Strategies for Treatment-Resistant Depression: Lessons Learned from Animal Models

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Abstract

Around 300 million individuals are affected by major depressive disorder (MDD) in the world. Despite this high number of affected individuals, more than 50% of patients do not respond to antidepressants approved to treat MDD. Patients with MDD that do not respond to 2 or more first-line antidepressant treatments are considered to have treatment-resistant depression (TRD). Animal models of depression are important tools to better understand the pathophysiology of MDD as well as to help in the development of novel and fast antidepressants for TRD patients. This review will emphasize some discovery strategies for TRD from studies on animal models, including, antagonists of N-methyl-D-aspartate (NMDA) receptor (ketamine and memantine), electroconvul-

sive therapy (ECT), lithium, minocycline, quetiapine, and deep brain stimulation. Animal models of depression are not sufficient to represent all the traits of TRD, but they greatly aid in understanding the mechanism by which therapies that work for TRD exert antidepressant effects. Interestingly, these innovative therapies have mechanisms of action different from those of classic antidepressants. These effects are mainly related to the regulation of neurotransmitter activity, including general glutamate and increased connectivity, synaptic capacity, and neuroplasticity.

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Introduction

Major depressive disorder (MDD) is the most common of all mental disorders, affecting over 300 million people all around the world, and ranks among the top causes of disability [1]. Abnormalities in the domains of learning/memory, executive function, attention, concen-

tration, and processing speed are consistently reported in patients with MDD [2]. In addition, treatment-resistant depression (TRD) is among the most important public health problems and commonly associated with significant disability and psychosocial impairment [3]. Although there have been recent advances in identifying the neurobiological correlates of these complex conditions, their pathophysiology still remains unclear [3].

The treatment options for patients with MDD depend on the use of antidepressants, most of which are monoaminergic agents, such as selective serotonin reuptake inhibitors, tricyclic antidepressants (TCAs), selective norepinephrine or dual serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors (MAOIs) [4]. Only 2 antidepressants (i.e., duloxetine and vortioxetine) have established procognitive effects utilizing rigorous methodology in MDD. Most antidepressants improve cognitive function(s), but the extent to which they directly exert procognitive effects is not yet understood [2]. In addition, the positive effects of the most antidepressant agents are related to the hypoactivity of the monoamine neurotransmitter systems (predominantly serotonin, norepinephrine, and dopamine), especially in brain regions implicated in the pathophysiology of MDD, such as the hippocampus and prefrontal cortex (PFC) [5, 6].

Unfortunately, drug treatment has important shortcomings, such as a delayed onset of therapeutic effects and limited efficacy [7]. In fact, monoaminergic agents are related to a time lag of 2 or more weeks before a therapeutic effect is observed [8]. In addition, studies have shown that more than 60% of patients with MDD fail to obtain a clinical important response or sustained remission with a traditional antidepressant, with approximately one-third of all depressed patients failing to respond to 2 or more first-line antidepressant treatments and thus being characterized as having TRD [9]. In this way, treatment resistance is a common problem in MDD therapy [10], which demonstrates a great need for the development of safer and more effective antidepressant agents [11].

An animal model is defined as any experimental preparation developed in an animal for the purpose of studying a human condition [12]. For preclinical studies, animals are essential for developing novel treatments. Symptoms like feelings of sadness, guilt, or suicidal thoughts cannot be observed in rodents; however, some criteria have been established to define depressive mood disorders, such as depressed mood and/or anhedonia, changes in appetite, sleep disturbances, fatigue, and other behavioral alterations [13]. Most animal models of MDD demonstrate the efficacy of antidepressant agents using behav-

