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Commentary

A role for AMPA receptors in mood disorders

Andrew Alt, Eric S. Nisenbaum, David Bleakman, Jeffrey M. Witkin *

Neuroscience Discovery Research, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

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Abbreviations:
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
cAMP, adenosine 3′,5′-cyclic monophosphate
CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione
CX516, piperidine, 1-(6-quinoxalinylcarbonyl)-(9CI), Ampalex, BDP 12
CX691, piperidine, 1-(2,1,3-benzoxadiazol-5-ylcarbonyl)-(9CI), Farampator, Org 24448
DARPP-32, dopamine- and cAMP-regulated phosphoprotein of M_r 32,000
DNQX, 6,7-dinitroquinoxaline-2,3-dione
GCPR, G-protein-coupled receptor
GYKI 53655, *7H*-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carboxamide, 5-(4-aminophenyl)-8,9-dihydro-*N*,8-dimethyl-monohydrochloride-(9CI)

ABSTRACT

Major antidepressant agents increase synaptic levels of monoamines. Although the monoamine hypothesis of depression remains a cornerstone of our understanding of the pathophysiology of depression, emerging data has suggested that the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subtype of glutamate receptor may also play a pivotal role in depression. Positive allosteric modulators of AMPA receptors increase brain levels of brain-derived neurotrophic factor (BDNF) that impacts the viability and generation of neurons in key brain structures. AMPA receptor potentiators are active in rodent models predictive of antidepressant efficacy. The mechanisms by which AMPA receptor potentiators produce these biological effects, however, are uncertain. Current evidence points to an antidepressant mechanism that is independent of monoaminergic facilitation that is driven by neurogenesis, a process facilitated by increased BDNF expression. However, alternative hypotheses need to be considered given uncertainties in the relationship between BDNF increases and the effects of conventional antidepressant medications. Electrophysiological and protein conformational data indicate that structural variants of AMPA receptor potentiators can differentially modulate AMPA receptor-mediated currents, although the manner in which this impacts antidepressant efficacy is yet to be understood. Conventional antidepressants such as fluoxetine positively modulate AMPA receptors. This potentiation is engendered by specific phosphorylation pathways activated through the dopamine- and cAMP-regulated phosphoprotein of M_r 32,000 (DARPP-32). Other novel compounds with antidepressant-like effects in rodents may also produce their in vivo effects through potentiation of AMPA receptors. Thus, AMPA receptor potentiation might be a general mechanism through which the clinical outcome of antidepressant efficacy is achieved.

* *Corresponding author at:* Psychiatric Discovery Group, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN 46285-0501, USA. Tel.: +1 317 277 4470; fax: +1 317 276 7600.
E-mail address: jwitkin@lilly.com (J.M. Witkin).

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LY392098, *N*-2-(4-(3-thienyl)phenyl)propyl 2-propanesulfonamide
LY404187, *N*-2-(4-(4-cyanophenyl)phenyl)propyl 2-propanesulfonamide
LY451646, *N*-[2-(4′-cyano[1,1′-biphenyl]-4-yl)propyl]-(9CI)
LY503430, 4′-[(1R)-1-fluoro-1-methyl-2-[[(1-methylethyl)sulfonyl]amino]ethyl]-*N*-methyl-(9CI)
MGS0039, 2-amino-3-[(3,4-dichlorophenyl)methoxy]-6-fluoro-, (1R,2R,3R,5R,6R)-(9CI)
NMDA, *N*-methyl-D-aspartate

