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MINI REVIEW

AMPA receptor modulation in depression: from molecular mechanisms of plasticity to therapeutic translation

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Abstract

The glutamatergic system, particularly N-methyl-D-aspartate (NMDA) receptors, has long been a significant focus of research into new strategies for treating depression, and the clinical success of ketamine, an NMDA receptor antagonist, has been a significant breakthrough. In parallel, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, another key component of the glutamatergic system, have been studied for decades, and renewed interest stems from evidence linking their activation to the rapid antidepressant effects and synaptic plasticity observed after ketamine administration. Among pharmacological agents targeting AMPA receptors, the class of positive allosteric modulators, AMPAkines, has attracted particular interest. These compounds act by prolonging AMPA receptor channel open time, thereby enhancing excitatory neurotransmission and upregulating brain-derived neurotrophic factor (BDNF) expression. Preclinical studies consistently demonstrated antidepressant-like effects of low-impact AMPAkines, which offer a favorable safety profile in contrast to high-impact compounds that carry seizure risk. Although preliminary clinical trials support these findings, their limited scope highlights persistent translational challenges. These include a narrow therapeutic window, suboptimal pharmacokinetic properties, and the limited predictive validity of animal models. AMPAkines thus represent a potentially promising class of rapid-acting antidepressants, although significant translational hurdles remain. This narrative review aims to synthesize evidence on the role of AMPA receptors in neuroplasticity, the therapeutic potential of AMPA receptor modulators (AMPAkines) in influencing neuroplasticity, and their potential therapeutic applications in depression.

Keywords AMPA receptors · AMPAkines · Neuroplasticity · Depression · Rapid antidepressant response · Clinical translation · Pharmacokinetics · Safety profile

Clinical trial number

Not applicable.

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAkine	AMPA receptor modulator
ANN	Artificial neural network
ARC	Activity-regulated cytoskeleton-associated protein
BAX	B-cell lymphoma 2–associated X protein
BCL-2	B-cell lymphoma 2
BDNF	Brain-derived neurotrophic factor
Ca2+	Calcium ion
CaMKII	Calcium-dependent protein kinase II

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CMS	Chronic Mild Stress
CNS	Central nervous system
CYP3A	Cytochrome P450 3 A
DAG	Diacylglycerol
EEG	Electroencephalography
ERK	Extracellular signal-regulated kinase
FST	Forced Swim Test
GABA	Gamma-aminobutyric acid
GluA1	Glutamate receptor subunit AMPA 1 (GRIA1)
GluR1 mRNA	Glutamate receptor 1 messenger RNA
Group I mGluR	Metabotropic glutamate receptor 1,2,3,4, and 5
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
IP3	Inositol-1,4,5-triphosphate
LTD	Long-term depression
LTP	Long-term synaptic potentiation
MADRS	Montgomery–Åsberg Depression Rating Scale
MAGUK	Membrane-bound guanylate kinase
MDD	Major Depressive Disorder
MEK	Mitogen-activated protein kinase kinase
Mg2+	Magnesium ion
mGluR	Metabotropic glutamate receptor
mGluR-LTD	Metabotropic glutamate receptor-dependent long-term depression
mPFC	Medial prefrontal cortex
MTD	Maximum tolerated dose
mTOR	Mechanistic target of rapamycin
NeuroCARD	Neurocognitive Assessment for Reaction, Detection, and Decision
NGF mRNA	Nerve Growth Factor messenger RNA
NMDA	N-Methyl-D-Aspartate
NMDA-LTD	N-methyl-D-aspartate receptor-dependent long-term depression
p38-MAPK	p38 mitogen-activated protein kinases
PKA	Protein kinase A
PKC	Protein kinase C
PLC	Phospholipase C
Protein 4.1N	Neuronal isoform of protein 4.1
PSD-95	Postsynaptic density protein 95
RSBM test	Rat Social Behavior Model test
S831, S845	Serine 831 and Serine 845 phosphorylation sites on GluA1 subunit
SSRIs	Selective serotonin reuptake inhibitors
TARP	Transmembrane receptor regulatory proteins
TrkB	Tropomyosin receptor kinase B
TrkB-Fc	TrkB-Fc fusion protein
TST	Tail Suspension Test

Introduction

Depression is a major mental disorder with long-term health consequences, being one of the leading sources of reduced quality of life and lost productivity worldwide [1]. According to current estimates, up to 5% of adults suffer from depressive disorders [2]. Typical symptoms of depression include low mood, anhedonia, sleep and appetite disturbances, fatigue, and impaired concentration [3, 4]. Due to the absence of validated biological markers, a diagnosis is established through clinical assessment (history and mental status examination). Whilst response to pharmacotherapy is variable. Risk factors for the development of depression include both genetic and environmental influences, such as a family history of the disorder, adverse childhood experiences, and stressful life events [5, 6].

