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·Review·

Rapid-onset antidepressant efficacy of glutamatergic system modulators: The neural plasticity hypothesis of depression

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Depression is a devastating psychiatric disorder widely attributed to deficient monoaminergic signaling in the central nervous system. However, most clinical antidepressants enhance monoaminergic neurotransmission with little delay but require 4−8 weeks to reach therapeutic efficacy, a paradox suggesting that the monoaminergic hypothesis of depression is an oversimplification. In contrast to the antidepressants targeting the monoaminergic system, a single dose of the N-methyl-*D*-aspartate receptor (NMDAR) antagonist ketamine produces rapid (within 2 h) and sustained (over 7 days) antidepressant efficacy in treatment-resistant patients. Glutamatergic transmission mediated by NMDARs is critical for experience-dependent synaptic plasticity and learning, processes that can be modified indirectly by the monoaminergic system. To better understand the mechanisms of action of the new antidepressants like ketamine, we review and compare the monoaminergic and glutamatergic antidepressants, with emphasis on neural plasticity. The pathogenesis of depression may involve maladaptive neural plasticity in glutamatergic circuits that may serve as a new class of targets to produce rapid antidepressant effects.

Keywords: depression; stress; neural plasticity; glutamatergic transmission; monoamine-based antidepressant; ketamine

Introduction

Depression is a common psychiatric disorder, with prevalence rates of 19% in Beirut and 16.2% in the United States[1]. Depression is also one of the leading causes of severe mental disability, suicide, and socioeconomic burden, and its diagnosis sometimes relies on self-reported symptoms in the major depressive inventory[2, 3]. The pathogenesis of depression is still not clear, and currently available antidepressants are far from satisfactory. Most antidepressants target the monoaminergic system[4]; however, 30%–40% of patients are resistant to monoamine-based antidepressants (remittance rates of 13% to 36.8% with citalopram[5]), and a clinically significant reduction of depressive symptoms in responders usually requires 4−8 weeks of daily treatment[6]. These limitations result in a large proportion of patients at high risk of suicide even after diagnosis. Thus, it is necessary to search for new antidepressants outside the monoaminergic system. Recent clinical studies have demonstrated that a single dose of the N-methyl-*D*-aspartate receptor (NMDAR) antagonist ketamine has rapid antidepressant efficacy within 2 h that can be sustained for over 7 days in patients with treatment-resistant depression[7, 8]. This finding suggests that depression could be directly associated with deficits in glutamatergic synaptic transmission and plasticity.

The monoaminergic hypothesis of depression, based on the efficacy of antidepressants that enhance monoaminergic transmission and signaling, has dominated the field of depression research for nearly half a century. However, the primacy of monoaminergic dysfunction in depression is inconsistent with the delay between enhancement of synaptic monoamines conferred by drugs such as specific serotonin re-uptake inhibitors, serotonin–noradrenalin re-uptake inhibitors, and monoamine oxidase inhibitors, and clinically significant antidepressant efficacy[9].

Many studies have revealed that these antidepressants have multiple pharmacological effects in addition to increasing monoaminergic function, such as enhancing adult hippocampal neurogenesis and rescuing stress-impaired NMDAR-dependent long-term potentiation (LTP)[10-12]. Neurogenesis enhances hippocampus-dependent memory and LTP, while stress impairs neurogenesis and alters hippocampus-dependent memory and LTP. Thus, the mechanisms underlying the clinical response to antidepressants may include effects on neural plasticity. This point of view is strongly supported by the rapid onset of antidepressant efficacy of ketamine in clinical trials, because NMDAR activation is critical for both LTP and hippocampus-dependent memory[8, 13, 14]. These developments suggest an alternative etiology for depression due to functional disturbances of neural plasticity in the glutamatergic system. In this paper, we review recent studies that implicate aberrant neural plasticity in depression and suggest that mitigation of these deficits underlies the efficacy of antidepressant medications. We predict that a