1. Overview

The present commentary discusses the possibility that AMPA receptor activation might produce antidepressant effects. A corollary is that AMPA receptors play a role in the control of mood. The data suggest that positive allosteric modulators of AMPA receptors could function as a novel class of antidepressant agents. However, this idea is contradictory to a number of ideas: (i) the prevailing hypothesis for depression is the biogenic amine hypothesis, which suggests that depressed mood results from a decrease in the synaptic availability of monoamine neurotransmitters, which are increased with antidepressant treatments (cf., [1,2]); (ii) glutamate levels have been reported to be increased in patients with major depression [3]; (iii) NMDA receptor blockade has been associated with antidepressant-like effects [4]. One of the keys to the AMPA receptor potentiation hypothesis originally forwarded by Skolnick (cf., [5,6]) rested on the observations that AMPA receptor activation can increase BDNF levels in neuronal culture (e.g., [7,8]) and in vivo [9]. Increases in BDNF levels have been associated with the activity of a broad array of antidepressant agents and with neurogenesis, which may be a critical component of antidepressant efficacy (cf., [10–12]). It is important to note that inconsistencies exist in the linkage between BDNF and antidepressant activity (cf., [13–15]). Nonetheless, AMPA receptor potentiators have been shown to increase BDNF levels in vitro and in vivo and to promote cell proliferation within the central nervous system. The neurotrophic effects of AMPA receptor potentiators have been extended experimentally to models of Parkinson's disease where beneficial effects of AMPA receptor potentiators have been demonstrated (cf., [16]). Further, data will be discussed that raise the possibility that altering AMPA receptor function could be a part of the mechanism of action conventional, biogenic amine-based antidepressants like fluoxetine (Prozac). Given the arguments that both direct activation of AMPA receptors by potentiators and indirect positive modulation of AMPA receptors by biogenic amine receptors may engender antidepressant effects, these processes might converge upon a common final pathway and facilitate one another to provide enhanced antidepressant efficacy and/or a decrease in the lag time required to reach full therapeutic benefit (for more detailed reviews of literature, see [4–6,16–18]).

2. Medicinal therapies for mood disorders

Mood disorders constitute one of the world's major psychiatric maladies. Mood disorders are diagnostically categorized by depressed mood, greatly reduced interest and pleasure in life, changes in weight and sleep, a diminished ability to think and make decisions, and suicidal ideation. Formal classification as a mood disorder (DSM-IV of the American Psychiatric Association) requires that at least some of these symptoms are not transient or due to external factors (e.g., bereavement, medical conditions, or drug use or withdrawal). A host of disorders are subsumed under the category of mood disorders such as bipolar disorders, major depression, masked depression, dysthymic disorder, psychotic depression, and cyclothymic disorder (cf., [19]).

Modern medicinal treatments for depression have been in use only since the introduction of the monoamine oxidase inhibitors and the tricyclic compounds into clinical practice in the 1950s. However, in addition to changing remarkably the management of these disorders, a great deal of our understanding of the neurobiology of depression derives from analysis of the biochemical mechanism of action of drugs that are effective in the treatment of depression (cf., [19]). The observation that a structurally and pharmacologically diverse group of antidepressant molecules all increase the concentration of biogenic amines (norepinephrine, serotonin, and/or dopamine) is one of the foundations of the biogenic amine theory of depression (see [2]). It has been argued that by increasing synaptic availability of monoamines, antidepressants restore the neurochemical milieu of the brain with an environment more conducive to normal affective tone and adaptability (cf., [11,19]). Although marked improvements in the safety and side effect profile of antidepressants have been engineered into modern medicines, there are still a number of critical dimensions along which improvements are needed. One important dimension

is efficacy. Older and yet more toxic or controversial antidepressant treatments such as the tricyclic molecules, monoamine oxidase inhibitors or electroconvulsive therapy have generally shown better efficacy over the safer and more widely prescribed selective monoamine uptake inhibitors (cf., [19]). However, even with the former agents, some patients continue to be treatment-resistant. In addition, although antidepressant effects of compounds can be seen rather soon after dosing, the full efficacy of these compounds is generally observed only after several weeks of treatment [20], leaving the risk of suicide incompletely managed. Finally, unwanted side effects continue to be a problem.

3. Molecular biology of AMPA receptors

The family of ionotropic glutamate receptors can be segregated into three distinct subtypes on the basis of molecular and pharmacological properties: (1) α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), (2) *N*-methyl-D-aspartic acid (NMDA), and (3) kainic acid (KA) receptors [21–23]. AMPA receptors are expressed ubiquitously throughout the central nervous system and mediate the majority of rapid excitatory neurotransmission. In addition to their role in postsynaptic depolarization and neuronal firing, AMPA receptors are intimately involved in a variety of other cellular responses, including the recruitment of voltage-gated ion channel and NMDA receptor activity and the development and expression of long-term synaptic plasticity [24], as well as the induction of neurotrophic factors such as brain-derived neurotrophic factor (BDNF; see Section 5).

