Animal Models of Anxiety Disorders

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Animal models may be useful in investigating the fundamental mechanisms underlying psychiatric disorders, and may contribute to the development of new medications. A computerized literature search was used to collect studies on recently developed animal models for anxiety disorders. Particular cognitive-affective processes (eg, fear conditioning, control of stereotypic movements, social submissiveness, and trauma sensitization) may be particularly relevant to understanding specific anxiety disorders. Delineation of the phenomenology and psychobiology of these processes in animals leads to a range of useful models of these conditions. These models demonstrate varying degrees of face, construct, and predictive validity.

Introduction

Animal models can contribute to understanding the mechanisms underlying anxiety disorders and to screening and developing new medications for their treatment [1,2]. An initial focus of preclinical work was on the broad construct of "anxiety," and, in particular, in addressing the issue of determining whether novel agents had anxiolytic properties [3,4]. Barbiturates and benzodiazepines, for example, had anxiolytic properties in particular paradigms, and the efficacy of new molecules could be compared with these agents. This approach was, however, problematic insofar as it was not always based on specific cognitive-affective processes relevant to anxiety disorders, and as it was unable to predict the value of various medications (*eg,* antidepressants) for human anxiety disorders.

Some models of anxiety have focused on changes associated with acute stress, whereas others have aimed at understanding the neurobiology of chronic stress (*eg,* models of learned helplessness). Models of chronic stress arguably have applicability across a range of psychiatric conditions, including mood [5] and anxiety disorders [6]. Conversely, it has been argued that although these models have provided valuable insights about the neurochemistry and neuroendocrinology of stress responses, they have not led to insights into individual psychiatric disorders. The broad concept of a general stress response arguably needs supplementation by more specific understanding of the mechanisms underlying particular cognitive-affective processes (*eg,* fear conditioning) involved in particular anxiety disorders. Because these disorders differ with respect to symptoms and age of onset, prevalence in men and women, and treatment response, the interface between existing behavioral models of anxiety and the clinical profile of anxiety disorders is of considerable relevance, as is the important issue of accurately modeling developmental risk factors, such as emotional neglect, family strife, maternal separation, and overcrowding [1].

Given the increased evidence that anxiety disorders may have distinctive symptomatology and neurobiology, specific cognitive-affective processes may be particularly relevant to each of the different anxiety disorders. Furthermore, although some of the anxiety disorders seem specific to humans, a number of these cognitive-affective processes can be studied in lower animals. This paper discusses models of generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder (PD), social phobia (SP), and post-traumatic stress disorder (PTSD) [7], in each case emphasizing a cognitive-affective process that may be especially relevant to that disorder. A computerized literature search was used to search for studies on recently developed animal models for anxiety disorders.

Generalized Anxiety Disorder

Generalized anxiety disorder is characterized by excessive and uncontrollable worries about life events. These worries are accompanied by motor tension or hypervigilance [7]. Clinical studies point to dysregulation of monoamine [8] and gamma-aminobutyric acid (GABA) [9] neurotransmitter systems in GAD. Complementing these findings are clinical trials showing that GAD responds reasonably well to benzodiazepines, buspirone, and antidepressants [10].

Development of a behavioral model of GAD is complicated, because core diagnostic criteria for GAD have changed over time [11]. Generalized anxiety disorder was originally conceptualized as a residual category for patients whose anxiety symptoms did not meet criteria for other anxiety disorders. Subsequent *Diagnostic and Statistical Manual of Mental Disorders* definitions of GAD have increasingly focused on "worry," a cognitive

symptom that may not have a clear behavioral analogue. Another way of conceptualizing GAD, however, is in terms of heightened activation of innate general avoidance behaviors [6].

General avoidance behaviors

A number of animal models based on this principle have been developed. Among the best known is the elevated plus maze, but other widely used paradigms include the open-field test [12], stress-induced vocalization model [13], the light-dark compartment test, and the social interaction test [1]. In the elevated plus maze, a rat or mouse is placed in the center of a maze, which has two open and two closed arms, and the animal is allowed to explore freely. The natural fear of open spaces is responsible for the reluctance to explore the maze, and fear is measured by the decreased percentage time spent in an open arm [3]. The elevated plus maze is sensitive to anxiogenic and anxiolytic agents that act on GABA receptors [3] and to corticotropin-releasing factor receptor antagonists [14,15].

