Revista Brasileira de Psiquiatria. 2013;35:S121–S131

doi:10.1590/1516-4446-2013-1168

UPDATE ARTICLE

Contributions of animal models to the study of mood disorders

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Mood disorders are a leading cause of morbidity and mortality, yet their underlying pathophysiology remains unclear. Animal models serve as a powerful tool for investigating the neurobiological mechanisms underlying psychiatric disorders; however, no animal model developed to date can fully mimic the ''corresponding'' human psychiatric disorder. In this scenario, the development of different animal models contributes to our understanding of the neurobiology of these disorders and provides the possibility of preclinical pharmacologic screening. The present review seeks to provide a comprehensive overview of traditional and recent animal models, recapitulating different features and the possible pathologic mechanisms of mood disorders emulated by these models.

Introduction

Mood disorders are common and potentially devastating conditions, associated with high rates of suicide and disability.[1,2] Even with proper use of current pharmacological treatments, most patients continue to have recurrent mood episodes, residual symptoms, functional impairment, psychosocial disability, and significant medical and psychiatric comorbidities. A better understanding of the pathophysiologic mechanisms of these disorders is a prerequisite for the design of new drugs and their implementation in clinical practice.[3]

Recent advances in genetic, neurobiological, and pharmacological methodologies have helped the development of animal models, which has been an important tool to investigate new intracellular systems that may be involved in the specific pathophysiology of psychiatric disorders.[4,5] However, no animal model developed to date can fully mimic the ''corresponding'' human psychiatric disorder. A particular challenge of bipolar disorder (BD) is its complex, alternating clinical course, with recurrent mood swings, including manic, depressive, and mixed episodes, which make the development of an adequate animal model challenging.[6] Nevertheless, traditional and promising new animal models that mimic certain attributes of depression or mania have been established and are being used to deepen our understanding of the underlying mechanisms of distinct mood disorders.

Ellenbroek & Cools[7] have proposed that the validity of animal models in psychiatric disorders should demonstrate the following three major criteria: face validity, construct validity, and predictive validity. Face validity represents how similarly the model can mimic the symptoms of a given illness, whereas construct validity is related to the ability of the model to reproduce some pathophysiological aspects of the illness. Finally, predictive validity evaluates whether the therapeutic agents used in the treatment of an illness can reverse the symptoms induced in the animal model.

For decades, the monoaminergic hypothesis of mood disorders has explained both their pathophysiology and the mechanisms of action of psychopharmaceuticals, and it has led to the production of several generations of antidepressants and mood stabilizers. Nevertheless, there are serious limitations to the current monoamine theory, and additional mechanisms, including hypothalamic-pituitary-adrenal (HPA) axis dysfunctions and neurodegenerative and inflammatory alterations, are potentially associated with the pathogenesis of mood disorders. Furthermore, recent studies have showed that epigenetic mechanisms such as histone modifications and DNA methylation could affect diverse pathways leading to depression-like behaviors in animal models.

This review seeks to provide a comprehensive overview of traditional and recent animal models, recapitulating their different features and the possible pathophysiology of mood disorders emulated by those models.

How can depressive-like and manic-like behaviors be evaluated in laboratory animals?

Researchers have long attempted to develop animal models that mimic the greatest possible number of specific physiological and behavioral changes observed in mood disorders. Some behavioral tests are of utmost importance to assessment of the face validity of an animal model, which demonstrates its ability to mimic the

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symptoms of depression or mania. These behavioral tests include the forced swimming test (FST), tail suspension test (TST), sucrose consumption test, and open-field test.

The FST is a behavioral test described first by Porsolt et al.[8] in the rat and subsequently in the mouse.[9] It is the most commonly used test to screen for antidepressant activity and to evaluate depressive-like behavior in animal models of depression. The test involves two individual exposures to a cylindrical tank filled with water in which rats cannot touch the bottom of the tank or escape. Rats are individually placed in the water-containing cylinder for 15 min (pre-test session), and when re-exposed 24 h later to the apparatus, are tested for 5 min (test session). The test session measures the time the animal spends without moving.[8] In the mouse FST, the animals are individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm) containing 19 cm of water (depth), and the total duration of immobility is measured for 6 min.[9,10] Immobility in the FST has been interpreted as a manifestation of negative mood, representing a kind of hopelessness in the animal, reflecting lack of motivation, which is a frequently reported symptom of depression.[8,9,11] As the FST, the TST was first described, by Steru et al.,[12] in mice. It is also widely used to screen for antidepressant activity. The tail suspension-induced state of immobility in animals is similar to human depression and is amenable to reversal by antidepressant drugs.[12,13] This animal model is also based on despair or helpless behavior in response to an inescapable and confined space.

