Review

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Dysfunction of Glutamatergic Synaptic Transmission in Depression: Focus on AMPA Receptor Trafficking

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ABSTRACT

Pharmacological and anatomical evidence suggests that abnormal glutamatergic neurotransmission may be associated with the pathophysiology of depression. Compounds that act as NMDA receptor antagonists may be a potential treatment for depression, notably the rapid-acting agent ketamine. The rapid-acting and sustained antidepressant effects of ketamine rely on the activation of AMPA receptors (AMPARs). As the key elements of fast excitatory neurotransmission in the brain, AMPARs are crucially involved in synaptic plasticity and memory. Recent efforts have been directed toward investigating the bidirectional dysregulation of AMPAR-mediated synaptic transmission in depression. Here, we summarize the published evidence relevant to the dysfunction of AMPAR in stress conditions and review the recent progress toward the understanding of the involvement of AMPAR trafficking in the pathophysiology of depression, focusing on the roles of AMPAR auxiliary subunits, key AMPAR-interacting proteins, and posttranslational regulation of AMPARs. We also discuss new prospects for the development of improved therapeutics for depression.

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Major depressive disorder (MDD) is a severe psychiatric disorder affecting approximately 5% of the world population and contributing significantly to global economic and health burdens (1,2). Clinical antidepressants, including selective serotonin reuptake inhibitors (SSRIs), are widely used for the treatment of depression. However, there is a significant time lag of several weeks before the benefit for patients with MDD, and approximately one third of patients do not experience therapeutic benefits following treatment with SSRIs (3). Therefore, the development of robust and rapid-acting antidepressants is urgent to improve symptoms and suicidal ideation in patients with MDD.

Glutamate is the major mediator of excitatory synaptic transmission in the mammalian brain. Glutamate released by the presynaptic terminal binds to and activates specialized ionotropic and metabotropic receptors in the postsynaptic membrane, producing wide-ranging effects on neuronal excitability. The role of the glutamatergic system in the pathophysiology and treatment of depression has been investigated (4). The antidepressant effects of ketamine have attracted increasing attention owing to their rapid-acting and long-lasting effects. Although ketamine acts as an NMDA receptor (NMDAR) antagonist, its antidepressant effects may be independent of NMDAR inhibition and rely on the activation of AMPA receptors (AMPARs) (5,6).

AMPARs are composed of glutamate receptor subunits (GluA1–GluA4) that form tetramers (mainly GluA1/GluA2 and GluA2/GluA3 heteromers) to participate in excitatory neurotransmission and activity-dependent synaptic plasticity and synaptogenesis (7). In contrast to NMDARs, AMPARs are highly mobile, and their synaptic abundance is tightly regulated, such as trafficking to/from the synapse, mobility along the plasma membrane, and synaptic stabilization. The components of AMPAR subunits are developmentally regulated and region specific (8). Chronic stress breaks the homeostasis of AMPAR trafficking via numerous protein molecules and signaling pathways, such as AMPAR auxiliary subunits, key AMPAR-interacting proteins, and posttranslational regulation of AMPARs. Chronic physical and psychological stress is a major risk factor for psychiatric disorders such as depression (9). Prolonged stress impairs neuronal structure and function and leads to psychiatric disorders. Several animal models of chronic stress have been established to explore the potential mechanism of depression, such as chronic social defeat stress (CSDS), chronic restraint stress (CRS), and chronic unpredictable stress (CUS) (10).

This review presents an integrative overview of the current literature surrounding the disturbance of surface stability of AMPARs under stress conditions. It delineates the functional implications of this process in depression by focusing on the mechanisms of AMPAR trafficking in the pathophysiology, which will be helpful for identifying potential drug targets for the therapeutics of MDD.

AMPAR-MEDIATED SYNAPTIC TRANSMISSION IN DEPRESSION

Stress-induced alterations in AMPAR-mediated synaptic transmission result from changes in expression or subunit

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composition of AMPARs. However, opposite findings often appear in the literature (11), which may be due to the considerable heterogeneity among brain regions and the variability of stress. We summarize functional changes in AMPARs in brain regions that are closely related to MDD based on preclinical and clinical studies (Table 1).

