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# Experimental modeling of anxiety and depression

Review

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**Abstract.** Anxiety and depression have dramatic impact on human and animal behaviors. We take an interdisciplinary approach and review the existing experimental models of anxiety and depression in order to promote further understanding of neurobiological aspects of anxiety and depression.

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**Key words:** anxiety, depression, experimental models

## INTRODUCTION

Stress plays the main role in pathogenesis of mental disorders (McKinney 1984, Willner 1997). Anxiety and depression are extremely common, dramatic and debilitating multifacetic disorders, and it is now becoming clear that without knowledge of both clinical and biological aspects of anxiety and depression, it is impossible to offer effective treatment strategies for the patients (Arborelius et al. 1999, Paterson et al. 2001, Willner 1997). According to McKinney (1984), we use animal models as "experimental preparations developed in one species for the purposes of studying phenomena occurring in another species". Over the past decades, there has been intensive study of a variety of neurobiological aspects of depression and anxiety (Nemeroff 2004, Raison and Miller 2003). Mice and humans share more then 90% of their genes, and animal models seem to be a useful tool in biomedical sciences, as evidenced by a notable increase in the number of active laboratories working in the field (Belzung 1999, Borsini et al. 2002). Furthermore, animal models are particularly of help in situations when the impact of stress cannot be studied in humans because of ethical and other like reasons. However, the choice of which biological correlates to study is not easy, since problems with animal models of human psychic disorders include: (i) the difference between human's and non-human's nervous systems; (ii) the difficulty in determining analogous behaviors among species; and (iii) the need in extrapolation of results from animals to humans. Such problems most likely reflect a significant difference in etiology and complexity of anxious or depressive behaviors. In addition, it is important to know that the data derived from animal models are of value only to the extend that the models are valid, and that the level (severity) of the disorder evoked in animals may not be the level of human disorder we want to model (Willner 1997). One of the current challenges is therefore to utilize the best of both clinical and neurobiological approaches to anxiety and depression. Here we focus on a comprehensive and systematic approach to the existing neurobehavioral markers and experimental models of anxiety and depression.

## GENERAL CONCEPTS IN THE EXPERIMENTAL MODELING

Behavioral repertoire of animals has long been used to detect effects on, and impact of, anxiety and depression (Arborelius et al. 1999, McKiney 1984, Paterson et al. 2001). A number of models, based on animal emotional reactivity, have been designed and proven to be bidirectionally sensitive to stressful manipulations, including those of anxiety and depression (Espejo 1997) (Tables I and II). Many of these models have been successfully used to test new anxiolytic or antidepressant drugs and understand the underlying neural mechanisms (Arborelius et al. 1999, Paterson et al. 2001, Willner 1997) by simple, rapid and inexpensive ways of evaluating an animal's condition (Table III). Although a substantial progress has been made in our understanding which stressors may affect behavior and how, there are several key questions in this field which still remain open. Can we distinguish between animal anxiety and depression? Do we have reliable neurobehavioral tools to assess anxiety and depression in animals? Do we always provide correct interpretations of behavioral changes seen in experiments? This paper reviews the traditional animal models of, and discusses neurobehavioral approaches to, experimental anxiety and depression.

Since classification of experimental animal anxiety and depression is as difficult as classification of human anxiety and depression spectrum disorders (Nemeroff 2004, Raison and Miller 2003), the main task is therefore to differentiate between common and specific stress-related pathogenic mechanisms of the disorders belonging to this spectrum. Animal anxiety and depression taxonomy can be based on the nature and type of stressors employed (Tables I and II), with the continuum of animal models used in experimental research ranging from "basic" animal assays to sophisticated homologous models (Newport et al. 2002). The former are based on animal behaviors that do not need to be similar to human symptoms while the latter share some functional similarity with human behavior. Depending on the aim of research, one can use simple models that utilize relatively primitive manipulations, complex models which incorporate both neurobehavioral and behavioral/cognitive aspects, or hybrid models that mechanically combine two working simple models in one new (Dere et al. 2002, Kalueff 2003, Sarter and Bruno 2002). Experimental models of anxiety and depression can be acute, sub-chronic or chronic (Willner 1997); inducing (e.g., by drugs, targeted gene mutations, brain lesions/stimulation or stressful external factors) or measuring pathology (in terms of behavioral and physiological reactions); "state" or "trait"; and those

