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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.

Keywords

Rodents; depression; model; behavior; review

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

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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 postmortem brain samples from human subjects; however, their availability is scarce and is often associated with confounding variables such as prior or current antidepressant treatment, postmortem interval, agonal state, and pH of the brain (Bunney et al., 2003; Lewis, 2002). In a majority of the cases, postmortem 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 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.

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 ~55dB), 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).

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 minutes and the time of immobility is observed. If the subject shows more depressive-like behavior, it will exhibit an increase in the amount of immobility time. To be noted, the TST is used only in mice, but not in rats due to the larger size and weight; in a majority of cases, TSTs are used to detect the antidepressant response (Steru et al., 1985).

2.3. Hopelessness

Shock avoidance, which is a measure of escape latency to aversive, electrical stimuli, is a measure of depressive behavior (Seligman, 1972). Mice or rats are presented with an

inescapable shock (0.6 mAmp, 100 times at random intervals for about 5 seconds each); typically, this is to the tail via electrodes or to the paws via an electric grid. The subjects are then placed in a shuttle escape chamber 24 hours after the initial inescapable shock. A very mild electric current is passed through the grid on the floor of the shuttle box. The subject must cross from one side of the chamber to the next in order to inactivate the shock; this is the acclimation period which lasts for five shocks. During the testing period, which begins immediately after the acclimation, the animal must cross one side of the chamber to the other then return to the original side to deactivate the shocking floorboard. Typically, a non-depressed animal will escape from the shocks successfully immediately or within ~5 seconds. An animal that is depressed will typically have a delayed escape time which in mild cases can range from 10–19 seconds while a severely depressed rat will delay its escape as late as 20 to 30 seconds. In some cases, severely depressed subjects do not escape the shock at all, enduring it for the full 30 second period, which is generally the cutoff point of electric current (Maier and Seligman, 1976).

2.4. Anxiety-like symptoms

Elevated plus maze (EPM) is used to assess anxiety. In the EPM, a mouse or rat is placed at the center of an elevated four-arm “maze.” The anxiety is measured by the amount of time the rodent spends in the closed arms versus the opened arms. Typically a non-anxious rodent will explore the open arms while an anxious one will either stay completely within the closed arms or only peek out from the center while its body is concealed within the closed arm (Pellow et al., 1985).

2.5. Anxiety and locomotor activity

Open field test (OFT) is often used to test both anxiety and locomotor activity. In OFT, a rodent is placed in a large circular or square enclosure and allowed to move ad-libitum. Anxiety is determined by the ratio of “wall hugging” to center exploration. A non-anxious rodent will explore the center of the enclosure more than an anxious one, which will cling to the walls or simply stay in one place like a corner (Denenberg, 1969).

2.6. Anhedonia

Anhedonia, a loss of interest in things that were once pleasurable, can be assessed by means of the sucrose preference test. Mice and rats have a preference for water with sucrose dissolved in it over regular water. When a rodent shows a lack of interest in the sucrose solution, it is said to be exhibiting anhedonia which is a classic attribute of depression (Klein, 1974).

Intracranial self-stimulation (ICSS) is an important tool which is used for detecting anhedonia and aversion (dysphoria). In this test, the brief electrical pulses are delivered into the specific brain regions to affect the reward-pathway activity. Lowering of ICSS thresholds represents a strong brain stimulation reward, whereas the relative higher ICSS thresholds reflect the diminished reward value of the stimulation and an anhedonia state. Like sucrose preference test, reduced self-stimulating reward reflects loss of interest, fatigue, desire and energy along with depressive-like behavior (Cryan et al., 2003).

There are other simple measures, after behavioral batteries, like assessing animal weight gain/loss or corticosteroid levels compared to controls. When considering animal models and methods to test them, one should consider that the model must fulfill certain criteria, namely phenomenological similarities, pathophysiological (face validity), similar etiology (construct validity) and common treatment for rescuing the behavioral despair (predictive validity) (Anisman and Matheson, 2005; Vollmayr et al., 2007; Willner and Mitchell, 2002). Also, no single test or model is an acceptable, stand-alone diagnostic measure. Rather, combinations of anxious, depressive, despair, and anhedonia behaviors can be used to assess the occurrence and severity of depression. Using these assessments, a researcher may be able to study different aspects of depression in order to further knowledge and treatment of depression as a whole.

3. Animal Models of Depression

3.1. Learned Helplessness (learned helpless, LH)

Learned helplessness (LH) is a phenomenon discovered and explored initially by Seligman and his colleagues in the 1970s (Seligman, 1972). For the first experiments, dogs were placed in chambers where electric shocks were applied to their paws from which they were unable to escape. They were then tested in a chamber where they had a visible escape route; they needed to jump over a hurdle when the shock was applied to escape the shock. According to Seligman, 2/3 of the 150 (or 100 dogs) dogs subjected to the inescapable shock would not attempt to escape the shock when placed in the escape shuttle box. He coined the term “learned helplessness” in the wake of this study. Seligman also defined a “cure” of sorts in his paper. If a learned helpless dog was placed in a chamber with no barrier and shocked, it would simply lie down and wait for the termination of the shock. If a handler were to repeatedly drag the dog by leash to the side of the box where electric shock was not being applied, the dog would eventually learn to escape the shock on its own. He proposed that this was a strong model for depression as it created a hopeless, inescapable and uncontrollable scenario, a resulting depressive reaction, and a method to ameliorate learned behavior. It should be noted that Seligman and his colleagues did compare these dogs to groups that had the ability to control their environment: i.e. the dog could press a lever and terminate the shock. These dogs had no problem escaping the shock when placed in the shuttle escape box. Seligman concluded that it was the inability to control traumatic events, like the shocks, that led to a learned helpless phenotype. One of the major attractions of this model is that it is derived from the cognitive view of depression in which events are viewed negatively and interpreted as not controllable, leading to feelings of anxiety and helplessness when dealing with them. Later, this phenomenon was applied in rodents and similar results were found when these animals were subjected to random inescapable shock.