Prefrontal Cortex

The prefrontal cortex (PFC) is an important brain subregion in which the controllability of a stressor or the pleasantness of a stimulus can influence mood and reward (11). Chronic stress induces the loss of dendritic spines in the PFC and a decrease in AMPAR expression, leading to the attenuation of AMPAR-mediated synaptic transmission (12–14). Sutton *et al.* (13) found that CUS increased the expression of orphan receptor GPR158 via a glucocorticoid-dependent manner. GPR158-induced activation of cAMP-dependent protein kinase A (PKA) may be responsible for the decreased phosphorylation of GluA1 and AMPAR-mediated synaptic transmission (13). In the CSDS model, reduction of the ephrin B2 receptor and activation of the miR-214-β-catenin signaling pathway in the mPFC induce a decrease in AMPAR and spine remodeling (12,14). A potential involvement of the mTOR (mechanistic target of rapamycin) signaling pathway in depression has been suggested by postmortem studies, which report a significant reduction in mTOR and S6K protein levels in the PFC of subjects with MDD (15). In the chronic behavioral despair mouse model of depression, the decreased Homer1a-mGluR5 signaling downregulates AMPAR function via damping GluA1 protein translation and trafficking (16). More detailed studies have found that selective loss of p11 in the dopamine D_2 receptor–expressing glutamatergic neurons in the prelimbic cortex induces the attenuation of AMPAR-mediated synaptic transmission in the CRS model, which can be restored by antidepressants, such as fluoxetine or imipramine (17). The biochemical changes in AMPAR expression under stress conditions are varied among different reports. Some studies observed a decrease in both GluA1 and GluA2 expression (12,18,19). However, other studies observed a specific decrease in GluA1 or GluA2 (13,16,20). In addition, chronic stress also weakens the miniature excitatory postsynaptic current, which is a critical indicator of AMPAR function. In these studies, GluA1- or GluA2-containing receptor–mediated currents cannot be distinguished due to the absence of specific AMPAR blockers (14,17). Seo *et al.* (17) showed that AMPAR-mediated glutamatergic transmission was depressed only in D_2 receptor–expressing glutamatergic neurons in the PFC. Wei *et al.* (21) observed diminished glutamatergic transmission in pyramidal neurons projecting to the basolateral amygdala (BLA) in animals exposed to prolonged severe stress, which can be restored by chemogenetic activation of pyramidal neurons in the PFC. Collectively, these results reveal impaired AMPAR-mediated synaptic transmission in the PFC under chronic stress conditions, which is closely related to depressive-like behaviors in rodents.

Nucleus Accumbens

More than 95% of neurons in the nucleus accumbens (NAc) are primarily composed of two types of medium spiny neurons (MSNs) enriched with D_1 or D_2 receptors (D1-MSNs and D2-MSNs, respectively). CSDS induces decreased binding of ΔFOSB to the GluA2 promoter and the subsequent higher

Table 1. Summary of AMPAR Expression in Preclinical Models of Depression and Patients With Depression

AMPA Receptor	Brain Region	Expression	Stress or Sample	References
Preclinical Studies				
GluA	NAc	↑	CSDS, FSS	(26,27,115)
	NAc	↓	CUS	(25)
	PFC	↓	CRS, CSDS	(12,14,17)
GluA1	PFC	↓	CRS, FST	(13,16,18)
	Hippocampus	↓	LPS, CUS, CSDS	(30,33–35,116,117)
	PFC, Hippocampus	↓	CMS	(118)
	NAc	↑	CSDS	(22)
	Amygdala	↓	CUS	(48)
	BLA	↑	CSDS, FSS, CRS	(45–47)
GluA2	PFC	↓	CRS, CUS	(18,20)
	Hippocampus	↓	CSDS	(30,32)
	Hippocampus	↑	CRS	(119)
	NAc	↓	CRS, CSDS	(22,23)
Patients With Depression				
GluA	ACC	↑	MDD	(51)
GluA1/3	Hippocampus	↓	MDD	(117)
GluA1	DLPFC	↑	MDD	(50)
GluA2	NAc	↑	MDD	(22)

ACC, anterior cingulate cortex; AMPAR, AMPA receptor; BLA, basolateral amygdala; CMS, chronic mild stress; CRS, chronic restraint stress; CSDS, chronic social defeat stress; CUS, chronic unpredictable stress; DLPFC, dorsolateral prefrontal cortex; FSS, footshock stress; FST, forced swim test; LPS, lipopolysaccharide; MDD, major depressive disorder; NAc, nucleus accumbens; PFC, prefrontal cortex.

proportion of GluA2-lacking AMPARs in susceptible mice followed by CSDS (22). Lim *et al.* (23) showed that endocytosis of GluA2 and insertion of GluA2-lacking AMPARs were specifically restricted to D1-MSNs but not D2-MSNs after CRS owing to the activation of melanocortin 4 receptor and the downstream exchange proteins activated by cyclic AMP. The NAc is critical to integrating input from the hippocampus and ventral tegmental area (24). Chronic stress also decreases the AMPAR/NMDAR ratio, an index of change in postsynaptic function, on D1-MSNs receiving projections from the hippocampus, which can be rescued by fluoxetine treatment (23,25).

