Models of Depression

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Contents

Abstract

The incidence of depressive illness is high in the United States and worldwide, and the inadequacy of currently available drug treatments contributes to the significant health burden associated with depression. A basic understanding of the underlying disease processes in depression is lacking, and therefore, recreating the disease in animal models is not possible. Currently used models of depression attempt to produce quantifiable correlates of human symptoms in experimental animals. The models differ in the degree to which they produce features that resemble a depressive-like state, and models that include stress exposure are widely used. Paradigms that employ acute or subchronic stress exposure include learned helplessness, forced swim test, and tail suspension test, which employ relatively short-term exposure to inescapable or uncontrollable stress and can reliably detect antidepressant drug response. Longer-term models include chronic mild stress models, early-life stress models, and social conflict models, which may more accurately simulate processes that lead to depression.

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These models each have varying degrees of face, construct, and predictive validity for depression and contribute differently to our understanding of antidepressant processes.   © 2010 Elsevier Inc.

I. Introduction

Major depressive disorder is a leading cause of disability worldwide, with a lifetime population prevalence as high as 20% (Kessler *et al.*, 2005). Depression is a heterogeneous group of illnesses that vary in symptomology and most likely in etiology. Symptoms of depression include depressed mood, loss of pleasure, inability to concentrate, lack of energy, dysregulated sleep or appetite, feelings of worthlessness or guilt, and thoughts of suicide (DSM-IV). In addition to the personal suffering and loss associated with depression, the high incidence and chronic nature of depressive illness result in a significant public health burden. This is estimated to be tens of billions of dollars each year for the United States, largely due to loss of productivity in the workplace (Wang *et al.*, 2003).

The public health impact of depression is partially due to the fact that available treatments are suboptimal. Antidepressant drugs in use today are based on the strategy of blocking the reuptake or degradation of monoamine neurotransmitters (Morilak and Frazer, 2004). Tricyclic antidepressants and monoamine oxidase inhibitors were used as antidepressants starting several decades ago and led to the development of the serotonin-selective and nor-epinephrine-selective reuptake inhibitors (SSRIs and NRIs, respectively) that are widely used today. Significant percentages of depressed patients do not respond to any of the available drugs. For patients that do respond, therapeutic effect develops slowly, usually over several weeks of chronic drug treatment and patients are at risk during this time. The SSRIs and NRIs have improved safety and side-effect profiles compared to the older drugs, but because the primary mechanisms are similar, the therapeutic efficacy and the drawbacks (slow therapeutic onset, low remission rates, and treatment resistant patients) are also similar (Nestler *et al.*, 2002; Sonawalla and Fava, 2001). Improvement of therapeutic options (especially designing treatments for patients that do not respond to currently available drugs) depends on the identification of under-lying pathological processes in depression and potential mechanisms for their reversal. Both human and animal studies are essential to these goals.

II. General Considerations in Modeling Depression

A basic understanding of the underlying disease processes in depres-sion is currently lacking, and therefore recreating the disease in animal models is not possible. Currently used models of depression attempt by

various means to produce quantifiable correlates of human symptoms in experimental animals. Some of the most prominent symptoms of depression are subjective feelings, which are not readily assessed in animals. This makes it necessary to model symptoms of depression that can easily translate to behaviors that are measurable in animals. Psychomotor, sleep, and appetite changes are not uniformly useful for the investigation of neurobiological mechanisms as these behavioral alterations can occur in either direction in depression. Currently used animal models for depression research vary considerably in the extent to which they produce features that resemble a depressive-like state. Examples of measures that can be assessed in rodent behavioral models include motor responses to stress, reward–related responding and social interaction, with the rationale that they reflect levels of helplessness or despair, anhedonia, and social withdrawal, respectively, all relevant to human depression.