There are many similarities between the LH animal and human depression. For example, uncontrollable stressful events, which precipitate depression-like behaviors observed in rodents, similarly precede the onset of some clinical depression in humans (Gold et al., 1988; Lloyd, 1980). Moreover, exposure of animals to similar but controllable events does not produce relevant behavioral changes (Corum and Thurmond, 1977; Weiss et al., 1982). Several of the principal symptoms that characterize clinical depression are seen in stressed

animals. These include decreased motor activity (Seligman and Maier, 1967; Weiss et al., 1980), decreased eating and drinking, weight loss/lack of weight gain (Ritter and Balch, 1978), decreased grooming (Zacharko et al., 1983), decreased competitive behavior (Corum and Thurmond, 1977; Peters and Finch, 1961), increased errors in a choice/discrimination task (Sherman and Petty, 1982), decreased response to rewarding brain stimulation (Zacharko et al., 1983), and sleep disturbances (Weiss et al., 1985). These symptoms closely resemble those typically used for the diagnosis of depression. In summary, the exposure of animals to highly stressful uncontrollable events produces a model of depression characterized by an etiology and symptomatology that resembles clinical depression in humans and makes this an interesting and reliable model to explore the pathophysiology of depression.

Our laboratory has reported a unique finding with Holtzman Sprague-Dawley rats when they are exposed to inescapable shock. Generally, ~50% of rats exposed to this stress become learned helpless and have delayed escape latency in an escape chamber. The remaining rats, however, are resilient, and escape from the shock with escape latencies that mirror the tested control rats who received no tail-shock. This unique feature allows the studying of a resilient group. This can be looked at in one of two ways: either there is something intrinsically unique about the non-helpless rats which prevents them from becoming helpless or that the rats that become learned helpless have maladaptive features which makes them susceptible to the depressed phenotype (Dwivedi et al., 2004).

Neurochemical studies have been performed to unveil the underlying mechanisms of learned helplessness. For decades, research directed at understanding the neurochemical mechanisms underlying learned helplessness has focused on the monoamines.

Uncontrollable stress may activate and sensitize 5-HT-neurons in the dorsal raphe nucleus and reduce the release of norepinephrine in the locus coeruleus (Amat et al., 2005; Weiss and Simson, 1986). In addition, decreased dopamine signaling and over activation of the habenula in response to prediction and escape suggested coping deficits in learned helplessness (Ilango et al., 2012; Shumake et al., 2010). Learned helplessness can be reversed by chronic, but not acute, treatment with monoaminergic antidepressants. BDNF signaling plays an important role in the pathophysiology of learned helplessness. Infusion of BDNF into the dentate gyrus of hippocampus produced an antidepressant-like effect in the LH. In response to uncontrollable stress, BDNF mRNA and protein are significantly increased in sub regions of the medial prefrontal cortex (mPFC) and the hippocampal formation (HF) of male Sprague-Dawley rats (Aznar et al., 2010; Bland et al., 2007; Schulte-Herbrüggen et al., 2006; Vollmayr et al., 2001). A study of heterozygous BDNF knockout mice was also shown to have learned helplessness behavior (MacQueen et al., 2001). Also, stress-induced or genetically modified downregulation of BDNF may increase learned helplessness in rodents (Chourbaji et al., 2012; Chourbaji et al., 2005).

Recently, Li et al. (2013) utilized congenitally learned helpless (cLH) rats and found that β -CaMKII expression was significantly upregulated in the LH animals, and downregulated by antidepressants. Downregulation of β -CaMKII levels, by blocking its activity or its target molecule GluR1, reversed the depressive symptoms. This study provided new insights into

the molecular mechanism for depression based on the learned helplessness rodent model (Li et al., 2013).

Kohen et al. (2005) performed gene expression profiling of acute LH vs. NLH vs. sham (tested controls) vs. cage-control (naive) rats in hippocampus. They reported that LH rats resembled the TC and cage-control rats in their gene expression profile, whereas the NLH rats showed numerous significant mRNA changes (mostly down-regulation). Thus, the NLH rats showed a robust adaptive response to inescapable shock whereas the LH rats failed to show this response. As a group, the down-regulated mRNAs tended to be correlated with each other across individuals, and they shared certain AT-rich motifs in their 3'-UTR regions, which they suggested could represent potential miRNA target sites (Kohen et al., 2005).