It is worth noting that some conflicting results exist on the excitatory synaptic transmission on D1-MSNs in the NAc under chronic stress. Ventral hippocampal synapses onto D1-MSNs are potentiated by footshock stress, and the elevated AMPAR/NMDAR ratio is due to increased AMPAR-mediated synaptic currents (26). Kim *et al.* (27) also found that CSDS increased AMPAR-mediated neurotransmission on D1-MSNs, which received projections from the ventral tegmental area. The potent AMPAR function is due to the cell-specific upregulation of Shisa6, a transmembrane adapter protein of AMPARs (27). However, Francis *et al.* (28,29) found no significant changes in the amplitude of AMPAR-mediated synaptic currents on D1-MSNs in susceptible mice, but the frequency was decreased. They showed that an early growth response family member, EGR3, mediated the susceptibility of mice to stress by controlling stress-driven dendritic morphological adaptations in D1-MSNs. EGR3-mediated dendritic changes lead to functional alterations in excitatory synaptic transmission (29). These conflicting results highlight the complex nature of the NAc circuit in depression. The impact of stress on MSNs in the NAc varies with cell specificity.

Hippocampus

The hippocampus is a key brain region in the neuronal circuit that regulates cognitive and emotional behaviors. Chronic stress (CSDS or CRS) decreases AMPAR expression and miniature excitatory postsynaptic current amplitude in the hippocampus (30–32). Ma *et al.* (33) showed that CUS induced reduction in spine density, dendritic complexity, and synaptosomal AMPARs in the ventral CA1. This pathological changes were reversed by stimulation of posterior BLA–ventral CA1 innervation via chemogenetics or administration of cannabidiol, indicating the dependence of neuronal activity and circuit-specific regulation (33). In CSDS or CUS models, the phosphorylation of AMPAR subunit GluA1 is also reduced, leading to a decrease in synaptosomal AMPAR level (33–35). The decrease in GluA1 expression relies on the CaMKIIβ-mediated phosphorylation of GluA1 or the AMPAR auxiliary subunit TARP-γ8 (35). The neurogenesis hypothesis of depression suggests that chronic antidepressant treatment, such as by using SSRIs, alleviates depressive-like behaviors through increasing neurogenesis in the hippocampus. However, more current literature has disputed those findings and concludes that neurogenesis can be affected by stress and antidepressants under certain conditions (36,37). Neuropeptides and anti-inflammatory action may be relevant to the mechanism of action of SSRIs (38,39). In addition, enhanced AMPAR-mediated synaptic transmission in the hippocampus also responds to chronic antidepressant treatment, underlying the mechanism for ameliorating depressive-like behaviors in mice (32,34,40). Recent studies also show that the dynamic expression of AMPARs in specific interneurons in the dentate gyrus responds to stress-induced depressive-like behaviors (32,41). CSDS represses the SMARCA3/Neurensin-2 pathway in cholecystokinin- or parvalbumin-expressing interneurons to induce endocytosis of AMPARs (32,41). In addition, activation of the SMARCA3/Neurensin-2 pathway and subsequent AMPAR localization to synapses in parvalbumin-expressing interneurons mediates the response to chronic antidepressant treatment (41). Regular exercise-induced neurophysiological adaptation is beneficial to multiple brain functions such as cognition and mood (42). Leem *et al.* (43) found that regular exercise improved prolactin responsiveness in the hippocampal CA1 region, which led to prolactin-dependent enhancement in phosphorylated signal transducer and restored decreased GluA1 expression. These lines of evidence suggest that chronic stress weakens AMPAR-mediated synaptic transmission in diverse cell types in the hippocampus. Recovery of the deficit in synaptic transmission may be the key target of antidepressants.