ioral tests that show robust responses clinically [4]. Ideally, an animal model of TRD should be validated by demonstrating that populations resistant to traditional antidepressants would respond to treatments shown to be effective in patients with TRD [14]. One of the main objectives for the development of animal models for MDD is to better understand the neurobiological mechanisms of depression in resistant patients [4]. In addition, they provide a framework for improved translation between preclinical research and clinical trials [4]. Preclinical models, with face, construct, and predictive validities, will allow a better understanding of the genetics and underlying neurobiology of TRD and provide a translational valid model for the development and testing of novel antidepressant therapeutics [15]. Currently, some studies have focused on the understanding of which antidepressant responsiveness and resistance mechanisms are present in animal models [16]. In accordance, animal models of antidepressant resistance have used 3 basic approaches: (1) separation of rodents into bimodal subpopulations that respond or are resistant to traditional antidepressant treatments, which is often used following a behavioral stressor such as chronic mild stress (CMS) [17] or chronic social defeat [18]; (2) treatments that render rodents resistant to antidepressants (e.g., adrenocorticotrophic hormone [ACTH]) [19] or inflammation [20]); and (3) genetic models that show resistance to traditional antidepressant treatment (e.g., use of genetically modified mice).

Thus, in the development of animal models of MDD, researchers have typically relied on pharmacological validation by determining if classical antidepressants can reverse a stress-induced behavioral change in normal animals [4]. Utilizing animal models that do not respond to classical antidepressants but are responsive to drugs that have shown efficacy in refractory patients in the clinic may offer an improved framework to test new pharmacological therapies for TRD [4]. Thus, the purpose of this review was highlighting the new drug strategies with a novel mechanism of action to TRD in animal models of depression.

Methods

We conducted a review of computerized databases (i.e., PubMed) from 1980 to 2017. "MDD" was cross-referenced with the subsequent words: treatment-resistant depression, treatment, and animal models of treatment-resistant depression. Treatment-resistant depression was cross-referenced with the subsequent words: depression and ketamine, depression and memantine, depression and quetiapine, depression and minocycline, depression and lithium, depression and electroconvulsive therapy, and de-

pression and deep brain stimulation. Bibliographies from identified papers were also verified to detect any other original article that was associated with the goals of this review.

Results

Ketamine

Due to the therapeutic limitations of current antidepressant treatments, studies on the pathophysiology of MDD have focused on new targets for antidepressant action, especially in the glutamatergic system [9]. Studies with animals found that N-methyl-D-aspartate (NMDA) receptor antagonists have antidepressant effects in the forced swimming test (FST) and tail suspension test, in learned helplessness paradigms, and in animals exposed to chronic stressors [15, 21–23]. In fact, ketamine, a nonselective NMDA receptor antagonist, has been studied as an alternative antidepressant with fast onset and long-lasting therapeutic action [24, 25]. Its limitations include poor bioavailability, rapid but short-lived effects, and little information about long-term benefits and safety of repeated administration [25].

Moreover, Hirota and Lambert [26] showed that ketamine alters voltage-operated calcium channels and receptors for opioids, α -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor, and muscarinic acetylcholine receptor. Since the discovery that ketamine is a fast-acting antidepressant in MDD patients, there are pre-clinical studies assessing its effects using ketamine to investigate different mechanisms of this drug to treat TRD in rodents [16]. An initial study found that ketamine shows rapid antidepressant-like properties in mice exposed to a learned helplessness paradigm and FST [27]. In some studies, ketamine produced antidepressant-like behavior effect in animals exposed to several different stressors [28, 29]. In addition, in rats submitted to the maternal deprivation protocol, ketamine was able to produce antidepressant effects in the FST [30–32].

Studies have used MDD animal models to assess the mechanisms underlying the antidepressant effects of ketamine. In brain-derived neurotrophic factor (BDNF) heterozygous null mice, where imipramine had no effect in the FST, ketamine produced a robust antidepressant-like response [33]. Contrarily, conditional BDNF-knockout mice (with loss specific to the hippocampus and cortex) did not respond to ketamine in the FST [34], showing that ketamine antidepressant effects could be mediated by BDNF pathways. In fact, a previous study showed that ketamine at different doses was able to increase the levels of BDNF, cAMP response element binding (CREB), pro-

tein kinase C, and protein kinase A in some brain structures related to MDD, including PFC, hippocampus, amygdala, and nucleus accumbens (NAc) [35]. Wei et al. [36] have also reported that the enhancement of the phosphorylation of CREB Ser¹³³ and expression of CREB and glutamate receptor 1 (GluR1) are necessary for the antidepressant actions of ketamine.

