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Signaling Pathways Underlying the Pathophysiology and Treatment of Depression: Novel Mechanisms for Rapid-Acting Agents

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Abstract

Basic and clinical studies demonstrate that stress and depression are associated with atrophy and loss of neurons and glia, which contribute to decreased size and function of limbic brain regions that control mood and depression, including the prefrontal cortex and hippocampus. Here, we review findings that suggest that opposing effects of stress/depression and antidepressants on neurotrophic factor expression and signaling partly explain these effects. We also discuss recent reports that suggest a possible role for glycogen synthase kinase 3 and upstream Wnt-Fz signaling pathways in mood disorders. New studies also demonstrate that the rapid antidepressant actions of NMDA receptor antagonists are associated with activation of glutamate transmission and induction of synaptogenesis, providing novel targets for a new generation of fast-acting, more efficacious therapeutic agents.

Introduction

Depression and stress-related mood disorders impact approximately 17 percent of the population, resulting in enormous personal suffering, as well as social and economic burden [1-3]. The neurobiology underlying depression has not been fully identified, but is thought to result from molecular and cellular abnormalities that interact with genetic and environmental factors [4]. This complexity and heterogeneity have made it difficult to define, diagnose, and treat this widespread illness. Currently available antidepressants, although widely prescribed for depression and other mood and anxiety related illnesses, have significant limitations, including a long time lag for a therapeutic response (weeks to months) and low response rates (only a third respond to the first drug prescribed, and up to two thirds after multiple trials, often taking months to years) [5]. This is particularly problematic for an illness associated with high rates of suicide.

Typical antidepressants acutely block the reuptake or breakdown of the monoamines 5-hydroxytryptamine (5-HT or serotonin) and norepinephrine (Figure 1), with 5-HT selective reuptake inhibitors (SSRIs) representing the most highly prescribed medication for depression, and related mood disorders. This acute mechanism of action led to the monoamine hypothesis of depression, but the time-lag for treatment response indicates that

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slow onset adaptations of downstream signaling pathways and regulation of target genes underlie the therapeutic actions of antidepressants (Figure 1). These signaling pathways and target genes in turn result in regulation of multiple physiological processes, including neuroplasticity, neuroprotection, and neurogenesis in the adult brain [4, 6].

Significant efforts have been directed toward characterization of the downstream targets of antidepressant treatment, with the promise of identifying novel therapeutic targets. A number of signaling pathways and targets have been identified, and here, the focus is on a few of the best-characterized and validated systems, including neurotrophic factor, Wnt, and glycogen synthase kinase 3 (GSK3) pathways. The functional consequences of these systems in the context of the damaging effects of chronic stress, including atrophy and loss of neurons and glia, effects also observed in brain imaging and postmortem studies of depressed patients, will be discussed.

In addition to advances made in understanding the actions of typical antidepressants and conversely the damaging effects of stress and depression, recent studies have begun to elucidate the mechanisms underlying a novel class of antidepressants, NMDA receptor antagonists. These agents, notably ketamine, produce a rapid antidepressant action, an effect not seen with any previous agent, in severely depressed patients who are resistant to typical antidepressants [7, 8]. Moreover, this rapid, efficacious response occurs via a completely different pathway, involving increased glutamate transmission and induction of synaptogenesis [9]. This pathway, and related ketamine-induced signaling pathways, will be discussed.

Together these findings underscore the importance of characterizing the intracellular signaling pathways that underlie the actions of antidepressants, as well as stress and depression. Importantly, comparison of typical antidepressants with novel, rapid acting NMDA antagonists also highlights the difference between agents that act on neuromodulatory systems (i.e., monoamines) compared to those that act on the major excitatory neurotransmitter system (i.e., glutamate) (Figure 1). The pros and cons of these approaches will be discussed, including response time, efficacy, and safety.

