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Depression and treatment response: dynamic interplay of signaling pathways and altered neural processes

Vanja Duric and Ronald S. Duman

Department of Psychiatry, Yale University, 34 Park Street, New Haven, CT 06508, USA

Ronald S. Duman: ronald.duman@yale.edu

Abstract

Since the 1960s, when the first tricyclic and monoamine oxidase inhibitor antidepressant drugs were introduced, most of the ensuing agents were designed to target similar brain pathways that elevate serotonin and/or norepinephrine signaling. Fifty years later, the main goal of the current depression research is to develop faster-acting, more effective therapeutic agents with fewer side effects, as currently available antidepressants are plagued by delayed therapeutic onset and low response rates. Clinical and basic science research studies have made significant progress towards deciphering the pathophysiological events within the brain involved in development, maintenance, and treatment of major depressive disorder. Imaging and postmortem brain studies in depressed human subjects, in combination with animal behavioral models of depression, have identified a number of different cellular events, intracellular signaling pathways, proteins, and target genes that are modulated by stress and are potentially vital mediators of antidepressant action. In this review, we focus on several neural mechanisms, primarily within the hippocampus and prefrontal cortex, which have recently been implicated in depression and treatment response.

Keywords

Depression; Stress; MKP-1; Neurotrophins; Ketamine; Molecular mechanisms

Introduction

Major depressive disorder (MDD) is one of the most common and devastating psychiatric disorders with high lifetime prevalence (more than 16 %) [1], as well as a very significant socioeconomic burden [2, 3]. From a clinical perspective, MDD is characterized as a heterogeneous mental illness with a broad range of symptoms, including the inability to experience pleasure (i.e., anhedonia), feelings of helplessness, sadness, and despair, and is thought to result from a combination of environmental (e.g., stress or trauma) and genetic factors. The complexity of MDD pathophysiology is also evident from treatment limitations, as currently available antidepressants, which mainly target the reuptake or breakdown of monoamines, are effective in only a subset of MDD patients (approximately one-third respond to the first medication prescribed, up to two-thirds with multiple drug prescriptions) and require long-term treatment (weeks to months) to achieve therapeutic response [4, 5].

Although the principal molecular and cellular events contributing to the etiology and treatment of MDD are not well characterized, growing preclinical and clinical evidence suggests that stress and depression induce changes in intracellular signaling, gene

expression, neuronal function, and cellular architecture within the limbic brain regions that control mood, cognition, and executive functions (Fig. 1). Here, we describe morphological alterations, at the cellular and regional levels, in depressed patients, rodent stress/depression models and recently identified molecular pathways that potentially underlie these changes, as well as the actions of antidepressants. Further characterization of the key signaling molecules that underlie the synaptic plasticity alterations to stress, depression, and antidepressant treatment will provide new avenues for development of novel therapeutic interventions.

Cellular changes caused by depression and chronic stress

Stressful events affect a number of different, reciprocally connected brain areas that make up the mood-regulating circuitry [6]. However, the most consistent structural and molecular adaptations associated with depression and chronic stress are found in neuronal and glial populations in the forebrain within the limbic system, especially the hippocampus and more recently the prefrontal cortex (PFC). Hence, the primary focus of this review is on studies describing alterations in these two brain regions.

Human imaging and postmortem studies

Human brain imaging studies and postmortem histopathological analysis in subjects diagnosed with MDD show significant functional deficits accompanied by atrophy of hippocampal pyramidal neurons, decreased neuropil, altered morphology, and reduction in overall hippocampal volume [7–15]. These cellular hippocampal deficits are further supported by molecular abnormalities, mainly alterations in glutamatergic, monoaminergic, and GABAergic signaling, as well as modifications in neuronal synaptic density and expression of neurotrophic factors [16]. Similar neuronal atrophy and cell loss, including reductions in dendritic arborizations and spine density, have also been observed in depressed PFC and anterior cingulate cortex [17]. Additional cellular events that may play an important role in stress responses and antidepressant treatment are production of new neurons and glia throughout the brain [18]. The hippocampus is one of several regions where neurogenesis occurs in adulthood. In a recent study, the number of hippocampal neural progenitor cells (NPCs) was reported to be increased in depressed subjects treated with antidepressants at the time of death compared to non-medicated MDD patients [19]. However, overall clinical evidence is limited and inconsistent; thus, the functional role of neurogenesis in development and treatment of MDD is yet to be fully determined. Conversely, diminished density and number of glial cells have been consistently found in the postmortem brains from depressed and bipolar subjects, mainly in the dorsolateral PFC, orbitofrontal cortex [17, 20], and anterior cingulate cortex [21, 22]. Alterations in the number of glial cells, both astrocytes and oligodendrocytes, may functionally contribute to mood regulation, especially since it is now well established that glia are critical for maintaining metabolic and synaptic support for neurons [23]. These cellular observations are further supported by alterations of glial markers, including decreased levels of glial fibrillary acidic protein (GFAP) in PFC of depressed subjects [24]. A recent microarray gene expression study also showed significantly dysregulated expression of astroglial genes in the locus coeruleus of subjects with MDD [25].