Table I

Animal models in the study of anxiety and depression

| | | | |
|---|---|---|---|
| I. Depression | Acute | 1) Pharmacologic | Reserpine- or clonidine-induced (c) |
| | | 2) Stress-evoked | Porsolt test (forced swimming) behavioral despair task, tail suspension test, inclined and vertical screen test (c-e, l), pinch-induced catalepsy (m) |
| | Chronic | 3) Stress-evoked | Learned helplessness (unsignalled inescapable shock) Vogel/Gellert tests (p) |
| | | 4) Social disruption | Maternal or peer separation (c, u) |
| | | | Social defeat, altered group hierarchy, reduced submissive behavior (c) |
| | | 5) Chronic stress-evoked depression models (c), see also p. 7 | |
| | | 6) Sensory models | Olfactory bulbectomy (k) |
| | | | Long-term $ZnSO_4$-induced anosmia (s) |
| | | 7) Anhedonic models | Willner's test (sucroze consumption) |
| | | | Hedonic behavior suppression (q) |
| II. Anxiety | Acute | 1) Pharmacologic | Convulsant/stimulant-induced anxiety (c) |
| | | 2) Stress-evoked | "Forced" single-factor (novelty) or multi-factor tests (e.g., novelty and aversion): open field, elevated plus or zero-maze, light-dark box, holeboard, inclined or vertical screen test (a-i, n, p), seed seeking behavior in hamsters, shock-probe defensive burying, etc. (t, q) |
| | | | Free exploration paradigms (h, i) |
| | | 3) Social models | Social interaction (File's) paradigm (c) |
| | Chronic | 4) Stress-evoked | Learned anxiety (Geller conflict test) (p) |
| | | | Chronic forced exposure to various acute stressors (c) |
| | | 5) Social models | Chronic social defeat test (c) |
| | | 6) Prenatal stress-evoked "state" anxiety models (c, u) | |
| | | 7) Sensory models | Short-term ZnSO4-induced anosmia (s) |
| | | | Exposure to novel or predator odors, |
| | | | Amputation of vibrissae (c, s) |
| | | 8) Innate anxiety | Selected "high-anxiety" strains (d, p) |
| III. Transitory models: initially anxiety then depression | | | Anosmia-induced anxiety-depressive symptoms (s), partition social test (q) |
| IV. Combination models: anxiety and depression states to be measured simultaneously (c, q) ** | | | |
| V. Comorbidity models: allows to model anxiety or depression in comorbidity with other psychiatric illnesses (e.g., epilepsy, addiction, etc.) (a, c, q-s) | | | |

** e.g., Porsolt's swim and tail suspension depression tests are also sensitive to anxiolytics. References: (a) Kalueff et al. 2001; (b) Aguilar et al. 2002; (c) Kalueff 1999; (d) Moyaho et al. 1995; (e) Lapin 2000; (f) Andrade et al. 2003; (g) Kalueff 2002; (h) Belzung 1999; (i) Chapillon et al. 1999; (j) Salome et al. 2002; (k) Kelly et al. 1997; (l) Mayorga and Lucki 2001; (m) Fundarro 1998; (n) Chen et al. 2003; (o) Bouwknecht et al. 2000; (p) Flint 2003; (q) Kalueff 2003; (r) Rezvani et al. 2002; (s) Makarchuk and Kalueff 2000; (t) King et al. 2002; (u) Newport et al. 2002.

based on unconditioned or conditioned stress responses (King et al. 2002, Overall 2000). Wall and Messier (2001) suggest that anxiety models can be based on: (i) exploratory; (ii) social; (iii) defensive; (iv) novelty-evoked; (v) conditioned (active/passive avoidance); (vi) anhedonic behavior; and (vii) conditioned fear-related behaviors. In addition, there are numerous models of anxiety and depression based on prenatal and neonatal manipulations, including acute and chronic exposure to various stressors or different drugs (for a de-

Table II

Summary of animal conditioned response-based models (Flint 2003)

| | |
|---|---|
| Two way avoidance conditioning test “Shuttle box” | Rate of acquisition response |
| Acoustic startle | Contraction in response to loud noise |
| Foot shock induced freezing | Contraction in response to conditioned stimuli |
| Fear-potentiated startle | Contraction in response to loud noise in conjunction with loud noise |
| Geller (Geller-Seifnert) conflict test | Frequency of conditioned response coincidental to an electrical shock |
| Vogel conflict test | Frequency of conditioned licking coincidental to an electrical shock |

tailed review see Espejo 1997). Moreover, models of anxiety and depression can be "natural", based on measuring natural animal behaviors, or "artificial", utilizing behaviors not normally seen in natural conditions (Tables I and II) (see also Kalueff 2003, King et al. 2002). Natural animal models aim to reproduce behavioral and pathological aspect of the disorder, to investigate the neurobiological mechanisms that are not easily amendable to study in humans, and allow a reliable evaluation of a number of external factors including pharmacological agents (Overall 2000). Such ethologically based paradigms are more sensitive to stress compared to "artificial" animal conditioned behavior models which usually use strong and often painful stressors (Table IV). Clearly, the stressfulness of the test has to be taken into account when analyzing the behavior, as it may significantly affect behavioral performance. Since extreme stressors suppress general activity and result in non-specific alterations in animal performance (Sarter and Bruno 2002), our paper will focus on the first, more suitable, group of models of anxiety and depression.