Brain Regions and Circuits That Regulate Emotion and Mood

Basic research and clinical imaging and postmortem studies have reported alterations of limbic brain regions, including the prefrontal cortex (PFC), hippocampus and amygdala in mood disorders [10, 11]. These and additional deep brain stimulation and mapping studies have identified depression circuit models, that link alterations of these and additional brain regions with the major symptoms of depression, including depressed mood, pleasure (i.e., anhedonia), cognition, and motivation, and altered sleep, libido and eating. Brain imaging studies consistently report reductions of PFC and hippocampus volumes that are associated with the length of illness and time of treatment [11-13]. Postmortem studies report reduced size of pyramidal neurons, decreased number of GABAergic interneurons and glia (both astrocytes and oligodendrocytes) in the PFC [14]. Many of these effects also occur in response to chronic stress exposure in rodents and nonhuman primates, including atrophy of dendrites and spines in the PFC and hippocampus, and decreased glia and neurogenesis in the adult hippocampus [15-18]. These findings support the notion that depression can be viewed as a mild neurodegenerative disorder, but with the possibility that the neuronal and glial decrements can be reversed by treatment or alleviation of stress.

Studies of the amygdala provide evidence of neuronal hypertrophy, including increased dendrite complexity of neurons in the basolateral nucleus [19]. These changes could result from direct actions of stress on amygdala or from PFC hypofunction and reduced inhibitory control, highlighting the importance of dysfunctional circuits in depression [18]. In either

case, the result is a hyperactive state of the amygdala that could contribute to increased anxiety, fear, and emotion [20].

Recent studies have also demonstrated a key role for the mesolimbic dopamine system in depression, particularly disruption of motivation, reward and pleasure, as well as social behavior [4]. Major advances have been made characterizing mesolimbic dopamine signaling pathways controlling behaviors related to depression, including epigenetic alterations [21, 22], and adaptations underlying resilience and susceptibility to depressive behaviors [4, 23, 24].

Neurotrophic Responses in Depression

Neurotrophic factors were identified as critical signaling molecules for nervous system development [25], but continue to play an important role in the survival, function, and adaptive plasticity of neurons in the adult brain [26-28]. Of the different families of neurotrophic/growth factors expressed in brain, the most extensively studied in depression is the nerve growth factor (NGF) family, which includes NGF, brain derived neurotrophic factor (BDNF), neurotrophin 3 and 4 (NT3 and NT4). Most notable of these has been BDNF and its receptor tropomyosin related kinase B (TrkB), a transmembrane receptor with an intracellular tyrosine kinase domain. BDNF-TrkB downstream signaling includes activation of phosphatidylinositol-3 kinase (PI3K)-Akt (serine threonine kinase or protein kinase B), Ras-microtubule associated protein kinase (MAPK), and the phospholipase C γ (PLC γ)-Ca²⁺ pathways [29, 30], (Figure 2). The Ras-MAPK pathway includes extracellular signal regulated kinase (ERK) and MAP/ERK kinase (MEK).

There are several additional neurotrophic/growth factors that have been implicated in depression, treatment response, and as biomarkers, including vascular endothelial growth factor (VEGF), insulin like growth factor 1 (IGF1) and fibroblast growth factor 2 (FGF2) [31-34]. Some of these factors are expressed primarily in peripheral tissues (i.e., VEGF and IGF1) and are transported into the brain, while others (i.e., BDNF) are primarily expressed in the brain but are also expressed in peripheral tissues, demonstrating interactions between peripheral and central systems.

Opposing Actions of Stress and Antidepressants on BDNF: Functional Consequences

Early studies implicating BDNF demonstrated that stress decreases and antidepressant treatment increases the expression of BDNF in the hippocampus and PFC [4, 16, 29, 35]. Antidepressant induction of BDNF occurs via increased mRNA expression and requires chronic treatment. However, typical antidepressants do not increase BDNF release, which could further contribute to the delayed response, as well as limited efficacy of these agents (Figure 1). These basic research findings, coupled with brain imaging studies reporting decreased volume of limbic brain regions, have led to a neurotrophic hypothesis of depression and a wide range of basic and clinical studies of BDNF in depression [6, 16, 35].

Some of the key questions regarding this hypothesis are whether decreased BDNF underlies the deleterious effects of stress and depression, and conversely if induction of BDNF mediates the beneficial effects of antidepressants? The results indicate that BDNF is sufficient to produce an antidepressant response in behavioral models of depression, and that genetic deletion or blockade of BDNF blocks the effects of antidepressant treatments [16, 36]. However, deletion of BDNF is not sufficient to induce depressive behavior in rodent models [16, 35]. There are a few exceptions, including reports that conditional deletion of BDNF causes depressive behavior in female mice [37, 38], and that short-hairpin RNA (shRNA) knockdown of BDNF causes depressive behaviors in rats [39]. The latter could be due to targeted deletion in the hippocampus compared to the global deletion of BDNF in

mutant mice that could result in opposing effects in different brain regions. For example, BDNF in the mesolimbic dopamine system produces pro-depressive effects and increases susceptibility to social defeat, effects that could oppose the antidepressant actions of BDNF in the PFC and hippocampus [4, 23]. Interestingly, BDNF administration by routes that would effect multiple brain regions (intracerebroventricular or systemic) produce antidepressant responses [40, 41].