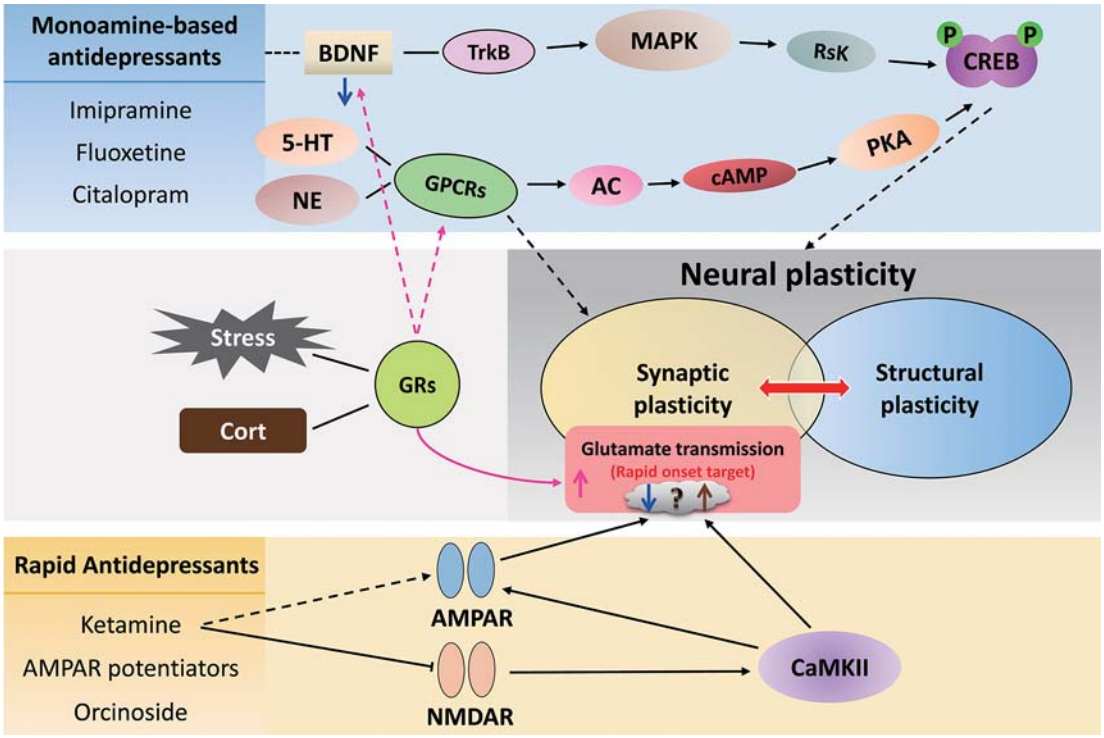

Fig. 1. Effects of stress and antidepressants on neural plasticity. Major signaling pathways critical for memory and neural plasticity are also regulated by stress and antidepressants. See text for details and references. Pink arrow, pathological status; solid arrows, direct action; dashed arrows, indirect action. Abbreviations: BDNF, brain-derived neurotrophic factor; TrkB, BDNF receptor; MAPK, mitogen-activated protein kinase; Rsk, ribosomal S6 protein kinase; CREB, cAMP response element-binding protein; 5-HT, 5-hydroxytryptamine (serotonin); NE, norepinephrine; GPCRs, G-protein coupled receptors; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; Cort, corticosterone; GRs, glucocorticoid receptors; AMPAR, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid glutamate receptor; NMDAR, N-methyl-*D*-aspartate glutamate receptor; CaMKII, calcium-calmodulin-dependent kinase II.

new class of drugs targeting neurogenesis and synaptic plasticity within the glutamatergic system could produce rapid antidepressant responses (Fig. 1).

Dysfunctional Neural Plasticity in Depression

Neuroplasticity often refers to the functional and structural synaptic plasticity that is a prominent feature of glutamatergic neuronal circuits and crucial to adaptive behavioral responses and survival[15, 16]. Experience-dependent changes in glutamatergic synaptic transmission, notably LTP and long-term depression (LTD), are widely believed to encode hippocampus-dependent associative memories. However, both LTP and LTD are sensitive to stress-associated emotional states[17]. Dysfunction of synaptic plasticity is associated with many psychiatric disorders, such as depression, autism, and drug addiction[18-20].

