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The recent progress in animal models of depression

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ABSTRACT

Major depression disorder (MDD) is a debilitating mental illness with significant morbidity and mortality. Despite the growing number of studies that have emerged, the precise underlying mechanisms of MDD remain unknown. When studying MDD, tissue samples like peripheral blood or post-mortem brain samples are used to elucidate underlying mechanisms. Unfortunately, there are many uncontrollable factors with such samples such as medication history, age, time after death before post-mortem tissue was collected, age, sex, race, and living conditions. Although these factors are critical, they introduce confounding variables that can influence the outcome profoundly. In this regard, animal models provide a crucial approach to examine neural circuitry and molecular and cellular pathways in a controlled environment. Further, manipulations with pharmacological agents and gene editing are accepted methods of studying depression in animal models, which is impossible to employ in human patient studies. Here, we have reviewed the most widely used animal models of depression and delineated the salient features of each model in terms of behavioral and neurobiological outcomes. We have also illustrated the current challenges in using these models and have suggested strategies to delineate the underlying mechanism associated with vulnerability or resilience to developing depression.

1. Introduction

Major depressive disorder (MDD) is one of the most debilitating mental illnesses with a 12-month life-time prevalence of ~17% (Kessler et al., 2003). About 350 million people worldwide suffer from MDD (World Health Organization, 2003), whereas within the United States, about 15 million people are affected with this mental illness (Hedden et al., 2015). MDD is associated with significant morbidity and mortality (Carney et al., 2002). About 50% of depressed patients show suicidal ideation or thought and ~10% commit suicide (Kovacs and Garrison, 1985). The existing mechanisms for the development of therapeutic drugs are mostly based on "monoamine hypothesis" which suggests that decreased concentration of monoamine neurotransmitters plays a role in MDD (Tran et al., 2003). These drugs include selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAS) and inhibitors of degradation of neurotransmitters such as monoamine oxidase inhibitors (MAOIs) (Brunello et al., 2002). However, a significant population of depressed patients (20% to 30%) does not respond to these medications. This is partially due to our limited understanding of the precise neurobiological mechanisms associated with depression (Krishnan and Nestler, 2008). Recent evidence suggests that the incidence of depression is caused by alterations in the complex signaling networks. These networks cover monoamine neurotransmitter systems, neuroendocrine system, neurotrophic factors, neurogenesis, altered immune system, and epigenetic modifications (Abrous et al., 2005; Butler et al., 1989; Calvano et al., 2005; Castrén et al., 2007; Kim et al., 2006; Ponomarev et al., 2012). There is also a considerable contribution of genetic factors to the pathogenesis of depression (Shi et al., 2011). In addition, the interaction of susceptible genes and stress environment also plays a major role in the etiology of this disorder (Ohadi et al., 2012).

The major limitations in delineating the precise neurobiological mechanisms of depression lie in its complex nature, its heterogeneity, and its association with other comorbid psychiatric disorders (Krishnan and Nestler, 2008). The use of peripheral tissues from patients, such as blood, has limited value. Some of the limitations have been overcome by using post-mortem brain samples from human subjects; however, their availability is scarce and is often associated with confounding variables such as prior or current antidepressant treatment, post-mortem interval, agonal state, and pH of the brain (Bunney et al., 2003; Lewis, 2002). In a majority of the cases, post-mortem tissues are available from depressed patients who committed suicide, which may have its own or overlapping neurobiological mechanisms (Krishnan and Nestler, 2008). In this regard, animal models provide a crucial avenue to examine neural circuitry along with molecular and cellular pathways that may be critical in the pathogenesis of depression. There has been

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skepticism of the use of animal models because animal cognition is dissimilar to the higher cognitive and emotional prowess of humans. However, over the years, these models have been refined to cover several aspects of depression-like and cognitive behavior that closely resemble human depression (Nestler and Hyman, 2010; Wong and Licinio, 2001). Animal models are also helpful not only in avoiding obstacles in human studies of depression-related ethical concerns, but also in issues with obtaining adequate sample sizes (Pryce et al., 2005).