Another possibility is that deletion or mutation of BDNF may result in a state of increased susceptibility to other factors (e.g., stress). This type of gene $\times$ environment interaction is supported by studies demonstrating that BDNF heterozygous deletion mutant mice display depressive behavior only when exposed to mild stress that has no effect in wild type mice [42]. Additional studies of chronic stress and other environmental challenges are needed to further test this hypothesis. However, a single nucleotide polymorphism (SNP) of BDNF, Val66Met provides supporting evidence from human, as well as rodent studies, for a role in depressive behavior (as discussed further below).

BDNF Val66Met: A Functional Polymorphism

The BDNF Val66Met polymorphism is found in 25-30 percent of humans [43, 44]. The G196A nucleotide mutation is located in the pro-domain of BDNF and decreases the processing and trafficking of BDNF transcripts to dendrites [43, 45]. The Val66Met SNP thereby decreases the amount of BDNF transcripts available for local translation in dendrites and reduces the activity-dependent release of BDNF that contributes to synaptic plasticity (Figure 1). Clinical studies demonstrate that the Met allele is associated with decreased hippocampal volume in both normal and depressed patients [12, 46-48], and with decreased executive function and cognition [44, 49, 50]. A recent study has also shown that the Met allele reduces fear extinction in human subjects, and that this effect is associated with altered PFC-amygdala activity [50]. There is also evidence that Met carriers have increased rumination, a symptom of depression, at baseline and in response to stress [51], and that Met carriers exposed to early life stress or trauma are at increased risk for depression and cognitive dysfunction [52]. Studies in rodent models also demonstrate increased sensitivity to stress [53, 54] and to fluctuations of ovarian hormones [55]. Paradoxically, clinical studies report a higher incidence of depression in Val, not Met carriers, and greater antidepressant response rates in Met carriers [48].

The cellular effects of this polymorphism have also been examined in mice with a knock-in of the Met allele [54]. Met knock-in mice have fewer spines and dendrites in pyramidal neurons in the CA3 region of the hippocampus and layer V of the PFC compared to controls [54, 56, 57]. BDNF heterozygous deletion mutants display similar deficits [54, 58], and there is no further atrophy of hippocampal neurons, indicating that BDNF either underlies or occludes the effects of stress [58]. The survival of new neurons in the subventricular zone is decreased in BDNF Met mice, but the rate of proliferation is not changed [59]. This is consistent with reports that BDNF is required for increased survival of hippocampal newborn neurons in response to antidepressant treatment [60]. However, conditional deletion of TrkB in neural progenitor cells blocks antidepressant-induction of cell proliferation in adult hippocampus, suggesting that BDNF or a related neurotrophic factor that can bind TrkB (e.g., NT4) can regulate proliferation [61].

The anxiolytic actions of SSRI antidepressants are blocked in BDNF Met knock-in mice [53], confirming previous studies that BDNF is required for the actions of antidepressants [16]. This appears to contradict the reports that depressed patients with the Met allele respond better to antidepressants than Val carriers [48]. The reasons for these differences between rodent and human studies will require further studies, including analysis of different classes of antidepressants, prior history of stress, and state-dependent responses.