Using microRNA approach, we have recently used this model to delineate the molecular mechanisms associated with vulnerability and susceptibility to developing depression. We found that a subgroup of rats that displayed hopelessness had a blunted response in frontal cortical miRNAs compared to resilient rats, suggesting that aberrant miRNA expression can lead to deficits in the coping response to stress (Smalheiser et al., 2011). We also identified a core miRNA co-expression module consisting of 36 miRNAs that were highly correlated with each other across individuals of the LH group (but not in the NLH or TC groups), suggesting that miRNAs participate in the alterations of gene expression networks that underlie the normal (NLH) as well as aberrant (LH) response to inescapable shocks (Smalheiser et al., 2011).

Acute and chronic restrained stress can also cause differential changes in miRNA expression in a brain region-specific manner. For example, acute stress induced a transient increase in the expression of selected miRNAs (miR-9, miR-9*, miR-26b, miR-29b, miR-30b, etc.) in the frontal cortex, but not in the hippocampus. Using unpredictable chronic mild stress combined with separation, Cao et al. (2007) found changes in 13 specific miRNAs in the rat hippocampus. These included downregulating miRNAs (miR-298, miR-130b, miR-135a, miR-323, miR-503, miR-15b, miR-532, and miR-125a) and upregulating miRNAs (miR7a, miR-212, miR-124, miR-139, and miR-182). Among these, miR-125a and miR-182 recovered to normal levels after intervention with antidepressant medication (Cao et al., 2013). Some studies have also shown that miRNAs can induce depressive-like phenotype. Recently, Bahi et al. 2014 found that hippocampal miR-124a overexpression can contribute to social stress-induced depression through suppressing BDNF expression. The study also showed that miR-124a was up-regulated in the hippocampus but not in the cortex and BDNF transcripts were down regulated. Interestingly, BDNF and anti-miR-124a acted as antidepressants when miR-124a silencers were injected into hippocampus (Bahi et al., 2014). Another study utilized mice exposed to chronic ultra-mild stress, which exhibited induced depression-like behaviors. miR-124 was reduced in hippocampal of these mice. Behavior experiments showed that viral-mediated miR-124 overexpression in hippocampal neurons induced resilience to chronic unpredictable mild stress, whereas a defect in miR-124 induced behavioral susceptibility to a milder stress paradigm (Higuchi et al., 2016). Another study suggested that maternal deprivation and chronic unpredictable stress could induce different depression-like behaviors in rats. Depression induced by maternal deprivation but

not chronic unpredictable stress was significantly associated with upregulation of miR-16 and possibly subsequent downregulation of BDNF in hippocampus, suggesting that environmental stressors can lead to the onset of depression via inhibiting hippocampal BDNF expression mediated by miR-16 (Bai et al., 2012). Baudry et al. 2011 reported that miR-16 targeting serotonin transporter (SERT) is involved in the negative modulation of hippocampal neurogenesis and consequent depression-like behaviors (Baudry et al., 2010).

3.2. Unpredictable chronic mild stress (UCMS)

The first UCMS model was developed by Katz and colleagues (Katz et al., 1981). Subsequently, the paradigms were improved by the Willner lab (Willner, 1991), which was based on the following two strategies: one is decreasing stressor and the other is to introduce the anhedonia as appraisal standard. Generally, the rat or mouse received a series of different stressors over a period of several weeks. The stressors mainly include food and water deprivation, overnight illumination, cage tilt, and other similar unpredictable stresses. The aim of UCMS method is to chronically develop the depressive state in response to unpredictable stress stimuli. The most important point in this model is a decrease in reward sensitivity and the development of anhedonia. The symptoms of the UCMS rodent model mainly include the decrease of sugar consumption, the increase of intracranial self-stimulation threshold, the loss of weight and appetite etc. With respect to neurobiology, acute stresses activate the hypothalamic-pituitary-adrenal axis (HPA) axis and consequently increase the circulating glucocorticoids. The high level of glucocorticoids may result in atrophy and apoptosis in the prefrontal cortex and hippocampal regions.

With the releasing corticosterone and the down regulation of glucocorticoid receptor expression, the cognitive impairment associated with depression is changed (Boyle et al., 2005). The animals exposed to UCMS demonstrate a significant reduction of diffusion of astrocyte gap and abnormal gap junctional ultrastructure in the PFC. Antidepressants reverse the gap junction dysfunction and connexin 43 gene expression (Quesseveur et al., 2015).

Based on the UCMS rodent model, a recent study shows that low level of endogenous ATP in the mice brain is responsible for the depressive-like behavior. On the other hand, stimulation and subsequent release of endogenous ATP in the astrocytes cells cause the antidepressant-like behavior (Crema et al., 2010). You et al. (2011) also utilized the UCMS model and found that levels of pro-inflammatory cytokines were upregulated in these stress-exposed rats. On the other hand, the anti-inflammatory cytokines, including TGF- β and IL-10, were inhibited (You et al., 2011).

