiomyopathies typical of stress-related disorders (Rupp et al. 1997).

Antidepressant drugs such as SSRIs attenuate expression of schedule-induced polydipsia and these effects are characterized by remarkable delay of onset (Fig. 2; see also Hogg and Dalvi 2004). In addition to its usual significance (i.e., parallels to clinical effect), delayed onset of action in these studies helps to argue for specific mechanism of action because, when given at high-enough doses, most CNS active drugs attenuate polydipsia (via non-specific sedation or motor inhibition). Therefore, development of data analysis techniques is necessary for drugs that are expected to act faster than modern antidepressants.

3.8.3 Beyond Chronic Stress Procedures

Elevated baseline anxiety levels (i.e., disease states prior to the drug treatment) are described for a number of mouse strains where trait anxiety results from either genetic deletion of a known gene (e.g., genes for 5-HT1A, 5-HT2C receptors or neuropeptide Y) or more complex and most likely randomly introduced alterations in various neurotransmitter circuits that may be more akin to the clinical situation (e.g., BALB/c mice; Belzung and Griebel 2001). It remains to be evaluated whether such animals with trait anxiety will be in classical tests or whether they still require novel tests.

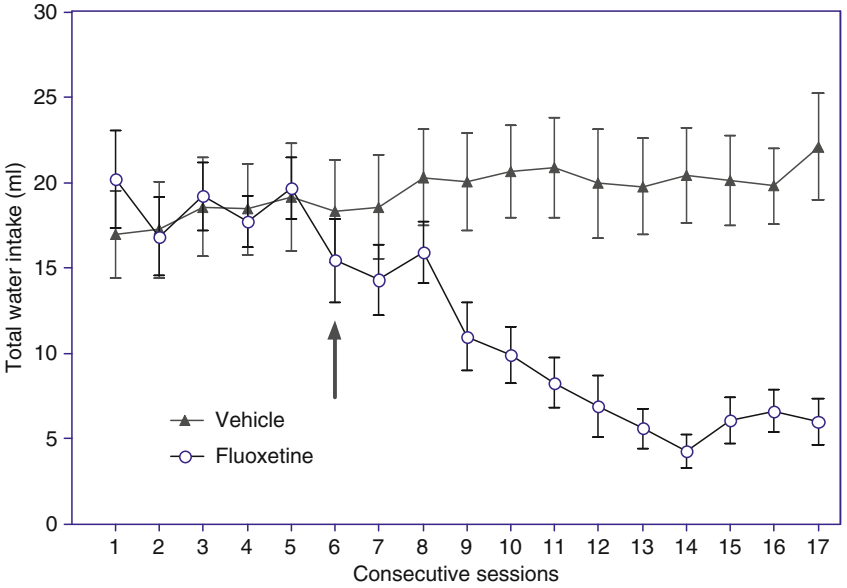

Fig. 2 Effects of repeated fluoxetine treatment on polydipsia induced by intermittent schedule of food delivery (fixed time 60 s) in rats. When water intake stabilized (ca. 3 weeks), rats received daily injection of fluoxetine (10 mg·kg^{-1}) or its vehicle prior to the 1-h long sessions (indicated by the *arrow*). Fluoxetine attenuated schedule-induced polydipsia starting after the fourth injection ($P<0.05$)

Overall, there are a number of new "anxiolytic" tests emerging that may be sensitive to antidepressant drug treatment and will therefore be very useful in the drug development process. All that has to be done is that these promising results need to be replicated by independent laboratories and evidence on predictive validity has to be extended.

As summarized in Table 2, not too many preclinical models exist where antidepressant drugs produce effects that may be interpreted as predictive of and relevant to their clinical efficacy in the treatment of anxiety disorders. Despite this generally disappointing situation, such analysis seems to suggest that treatment with SSRIs is more often associated with signs of preclinical efficacy than any other type of antidepressants. This may of course be due to the fact that SSRIs have been the most popular antidepressant medications dominating clinical use and this has affected the design and focus of preclinical studies favoring the use of SSRIs. However, this evidence may also be suggesting that, similar to the clinical situation, preclinically SSRIs are superior to other antidepressant drug classes and enhanced serotonergic function is indeed crucial for the anxiolytic properties of current antidepressants. Further, while the methodological portfolio certainly needs further work, available data on preclinical efficacy of SSRIs suggest that useful animal models are available and point at these directions for new model development.