The models are generally evaluated for their reliability or reproducibility, their ability to accurately predict outcome in humans (predictive validity), their ability to reproduce in animals aspects of the illness in humans (face validity), and the extent to which they model the true disease process or its etiology in humans (construct or etiologic validity) (McKinney, 2001; Willner, 1984, 1997). Predictive validity includes the ability of a model to accurately detect treatments that are useful clinically. While the utility of many of the models to be discussed here is based on their predictive validity for pharmacological treatments, an important feature that has been lacking in the more widely used models is an accurate reflection of the temporal characteristics of treatment effectiveness as it occurs in humans. This consideration has become increasingly important as mechanisms of neural plasticity are implicated as central to antidepressant effectiveness (Pittenger and Duman, 2008).

The degree of construct and/or etiologic validity is generally low in most currently used animal models for depression, mainly because the pathophysiological basis for depression is not known. Although the models attempt to produce specific behavioral or physiological features of depression, the features in the animal models likely come about through processes that are very different from those operative in human depression. Therefore, results need to be carefully interpreted for relevance that may be more specific to the model than for human depression. This is an important limitation of currently used models. Because they are used largely based on their abilities to detect mechanisms of current antidepressant drugs, they select for those (known) mechanisms and may lack the ability to detect potentially novel mechanisms. This emphasizes the importance of using animal models with features that result from processes believed to be relevant to human depression.

III. Stress and Models of Depression

Exposure to stress is a main environmental risk factor associated with the occurrence of depression (Keller *et al.*, 2007; Kendler *et al.*, 1999; Kessler, 1997). Recent work has indicated that stress exposure may interact with genetic risk factors to increase susceptibility to depression (Caspi *et al.*, 2003; Kaufman *et al.*, 2006). For these reasons, many animal models have attempted to reproduce some core components of major depressive disorder through exposure to stress. Experimentally, the outcome of stress exposure is influenced by several variables, including the nature of the stress (physical/systemic vs. cognitive/psychological), the severity of the stress, and exposure parameters. Different neural circuits are activated by different types of stressors. For example, differential involvement of limbic pathways is thought to occur for the processing of stressors that differ in their systemic versus cognitive/psychological nature (Anisman and Matheson, 2005; Herman and Cullinan, 1997). The degree of control an animal has over stress exposure has been demonstrated to be important to the consequences of stress exposure, for example, behavioral impairment and increased brain amine utilization can be seen after exposure to uncontrollable stress but are not apparent when a subject is able to control the stress exposure (Anisman and Matheson, 2005). The degree of predictability is also thought to affect the outcome–repeated stress exposure. Greater unpredictability can reduce the probability of adaptive processes occurring upon repeated stress exposure and promote the appearance of stress effects such as brain monoamine utilization and behavioral changes (Anisman and Matheson, 2005; Willner *et al.*, 1987).

The inclusion of a stress component and an appropriate temporal profile can strengthen the validity of a model. This chapter discusses rodent behavioral models of depression that include a stress component, including learned helplessness (LH), forced swim test (FST), and tail suspension test (TST), in which rodents are exposed to relatively acute or subchronic stress. The FST and TST have been widely used as screening tests for antidepressant activity. Chronic paradigms such as chronic unpredictable mild stress exposure, early–life stress (ELS) paradigms, and social defeat/conflict models are also discussed (Table 1.1). These models are considered more naturalistic in the induction of a depressive-like state and are suggested to have better potential homology to the human situation. Surgical, pharmacological, immune, or genetic models, while useful to the field, have been reviewed elsewhere and are not covered in this chapter (Crowley and Lucki, 2005; Dunn *et al.*, 2005; El Yacoubi and Vaugeois, 2007; Henn and Vollmayr, 2005; Overstreet *et al.*, 2005; Song and Leonard, 2005).