Given the diverse causes of depression, several hypotheses have been proposed to explain its pathophysiology, including the widely accepted neurotransmitter and receptor hypothesis, among others [7]. The most prominent is the monoamine hypothesis, which suggests that depression results from the depletion of brain neurotransmitters such as serotonin and noradrenaline [8]. This hypothesis guided pharmacotherapy, with selective serotonin reuptake inhibitors (SSRIs) or noradrenaline reuptake inhibitors(NRIs) as the mainstay of treatment. Such drugs act to increase extracellular monoamine levels [1, 9, 10]. However, monoamine-based treatments have several limitations, including a delayed onset [11] and unwanted side effects [12], prompting research into non-monoaminergic mechanisms. In particular, targeting glutamatergic and GABAergic neurotransmission has been prioritized. Recent evidence indicates that disturbances in glutamatergic and GABAergic neurotransmission play a key role in the pathophysiology of depressive disorders [12–14].

Within the glutamatergic system, N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are central nodes linking glutamate signaling to rapid changes in synaptic efficacy and plasticity [15]. AMPA receptors are mainly responsible for fast excitatory transmission in the cerebral cortex and hippocampus [16], whereas NMDA receptors act as voltage-dependent coincidence detectors and are crucial for neuroplasticity [17]. In contrast to NMDA receptors, which predominantly initiate plasticity-related signaling pathways, AMPA receptors directly determine synaptic strength by regulating postsynaptic function through receptor trafficking, thereby shaping functional neural connectivity [16, 17].

Importantly, AMPA receptor function is strongly influenced by its subunit composition, particularly the relative contribution of GluA1 and GluA2 subunits. Receptors

lacking the GluA2 subunit are permeable to Ca^{2+}, whereas the presence of GluA2 renders the receptor largely Ca^{2+}-impermeable due to RNA editing at the Q/R site [18, 19], This Ca^{2+} permeability increases the capacity of GluA2-lacking receptors to drive synaptic plasticity but also raises susceptibility to excitotoxicity [20]. In contrast, GluA2-containing receptors contribute to more stable synaptic transmission [18] but also to the excitotoxicity [18]. Importantly, the distribution of these receptor subtypes is not uniform across neuronal populations and synaptic connections. Ca^{2+} Permeable AMPA receptors are expressed in a synapse-specific manner at excitatory inputs onto selected interneuron subtypes, such as basket cells but not Martinotti cells, indicating that AMPA receptor composition and function vary across distinct microcircuits [21]. This subunit-dependent functional diversity is highly relevant for pharmacological modulation [20].

In patients with depression, synaptic plasticity-related pathways, controlling the brain's ability to adapt in response to neuronal activity and past experiences [22, 23], are impaired in the amygdala, prefrontal cortex, and hippocampus. The latter two regions have been strongly linked to depressive symptoms, including cognitive impairment, rumination, and anhedonia [24, 25]. This association is reflected in the structural reduction and functional weakening of these brain areas [26].

While numerous reviews have focused on the role of NMDA receptors and their modulators (especially ketamine) as potential targets for novel antidepressant therapies, much less attention has been paid to the AMPA receptors, which play an equally important role in regulating synaptic plasticity and excitatory neurotransmission. Therefore, this mini-review aims to analyze the potential use of the glutamatergic system, and AMPA receptors in particular, as a potential therapeutic target in the treatment of depression. The paper attempts to synthesize existing research involving neuroplastic changes associated with the action of the new class of antidepressant agents - AMPAkines, and the efficacy and mechanisms of action of AMPAkines based on preclinical and clinical data. We also discuss perspectives on why promising preclinical research results have not yet been translated into therapeutic success in clinical trials.

Methods

This narrative mini-review was conducted in accordance with the SANRA protocol [27]. The primary aim of this work was to provide a concept-driven narrative synthesis of the available literature. Given the heterogeneity of the available evidence (preclinical studies, early-phase clinical trials, and mechanistic investigations), a fully systematic review approach was not considered appropriate. Therefore, the present work should be regarded as a narrative review supported by a structured literature search, rather than a systematic review.

Search strategy

A literature search was performed in Scopus, PubMed, and Google Scholar, covering the period from 1990 to 2025. A total of 82 peer-reviewed English-language articles (original research and reviews) were selected as most relevant to the scope of this narrative review. The search terms included "neuroplasticity," "glutamate and depression", "Neuroplasticity and depression", "AMPAkines", "AMPA potentiators in depression", "AMPA ligands", "AMPA BDNF", "AMPA and neuroplasticity", "Farampator", "Farampator depression", "AMPAkines depression", "AMPAkines depression human study". Additionally, ClinicalTrials.gov was searched for registered AMPA receptor modulator studies in depression.