Although these behavioral tests have been widely utilized in many preclinical trials to screen new antidepressant-like drugs,[14,15] they do not necessarily provide any insights about neurobiological aspects of depression.[16] The three major criticisms of these tests as a tool for preclinical studies focusing on discovery of new antidepressant-like drugs are: i) the stress is usually applied for only 5 min to normal rodents, which is very different from human depression; ii) classical antidepressants have an acute antidepressant-like effect, whereas in humans, a clinical response to antidepressant medication takes at least 3 to 4 weeks; iii) it remains unclear whether these tests are sensitive to non-monoaminergic drugs.[14,17]

Another important preclinical test is the foot shock escape task, which evaluates the animal's ability to learn to escape when exposed firstly to an inescapable foot shock and, at a predetermined time in the future, to an escapable foot shock. Acute antidepressants are able to reduce escape latency and failures. This test is subject to the same criticisms as the FST and TST. Nevertheless, it has been proposed as a model of learned helplessness in mice.[14,18] Many issues can be raised regarding the utility of learned helplessness/behavioral depression as a model of depression or antidepressant activity. Furthermore, as learned helplessness is sensitive to both antidepressant and anxiolytic drugs, it may be an animal model of either depression or anxiety.[19]

According to the DSM-IV-TR, one of the major symptoms of depression is anhedonia, the loss of interest or pleasure in daily activities.[20,21] In rats or mice, anhedonic-like behavior is commonly assessed by evaluating sucrose intake. Thus, a reduction in consumption of palatable liquids or food is generally considered to represent anhedonia.[22,23]

The open-field test was developed by Calvin S. Hall in 1932[24] to test rodent emotionality. This test is commonly used to provide a qualitative and quantitative measurement of exploratory and locomotor activity in rodents. The apparatus consists of an arena surrounded by high walls, to prevent escape, and the floor of the open field is divided into squares. In the test session, the number of square crossings, rearing, and time spent moving are used to assess the activity of the rodent. Automatic open-field apparatuses, which have software-linked infrared beams or video cameras to make the process easier and more accurate, are currently available. The open-field task is also often used to assess anxiety by including additional measures of defecation, time spent in the center of the field, and evaluation of the first few minutes of activity. The effects of stimulants on behavior have been widely used as an animal model of mania, because they induce psychomotor agitation, which is commonly observed during mania; besides, locomotor activity is easily measured in rats or mice using the open-field test.[25-27]

It is important to mention that these behavioral tests in animals are not animal models of depression, as they only mimic some aspects of the depressive symptoms seen in humans, whereas animal models mimic a whole specific system disturbance related to the phenotype of depression.[12]

Animal models of depression

In accordance with the first theory of depression, the so-called monoaminergic hypothesis, many studies have demonstrated that patients with major depression have abnormalities in the neurotransmitters of the brain, particularly serotonin (5-hydroxytryptamine, 5-HT), noradrenaline, and, as demonstrated more recently, dopamine (DA). However, this theory alone cannot fully explain the neurobiology of depression; therefore, other neurotransmission systems and signaling pathways have been implicated in the pathophysiological mechanisms of depression, such as acetylcholine (ACh), glutamate, gamma-aminobutyric acid (GABA), and endogenous opiates.[28-32] Functional imaging studies have shown that blood flow and glucose levels are higher in some parts of the brain (e.g., the frontal cortex, amygdala, thalamus, and lower parts of the striatum) of patients with major depression as compared with controls.