Several brain regions critical for memory and emotion, most notably the hippocampus, amygdala and the prefrontal cortex (PFC), exhibit robust neural plasticity, which is disrupted in stress-induced animal models of depression. Moreover, hippocampal and amygdala functions are disrupted in clinical depression, suggesting a causal link between dysfunctional neural plasticity, memory, and mood regulation. Neuroimaging studies have demonstrated a reduced hippocampal volume in depressed patients that can be restored by antidepressant treatment[21-24]. In contrast, both the size and the activity of the amygdala, a structure critical for fear-associated memories, are increased in depressed patients[25-28]. Consistent with brain imaging studies, depressed patients exhibit deficits in hippocampus-dependent memory tasks and are more sensitive to stressful events[24, 29, 30]. Changes in neurotransmitter levels, receptors, and serotonin reuptake transporters have also been found in depressed patients, such as increased glutamate, decreased serotonin 1A receptors and impaired serotonergic neurotransmission[31-35]. However, due to the technical and ethical limitations of clinical research, most of this evidence has been obtained from studies of animal models of depression.

While the most-widely used animal models of depression have been established using chronic or acute stress, the relationship between stressful life experiences and depression risk in humans is complex. Nevertheless, stressful life-events do contribute to the development of depression[36]. Indeed, some individuals become depressed in response to stressors that may have no serious impact on others. Memory or synaptic plasticity related to beneficial or harmful experiences can be affected by stress. Both acute and chronic stressors have profound effects on the brain, causing increases of extracellular glutamate levels and changes in structural and functional plasticity.

Neurogenesis is maintained in the hippocampus throughout adulthood. At the structural level, chronic stress alters the neural morphology in the hippocampus and the medial PFC, including loss of dendritic spines and retraction of dendrites, and reduces neurogenesis in the dentate gyrus (DG)[37-40].

Certain types of stress impair NMDA-dependent LTP and facilitate LTD in the hippocampal CA1 region, processes that are critical for learning and memory. Stress can cause rapid glucocorticoid receptor-mediated alterations in presynaptic glutamate release and slower changes in postsynaptic glutamate receptor expression and function[41], which can affect LTP and LTD. In addition, stress may induce changes in functional plasticity by shifting the balance between synaptic and extrasynaptic glutamate receptors that are thought to contribute to potentiation and depression, respectively[42, 43]. Learned helplessness in rats is a widely-used behavioral model of depression. The underlying mechanism is associated with a marked increase in depolarization-evoked glutamate release in the PFC, which can be mitigated by monoamine-based antidepressants[44-46]. Moreover, antidepressants reduce the release of glutamate, possibly by decreasing phospho-activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)[47].

Antidepressants can enhance structural plasticity and neurogenesis. A few days (~5 days) of fluoxetine administration increases synaptic density in the hippocampal CA1 pyramidal cell layer, and 14 days of treatment has similar effects in the CA3 pyramidal cell layer[48]. In the olfactory bulbectomy model of depression, chronic treatment with the tricyclic antidepressant amitriptyline blocks the stress-induced decrease in spine density in hippocampal DG, CA1, and CA3 neurons[49]. In addition to the monoamine-based antidepressants, NMDAR antagonists rapidly reverse the low levels of synaptic proteins and spine loss in the medial PFC[50].