The AMPA receptor family includes four different genes, termed $GLU_{A1–4}$ (alternatively, GluR1-4 or GluRA-D) that each encode subunits containing a large extracellular NH_2-terminus domain and four hydrophobic domains labeled M1–M4 [23] (Fig. 1A). Evidence indicates that functional AMPA receptors are tetramers that can be generated by the assembly of one or more subunits, yielding either homomeric or heteromeric configurations, respectively [22]. Further diversity among AMPA receptors can arise from post-transcriptional modifications of $GLU_{A1–4}$ subunits at two different positions within the AMPA receptor genes. A glutamine residue (Q) in the pore region (TM2) of GLU_{A2} is edited to an arginine (R) in adult tissue and confers a significant reduction in calcium permeability, decreased single channel conductance and rectification of the AMPA receptor current–voltage relationship [25,26]. A second site in the S2 extracellular domain between TM2 and TM3 is edited from an R to a glycine (G) in GLU_{A2}, GLU_{A3}, and GLU_{A4} and this alteration can alter the time course of recovery from desensitization [27].

Additional complexity among AMPA receptors results from alternative splicing in the extracellular S2 region in $GLU_{A1–4}$. This region can contain one of two different exons, referred to as flip (i) and flop (o). The flip and flop exons encode a 38 amino acid sequence that differs between the two isoforms by 7–10 residues depending on the subunit. Crystallographic data has revealed that the flip/flop region is located at the ''hinge'' of the clam shell-like ligand-binding core [28,29]. Functionally, flip and flop isoforms of homomeric $GLU_{A2–4}$ receptors display markedly different kinetics of desensitization in the continued presence of glutamate with the flip isoform desensitizing 2–5-fold more slowly than the flop variant for these subunits [30].

On the basis of recent structure–function studies, a model of the mechanisms by which AMPA receptors gate synaptic current has emerged. Evidence indicates that the tetrameric receptor is formed by dimerization of two adjacent subunits that in turn dimerize with two additional subunits [29] (Fig. 1B).

The function of AMPA receptors is also highly regulated by the trafficking of these receptors and the scaffolding proteins to which they are associated. The insertion and removal of AMPA receptors from synapses, which in turn controls excitatory tone and synaptic plasticity, are under complex regulatory control that is only beginning to be mapped (see [31] for a review). These functions can be influenced by the external milieu (e.g., [32]) and are likely also controlled by stress, biological events associated with depression, and antidepressant agents. For example, neuronal activity-regulated pentraxin (NARP) is a secreted neuronal pentraxin implicated in regulating clustering of AMPA receptors that is increased with antidepressant electroconvulsive treatment [33].

Among the many proteins involved in the regulation of AMPA receptor expression, the transmembrane AMPA receptor regulatory proteins (TARPs) are particularly interesting. These include stargazin, γ-3, -4, and -8 (for review see [34]). These proteins display a striking differential expression in the brain. For example, γ-8 appears to be expressed specifically in the hippocampus [35] and therefore may be particularly relevant in the context of depression. Generation of γ-8 knockout mice could provide important clues as to the role of hippocampal AMPA receptors in depression and the actions of antidepressant drugs. In this regard, it is noteworthy that BDNF protein levels are dramatically reduced in the cerebellum of stargazer mice [36,37]. BDNF may play a key role in the actions of antidepressants, as discussed below. It is important to note that in addition to their functional role in AMPA receptor trafficking, TARPs also regulate ion flux through AMPA receptors [38,39]. The role of these regulatory proteins in the action of antidepressant agents, however, is not currently known.