Table 1.1 Stress-based models of depression and antidepressant response

Model	Stress	Test duration	Primary endpoint	Advantages
LH	Inescapable footshock	Subchronic	Active avoidance	Depression-like syndrome
FST	Water immersion	Acute	Immobility	Ease of use Predictive validity
TST	Suspension	Acute	Immobility	Ease of use Predictive validity
NSF/NIH	Environmental change	Acute	Feeding	Predictive validity No food restriction
CUS	Varied mild	Chronic	Anhedonia	Construct and Predictive validity
ELS	Deprivation	Chronic	Endocrine or behavioral	Etiologic validity
Social defeat	Conflict/defeat	Acute or chronic	Social avoidance	Construct and Predictive validity

LH: learned helplessness, FST: forced swim test, TST: tail suspension test, NSF: novelty-suppressed feeding, NIH: novelty-induced hypophagia, CUS: chronic unpredictable mild stress, ELS: early-life stress.

IV. Models

A. Learned helplessness

The LH paradigm uses a stress-exposure period in which rats or mice are exposed to inescapable stress (e.g., electrical footshock) in one or more sessions. In a subsequent session, the animals are tested for their performance in an active avoidance test. In a typical active avoidance test, animals are confined to one side of a shuttle box chamber where footshocks are delivered but the animal has the opportunity of actively escaping the footshock. Animals previously exposed to inescapable stress show reduced abilities to escape in this model. The reduced ability to escape is restored by different forms of antidepressant treatment, including tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and electroconvulsive shock therapy (Martin *et al.*, 1990; Sherman *et al.*, 1982). This model has good validity for predicting antidepressant efficacy (Willner, 1984), and there are few reports on false positives. This model has been used to demonstrate the importance of controllability of the stressor as a key psychological component in inducing the behavioral deficit (Anisman and Matheson, 2005). Animals that are helpless in this model also show several features that have similarity with human depression, including decreased motor activity, weight loss, altered sleep, decreased motivation, and increases in stress hormones (Maier, 1984). Despite the presence of these features along with behavioral helplessness, there is no way of knowing if the LH model reproduces the pathophysiology of depression.

The time course for induction and for treatment effect in LH paradigms is improved (subchronic) compared with the acute responsiveness of the FST and TST (explained later). LH models can identify subgroups of stress-exposed animals that are more prone to becoming helpless. Using LH to identify vulnerable and resistant subgroups can be a useful strategy for investigating mechanisms underlying differential susceptibility and has analogy to the human situation. Limitations of LH models include low reproducibility and the relevance of the induction methods has been questioned (Nestler *et al.*, 2002).

B. Forced swim test

The FST involves placing a rat or mouse in a cylinder with enough water so that it cannot touch the bottom with its hind paws (Porsolt *et al.*, 1977a,b, 1978). A normal animal will show an immediate burst of activity, try to escape, and then eventually adopt an ''immobile'' posture, where it will make only those movements necessary to keep its head above water. The development of immobility may be facilitated by prior exposure to the test

and a 24-h prior preexposure to the test is often used (Porsolt et al., 1978). Immobility is quantified during brief test periods and classical antidepressants such as the monoamine oxidase inhibitors, tricyclics, and atypical antidepressants all decrease the duration of immobility in rats and mice in a dose-dependent manner (Borsini and Meli, 1988; Porsolt et al., 1977a,b). A modified FST procedure is often used in rats that allows behavior in response to norepinephrine-selective drugs to be distinguished from behavior after treatment with serotonin-selective antidepressants. The modification involves separately quantifying the predominant active behaviors as either swimming or climbing. Swimming behavior predominates for serotonergic antidepressants and climbing predominates for drugs that are primarily noradrenergic, allowing the FST to detect this distinction (Detke et al., 1995; Lucki, 1997). The FST may yield false positive results with drugs that increase locomotor activity, and correspondingly, decrease immobility (e.g., amphetamine). In addition, the FST does not uniformly distinguish acute from chronic antidepressant effects. The FST is sensitive to genetic variation as indicated by strain differences in performance and drug effects in rats and mice (López-Rubalcava and Lucki, 2000; Porsolt et al., 1978).