Amygdala

The amygdala is a series of nuclei complexes and usually is divided into the BLA, the medial amygdala, and the central amygdala. Hyperactivity of the amygdala contributes to stress-induced neuropsychiatric disorders, such as anxiety and depression (44). It is shown that GluA1 phosphorylation in the BLA synaptosome is increased in a PKA-dependent manner after exposure to chronic stress, leading to the insertion of GluA1 (45–47). Endogenous cannabinoid signaling modulates glutamatergic neurotransmission in the BLA. Chronic stress and corticosterone treatment reduce cannabinoid receptor type 1–mediated attenuation of glutamatergic synaptic transmission in the BLA through presynaptic mechanisms (48,49). Another study has found that CUS exposure decreases the phosphorylation of mTOR and its downstream signaling components extracellular signal–regulated kinases 1/2 and GluA1 (48). In this study, the whole amygdala was not subdivided into the BLA subregion, which may explain the discrepancy.

Taken together, the preclinical available data suggest that region- and subunit-specific changes in AMPAR-mediated synaptic transmission are closely related to depressive-like behaviors. Chronic stress induces AMPAR-mediated transmission in the PFC and hippocampus but potentiates AMPAR-mediated transmission in the amygdala.

Clinical Study

There is relatively less AMPAR-related research in postmortem studies in MDD compared with the abundant results in animal models. These clinical and preclinical results are not always consistent. For example, different from the reduction in preclinical animal models, AMPAR expression is increased in the PFC in depression and postmortem studies (50–52). The paradoxical results between preclinical and clinical studies may be due to the heterogeneity of samples. The preclinical studies mostly analyze the mPFC sample, while the clinical data mainly

come from the dorsolateral PFC and anterior cingulate cortex. Furthermore, the subjects were not drug naïve, and antidepressant treatment may have an impact on the results. Moreover, there may be physiological changes in the postmortem studies. Therefore, detecting changes in AMPARs in living human brains would confirm the postmortem studies. Recently, Miyazaki *et al.* (53) developed a positron emission tomography tracer, [^{11}C]K-2, for AMPARs in living human brain. The increased tracer uptake can be detected in the epileptogenic focus of patients with epilepsy, which was correlated with the density of AMPAR protein examined by biochemical study after surgery. With this tracer, we will explore the number and function of AMPARs in the living human brains of patients with MDD.

AMPAR TRAFFICKING–RELATED PROTEIN IN DEPRESSION

Functional AMPARs are assembled from four core subunits (GluA1–GluA4) with different combinations and additional proteins, such as AMPAR auxiliary subunits and AMPAR trafficking–related protein. AMPAR-interacting proteins exhibit different roles in regulating AMPAR trafficking and function, attracting more and more attention over the past few years. Their temporally and spatially regulated expression leads to different combinations according to brain region and neuronal type and also provides a molecular framework underlying the spatiotemporal-specific features of AMPAR trafficking (8,54).

AMPAR Auxiliary Subunits

The category of AMPAR auxiliary subunits comprises the family of TARPs, Shisas, cornichon homolog proteins, synapse differentiation-induced gene 1/4, and germ cell-specific gene 1 like protein (55). Auxiliary subunits interact directly with AMPARs and affect various functions, such as channel gating, conductance, subunit composition, and trafficking (56).

TARPs are the first identified auxiliary proteins for neuronal AMPARs (57). TARPs are enriched in the postsynaptic density and are important for surface expression of AMPARs in the brain regions where they are expressed (58,59). The deletion of TARP-γ2 leads to a total loss of surface AMPARs on cerebellar granule cells, and TARP-γ8 loss leads to about 85% reduction of AMPARs in the hippocampus (60,61). TARP-γ8 knockout mice also exhibit reduced marble-burying behaviors and immobility time, indicating its anxiolytic and antidepressant effects. Furthermore, the antidepressant-like effects of LY392098, an AMPAR potentiator, are abolished in TARP-γ8 knockout mice (62). Recently, Sakai *et al.* (35) demonstrated that CaMKIIβ-mediated TARP-γ8 phosphorylation enhanced the expression of GluA1 in hippocampal CA1 neurons to promote stress resilience. These studies indicate the role of the TARP-γ8–AMPAR complex in depression. In view of the predominant expression of TARP-γ8 in the hippocampus, compounds specific for AMPARs associated with TARPγ-8 are being developed, leading to the discovery of LY3130481 and JNJ55511118, the antagonists of TARPγ-8–containing AMPARs (63,64). JNJ55511118 treatment increased the susceptibility to stress (35). More importantly, in contrast to perampanel, the blocker of AMPARs in all brain regions, LY3130481 significantly reduces the incidence of side effects such as dizziness (63). Considering a better understanding of the precise stoichiometry and architecture of the TARP-γ8–AMPAR complex through cryoelectron microscopy in recent years (65,66), we look forward to more JNJ55511118-like drugs being developed.