This model can be used to investigate a range of potential neurobiologic dysfunctions relevant to GAD. For example, mice lacking the serotonin 5-hydroxytryptamine (5-HT_{1A}) receptor, or 5-HT_{1A} knockouts (5-HT_{1A} KO), show more anxious behavior in the elevated plus maze [16•]. It was also found that diazepam proved anxiolytic in this paradigm, but the effects varied according to the mouse species [17,18]. Although the gross dysfunction produced by a KO model may differ from the more subtle dysfunction seen in human psychopathology, KOs have the advantage of being able to study the effects of a single genetic change.

From a phenomenologic perspective, it is unclear if the elevated plus maze models the core symptom of GAD, that is, excessive "worry." Furthermore, the elevated plus maze has a range of methodologic problems. These include inter-laboratory differences and differences among animal strains [19]. Finally, although benzodiazepines reliably reduce anxiety in the elevated plus maze [3,19], studies with 5-HT_{1A} agonists and selective serotonin reuptake inhibitors (SSRIs) have proven inconsistent [20]. This is in contrast to clinical studies that regularly demonstrate that serotonergic anxiolytics are effective in treating GAD [10]. Given these limitations, preclinical work that is intended to address GAD may need to use a combination of different behavioral models (*eg,* elevated plus maze and open-field test).

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is characterized by obsessions (recurrent and persistent thoughts) and compulsions (repetitive behaviors or mental acts in response to obsessions) [7]. Clinical studies have emphasized the importance of corticostriatal circuits in mediating OCD, and have supported the hypothesis that serotonin and dopamine play important roles in mediating the disorder [21,22]. Selective serotonin reuptake inhibitors are currently the first-line agent in the treatment of OCD [23], and patients refractory to these agents may respond to augmentation with dopamine blockers [24••]. Autoimmune processes may play a role in the corticostriatal dysfunction seen in some patients with OCD [25].

Stereotypy is arguably central to OCD, because stereotyped behavior with its repetitive, topographically invariant movements is reminiscent of the compulsions of OCD. Animal models that focus on this phenomenon include the behavioral model of spontaneous stereotypy in deer mice [26••,27–29], veterinary disorders characterized by stereotypy, such as acral lick dermatitis in canines [30••], and a number of anatomic and molecular models of repetitive behavior [31–33].

Control of repetitive movements

In the rodent model of spontaneous stereotypy, deer mice (*Peromyscus maniculatus bairdii*) express patterns of motor behaviors that are repetitive, excessive, and topographically invariant. These behaviors lack any obvious function and purpose [26••,27–29]. The patterns of motor behavior include patterned running, jumping, and backward somersaulting. Apomorphine has been found to induce behaviors in nonstereotypic mice that are topographically distinct from behaviors emitted by stereotypic mice. Furthermore, apomorphine only increases two of the three stereotypic behaviors usually emitted by deer mice with no increase in dopamine receptor sensitivity. Thus, although dopamine dysfunction may underlie certain aspects of OCD, spontaneous stereotypy is only partially mediated by the dopamine system [27]. The role of the serotonergic system in mediating deer mice stereotypy, as well as its response to administration of different agents, remains to be fully clarified.

Acral lick dermatitis (ALD) is a veterinary disorder characterized by repetitive paw licking and biting of the extremities in different mammalian species, particularly in large dogs. Acral lick dermatitis has some face validity as a model for OCD, insofar as the conditions can arguably be conceptualized as grooming disorders. Furthermore, like OCD, ALD responds more robustly to SSRIs than to noradrenergic agents [30••]. Although the phenomenology of ALD differs from some subtypes of OCD, stereotypic behaviors in other species are arguably reminiscent of such subtypes (*eg,* rodent hoarding) [34]. Various stereotypes in other animals (*eg,* primates) may also respond to SSRIs [35••]. There is a need for additional research to delineate the neurobiologic dysfunctions that underlie ALD, and to see whether these are analogous to those responsible for OCD.

Dopamimetic agents, such as dexamphetamine and apomorphine, administered orally or injected into brain regions such as the striatum, have been extensively used to study the neurobiology of stereotypy [36–38].

For example, rats treated chronically with the dopamine D2/D3 receptor agonist, quinpirole, develop compulsive checking behavior [31,32] and perform ritual-like behavioral acts at specific places in an open field. Clomipramine, another SSRI, partially attenuates quinpirole-induced compulsive checking [31], suggesting at least a partial role for 5-HT in this behavior, and supporting the regulatory role of striatal 5-HT on dopamine-driven behaviors [22]. Although drug-induced stereotypy is only partly reminiscent of the phenomenology of OCD, it does appear to model some aspects of the neurobiology of this condition.