Neurotrophic Factor Signaling in Depression

BDNF-stimulated signaling cascades, including Ras-MAPK and PI3K-Akt, have also been implicated in depression and treatment response (Figure 2). There have been conflicting reports on inhibitors of the Ras-MAPK pathway, with findings of both antidepressant-like responses [62, 63] and blockade [42]. This discrepancy may be due to the treatment paradigm, as acute dosing of MEK-ERK inhibitors can have locomotor activating effects that could be interpreted as antidepressant responses in behavioral models that are influenced by activity (e.g., the forced swim or tail suspension tests). These behavioral models, although used as rapid screens for antidepressants, have limited validity as models of depression. Recent studies demonstrate that ERK signaling is reduced by chronic stress and reversed by antidepressant treatment [64], and show that blockade of ERK signaling produces depressive and anxiety behaviors [65]. Postmortem studies have reported decreased levels of Raf, MEK, and ERK in the hippocampus of depressed suicide subjects, consistent with the hypothesis that reductions of this pathway contribute to depressive symptoms [66-68]. In addition, expression of a negative regulator of MEK-ERK signaling, MAP kinase phosphatase 1 (MKP1), a dual specificity phosphatase, is increased in postmortem hippocampus of depressed subjects (Figure 2) [69]. MKP1 expression in rodent hippocampus is also increased by chronic stress and normalized by antidepressant treatment. Importantly, viral expression of MKP1 in the hippocampus is sufficient to produce the same depressive behaviors caused by chronic stress, while MKP1 deletion results in resilience to chronic stress exposure [69].

Levels of Akt are also decreased in depressed suicide subjects, including in the PFC and occipital cortex [70, 71]. Akt phosphorylation and catalytic activity are decreased in the hippocampus and PFC of suicide subjects, which could result from increased expression of phosphatase and tensin homologue (PTEN), an upstream negative regulator of Akt (Figure 2) [72]. There have been limited rodent studies, with reports that Akt is decreased in ventral tegmental area and that Akt blockade in this region increases susceptibility to depressive-like behaviors [23]. A role for Akt in the actions of the rapid antidepressant action of ketamine has also been reported [9] (see below).

GSK3 Signaling in Mood Disorders

GSK3 is widely expressed in the brain and is found in two isoforms, α and β , both of which are inhibited by phosphorylation (Figure 3). Lithium directly inhibits the catalytic activity of GSK3, but also increases its phosphorylation at relevant therapeutic doses [9, 73, 74]. There are several kinases that phosphorylate and inhibit GSK3, most notably Akt. Lithium induction of GSK3 phosphorylation occurs via disruption of an Akt/b-arrestin/protein phosphatase 2A (PP2A) complex (Figure 3) [75]. GSK3 is also phosphorylated and inhibited by SSRI antidepressants via activation of 5-HT_{1A} receptors (Figure 3) [76]. SSRI-induction of GSK3 phosphorylation occurs rapidly, within hours, but could lead to a cascade of slower onset effects, although this hypothesis requires further testing.

One of the primary downstream targets of GSK3 is β -catenin, that when phosphorylated is targeted for proteasomal degradation [77]. Inhibition of GSK3 reduces degradation and increases β -catenin availability for cell structural support or regulation of gene transcription, depending on the cellular localization (i.e., membrane or cytoplasmic/nuclear) (Figure 3). The transcriptional effects of β -catenin are mediated by interactions with T-cell factor (Tcf) and lymphoid enhancer-binding protein (Lef), resulting in cell specific target gene expression (Figure 3). GSK3 also regulates cAMP response element-binding (CREB), hippocampal neurogenesis, and neuroprotection, which have been implicated in the actions of antidepressant treatments [76, 78] GSK3 increases the production of amyloid β -peptides [79], and contributes inflammatory responses in monocytes, microglia, and astrocytes [80,

81], which could contribute to increased inflammatory cytokines in depression [82]. GSK3 is a downstream target of DISC1 (disrupted in schizophrenia 1), a gene identified in a Scottish family with increased incidence of depression, bipolar disorder, and schizophrenia [83] (Figure 3). DISC1 loss of function results in reduced proliferation of neural progenitors and behavioral deficits that are reversed by GSK3 inhibition [83].

These studies demonstrate that GSK3 is at the intersection of several signaling pathways and downstream targets relevant to mood, as well as other disorders. GSK3b SNPs have also been associated with altered structural and behavioral characteristics in depressed patients [84, 85]. Recently developed small molecule GSK3 antagonists are reported to produce antidepressant as well as anti-manic responses in rodent models, as assessed by the forced swim and amphetamine-induced locomotion tests, respectively [86-88], but more rigorous studies are required to demonstrate the efficacy of these agents (e.g., chronic unpredictable stress/anhedonia-based tests) (see also [119] in this Issue).