Shisas constitute a family of four proteins that influence the trafficking and subcellular localization of AMPARs (67). Shisa9 has been recently identified as a gene related to major depression by large-scale genome-wide association study (68). Shisa6 is expressed in the principal cell layers of the hippocampus and in the Purkinje layer of the cerebellum (69,70). A recent study has found that chronic stress increased Shisa6 expression in D1-MSNs in the NAc, contributing to the depressive-like phenotypes of susceptible mice (27). Cell-type action of Shisa6, which directly modulates excitatory synaptic transmission that encodes aversive information, identifies the protein as a potential antidepressant target.

AMPAR–Interacting Proteins

The four AMPAR subunits (GluA1–GluA4) are embedded into a dynamic network of distinct sets of interacting proteins. Many of these proteins are known to modulate receptor gating, trafficking, and subcellular localization, including direct and indirect protein-protein interactions.

AMPAR subunits GluA1 and GluA3 share a common sequence at the end of their C-terminus through which they can interact with PDZ domain–containing proteins (71). Two groups have been identified so far: the glutamate receptor–interacting protein family of proteins and PICK1 (72). Grip1 knockout mice exhibit impaired hippocampal long-term potentiation, as well as deficits in learning and memory, which is associated with decreased phosphorylation of GluA2 (73). GRIP1/2 double knockout mice show anxiety behavior and increased sociability and preference for social novelty (74). Moreover, CUS increases the expression of GRIP1 in the PFC (75). It is well established that PICK1-GluA2 interaction is required for both hippocampal and cerebellar long-term depression (76,77). PICK1 polymorphisms may be associated with cognitive impairment in patients with schizophrenia (78). In addition, PICK1 knockout mice show attenuated reward-related behaviors characterized by decreased behavioral sensitization to a single injection of cocaine and diminished cocaine intake in a self-administration paradigm (79).

N-ethylmaleimide sensitive factor (NSF) interacts with the C-terminus of GluA2. Blockade of GluA2-NSF interaction results in decreased AMPAR-mediated excitatory postsynaptic currents, supporting a role of NSF in the synaptic abundance of GluA2-containing AMPARs (80), as well as its rapid incorporation and stabilization at synapses (81). Moreover, infusion of a specific peptide, TAT-pep-R845A, which disrupts GluA2-NSF interaction, inhibits the formation of fear memory in the lateral amygdala and increased the locomotor response of rats to cocaine in the NAc (82,83). Exposure to stressful events increases the synthesis and release of glucocorticoids. Xiong *et al.* (84) found that corticosterone increases the synaptic transmission and surface expression of AMPARs in hippocampal neurons, which was also prevented by TAT-pep-R845A.

Syndapin is an F-BAR and SH3 domain–containing protein that is capable of remodeling the plasma membrane and mediating protein-protein interactions. Syndapin-1 associates with AMPARs via an interaction with PICK1 and regulates the activity-dependent endocytosis of AMPARs (77,85). Patients with schizophrenia or bipolar disorder display reduced levels of syndapin-1 protein in the dorsolateral PFC (86,87). Targeted multiplexed proteomic research also found that acute ketamine treatment induced the expression of syndapin-1 in the hippocampus of rats (88).

SAP97 protein belongs to AMPAR native macromolecular complexes (89). SAP97 specifically binds to GluA1 but not GluA2 through GluA4, which depends on a small sequence outside of PDZ-binding sequence (90). SAP97 appears to be involved in the regulation of AMPAR trafficking between extrasynaptic and synaptic pools. Upregulation of SAP97 was negatively correlated with hippocampal long-term potentiation, contributing to the deficits of learning and memory (91). Ketamine treatment reduces the expression of SAP97 in the medial PFC and hippocampus of rats (92,93).