Table 2 Summary of the preclinical efficacy of antidepressant drugs in animal models of anxiolytic activity

Animal model	TCA	MAOI	SSRI	SNRI & NRI
Ethological models				
Exploratory activity				
Social behavior			±	
Unconditioned non-social stress-induced responses				
Conditioned fear (non-social)			+	
Social stress	+		+	
Social hierarchy	+	+	+	+
Conflict tests				
PAG stimulation	+		+	
Stress sensitization		+	+	

+ positive evidence; ± mixed evidence; empty cell indicates lack of positive evidence

4 Mechanisms of Anxiolytic Action of Antidepressant Drugs

It has been repeatedly discussed that depression and anxiety disorders share a number of overlapping clinical signs and symptoms such as sleep disturbances, restlessness, irritability, difficulty concentrating, loss of control, fatigue, fear distress, etc. Many patients complaining of symptoms of anxiety in fact have depression, which is often overlooked (Fineberg and Drummond 1995). Extremely high degree of comorbidity of depression with anxiety disorders, overlapping symptoms as well as similar time-course of antidepressant drug effects in patients with depression or anxiety point at the most obvious explanation of the anxiolytic properties of antidepressant drugs: mechanisms responsible for anxiolytic effects are similar, if not identical, to those responsible for antidepressant effects of these medications.

4.1 Changes in the Neurotransmitter Systems

Acute administration of antidepressant drugs suppresses the firing rate of 5-HT neurons (Blier 2001). For both reuptake inhibitors and MAO inhibitors, these effects are explained by the density of 5-HT being greatest in the raphe nuclei. This suppression results in increased activation of 5-HT1A autoreceptors on the cell body of 5-HT neurons, which in turn exert a negative feedback action on their firing activity. This increased activation of 5-HT1A autoreceptors and resulting negative feedback occur because the firing rate of 5-HT neurons is generally proportional to 5-HT release throughout the brain. In projection areas, there is also an increase in the synaptic availability of 5-HT due to reuptake inhibition or MAO inhibition, but this enhanced level is limited by the suppression of the firing activity of 5-HT neurons. However, with prolonged treatment, the spontaneous firing of 5-HT neurons gradually returns to normal because of the desensitization of 5-HT1A autoreceptors. This desensitization is also expected to be proportional to receptor stimulation (i.e., local 5-HT levels) and therefore 5-HT1A receptors in the projection areas are affected

less than autoreceptors in somatodendritic fields. Downregulation of the latter leads to an increase in 5-HT neurotransmission and this increase is seen as the main neurochemical substrate of effects of currently used antidepressant drugs. Indirect support of this view is provided by the data indicating rapid relapse of symptoms in SSRI-sensitive depressed patients who undergo a dietary 5-HT depletion paradigm (Delgado et al. 1999). However, one should also note that there is still no convincing clinical evidence that 5-HT1A blockade accelerates onset of action of antidepressants. Thus, 5-HT1A desensitization remains a hypothesis awaiting final validation.

While 5-HT1A desensitization accounts appear to dominate the current way of thinking about antidepressant drug action, it is unclear whether this is the mechanism that is also responsible for these drugs' anxiolytic effects. Sustained administration of antidepressant drugs also enhances 5-HT transmission to NE neurons of the locus coeruleus (Szabo et al. 1999). This enhanced transmission is indicated by a marked suppression of the firing activity of these neurons resulting from an enhanced inhibitory tone exerted by 5-HT. Such inhibitory effect is, however, indirect, and is mediated by increased activation of excitatory 5-HT2A receptors on inhibitory GABAergic interneurons, the latter in turn suppressing the firing of NE neurons (Szabo and Blier 2001). Obviously, this GABAergic activation as well as attenuation of noradrenergic firing could explain at least in part the anxiolytic effects of antidepressant drugs. However, there is not much evidence directly supporting such accounts (e.g., no benzodiazepine-like anxiolytic effects of antidepressants or agents reducing the firing activity of NE neurons such as α2 agonists). It is likely that there are other neurochemical adaptations triggered by enhanced 5-HT neurotransmission that may contribute to anxiolytic activity (e.g., adaptations in β-adrenoreceptors or glutamate/NMDA receptors).

Enhanced 5-HT levels may also be responsible for clinical efficacy of drugs whose primary receptor targets are outside this neurotransmitter system. For instance, prolonged administration of selective NE reuptake inhibitors is expected to desensitize α2 receptors located on 5-HT terminals (Mongeau et al. 1994). Such indirect effects on 5-HT perhaps explain the weaker anxiolytic profile of NE reuptake inhibitors compared with SSRIs.