## SOME METHODOLOGICAL ISSUES

Are animal anxiety and depression a good approximation of human disorders? Which tests can be good models, and which particular subtypes of anxiety of depression they model? These questions are relatively rarely asked, but are fundamentally important. The use of nearly all animal models has been extensively criticized in the literature for several reasons. First, many clinically important, especially cognitive-based, symp-

Table III

Principal behavioral profiles in experimental models of anxiety and depression

| Behavioral Indices | Anxiety | Depression |
|---|---|---|
| General locomotion | + | - * |
| Exploration | - | - |
| Self-grooming | + (frequency) | + (duration) |
| Immobility | + (freezing) | + (despair)** |
| Defecation, urination | + | ? |
| Aggression | + | + |
| Self-aggression | 0 | + |
| Transitions between behaviors | + | - |
| Risk assessment | + or - *** | - |
| Some other “specific” behaviors **** | + | 0 |

(+) increased; (-) decreased; (?) unclear or inconsistent effects; (0) no effects; *activated in the open field in olfactory bulbectomy model of depression; **in Porsolt’s swim and tail suspension tests; ***depending on the model; **** e.g., seed finding, shock-probe defensive burying, etc., see King et al. (2002) for details.

Table IV

Major behavioral measures in experimental models of anxiety and depression

| Tests | Neurobehavioral Parameters | Anxiety | Depression | Refs |
|---|---|---|---|---|
| Open field | Defecations/urinations number and duration | + | - | |
| (circular, square or rectangular | Total distance traveled or squares crossed | - | +* | |
| open lit arenas) | Speed of movements | + | - | |
| | Distance in the inner area | - | | |
| | Number of squares crossed in the inner area | - | + | (a-c) |
| | Distance in the outer area | - | + | |
| | Self-grooming latency | - | - | |
| | Self-grooming duration | + | +? | |
| | Self-grooming frequency | + | ** | |
| | Interrupted (aborted) or incorrect grooming (%) | + | + | |
| | Average duration of a single grooming | - | | |
| | Stretch Attend postures | + | - | |
| | Latency of the 1st and the 2nd visits to the central area | + | ? | |
| | Latency to leave the central area | + | ? | |
| Open field with novel objects | Approach latency | + | 0 | |
| | Number of contacts | - | 0 | (a) |
| | Duration of exploration of the novel object | - | 0 | |
| Elevated plus maze | Latency to leave the centre | + | | |
| (plus- or zero-shaped maze) | Total arms entries (4 paws criterion) | + | - | (b-g) |
| | Enclosed arms entries | ? | | |
| | Open arms entries (4 paws) and rears (2 paws) | - | | |
| | Time spent in the open arms | - | | |
| | Time spent in the enclosed arms | + | | |
| | Open arms entries (%) | - | | |
| | Time spent in the open arms (%) | - | | |
| | Head dips | - | | |
| | Defecations, urinations | + | + | |
| | Self-grooming latency | + | - | |
| | Self-grooming duration | + | + | |
| | Self-grooming frequency | + | - | |
| | Central platform crossings and time spent | - | ? | |
| Hole board test | Head dipping (hole poking) | - | ? | (a-c) |
| (open field arena with | latency | + | + | |
| "exploratory" holes) | number, duration | - | - | |
| | Defecations, urinations, total distance traveled/squares crossed, distance/squares crossed in the inner area, distance in the outer area, self-grooming, rears | as in the open field | as in the open field | |
| Light/dark box | Light box entries number (4 paws criterion) | - | - | |
| (two boxed interconnected with | Light box time spent | - | - | (c, g) |
| a sliding door) | Light box rears number (2 paws criterion) | - | - | |
| | Duration of light box rears | - | - | |
| | Latency of the first rear and entry | - | - | |
| | Vertical activity in the light box (c) | + | ? | |
| | Urinations, defecations, grooming | + | ? | |