Clinical research suggests that OCD and tics may be mediated by corticostriatal circuits. One possibility is that such dysfunction involves autoimmune processes [39], and in a preclinical model of this phenomenon, rats were injected with sera from patients with Tourette's syndrome with high levels of autoantibodies in the ventrolateral striatum, an area associated with oral stereotypy [37]. Experimental animals exhibited significantly higher oral stereotypy scores (wood chip eating, self-gnawing, biting, licking not associated with grooming, and repetitive paw-to-mouth movements) compared with animals injected with sera from normal individuals or patients with Tourette's syndrome with low autoantibody titers [40]. Although there is evidence that certain immunotherapies may be useful in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections [39], parallel preclinical data is not yet available. This model has phenomenologic and neurobiologic aspects reminiscent of OCD and deserves further study.

Panic Disorder

Panic disorder is characterized by recurrent unexpected panic attacks followed by persistent concern about additional attacks, worry about the implications of the attack or its consequences, and a significant change in behavior related to the attacks [7]. A panic attack is normally accompanied by a range of sympathetic symptoms and clinical studies suggest dysregulation of the noradrenergic [41–43] and serotonergic [44,45] neurotransmitter systems. Patients with PD respond to various antidepressants, including tricyclics, monoamine oxidase inhibitors, SSRIs, and certain benzodiazepines [46].

Modeling neurobiologic processes related to anxiety can provide important information relevant to many mental disorders. It is imperative that brain mechanisms involved in the development and maintenance of fear and anxiety are understood and closely reproduced in the animal model [1]. Fear conditioning and extinction are processes that may be relevant to the pathogenesis of a number of different anxiety disorders and their treatment [47]. Nevertheless, certain phenomena seen after fear conditioning, such as fear-potentiated startle, are reminiscent of the symptoms of PD (and of the arousal symptoms of PTSD). In this section, the authors discuss how preclinical studies of fear conditioning may shed light on the neuoroanatomic and molecular basis of panic disorder.

Fear conditioning

Animal models of conditioned fear examine behaviors that are provoked by stimuli associated with an aversive stimulus, for example, an electric foot shock. Fear conditioning is a form of Pavlovian conditioning where a neutral stimulus is paired with an aversive stimulus (unconditioned stimulus). After a number of pairings, the neutral stimulus (conditioned stimulus) elicits fear behaviors without the presence of the aversive stimulus. A major advance has been the delineation of the role of the amygdala and other limbic structures in mediating innate and conditioned fear responses [48–50].

In animals, stimulation of the amygdala results in behavioral [51] and physiologic [52] patterns associated with fear and anxiety, whereas stimulation of specific target areas of the amygdala produces more selective effects [50]. The extended amygdala may be particularly relevant to anxiety (rather than fear), and the hippocampus plays an important role in contextual fear conditioning. Finally, medial prefrontal cortex (anterior cingulate) plays a crucial role in mediating the extinction of fear-conditioned responses. Neurotransmitters that are crucial in this circuitry include the serotonergic, glutamatergic, and GABAergic systems.

The fear-potentiated startle response, which consists of fast muscle contraction, especially around the face, neck, and shoulders [53], is arguably reminiscent of a panic attack. One of the regions that play an important role in the fear-potentiated startle response is the periaqueductal gray (PAG) [54]. Stimulation of the dorsal periaqueductal gray (dPAG) elicits fear behaviors and autonomic arousal [55,56], and lesions of the PAG prevent fear-potentiated startle [57]. Fear-potentiated startle is sensitive to fear-modulating drugs, for example, benzodiazepine agonists [58], 5-HT_{1A} agonists [59] and *N*-methyl-D-aspartate (NMDA) receptor antagonists [60]. Panicogenic drugs, such as yohimbine and caffeine, lead to an increase in dPAG-induced aversion, whereas a number of antipanic drugs, including clonazepam and alprazolam, lead to a decrease [55].

Fear conditioning appears relevant to understanding the development of agoraphobia in patients with PD, and arguably provides a conceptual foundation for an integrated approach to extinguishing fear by means of medication or desensitization. Although a fear-potentiated startle model is partly reminiscent of the phenomenology of PTSD, there is arguably overlap with the responses to impending danger also seen in PD [61]. Clinical studies of PD indicate that the neurocircuitry of PD is broader than simply the dPAG. Nevertheless, the dPAG component of this model may have some predictive validity; as with PD, it responds to clonazepam, alprazolam, imipramine, and fluoxetine [62].