Rescuing neurogenesis in depression is crucial for the antidepressant effects. Reduced neurogenesis by both acute and chronic stress can be rescued by chronic administration of antidepressants, while abolishing neurogenesis by x-irradiation makes antidepressants behaviorally ineffective[51, 52]. Suppression of neurogenesis in the hippocampus by genetic manipulation or radiation in mice results in deficits in the hippocampal negative feedback control of corticosterone, and they develop anxiety and depressive-like behavior such as anhedonia[53]. The changes described in structural plasticity may result from or lead to alterations of functional plasticity, such as reduced LTP or enhanced LTD in the hippocampus[54, 55]. Thus, aberrant neural plasticity such as decreased neurogenesis in the DG, impaired LTP and facilitation of LTD, and dysfunction of glutamatergic neurotransmission may all contribute to the development of depression.

From Stressful Events to Depression: Clues from Maladaptive Neural Plasticity to Negative Memory

Dysfunctional learning and memory links neural plasticity with depression. Stressful events can change behavioral and cognitive patterns according to the learned helplessness cognitive model and Beck's cognitive model of depression[56, 57]. Memory dysfunction has been reported in depressed patients using paradigms such as the virtual reality spatial navigation task or paragraph recall, and the impairments are highly correlated with illness chronicity[58, 59]. In free-recall tests of biographical information, depressed patients show enhanced recall for negative events, a phenomenon termed mood congruent memory[29, 30]. This suggests that both hippocampal and the amygdala functions are altered in depression, and these changes are correlated with changes in functional neural plasticity.

There is compelling evidence that stress-related memory is essential to the development of depression, at least in animal models. Uncontrollable and unpredictable stress is commonly used to model depression in laboratory animals. These models include the forced-swim test (FST), tail suspension test (TST), learned helplessness, chronic mild stress, and social defeat[60]. Stress and the stress hormone corticosterone have profound impacts on both synaptic plasticity and memory, consistent with the role of memory in depression-associated behavioral changes. Stress or corticosterone treatment enhances the acquisition of spatial information[61], but also impairs the retrieval of memory[62]. Stress also enhances the acquisition of fear memory but impairs its extinction[63]. If stress occurs before a spatial learning task, it impedes both memory formation and retrieval[64]. However, briefly exposing the rats to acute stress, as measured by the T-maze, increases working memory performance, and the effects are acute, lasting <2 days[41]. Therefore, stress can either facilitate or impair memory formation and (or) retrieval depending on the timing and the severity, possibly due to the effects on neural plasticity[65]. At the functional level, stress blocks LTP induction and facilitates LTD induction, and the formation of fear memory and one-trial avoidance memory implicate possible stress-induced endogenous LTP in the amygdala and hippocampus, respectively[66, 67]. At the structural level, stress or corticosterone induces neuronal shrinkage in the hippocampus but enhances dendritic arborization in pyramidal and stellate neurons in the basolateral amygdala[68]. These changes may result from an overreaction of memory systems to stressful events. In other words, depression may result from over-activation of a highly conserved mechanism critical for survival (although stress-facilitated storage of pivotal information) which is one of the conserved mechanisms beneficial to survival competition but may lead to the development of depression. Antidepressants can mitigate the effects of stress on memory, and are associated with the restoration of neural plasticity. Fluoxetine treatment acts synergistically with extinction to erase conditioned fear in mice, possibly by enhancing LTP and brain-derived neurotrophic factor (BDNF) expression in the lateral amygdala. Indeed, this effect was not observed in $BDNF^{-/+}$ mice, while the effects of fluoxetine were mimicked by BDNF overexpression[69]. Antidepressants can also restore impaired memory performance in depression models by rescuing impaired LTP induction and by maintaining dendritic morphological complexity and hippocampal neurogenesis.

Changes in neural plasticity caused by chronic stress may alter cognition and behavior in humans, and this may lead to depressive symptoms. In depression, the encoding and retrieval of negative memories may be facilitated, and so come to dominate cognition and exert a prominent influence on behavior. Depressed patients may accumulate negative memories in a stressful environment

and ultimately are unable to update new memories due to dysfunctional neural plasticity. Antidepressants may restore maladaptive neural plasticity, allowing for normal memory function, as discussed below.

