Appendix A14.5

Modeling Psychopathology in Animals: Theoretical Considerations and Future Directions

Modeling in animals is an invaluable tool in exploring the underlying pathologies of human diseases and in developing better therapies. However, modeling psychopathology is a much more difficult task compared to other somatic diseases, primarily because of three major considerations (Einat et al., 2002; Nestler et al., 2002):

1. Much of the diagnosis of psychiatric disorders is based on reports of symptoms, rather than specific, objective measures
2. There are no adequately validated biological markers for psychiatric disorders
3. Many features of major psychiatric illnesses can only be fully appreciated in humans, wherein the cortical mantle has evolved to such an extent as compared to other species

In developing appropriate animal models, it is imperative always to be cognizant of the question, "Models for what?" Overall, existing models in psychiatry can be divided to three major groups:

A. Heuristic models that infer the existence of a common primary mechanism behind an animal behavior and a human pathology. These models can then be used to study the biological mechanisms underlying those symptoms and to develop new treatments that alleviate the symptoms. Most animal models for mood disorders fall into this category. By use of a variety of stressful conditions and/or pharmacological manipulations, they induce in animals certain symptoms that are inferred to be "depression-like" or "manic-like." The main limitation of these models is that they may poorly reflect mechanisms involved in the human situation. As a result, the biological basis of the animal symptoms may be very different from the biological basis of human symptoms and drugs that treat the former may not treat the latter.

B. Theory-driven, evidence-based models, which emphasize a common etiological or behavioral feature of both the model and the pathology. In the case of depression, for example, one could replicate in a laboratory animal the etiological factors that cause depression in humans and, consequently, many of the symptoms as well. A related approach is to model a disease mechanism in a laboratory animal and recreate particular features of the disorder. Both of these approaches have been used with considerable success in recent years in creating animal models for several neurological conditions (e.g., Huntington's disease; familial Alzheimer's and Parkinson's diseases) for which the underlying genetic abnormalities are known. However, our understanding about the complex neurobiology of bipolar disorder has precluded the use of such strategies at this time. Moreover, many of the core symptoms of depression and mania involve higher brain functions that cannot readily be modeled in animals.

C. Representative models that include generalization of validated behaviors to model the pathology (Overmier and Patterson, 1988; Ursin and Murison, 1986).

Choosing an appropriate model for a disease will depend on a number of factors, including the existing knowledge of the etiology of the disease, the specificity of available treatments, and the facilities needed to induce the model behavior in laboratory animals (Einat et al., 2002).

Validating Criteria for Animal Models

The process of validation of an animal model of psychopathology includes three criteria: face validity, predictive validity and construct validity (Willner, 1986; Willner, 1991).

1. *Face validity* represents the commonalties in overt behavioral features between the model and the modeled disorder.

2. *Predictive validity* represents the degree to which the specific drugs that are effective in treating the disorder will have a corresponding "therapeutic" effect on the behavioral model. Since the behavioral models are only gross approximations of psychiatric disorders, it is also critical to determine that non-therapeutic drugs do not also reverse the behavior in question.

3. *Construct validity* represents a possible common mechanistic theory that can explain both the model and the modeled disorder (Willner, 1991).

Most of the existing models have been developed from a face validity starting point—a researcher noticed the appearance of a rodent behavior that is similar to a human pathological behavior and undertook investigations of other aspects of validity. It is only recently that attempts have been made to develop models starting from a truly construct validity standpoint.

Since most models do not meet all three validation criteria, the choice for an appropriate model depends on the task on hand. When a researcher attempts to screen new drugs, a model with high predictive validity may be the best choice. However, when the goal is to explore the etiology of a disease, a model with high construct validity may be the most appropriate choice (Dixon and Fisch, 1998; Willner, 1995). For example, attempts to screen new antidepressant drugs are best suited to the predictive models that respond to acute treatment (to provide high throughput, and the ability to investigate larger numbers of agents) whereas attempts to study the mechanisms of depression should utilize models that respond only to chronic treatment (in a similar way to the pattern of responding in depressed patients).

Induction of Animal Models of Psychopathology

The major approaches to inducing animal models of psychopathology are pharmacological, behavioral/stress-related, and genetic (Einat et al., 2002). For example, depletion presynaptic stores of monoamines with reserpine treatment is frequently used as a pharmacological model of depression, as reserpine induces hypoactivity that can be reversed by antidepressant drugs (Einat et al., 1999). Behavioral models include analysis of spontaneous behaviors, or experimental manipulations that alter the behavioral repertoire of the animal. For instance, exposure of rats to chronic mild stress results in behavioral changes that have been suggested to constitute a depressive-like state that can be used to model depression (Willner et al., 1987). A genetically-induced model can be developed by breeding animals for a specific trait that characterizes a psychiatric disorder or, more recently, by directly manipulating genes that are thought to be related to the etiology of a psychiatric disorder (Crawley, 1999). For example, rats were bred for alcohol preference in order to model alcohol addiction (Overstreet et al., 1992).