Animal stress studies

In comparison to cellular events observed in depressed human subjects, studies using rodent models demonstrate that exposure to chronic stress evokes similar forms of cellular atrophy. In particular, stress causes spine loss and remodeling of dendritic structures in pyramidal neurons located in the hippocampus and medial PFC [26–30]. Besides treatment with tianeptine, an atypical antidepressant [27, 31, 32], there is little evidence that these

damaging effects of stress on neuronal structure are reversible with antidepressant treatment, and it is still unclear to what extent they contribute to development of core depressive symptoms, or deficits in memory and cognitive processing observed in depressed patients.

Stress-induced decreases in hippocampal neurogenesis are well documented and supported by a number of different rodent studies using various types of stress models of depression [33–35]. However, as in humans, the exact role of neurogenesis in the development of depressive behaviors in rodents is still unclear, since ablation of neurogenesis in vivo by either irradiation or genetic approaches does not produce a depressive-like phenotype [36–39]. This would suggest that loss of new neurons in the hippocampus may not be sufficient to mimic the effects of stress exposure [40]. However, another recent study further demonstrates that decreased neurogenesis increases the susceptibility to depressive behaviors caused by stress, such as anxiety, despair, and anhedonia [41]. Moreover, neurogenesis is induced by antidepressant treatments [37, 42–44] and is required for development of certain types of antidepressant behaviors [37]. Altogether, currently available clinical and preclinical data indicate that neurogenesis-dependent processes may be required for behavioral responses to antidepressant treatments. Similarly to depressed human subjects, rodents exposed to chronic unpredictable stress (CUS) also exhibit diminished glial production in the PFC, in particular decreases in the number of oligodendrocytes and endothelial cells [45]. In contrast, the decrease in oligodendrocytes caused by CUS and the accompanying behavioral anhedonia (i.e., deficit in sucrose preference) are reversed by chronic antidepressant treatment. Furthermore, infusion of an astrocyte-specific gliotoxin and subsequent ablation of glial cells in rat PFC is sufficient to cause depressive behavioral alterations (i.e., anhedonia, anxiety, and helplessness) similar to those caused by chronic stress [46]. Together, these findings provide a direct link between glial loss and depressive behavior, and further implicate glial function in actions of stress and MDD pathology. Future studies are needed to determine if glia and their cellular processes may also represent viable new targets for antidepressant treatment, especially in the light of recent findings indicating important roles of these cells in stress-mediated enhancement of glutamate excitotoxicity and diminishment of neurotrophic support (for full review, see [23, 47]).

Molecular mechanisms underlying the actions of stress and antidepressant treatment: neurotrophic factor signaling

Over the last two decades, many different intracellular signaling pathways have been implicated in the responses to stress, although the molecular adaptations that precede cellular remodeling events are still not well defined. Neurotrophic factors play an essential role in neuronal development (growth, differentiation, and survival), but continue to be important to growth, survival, and neuroplasticity in the mature brain [43, 48–52]. Evidence of depression-associated neuronal atrophy, cell loss, and reduced tissue volume occurring in human brains, combined with preclinical observations that stress robustly decreases hippocampal neurotrophic factor levels, suggests that the long-term effects of stress are mediated, at least in part, by a lack of sufficient neurotrophic support (Fig. 1). This idea led to formation of the neurotrophic hypothesis of depression [53], which identifies altered neurotrophic signaling as a key contributing factor underlying the etiology of depression, as well as neuronal plasticity promoted by antidepressant treatments [43, 54, 55]. Some of the key neurotrophic factor alterations are discussed in this section.

Brain-derived neurotrophic factor (BDNF)

BDNF belongs to the nerve growth factor (NGF) family, which includes neurotrophin-3 (NT3) and neurotrophin-4 (NT4). These factors stimulate intracellular signaling through

binding and activation of tropomyosin receptor kinases (TrkA-C) and the intracellular tyrosine kinase domain of these receptors [43]. The neurotrophic hypothesis of depression was based on observations that both glucocorticoid administration and exposure to stress result in significantly diminished expression of BDNF within the hippocampus [56, 57]. Conversely, chronic antidepressant treatments reverse these detrimental effects of stress and increase in vivo BDNF levels [58–61], while selective serotonin re-uptake inhibitors (SSRIs) can also induce expression of BDNF and other neurotrophic factors in cultured cortical astrocytes [62]. Additional studies show that intrahippocampal administration of BDNF is sufficient to produce antidepressant-like behavioral effects in several rodent models of depression, which are blocked by co-administration of K252a, an inhibitor of BDNF receptor signaling [63].