Overall, desensitization of auto- and heteroreceptors controlling the release of monoamines such as 5-HT is the most studied neurochemical adaptation induced by antidepressant drugs. It is unlikely to be the only possible mechanism to be exploited by future antidepressant/anxiolytic drugs. However, this knowledge is instrumental because novel target candidates can be searched by following the neuroanatomical organization of 5-HT system.

4.2 Neuroanatomical Aspects of Antidepressant Drugs' Anxiolytic Action

Serotonergic raphe cells project to a number of brain areas that are traditionally implicated in emotional processing and expression of anxiety (e.g., amygdala, hypothalamus) and the most straightforward explanation of anxiolytic properties

of antidepressant drugs would be based on inhibitory effects of elevated 5-HT on the function of these brain areas. Such account naturally leads to testing anxiolytic potency of novel drugs with alternative mechanisms of downregulating the activity of "anxiety" centers. For instance, antagonists acting at CRF1 receptors have long been hypothesized to possess anxiolytic activity (Steckler 2009). Indeed, these receptors are known to be essential in coordinating physiological response to stress and a number of studies have demonstrated the ability of CRF1 antagonists to inhibit stress-induced increases in HPA axis activity[3] (e.g., as shown by reduced corticosterone levels; Ising et al. 2007). Preclinical studies have also revealed a very appealing anxiolytic-like profile of CRF1 antagonists, which did not alter spontaneous anxiety when tested in traditional "benzodiazepine" tests (e.g., conflict tests) but were very active in tests taxing stress-facilitated anxiety (e.g., elevated plus-maze testing following the swim stress exposure; Chaki et al. 2004). Perhaps even more appealing is that CRF1 antagonists are effective in several other tests, which were claimed to be sensitive to antidepressant drug treatment (e.g., separation-induced vocalizations, mouse defensive test battery, etc.). However, as convincing as this evidence may appear, there is no clinical proof of anxiolytic activity of CRF1 antagonists and the first clinical data are rather disappointing (Coric et al. 2008) suggesting that anxiolytic effects of antidepressant drugs may have mechanisms other than simple suppression of stress-induced responses.

4.2.1 Hippocampus

One of the original members of Papez' circuit, the hippocampus, also receives relatively dense serotonergic innervation and, from a functional point of view, the hippocampus is one of the most interesting targets of anxiolytic drug action. It is well established that the hippocampus is hyperactive in anxiety disorders and there were several theories advanced to associate reduction in hippocampal activity with anxiolysis (e.g., McNaughton et al. 2007). Experimental evidence also speaks strongly in support of hippocampal involvement in anxiolytic drug action. For example, inhibition of hippocampal dentate gyrus granule cells selectively suppressed conditioned responses to ambiguous cues. In contrast, inhibition of neurons in the central nucleus of the amygdala suppressed conditioned responses to both ambiguous and non-ambiguous cues in the fear conditioning experiments (Tsetsenis et al. 2007).

For antidepressant drugs, the hippocampus is an especially important target. Over the recent 5–6 years, several studies have suggested that adult neurogenesis in the hippocampus is causally related to antidepressant drug action (see Drew and Hen 2007 for review). Several antidepressants were shown to stimulate hippocampal neurogenesis upon repeated administration. Ablation of neurogenesis via

[3]It is of note that subchronic treatment with SSRIs like fluoxetine may attenuate stress-induced behaviors but has little or no effects on stress-induced increases in ACTH and corticosterone levels (Zhang et al. 2000).

irradiation of a brain area containing the hippocampus prevented both neurogenic and behavioral (anxiolytic- and antidepressant-like) effects of antidepressants. Interestingly, non-drug inhibitors of conditioned fear (i.e., learned safety signals) enhance hippocampal neurogenesis as well (Pollak et al. 2008).