Posttranslational Regulation of AMPAR Trafficking and Function

Exocytosis, endocytosis, and channel gating of AMPARs are dynamically regulated by AMPAR-interacting proteins and various reversible posttranslational modifications that occur on the cytoplasmic domains of AMPAR subunits. The kinases and phosphorylation sites on AMPAR subunits and their roles in receptor trafficking and function have been intensively studied (94,95). Several protein kinases, including CaMKII, PKA, and protein kinase C, are critical modulators of biophysical properties and activity-dependent AMPAR trafficking (96). Sutton *et al.* (13) found that CRS upregulated the expression of orphan receptor GPR158 in the mPFC. GPR158 inhibited PKA-mediated phosphorylation of GluA1 at Ser845 and weakened excitatory synaptic strength. In contrast, GPR158 ablation led to a prominent antidepressant-like phenotype and promoted stress resilience (13). In the BLA, chronic stress enhances cAMP-dependent PKA activity and increases GluA1 phosphorylation at Ser845, facilitating the synaptic insertion of GluA1 (45,47). GluA1 Ser845 is also dephosphorylated by the calcium-dependent phosphatase calcineurin (also known as PP2B). PKA and PP2B are anchored at synapses by A-kinase-anchoring protein 150 (AKAP150) (the rodent ortholog of human AKAP79). Changes in the expression of AKAP79 protein are found in individuals with mood disorder (97). Recent evidence has shown that CRS facilitates the association of AKAP150 with PKA and increases GluA1 phosphorylation at Ser845 and surface insertion of GluA1 in the BLA, which contributes to depressive-like behaviors. Infusion of an interference peptide, Ht-31, which dissociates PKA from AKAP150, also displays antidepressant action (46). Phosphorylation of other synaptic proteins that directly interact with AMPARs are also involved in depression, such as TARP-γ8. Stress-induced CaMKIIβ upregulation in the lateral habenula mediates depressive-like behaviors through increasing the synaptic insertion of GluA1 (98). Long-term potentiation and memory formation are significantly impaired in mice lacking CaMKII phosphorylation sites of TARP-γ8 (99). A recent study has demonstrated that CaMKIIβ-mediated TARP-γ8 phosphorylation enhances the expression of GluA1 in the hippocampus and promotes stress resilience (35).

Ubiquitination is a posttranslational process that attaches a single ubiquitin or polymeric ubiquitin chains to lysine residues of a substrate protein. It is shown that repeated stress impairs glutamatergic transmission in the PFC of juvenile male rats and causes cognitive impairment (18). One of the underlying mechanisms involves glucocorticoid receptor–dependent transcriptional activation of E3 ubiquitin ligases Nedd4–1 and subsequent ubiquitination and degradation of AMPARs (18,19). It is well known that AKAP150 is regulated by a ubiquitin-proteasome system that depends on synaptic activity (100). A recent study also found that hippocampal long-term depression induced AKAP150 degradation that was associated with the ubiquitination of AKAP150 (101).

SUMMARY AND FUTURE DIRECTIONS

In this review, we summarized the brain region– and subunit-specific changes in surface stability of AMPARs under stress condition in MDD. Chronic stress breaks the homeostasis of AMPAR trafficking via numerous molecules and signaling pathways, such as AMPAR auxiliary subunits, key AMPAR-interacting proteins, and posttranslational regulation of AMPARs. We proposed that normalization of AMPAR expression and function through bidirectional modulation of AMPARs would indirectly show antidepressant outcome (Figure 1).

Nonselective NMDAR antagonists, such as ketamine, exert fast and long-lasting antidepressant-like effects; however, the psychomimetic effects limit their clinical application. Therefore, the downstream molecular and cellular mechanisms underlying the antidepressant actions of ketamine may hold great promise for antidepressant development. Ketamine is a racemic mixture of the enantiomers (*R*)-ketamine and (*S*)-ketamine. (*S*)-ketamine is an active isomer because of its higher affinity for NMDARs (Ki = 0.30 μM) and greater anesthetic potency than that of (*R*)-ketamine (Ki = 1.4 μM) (102). However, preclinical findings reveal that (*R*)-ketamine exerts greater potency and longer-lasting antidepressant-like actions than (*S*)-ketamine and appears to have fewer behavioral side effects and less abuse liability (103,104). Moreover, not all NMDAR antagonists exhibit rapid antidepressant efficacy. Notably, AZD6765, an NMDAR antagonist, shares several pharmacological profiles with (*R,S*)-ketamine at the NMDAR but does not show potent antidepressant-like effects (105,106). Therefore, it is unlikely that the different antidepressant effects of the two ketamine enantiomers are related to the differences in their pharmacokinetic properties. Recently, the disinhibition hypothesis suggests that the rapid antidepressant effects of ketamine are mediated through blockade of NMDARs located on GABAergic (gamma-aminobutyric acidergic) interneurons. This in turn leads to a disinhibition of pyramidal cells in the PFC and an acute glutamate release (107). The balance of neuronal activity in these regions is shifted toward excitatory transmission, which may underlie its antidepressant action. Indeed, ketamine exerts its antidepressant-like effects by initiating synaptogenesis in an AMPAR/BDNF (brain-derived neurotrophic factor)/mTOR complex 1–dependent manner, which