Some of the better-validated animal models for psychiatric disorders have a significant value both for drug development and for etiological studies. The relatively simple Porsolt forced swim test model of depression is used in both these contexts (Kirby and Lucki, 1997; Rossetti et al., 1993). This test is based on two exposures (in rats) or one exposure (in mice) to a water tank that does not permit escape (Borsini and Meli, 1988; Porsolt, 1979; Porsolt et al., 1978; Redrobe et al., 1996; Sanchez and Meier, 1997). The attempts to escape and activity levels during the second exposure (in rats) or the later part of the exposure (in mice) serve to model the level of "despair" of the animal, which represents its depressive-like state (Porsolt et al., 1977). The forced swim test has some face validity (reduced activity and motivation model human symptoms of depression), good predictive validity (treatment with antidepressant drugs but not other psychiatric drugs increase test activity levels), and some construct validity, since the test has been reported to influence brain monoaminergic systems (Willner, 1991).

The forced swim model is frequently used for the evaluation of new drugs both in academic and in industrial settings. Whereas pharmacologically- and behaviorally-induced models predominated research for many years, the significant recent advancements in molecular biological techniques and in the ability to produce targeted mutations in mice has resulted in much attention being directed towards genetically-induced models. As with other methods, models based on genetic modifications can be the outcome of both a mechanistic hypothesis or of a phenotype screen of many available mutants. Whereas both approaches contribute to the advancement of our understanding of specific disorders, it is noteworthy that the novel molecular techniques may offer great new possibilities to explore specific hypotheses (Tarantino and Bucan, 2000). Behaviorally-induced models have the advantage of being naturalistic and may resemble (somewhat extreme) environmental situations that precipitate affective-like behavior in animals and humans, but targeted mutations supply the tools to explore the interactions between specific molecules and behavioral outcome. Hypotheses-driven targeted mutation can be based on human linkage studies or on molecular theories of a disease, such as the serotonergic theories of anxiety disorders that led to in-depth studies of the behavioral phenotype of 5HT receptor mutants. Some of these studies indeed demonstrated that mice with null mutation of the 5HT1A (but not 5HT1B) gene display a variety of behaviors that can be interpreted as representing anxiety-like behavior (Ramboz et al., 1998).

Table A14.5a
Current Animal Models of Mood Disorders: Pros and Cons

Depression Models	**Pros**	**Cons**
Forced swim test (Porsolt test)	Responds to antidepressant treatment; relatively easy to perform; behaviorally relevant; Induces biochemical changes relevant to pathology of depression	Responds to acute drug treatment; may not identify drugs with novel actions; antidepressants effects may not be clear for some inbred strains of mice
Tail suspension test	Responds to antidepressant treatment; relatively easy to perform;	Responds to acute drug treatment; may not identify drugs with novel actions;
Learned helplessness	Results in neurovegetative symptoms reminiscent of depression; responds to some antidepressant treatments	Requires extreme stressors; may be better model of PTSD Depends on ability to learn
Chronic Mild stress	Causes some depression-like Symptoms; responsive to Antidepressants; relevant Etiology – life stresses	Difficult to produce; difficult to show antidepressant activity
Early life stress	Causes some depression-like symptoms; effective in rodents and primates	Changes in social behavior not well-characterized in rodents; effects of antidepressants need to be better established
Selective breeding	Focuses on individual differences in susceptibility to depression or depression-like behavior	Only the FSL rat line have been well validate. Prolonged process; animals that demonstrate depressive-like properties may also have other irrelevant changes.

Reward models	May provide measure of affective state and model motivational symptoms of depression	Not yet validated in more traditional models of depression and antidepressant action Also needs a pretreatment or intervention to produce a depressive-like state as antidepressants don't change the baseline behavior.

Mania and Bipolar Models	**Pros**	**Cons**
Psychostimulant-induced hyperactivity	Reproduces some mania-like symptoms; sensitive to Li^+ and possibly to anticonvulsant mood stabilizers	May not be useful for identifying drugs with novel actions; responses vary greatly across strains
Sleep deprivation	Causes some mania-like symptoms; sensitive to Li^+	Difficult to control for non-specific stress effects. A very short window of the behavioral phenomenon after a relatively long induction period.
Behavioral sensitization psychostimulants	Models progressive aspects of bipolar disorder	Equivocal findings regarding to the effects of mood stabilizers; models only mania.
Amygdala kindling	Models progressive aspects of bipolar disorder; seizures affected by Li^+	Not behaviorally relevant

Models of Depression and Bipolar Disorder: Opportunities for the Future

There is a clear need to develop better models in order to identify neural circuits in the brain related to depressive and manic symptomatology, pathophysiological mechanisms that underlie depression and mania, and the genetic and non-genetic underpinnings of normal mood regulation and of abnormal affective episodes (Nestler et al., 2002). Ultimately, such bona fide animal models may only be developed once the etiology and pathophysiology of human mood disorders are identified. For example, despite all attempts at studying animal models of Alzheimer's disease in previous generations, only now are adequate models becoming available based on the genetic and molecular lesions of the disease. Nevertheless, until such information is available for depression, several approaches are being investigated which have considerable potential to move the field along. Some of the most promising approaches include examination of neural circuits involved in mood disorders, gene-environment interactions, phenotype-based mutagenesis, quantitative trait locus analysis, candidate gene mutations, inducible and cell-targeted candidate gene mutations, and non-human primate models (discussed at length in Nestler et al., 2002).

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