The involvement of BDNF and other neurotrophic/ growth factors in mood disorders was further supported by postmortem studies showing a reduction in mRNA and protein levels of BDNF and its preferred receptor TrkB in the hippocampus, PFC and locus coeruleus of depressed patients when compared to those in nonpsychiatric control subjects [25, 64–66]. In contrast, these effects were not found in depressed subjects treated with antidepressant medication, as protein levels of BDNF and other neurotrophic factors were either increased or not changed, providing further support for the possibility that BDNF contributes to the actions of antidepressant treatment [67, 68].

Although comprehensive mechanistic details remain unclear, it is possible that antidepressant-like effects of BDNF involve stimulation of hippocampal cell proliferation, as suggested by findings that chronic intrahippocampal infusion of BDNF stimulates neurogenesis [69]. Another study, using BDNF mutant mice (BDNF^{+/-}), further demonstrates that BDNF signaling is required for antidepressant action, in particular the increases in long-term survival and function, rather than initial proliferation, of newly produced hippocampal neurons [70].

At the molecular level, activity-dependent expression of BDNF is regulated by activation of the cAMP response element binding protein (CREB) transcription factor [71, 72]. Protein and mRNA levels of CREB and cAMP response element (CRE)-DNA binding activity are significantly reduced in the frontal cortex and hippocampus of postmortem suicide brains [73]. Moreover, antidepressant treatments increase the phosphorylated/activated forms of TrkB and CREB in cortical and limbic brain regions [74]. In the same study, these effects were reduced in mice over expressing a truncated, dominant negative form of TrkB, indicating that TrkB activation and function are required for the behavioral responses to antidepressant treatment [74]. Together, this line of evidence indicates that hippocampal BDNF signaling is diminished in stress and depression, and is required for functional effects of antidepressant treatment.

In contrast to the antidepressant effects of BDNF in the hippocampus, increased activation of BDNF signaling in the mesolimbic dopamine system (i.e., ventral tegmental area and nucleus accumbens), a midbrain region implicated in reward, results in development of depressive-like phenotype [75]. Together, these findings demonstrate that BDNF can influence neuronal responses in different neuronal circuits with behavioral consequences that are dependent on that particular circuit. However, it is notable that administration of BDNF by routes that influence multiple regions (i.e., intracerebroventricular or systemic) produce antidepressant responses [76, 77].

Over the past decade, significant efforts have been devoted towards identifying additional neurotrophic factors that may be involved in stress pathways or antidepressant treatment. Newton et al. [78] used a custom growth factor microarray chip to examine the expression

of neurotrophic factors and other related signaling molecules within the hippocampus of rats exposed to electroconvulsive shock (ECS), still considered the gold standard for the treatment of depression, particularly treatment-resistant patients. In addition to BDNF and fibroblast growth factor 2 (FGF2), ECS also increased the expression of nerve growth factor (NGF), neuritin, vascular endothelial growth factor (VEGF) and VGF (nonacronymic).

Vascular endothelial growth factor (VEGF)

VEGF, a member of vasoactive growth factors, is a cell mitogen that binds and specifically activates tyrosine kinase receptors, including fetal liver kinase (Flk-1 or VEGFR2), located on vascular endothelial cells to promote vasculogenesis and angiogenesis [79]. However, over the last decade, new evidence has emerged indicating that VEGF also has direct effects on neural cells, where it promotes neurogenesis and is implicated in neuroprotective mechanisms [80, 81]. Cao et al. [82] further demonstrated that housing in an enriched environment or water maze learning experience robustly increase hippocampal VEGF mRNA and protein levels. Likewise, viral vector-mediated elevation of hippocampal VEGF levels promotes neurogenesis and enhances overall memory and cognitive performance, effects that are blocked by inhibition of VEGF expression. This was one of the first reports directly implicating VEGF signaling in neurogenic cellular mechanisms leading to alterations in cognitive function and behavior.

A potential role of VEGF signaling in depressive illness was suggested by observations that exposure to chronic stress produces a reversible decrease in both VEGF and Flk-1 protein levels within the granular cell layer of the hippocampus [83]. Recent studies further demonstrate that VEGF-mediated signaling is activated by a variety of antidepressant treatments and is required for antidepressant-induced neurogenic and behavioral effects in animal stress models [84, 85]. Indeed, VEGF mRNA levels and the number of hippocampal endothelial cells are increased following acute ECS treatment or after 14 days of antidepressant drug administration, a time course that is concurrent with increases in neurogenesis. Conversely, inhibition of Flk-1 receptor completely blocks the above-mentioned antidepressant actions, further implying that VEGF-Flk-1 signaling is necessary and may be sufficient for the development of neurogenic and behavioral responses following antidepressant treatments (for a full review please see [86]). However, further studies are needed to elucidate the precise cellular targets and neurogenic mechanisms involved in VEGF-mediated antidepressant actions.