Literature selection and evaluation

Inclusion criteria

The following inclusion criteria were applied to select the most relevant studies for the purpose of this narrative review: (1) experimental studies in animals and humans investigating AMPA receptor modulators in the context of depression and/or neuroplasticity, (2) reports presenting neuroplastic or molecular outcomes relevant to AMPA receptor modulators and depression, (3) clinical trials.

Exclusion criteria

(1) studies with low methodological quality, (2) non-original publications such as opinion pieces, letters to the editor, or duplicates of publications, (3) studies focusing exclusively on ADHD, cognition, schizophrenia, or epilepsy without a relevant indication for depression, (4) unavailability of full text.

Two independent reviewers screened titles and abstracts, assessed full texts for eligibility, and removed duplicates. No content editing of source texts was performed. Given the narrative nature of this review, formal risk-of-bias tools were not applied. However, studies were evaluated based on their relevance to the review objectives, Study design (with higher weight given to clinical and translational studies), and methodological clarity, the previously used numerical scoring system (0–2) was abandoned due to its limited interpretability and replaced with a descriptive appraisal approach. Priority was given to human studies and

well-characterized experimental models, while preclinical findings were interpreted with explicit consideration of their translational limitations.

Data extraction

Data were extracted into the following fields: study type: (preclinical or clinical), experimental model (human or animal), intervention or compound investigated, assessed endpoints including molecular (e.g., BDNF levels), behavioral (Forced swim test, e.g.,), and electrophysiological measures (e.g., LTP induction), as well as the key findings and conclusions reported by the authors.

The collected data were categorized by endpoints (e.g., changes in BDNF, antidepressant effects, animal models, and clinical trial outcomes) and analyzed as described above.

Diagnostic definitions of depression varied across the reviewed studies. When diagnostic criteria were not explicitly stated, we retained the terminology used in the original publications; studies explicitly referring to major depressive disorder (MDD) were categorized accordingly.

AMPA receptor-related mechanisms in depression: a focus on neuroplasticity

AMPA receptors are receiving increasing attention due to their versatile roles in regulating synaptic strength and adaptive changes in neuronal circuits. These changes involve activity-dependent modifications in the number, function, and biophysical properties of AMPA-type glutamatergic receptors at the postsynaptic membrane, as well as alterations in their subunit composition/structure [28, 29]. Long-term potentiation (LTP), initiated by glutamate binding to AMPA receptors, has been extensively studied in the context of depression [30], with evidence linking its dysregulation to impaired synaptic plasticity observed in MDD -thereby pointing to neuroplasticity enhancers [31], such as AMPAkines, as potential therapeutic agents.

Interestingly, preclinical studies using the chronic mild stress (CMS) animal model of depression demonstrated impaired AMPA receptor trafficking, reduced GluA1 expression, and a disrupted balance between LTP/LTD [32, 33]. Additionally, in the CMS model ketamine has been shown to enhance AMPA receptor function, promote mTOR signaling, increase dendritic spine density, and rescue synaptic markers - findings that support its rapid antidepressant effects via glutamatergic modulation [34]. While these effects are robustly observed in animal models, they require careful translation to clinical settings. Chronic treatment with conventional antidepressants, such as SSRIs, has also been shown to enhance synaptic plasticity in animal models, partly by upregulating BDNF, restoring dendritic spine density, and normalizing stress-induced LTP/LTD imbalance, as highlighted by Duman and colleagues [30]. These pharmacologically induced changes in structural and functional plasticity are thought to contribute to the delayed onset and consolidation of antidepressant efficacy.

While direct molecular studies on synaptic plasticity in depression in humans are limited, neurophysiological data provide key insights. For instance, patients with depression exhibit impaired cortical plasticity as measured by visual evoked potentials (VEPs) [35]. In a landmark study, Normann et al. [35] showed reduced long-term potentiation-like enhancement of VEPs in MDD, suggesting deficient synaptic adaptability. This finding represents one of the few direct human types of evidence of impaired plasticity in depression.

Additionally, patients with MDD often exhibit reduced levels of BDNF, a key mediator of activity-dependent synaptic plasticity and AMPA receptor trafficking [36, 37]. Reduced BDNF levels correlate with symptom severity and may reflect diminished neuroplasticity. Non-invasive stimulation protocols, such as TMS and tDCS, further support altered plastic potential in the depressed brain [38]. Several clinical studies further indicate that successful antidepressant treatment is accompanied by partial normalization of peripheral and central BDNF measures and by improvements in neurophysiological indices of cortical plasticity, as probed with non-invasive brain stimulation or sensory-evoked potential paradigms [39].