C. Tail suspension test

The TST is conceptually similar to the FST and is suggested to have greater sensitivity. A mouse is suspended by the tail in this test and observed for the extent of immobility versus active movement (Steru et al., 1985). Similar to the FST, the TST is also based on the adoption of a passive response in a stress situation. Acute antidepressant treatment given prior to the test reduces immobility time in the TST and it is considered to have good predictive validity (Cryan et al., 2005; Perrault et al., 1992; Steru et al., 1985). Although conceptually similar, the TST and FST do not show identical sensitivities to pharmacologic agents or to strain differences, suggesting that responding in these tests may be determined by nonidentical substrates (Bai et al., 2001). Different mouse strains respond differently to basal immobility in the TST, indicating that this test is sensitive to genetic influence (Ripoll et al., 2003). The strain response profile for antidepressant response is different from the profile for basal response, indicating that the determinants for basal and antidepressant responding are not identical (Liu and Gershenfeld, 2001; Trullas et al., 1989). Differential sensitivity between strains for antidepressant response is suggested to be related to variations in monoamine levels (Ripoll et al., 2003).

The TST is used only in mice and not in rats due to their larger size and weight. The TST has similar limitations to the FST, including a false positive response to psychostimulants and acute drug response. The high reliability of the FST and TST has also contributed to their use and they are

both considered useful for investigating differences between strains in reactivity to stress.

LH, the FST, and TST do not reproduce the pathophysiology of depression but they are useful in that they induce changes that are sensitive to therapeutic agents in a manner predictive of their effects in humans. The FST and TST have been used extensively for this purpose, but the selectivity of these tests for monoamine-based mechanisms may limit their ability to detect novel mechanisms (Lucki, 1997; Thiébot et al., 1992; Weiss and Kilts, 1995; Willner, 1990).

D. Hyponeophagia paradigms

Examples of hyponeophagia tests that are used in rats and mice are novelty-induced hypophagia (NIH) and novelty-suppressed feeding (NSF) paradigms. They are anxiety based and compare feeding behavior in an anxiogenic versus a nonanxiogenic environment. The stress employed in these models is very mild relative to most other tests for antidepressant action, and consists of placing the experimental animal in a novel environment to induce anxiety during testing. The animal experiences conflict between the desire to approach and feed or drink, and the anxiety-induced avoidance of the novel environment.

The NIH procedure described by Dulawa et al. (2004), measures latency and volume for consumption in a familiar (home cage) versus a novel environment. Mice are habituated to drink a palatable liquid (sweetened milk) and then given the opportunity to approach and consume it in two test sessions. The first session occurs in the home cage and serves as a control for potential treatment effects on appetite. The subsequent test session occurs in a similar cage except that additional parameters (location, lighting) are chosen to be mildly anxiogenic. Consumption measures from the novel cage are compared with the same measures obtained in the home cage and the difference score is the measure of hyponeophagia. The inclusion of the home cage control that utilizes equivalent measures in a home cage detects and controls for potential alterations in consumption-related variables. Using palatable food or drink as the test substance avoids the use of food deprivation, which can complicate interpretation. These hyponeophagia models have good predictive validity. They respond to the anxiolytic effects of benzodiazepines and barbiturates and respond to antidepressants which are anxiolytic (Dulawa and Hen, 2005). Importantly, the predictive validity also applies to the temporal course of response. The hyponeophagia paradigms detect the clinically relevant acute and chronic anxiolytic effect of benzodiazepines (Bodnoff et al., 1988). They detect anxiolytic effects of antidepressants only after chronic treatment, which agrees with the clinical profile for this effect in humans (Bodnoff et al., 1989; Dulawa and Hen, 2005). Additionally strengthening the predictive validity is the fact that

hyponeophagia paradigms can detect increased anxiety, including that resulting from acute SSRI treatment, an effect that is not reliably detected in other models but is clinically relevant (Dulawa and Hen, 2005). While being sensitive to chronic influences, the paradigms benefit from having no significant training requirement. Hyponeophagia models are sensitive to genetic influences on anxiety (Dulawa and Hen, 2005).