VGF

Neuropeptide VGF is another neurotrophic factor encoded by a gene originally discovered to be inducible by ECS in the hippocampus [78]. VGF is expressed primarily in neurons found throughout the brain and central nervous system (CNS), and was previously shown to be involved in hippocampal synaptic plasticity, regulation of metabolism, and peripheral energy expenditure [87, 88]. VGF was initially identified as a potential antidepressant target gene in the hippocampus of mice exposed to voluntary exercise, as physical activity is thought to have beneficial, mood-stimulating effects [89]. Moreover, infusions of VGF peptide into the mouse hippocampus produce robust, dose-dependent antidepressant effects in several behavioral models, including the forced swim test, tail-suspension test, and novelty-induced hypophagia. Interestingly, mutant mice with VGF deletion (*Vgf^{+/−}*) exhibit the opposite, depressive-like behaviors in the same testing paradigms [89].

VGF is also one of the several genes commonly induced by exposures to BDNF or serotonin in the hippocampal neuronal cultures [90]. Exposure to prenatal stress reduces hippocampal VGF expression, while chronic treatment with several different classes of antidepressant drugs (i.e., TCA, SSRI, and SNRI) increases VGF mRNA levels in the PFC and

hippocampus [91]. Furthermore, chronic intrahippocampal VGF infusions enhance progenitor cell proliferation, in particular neuronal differentiation, resulting in an antidepressant-like phenotype [90]. Since BDNF was shown to promote expression of VGF, it is possible that BDNF may induce antidepressant effects, in part, through activation of VGF, followed by downstream stimulation of neurogenesis. Moreover, the VGF gene contains a CRE domain within its promoter, raising the possibility that CREB not only activates BDNF but may also be a crucial regulator of BDNF-mediated VGF expression [87]. The VGF receptor and associated intracellular pathways are yet to be identified; however, analysis of regulated genes following either antidepressant treatment, exercise, or VGF stimulation suggests that putative downstream targets of VGF activation may include both MEK-ERK and phosphatidylinositol 3-kinase (PI3K)-Akt signaling cascades [88].

Besides antidepressant-like actions observed in animals, limited evidence is available to support the role of VGF in human mood disorders. VGF gene expression was robustly decreased in leukocytes from non-treated depressed subjects; however, 12 weeks of treatment with escitalopram fully restored VGF expression to non-depressed control levels, especially in subjects that responded behaviorally to antidepressant treatment [91]. Likewise, a recent postmortem analysis demonstrated a significant reduction of VGF mRNA levels in the hippocampus and PFC of subjects diagnosed with bipolar disorder [92]. Together, the combined evidence from preliminary human reports and preclinical stress studies provide initial support for VGF as potentially important factor in the etiology of mood disorders and antidepressant actions.

Other neurotrophic factors involved in mood regulation

Insulin-like growth factor 1 (IGF-1) and fibroblast growth factor 2 (FGF2) have recently been implicated in depression and treatment response. IGF-1 is a growth hormone produced in the liver and CNS where it is involved in regulation of brain growth and development, myelination, synaptogenesis, and hippocampal neurogenesis [43, 93–95]. FGF2 is also a vital growth factor that contributes to neuronal plasticity, proliferation, survival, and differentiation, as well as axonal branching, outgrowth, and synaptic function [96]. IGF-1 and FGF2 were both shown to promote neurogenic mechanisms and contribute to antidepressant responses. Chronic systemic administration of IGF-1 or overexpression of IGF-1 was shown to increase neurogenesis within the adult hippocampus [95, 97]. Conversely, the rate of neurogenesis is robustly attenuated in mutant mice lacking FGF2 [98]. Consistent with these findings, another study suggests that IGF-1 and FGF2 may both be required for maximal hippocampal cell proliferation [99].

Furthermore, chronic antidepressant treatments increase hippocampal IGF-1 protein levels [100], while intraventricular delivery of IGF-1 induces antidepressant- and anxiolytic-like effects in rodent behavioral models [101]. Peripheral administration of IGF-1 also produces antidepressant effects in mice exposed to chronic mild stress, while inhibition of peripheral IGF-1 attenuates the effects of exercise on hippocampal neurogenesis and development of antidepressant responses [102, 103]. Similar to IGF-1, chronic antidepressant treatments increase neuronal FGF2 protein levels in cortical and hippocampal brain regions [104]. This is in contrast to decreased mRNA levels of FGF2 and its receptor, FGFR1, found in the hippocampus of depressed human subjects [66, 105] and animals exposed to social defeat stress [106]. Moreover, decreased expression of FGF receptor 3 (FGFR3) and other neurotrophic signaling genes was found in the locus coeruleus of MDD subjects; these changes were unique to MDD and not present in bipolar disorder (BPD) [25]. Studies of rodent anxiety models also demonstrate reduced FGF2 mRNA levels in the hippocampus, while knockdown of hippocampal FGF2 by RNA interference promotes anxiogenic behavior [107, 108]. Conversely, chronic peripheral treatment with FGF2 produced an

anxiolytic effect, possibly through stimulation of hippocampal neurogenesis and gliogenesis [108].