This convergence of animal and human data supports the view that impaired neuroplasticity in MDD is not only a pathophysiological correlate but also a modifiable target of pharmacological and neuromodulatory interventions.

More direct in vivo evidence for synaptic pathology in MDD comes from positron emission tomography (PET) studies using ligands for synaptic vesicle glycoprotein 2 A (SV2A), which provide an index of presynaptic terminal density. In a pioneering [^{11}C]UCB-J PET study, patients with unmedicated MDD exhibited significantly lower SV2A binding in several fronto-limbic regions compared with healthy controls, and the degree of synaptic loss correlated with depression severity and large-scale network dysfunction. These findings support the model of stress- and depression-related synaptic pruning in cortico-limbic circuits and provide a mechanistic bridge between post-mortem evidence of reduced synapse number and functional imaging abnormalities in depression [40]. In addition to synaptic density imaging, several PET studies have directly targeted glutamate receptors *in vivo*. Using the metabotropic glutamate receptor 5 (mGluR5) radioligand [^{11}C]ABP688, Deschwanden et al. [41] reported reduced mGluR5 binding

in prefrontal and striatal regions in MDD patients, which was paralleled by lower mGluR5 protein expression in post-mortem prefrontal cortex. A subsequent multimodal study combining mGluR5 PET with ^{1}H-MRS demonstrated an inverse relationship between mGluR5 availability in the anterior cingulate and glutamate/Glx concentrations in individuals with MDD, further linking receptor-level abnormalities to neurometabolite changes. Together, these findings indicate that both synaptic density and postsynaptic glutamate receptor function are altered in MDD and may represent relevant targets for glutamatergic antidepressant strategies, including AMPA receptor modulators [41, 42].

Taken together, these observations suggest that restoring AMPA-dependent synaptic plasticity and its molecular mediators, including BDNF-regulated signaling cascades, may represent a common final pathway through which both conventional antidepressants and rapid-acting agents such as ketamine exert their therapeutic effects.

AMPAkines and their pharmacological potential

AMPAkines are allosteric modulators of the AMPA-type glutamate receptor [13]. Thus, they bind to the receptor's allosteric site and modulate the kinetics of channel deactivation and desensitization. This results in prolonged channel open time and enhanced excitatory synaptic transmission [43]. In contrast to agonists, they do not activate the receptor; rather, they potentiate the response to endogenous glutamate. Their activity can increase synaptic efficiency, promote neuroplasticity, upregulate brain-derived neurotrophic factor (BDNF), and stabilize synaptic connections [44].

Research on AMPAkines dates back to the early 1990s, when AMPA receptor subunits were first identified. At that time, it was acknowledged that aniracetam, a prototypical positive allosteric modulator of AMPA receptors, potentiates AMPA receptor-mediated currents. Subsequent work identified additional modulators, including diazoxide and cyclothiazide. It is noteworthy that none of these compounds were originally discovered for their action on the AMPA receptor [45]. The synthesis of later AMPAkines leveraged a shared pharmacophore, defined as a specific functional or structural feature of a compound that characteristically interacts with the biological target [46], in the present work, the AMPA receptor. Their pharmacophore is composed mainly of a 1,4-benzamide or pyridine group [47], although recent advances have identified molecules with novel pharmacophores, such as bispidine, which exhibit high potency at glutamatergic synapses [48].

AMPAkines are commonly classified as high- or low-impact agents based on differences in receptor binding sites, channel kinetics, modulation of glutamate binding, and pharmacological safety profiles [15]. Low-impact AMPAkines have minimal effect on receptor desensitization, but their main action is to accelerate AMPA channel opening. Significantly, they do not modify agonist binding affinity [49]. In contrast, high-impact AMPAkines act by binding to the tetrameric receptor complex and stabilizing its agonist binding [49]. Additionally, they increase channel open time and ion flow into the cell, counteracting receptor desensitization [49]. Notably, studies with CX-729 (a high-impact AMPAkine) suggest activity that can persist with minimal agonist exposure, raising concerns about the risk of excitotoxicity [15].

Critically, evidence that AMPAkines can modulate AMPA receptor kinetics, promote LTP, and upregulate BDNF signaling clearly indicates that this novel group of agents can enhance neuroplasticity [44]. These findings are particularly relevant in the context of mood disorders. Indeed, there is substantial evidence linking synaptic plasticity with depression [49]. These findings provide a broader picture of the mechanism underlying the development of depression, and are coherent with the contemporary view of depression as a disorder of neuroplasticity dysfunction [50]. Additionally, this perspective supports the adoption of more modern treatment strategies.