At first glance, this evidence appears to come into conflict with the data suggesting that learning (including aversive learning such as fear conditioning) enhances neurogenesis. This paradox is solved by studies demonstrating that learning increases or decreases the number of newly born cells depending on their birth date: For example, Dobrossy and colleagues (2003) divided water maze learning into two phases, an early phase during which performance improves rapidly, and a late phase during which asymptotic levels of performance are reached. The number of newly born cells increased contingently with the late phase and a large proportion of these cells survived for at least 4 weeks. In contrast, late-phase learning decreased the number of newly born cells produced during the early phase. This decline in neurogenesis was positively correlated with performance in the water maze. To understand these results, one may want to recall the difference between "perfect predictors" and ambiguous predicting stimuli mentioned above for fear conditioning studies. It is the ambiguous stimuli that are more relevant to anxiety modeling and are known to depend on hippocampal function. In case of the water maze, one could expect slower acquisition of the task in some individuals to be due to the greater ambiguity of guiding stimuli. Antidepressant drugs would be expected to reduce the impact of the ambiguous guiding stimuli, thereby enhancing hippocampal learning and neurogenesis.

Experimental support for this hypothesis would require additional studies with (sub)chronic treatment regimens of antidepressants given prior to and during the water maze training. Given that the repeated treatment with antidepressants enhances 5-HT neurotransmission and that this may inhibit hippocampal activity, it is very critical to see if anxiolytic effects can be separated from cognition-impairing properties. Such dissociation was shown for scopolamine-like muscarinic receptor antagonists and benzodiazepine anxiolytics, both of which have similar capacity to reduce hippocampal theta activity and cognitive functions. However, although benzodiazepines are anxiolytic, muscarinic receptor antagonists are not.

4.2.2 Prefrontal Cortex

Prefrontal cortex is another brain area that is critically involved in both cognitive processes and antidepressant drug action. For example, anti-OCD effects of antidepressant drugs are thought to result from increased 5-HT neurotransmission in orbitofrontal cortex (Nakao et al. 2005). OCD is often associated with hyperactivity in neuronal cortico-striato-thalamo-cortical loops and this hyperactivity can be dampened by enhanced action of 5-HT in the cortex. There is a growing body of evidence linking frontal cortical functions to other types of anxiety disorders as well. Stress-sensitization studies assessed expression of Fos protein in response to novel stressors several weeks after the repeated shock experience: in

shock-preexposed subjects, there was an elevated number of Fos-positive cells in the medial prefrontal cortex (Bruijnzeel et al. 1999). Prefrontal cortex may have an even more global function in controlling the response to stress. When a stressor is controllable (e.g., escapable), stress-induced activation of serotonergic dorsal raphe nuclei is inhibited by prefrontal cortex, and behavioral consequences of uncontrollable stress are prevented (Amat et al. 2005). It is to be noted that repeated treatment with antidepressant drugs reverses learned helplessness, the most commonly studied behavioral consequence of uncontrollable stress (Sherman et al. 1982).

The prefrontal cortex may also be involved in the mechanisms of attentional bias towards threat-related stimuli and poor inhibition of distractor processing which are characteristic of clinical anxiety (Bishop 2009). Both clinical and preclinical data indicate that prolonged stress exposure induces neuroanatomical changes in the prefrontal cortex and negatively affects performance on prefrontal cortex-dependent attentional flexibility task (Liston et al. 2006, 2009).

The above mentioned involvement of brain areas that are traditionally discussed in the context of cognitive functioning suggests contribution of learning and memory to pathophysiology of stress-related disorders as well as antidepressant drug action. Originally formulated over 40 years ago, the cognitive model of depression focuses on automatic thoughts, cognitive distortions, dysfunctional beliefs, and negative information-processing biases (Beck 2008). Traumatic experiences and the formation of dysfunctional beliefs in early life are viewed as predisposing events while congruent stressors in later life as precipitating factors. Such views can easily be transferred to describe the pathogenesis of anxiety disorders.

Is it possible that different anxiety disorders share neuroanatomical substrates? The answer is "yes and no." On the one hand, there is clearly a growing body of evidence that certain brain areas and connections are more important for some anxiety disorders than for others (e.g., cortico-striato-thalamic loops for OCD). On the other hand, antidepressant drug treatment induces neurochemical adaptations in the 5-HT system that are distributed in time and space in a manner that is not likely to depend on the type of anxiety disorder. It is possible that various anxiety disorders share some core "learning" mechanism with a specific neuroanatomical substrate and this mechanism is sensitive to antidepressant drug treatment.

4.3 Cognitive Model of Anxiety Disorders: Implications for Novel Drug Development

Even a superficial review of animal models sensitive to antidepressant drugs reveals several paradigms with strong cognitive load. For example, a number of antidepressants were shown to be effective in rats trained to press a lever to obtain food under differential reinforcement of low rates of responding schedule (DRL; Sokolowski and Seiden 1999). Under this schedule, rats need to withhold a response for a certain period of time (originally, 72 s but shorter versions are also used).