The studies described in this section provide considerable evidence that activation of neurotrophic/growth factor signaling is susceptible to stress and is dysregulated in MDD. Genetic manipulations and antidepressant studies suggest that several key neurotrophic factors may act simultaneously, possibly in an interactive and overlapping manner, to stimulate neural mechanisms required for reversal of damages induced by stress. Furthermore, recent studies indicate that glial cells also provide a significant source of secreted neurotrophins such as BDNF, FGF2, VEGF, and glial cell line-derived neurotrophic factor (GDNF) that have pleiotropic effects on protection and survival of neuronal cells (for full review, see [109]). Antidepressant-induced increases in glial neurotrophic expression and signaling further supports this hypothesis [62, 110]. However, the exact functions of individual neurotrophic factors in these complex inter- and intracellular interactions are yet to be fully characterized.

Molecular mechanisms of stress and antidepressants: intracellular signaling pathways implicated in mood disorders

MAP kinase cascade

Activation of neurotrophic factor receptors is directly coupled to several different intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK) cascade [111]. Postmortem studies show decreased activation and expression of extracellular signal-regulated kinases 1/2 (ERK 1/2), central MAPK proteins, in the hippocampus of depressed suicide subjects [112–114]. ERK signaling and function have been linked with synaptic plasticity as well as normal function and survival of neurons [115, 116], and sustained disruption of this pathway would be expected to have negative outcomes on the function of pyramidal and granule cells in the hippocampus. Findings in depressed brains are further supported by preclinical studies showing that antidepressant treatments activate MAPK signaling pathways [117, 118], while pharmacological blockade of this cascade results in a depressive-like phenotype and inhibits behavioral actions of antidepressants in animal models of depression [63, 119].

Role of MAP kinase phosphatase-1 (MKP-1)

Results of a recent whole genome microarray study demonstrated that expression of MAPK phosphatase 1 (MKP-1) is significantly (more than twofold) increased in the dentate gyrus and CA1 hippocampal subregions of subjects with MDD when compared to healthy controls [120]. MKP-1 is one of the main negative regulators of MAPK cascade, and it belongs to a family of dual-specificity phosphatases (DUSP) that dephosphorylate both threonine and tyrosine residues within a conserved TxY motif found in the catalytic core of MAPK proteins [121, 122]. MKP-1 regulates activation of the MEK–ERK signaling cascade during long-term potentiation (LTP) and glucocorticoid-mediated anti-inflammatory actions [123, 124]. Previous reports have shown increased levels of MKP-2 protein in postmortem limbic areas of depressed suicide subjects [112]; however, until now, MKP-1 has not been directly implicated in MDD etiology. Indeed, sustained induction of MKP1 could underlie, in part, the reduction in MAPK signaling that has been reported in MDD [112, 113].

MKP-1 is classified as an immediate-early gene and its expression is inducible by a variety of factors such as oxidative stress, heat shock, hypoxia, and mitogens [125–127]. MKP-1 has been implicated in immune responses and cancer development [122, 128]; however, the role of MKP-1 in the nervous system has not been well explored [129]. Structurally, it consists of a non-catalytic NH(2) terminus and a dual-specificity phosphatase domain on the

carboxylic terminus [121]. Intracellular activity of MKP-1 proteins is limited primarily to the nucleus, due to their amino-terminal LXXLL motif that is known to mediate nuclear targeting [130]; however, recently, it was demonstrated that in neuronal cells MKP-1 is primarily located in the cytoplasm [131]. Additional evidence of MKP-1-dependent regulation of MAPK signaling comes from studies using cell lines derived from mutant mice lacking MKP-1, where different external stimuli, such as exposures to endotoxins or cellular stress, evoked robust increases in activation of p38 MAPK, c-Jun N-terminal kinases (JNKs), and ERKs [132, 133]. Moreover, Jeanneteau et al. [131] have recently shown that MKP-1 is inducible by BDNF and is required for spatiotemporal BDNF-mediated regulation of axonal branching and remodeling in the cortex of developing brain. This group further demonstrated that MKP-1-induced deactivation of the JNK intracellular signaling cascade leads to microtubule destabilization in cortical neurons, which, if prolonged, may result in axonal degeneration. These findings suggest that long-term MKP-1 dysregulation and inhibition of MAPK signaling could significantly contribute to cellular atrophy found in stress and depression.