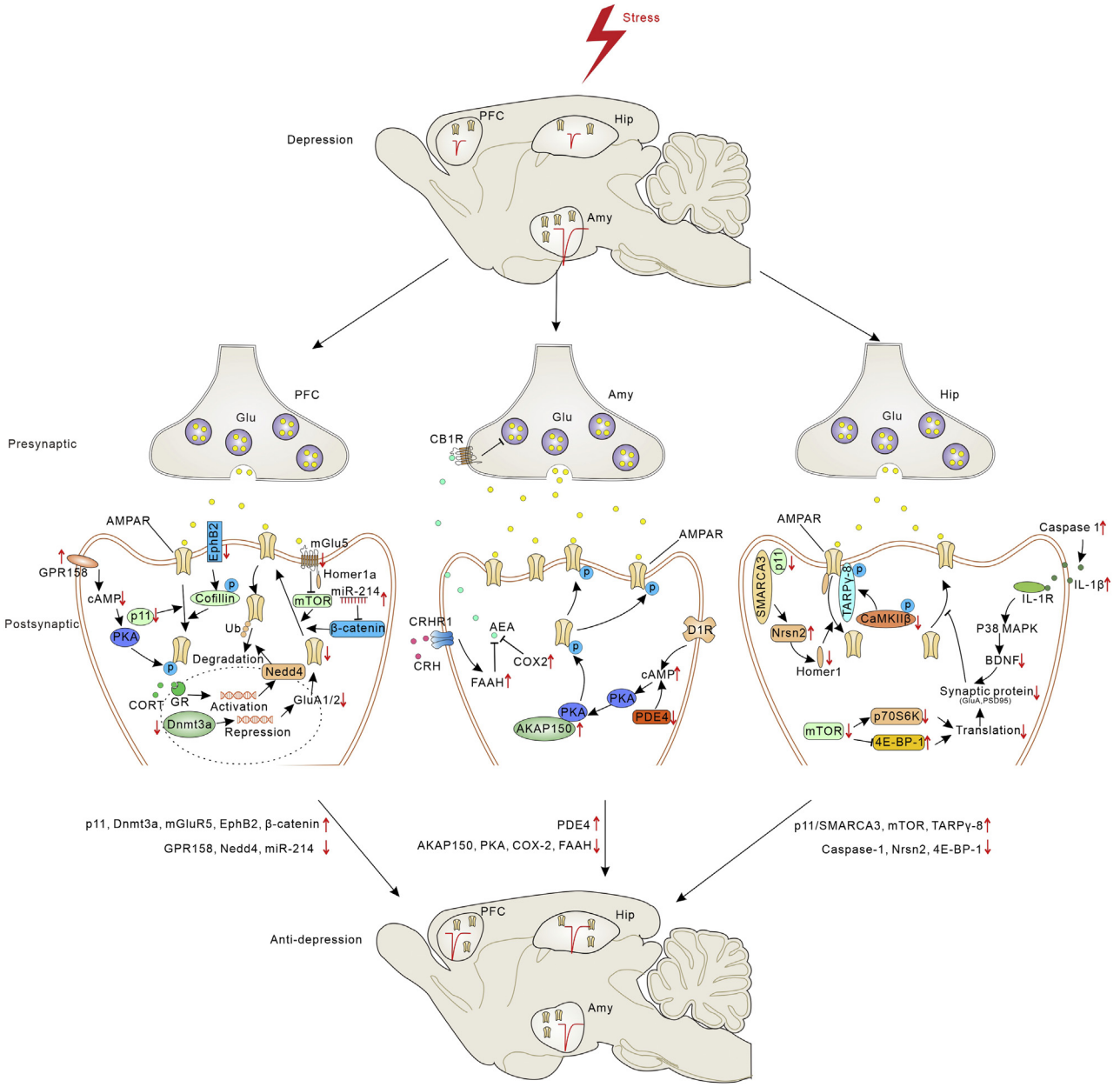

Figure 1. Dysfunction of AMPAR trafficking in depression. In the PFC and hippocampus, stress decreases AMPAR expression, which can be affected by the pathways including receptors (e.g., GPR158, GR, and mGluR5), neurotrophic factors (e.g., BDNF), cytokines (e.g., caspase-1 and IL-1β), transcriptional regulation (e.g., Dnmt3a, SMARCA3, and microRNA), posttranslational modifications (e.g., phosphorylation, ubiquitination), AMPAR-interacting proteins (e.g., homer1 and TARPγ-8) and mTORC1 signaling cascade. In the amygdala, stress enhances AMPAR-mediated synaptic transmission, which can be affected by the pathways including receptors (e.g., CRHR1 and D1R), posttranslational modifications (e.g., phosphorylation), AMPAR-interacting proteins (e.g., AKAP150), and endocannabinoids signaling cascade. Normalization of the abnormal synaptic AMPAR trafficking by genetic or pharmacological treatment represents antidepressant effect. 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; AEA, anandamide; AKAP150, A-kinase anchoring protein 150; AMPAR, AMPA receptor; Amy, amygdala; BDNF, brain-derived neurotrophic factor; CaMKIIβ, calcium/calmodulin-dependent protein kinase IIβ; CB1R, cannabinoid receptor type 1; COX2, cyclooxygenase-2; CRH, corticotropin-releasing hormone; D1R, dopamine 1 receptor; Dnm3a, DNA methyltransferase 3a; FAAH, fatty acid amide hydrolase; GPR158, G protein-coupled receptor 158; GR, glucocorticoid receptor; Hip, hippocampus; IL, interleukin; mGluR5, metabotropic glutamate receptor 5; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; Nedd4, neuronal precursor cell-expressed developmentally downregulated 4; Nrsn2, neurensin 2; PDE4 phosphodiesterase-4; PFC, prefrontal cortex; PKA, protein kinase A; SMARCA3, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin 3; TARPγ8, transmembrane AMPAR regulatory proteins γ8.

involves recruitment of eukaryotic translation initiation factor 4E-BP2 and sustained increases in AMPAR expression (108,109).

Despite this abundance of preclinical data regarding glutamatergic involvement in MDD, the results of subsequent clinical trials are dissatisfactory (110). Despite promising antidepressant effects at the preclinical stage, several alternative NMDAR agents, including GluN2B-selective allosteric modulators (CP-101,606, CERC-301, and RO 25-RO6981) and glycine binding site modulators (AV-101 and rapastinel) failed to achieve the rapid and robust antidepressant efficacy of ketamine. In addition, several AMPAR-positive allosteric modulators, including ORG 26576 and CX1632, did not improve depressive symptoms significantly or meet trial end points in subsequent phase 2 clinical trials for MDD (111,112).