3.3. Early life stress model

The principal of early life stress model is that adverse events in early life substantially affect the development of psychiatric illnesses in late life, such as depression (Kendler et al., 2002) and psychosis (Morgan et al., 2007). Maternal separation (MS), one of the early life stress models, has long-lasting effects on emotionality and stress responsiveness (Levine, 1967; Meaney, 2001; Plotsky et al., 2005). The procedure of MS was to separate the pups from their mothers during the postnatal period. Different laboratories used different duration of separation, which varied from few hours to several days. The MS model directly interrupts

the usual mother-pup interaction and damages the responsiveness of the HPA axis (Ellenbroek and Cools, 1998; Enthoven et al., 2008; Lyons et al., 1998; Nishi et al., 2013; Pryce et al., 2005). The activity of HPA axis and the response to stress is relatively low during early postnatal life (Levine, 2005; Walker et al., 1991); however, it is much more pronounced in later life. Interestingly, short time early-life stress, e.g. handling, mimic the situation where mother leaves her pups to find foods. This short-term MS not only decreases the HPA axis but also reduces anxiety-like behavior in adulthood (Levine, 2005; Plotsky et al., 2005). This is perceived as beneficial adaptations to stress. The Meaney group found that the corticosterone and adrenocorticotrophic hormone (ACTH) in the serum of MS rodent was significantly increased in the first 2 weeks of neonatal life whereas the expression of glucocorticoids receptors in hippocampus and prefrontal cortex was significantly altered (Meaney and Szyf, 2005). MS also induced changes in 5-HT system and down-regulated BDNF expression in the prefrontal and hippocampus. Taken together, many studies of repeated MS during the first 2 weeks of neonatal life showed depression- and anxiety-like behaviors in adulthood (Daniels et al., 2004; Lee et al., 2007; Newport et al., 2002; Ryu et al., 2009).

Recent studies also suggest that exposure to early-life stress can persistently change DNA methylation in the brains of adult mice or rodents (Mueller and Bale, 2008). Weaver et al. (2004) reported that low maternal care using pup licking and grooming and arched-back nursing altered DNA methylation in the promoter regions of *Nr3c1* gene hippocampus area of offspring, which persistently affected the transcription patterns and stress responses in the adulthood (Weaver et al., 2004). Another study validated *NR3C1* methylation in hippocampus regions in maternal separated male mice and found that epigenetic changes may be involved in depressive like behavior (Kember et al., 2012). A sustained hypomethylation in arginine vasopressin (*AVP*) gene accompanied by a significant increase in *AVP* expression have been reported in early life stress mice (Murgatroyd et al., 2009). In rats, early maltreatment produced persistent methylation changes in *BDNF* promoter accompanied by altered *BDNF* gene expression within the developing and adult prefrontal cortex (Roth et al., 2009). Epigenetic changes following neglect and abuse adversity have also been reported in other genes such as *Crh* (Elliott et al., 2010), *Dlgap2* (Chertkow-Deutsher et al., 2010), *Mecp2*, *Cnr1*, and *Crhr2* (Franklin et al., 2010), indicating that interaction of early life stress and DNA methylation can induce alterations in multiple neurobiological pathways leading to behavioral changes.

Epigenetics mechanisms also contribute to behavior transmission of maternal care from one generation to the next. The different level of maternal care received during postnatal development may transmit multigenerational effects of maternal behavior. The elevated expression of *esr1* in the MPOA brain area, the gene encoding estrogen receptor alpha, was found in the female offspring which experienced higher maternal licking/grooming (LG) compared with lower LG. It was also found that DNA methylation within the *esr1* gene also emerged during the first week postnatal (Peña et al., 2013). As a result of epigenetic changes, adult female offspring with the lower maternal care showed decreased sensitivity to *estrogen* and the offspring also displayed lower LG (Champagne et al., 2001). Additionally, abusive caregiving also resulted into the increased BDNF methylation in the prefrontal

cortex and the offspring with abusive caregiving experience transmitted these behaviors into next generation (Roth et al., 2009).

3.4. Olfactory bulbectomy (OBX) model

The rat olfactory system as well as amygdala and hippocampus, that form the limbic region, are responsible for memory and emotion (Halász, 1990; Leonard and Tuite, 1981). The removal of olfactory bulb induces neurochemical, neuroanatomical, physiological, endocrine and behavioral changes, which are similar to symptoms in human patients with major depression (Kelly et al., 1997; Song and Leonard, 2005). Antidepressant treatment can reverse the depressive behavior of OBX rats to the normal phenotype (Jarosik et al., 2007; Song and Leonard, 2005). Clinical studies have also demonstrated that depressed patients show a marked reduction in the sensitivity to olfactory cues, the extent of the reduction being associated with the severity of the symptoms (Pause et al., 2001). The olfactory bulb of rats subjected to UCMS show altered gene expression and signal transduction pathways. Thus, there is a strong link between the dysfunction of olfactory system and depressive behavior. The olfactory bulbectomy leads to anhedonia and behavior changes, combined with deficits in spatial learning, avoidance learning, conditioned taste aversion and food-motivated behaviors (Harkin et al., 2003; Kelly et al., 1997; Song and Leonard, 2005). The surgical removal of the olfactory bulbs also produces changes at the cellular levels. For example, the number of synapses and dendritic spines and shafts are reduced in the olfactory bulbectomized rats (Hall and Macrides, 1983). The brain content of serotonin and 5-HIAA are also significantly reduced and the chronic antidepressant treatments reverse the changes in serotonin and 5-HIAA levels (Jancsar and Leonard, 1984; Lumia et al., 1992; Song and Leonard, 1995). Besides serotonin, the level of neuropeptide Y, ChAT, noradrenaline and glutamate are also reduced in the olfactory bulbectomized rats. Increase in BDNF level in the hippocampus (+108%) and frontal cortex (+48%) 16 days after olfactory bulbectomy in mice have also been reported (Hellweg et al., 2007). Such evidence demonstrates that OBX models provide a tool to investigate the neurobiology of depression and the mechanism of antidepressant action.