Table IV (continued)

| Tests | Neurobehavioral Parameters | Anxiety | Depression | Refs |
|---|---|---|---|---|
| Exploration of novel objects | Number of approached and contacts | - | - | |
| | Duration of contacts | - | - | (b, h) |
| | Latency of the first approach/contact | + | + | |
| Free exploratory paradigm | Number of entries to the novel compartment | - | ? | |
| | Time spent in the novel environment | - | ? | (i) |
| | Latency to enter the novel compartment | + | ? | |
| | Stretch attention, rearing to the novel box | - | ? | |
| Porsolt's swim test | Immobility latency (until first floating) | ? | - | |
| (water tank) | Immobility duration in the water tank | ? | + | (b, j) |
| | Swimming average speed and distance | - | - | |
| Olfactory bulbectomy | Behavioral hyperlocomotion in the open field | - | + | |
| | Aggression | | + | (c, k) |
| Tail suspension test | Immobility latency | +? | + | |
| | Immobility duration | +? | + | (c, l) |
| | "Tail-climbing" | - | - | |
| Inclined screen retention test | Time spent on the screen (falling latency) | - | - | |
| | Urinations, defecations | + | - (?) | (c) |
| Pinch-induced catalepsy | Duration of catalepsy | +? | +? | |
| | Required number of pinches | +? | +? | (m) |
| Stress-induced hyperthermia | The amplitude of hyperthermia | + | ? | |
| | The duration of hyperthermia | + | ? | (n, o) |
| Hypo-neophagia | Latency to start eating novel food | + | ? | (p) |

(+) activation; (-) inhibition of a behavioral pattern; (?) unclear effects; *olfactobulbectomy model; **different effects of anxiety (shortened, reversed) and depression (prolonged, stereotypic). References as in Table I.

toms of anxiety and depression can not be directly modeled in animals. Second, behavioral measures are often confounded and reflect changes in general activity, exploration and anxiety-depression levels (Belzung and Griebel 2001, File 2001, Lapin 2000, Rodgers and Cole 1994). Third, we often see poor correlation between different behavioral measures taken in the same test, or the same measures taken in several different tests (Kalueff 2003). For example, grooming and defecation can often be seen as the only behaviors that change in the tests designed to measure anxiety behaviors (Kalueff 2002, Kalueff et al. 2001). Even the simplest task – distinguishing between horizontal exploration and locomotion in the open field, often mistakenly used synonymously in the literature – still requires further elaboration (Choleris et al. 2001). Thus, since it is difficult to interpret a subjective anxiety or depression levels based on a single behavioral measure, proper understanding of animal state is only possible through assessment of interaction between behavioral and physiological variables in the multivariate analysis (Catalayud and Belzung 2001). Since various forms of psychopathologies in animals and humans can be characterized as context-regulation disorders, subjects may sometimes produce "normal" behavior in inappropriate contexts. Thus, special analysis of behavioral contexts may be needed in the field of animal anxiety and depression. Finally, it should be noted that animal emotional behavior is not just "plus" or "minus", but has several dimensions including anxiety, exploration, locomotion, risk assessment, general arousal and coping (Salome et al. 2002). These dimensions interact with each other as well as with cognitive functions, giving a complex mosaic picture of behavior. Therefore, the traditional quantitative behavioral methods (i.e., latency, frequency and duration parameters and their spatial, temporal or sequential patterns) to study animal stress are now combined with sophisticated analysis of "not just the presence or absence of these behaviors, but also whether or not the … acts, postures and gestures are fully developed in intensity, la-

tency and patterning" (Barrett and Miczek 2000). Finally, because not all robust behavioral changes seen in experiments represent meaningful parameters for assessment of animal anxiety and depression, there is a need for clear-cut measures resistant to experimental conditions or apparatus design of particular laboratories but showing reliable and predictable changes following experimental manipulations affecting anxiety and depression states (Table IV).

However, here appears a new cluster of issues. First, can we possibly model different subtypes of anxiety and depression? For example, distinct subtypes of anxiety can be modeled in the same test, as suggested by Holmes and Rodgers (2001) for the elevated plus maze (single vs. repeated testing). Second, although depression and anxiety are considered to be separate entities according to current diagnostic classifications, in clinical practice these two conditions often co-exist. "Ideal" modeling of anxiety or depression in animals presumes that in order to achieve better results we model either pathology separately. However, the important problem now is whether animals may possibly have comorbidity of depression and anxiety. Theoretically, there are no reasons to rule out this possibility, and modeling comorbidity may represent certain interest for the researchers. Relatively few such studies have been conducted, and there is a great need in developing specialized models which will allow to assess comorbidity in animals. For example, Wistar-Kyoto rats have been recently suggested as an animal model of anxiety and depression based on their frequent anxiety-like freezing and depressive-like swim immobility (Tejani-Butt et al. 2003). Gass et al. (2001) suggested that mice with targeted mutations of gluco/mineralocorticoid receptors can also be the model of anxiety and depression. Recently high-anxiety HAB rats (Salome et al. 2002) have been suggested to be a reliable model of trait anxiety and depression. Thus far, measuring comorbidity of anxiety and depression or their comorbidity with other pathologies (e.g., addiction, alcoholism, etc.) may present an important direction for future studies.