Animal models are established based on three basic constructs: face validity (phenotype similar to humans who have the illness), construct validity (processes that result in human pathology are recapitulated with the model), and predictive validity (sensitivity to pharmacological and non-pharmacological interventions that are effective for the disease or condition in humans) (Nestler and Hyman, 2010). However, some of the studies propose to include other features such as homological validity (species and strain validity), mechanistic validity (similar cognitive or biological mechanisms) and pathogenic validity (etiological and biomarker validity) (Belzung and Lemoine, 2011). Based on the etiology of depression, the animal models have been developed on the basis of acute or chronic stress exposure, gene-environmental interaction, exogenous administration of glucocorticoids, and genetic manipulations (Caspi and Moffitt, 2006; McGonagle and Kessler, 1990; Surís et al., 2010; Uher and McGuffin, 2010). Each model has its own set of advantages and disadvantages. We have reviewed the often used depression models in rodents and their usefulness in delineating the neurobiological and molecular mechanisms. It is difficult to cover every aspect of each model described here; however, our approach has been to provide an overview of the salient features that can be used to advance research designed to improve our understanding of neurobiology and treatment of depression. The salient features of each model is listed in Tables 1 and 2.

2. Behavioral batteries often used to establish depression models in rodents

2.1. Cognition and emotion

When considering the use of animals for studying depression, one must take into account the assessment methods for evaluating behavioral changes. Several aspects of cognitive and emotional features can be assessed including fear conditioning which can be used to measure fear response, memory, and anxiety (Dibbets et al., 2015; LeDoux et al., 1990; Phillips and LeDoux, 1992). The general setup of fear conditioning is that the rat is placed in a fear conditioning chamber. It is then presented with an aversive stimulus like foot shock or a loud noise (white noise at ~55 dB), which is paired with a neutral stimulus like a light in the chamber box or a lower-level tone (Helmstetter and Bellgowan, 1994). Typically, the animal in the chamber will be conditioned to associate the neutral stimulus with the aversive one and will react with a freezing behavior along with physiological responses like increased heart rate. Animals with an anxiety/depressive phenotype will have longer periods of freezing as well as a greater incidence of anticipatory freezing compared to controls (LeDoux et al., 1983; Brandão et al., 2008; de Oliveira Galvão et al., 2011) (Tables 1 and 2).

2.2. Behavioral despair

The forced swim test (FST) assesses despair based on how a rodent reacts to an unpleasant environment (Porsolt et al., 1977). For instance, a rat that is placed in water typically tries to escape. However, if it exhibits a more depressive behavior, it will simply float without attempting to escape until rescued.

Tail suspension test (TST) is another important behavior test to measure the response on the stress situation. The rodent tails are suspended with adhesive tape to a horizontal bar for 6 min and the time

Table 1
Assessment of various behavior and their advantages and disadvantages.

Behavioral assessment	Emulated MDD behavior	Suitable strains	Test advantages	Test disadvantages
Shock avoidance/escape latency (ET)	Hopelessness	Holtzman	Creates depression susceptible (LH) and resilient (NLH) groups for comparison	Requires additional rats due to the differentiation of LH and NLH rats; requires specific equipment and program administration and analysis
		cLH	Similar to human patients with treatment-resistant MDD	Does not allow for comparison of LH and NLH rats
Forced swim test (FST)	Despair	Most rodents	Quick and inexpensive; simple drug screening test	Weak validity and high variability depending on factors like temperature of water, size of cylinder, depth of water; results can be compounded by motor deficits
Tail suspension test (TST)	Despair	Mouse models	Inexpensive; simple drug screening	Only tested in mice; results can be compounded by motor deficits
Open field test (OFT)	Anxiety/motor-locomotion	Most rodents	Quick and inexpensive; simple drug screening test	Does not specifically test depression - only anxiety
Sucrose preference test (SPT)	Anhedonia	Most rodents	Inexpensive; simple drug screening test	Weighing or measuring methods may vary from one lab to another; spillage can occur
Elevated plus maze (EPM)	Anxiety	Most rodents	Simple process for anxiety assessment	Does not specifically test depression - only anxiety
Intracranial self-stimulation (ICSS)	Reward sensitivity/ anhedonia	Most rodents	Precise administration and drug localization is known to the researcher	Requires surgery, canula and proper administration equipment
Operant fear conditioning	Fear/anxiety	Most rodents	Inexpensive; simple drug screening	Does not specifically test depression - generally for anxiety

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