3.5. Social defeat model

Social stress is a significant type of adversity and is critically involved in the development of depression and other psychopathology in humans (Agid et al., 2000; Björkqvist, 2001; Huhman, 2006). The social defeat model uses social conflict as a stressor to yield emotional and psychological stress. In this model, a male rodent is introduced into the home cage of an older, aggressive and dominant male rodent. The intruders are attacked and defeated by the residents. To ensure the defeated rodent to be produced, the residents should be selected according to the body weight, strain, social status, etc. Once the physical attack or threat attack has happened, the residents and intruders are separated with a barrier. Subsequently, the test rodent is exposed to a different aggressor. After several physical attacks, the intruder receives different behavioral tests. The defeated rodents show anhedonia as well as a series of physiological changes including 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 functions (Bohus et al., 1993; Koolhaas et al., 1997; Martinez et al., 1998;

Meerlo et al., 1996). The HPA axis is also activated in the defeated rodents, which is similar to the other depression models.

Although the social defeat model has some drawbacks, one prominent disadvantage is its inability to be studied in female subjects. The other one is that test subjects are restricted in the adult animals. Social defeat has proven useful in identifying molecular mechanisms that can induce stable changes in phenotype (Meerlo et al., 1996). Golden et al. (2013) reported that mRNA and protein levels of RAC1, a small Rho GTPase that controls spine synapse stability, are decreased in the nucleus accumbens of mice exposed to social defeat, and in the postmortem nucleus accumbens of patients with depression (Golden et al., 2013). Long-term reduction in RAC1 gene expression in both mice after social defeat and humans with depression is associated with chromatin remodeling that represses Rac1 gene promoter activity. Inhibition of this repressive transcriptional state reverses the deficit in RAC1 mRNA levels and depressive behaviors. The authors also show that decreased Rac1 expression is necessary and sufficient for the development of altered spine synapses in the nucleus accumbens and the induction of depressive behavior (Golden et al., 2013).

3.6. Chronic restraint stress model

Whilst not explicitly mentioned, one of the types of mild stressors used in unpredictable chronic mild stress (CMS), restraint is a very well established source of stress that results in depressive behavior in rats. For a more chronic, predictable stressor, animals are restrained for a minimum of 2 hours per day for 14 to 21 days; days 1 and 7 have shown no significant changes in behavior compared to controls, so 14 or 21 are the standard. The results of this stress are varied, but all converge in the following: damage or atrophy to hippocampal CA3 pyramidal cells (Conrad et al., 1999; Magarin and McEwen, 1995; Magariños et al., 1999; Watanabe et al., 1992), increased corticosteroid levels along with increased aggressive behaviors (Wood et al., 2003), depressed behavior, and apoptotic cell death (Zhang et al., 2014). This is a strong model as all the rats subjected to this show genetic and protein changes that are established in depression. This allows one to research a primary, progressive state of depression without any confounds of resilience or other factors. Typically, Sprague-Dawley rats are selected for this form of behavioral stress. One might liken this type of stress to a continuous, predictable stress people experience every day. Stresses of this nature may include daily repetition of a stressful job, social or financial stress, familial stresses, or day to day stresses that are repeated and constantly stacked upon the previous day's workload.

3.7. Glucocorticoid/corticosterone model

Dysregulated levels of corticosteroids (CORT) are strong indicators of stress. Not only can CORT be a diagnostic tool, but it can be pharmacologically manipulated to evoke an anxiety-depressive state in animals via the synthetic hormone corticosterone. Gregus et al. (2005) showed that rats who were repeatedly injected with CORT gained weight less quickly or even lost weight when compared to: rats that underwent 6 hr daily restraint, rats that were handled daily, and rats that were vehicle injected (Gregus et al., 2005). They also showed that CORT treated animals had a longer immobility period when subjected to the forced swim test.

Previous studies found that the depression-like behavior in CORT-treated animals was attributed to the catabolic effects of CORT on muscle tissue. In our lab, we conducted forced swim test and sucrose preference test to assess the depression-like behavior. We found that the length of immobility time was greater whereas sucrose preference was lower in CORT treated animals than the vehicle-treated rats. The locomotor activity in open field test showed no changes in the CORT-treated rats, which suggests that depression-like behavior in the CORT animal is not associated with nonspecific motor behaviors. In this study, we also found the chronic CORT may induce depression phenotype by altering a select group of miRNAs and associated networks (Dwivedi et al., 2015).

