Animal Models of Anxiety Disorders

Joachim D. K. Uys, MS, Dan J. Stein, MD, PhD, Willie M. U. Daniels, PhD, and Brian H. Harvey, PhD*

Address
Division of Pharmacology, School of Pharmacy, University of Potchefstroom, Potchefstroom, South Africa.
E-mail: fklbhh@puknet.puk.ac.za

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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 (e.g., antidepressants) for human anxiety disorders.

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 (e.g., 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.

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
studies with 5-HT1A agonists and selective serotonin 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-HT1A) receptor, or 5-HT1A knockouts (5-HT1A KO), show more anxiety 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-HT1A 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).

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].

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Obsessive-Compulsive Disorder
Obsessive-compulsive disorder is characterized by obsessions (recurring 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.

Dopaminergic 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].