Antidepressants shift distribution of the inter-response times to the right, enhancing the total number of food reinforcers earned and reducing the overall response rate. These effects are quite characteristic of this drug class because opposite results are typically seen with psychostimulants as well as benzodiazepine anxiolytics. Specific analysis methods were developed for characterizing antidepressant drug action besides the increase in reinforcement rate. Successful performance in the DRL task requires inhibition of prepotent responses. Such inhibitory control is one of the core functions attributed to prefrontal cortex and this makes the DRL task one of the candidates for evaluating cortical cognitive aspects of antidepressant drug effects. This example of DRL indicates that strong face validity may not be necessary for tests predictive of antidepressant/anxiolytic action.

Effects of antidepressants in the DRL task are seen after the first injection. At first glance, acute efficacy speaks against the validity of this task. Indeed delayed onset of action in preclinical tests is mandated by delayed onset of clinical efficacy and is further reinforced by the current way of thinking dominated by 5-HT1A desensitization accounts. However, delayed onset of action may have other mechanisms not directly related to changes in the receptor and/or second messenger systems. For instance, any learning requires time and should the antidepressant drug action involve improved inhibitory control or any other cognitive function, it would take a certain period of time and a number of training sessions for these "cognitive" effects to be translated into improved behavioral performance in "anxiolytic" tests. If this is true, anxiolytic/antidepressant-like activity of novel drugs may not necessarily require sub(chronic) treatment and can be predicted based on the results of acute tests.

5 Summary

Antidepressant drug treatment is the clinical standard of care for all types of anxiety disorders. As discussed above, this stands in a sharp contrast to preclinical practice where most "anxiolytic" drug tests are not sensitive to antidepressants. There are at least two factors contributing to this situation.

First, traditionally "anxiolytic" drug tests have been validated by confirming their sensitivity to benzodiazepine drugs (i.e., establishing predictive validity). This approach is clearly not the most effective because it does not fully establish that classical benzodiazepine-sensitive test really reflect on therapeutic efficacy of these drugs and not their side-effects and because there may be more than one pathophysiological mechanisms via which "anxiolysis" may be produced (i.e., benzodiazepine-sensitive and benzodiazepine-insensitive).

Second, development of "anxiolytic" drug tests was often a victim to face validity requirements. For instance, laboratory rodents do avoid open spaces because for them, engagement in otherwise risky behaviors is biologically not justified. In contrast, human anxiety disorders are clearly maladaptive and reducing anxiety in diseased individuals serves a clear biological role. Another example

concerns the selection of the stress procedures for inducing anxiety states in laboratory animals. It is often assumed that only aversive stimuli that induce visible and markedly pronounced physical suffering are relevant and stressful enough. In contrast, in humans, exposure to such noxious stimulation is often difficult to reveal and document. Rather, what is common for true stress stimuli are specific characteristics imposed by intermittent reinforcement contingencies (i.e., positive or negative reinforcers are delivered in a manner, which is not controlled by the subjects). Uncertainty in a broad sense (including unstructured time) is the hallmark of human stress and may have different expressions ready for experimental modeling. These possibilities include schedule-induced behaviors that are directly based on intermittent reinforcement, conditioning to ambiguous stimuli, social stress where agonistic confrontations are possible but not predictable and not controlled by the subject, and an even larger class of behaviors that are critically dependent on the inhibition of the prepotent responses in exchange for the ambiguous possibility of later gain in reinforcement. As reviewed above, in all of these cases, antidepressant drug treatment is clearly effective.

Face validity of the model further dictates that antidepressant drug have a delayed onset of action. As argued above, the cognitive model of antidepressant drug action may be extended to cover their anxiolytic properties as well. Cognitive effects of antidepressants and any learning induced by this treatment will certainly require time for translation into improved behavioral performance and anxiolysis. One of the cognitive functions that appears to be affected by antidepressant drugs is inhibitory control. Inhibition of prepotent responding has beneficial effects in the "uncertainty" stress situations discussed above and therefore it is this cognitive function that may be critical for anxiolytic effects of antidepressants and novel anxiolytic drug development.

In conclusion, as heterogenous as they may appear, anxiety disorders share certainly more than just the label "anxiety." Their sensitivity to treatment with antidepressants such as SSRIs suggests common pathophysiological mechanisms. When these mechanisms are fully revealed and understood, truly specific anxiolytic drug tests will help identifying novel medications with improved therapeutic properties.

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