Moreover, the rapid actions of ketamine in behavioral models of depression and antidepressant responses have been linked to increased synapse number and function in the medial PFC (mPFC) [37, 38]. These studies also demonstrate that ketamine increases the mechanistic target of the rapamycin complex 1 (mTORC1) signaling pathway that regulates translation and synaptic protein synthesis [37]. In addition, Abela et al. [38, 39] reported that the activation of mammalian target of rapamycin (mTOR) in the PFC is involved in the antidepressant-like effects of ketamine, and the inhibition of this pathway by rapamycin (an mTOR inhibitor) was able to protect certain brain areas against oxidative stress and regulate the endoplasmic reticulum (ER) stress pathway.

Taken together, these studies demonstrate that ketamine also shows rapid antidepressant effects in rodents and in some signaling pathways that are potential targets for novel therapeutic interventions. Future animal studies into the mechanisms underlying the antidepressant effects of ketamine should lead to additional targets for new antidepressants that are fast acting and elicit high response rates [16].

Memantine

Memantine (1-amino-3,5-dimethyladamantane) is a low-to-moderate-affinity, noncompetitive NMDA receptor antagonist currently prescribed for the treatment of Alzheimer's disease [40]. In fact, in patients with Alzheimer's disease, Emre et al. [41] demonstrated that treatment with memantine significantly improved cognition and memory compared to placebo. Besides dementia in the elderly, during the past 10 years, this drug has been used for the treatment of Parkinson's disease [42], which is associated with the loss of dopaminergic neurons located in substantia nigra pars compacta [43, 44].

In contrast to ketamine, memantine is devoid of psychotomimetic effects at therapeutic doses (5–20 mg/day) [45]. Moreover, preliminary clinical observations report promising antimanic and mood-stabilizing effects of memantine also in treatment-resistant bipolar disorder, presumably via blockade of an NMDA-receptor-mediated phenomenon of dopamine D2 receptor sensitization [46].

Clinical studies have shown controversial results regarding the antidepressant effects of memantine in pa-

tients with MDD. Ferguson and Shingleton [47] showed that memantine administered during 12 weeks leads to a rapid and effective improvement in depressive symptoms in MDD patients. However, Zarate et al. [48] demonstrated that monotherapy during 8 weeks with memantine did not have efficacy in the treatment of MDD.

Preclinical investigations have described that memantine possesses antidepressant-like properties in animal models of depression [49, 50]. In rats submitted to the CMS protocol, Papp et al. [50] demonstrated that memantine presented anxiolytic and procognitive effects but did not reverse CMS-induced anhedonia. However, Quan et al. [51] showed that memantine increases sucrose consumption in stressed rats. In addition, memantine reversed learning deficits and PFC synaptic plasticity but impaired spatial memory; these effects are probably due to different upregulation of NMDA receptor subtype 2B (NR2B) expression in PFC and hippocampus of stressed rats. Marvanová et al. [52] have shown that memantine increases the levels of both BDNF and its receptor, tyrosine kinase B (trkB), in the rat limbic cortex. A previous study reported that acute administration of memantine at a higher dose (20 mg/kg) increased BDNF protein levels in the rat hippocampus. Still, combined treatment with memantine and sertraline decreased the immobility time in the FST and produced stronger increases in the BDNF protein levels in the hippocampus and PFC [53], suggesting that glutamate acting on NMDA receptors may play a role in regulating the expression of BDNF levels [54]. A synergistic antidepressant-like effect was observed when imipramine and fluoxetine were administered in combination with memantine in the FST [55]. Interestingly, fluoxetine, which was inactive when given alone, displayed a positive effect when co-administered with aminoadamantanes, such as amantadine and memantine, suggesting that the combination of traditional antidepressants and NMDA antagonists may produce an enhanced antidepressant effect [54]. This assumption could be of particular relevance for TRD.