Monoamine-Based Antidepressants Restore Neural Plasticity

Monoamine-based antidepressants, fortuitously discovered from clinical observations in the 1950s, represent a milestone in the treatment of depression[6, 70, 71]. Moreover, they provide clues to the biological basis of depression. Iproniazid and imipramine were first developed for non-psychiatric conditions, but were discovered to have potent antidepressant efficacy[22]. It was found that these monoamine-based antidepressants either enhanced central 5-HT/norepinephrine (NE) transmission or depleted monoamine stores in the brain. The monoaminergic hypothesis has guided drug development for decades and resulted in the development of a myriad of antidepressants that share similar mechanisms and limitations. More specific drugs to inhibit 5-HT and NE reuptake have been developed, such as fluoxetine, citalopram, and tranylcypromine[22], all with similar limitations, most notably a 4−8-week delay for clinical effect. This delay likely increases the risk of suicide in the interim[72].

Brain-Derived Neurotrophic Factor

BDNF is critical for synaptic plasticity and memory. It is also the most important target for antidepressant efficacy. BDNF promotes synaptic and morphological plasticity, and regulates synaptic transmission and neuronal growth[73]. The neurotrophic hypothesis of depression is based on clinical and preclinical observations that include three lines of evidence: a low concentration of BDNF in the hippocampus of postmortem samples from depressed suicide victims[74], depression-related behaviors caused by impaired BDNF signaling in rodent hippocampus[75, 76], and the antidepressant effects of increased hippocampal BDNF[77, 78]. BDNF is critical for stabilizing synaptic plasticity. BDNF mRNA expression is reduced by stress, leading to impaired hippocampal synaptic plasticity[79]. Antidepressant effects mediated by slow changes in BDNF expression and downstream signaling, leading to morphological plasticity and enhanced neurogenesis, may explain the delay between drug administration and antidepressant efficacy. However, the neurotrophic hypothesis of depression is over-simplistic, as neuronal survival and plasticity depend on the connections to other cells and the activation of many additional signaling pathways.

CREB Signaling Cascade under Monoamine-Based Antidepressants

Since the 1990s, the cAMP response element binding protein (CREB) gene has been considered as a central “memory gene”. CREB activation and the ensuing CREB-dependent *de novo* protein synthesis are required to stabilize structural and functional changes in synaptic strength, which participate in long-lasting late-LTP and long-term memory[80-82].

The cAMP-PKA-CREB signaling cascade has been implicated in synaptic plasticity, memory, and antidepressant drug responses. Modulatory neurotransmitters such as 5-HT, NE, and dopamine increase the intracellular cyclic adenosine monophosphate (cAMP) concentration and activate cAMP-dependent protein kinase (PKA) through G-protein coupled receptors (GPCRs)[83]. Chronic antidepressant administration enhances the coupling of GPCRs to adenylyl cyclase, PKA activation, and expression of CREB[19]. Furthermore, the cAMP-PKA-CREB signaling cascade is critical for long-lasting forms of synaptic plasticity, notably late-LTP, and for long-term memory formation[84].

The mitogen-activated protein kinase (MAPK) pathway also regulates synaptic plasticity in the hippocampus, amygdala, and neocortex[85-88]. BDNF *via* its receptor TrkB activates the MAPK-RsK-CREB cascade, and this signaling cascade is altered by antidepressant treatment[89].

Activation of CREB promotes adult hippocampal neurogenesis, suggesting that antidepressants promote neurogenesis through activation of the cAMP-PKA-CREB pathway[90]. Postmortem studies on depressed patients have demonstrated reductions of CREB expression and phosphorylation in suicides[91, 92]. Animals overexpressing CREB in the hippocampus exhibit a shorter immobility time in the FST and fewer escape failures in the learned helplessness paradigm[93]. In addition, chronic antidepressant administration increases CREB phosphorylation and transcriptional activity[94, 95]. These studies provide a compelling rationale for the development

of new antidepressants targeting CREB activation and transcriptional activity.