3.8. Genetic models

3.8.1. Sprague-Dawley—The Sprague-Dawley albino rats may be considered the “standard” of animal research rodents; this is especially true when analyzing behavior. These rats are fairly calm and have a slightly longer body length than other strains like Wistar rats (Etzersdorfer et al., 2015). In the context of behavioral paradigms, SDs is typically selected for behavioral tests such as chronic restraint stress, chronic unpredictable stress, or genetic manipulation (knock-in/knock-out). They are not selected for paradigms like learned helplessness as they have a greater ratio of resilience to LH-susceptible in comparison to their Holtzman counterparts, which are genetically more susceptible to a depressive phenotype. Studies in SD rats attempting to create the LH model have not been as successful because these rats show greater resilience to stress (Padilla et al., 2010). Similarly, Wistar rats are also resilient to stress-induced behavioral depression (Nam et al., 2014). These rats are an excellent base for study if the investigator wishes to start with an easy-to-handle, base-line rat that responds well to being handled and performs behavioral tasks very well.

3.8.2. Flinders sensitive line—The FSL rat model of depression has been widely and successfully used for well-known behavioral test and putative antidepressant responses. The rat of FSL model was selectively bred from the Sprague-Dawley strain, because the SD rat developed a strain showing hypersensitivity to the di-isopropyl fluorophosphates (Overstreet and Russell, 1982; Overstreet et al., 2005). From the behavior characteristic, the FSL rats exhibit hypoactivity in the forced swim test and in the open field arena (Overstreet and Russell, 1982). Under acute or chronic stress, the FSL rats also exhibit a significantly greater decrease in saccharin preference, whereas the Flinders resistant Line (FRL) rats has no change in the sucrose preference for stress (Pucilowski and Overstreet, 1993). For the neurochemical characteristics, the FSL rats show lower 5-HT synthesis in brain compared to FRL rats (Zangen et al., 1997). Treatment with 5-HT_{1A} receptor agonist (e.g., buspirone) also alters 5HT synthesis differently between FRL and FSL. Buspirone produces a significant elevation of 5-HT synthesis in the FSL rats, whereas 5-HT synthesis in the FRL rats was significantly decreased. The alterations in dopaminergic and noradrenergic systems have also been observed in different brain areas of the FSL rats (Nishi et al., 2009). Recently, the FSL model has been used for the gene × environment interaction studies for the development of depression. The study using maternal separation in FSL and FRL pups reported differences in the expression of genes in several brain regions that may predispose these animals to develop depressive behavior.

3.8.3. Holtzman Albino strain—Holtzman strain of Sprague Dawley rats are typically selected when studying learned helplessness susceptibility. Padilla et. al (2009) compared susceptibility to helpless-depressive behavior in Sprague Dawley, Long Evans (LE), and Holtzman (HO) rats. It was shown that HO and LE both showed greater escape latency than SD rats; of the two, HO rats had the highest escape latency average. Also, these rats had the highest number of “failed trials” or escape test trials where the rat does not escape the shock. HO rats are excellent rats to use when considering learned helplessness as a model to study depression. Their susceptibility ratios average from 1/3 to 1/2 of the shocked rats with the remaining showing resilience. Studies can then be directed at examining the differences between resilient and susceptible rats and rescuing the depressive behavior (Padilla et al., 2009).

3.8.4. Congenital learned helplessness—An excellent review by Willner and Belzung (2015) described work from several labs that sought to create a genetic approach with the LH model known as the congenital learned helplessness (cLH) strain (Willner and Belzung, 2015). In this case, rats are subjected to inescapable shock and those who show the most depressive behavior (escape latency/test failures) are selected to breed. After generations of breeding like this, the cLH line will fail escape test without the need for an inescapable-stress trigger. They also show resistance to antidepressants (except for a high dose of MAO-B inhibitors). This is a strongly translational model as neuroimaging of these rats show very similar changes to human patients who suffer from major depression and treatment-resistant depression.

3.8.5. Wistar-Kyoto (WK) strain—Generally, WK rats are studied under the context of post-traumatic stress disorder, hyperactive disorders, and anxiety, but they have ties to depressive studies as well. Jiao et al (2011) compared WK rats to SD rats to determine strain differences in anxious-like behavior. They showed that WK rats had a higher avoidance percentage (by lever pressing) than SD rats. They also showed a higher rate of anticipatory lever pressing than their SD counterparts; this was especially prevalent in females. WK rats also exhibited an elevated acoustic startle response compared to SD rats (Jiao et al., 2011). Recently, Nam et al. found that WKY rats capture specific functional domains relevant to clinical depression which include psychomotor retardation, behavioral inhibition, learned helplessness, social withdrawal, and physiological dysfunction. These rats are resistant to early-life manipulations (i.e., neonatal handling) that are therapeutic in other strains, and may be a useful model for the development of personalized anti-depressant therapies for treatment resistant depression (Nam et al., 2014). One disadvantage is that WK rats show high variability in behavioral phenotype. However, this shortcoming is overcome by selective breeding of WKY rats based on immobility in forced swim stress, which results into two sub-strains: WKY most immobile (WMI) and WKY least immobile (WLI). These two sub-strains show less variability and different responsiveness to antidepressants. For example, subacute treatments of males with several classes of antidepressants show different effects on FST behavior in the two sub-strains. Both desipramine and phenelzine significantly and drastically decrease FST immobility in WMI; in contrast, WLI show a limited response to these antidepressants. In addition, male WMI rats show decreased

activity in the open field test than male WLI rats. Plasma CORT in response to restraint stress is also lower and less variable in WMI compared to WLI males (Will et al., 2003).