Consistent with findings in depressed human brains, hippocampal MKP-1 mRNA levels are significantly increased in rodents subjected to chronic unpredictable stress (CUS). In contrast, chronic antidepressant treatment reverses stress-induced MKP-1 expression and related depressive-like behaviors [120]. Moreover, viral vector-mediated overexpression of hippocampal MKP-1 was sufficient to produce a robust depressive-like phenotype in non-stressed rats. However, mutant mice lacking MKP-1 (*Mkp-1*^{-/-}) that displayed a normal behavioral phenotype under standard housing conditions, exhibited resilient behaviors when exposed to chronic unpredictable stress [120]. These findings directly link MKP-1 expression with depressive behavioral outcome, and further support previous reports that inhibition of MEK-ERK signaling blocks antidepressant responses and promotes development and maintenance of depressive states [119, 134–137].

Expression and activation of phosphatases such as MKP-1 are tightly controlled processes that, if continuously dysregulated, may have severe negative consequences on the activity of intracellular pathways, such as the MAPK cascade, resulting in abnormal behavioral responses (Fig. 2). The resilience to stressful stimulation observed in MKP-1 null mice suggests that pharmacological blockade of MKP-1 may have similar antidepressant effects. In addition, identification of other phosphatases that effectively block MAPK intracellular signaling may elucidate additional key drug targets for MDD treatment.

Wnt and GSK-3 pathway

Wnt signaling plays an important role in a number of cellular and physiological events ranging from embryonic development, cell proliferation, and fate determination to adult neuroplasticity, synaptogenesis, and neuronal remodeling [138–140]. Wnts are glycoproteins that bind to Frizzled (Fzd) receptors and, through activation of Dishevelled phosphoproteins, inhibit glycogen-synthase kinase-3 (GSK-3) activity [141, 142]. GSK-3 is one of the main regulators of neuronal survival, when active GSK-3 promotes cell cycle arrest and apoptosis, while inhibition of GSK-3 activates β -catenin and leads to increased cell proliferation, growth, and resiliency [111]. Pharmacological blockade of GSK-3 activity via either specific pharmacological inhibitors or mood stabilizing agents, such as lithium, produces antidepressant-like effects in behavioral models of depression [143–146]. Several recent studies provide additional evidence implicating Wnt–Fzd–GSK-3 signaling in mood disorders and antidepressant actions. A study by Okamoto et al. [147] identified Wnt2 expression as a common signaling target of several different classes of antidepressant treatments, including both ECS and chemical agents. Moreover, virus-mediated expression of Wnt2 in hippocampus was sufficient to evoke antidepressant-like behavioral responses.

Involvement of Frizzled receptor subtypes in stress and antidepressant treatment has also been indicated. The expression of Fzd6 receptor is increased in the hippocampus of rats subjected to chronic ECS treatment, while exposure to CUS decreased Fzd6 expression levels [148]. Moreover, similar to the effects of stress, viral-mediated knockdown of hippocampal Fzd6 produced a depressive-like phenotype in several behavioral models [148]. Besides the hippocampus, there is also evidence that the Wnt–Fzd–GSK-3 signaling pathway plays a role in the brain's reward circuitry, especially in regulation of susceptibility to stress. The Dishevelled protein and mRNA levels are significantly decreased in postmortem nucleus accumbens of depressed human subjects, as well as in mice susceptible to social defeat stress [149]. Another study directly implicates the GSK-3 cascade in rapid antidepressant actions of ketamine, an NMDA receptor antagonist. Beurel et al. [150] showed that GSK-3 is inhibited by ketamine in the cortex and hippocampus, while mutant mice that express constitutively active GSK-3 are resistant to ketamine treatment in the learned helplessness model of depression. These results imply that specific GSK-3 inhibitors could also potentially produce a similar rapid antidepressant response.

Molecular mechanisms underlying the actions of rapid-acting antidepressants: mTOR signaling and synaptogenesis

Synaptic plasticity is an essential neuronal property that underlies neuronal communication, information processing, and overall responsiveness. This dynamic process, based on changes in synaptic release of neurotransmitters and alterations in number of their respective receptors, involves modulation of the existing synapses (strengthening and weakening) and structural remodeling that includes both synapse formation and elimination [151]. Particular attention in depression research has recently been given to studying the role of synaptogenesis in adult neural circuitry, a process characterized by increases in dendritic spines and stabilization of synapses [151, 152]. This idea was perpetuated by observations that exposure to chronic stress causes robust decreases in the density of spines, and the number and length of dendrite branches, as part of the overall neuronal atrophy occurring in limbic brain regions such as the PFC and hippocampus [153, 154]. Likewise, synaptic plasticity and synaptogenesis may also play a vital role in stress-related mood disorders in humans, since alterations in neuronal morphology and volume of PFC and hippocampus were observed in depressed individuals [10, 155].