Moreover, no other glutamate modulators are currently approved for the treatment of depression worldwide. To date, major pharmaceutical efforts to develop novel antidepressant drugs directly target glutamate receptors. Although the strategy that directly targets the receptor has enabled the discovery of most drugs developed to modulate receptor signaling, obvious disadvantages still exist. First, glutamate receptors are widely distributed in the brain and fundamental to brain function. Meanwhile, stress induces brain region–specific bidirectional dysregulation of AMPAR-mediated synaptic transmission. Therefore, drugs that directly target the receptor lack specificity in the brain. Second, the use of an antagonist that directly blocks receptors is often accompanied with internalization and homeostatic regulation (113). With the continuous progress of novel drugs, an innovative approach targeting receptor complexes has recently garnered great interest (54,114). AMPAR complexes consist of AMPAR subunits and receptor-associated proteins, which reveal relative spatiotemporal diversity of expression and have profound effects on the overall function and localization of receptors. Targeting AMPAR-associated proteins may provide a more selective pharmacology, increase the safety of depression treatment, and reduce side effects. As exemplified by the TARPγ-8 modulators LY3130481 and JNJ55511118, targeting AMPAR-associated proteins can provide brain region selectivity (63,64). The regional expression of TARPγ-8 explains why they preferentially block hippocampal and cortical AMPARs. TARPγ-8 in the hippocampus is required for the synaptic localization of CaMKIIβ-mediated GluA1 and subsequent stress resilience (35). Further progress in AMPAR structural biology, especially by using cryoelectron microscopy approaches, will contribute to revealing the structure-guided medicinal chemistry of macromolecular receptor targets. Targeting AMPAR-associated proteins may be of value for the development of novel drugs for depression.

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