The anxiety component in hyponeophagia models provides a degree of face validity. There is significant comorbidity of major depression and anxiety disorders (Fava *et al.*, 2000; Kaufman and Charney, 2000). Anxiety and depression may result from closely related mechanisms as suggested by their common symptomology, family and population studies that suggest that vulnerability may result from common genetic factors, imaging studies that indicate ADT-responsive abnormalities in similar brain areas for the two disorders, and comparable efficacy of ADT in the treatment of both disorders (Drevets *et al.*, 2008; Kaufman and Charney, 2000; Ressler and Nemeroff, 2000; Serretti *et al.*, 2009). These considerations suggest vulnerability of common neural substrates and support the growing body of evidence for overlap in the neural circuitry that modulates anxiety and mood. They further validate the appropriate use of anxiety components in antidepressant models.

E. Chronic unpredictable mild stress

In comparison to LH and FST/TST procedures that rely on relatively short-term aversive stress exposure, the chronic unpredictable mild stress (CUS) paradigm was developed to study neural changes that result from stress of a more chronic nature. CUS paradigms aim to model a chronic depressive-like state that develops gradually over time in response to stress, and is thus considered more naturalistic in the induction. A CUS paradigm was first studied by Katz and colleagues, and this idea was further developed by Willner (Katz *et al.*, 1981a,b; Willner, 1997; Willner *et al.*, 1987) providing the basis for most of the currently used paradigms. Most of the procedures employed for CUS share certain common features such as use of a stressor variety, use of stressors that are mild in severity, and use of stress exposure schedules that are semirandom and unpredictable. Rats or mice are exposed to a series of different stress conditions over a period of several weeks. Several stressors (6–8) are applied (1 or 2 per day) for several hours each day. Typical stressors include overnight illumination, periods of food or water restriction, cage tilt, and isolation or crowded housing. The sequential and unpredictable stress exposure decreases the likelihood of the animals habituating to any one reoccurring condition (Aguilera, 1998; Magariños and McEwen, 1995; Tannenbaum *et al.*, 2002).

The gradual development of a decrease in reward sensitivity or anhedonia is a central focus of CUS paradigms. Decreased ability to experience

reward is a characteristic common to all forms of depression and it is amenable to repeated measurement as a quantifiable endpoint for assessing the effectiveness of CUS. Exposure to CUS can result in several other behavioral and physiologic changes that have analogy with symptoms of depression, such as decreased reward-related behavior, decreased self-care, and changes in sleep that respond to antidepressant treatment. These and other abnormalities, including increased hypothalamic–pituitary–adrenal (HPA) axis activation and immune system abnormalities, support face validity of this model (Willner, 2005). These changes develop gradually over time with CUS exposure and suggest improved face validity of this compared with the more acute stress models. Construct validity for CUS is largely based on the development of reduced sucrose preference, which is interpreted to reflect anhedonia, a core symptom of depression (Willner, 1997).

Anhedonia in the CUS model responds to chronic but not acute treatment with several classes of antidepressant drugs, indicating good predictive validity (Papp *et al.*, 1996). Hedonic measures are not altered by antidepressant treatment in the control animals in the model, in agreement with the lack of effect of antidepressants in altering hedonic response in humans (Willner *et al.*, 1987). False positive responses are reported but predictive validity for CUS is strengthened by the time course and the general lack of effectiveness of nonantidepressants. Reliability had been questioned for the CUS model, but is considered significantly improved, as reviewed by Willner (1997, 2005). The CUS paradigms are time-consuming to perform, but the growing reliability and the temporal characteristics as well as the validity of using anhedonia as an endpoint has resulted in increasing use of CUS models.