GSK3 is also reported to be required for the rapid antidepressant actions of ketamine [89]. Ketamine increases GSK3 phosphorylation in the hippocampus and cerebral cortex in mice, and the behavioral responses to ketamine are blocked in GSK3 phosphorylation mutant knock-in mice [89]. Increased phosphorylation of GSK3 by ketamine could occur via stimulation of Akt, possibly by activity-dependent release of BDNF [90]. GSK3 in monocytes can be phosphorylated by the mammalian target of rapamycin (mTOR) pathway (Figure 3) [91], which is stimulated by ketamine [9].

Although there are reports that valproic acid leads to increased phosphorylation of GSK3, there have also been negative findings [76]. Valproic acid is an inhibitor of histone deacetylase (HDAC) [92], and selective inhibition of HDAC can indirectly increase the phosphorylation and inhibition of GSK3, raising the possibility that the actions of valproate could involve both mechanisms [76, 93, 94]. Epigenetic mechanisms have also been implicated in the actions of typical antidepressants, including in the regulation of BDNF, via inhibition of HDAC [4].

Wnt-Frizzled Signaling In the Actions of Antidepressants

Another upstream regulator of GSK3 that has been implicated in the actions of antidepressants, based on studies in rodent models, is the Wnt (drosophila wingless) and frizzled (Fz) receptor signaling system [95]. Wnt signaling plays a role in cell growth and differentiation during development, but many Wnt isoforms, Fz receptor subtypes, and related signaling molecules are also expressed in the adult brain, where they play roles in the survival, function and plasticity of neurons [96-99]. The current review will focus on the canonical Wnt-Fz-GSK3- β -catenin pathway, but the non-canonical Wnt/Ca²⁺ pathway could also play an important role in depression via regulation glutamate receptors and synaptic plasticity [95-97].

Wnt secretion and binding to Fz receptors leads to activation of the scaffolding protein dishevelled (Dsh) and inhibition of GSK3 (Figure 3). Microarray studies demonstrate that antidepressants differentially regulate the expression of Wnts, Fz, Dsh receptors, and downstream transcription partners in the rodent hippocampus [100]. Chronic, but not acute antidepressant treatment, including SSRIs, dual reuptake inhibitors, and electroconvulsive seizures (ECS), increase Wnt2 expression in the hippocampus. Moreover, viral expression of Wnt2 in the hippocampus produces an antidepressant response in the learned helplessness and sucrose preference tests [100]. Other Wnt-Fz proteins, including Wnt7b, Fz9, FzB (Fz related protein 3) and Dvl1 (a member of the Dsh family), as well as transcription factor-15 (Tcf15), TcfL1, and Lymphoid enhancer-binding factor 1 (Lef1), are differentially regulated by antidepressants [100]. Wnt3a is also increased by SSRI treatment and is associated with

the induction of adult hippocampal neurogenesis [101]. ECS treatment, still considered the most efficacious treatment for depression, increases the expression of Fz6 in rat hippocampus [102], and Fz6 knock-down results in depressive and anxiety behaviors in rodent models [102]. Conversely, social defeat decreases the expression of Dvl2 in mouse nucleus accumbens (Nac), and blockade of Dvl2 in this region increases vulnerability to social defeat and depressive behaviors [103]. Dvl2 is also decreased in postmortem Nac of depressed subjects, providing evidence of altered Wnt signaling in humans [103]. These findings demonstrate complex, differential effects of antidepressants on Wnt-Fz-Dvl-Tcf/Lef signaling, and a role for selected signaling molecules in the behavioral and neurogenic actions of antidepressant treatment.

Rapid Acting Antidepressant Actions of NMDA Receptor Antagonists

Recent clinical studies have made significant progress addressing the major limitations of current antidepressant medications, demonstrating that a low dose of ketamine produces rapid (within 2 hrs) and sustained (up to 7 days) antidepressant effects in depressed patients [7, 8]. Moreover, approximately 70% of depressed patients tested reported significant improvement, a remarkable response given that the patients tested were considered treatment resistant (i.e., failed to respond to two or more typical antidepressants). Ketamine is also a rapid and effective treatment for bipolar depression [104] and suicide ideation in treatment-resistant depressed and suicide patients in the emergency room [104-106]. Ketamine is a nonselective NMDA receptor antagonist with dissociative anesthetic and psychotomimetic properties. The discovery of the rapid antidepressant actions of ketamine, which acts by a mechanism completely different from typical monoamine reuptake inhibitors, represents a major advance in the field of depression.