Memantine could be considered an option for TRD patients. However, more studies should be conducted, mainly in animal models, to investigate the mechanisms by which other NMDA receptor antagonists have shown better responses. An alternative could be memantine combined with classical antidepressant drugs. The contradictory results in clinical studies might be related to differences in patient characteristics or exclusion criteria, and also differences in the follow-up period, sample size, dosage regimens, and duration of previous medical therapy [56]. In addition, the pharmacological effect of me-

mantine includes weak open-channel blockers with low-affinity and fast dissociating properties that might explain the lack of its antidepressant activity reported in some of the above-mentioned literature publications [57].

Quetiapine

Quetiapine is an atypical antipsychotic drug that was approved for the treatment of schizophrenia by the Food and Drug Administration (FDA) in 1997 [58]. Several studies characterize quetiapine as adjunctive therapy for MDD, TRD, and for the treatment of acute depressive episodes associated with bipolar disorder [59–61]. The main antipsychotic effect of quetiapine is due to its antagonism on D2 and 5-HT₂ receptors; also, quetiapine acts by blocking 5-HT_{1A}, 5-HT₂, D₁, D₂, H₁, A₁, and A₂ receptors [62]. Among broad pharmacological properties, the antidepressant effect of quetiapine may be mediated through α_2 -receptor blockade, which results in increased noradrenergic transmission [63]. Besides, quetiapine acts as a partial agonist of 5-HT_{1A} receptors and as an effective norepinephrine reuptake inhibitor by N-desalkyl-quetiapine, a metabolite present in this drug [64].

A clinical study reported that quetiapine has antioxidant properties in human plasma [65]. Acute and chronic treatments with quetiapine in adult rats demonstrated antidepressant-like effects through the reduction in the FST immobility time [66]. Furthermore, quetiapine exhibited an antioxidant profile and decreased oxidative damage, mediated by the reduction in myeloperoxidase activity and the levels of thiobarbituric acid-reactive species, as well as increases in antioxidant enzymes, superoxide dismutase and catalase activities in brain structures involved in MDD pathophysiology [66].

Quetiapine add-on therapy can significantly improve the depressive behaviors induced by CMS in rats resistant to fluoxetine [67]. A 3-week add-on treatment with quetiapine prevented the anhedonic state in rats exposed to CMS, as observed by the increased sucrose consumption, decreased immobility time in the FST, and the shortened latency to chew the pellet in fluoxetine-resistant depressive rats [67]. Furthermore, the combination with quetiapine and fluoxetine demonstrated a potential mechanism of action on precognitive effects by increasing cell proliferation in the hippocampus of fluoxetine-resistant depressive rats [67].

It was revealed that one of the putative antidepressant effects of quetiapine is the presence of norquetiapine, a metabolite that activates extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signaling pathways, generating the release of the glial cell-

derived neurotrophic factor [68]. In addition, chronic treatment with quetiapine and repetitive transcranial magnetic stimulation was determined not only to reverse the depressive-like behaviors of rats exposed to CMS but also to restore the protein expression of pERK1/2 and BDNF and cell proliferation in the hippocampus [69].

Minocycline

Minocycline hydrochloride is a semisynthetic tetracycline derivative with antibiotic and anti-inflammatory properties, which also exhibits potent neuroprotective activities [70]. It can potentially affect a wide variety of secondary injury mechanisms and can also protect neural tissue via anti-inflammatory, antioxidant, and antiapoptotic effects after a traumatic spinal cord injury, for example [70–75].