Effects of Antidepressants Mediated by Glutamate Receptor Stimulation

Monoamine-based antidepressants interfere with NMDAR activation[96]. Chronic administration of antidepressants such as fluoxetine, desipramine, and reboxetine significantly reduces depolarization-evoked glutamate release in the hippocampus[97], and animal studies have shown that chronic antidepressant treatment reduces glutamatergic transmission and field potentials in rat frontal cortex[98, 99], thereby reducing NMDAR activation (which requires both synaptic glutamate and postsynaptic depolarization). Antidepressants also affect α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptor (AMPAR) trafficking. Riluzole increases the surface expression of the AMPAR subunits glutamate receptor 1 (GluR1) and GluR2, and reversibly attenuates AMPAR-mediated synaptic currents in cultured cells[100, 101]. Fluoxetine regulates the phosphorylation state of AMPARs[102]. Cai *et al.* provided the first evidence that endogenous serotonin selectively potentiates temporoammonic-CA1 excitatory synapses *via* the activation of serotonin 1B receptors. This potentiation requires postsynaptic AMPAR expression and CaMKII-mediated phosphorylation of GluR1 subunits[103]. While many forms of LTP and LTD are triggered by stimulation of NMDARs, LTP and LTD expression depend on selective up- or down-regulation of AMRAR currents, respectively, due to changes in both channel ion permeability and postsynaptic surface expression. Therefore, changes in both AMPAR and NMDAR function and expression may relate directly to depression and the clinical effects of antidepressants. Thus, AMPARs as well as NMDARs are promising targets for antidepressant research and development.

Glutamate Receptors as Direct Targets for Rapidly-Acting Antidepressants

Glutamate was not acknowledged definitely as a neurotransmitter in the mammalian central nervous system until the early 1980s[104]. Prior to this, the conceptual framework of depression was dominated by the monoaminergic hypothesis, so most of the antidepressants developed for clinical therapy target monoaminergic transmission. However, stress affects glutamate release, clearance, metabolism, receptor function, and receptor expression, strongly implicating glutamatergic transmission and plasticity in the pathogenesis of depression[46]. Glutamate signaling is mediated by both ionotropic (AMPARs and NMDARs) and metabotropic glutamate receptors (mGluR1 to mGluR8). Excitatory synaptic efficacy is determined by the single-channel conductance, the number, and the stability of glutamate receptors at the postsynaptic membrane[46]. Acute stress enhances glutamate transmission by increasing the surface expression of NMDARs and AMPARs at the postsynaptic membrane, which dynamically regulates metaplasticity (e.g., LTP/LTD induction thresholds) at glutamatergic synapses[105]. Chronic stress further alters glutamatergic circuits and the survival of newborn glutamatergic neurons[106, 107]. Thus, disturbed glutamatergic neurotransmission is likely a core feature of stress-related mental illnesses. Drugs influencing basal transmission, plasticity, and metaplasticity may be effective antidepressants that act rapidly[46, 108, 109].

Ketamine Has Rapid-Onset Antidepressant Efficacy

The discovery of ketamine's fast antidepressive effects not only allowed exploration of new research of the brain circuits involved in depression but helped to develop new pharmaceutical approaches of a disease that for many decades showed no advance, and any new approach for psychiatric diseases should consider the past long-term mistakes to avoid them[110].

Preclinical and clinical studies have reported that low doses of the noncompetitive NMDAR antagonist and psychotomimetic ketamine have a rapid antidepressant action: a rapid (within hours) and sustained (up to 1 week) antidepressant effect on core symptoms can be induced by a single subanesthetic dose of intravenously-infused ketamine in patients with treatment-resistant depression[7, 8, 14, 111]. A recent report also emphasized that a single dose can have long-lasting effects on the FST behavior of rats[112]. This unanticipated finding suggests that ketamine could be an alternative treatment for depressed patients who have not previously responded to pharmacotherapy. Though ketamine is a hallucinogenic drug similar to lysergic acid diethylamide, it is relatively safe as an antidepressant because a low dose is used (0.5 mg/kg