Preclinical evidence on antidepressant-like effects of AMPAkines

Understanding the mechanisms of action and structures of AMPA receptors, in particular, modulation of neuroplasticity and trophic activity in the brain, has enabled the development of new molecules that modulate them. For example, Jin et al. reported that CX614, a high-impact benzamide-type AMPAkin decelerates AMPA receptor deactivation and prolongs channel opening in the presence of glutamate [51]. Notably, cyclothiazide, known for its strong inhibitory effect on AMPA receptor desensitization, acts preferentially at "flip" isoforms, whereas CX614 modulates both "flip" and "flop" isoforms (with a preference for "flop". Additionally, CX614 also reduced desensitization [51]. Using rat hippocampal slices, Lauterborn et al. [52] found that long-term treatment (12–24 h) with CX614 reduced GluR1-mRNA and protein levels in hippocampal cultures-consistent with homeostatic responses to sustained neuronal activation (also evoked by cholinergic agonist carbachol). They further showed that BDNF expression is optimally upregulated by shorter exposures and lower doses; reducing

exposure to ≤3 h increased BDNF without altering AMPA receptor expression.

Additionally, an enhanced TrkB-Fc signaling at dendritic tips was observed, indicating increased tropic activity [52]. However, this compound has not been directly studied in behavioral tests for its antidepressant effects. Increasing BDNF via AMPAkine was also demonstrated with another benzamide-type AMPAkine CX546 in mouse entorhinal cortex/hippocampus slices. Prolonged infusion of the compound resulted in increased mRNA for BDNF and sustained BDNF elevation for the next 48 h. The same group reported that intraperitoneal injection of CX546 increased BDNF mRNA levels in aged rats and middle-aged mice [53]. These findings suggest that sustained AMPA receptor activation may lead to compensatory downregulation of receptor expression, while brief, low-dose exposure to AMPAkines such as CX614 enhances BDNF expression without affecting AMPA receptor expression levels, thereby supporting a more favorable neuroplastic environment.

Further evidence supporting the therapeutic relevance of AMPA receptor activation comes from (2R,6R)-hydroxynorketamine (HNK), a pharmacologically distinct and major active metabolite of ketamine. Unlike ketamine, HNK does not primarily act through NMDA receptor inhibition. Instead, studies by Zanos et al. [54] demonstrated that HNK produces rapid and sustained antidepressant-like effects in animal models by enhancing AMPA receptor activity and increasing BDNF expression. Importantly, these effects are reduced by selective AMPA receptor antagonists, highlighting the critical role of AMPA receptor-mediated signaling in HNK-induced antidepressant effects [54]. Complementing the above-mentioned results, behavioral assessments were used to evaluate the antidepressant-like activity of AMPAkines. In the forced swim test (FST), CX614 reduced immobility time, consistent with an antidepressant-like profile [55]. In an ethanol-induced depression model, Yao et al. [55] reported that CX516 (Ampalex), a first-generation low-impact AMPAkine characterized by relatively low potency and a short half-life, decreased hippocampal IL-6 and IL-1β levels and modulated apoptotic markers (BAX and BCL-2), suggesting anti-inflammatory and neuroprotective effects. CX516 also attenuated the suppression of the ERK1/2-BDNF-TrkB pathway in the hippocampus, a signaling axis closely linked to synaptic plasticity and LTP [55]. In the submissive behavior model, Knapp et al. [56] found that administration of CX516, CX691, and CX731 increased time at the feeder compared with placebo and with piracetam or aniracetam, which the authors interpreted as reduced submissive behavior and improved social functioning [56]. Notably, CX516 reduced submissive behavior after 2 weeks, whereas piracetam and aniracetam were effective only after 4 and 2 weeks, respectively. CX731 and CX691 demonstrated significant effects after one week [56]. Although CX516 did not advance to clinical trials due to its low potency, short half-life, and extensive metabolism, recent studies have reported promising findings in intellectual disability and ADHD, and have suggested potential utility in neurodegenerative disorders [57]. CX691 (also known as ORG-2448 or Farmapator) is a low-impact AMPAkine that has been investigated as a potential antidepressant. The drug exhibited both anti-anxiety and antidepressant-like activity in a submissive behavior model with greater efficiency than that of aniracetam or piracetam [56]. Subsequently, it has been studied in animal models of Alzheimer's disease, where it has shown pro-cognitive effects, including increased BDNF levels in the hippocampus and improved spatial learning and memory. Administration of CX-691 increased extracellular acetylcholine in the dorsal hippocampus and both dopamine and acetylcholine in the medial prefrontal cortex [58]. These findings are consistent with those reported by Radin et al. [59] who found that CX691 upregulated BDNF and NGF mRNA (Nerve Growth Factor) in the dentate gyrus, amygdala, and piriform cortex [59]. Similarly, CX-717 was also studied as a potential antidepressant. However, despite the positive effects observed in animal studies, it appears to be more potent as a cognitive enhancer. Gordlilo-Salas [60] reported that CX-717 significantly reduced immobility in FST [60]. These findings support the compound's antidepressant activity. Notably, the effect persisted for up to 7 days after a single injection, but was not long-lasting. Although CX-717 did not affect monoamine levels (e.g., dopamine, serotonin, noradrenaline), it increased BDNF in the medial prefrontal cortex (mPFC) [61]. Unfortunately, the compound showed only short-lasting antidepressant-like effects and is being pursued primarily for ADHD in clinical studies. The transient efficiency is likely due to its narrow therapeutic window. It can be hypothesized that insufficient receptor engagement results in weak or absent behavioral effects. In contrast, higher levels of potentiation may trigger receptor desensitization or homeostatic compensatory mechanisms, limiting sustained efficacy [29, 61]. This pharmacodynamic pattern led to the redirection of CX-717's development from antidepressant use to cognitive enhancement, in which brief AMPA receptor potentiation is sufficient and better tolerated [61].