Furthermore, the majority of antidepressants currently prescribed are 5-HT reuptake inhibitors (SSRIs), which make more 5-HT available to synapses, and drugs acting selectively on both norepinephrine and 5-HT transporters (mixed 5-HT/norepinephrine reuptake inhibitors, SNRIs), which increase the concentration of both norepinephrine and 5-HT in the synaptic cleft. Chronic therapy with antidepressants decreases the anhedonic symptoms

observed in depressive patients, reverses cognitive impairment, and increases neurogenesis.[33,34]

Animal models of depression are widely used to induce depressive-like symptoms in such a way that these can be reversed by classic antidepressants. Therefore, it is necessary that these models have predictive, face, and construct validity. It has not yet been possible to develop an animal model that completely mimics the biopsychosocial characteristics of depression in humans. However, many animal models reproduce some important aspects of the disorder, and are a used in research of new therapeutic targets for depression.[12,35]

Preclinical models of depression based on induction of chronic or acute stress, such as unpredictable chronic mild stress, early life stress (maternal deprivation), and restraint stress, are important to replicate etiological conditions of depression.[36-42] Animal models based on unpredictable chronic mild stress,[38,40,41,43,44] maternal deprivation,[45-48] and restraint stress[36,49] (different duration and stimuli type of stressful events) induce HPA axis hyperactivity. HPA axis hyperactivity is closely related to stressful life events, which are key factors in the etiopathogenesis of depressive episodes in patients. Stress hormone release in the bloodstream is usually observed in these individuals.[50-53] In rodents, stress induces reduction of MR (mineralocorticoid receptor) mRNA expression and of the MR/GR (glucocorticoid receptor) ratio.[54] Moreover, rats subjected to chronic mild stress have shown elevation of serum corticosterone concentration[40,44,55] and hypothalamic CRH (corticotropin-releasing hormone) mRNA expression.[40,55] The maternal deprivation- or restraint stress-induced animal models of depression have also been associated with elevated plasma levels of corticosterone and/or ACTH (adrenocorticotropin hormone).[45-49] The induction of stress in animals can cause remodeling of synaptic contacts on CRH neurons, contributing to the development of animal models of stress-related psychiatric disorders such as depression.[56] The administration of classical antidepressants reverses stress-induced biochemical and behavioral changes.[42,57-61]

The animal models of depression induced by different stressful stimuli (chronic mild stress, maternal deprivation, and restraint stress) reproduce alterations in the immune system,[42,62,63] another pathophysiological aspect found in depressive patients.[64] Classical antidepressants can improve mood and response to treatment in these individuals.[64,65] Rodents subjected to stressful stimuli such as chronic mild stress have shown elevated levels of interleukin (IL) 1β, IL-6 and tumor necrosis factor-alpha (TNF-α), indicating changes in the immune system.[62] Moreover, our group found increased TNF-α and IL-β levels in the serum and CSF of maternally deprived rats. By contrast, this same animal model of depression induced reduction of serum IL-10 levels. These changes in immune markers were reversed by imipramine.[42] Corroborating the idea that cytokines are involved in the depressive-like symptoms of animal models of depression, Karson et al.[66] showed that administration of the TNF-α inhibitor infliximab in rats subjected to chronic mild stress caused a reduction of the depressive-like effect observed on this animal model of depression (increased immobility time during FST and anhedonia on sucrose preference test). The pathophysiological mechanisms of chronic restraint stress also involve inflammation, since Voorhees et al.[63] showed that prolonged restraint stress elicited an increase in circulating IL-6 and decrease in serum IL-4 and IL-10 in mice. It is important to note that interleukins, especially IL-10, play an important role in regulation of the HPA axis. Therefore, reduced production of IL-10 can induce hyperactivity of the HPA axis as seen in depressed patients[67] and can be reproduced in animal models of depression.[63]

Considering that depressed patients have lower levels of brain-derived neurotrophic factor (BDNF) and that antidepressant therapy has reversed this effect,[68] animal models based on stress induction have also replicated this pathophysiological feature. In animals exposed to unpredictable chronic mild stress, BDNF (an important neurotrophic factor) is decreased, and this effect is reversed by antidepressant therapy.[69] Moreover, reductions in both BDNF and cyclic AMP response element binding protein (CREB) expression are proposed to be associated with the anhedonic symptoms and learning-memory impairments observed in stressed animals.[70] Furthermore, an animal model of depression induced by maternal deprivation and restraint stress was associated with a reduction of BDNF levels in rodent brains.[37,42,44,48]

It is important to note that chronic mild stress and maternal deprivation are among the most widely used preclinical models of depression. Chronic mild stress exposure induces depressive-like behaviors in rats, such as anhedonia and increased immobility in the FST. The reversion of these effects by chronic antidepressant treatment makes chronic mild stress one of the most valid models of depression.[71] The maternal deprivation paradigm is an animal model that has been used to study the long-term effects of child abuse and neglect. Experiments showed that rats subjected to trauma and stress early in life exhibit depressive behavior at a later stage in life; these findings mimic the clinical conditions seen in humans. It is apparent that adverse events occurring early in life may affect the development and maturation of the brain.[72]