Ketamine Increases mTOR Signaling and Synaptogenesis

The rapid actions of ketamine raise the possibility that fast changes in synaptic plasticity may underlie the therapeutic actions. One possible signaling pathway that has been implicated in protein synthesis dependent long-term memory is the mTOR pathway (Figure 4) [107]. Ketamine rapidly (within 30 min), but transiently increases the phosphorylation and activation of mTOR in the PFC of mice, leading to a delayed, but sustained induction of synaptic proteins with a time course (2 hr to 7 d) similar to its therapeutic response [9, 57, 108]. This increase in synaptic proteins is accompanied by an increase in the number and function of spines in layer V pyramidal neurons of the PFC and antidepressant behavioral responses in several different models of depression [9]. The induction of synaptic proteins, spine density and function, and antidepressant behaviors are blocked by infusion (intracerebroventricular) of rapamycin [9, 109], an inhibitor of the mTOR pathway, confirming that mTOR signaling is required for the actions of ketamine.

Another striking finding is that a single dose of ketamine produces a rapid reversal of the synaptic, spine, and behavioral (anhedonia) deficits in a chronic (3 weeks) unpredictable stress model of depression, in which responses to typical antidepressants are observed only after 3 weeks of treatment [57]. In contrast to the beneficial effects of rapid, transient activation of mTOR, genetic mutations that lead to sustained induction of mTOR signaling can underlie a number of neurological disorders, including Fragile X syndrome, tuberous sclerosis complex, and autism [110]. Rapamycin also reverses damage in neurodegenerative disease models via activation of autophagy and is a tumor suppressor [111], further demonstrating the complexity of targeting mTOR signaling for treatment of depression.

Role For Glutamate and BDNF in the Actions of Ketamine

The ability of ketamine to stimulate mTOR signaling and synaptogenesis is likely more complicated than simple blockade of NMDA receptors. Previous studies have demonstrated that ketamine increases extracellular glutamate in the PFC [112], with a time course and dose response similar to that for induction of mTOR and synaptic protein synthesis [9]. This could occur via blockade of NMDA receptors on tonically active GABAergic interneurons and disinhibition of glutamate transmission [113]. Ketamine activation of mTOR, synaptogenesis, and behavior is blocked by pretreatment with an AMPA receptor antagonist [9, 114]. Stimulation of AMPA receptor-mediated fast excitation most likely accounts for its rapid antidepressant actions compared to typical antidepressants that act via slower neuromodulatory monoamine mechanisms (Figure 1).

Studies in cultured cells demonstrate that AMPA receptor activation increases mTOR signaling and synaptogenesis via increased release of BDNF and activation of Akt (Figure 4) [90]. The possibility that BDNF signaling is involved in the synaptogenic and behavioral actions of ketamine is supported by studies demonstrating that these effects are blocked in BDNF Val66Met knock-in mice and BDNF conditional deletion mice, as well as by inhibition of PI3K/Akt [9, 56, 115]. However, another study [115] did not find evidence for mTOR signaling in the actions of ketamine, although this may be explained by technical and procedural differences (i.e., mTOR signaling was examined in crude homogenates of the hippocampus, not synaptosomal preparations of PFC, and the behavioral studies were conducted 30 min after ketamine administration, when extracellular glutamate is increased and before synaptogenesis occurs).

Novel, Rapid Acting Antidepressant Targets

Although the rapid therapeutic actions are promising, ketamine is a psychotomimetic and drug of abuse that may also cause toxicity with repeated, higher dosing [116]. However, characterization of the signaling pathways underlying the actions of ketamine provides novel targets for drug development. Clinical and basic research studies demonstrate that selective antagonists of NR2B-containing NMDA receptors have antidepressant actions [9, 114, 117]. Surprisingly, memantine, another NMDA antagonist, does not produce rapid responses, although this could be due to differences in NMDA receptor affinity, subtype selectivity, channel blocking properties, or doses tested [8]. As mentioned, AMPA receptor potentiating agents increase mTOR and synaptogenesis in cultured cells and are currently being tested for rapid actions in rodent models [90].