antidepressant dose *versus* 2.0 mg/kg psychedelic dose)[8]. Furthermore, repeated ketamine infusion also has a sustained antidepressant effect, with no clinically significant psychotomimetic effects[113]. In contrast to most approved antidepressants which target the monoaminergic system, ketamine has a direct and rapid effect on the glutamatergic system and synaptic plasticity[47]. Ketamine rapidly increases the expression of synaptic proteins and the number of excitatory spine synapses in the PFC[50, 114, 115]. In the FST, ketamine reduces immobility (a behavioral endophenotype reversible by antidepressants) concomitant with a rapid increase in glutamate release, activation of AMPARs, and increased hippocampal BDNF concentration[116, 117]. From this evidence, a glutamatergic hypothesis of depression is proposed in which the glutamatergic system is the primary mediator of depression and serves as a final pathway in antidepressant therapy. By directly targeting NMDARs and rapidly restoring glutamatergic function, ketamine has fast antidepressant effects.

Targeting NMDARs

The NMDAR as an antidepressant target was first suggested by the findings that inescapable acute stress impairs hippocampal LTP and facilitates LTD. Thus, before the discovery of ketamine's antidepressant effect, several other NMDAR regulators had been evaluated for their antidepressant effect in animal models, such as MK-801 (a non-competitive antagonist), AP-7 (a competitive antagonist), and RO25-6981 (an NR2B antagonist)[118, 119]. While antidepressant effects occurred with these agents, they were not as sustained as those of ketamine[116]. Recent studies have found that the NMDAR agonist GLYX-13 has effects similar to ketamine but without the adverse effects, such as the psychotomimetic consequences and impaired cognition that limit its clinical use[120]. Further studies are required to determine how both agonists and antagonists of NMDARs exhibit antidepressant efficacy. One possibility is that agonists promote synaptic plasticity and improve cognition, while antagonists serve to protect neurons against stress-induced degeneration.

Targeting AMPARs

Glutamatergic synaptic strength is determined by AMPARs, as these receptors contribute to the majority of postsynaptic current. The function of AMPARs is rapidly modulated by phosphorylation at two sites on the GluR1 subunit, and both sites are implicated in the expression of synaptic plasticity and memory[121]. GluR1 phosphorylation is transiently increased by stress, possibly contributing to the stress-induced facilitation of memory[122]. In addition, the AMPAR potentiators LY392098 and LY451646 have antidepressant effects in the FST and TST[123-125]. Enhanced phosphorylation of GluR1 has been detected following fluoxetine, imipramine, and ketamine treatment, and ketamine rapidly increases postsynaptic AMPAR expression[103, 104, 115]. Moreover, the onset of ketamine effects requires AMPARs, as the antidepressant-like behaviors are attenuated by pre-treatment with the AMPAR antagonist NBQX in mouse models of depression[116]. Considering their importance in memory and synaptic plasticity, AMPARs may be another target for fast antidepressant effects.

Orcinoside

Orcinoside is a small compound extracted from a traditional Chinese herb that has been used to treat depression-like symptoms, lack of mental energy, and memory defects for over 100 years. A fruitful collaboration by the Kunming Institute of Zoology and Kunming Institute of Botany, Chinese Academy of Sciences, has identified orcinoside as a potent antidepressant[126].

Conclusion and Future Prospects

Depression is a functional illness. Stress-induced effects on neural plasticity and memory appear critical for disease pathogenesis as evidenced by the actions of stress, monoamine-based antidepressants, and glutamate receptor modulators on memory pathways. The NMDAR is necessary for many forms of neural plasticity and memory, and thus may be a feasible target for a new class of antidepressants with more rapid efficacy than currently achieved using monoaminergic modulators. Indeed, the antidepressant efficacy of the NMDAR antagonist ketamine may provide proof of principle. A key question is why the efficacy of ketamine, while rapid, also wears off in time. Moreover, how different changes in synaptic plasticity and metaplasticity contribute to the development and (or) amelioration of specific depressive behaviors requires much future study.

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