Minocycline has been shown to have an inhibitory system in the inflammatory process that results in the progression of secondary injury [76]; it causes neuroprotection from oxidative stress and scavenges free radicals [76]; inhibits the nitric oxide (NO) synthase enzyme that is responsible for NO production [77]; prevents the apoptosis of neurons caused by glutamatergic neurotoxicity via NMDA-induced excitotoxicity by diminishing NMDA-induced Ca^{2+} influx and mitochondrial Ca^{2+} uptake [78, 79]; prevents apoptosis by inhibiting mitochondrial cytochrome C [80]; inhibits oligodendrocyte apoptosis and improves functional recovery [81]; protects gray and white matter from spinal cord ischemia [82]; protects neurons from hemorrhage-induced toxicity [82]; and protects the blood-brain barrier and reduces edema following intracerebral hemorrhage [83].

Only one-third of patients treated with antidepressant monotherapy obtain complete effective remission of depressive symptoms and functional recovery [84]. Therefore, minocycline has been investigated as a potential new agent to obtain a better response for TRD, since this drug presents powerful anti-inflammatory and neuroprotective effects [85]. In fact, minocycline regulates some pro-inflammatory agents that have been reported to be increased in depressed patients, such as NO, tumor necrosis factor- α , and interleukin-1 β [86, 87]. In addition, a study showed that minocycline displayed a neuroprotector action by the reduction in oxidative damage and regulation of energy metabolism in specific brain areas [88]. In a preclinical study, the early-life isolation, a model of early-life stress, induced depressive-like behavior in rats, and minocycline administration reversed these effects and blocked microglial activation induced by the stress in the early life period [89].

The results of these studies indicate that minocycline has a potential role in TRD. It is already available for sale and an easy to access, off-patent drug that has low probability to cause antibiotic resistance [90]. However, future studies are required to elucidate the mechanism of action of minocycline in TRD.

Lithium

Lithium is an alkali metal that is in the same family as sodium and is one of the lightest elements in the periodic table [91]. It has been used over decades in medicine. Studies have shown that treatment with lithium showed efficacy in the treatment of acute mania and MDD and in the prevention of recurrent mania and depression [92]. Lithium was approved by the FDA in the 1970s and is recommended for the treatment of bipolar and MDD disorders [93]. Moreover, evidence showed that the treatment with lithium reduced the suicide risk in MDD patients [94].

Preclinical studies have investigated the physiological, biochemical, and behavioral effects of this drug [95]. The mechanisms of action of lithium are involved in many pathways, including inhibition of cytosolic phosphatases as low-K-induced phosphatase, activation of phosphoinositol-3-kinase and serine-threonine protein kinase B (Akt), and inhibition of inositol monophosphatase and glycogen synthetase kinase (GSK)3 β [95–99]. It was reported that chronic treatment with lithium in rats induced a decrease in immobility time in the FST [100]. A study evaluated the effects of lithium alone in a subactive dose or in combination with gepirone (a 5-HT_{1A} agonist). The results showed that lithium administered acutely at doses of 2, 4, and 8 mEq/kg had a small effect on immobility time in rodents. However, lithium at a dose of 1 mEq/kg in combination with a subactive dose of gepirone led to a reduction in immobility time, showing a stronger antidepressant effect [101]. Recent studies have shown that long-term administration of lithium in rats also decreases immobility time [102–105]. Another study investigated the synergistic antidepressant effect of lithium with agmatine, a drug with multiple action mechanisms, including modulations in NO and NMDA receptors, and demonstrated that lithium administered at a dose of 30 mg/kg decreased the immobility time in FST in mice, but when administered at a dose of 3 mg/kg (a subeffective dose) with agmatine at a dose of 0.01 mg/kg (a subeffective dose), the antidepressant effects of lithium were potentiated [106].

On account of its antidepressant effect, lithium can be used in TRD, although the number of studies using lithi-

um only for this purpose is quite small. Most of the reports published studied lithium in combination with TCAs, and there are fewer data on serotonin reuptake and serotonin-norepinephrine reuptake inhibitors for antidepressant treatment, but, nevertheless, it could be an important pharmacological strategy for TRD [107].