In addition to studying different ways to manipulate animals in order to induce depressive symptoms, the removal of brain structures may be an effective alternative to study behavioral and neurobiological parameters associated with depression. In this regard, the bilateral removal of the olfactory bulbs in rodents has been widely used as an animal model of depression. This results in serious behavioral, neurochemical, neuroendocrine, and neuroimmune alterations that tend to co-occur in clinically depressed patients[73-76] and can be restored by treatment with classical antidepressants.[77-80] In rats, olfactory bulbectomy induces depressive-like behavioral and physiological alterations such as anorexia, nutritional disorders, weight loss, psychomotor retardation, sexual aversion, decreased grooming behavior, reduced social

interaction, increased immobility time in the FST, and anhedonia.[74-76,81] Rodents subjected to ablation of the olfactory bulbs display HPA axis hyperactivity[81-84] as well as a reduction[76] or increase[74,85,86] of BDNF levels in brain areas. Moreover, olfactory bulbectomy also induces elevation of TNF-α and IL-1β levels in the rat brain.[76,84]

The interaction between genes and the environment plays a significant role in the pathogenesis of depression. Preclinical models of depression based on genetic manipulation can be powerful tools for exploring this relationship and possible therapeutic strategies.[87] In the field of genetic engineering, it is noteworthy that studies in humans provide the identification of genetic targets, which can contribute to the reproduction of transgenic animal models of depression that can be successfully translated to humans (construct validity).[25,88] As depressed patients have reduced levels of 5-HT, as noted earlier, mice have been engineered to express a loss-of-function of Tph2, the rate-limiting enzyme in the brain 5-HT synthesis pathway, similar to that seen in humans.[89] This genetic modification induced hyposerotonergia; in other words, it is a naturalistic model of 5-HT deficiency.[90-92] Beaulieu et al.[90] showed that homozygous and heterozygous Tph2 knockin mice displayed increased immobility time in the TST and elevated latencies to cross to the lighted compartment, as well as a reduction of activity in this compartment, on the dark-light emergence test. On the face of it, it can be inferred that 5-HT deficiency elicits anxiety-like and depressant-like behavior. These behavioral effects can be mediated by activation of glycogen synthase kinase 3 (GSK3),[90] an important signaling molecule involved in depression.[93]

Another potential target is the cannabinoid type I (CB1) receptor. CB1 knockout mice are another preclinical model of depression, based on the fact that activation of CB1 receptors is involved in the control of mood and emotion.[94] These mice have shown anxiety-like[95,96] and depressive-like behavior[97-99] accompanied by increase in serum corticosterone levels and decreased BDNF levels in the hippocampus,[97] as well as alteration of serotonergic function.[98] In addition to Tph2 and CB1, other gene polymorphisms can be found in depressive patients, involving the genes coding for the 5-HT transporter (5-HT1A, 5-HT1B, and 5-HT2A) and endocannabinoid 1 (CB1) receptors, tryptophan hydroxylase-2 (Tph2), *CREB1*, *BDNF*, and G protein-coupled inwardly-rectifying potassium channel (GIRK) genes, which are important to the development of mutant animal models of depression based on these genes.[88]

Nevertheless, these mutant animal models present several problems: i) genetic lesions in mice do not replicate all of the robust phenotypes seen in humans; ii) mutations are usually common to different psychiatric disorders, producing different phenotypes; iii) depression involves multiple genes of small and rare effect, while mutant animal models usually involve only one gene; iv) the manipulation of a single gene involved in depression, alone, contributes with a small risk of development of the disorder; therefore, mutant animal models can be considered as animal models of risk for the disorder rather than of the disorder itself.[35] Therefore, it is important to emphasize that there is great controversy about the use of genetic animal models as a tool for depression research, as the genetic association of known polymorphisms with depression is often weak. Furthermore, mutant models are only available for a small group of genes involved in the pathological mechanisms related to depression susceptibility. Nevertheless, genetic animal models are widely used.