Beyond CX-717, antidepressant-like properties have also been investigated for LY392098 - biarylpropylsulfonamide-derived ampakine. In an animal model of unpredictable chronic mild stress (UCMS), LY392098 reduced weight loss and immobility time in the tail suspension test (TST) [62]. These data are consistent with findings by Li et al., who also demonstrated that LY392098 reduced immobility in the FST and TST in a dose-dependent manner [63]. ORG-26,576 (low-impact ampakine) is an example of a compound

Table 1 Preclinical and clinical evidence for the antidepressant-like effects of AMPA receptor positive allosteric modulators (AMPAkines)

Compound (AMPAkine)	AMPAkine class and chemical name	Model	Endpoints	Findings/ conclusions	References
CX614	high-impact AMPAkine. IUPAC name: 4,7,11-trioxa-16-azatetracyclo[8.7.0.03,8.012,16]heptadeca-1,3(8),9-trien-17-one)	in vitro rat hippocampal and entorhinal cortical slice cultures	BDNF mRNA and protein expression; GluR1 expression	short exposure: ↑ BDNF expression; prolonged exposure: ↓ GluR1 expression	[53, 73]
CX546	low-impact AMPAkine, IUPAC name: 2,3-dihydro-1,4-benzodioxin-6-yl(piperidin-1-yl)methanone	in vitro and ex vivo hippocampal and cortical neuronal preparations	neurotrophin gene/protein expression (BDNF, NGF); activity-dependent gene expression	↑ BDNF and NGF expression; ↑ activity-dependent gene expression	[53, 73]
CX516 (anaplex)	low-impact AMPAkine, IUPAC name: piperidin-1-yl(quinoxalin-6-yl)methanone	in vivo rodent submissive behavior model	behavioral assessment of depressive-like behavior	↓ submissive behavior	[56, 73]
CX691 (farampator)	low-impact AMPAkine, IUPAC name: 2,1,3-benzoxadiazol-5-yl(piperidin-1-yl)methanone	in vivo rodent cognitive impairment model	learning and memory performance	↑ learning and memory performance	[58, 73]
LY392098	low impact AMPAkine, IUPAC name: N-[2-[4-(2-fluorophenyl)phenyl]propyl]propane-2-sulfonamide	in vivo rodent chronic mild stress (CMS) model	anhedonia-like behavior; stress-induced behavioral deficits	↓ anhedonia-like behavior; reversal of stress-induced behavioral deficits	[62, 73]
CX717	low-impact AMPAkine, IUPAC name: 2,1,3-benzoxadiazol-5-yl(morpholin-4-yl)methanone	in vivo rodent depression model	depressive-like behavior; glutamatergic signaling	↓ depressive-like behavior; ↑ AMPA receptor-mediated glutamatergic signaling	[60, 73]
TAK-653 (osavampator)	low-impact AMPAkine, IUPAC name 9-(4-cyclohexyloxyphenyl)-7-methyl-3,4-dihydropyrazino[2,1-c][1,2,4]thiadiazine 2,2-dioxide	in vivo rodent chronic stress model	anhedonia-like behavior; motivation; social interaction; BDNF and IL-6 levels	↑ motivation and social interaction; ↓ anhedonia-like behavior; ↑ BDNF; ↓ IL-6	[67, 68, 73]

Table 1 (continued)