Metabotropic glutamate receptor 2/3 (mGluR2/3) antagonists, which regulate presynaptic release of glutamate, increase mTOR signaling and synaptic protein levels in the hippocampus, and produce rapamycin-dependent antidepressant behavioral responses in mice [109, 118]. As discussed above, ketamine increases GSK3 phosphorylation, and the behavioral actions of ketamine are blocked in GSK3 knock-in mice, indicating that GSK3 selective inhibitors could also produce rapid antidepressant actions [89].

Conclusions

Significant progress has been made toward understanding the molecular and cellular signaling pathways underlying the deleterious effects of stress and depression. Conversely, antidepressant treatments can block or even reverse these effects, in part via regulation of the intracellular pathways discussed, notably neurotrophic factor cascades. The ability of ketamine to rapidly activate mTOR signaling and synaptogenesis, and reverse the actions of chronic stress, further demonstrate the significance of neuronal atrophy in depression and the functional impact of treatments that can rapidly increase synaptic connections between

neurons. However, it is important to recognize that we are still at an early stage in characterizing the complex signaling pathways that underlie the pathophysiology and treatment of depression, and that many questions remain regarding disease etiology, the role of specific signaling molecules, and the efficacy and safety of novel treatments that directly target these systems (Box 1).

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Box 1. Outstanding Questions

- Why do BDNF Met allele carriers have increased vulnerability to depression when exposed to early life stress/trauma, but carriers of the Val allele have a higher incidence of depression? Also, is ketamine (which requires BDNF), effective in Met carriers, or is the effect of ketamine blocked, as reported in Met allele knock-in mice?
- How does BDNF signaling interact with other neurotrophic/growth factors that are also implicated in depression and treatment response (eg. VEGF, FGF2, IGF1)? Are there “double-hit” (i.e., when two or more factors are mutated), gene association, and environmental interaction effects?
- Does inhibition of GSK3, which is required for the actions of ketamine in rodent models, also produce rapid, efficacious responses in depressed patients, or enhance the response to ketamine? What are the pathways that lead to ketamine-inhibition of GSK3 (e.g., BDNF-Akt pathways)?
- What are the contributions of the different Wnt-Fz-b-catenin signaling molecules in mood and anxiety behavior in rodent models and in human illness? How do genetic polymorphisms of this system interact with neurotrophic factors and early life stress or trauma?
- Are the actions of ketamine explained only by disinhibition of glutamate transmission or are there also direct postsynaptic effects (e.g., postsynaptic regulation of glutamate receptor insertion)? Conversely, are there other lifestyle strategies that enhance neuronal survival, function, and synaptogenesis (e.g., exercise, enriched environment, and diet)?
- Do other systems, including stress hormones, energy imbalance and metabolic dysfunction (e.g., insulin resistance and diabetes), lead to depressive behavior via inhibition of mTOR signaling and synaptogenesis?
- Do other agents that produce ketamine-like effects via regulation of glutamate transmission (e.g., mGluR2/3 antagonists and NR2B-containing NMDA receptor antagonists) also produce psychotomimetic and neurotoxic effects?
- Is it possible to reduce the side-effects of ketamine by using drug combinations that sustain the actions of ketamine or that are effective at lower doses of ketamine?
- What are the relevant brain circuits that underlie the actions of antidepressants, particularly rapid acting agents (e.g., PFC-inhibition of the amygdala)?

Figure 1. Signaling pathways regulated by chronic antidepressant treatments

Typical antidepressants, such as SSRIs, block monoamine reuptake by the 5-HT transporter (SERT). This leads to regulation of postsynaptic G protein coupled receptors, which couple to a variety of second messenger systems, including the cAMP-PKA-CREB pathway [4, 6]. These effects require chronic SSRI treatment, due to the requirement for desensitization of 5-HT autoreceptors, and because 5-HT is a neuromodulator that produces slow neuronal responses. In contrast, glutamate produces fast excitation of neurons via stimulation of ionotropic receptors, including AMPA and NMDA receptors, resulting in depolarization and rapid intracellular signaling, such as induction of Ca²⁺-calmodulin dependent protein kinase (CAMK). Glutamate and 5-HT signaling lead to regulation of multiple physiological responses including regulation of synaptic plasticity, as well as gene expression. One target of antidepressant treatment and CREB signaling is BDNF [16]. BDNF transcripts may remain in the soma or are targeted for transport to dendrites where they are subject to activity-dependent translation and release. A common BDNF polymorphism, Val66Met, which is encoded by G196A, blocks the trafficking of BDNF to dendrites [44, 45]. The induction of BDNF and other neurotrophic factors contributes to the actions of antidepressant treatments, including neuroprotection, neuroplasticity, and neurogenesis.