In summary, preclinical models of depression still present several limitations, such as the acute nature of tests or models; the fact that many symptoms seen in humans cannot be assessed in animals; and the gender of animals. It is known that the prevalence of depression in humans is significantly higher in females, but most animal models of depression are replicated in males.[100-102] Despite these limitations, preclinical models of depression are extremely important tools for studying the neurobiology of depression and developing more effective therapeutic strategies.

Animal models of bipolar disorder

Researchers do not yet fully understand the underlying mechanism of BD pathophysiology, and a number of environmental factors may be involved, although a genetic predisposition has been clearly established. One theory is that BD might be linked to neurotransmitter system dysfunction. The neurotransmitter systems that seem to be involved in this psychiatric disorder are the dopaminergic, cholinergic, noradrenergic, serotoninergic, GABAergic and glutamatergic systems.[103-107]

BD presents a complex, alternating clinical course, with recurrent mood swings including manic and depressive episodes, making the development of an adequate animal model a challenge. Currently, there are no animal models with sufficient face, construct, and predictive validity to be considered an animal model of BD. However, the hallmark of BD is manic symptoms, which are related to dopaminergic hyperactivity. Thus, the animal model of mania induced by amphetamine (AMPH), even though it addresses only one pole of the disorder, is still the most useful model to study BD.[108]

AMPH acts on the central nervous system by increasing DA efflux, inhibiting DA reuptake and inhibiting DA degradation by the enzyme monoamine oxidase.[109-111] A study showed that acute administration of 10 μM AMPH is sufficient to increase DA levels in striatal slices of rat.[112] Dopaminergic drugs, such as AMPH, are able to induce manic symptoms in both normal human volunteers[113] and BD subjects.[114] Interestingly, higher urinary DA levels have been associated with the emergence of manic symptoms.[115] In addition, a study has demonstrated that BD patients exhibit modifications in an allele of the DA transporter encoder, which may enhance DA levels in the brains of BD patients.[103] Moreover, Pantazopoulos et al.[116] showed abnormal expression of the D1 receptor in BD patients. In the same study, the researchers described an increase in the number of neurons expressing the D1 receptor.

Another important fact associated with AMPH-induced hyperactivity is the alteration in BDNF levels in the rat brain.[117-119] Several studies have demonstrated that the chronic administration of AMPH decreases BDNF levels in the cerebral tissues of rats.[117-119] BDNF is a protein secreted by the brain responsible for regulating neural circuit development and function. The actions of BDNF are controlled by neural activity and its functions include neuronal differentiation, growth, and plasticity. For this reason, the impairment in BDNF levels observed in BD patients may contribute to brain atrophy and progressive cognitive changes, both of which are observed in BD.[120]

Several clinical studies have shown changes in BDNF levels in the brain and blood of BD patients. Dunham et al.[121] showed decreased expression of hippocampal BDNF and its receptors in patients with BD and major depression. The studies of Rao et al.[122] and D'Addario et al.[123] suggest that changes in BDNF levels in BD patients are linked to epigenetic changes, such as hypo- and hypermethylation of DNA regions associated with BDNF expression. Additionally, histone deacetylases (HDAC) have been described as a potentially promising target for treatment of several neurological disorders.[124] HDAC inhibitors (HDACi) increase histone acetylation, which diminishes the affinity between histone proteins and DNA and thus facilitates gene transcription.[125,126]

Valproate (VPA), an anticonvulsant and mood-stabilizing drug, has been characterized as an HDACi.[127] Several studies have shown that VPA has neuroprotective effects, suggesting that the therapeutic mechanisms of this drug involve, at least in part, the inhibition of HDAC.[128-130] Recently, it was demonstrated that microinjection of sodium butyrate (SB) and VPA, two HDACi, in the ventricle, amygdala, striatum, and prefrontal cortex blocked the hyperactivity induced by methamphetamine.[131] In addition, it was also demonstrated that intraperitoneal SB and VPA administration reversed and prevented dextroamphetamine (d-AMPH)-related manic behavior. In addition, SB protected against d-AMPH-induced mitochondrial complex damage and oxidative stress in the brains of rats.[132,133]

Oxidative stress is an important marker present in BD and, interestingly, appears to be associated with BDNF. There is evidence showing that oxidative stress may be increased in conditions where BDNF is described to be decreased in BD.[134,135] Furthermore, preclinical studies using animal models of mania induced by AMPH have shown that the mood stabilizers lithium and VPA increase BDNF levels and protect the rat brain against oxidative damage.[119,136] Therefore, we suggest that a good mood-stabilizing drug, besides acting on behavior, must act against oxidative stress and modulate BDNF levels in BD patients.