Compound (AMPAkine)	AMPAkine class and chemical name	Model	Endpoints	Findings/ conclusions	References
ORG-26,576	low impact AMPAkine, IUPAC name: (7 S)-9-oxa-3,11-diazatricyclo[8.4.0.03,7]tetradeca-1(10),11,13-trien-2-one	in vivo adult rodent neurogenesis model	cell proliferation (BrdU); neuronal survival and differentiation	↑ progenitor cell proliferation; ↑ survival of newly generated neurons; ↑ neuronal differentiation	[64, 73]
		randomized double-blind placebo-controlled clinical trial in patients with major depressive disorder	MADRS scores; executive function; processing speed; safety/ tolerability	improvement in depressive symptoms; ↑ executive function and processing speed; well tolerated	[69, 70, 73]

Abbreviations: AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAkine – AMPA receptor positive allosteric modulator; BDNF – brain-derived neurotrophic factor; BrdU – 5-bromo-2′-deoxyuridine; CMS – chronic mild stress; GluR1 – glutamate receptor 1; IL-6 – interleukin-6; MADRS – Montgomery–Åsberg Depression Rating Scale; NGF – nerve growth factor; ↑ increase/increased; ↓ decrease/decreased

that has been qualified for clinical trials. In animal models, it upregulated hippocampal neurogenesis and prelimbic cortical cell proliferation. Specifically, chronic administration of ORG-26,576 increased proliferation in the rat dentate gyrus (40%) and prelimbic cortex (35%). Newly generated dentate gyrus neurons exhibited a high survival rate (approximately 30%) [64]. Further studies demonstrated that subchronic administration of ORG-2657 improved spatial memory acquisition and retrieval in the Morris water maze, without confounding effects [65]. Under swim-stress conditions, ORG-2657 increased total BDNF mRNA in rats' hippocampus [66]. Belonging to the low-impact AMPAkines class, TAK-653 (known as osavampator), which possesses no agonistic activity, activated the mTOR pathway and increased BDNF levels in primary rat cortical cultures -but only in the presence of agonist. Using a resident-intruder submissive behavior model (RSBM), TAK-653 was found to be effective in both the presence and absence of an agonist. Unlike ketamine, it did not induce hyperactivity, suggesting a more favorable safety profile [67]. A recent study confirmed antidepressant-like activity of TAK-653 in monkey depression models. Animals were subjected to chronic stress for 12 weeks, leading to reduced food motivation, diminished activity, a tendency to remain at lower levels of the enclosure, and increased huddling. Hematological assessments showed elevated cortisol levels, as well as IL-6 and IL-8, compared with baseline. Treatment with TAK-653 improved food motivation and movement and reduced huddling behavior. Repeated plasma tests showed decreased interleukin concentrations and increased BDNF levels [68]. Taken together, these findings are consistent with the compound's antidepressant properties.

Antidepressant activity of AMPAkines - insights from early clinical trials

Although numerous AMPAkine compounds have been synthesized and extensively evaluated preclinically, only a few have progressed to human studies for depression.

As noted above, ORG-26,576 was studied in exploratory, randomized, double-blind, placebo-controlled trials evaluating its pharmacokinetics, pharmacodynamics, safety, and tolerability. In these studies, a dose of 450 mg BID was selected based on tolerability. Participants receiving ORG-2657 at this dose exhibited improvement on the Montgomery-Asberg Depression Rating Scale (MADRS). Administration of 400 mg BID was associated with improved executive functioning and processing speed on cognitive tests. Additionally, treatment was associated with increased growth hormone and reduced cortisol levels. Early encephalography (EEG) measures in the first week were reported as predictors of endpoint system change. Overall, the drug was well tolerated and considered a potential antidepressant agent for future proof-of-concept study trials [69]. In a subsequent bridging study conducted by the same team, the maximum tolerated dose (MTD) was estimated at 450 BID in adults with major depressive disorder (MDD) during a 28-day trial ($n = 54$) [70]. According to available sources, the clinical development of ORG-26,576 as an antidepressant was discontinued after its phase II trial. TAK-653 (Osavampator) in a randomised, double-blind, placebo-controlled, three-way crossover study in healthy volunteers ($n = 24$) exhibited a psychostimulant-like pharmacodynamic effect. TAK-653improved visual and cognitive parameters measured using NeuroCard without affecting subjective psychoactive sensations or balance [71]. The further parallel-arm phase I study was a drug-drug interaction study. It was demonstrated that TAK-653 does not induce cytochrome CYP3A and does not affect the pharmacokinetics of midazolam or ethinyl estradiol-levonorgestrel, indicating its compatibility with other drugs metabolized by this cytochrome [72]. Clinical trials are currently underway to evaluate the efficacy and safety of TAK-653 as an adjunctive treatment for depression (ClinicalTrials.gov).