There is increasing evidence for a function of amygdala glutamate receptors in fear learning, fear-potentiated startles, and fear extinction [50,63]. More specifically, amygdala NMDA receptors may be involved in the neural changes that support fear learning and also loss of fear that accompanies extinction training [64•]. For example, mice lacking a fully functional glutamate NMDA receptor have been less sensitive to stress induced by the elevated plus maze, light-dark box, and forced swimming tests [65]. Amygdala alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors also participate in fear learning [66], and glutamate metabotropic group II receptor agonists block fear learning, as well as fear-potentiated startle [67].

Augmentation of traditional antidepressants with NMDA antagonists in various animal models of stress and depression [68], and their ability to re-establish anti-stress efficacy after antidepressant withdrawal [69], hints at the potential of future treatment strategies with glutamatergic agents [70,71]. Nevertheless, there is limited evidence for the role of glutamate in PD and for the efficacy of NMDA antagonists in the treatment of this disorder.

Social Phobia

Social phobia is characterized by excessive fear of social and performance situations. Patients may experience panic attacks, and they tend to avoid such situations [7]. Patients with SP respond to SSRIs [10], which suggests an involvement of the 5-HT system, although there is also evidence from clinical studies of dopaminergic involvement [72].

Some authors have suggested that SP is a uniquely human condition. Nevertheless, social submissiveness is seen in lower animals, and may constitute a cognitive-affective process that proves useful for studying the neurobiology of SP.

Social submissiveness

Social submissiveness has been a particular focus of attention in studies of nonhuman primates. For example, social status and degree of social affiliation are associated with altered hypothalamic-pituitary-adrenal axis function among free-range wild baboons [73•]. Socially subordinate baboons exhibit hypercortisolism and resistance to feedback inhibition after dexamethasone treatment. Nevertheless, it is unclear that SP is characterized by hypothalamic-pituitary-adrenal axis dysfunction [74].

Lower social status in monkeys is, however, associated with lower dopamine D2 striatal receptor density [75], a finding that is consistent with clinical research on SP [76]. Furthermore, social submissiveness in nonhuman primates decreases in response to administration of SSRIs [77]. These data lend support to the thesis that SP can be conceptualized in terms of an appeasement display [78].

Post-traumatic Stress Disorder

Post-traumatic stress disorder develops after an individual has experienced or witnessed a life-threatening traumatic event. The symptoms include reexperiencing the traumatic event (*eg,* flashbacks and nightmares), generalized arousal, and avoidance of stimuli associated with the trauma [7]. Clinical studies have implicated the amygdala and hippocampus [79], and have demonstrated enhanced negative feedback of the hypothalamic-pituitary-adrenal axis [80] and dysregulation of catecholamine neurotransmitter systems [81]. Patients diagnosed with PTSD respond to a range of medications, including tricyclic antidepressants, monoamine oxidase inhibitors, and SSRIs [10].

Animal models of PTSD have used intense stressors, aversive challenges, and situational reminders of a traumatic stress in an attempt to model long-term effects on behavioral, autonomic, and hormonal responses seen in humans with PTSD. Examples include electric shock [82], stress-restress or time-dependent sensitization (TDS) [83••], underwater trauma [84], and exposure of animals to a predator [85,86]. Models of early developmental trauma [87,88] may also be relevant to understanding PTSD. Relevant to this review, the authors will focus on the process of TDS.

Time-dependent sensitization

The behavioral model of stress-restress or TDS has been proposed as a useful model for PTSD [89••]. In this model, animals are exposed to single session of prolonged stress (*eg,* 2 hours of restraint followed by a 20 minute forced swim, followed by exposure to ether or halothane vapors). The animals are allowed to recover for a week, then they are subjected to a brief restress on day 7 (30 minutes of restrain stress or 20 minutes swim stress). The rationale being that the frequency of exposure to situational reminders contributes to the maintenance of fear-related behavioral disturbances over time.

The model has proved valuable for studying hypothalamic-pituitary-adrenal abnormalities relevant to PTSD [83••,90]. Animals subjected to TDS display the enhanced sensitivity to negative glucocorticoid feedback that is characteristic of PTSD while also demonstrating distinct changes in mineralocorticoid and glucocorticoid receptor expression in the hippocampus [90]. In addition, stress-restress evokes significant spatial memory deficits together with lowered plasma corticosterone, which is again consistent with clinical findings [91]. Stress-restress leads to changes in hippocampal 5-HT_{1A} and prefrontal cortex 5-HT_{2A} receptors [91], brain areas that are intimately involved in memory and stress responsiveness.