3.8. Transgenic model

Because serotonin (5-HT) agents are commonly used for treating depression, and decreased 5-HT plays a pathophysiological role in major depression (Heninger et al., 1984; Krishnan and Nestler, 2008), most genetic models of depression are based on manipulating 5-HT system. Here, we briefly describe major genetic rodent models of anxiety and depressive-like behavior based on the constitutive knockout and transgenic approaches.

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in 5-HT biosynthesis. Two isoforms of the enzyme tryptophan hydroxylase, TPH1 and TPH2, are involved in catalyzing the 'serotonergic system if their expression is silenced in vivo. Walther et al. (2003) constructed constitutive *Tph1*^{-/-} mice and found no significant differences in 5HT-related behaviors. These mice expressed normal levels of 5HT in serotonergic brain regions. However, *Tph*-null mice lacked 5HT in the periphery, except for the duodenum. They found that *Tph2*, but not *Tph1*, is the predominant isoform expressed in mouse brain.

With the *Tph2*^{-/-} mice, increased immobility in the TST (tail suspension test) demonstrated pro-depressive effects. The increasing number of marbles in the marble-burying test also suggested higher anxiety levels (Walther et al., 2003). In this study, the double knockout *Tph1/Tph2* mice were generated. These mice showed significantly reduced levels of 5-HT in the brain and periphery. Behavioral tests of double knockout *Tph1/Tph2* mice showed greater marble burying, reduced immobility in the FST, and increased immobility in the tail suspension test. A knock-in of TPH2 variant (R439H) in mice showed pro-depressive behavior, as demonstrated by increased immobility times in the tail suspension test. Recently, Gutknecht et al. (2015) reported that *Tph2* null mutants (*Tph2*^{-/-}) mice displayed increased general metabolism, marginally reduced anxiety- and depression-like behavior, but strikingly increased fear conditioning responses. *Tph2*^{-/-} male mice displayed increased impulsivity and high aggressiveness, whereas *Tph2*^{-/-} female mice showed greater emotional reactivity to aversive conditions as reflected by changes in behaviors at baseline including increased freezing and decreased locomotion in novel environments (Gutknecht et al., 2015). However, both *Tph2*^{-/-} male and female mice were resilient to CMS-induced hyper-locomotion, while CMS intensified fear conditioning responses in a gene × environment-dependent manner. This suggests that 5-HT mediates behavioral responses to environmental adversity by facilitating the encoding of stress leading to increased vulnerability for negative emotionality.

The vesicular monoamine transporter (Vmat) is comprised of two proteins: Vmat1 and Vmat2. Vmat1 is enriched in the chromaffin, whereas Vmat2 is mainly expressed in monoaminergic neurons (Mahata et al., 1993). The growth of homozygous *Vmat2*^{-/-} mice show major retardation and these mice die within a few days after birth. Severe impaired monoamine and vesicular release have been found in *Vmat2*^{-/-} mice (Alvarez et al., 2002; Fon et al., 1997; Wang et al., 1997). On the other hand, the heterozygote *Vmat2*^{+/-} mice, that have 34% decreases in brain 5-HT, are viable and show normal growth rate, feeding and reproductive behavior. These animals also showed significant reduction in levels of

dopamine, and norepinephrine (Fon et al., 1997). Interestingly, Vmat2+/- mice show pronounced depressive-like phenotype characterized by increased immobility in the FST and TST, anhedonia responses to sucrose and higher sensitivity in the learned helplessness paradigm; these behavior deficits are alleviated by antidepressants (Fukui et al., 2007). Interestingly, no anxiety-like behavior was detected in the open field, light-dark exploration, zero maze, and novelty-suppressed feeding tests in Vmat2+/- mice (Fukui et al., 2007). Altogether, the genetic rodent models may provide proof of concept of the involvement of specific gene in depression pathophysiology.

4. Discussion and Conclusion

Depression is a heterogeneous and complex disorder. Several factors alone or in combination may predispose a person to the risk of depression. Animal models allow one to study the neurobiological basis of depression and provide a promising and much needed approach. Although there are some limitations in the existing depression rodent models, such that the feelings of sadness, guilt, suicidal thoughts cannot be fully captured, the existing models of depression to some extent provide the important tools for investigating molecular, genetic, epigenetic, and environmental risk factors in understanding the pathogenesis of depression. The animal models can also be used for the identification of novel targets for antidepressants and treatment responses.