Figure 2. BDNF-TrkB signaling pathways

BDNF binding to the extracellular domain of TrkB induces dimerization and activation of the intracellular tyrosine kinase domain [30]. This results in autophosphorylation of tyrosine residues that then serve as sites for interaction with adaptor proteins and activation of intracellular signaling cascades, including the Ras- microtubule associated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K)/ serine threonine kinase (Akt), and phospholipase C (PLC)- γ pathways. Phosphorylation of tyrosine 515 of TrkB leads to recruitment of the **Src homology 2 domain containing** (Shc) adaptor protein, followed by recruitment of Growth factor receptor-bound protein 2 (Grb2) and son of sevenless (SOS) and activation of the Ras-MAPK pathway (right). Shc-Grb2 can also lead to recruitment of Grb2-associated binder-1 (GAB1) and activation of the PI3K-Akt pathway (left). Phosphorylation of the TrkB tyrosine residue 816 results in recruitment of PLC γ , which leads to the formation of inositol triphosphate (IP3) and regulation of intracellular Ca^{2+} and diacylglycerol (DAG), which activates CAMK and protein kinase C (PKC). These pathways control many different aspects of cellular function, including synaptic plasticity, survival, and growth/differentiation. Basic and clinical studies demonstrate that BDNF and components of the Ras-MAPK and PI3K-Akt pathways are decreased by stress and depression, and increased by antidepressant treatments [16, 66, 67]. Abbreviations: ERK, extracellular signal regulated kinase; MEK, MAP/ERK kinase; MKP1, MAP kinase phosphatase 1; PDK1, 3-phosphoinositide-dependent protein kinase 1.

Figure 3. Signaling pathways involving Wnt-Fz and GSK3

Wnt is a secreted protein that binds to Fz, a seven transmembrane spanning domain receptor and a co-receptor for low-density lipoprotein receptor-related protein 5 (LRP5). Activation of Wnt leads to activation of Dvl and inhibition of GSK3. The activity of GSK3 is decreased by phosphorylation, which can occur via a number of different kinases, most notably Akt. One of the key targets of GSK3 is β -catenin (β -Ctnn), which is targeted for proteosomal degradation [97]. β -catenin can be translocated to the nucleus, where it enhances gene transcription via interactions with TCF/LEF, or it can have structural actions at the cell membrane. The activity of GSK3 is inhibited by the mood stabilizing agent lithium and by a number of other signaling pathways, most notably Akt [76]. Lithium also blocks GSK3 via disruption of an Akt/ β -arrestin2/PP2A complex that keeps Akt in a dephosphorylated and inactive form [86]. G protein coupled receptors, including 5-HT1A can also influence GSK3 via this mechanism. GSK3 is also blocked by a number of other signaling pathways that produce antidepressant responses.

Figure 4. Signaling pathways underlying the rapid antidepressant actions of ketamine
Ketamine rapidly increases extracellular glutamate, resulting in fast excitation/depolarization [112]. Studies in cultured neurons demonstrate that this leads to activation of voltage-dependent Ca^{2+} channels (VDCC) and activity-dependent release of BDNF, which subsequently stimulates TrkB and downstream signaling pathways (PI3K-Akt and Ras-MAPK) [90]. These pathways stimulate mTOR signaling and the mTOR complex 1 (mTORC1), which increases S6 kinase (S6K, a member of the ribosomal S6 kinase family) and local translation of transcripts, including expression of synaptic proteins, postsynaptic density-95 (PSD95) and the AMPA receptor GluA1 subunit. GluA1-containing AMPA receptors are subsequently inserted into the membrane, contributing to synaptogenesis. Ketamine-induction of mTOR signaling and behavioral responses are blocked by inhibition of AMPA receptors, PI3K-Akt, or MEK-ERK [9, 114]. In addition, the synaptogenic and behavioral actions of ketamine are blocked by rapamycin, a selective inhibitor of mTOR, and in BDNF Val66Met knock-in or BDNF conditional deletion mice [9, 56, 115]. Ketamine also increases the phosphorylation of GSK3 via an unknown mechanism [89], possibly by stimulation of Akt and/or S6K.