F. Hedonic sensitivity

Methods for quantifying hedonic sensitivity include conditioned place preference procedures in which animals learn to associate a particular environment with reward experience, brain-stimulation reward (BSR) paradigms, and quantifying consumption of sweet solutions. Quantifying consumption of sweetened fluids (sucrose or saccharin) is the most commonly employed endpoint for assessing CUS effectiveness. Rats previously habituated to sucrose are typically given a choice of drinking sucrose versus water in a two-bottle test. While control rats typically show a preference for drinking weak sucrose solutions, rats exposed to CUS loose this preference. The development of this effect can be demonstrated by repeated sucrose preference testing during the course of CUS exposure. The time-dependent reversal of this effect with chronic antidepressant treatment can also be demonstrated by repeated testing. The dependence of sucrose consumption/preference on several experimental variables has been investigated,

including sucrose concentration, temporal parameters, test duration, and body weight (D'Aquila *et al.*, 1997; Muscat and Willner, 1992; Willner *et al.*, 1996). Compared to rats, stress–sensitive changes in sucrose preference are more difficult to establish in mice. Decreases in sucrose consumption in a one-bottle test rather than preference can be demonstrated in mice after CUS, but this measure does not have the advantage of the simultaneous control measure for water drinking, which is a component of preference tests (Monleon *et al.*, 1995; Pothion *et al.*, 2004). Anhedonic measures after CUS are sensitive to strain effects for both rats and mice (Nielsen *et al.*, 2000; Pothion *et al.*, 2004).

In BSR paradigms, animals with implanted electrodes are trained to perform a specific operant response that results in the administration of rewarding electrical stimulation into a specific area of the brain. Operant responding relative to the stimulation intensity is quantified as a measure of reward system sensitivity and the motivation to obtain reward. BSR paradigms can be used to investigate stress effects on reward function, including effects of CUS and ADT, although results can be variable and subject to individual differences (Moreau *et al.*, 1992; Nielsen *et al.*, 2000). BSR paradigms are useful in that they can distinguish elevations in reward function from aversion, and a BSR paradigm has been developed in which alterations in reward function can be distinguished from treatment-induced influences on response performance (Markou *et al.*, 1992; Todtenkopf *et al.*, 2004; Carlezon and Chartoff, 2007). BSR paradigms avoid the appetitive and satiation effects that can complicate interpretation of behavioral responding for consummatory rewards such as food. Despite the positive features of BSR paradigms, they require surgery, training, and are less widely used than sucrose testing.

G. Early-life stress

Early–life adverse experience is an important predisposing factor for psychopathology in humans. Several human studies indicate that exposure to stress or adversity early in life increases the risk for depression, and that stress exposure may interact with genetic risk factors (Agid *et al.*, 1999, 2000; Caspi *et al.*, 2003; Kaufman *et al.*, 2006; Weiss *et al.*, 1999). Experimental paradigms have been developed in an effort to model ELS, and are used as models in which to investigate determinants of experience-dependent susceptibility to depressive illness. The ELS models typically employ stress exposure during critical periods of development and result in stable phenotypic changes. ELS-induced changes that have been particularly replicable involve alterations in neural systems that regulate or respond to stress such as the HPA axis and include endocrine, neurochemical, and behavioral alterations. Changes in stress–responsive systems after ELS could be relevant

to consequences in humans after ELS and may suggest mechanisms that predispose to depressive illness. Improved construct/etiological validity of ELS models will depend on further phenotyping of ELS animals in depression models and improvements in the validity of research models or assessing depression-related traits after ELS (Heim et al., 2004; Pryce et al., 2005).

Maternal separation. Parental care is increasingly implicated as an important modifier of stress effects during development in humans, and maternal deprivation paradigms are useful as developmental animal models of predisposition to affective disorders/depression (Heim and Nemeroff, 2001; Holmes et al., 2005; Kendler et al., 2002; Newport et al., 2002). A role of maternal behavior in programming emotion-related behavior in the offspring has been suggested to have evolutionary/survival value by ''translating'' the stress level in the environment into offspring emotional reactivity that is suited to that environment (Zhang et al., 2006).