From a phenomenologic and biologic perspective, the TDS model emphasizes the role of past trauma in predicting subsequent dysfunction, allows for the study of bidirectional expression of symptoms (enhanced or reduced responsiveness to environmental stimuli), and provides credible intrasubject variation [89••]. Time-

Table 1. Cognitive-affective processes relevant to the molecular and anatomic basis of anxiety disorders as modeled by various preclinical models of anxiety

Disorder	Cognitive-affective process	Paradigm	Anatomy	Molecular
Generalized anxiety disorder	General avoidance behaviors	Elevated plus maze	Poorly defined	Serotonin, gamma-aminobutyric acid
Obsessive-compulsive disorder	Control repetitive movements	Spontaneous stereotypy (deer mice), acral lick dermatitis (canines), and drug-induced stereotypy	Corticostriatal circuits	Serotonin, dopamine, autoimmune
Panic disorder	Fear conditioning	Fear-potentiated startle	Amygdala, hippocampus, medial prefrontal cortex, dorsal periaqueductal gray	Serotonin, glutamate, gamma-aminobutyric acid
Social phobia	Social submission	Primate hierarchy	Amygdala, corticostriatal circuitry	Serotonin, dopamine$_2$
Post-traumatic stress disorder	Time-dependent sensitization	Rodent time-dependent sensitization	Hippocampus, prefrontal cortex	Hypothalamic-pituitary-adrenal axis, serotonin

dependent sensitization–induced stress effects on spatial memory are attenuated by fluoxetine and ketoconazole [92]. Moreover, in line with the increasing evidence for an involvement of glutamatergic mechanisms in the pathology and pharmacology of stress and anxiety [70,71], it is of interest that stress-restress evokes a significant increase in hippocampal nitric oxide synthase activity with marked changes in hippocampal NMDA receptors [93]. The efficacy of other anti-PTSD agents in the TDS model still needs further research.

With advances in genomics, it will be possible to explore the specific genetic basis of individual differences in processes such as TDS and susceptibility to PTSD [94]. A genetic animal model of congenital learned helplessness (cLH), for example, has been used to explore the role of genetic predisposition in PTSD [95••]. The first cLH breeding line was selected by subjecting out-bred Sprague-Dawley rats to random electric foot shocks. Twenty-four hours later, the animals were tested in a shock-escape paradigm where foot shock could be eliminated by a single bar press. Failure to eliminate the shock in 20 seconds counted as a failed trial. Rats scoring 11 to 15 failed trials in a 15-trial session were labeled cLH. Animals from the breeding line 33 of cLH animals were monitored for changes in pain tolerance, spatial memory, and hypothalamic-pituitary-adrenal function after reexposure to intermittent stress. Stress-induced analgesia was significantly increased in cLH animals. Congenital learned helplessness animals also exhibited significant deficits in spatial memory as measured by the Morris water maze. In addition, cLH animals exhibited hypothalamic-pituitary-adrenal hyporesponsitivity to major stressors, possibly because of enhanced negative feedback sensitivity [95••]. A decrease in pain sensitivity [96], impairment in memory [97], and enhanced negative feedback sensitivity [80] are features of PTSD. Further work is needed to determine if these animals are more at risk for developing adverse consequences after TDS, and if pharmacotherapy is effective in reversing dysfunction in cLH animals.

Conclusions

There is a growing understanding of the phenomenology and psychobiology of specific cognitive-affective processes (*eg,* fear conditioning, social submissiveness, and trauma sensitization) that may be relevant to the anxiety disorders. Although some of these processes are relevant to several different anxiety disorders, others (*eg,* control of stereotypic behaviors) are particular pertinent to specific conditions. Although cognitive-affective processes in humans may have unique attributes, it is possible to study such processes in other animals.

Such work has led to a number of animal models of anxiety that demonstrate varying degrees of face, construct, and predictive validity (Table 1). These models have broadened the understanding of the neuroanatomy and neurochemistry of anxiety disorders, highlighting regions such as the amygdala and hippocampus and systems such as serotonergic and glutamatergic circuitry. In the future, as new technologies become available to explore the precise molecular and genetic bases of cognitive-affective processes relevant to anxiety disorders, researchers can expect further progress. Ultimately, such work may lead to the development of novel treatment approaches.

Acknowledgments

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