Clinical reports demonstrate that a low dose administration of ketamine produces a rapid (within hours) and lasting (up to 7 days) antidepressant response [156, 157]. Moreover, these rapid actions of ketamine were observed in treatment-resistant depressed patients (i.e., failed to respond to two or more typical antidepressants). Ketamine is a drug of abuse with limited potential of being used in treating mood disorders; however, deciphering the downstream cellular events leading to an antidepressant effect could enhance development of novel, fast-acting agents. A recent preclinical study demonstrates that ketamine increases synaptogenesis in PFC pyramidal neurons that may underlie rapid antidepressant actions of ketamine in rodents [158].

At the molecular level, ketamine rapidly stimulates PI3K–Akt and MEK–ERK signaling cascades to activate mammalian target of rapamycin (mTOR) pathway, which stimulates downstream production of synaptic proteins such as activity-regulated cytoskeletal protein (Arc), glutamate-AMPA receptor-1 (GluR1), postsynaptic density protein-95 (PSD95), and synapsin I. This rapid induction of synaptic proteins may, in part, underlie an increase in number of functional mature spine synapses, or synaptogenesis in layer V pyramidal neurons of the PFC that was observed 24 h after ketamine administration [158]. Furthermore, ketamine also produced a robust antidepressant behavioral effect in a CUS model of depression by rapidly reversing stress-evoked spine atrophy in the PFC [159].

Conversely, selective pharmacological blockade of mTOR with rapamycin completely inhibits the ketamine-induced synaptogenic events and development of antidepressant response in animal models. These results directly implicate the mTOR pathway in the response to ketamine, and show that mTOR signaling is required for development of rapid antidepressant effects (for full review, see [160]).

Human postmortem studies also demonstrate dysregulation of glutamate levels and related signaling pathways in depressed subjects [25, 161]. Alterations in NMDA receptor function has been linked to a depressive state; in particular, decreases in NMDA receptor binding and expression of NR1 and NR2A subunits have been reported in the hippocampus, prefrontal cortex, or superior temporal cortex of subjects with MDD and bipolar disorder (BPD) [162–165]. Regulation of AMPA receptors has also been observed in postmortem brains of depressed subjects, primarily reduction of striatal GluR1 in individuals with bipolar disorder and decreased GluR3 levels in the dorsolateral prefrontal cortex of individuals with MDD [166, 167]. In addition, decreased expression levels of both GluR1 and GluR3 were recently found in the CA1 and dentate gyrus subregions of depressed hippocampus [168]. Consistent with human postmortem findings, preclinical studies further demonstrate that GluR1 expression and function in the rat hippocampus is increased by chronic antidepressant treatment [169–171]. The GluR1 subunit plays a crucial role in AMPA receptor intracellular trafficking and synaptic delivery, while targeted ablation of GluR1 significantly diminishes long-term potentiation (LTP) and hippocampal-mediated learning [172, 173].

Recent findings suggest that AMPA receptors also play an important role in ketamine treatment. Selective inhibition of AMPA receptor function completely blocked ketamine-mediated induction of mTOR signaling, as well as activation of its upstream activators (Akt and ERK) and downstream target proteins (p70S6 and 4E-BP1) [158]. Furthermore, AMPA receptor blockade also inhibits the rapid behavioral actions of ketamine [174]. Another recent study reported that fast-acting antidepressant effects of ketamine are dependent on rapid induction of hippocampal BDNF synthesis, as ketamine responses were blocked in conditional BDNF mutant mice [175]. Based on these findings, it is possible that ketamine, through inhibition of NMDA receptors on GABAergic interneurons [176], results in disinhibition of glutamate transmission (i.e., increased glutamate release), followed by postsynaptic activation of AMPA receptors. Subsequently, this could lead to increased BDNF release and stimulation of PI3K–Akt and MEK–ERK cascades and activation of mTOR pathway that results in increased synaptogenesis and synaptic plasticity observed in rodent PFC (for full review, see [160]). As discussed above, sustained elevation of MKP-1 may contribute to decreased BDNF–ERK signaling in MDD and in response to chronic stress [120] (Fig. 2). This could lead to diminished activation of mTOR signaling, which was recently reported in PFC of subjects diagnosed with MDD [177].