## VALIDITY AND RELIABILITY ASPECTS

The discussion focusing on different aspect of animal models validity is crucial for experimental modeling of anxiety and depression. Validation is usually defined as the process by which the reliability and relevance of a method are established for specific purposes. Reliability is characterized by the reproducibility of a test within and between laboratories and over time. Since numerous differences exist between laboratories, good reproducibility at least within the same laboratory has to be established (Salome et al. 2002). As summarized in Table V, three principal and some additional validity

Table V

Summary of validity of animal models of anxiety and depression

| Validity | Importance | Brief description |
|---|---|---|
| **Major** | | |
| Face | - | Reflects phenomenological similarities (isomorphism) between the model and human pathology to be modeled |
| Predictive | + | Based on ability to predict drugs or manipulations effective in animal models to be effective in humans. May be limited to the drugs or manipulations it has been designed for |
| Construct | ++ | Based on similar theoretical rationale (homology) behind the pathology in animals and humans. May be limited to the extend of our knowledge of pathological mechanisms |
| **Additional** | | |
| Discriminant | - | Degree to which a test measures aspects of a phenomenon that are different from other aspects of the phenomenon that other tests assess |
| Convergent | - | Degree to which a test correlates with other tests to measure the same construct |
| Etiological | - | Degree of similarity of etiology of animal and human states |
| Genetical | + | Degree of similarity of the genes involved in anxiety or depression induced in a particular test |

(-) not important; (+) important; (++) critically important

criteria have been formulated and substantiated for animal models of anxiety and depression, including predictive, construct, concurrent or convergent, discriminant, etiological and face validity (Geyer and Markou 2000, Sarter and Bruno 2002). In addition, genetical validation based on behavioral phenotyping approach, is becoming increasingly important (Flint 2003). A "behavioral phenotype" refers to the specific and characteristic behavioral repertoire exhibited by animals with a specific genetic/chromosomal disorder (Flint 2003). However, the question whether certain behaviors shall be a part of behavioral phenotype, is not clearly understood, especially since an association between behavior and syndrome, and between the syndrome and the gene, is not always clear-cut and linear (Flint 2003).

On validity basis, animal models can be classified as: (i) correlational – based on predictive validity; (ii) isomorphic – based on face validity; and (iii) homologous – based on construct validity. In general, a model shall fulfill all 3 criteria in order to be good model (Bai et al. 2001, Clement et al. 2002) which means to be correlational, isomorphic and homologous at the same time. However, this situation is not seen in animal modeling very often. For example, traditional models of depression, such as Porsolt's forced swim and the tail suspension tests, lack face and construct validity but are extremely good at predictive validity (Bai et al. 2001). In general, despite the fact that some animal models have poor construct and predictive validity, and there is a disconnect between predictive validity and face validity (Overall 2000), construct validity seems to be the most important for the animal model of anxiety and depression.

## CONCLUSIONS

As it was mentioned earlier, all animal models are generally seen as an attempt to reproduce a human disorder in a laboratory animal (McKinney 1984). However, since the symptoms of psychiatric disorders are often being revised and their pathogenesis revisited (Borsini et al. 2002, Boyer 2000, Geyer and Marko 2001, Sarter and Bruno 2002), some caution is needed before claiming or using an animal model of anxiety or depression. With this in mind, we shall always remember that, as McKinney (2001) incredibly timely and rightly noted, generating the perfect animal model does not represent a separate goal of research, rather the model and its constant evolution represents an integral part of neuropsychobiology. Moreover, modeling proceeds most effectively when psychiatrists, who are experts in the phenomena in question, join forces with neuroscientists, who know and understand available modeling tools (Davidson et al. 2002). Today, with the growing number of medical professionals being involved in basic research, and neuroscientists involved in clinically-oriented studies, an interdisciplinary view of neurobiology of anxiety and depression, linking human data to animal experimentation, is becoming extremely important.

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