A number of maternal deprivation paradigms exist that utilize repeated periods of separation of preweanling rats from the mother. Preweanling rats are exposed to daily episodes of 3–6 h separation during a critical period in the first 2 postnatal weeks and the separation can include the intact litter from the mother, or individual pups can be separated from littermates and the mother. Previously separated animals are then allowed to develop under normal conditions through adulthood, when phenotypic characteristics are evaluated. As adults, previously separated rats show behavioral abnormalities, including increased anxiety and fear responses, reduced motor activity, reduced social motivation, reduced hedonic responding, sleep and appetite disturbances, and endocrine and neurochemical alterations in stress–relevant systems (Ladd et al., 2000; Levine, 1957; Mintz et al., 2005; Plotsky and Meaney, 1993; Rüedi–Bettschen et al., 2005, 2006). Stress responsiveness of the HPA axis is a consistent finding, but traits in depression tests are more variable and appear to depend on rat strain (Pryce et al., 2005). Many of the behavioral changes in maternal separation models have analogy with symptoms of depression and the neuroendocrine changes are consistent with depression (Heim et al., 2004; Pryce et al., 2001, 2005). The stability of the phenotypic changes allows these models to be useful for investigation of mechanisms, including gene expression, related to mood disorders (Law et al., 2009). Some effects of maternal separation are counteracted by chronic antidepressant drug treatment or ECT (Leventopoulos et al., 2009), but establishment of predictive validity requires further studies. Maternal separation paradigms in rodents target critical periods of postnatal development when the brain is very susceptible to experience-dependent alterations. These models are suggested to have face validity for disrupted parenting behavior in humans that can result from a number of situations, including parental depression, also likely to occur during critical periods of development (Newport et al., 2002).

A variation on maternal separation paradigms is a related paradigm that uses the quantification of levels of maternal care as it occurs naturally rather than experimentally manipulating maternal care (Francis *et al.*, 1999; Liu *et al.*, 1997). In this work, licking/grooming of pups and arched back nursing have been identified as important features of maternal behavior in female rats. Naturally occurring variations in these maternal behaviors are quantified and low levels are considered to represent a stress condition for the offspring. Levels of maternal care have been demonstrated to correlate with levels of stress–reactivity (HPA activity and anxiety-related phenotype) in the adult offspring (Liu *et al.*, 1997). This result has analogy to the maternal separation paradigms described above and with the correlation of HPA reactivity in humans with prior ELS (Heim *et al.*, 2001). Alterations in HPA axis responsiveness in humans after ELS may predispose to later depression (Heim *et al.*, 2001, 2004; Kendler *et al.*, 2002). This paradigm thus represents a way to identify a population of depression/anxiety-susceptible individuals in an experimental setting and the stable phenotype allows for the study of mechanisms that may underlie features of the phenotype.

ELS paradigms are sensitive and time-consuming and results obtained depend on choice of comparison control groups used. But, unlike some of the shorter-term stress models, the ELS paradigms produce animals with lasting depression-related features and can therefore inform the study of stress contributions in predisposing individuals to chronic anxiety and depressive illness. Familial transmission of depression is likely to involve both genetic and environmental components, and individuals who inherit genetic susceptibility to depression may also be exposed to adversity in the early environment as a result of depression-related behavior in the parents (Kendler *et al.*, 2002; Newport *et al.*, 2002). The work of Meaney and colleagues, with their paradigm of variation in maternal care and cross-fostering, has made significant advances in describing detailed molecular mechanisms whereby stress-related phenotype can be transmitted from mother to offspring via stable changes in gene expression (Kaffman and Meaney, 2007).