Role of pro-inflammatory cytokines

Clinical reports show increased levels of pro-inflammatory cytokines in depressed patients indicating that dysregulation of inflammatory system may also play an important role in responses to stress and the pathophysiology of MDD. Pro-inflammatory cytokines have been shown to contribute to the effects of stress on the CNS, causing development of symptoms common to both infection and depression, such as anhedonia, and eating and sleeping abnormalities [178]. Elevated blood levels of several different inflammatory mediators, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF α), have been shown in MDD patients [178, 179]. These peripheral observations were recently extended to brain by a microarray study of postmortem PFC of depressed subjects, where a large number of inflammatory cytokine genes were found to be significantly up-regulated [180]. Human studies support a relationship between elevated inflammatory

mediators and depressive state; however, the underlying mechanisms and pathways are not well understood. To directly address this issue, recent animal studies have identified IL-1 β as a potential key mediator of stress-induced behaviors. Similarly to depressed humans, hippocampal IL-1 β levels are significantly increased after stress. Furthermore, intraventricular administration of IL-1 β robustly suppresses hippocampal cell proliferation, while null mutation or pharmacological blockade of IL-1 β receptor completely protects against stress-induced anti-neurogenic effects of stress and inhibits development of depressive-like behaviors [181]. Additional studies report that the IL-1 β mediated pro-depressive effects occur through activation of the nuclear factor- κ B (NF κ B) signaling pathway [182]. Based on these findings, targeting proinflammatory cytokines and associated intracellular signaling pathways may elucidate additional novel avenues to treat MDD.

Conclusion

For more than four decades, researchers have been attempting to develop a comprehensive model of pathophysiology leading to depressive illness and the mechanisms underlying treatment response. Increasing evidence from human and animal studies links depression to cellular atrophy and altered morphology primarily observed within the limbic brain regions. Furthermore, a number of different molecular events that are affected by chronic stress and depression have been identified. Simultaneously, the search for common actions of antidepressant treatments beyond the enhancement of synaptic monoamine levels and related receptors has elucidated a myriad of intracellular signaling cascades that may be involved in therapeutic actions of antidepressants. Indeed, lack of neurotrophic support (i.e., decreased levels of neurotrophic factors such as BDNF and VEGF) has been characterized as one of the principal factors contributing to development and maintenance of depressive states in rodent models. In addition, significant progress has been made in identifying other novel systems that may be involved in stress actions, ranging from dysregulated activation of immune system to intricate mechanisms of synaptic plasticity that are required for rapid antidepressant responses (i.e., ketamine-induced activation of mTOR pathway and synaptogenesis). However, it is still not fully understood which brain circuits are relevant sites of interactions and convergence between these different intracellular signaling cascades in response to stress or antidepressant treatment. Moreover, the signaling pathways identified to date may also be affected in a number of different psychiatric disorders making it more difficult to elucidate mechanisms and events that are specific to MDD. Activation or inhibition of individual molecular targets can produce antidepressant responses in animal models, although examination of the therapeutic consequences of these signaling pathways has not yet been achieved in depressed patients. Translation from basic science research to clinical trials is further affected by genetic polymorphisms found in human subjects. Furthermore, many of described molecular and cellular events occur simultaneously and may have common regulators, such as MKP-1, which, if continuously dysregulated, may lead to destabilization of neuronal processes, decreased neuronal connectivity, and overall loss of neuronal function. Therefore, targeting specific regulatory molecules and downstream mechanisms evoked by rapid-acting agents such as ketamine may provide promising research directions that will lead to the development of new antidepressant drugs with improved treatment response and clinical efficacy.

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Fig. 1.

Initial molecular and cellular effects of stress can progress to severe structural modifications of neurons and limbic brain regions implicated in MDD. Consistent alterations at the molecular level (*green*), such as changes in levels of neurotransmitters, expression of key neurotrophic factors and signaling molecules can result in cellular destabilization and remodeling (*blue*). Long-term consequences of stress-induced molecular and cellular adjustments lead to morphological changes characterized by deficiencies in neuronal function and neural network connectivity (*red*). Therapeutic effects of typical antidepressant treatment (agents targeting monoamine system) coincides with the time course required to reverse the negative effects of stress at all three levels (molecular-cellular-morphological/tissue)

Fig. 2.

Interactions of neurotrophic factor and Wnt intracellular signaling cascades that mediate the negative cellular responses to stress/MDD and/or the therapeutic actions of antidepressant treatment. Wnt/Dishevelled-mediated blockade of GSK-3 signaling or neurotrophic factor-mediated activation of PI3K–Akt, MEK–ERK, and mTOR pathways lead to increased synaptogenesis, neuronal survival, growth and neuroplasticity, and resilience to stress, which contribute to antidepressant behavioral responses. *BAD* Bcl2-antagonists of cell death; *Bcl-xL* B cell lymphoma-extra large; *FRS* fibroblast growth factor receptor substrate; *GRB2* growth factor receptor-bound protein 2; *IRS* insulin receptor substrate; *MEK* MAPK kinase; *PDK1* 3-phosphoinositide dependent protein kinase-1; *RAF* v-raf-1 murine leukemia viral oncogene homolog 1; *RAS* RAT sarcoma; *RSK* ribosomal S6 kinase; *Shc* Src homology/collagen; *SOS* son of sevenless; *TCF/LEF* T cell-specific transcription factor, lymphoid enhancer factor