Preclinical and clinical evidence for the effects of selected AMPAkines is summarized in Table 1.

Table 1. Preclinical and clinical evaluation of selected AMPAkines in depression: models, molecular targets (BDNF, IL-6), and behavioral outcomes.

Barriers to clinical translation: from preclinical promise to therapeutic reality

Although AMPAkines have a faster onset than fluoxetine (animals treated with CX516 showed improvement in submissive behavior after one week, compared with two weeks with fluoxetine) [57] and may be used to accelerate treatment initiation in patients with severe depression, their bioavailability and short half-life remain significant pharmacokinetic drawbacks [58]. Importantly, AMPAkines can synergize with SSRIs, which may translate into faster treatment induction (and improved neuroplasticity and cognitive function), thereby motivating continued development of AMPA-receptor ligands [74].

Despite the promising outcomes of AMPAkines in preclinical studies, only a few have progressed to clinical trials. Key reasons for high failure rates include safety concerns. Namely, several AMPAkines - particularly high-impact agents - have shown epileptogenic potential, shifting development toward lower-impact compounds with more favorable profiles [15]. Additionally, as previously described in

the study of ORG26576 by Nations et al., in healthy volunteers, the maximum tolerated dose was lower than in patients with depression, suggesting a narrower therapeutic window and complicating dose selection for subsequent depression trials [69, 70].

Further, although animal research is a critical component of drug discovery, animal models differ meaningfully from human pathophysiology; for AMPAkines, promising preclinical signals have not consistently translated into clinical outcomes. An important aspect is interspecies differences. N-glycosylation of AMPA receptor subunits differs between rodents and humans [75], which may influence receptor function and activity [75, 76]. In addition, rodent cortical slice studies suggest faster glutamate turnover than in human cortical tissue, further limiting the direct extrapolation of preclinical findings to humans [77]. While animal models typically approximate depression by inducing chronic stress-related behavioral phenotypes (such as anhedonia and decreased activity), clinical depression is a heterogeneous, multidimensional syndrome diagnosed using symptom-based criteria, and no single model can capture its full complexity [78, 79]. An additional factor is the variability of human populations, whereas laboratory rodents are relatively homogenous [80]. Commonly used animal models remain valuable screening tools; however, they often assess the reversal of stress-induced behaviors rather than capturing the full clinical syndrome of human depression [81].

Looking ahead, research on AMPA-receptor modulators in depression should prioritize low-impact AMPAkines. Notably, several agents that showed insufficient efficacy in depression are now being explored for other indications (e.g., schizophrenia, ADHD, Parkinson's disease) as well as for reversing opioid-induced respiratory depression, an increasingly relevant clinical need. Collectively, these efforts underscore the continuing importance of this drug class in clinical pharmacology.

Conclusions

Dysfunction of the glutamatergic system has been identified as a significant factor in depression, particularly due to its association with neuroplasticity [82]. Both NMDA and AMPA receptors are key mediators of activity-dependent plasticity, and disruptions in these pathways have been linked to impaired synaptic strength and neuroplasticity observed in depression.

In recent years, numerous efforts have been undertaken to develop novel drugs targeting the glutamatergic system. Ketamine, a rapid-acting NMDA receptor antagonist, has yielded encouraging effects, prompting scientific interest in drugs that act on glutamatergic receptors. In this context, AMPA receptor potentiators (AMPAkines) – particularly those acting on GluA1/GluA2-containing receptors, which are critical determinants of synaptic strength and plasticity – have emerged as promising candidates. They are characterized by a rapid onset of action, which may be helpful as an augmentation and for treatment-resistant depression. Unfortunately, despite their promising pharmacology, no AMPAkine with a clinically viable pharmacokinetic profile and adequate bioavailability has yet been found. High-impact AMPAkines have been limited by seizure liability, which shifted development toward low-impact compounds. However, despite promising preclinical results, the development of low-impact AMPAkines has been constrained by limitations in bioavailability and duration of action. Although these compounds were designed to minimize the risk of seizures observed with high-impact AMPAkines, suboptimal pharmacokinetics – characterized by low bioavailability and short duration of action – have impeded their progression to larger, later-stage clinical trials.

To date, none of the synthesized and investigated AMPAkines has demonstrated clear and clinically meaningful efficacy in the treatment of depression, despite extensive preclinical support. This highlights a critical translational gap that remains unsolved.

Thus, future research directions for AMPAkines, should prioritize low-impact AMPAkines with greater selectivity and bioavailability, improved brain penetration, and robust safety profiles. While AMPA receptor modulation remains a biologically compelling strategy, future progress will depend on improved pharmacokinetic profiles, better target engagement, and the development of translational models that more accurately reflect human depressive pathology.

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Declarations

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