In addition to SB, several new possible mood stabilizers have been tested in animal models and some have demonstrated good results. In the absence of a precise pathophysiological characterization of BD, researchers have tested substances that act on the molecular targets of mood stabilizers, especially lithium and VPA. Protein kinase C (PKC) is a downstream biochemical target of lithium and VPA, and it has been suggested that the action of mood stabilizers on this protein may be the starting point for their antimanic effect.[3,137] PKC has many functions in the neuron, including that of facilitating neurotransmitter release, neuronal excitability, and neuronal plasticity.[138] Lithium and VPA attenuate PKC function, while promanic psychostimulants activate it, suggesting that PKC modulation plays a critical role in the treatment of mania.[139] In addition, several clinical studies have shown that tamoxifen (TMX) – a PKC inhibitor – is effective in treating acute mania.[140-142] Based on these observations, PKC inhibition was proposed as a promising therapeutic mechanism in the treatment of BD.[143] Recently, our laboratory showed that TMX protected against d-AMPH-induced hyperactivity, mitochondrial complex damage, and oxidative stress in the brains of rats. In addition, TMX as well as lithium increased levels of BDNF and Bcl-2, which are anti-apoptotic proteins.[118] The number of potential new drugs tested in animal models is growing, which helps further our knowledge of the pathophysiology of BD and supports the development of better drugs for the treatment of this disorder.

In 1983, El-Mallakh[144] described a hypothesis about BD pathophysiology. This new hypothesis was presented to explain and integrate experimental and clinical observations of bipolar psychosis. This model is based on alterations in the activity of the sodium, potassium-activated adenosine triphosphatase (Na^+, K^+-ATPase) pump. In his review, El-Mallakh suggested that a reduction in the activity of Na^+, K^+-ATPase can be responsible for both phases of BD.[144] The Na^+, K^+-ATPase is a major plasma membrane transporter for sodium and potassium that maintains and reestablishes, after each depolarization, the electrochemical gradient of the neuron.[145] Therefore, changes in Na^+, K^+-ATPase activity can lead to changes in neuronal activity and, consequently, behavioral changes.

It has been well established that blood Na^+, K^+-ATPase enzyme activity is reduced in BD patients.[146-148] Rose et al.[149] have demonstrated reduced expression of the $\alpha 2$ isoform of Na^+, K^+-ATPase in the brain of subjects with BD. Another study demonstrated that genetic variations in Na^+, K^+-ATPase are associated with BD.[150] In addition, it has been found that subconvulsive doses of ouabain (OUA), a potent Na^+, K^+-ATPase inhibitor, produce a dose-related increased in locomotor activity, which is considered a manic-like behavior, in rats.[151] Together, these studies suggest that a small reduction in sodium pump activity may alter the excitability of neurons, producing both manic and depressive symptoms.

More recently, the animal model of mania induced by OUA has gained considerable attention. The intracerebroventricular (ICV) injection of OUA in rats mimics some manic symptoms, which are reverted by administration of classical mood stabilizers, such as lithium and VPA.[152-154] Banerjee et al.[155] found a significant decrease in Na^+, K^+-ATPase activity and increased lipid peroxidation in the serum of BD patients. In the same study, the authors demonstrated that lithium induces improvement in enzyme activity and a significant reduction in lipid peroxidation.

Animal model studies have shown that manic-like hyperactivity induced by OUA is associated with severe brain damage by increasing formation of lipid and protein oxidation products and decrease of BDNF levels in the rat brain.[154,156]

Moreover, it has been shown that activity of the enzymes catalase (CAT) and superoxide dismutase (SOD) is altered in the brain and cerebrospinal fluid of rats subjected to the animal model of mania induced by OUA.[156-159] Brocardo et al.[157] also demonstrated that glutathione peroxidase and glutathione reductase levels are decreased in the hippocampus and cortex of rats after ICV OUA injection. Interestingly, lithium and VPA were able to protect the brain against the protein and lipid damage and SOD and CAT changes induced by OUA in rats.[156]