Prenatal stress. The impact of stress has also been modeled in prenatal stress paradigms. Maternal stress of various types, for example, noise exposure or restraint during gestation results in alterations in the offspring, including increased anxiety, increased indices of depression in depression models, and altered HPA axis activity (Alonso *et al.*, 1991; Maccari *et al.*, 2003; McCormick *et al.*, 1995; Morilak and Frazer, 2004; Morley-Fletcher *et al.*, 2003; Secoli and Teixeira, 1998; Smith *et al.*, 2004; Weinstock *et al.*, 1992). Behavioral alterations in the FST depression model, anxiety, and HPA axis changes that result from prenatal stress are reversible with chronic antidepressant treatment (Morley-Fletcher *et al.*, 2004; Poltyrev and Weinstock, 2004). Alterations in HPA axis are similar to those caused by

prenatal stress in humans (Weinstock, 1997). Prenatal stress paradigms have construct and face validity, but the anxiety and depression–related changes that are induced in the mothers complicate the interpretation as to the relative contributions of gestational versus postnatal care effects.

H. Social defeat

Social stress represents a significant type of adversity in many species and is thought to play a role in the development of depression and other psychopathology in humans (Agid *et al.*, 2000; Bjorkqvist, 2001; Huhman, 2006). The use of social conflict as a stressor and the use of social interaction as a quantifiable endpoint both have validity for depression (Heim and Nemeroff, 2001). Experimental models in rodents frequently utilize a conflict situation that results in one animal becoming or retaining dominant status and another ending up subordinate or ''defeated''. A phenotypic trait produced in these models is social avoidance, which can be quantified and is suggested to model social withdrawal in human depression (Berton *et al.*, 2006; Koolhaas *et al.*, 1997; Van Kampen *et al.*, 2002).

Social stress models are suggested to represent an induction of a depressive–like state that may be more relevant to human depression compared with models that employ acute or severe stressors. In these models, social conflict is created between male animals. This can be done by introducing an intruder animal into the home cage of another resident. The experiments are generally designed taking into account factors such as strain, body weight, and social status to ensure an outcome in which a defeated animal is produced. Paradigms are used which vary the number of conflict sessions and the nature of the conflict (psychological vs. physical). Physical attack and threat of attack (exposure to sensory contact with another animal but with a barrier to physical attack) can be used separately or combined within a paradigm. Control animals for these experiments should also be exposed to social contact but without conflict or defeat. Two important depression-related features that occur in defeated animals are anhedonia, measured as reduced preference for sweet solutions, and social avoidance in the presence of an unfamiliar animal (Meerlo *et al.*, 1996; Rygula *et al.*, 2005; Von Frijtag *et al.*, 2002). Other behavioral or physiologic changes include decreased sexual behavior and increased defensive behavior, increased anxiety, decreased locomotor or exploratory activity, changes in circadian rhythmicity, alterations in feeding and body weight, sleep disturbances, and impaired immune function (Bohus *et al.*, 1993; Koolhaas *et al.*, 1997; Martinez *et al.*, 1998; Meerlo *et al.*, 1996). The HPA axis is activated in defeated animals, which is similar to other stress models (Buwalda *et al.*, 1999).

Social avoidance and anhedonia that result from social defeat are long-lasting and are sensitive to chronic but not acute treatment with antidepressant drugs (Berton *et al.*, 2006; Huhman, 2006; Meerlo *et al.*, 1996, 2002;

Von Frijtag *et al.*, 2002). This indicates the utility of social defeat models in studying time-dependent neural processes relevant to depression. Animals can be identified as susceptible or resistant to the effects of social defeat, indicating further value of social defeat models for investigating substrates of individual vulnerability (Krishnan *et al.*, 2007). Social defeat has proven useful in identifying molecular mechanisms that can induce stable changes in phenotype (Krishnan *et al.*, 2007).

V. Concluding Remarks

The more rapid and acute antidepressant-responsive assays such as the FST and TST have been useful in identifying new drugs that share mechanisms with the older known drugs. While these assays are sensitive to the identified antidepressant mechanisms, it is possible that they are not sensitive to other mechanisms that could be of therapeutic value in treating depression. The identification of novel and improved antidepressant mechanisms depends on models that can recapitulate critical processes operative in depression. Until critical processes are identified, models that incorporate stress exposure, time-dependent induction and treatment response, and individual differences in susceptibility will be the most valuable in facilitating the study of mechanisms underlying depression and its treatment.

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