While no single animal model is the one-size-fits-all package answer for studying depression, different models have advantages over others for studying specific aspects of the disease. Many of the models were originally designed with drug testing in mind, but now, genetic, behavior, pathophysiology, etiology and social interaction and reaction have become far more important when deciding how to approach depression and its heterogeneity. Depending on one's approach to depression, one should consider using different models in combination. For a more anxiety-driven research, the WK inbred strain may be favorable while an approach to helplessness, anhedonia, despair and suicidal tendencies may be best studied in the LH outbred Holtzman rats. Future studies into depression should be less focused on drug response and more focused on models and systems that tease out underlying mechanisms. In the past, much research has been dedicated to treating symptoms by increasing the availability of monoamines – the monoamine hypothesis of depression (Delgado, 2000). It is well understood today, however, that depression is a far more complicated phenomena. In recent years, inflammation (Felger and Lotrich, 2013; Lotrich, 2012), apoptosis (McKernan et al., 2009), stress-signaling pathways (Timberlake and Dwivedi, 2015), growth factors (Dwivedi et al., 2003; Lotrich, 2012; Martinowich et al., 2007), genetics and epigenetic regulation (Abdolmaleky et al., 2005; Sun et al., 2013), environment (Schmidt, 2011), and nutrition (Rao et al., 2008) along with other compounding diseases and comorbidities (Yohannes and Baldwin, 2008) all contributed to the symptomatic pathophysiological state collectively known as depression. Once those underlying mechanisms have been better characterized and better understood, then individualized treatments should be designed that take the above into account.

Further, when selecting animal models and aspects of depression to study, one should consider similarities and translation, either direct or indirect, to human situations. Genetic

and epigenetic markers as well as other peripheral diagnostics that are found in both humans and in animal models should be considered important candidate targets for study and intervention. Studying resilience is also important for understanding what causes susceptibility. Models that include this aspect of the disease can be of great benefit in understanding depression. More comprehensive studies of depression may need to make use of several strains and multiple testing models, cross-compare genetic and epigenetic expressions and activity, and always collaborate with human data – both *ex vivo* and *post mortem* tissue.

Overall, animal models that can elucidate the neurobiology of depression, allow the testing of novel neurobiological hypotheses, and have translational value, can be applied in humans. On the other hand, based on available antidepressants, one can use animal models to test new hypothesis and identify novel targets for better and targeted therapy.

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Highlights

- Availability of current animal models of depression.
- Critical evaluation of behavioral paradigms being used to phenotype depression in animals.
- Availability genetic models of depression and their usefulness.
- Discuss current challenges and future studies to focus on the underlying mechanism on depression and resilience.

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
Forced Swim Test (FST)	Despair	cLH	Similar to human patients with treatment-resistant MDD	Does not allow for comparison of LH and NLH rats
Tail Suspension Test (TST)	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
Open Field Test (OFT)	Anxiety/Motor-locomotion	Mouse models	Inexpensive; simple drug screening	Only tested in mice; results can be compounded by motor deficits
Sucrose Preference Test (SPT)	Anhedonia	Most Rodents	Quick and inexpensive; simple drug screening test	Does not specifically test depression - only anxiety
Elevated Plus Maze (EPM)	Anxiety	Most Rodents	Inexpensive; simple drug screening test	Weighting or measuring methods may vary from one lab to another; spillage can occur
Intracranial Self-Stimulation (ICSS)	Reward Sensitivity/Anhedonia	Most Rodents	Simple process for anxiety assessment	Does not specifically test depression - only anxiety
Operant Fear Conditioning	Fear/Anxiety	Most Rodents	Precise administration and drug localization is known to the researcher	Requires surgery, cannula and proper administration equipment
		Most Rodents	Inexpensive; simple drug screening	Does not specifically test depression - generally for anxiety

Table 2

Assessment of various animal models and their advantages and disadvantages

Animal Model	Emulated MDD Characteristics	Suitable Strains	Model Advantages	Model Disadvantages
Learned Helplessness (LH)	Hopelessness, decreased motor activity, weight loss/lack of weight gain, decreased reward sensitivity	Holtzman	Creates depression susceptible (LH) and resilient (NLH) groups for comparison	Requires additional rats due to the differentiation of LH and NLH rats. Requires special equipment for IS/ET
Early Life Stress (ELS)	Anxiety, down-regulated BDNF expression	cLH	Strong translational model similar to human patients with treatment-resistant MDD	Does not allow for comparison of LH and NLH rats. Requires special equipment for IS/ET
Social Defeat	Anxiety, anhedonia	Sprague-Dawley	Stable change in phenotype	Requires special handling and rearing of pups
Olfactory Bulbectomy (OBX)	Anhedonia, reduction of serotonin and 5-HIAA in the brain	SD/WKY	Stable change in phenotype	Only adult males are used for this model
Unpredictable Chronic Mild Stress (UCMS)	Anhedonia, decrease in reward sensitivity	Sprague-Dawley	Produces many neurobiological changes allowing for investigation of mechanisms of antidepressants	Irreversible. Requires surgical extraction of olfactory bulb
Chronic Restraint Stress (CRS)	Anhedonia, increase in reward sensitivity	SD/WKY	Strong validity; phenotypic changes (both behavior and physiological) over time; good for drug screening	Long/complex procedure. Difficult to reproduce
Glucocorticoid/Corticosterone (CORT)	Atrophy in hippocampal CA3 pyramidal cells, increased corticosteroid levels	SD/WKY	Strong validity; phenotypic changes (both behavior and physiological) over time; good for drug screening	Changes in eating/drinking, anxiety and changes in weight are common
Transgenic Models	Anxiety, dysregulation of HPA Axis	SD/Wistar/WKY	More control over CORT levels which reduces experimental variability	Requires repeated administration of CORT to test subjects
	Dependent upon brain area and targeted genes	Most Rodents	Gene or brain area specific manipulation for specific aspects of disease state	Individual gene or area approach