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) was created by Ladislav Meduna and was introduced in 1938. The first idea was that ECT could chemically change the composition of the brain by inducing seizures in patients with schizophrenia [108, 109], but the mechanisms of action of this therapy have been studied for treating many mood disorders, including MDD and bipolar mood disorder. With the development of psychotropic drugs in the 20th century, ECT became unpopular, but due to TRD ECT recurred and is considered the last option for these patients [110].

The first study using ECT with an animal model of depression was made in 1980 by Katz [111]. In this study, rats were exposed to acute noise stress and treated with ECT; they were subjected to the open field test to evaluate their behavior, and it was demonstrated that the depressive effects on stressed rats were restored by ECT treatment [111]. Regulation in cortico-limbic circuits, inhibitory neurotransmitter systems, and monoamine neurotransmitters, neurogenesis, and endocrinological pathways are the most pertinent associated with ECT antidepressant mechanisms of action [112]. Another mechanism is supposed to be associated with an increase in the function of γ -aminobutyric acid (GABA), an inhibitory neurotransmitter [113]. In a study in rats receiving repeated ECT applications, GABA release increased in the cerebral cortex and striatum [114].

In another study, an association between ACTH and ECT was noted. In fact, it was shown that this hormone blocks the effects of TCAs [19]. Thus, to demonstrate the effects of ECT in an animal model of TCA-resistant depression, electroconvulsive stimuli were administered 30 min after ACTH administration for 6 or 14 days. In the FST, rats treated with ECT had a significant decrease in their immobility time in both saline and ACTH-treated rats after 6 and 14 days of treatment, and there was also an increase in BDNF protein levels in the hippocampus, suggesting that repeated ECT treatment has an antidepressant effect in an animal model of TCA-resistant depression by increasing BDNF levels [115].

It is evident that ECT is an effective treatment for MDD and TRD, but more studies are required to render it safer and more effective, and to reduce its side effects, such as headache, nausea, and memory loss.

Deep Brain Stimulation

Research has shown that deep brain stimulation (DBS) in specific brain areas is a promising new technique that may provide remission in TRD [116]. In TRD patients, DBS of the lateral habenula (LHb) resulted in therapeutic effects reported to correspond with periods of active stimulation [117].

Many experimental studies have been conducted to investigate the mechanism by which DBS exerts antidepressant effects. In an animal model induced by ACTH, it was demonstrated that the antidepressant effect induced by DBS on LHb was related to changes in Ca^{2+} /calmodulin-dependent protein kinase (CaMKII α/β), GSK3 α/β , and AMP-activated protein kinase [118]. Unilateral stimulation of the superolateral branch of the medial forebrain bundle in rats induced antidepressant-like effects in the FST and activated dopamine neurocircuitry in the PFC [119]. In addition, chronic DBS on the medial forebrain bundle displayed antidepressant effects in rats subjected to CMS and in a hemiparkinsonian rodent model [120]. Rummel et al. [121] used 2 animal models of depression, the Flinders sensitive line (FSL) and the therapy-refractory congenitally learned helpless rats, to study the DBS effects. The study revealed that DBS in the ventromedial PFC (vmPFC) and NAc improved depressive behavior in the FSL rat, while DBS in the subthalamic nucleus elicited depressogenic effects, and the antidepressant effects were associated with increased serotonergic turnover. Still, depleting transmitter release by repeated DBS of LHb afferents, using a protocol that can be effective on depressed patients, dramatically suppresses synaptic drive on ventral tegmental area (VTA)-projecting LHb neurons in brain slices and can significantly reduce learned helplessness behavior in rats [122]. Hamani et al. [123] also demonstrated that DBS in both vmPFC and NAc induced antidepressant effects in the FST. However, brain structures and circuits were differently influenced by DBS. Furthermore, antidepressant effects in the FST and a decrease in the anhedonic behavior in the sucrose preference test were reported in FSL subjected to DBS on vmPFC [124]. Also, antidepressant effects of DBS on vmPFC were not augmented when DBS was combined with buspirone, risperidone, and pindolol [125]. Another study investigated the anxiety and depressive effects of DBS in rodents; the results showed that DBS on the NAc area was effective to induce antidepressant- and anxiolytic-like responses, and, in addition, to increase neurogenesis, while selective serotonin reuptake inhibitors did not have any effect [126].