Machado-Vieira et al.[160] demonstrated an increase of lipid damage in the plasma of BD patients during initial episodes of mania, when compared with healthy controls. This study also reported an increase of SOD and CAT, which are natural antioxidant defenses. Treatment with lithium decreased the lipid damage and CAT and SOD level alterations, demonstrating an antioxidant effect and a potential role for these effects in the pathophysiology and treatment of BD. Some antioxidant substances have been tested in the animal model of mania induced by OUA. Administration of folic acid, a potent antioxidant, prevented OUA-induced behavioral alterations, lipid damage, and glutathione peroxidase and glutathione reductase changes in the rat brain.[157] Diphenyl diselenide, an organoselenium component of antioxidant enzymes, also reverted behavioral alterations attenuated lipid and protein damage, and prevented the increase of SOD and CAT induced by OUA.[159]

Recently, it was demonstrated that ICV administration of OUA alters synaptic plasticity and DA release in the rat medial prefrontal cortex (mPFC). These findings suggested that alterations in synaptic plasticity and DA release in the mPFC might underlie the mPFC dysfunctions that accompany OUA-induced manic-like behavior. These OUA-induced alterations in synaptic plasticity can be prevented by pretreatment with lithium. This study highlights important aspects of this animal model, which is able to mimic behavioral changes seen in BD as well as two important pathophysiological alterations observed in this disorder: a decrease in Na^+, K^+-ATPase activity and an increase in extracellular DA.[161]

Considering the search for animal models of BD that mimic the symptoms of this disorder more accurately, preclinical models based on circadian rhythm disturbances are being developed. Circadian rhythms are present in many organisms and are controlled by a central biological clock in the suprachiasmatic nucleus. Their main function is to regulate biological processes with circadian periodicity.[162-164] Circadian rhythm abnormalities have been associated with BD, but its potential role in the pathophysiology of BD is still poorly understood.[164] Studies have found that life events that disrupt the social rhythm are associated with the onset of manic episodes in BD patients. It bears stressing that disruption of daily routines leads to circadian rhythm instability, which can cause affective episodes.[165,166] Taking this into account, Frank et al.[167] showed that interpersonal and social rhythm therapy can prevented the emergence of new episodes. Therefore, considering that sleep abnormalities are seen in patients with BD, mainly in manic states,[168-170] an animal model of paradoxical sleep deprivation in rodents can reproduce mania-like symptoms.[171-174] In fact, Gessa et al.[171] showed that animals subjected to sleep deprivation exhibit hyperactivity, irritability, aggressiveness, hypersexuality, and stereotypy. The opioid and dopaminergic systems appear to be involved in these effects.[171] Moreover, the behavioral changes observed in this animal model may be mediated, at least in part, by interaction with the PKC pathway, which may contribute to the pathophysiology of mania.[173] More recently, Armani et al.[174] showed that sleep deprivation induces hyperlocomotion which is reversed by lithium.[174] These studies contribute immensely to the search for an animal model that is closer to the ideal representation of BD.

The more an animal model mimics the aspects of the disorder, the more it would accelerate BD research by improving our understanding of the pathophysiology of the disorder and providing the possibility of preclinical pharmacologic screening.[152]

Conclusion

This review has discussed how the multiple animal models of depression and BD can help our understanding of the pathophysiology of these psychiatric disorders and research new targets for their therapy. However, the challenge faced by researchers is to reproduce, in the animal model, the greatest possible number of the symptoms and pathophysiologic changes seen in the human disorder. BD, which features a complex, alternating clinical course with recurrent mood swings including manic, depressive, and mixed episodes, poses a particular challenge for the development of an adequate animal model. It is clear that the development of suitable animal models would accelerate mood disorder research by improving understanding of the pathophysiology of the disorder and providing the possibility of preclinical pharmacologic screening.[152] Just as BD, major depression also lacks an animal model that mimics all the symptoms observed in depressed humans. However, the available animal models of depression are able to reproduce a larger number of symptoms which resemble the human disorder than the models currently available for BD. Despite all of these limitations, animal models are an important tool for investigation of the neurobiological mechanisms underlying psychiatric disorders, and appear to be a promising vehicle for preclinical screening of mood-stabilizing and antidepressant drugs.

Acknowledgements

We thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo

à Pesquisa e Inovação do Estado de Santa Catarina (FAPESC), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and UNESC for the financial support provided. We also thank NM - Assessoria para Trabalhos Acadêmicos, who reviewed and corrected this article.

Disclosure

The authors report no conflicts of interest.

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