DBS on infralimbic PFC, a subregion of the mPFC, exerted antidepressant effects and increased the neurotrans-

mitters glutamate, serotonin, noradrenaline, and dopamine [127]. Another study investigated the effects of DBS on the VTA, and functional magnetic resonance imaging (fMRI) was used to observe changes induced by DBS on VTA. The results found by fMRI showed an increase in blood oxygen level-dependent signals (a method used to find more activity) in brain regions such as the anterior and posterior cingulate, insula, and striatum, and a decrease in the inferior temporal gyrus and primary somatosensory cortex, suggesting that DBS of the VTA could affect neuronal circuitry involved in the pathophysiology of MDD [128]. Wistar rats subjected to 21 days of ACTH administration (100 µg/day) presented evidence for treatment resistance to imipramine, accompanied by reduced mitochondrial capacity; on the other hand, DBS on NAc by 7 days was able to reduce immobility time in the FST and to restore mitochondrial capacity of ACTH-treated rats [129].

DBS appears to be promising for TRD. Animal models have helped to elucidate the mechanisms by which DBS exhibits antidepressant effects; these effects seem to be mainly related to the regulation of reward circuits and frontal cortical regions. In addition, the regulation of neurogenesis, energy metabolism, and signaling pathways appear to be important in the antidepressant effects of DBS.

Discussion/Conclusion

MDD is a common and often severe mental disorder associated with substantial illness-related burden. Most individuals receiving conventional pharmacotherapy fail to achieve and sustain remission, a critical determinant of full functional recovery. Several definitions and staging models have been proposed for TRD. However, animal models of depression are not sufficient to represent all the traits of TRD, but they greatly aid in understanding the mechanism by which therapies that work for TRD exert antidepressant effects. In fact, studies have shown that ketamine, quetiapine, and minocycline have potential antidepressant effects in animal models of TRD. In certain cases who do not respond to pharmacological treatments, ECT and DBS could be a therapeutic alternative. However, new studies using animal models of TRD are necessary for a better understanding of the pathophysiology of MDD and the mechanisms of action of the therapies, thereby helping in the treatment of those patients who do not respond to therapy.

Although there are many animal models of depression, few of them represent the characteristics of TRD, such as

CMS, chronic social defeat, learned helplessness, and FST. Most studies in animal models and clinical evidence have shown that a particular drug or technique exerts antidepressant effects for TRD patients. Animal models of depression demonstrate the mechanisms by which treatments for TRD have positive effects. Most studies show that drugs that have good effects seem to restore glutamatergic transmission, primarily mediated by the NMDA receptor, ultimately restoring intracellular signaling pathways that lead to increased brain cell survival and neuroplasticity (Table 1). The restoration of the immune system also appears to be an important factor involved in the antidepressant effects of drugs tested in animal models. Older techniques such as ECT and newer ones such as DBS, although more invasive, appear to have good effects for TRD, and the effects appear to be mediated by rapid regulation of the neurotransmitters involved in mood regulation and reward circuits of the brain.

The major finding in recent years for TRD appears to be ketamine, a drug with a very different mechanism of action compared to those approved for treating MDD, which act on the monoaminergic system. Results have been promising and help to understand the intrinsic mechanisms involved in antidepressant actions from animal models. The discovery of the antidepressant action of ketamine has fostered the development of other drugs. However, the psychomimetic effects induced by ketamine, as well as the lack of knowledge of its long-term effects, demonstrate the importance of further studies in this area. DBS has also shown good effects for TRD, but many brain regions appear to be involved. The discovery of specific circuits involved in the pathogenesis of TRD is very important, and animal models have helped elucidate such effects.

The goals in developing rodent models of TRD are to understand the neurobiological mechanisms involved in antidepressant resistance and to develop valid models to test novel therapies that would be effective in patients that do not respond to classical antidepressants. In the development of rodent models of depression, investigators have typically relied on pharmacological validation by determining if classical antidepressants can reverse a stress-induced behavioral change in normal animals. This may have led to underreporting of models that do not respond to classical antidepressants. Using animal models that do not respond to classical antidepressants but are responsive to drugs that have shown efficacy in refractory patients in the clinic may offer an improved framework to test new pharmacological therapies for TRD. However, there are some limitations to understand psychiatric dis-

Table 1. Effects of therapies used for TRD: evidence from animal studies

Animal model	Therapy	Main effect	Reference
Learned helplessness and FST	Ketamine	Rapid antidepressant effects	21
Chronic stress	Ketamine	Anti-anhedonic effects	22, 23
Maternal deprivation	Ketamine	Antidepressant effects	24–26
BDNF heterozygous null mice	Ketamine	Robust antidepressant effects	27
BDNF knockout mice	Ketamine	No antidepressant effects	28
FST	Ketamine	Increase BDNF, dendrites, and mTOR	30–33
CMS	Memantine	Anxiolytic effects	43
Chronic stress	Memantine	Increases BDNF levels, and upregulates NMDA receptor	44
FST	Memantine	Potentiates fluoxetine antidepressant effects	39
FST	Quetiapine	Antidepressant effects	61
CMS	Quetiapine	Anti-anhedonic effects and potentiates fluoxetine antidepressant effects	62
CMS	Quetiapine	Regulates BDNF levels and MAPK signaling pathway	64
CMS	Minocycline	Reduces oxidative stress	83
Early-life stress	Minocycline	Reduces microglial activation	84
FST	Lithium	Antidepressant effects	95
FST	Lithium	Potentiates agmatine antidepressant effects	101
Acute noise stress	ECT	Antidepressant effects	106
ACTH	ECT	Antidepressant effects, increases BDNF levels	111
FST	DBS	Antidepressant effects and restores dopamine neurocircuits in the PFC	113
CMS and Parkinson	DBS on MFB	Antidepressant effects	114
FSL	DBS on vmPFC and NAc	Antidepressant effects	19
FSL	DBS on STN	Depressive effects	19
FSL	DBS on vmPFC	Anti-anhedonic effects	116
ACTH	DBS on NAc	Antidepressant effects and restores mitochondrial capacity	121
ACTH	DBS on LHb	Alters CaMKII α/β , GSK3 α/β and AMPK	123

ACTH, adrenocorticotrophic hormone; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; CaMKII α/β , Ca²⁺ calmodulin-dependent protein kinase; CMS, chronic mild stress; DBS, deep brain stimulation; ECT, electroconvulsive therapy; FSL, Flinders sensitive line; FST, forced swimming test; GSK3 α/β , glycogen synthetase kinase 3 α/β ; LHb, lateral habenula; MAPK, mitogen-activated protein kinase; MFB, medial forebrain bundle; mTOR, mammalian target of rapamycin; NAc, nucleus accumbens; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex; STN, subthalamic nucleus; vmPFC, ventromedial PFC.

orders, such as the impossibility to identify mood changes, suicidal thoughts, and symptoms mainly specific to humans. The intriguing fact is that even with these new options there are still several patients who do not respond to these new therapeutic options, which is probably related to the individuality of each patient as well as to the triggers of MDD.

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Author Contributions

G.Z.R., A.B.M., L.A.B., H.M.A., and J.Q. wrote the manuscript. H.M.A. prepared Table 1. G.Z.R. contributed to the study design and manuscript revision.

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