4. Positive allosteric modulators of AMPA receptors

Understanding of the role of AMPA receptors in biochemical and behavioral processes has been facilitated by the discovery of systemically bioavailable agents that allosterically augment AMPA receptor signaling (Fig. 2). The development of positive allosteric modulators of AMPA receptors began with the demonstration [40] that the pyrrolidinone compound, aniracetam, could selectively enhance AMPA receptor-mediated currents in the presence of agonist, but had no effect on its own. Subsequent efforts have identified a variety of modulators from several structural classes, including the benzothiazides (e.g., cyclothiazide), the benzoylpiperidines (e.g., CX516), and the biarylpropylsulfonamides (e.g., LY392098) [17,41].

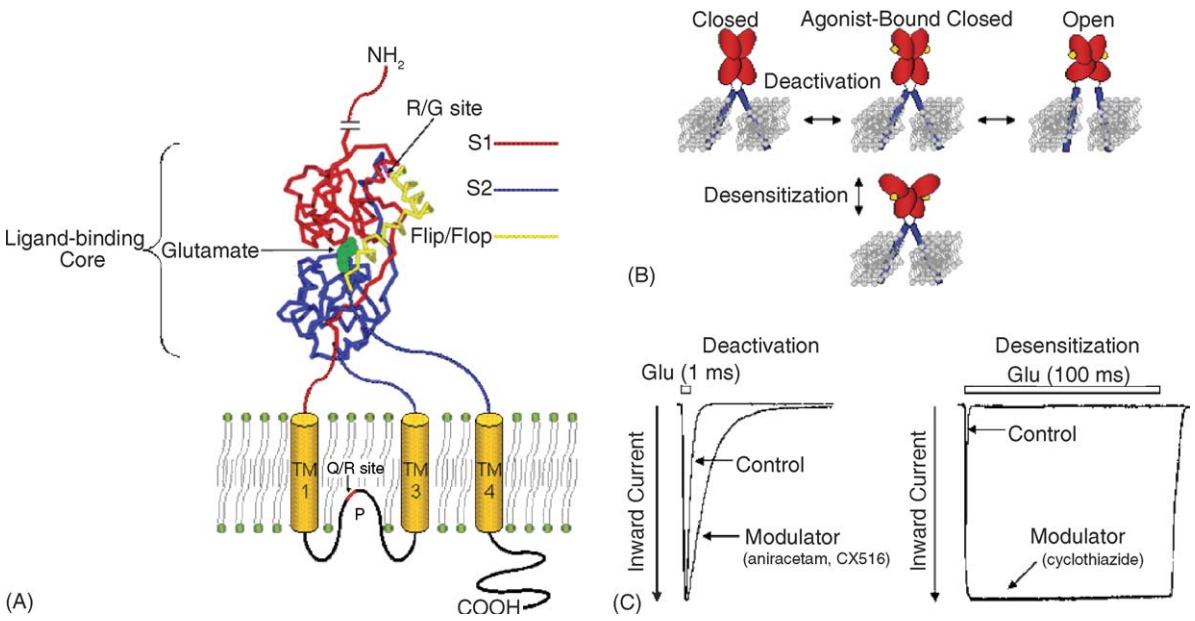

Fig. 1 – Schematic representations of an AMPA receptor subunit (A), the processes of receptor activation and deactivation (B), and the manner in which AMPA receptors modify AMPA receptor signaling (C). (A) Schematic representation of an AMPA receptor subunit. Crystallography studies have shown that glutamate (and other agonists) bind to a ligand-binding core defined by two extracellular domains: one just adjacent to TM1 (termed S1, red) and the second between TM3 and TM4 (termed S2, blue). The flip–flop splice variant region is present within the S2 domain (yellow) and regulates receptor desensitization and sensitivity to allosteric modulators. A post-translational modification from R to G (magenta) can occur at a residue just upstream from the flip–flop sequence. In addition, a Q to R modification (red) can occur in the pore (P) region of GLU_{A2} subunits. The region of the NH_2-terminus, immediately adjacent to M1 (designated S1), and the region between M3 and M4 (designated S2) has been crystallized and shown to form the glutamate ligand-binding core (LBC) having a clam shell-like configuration, similar to that for metabotropic glutamate receptors [28,135]. (B) Schematic representation of the relationship between the different conformation states of AMPA receptors and the biophysical processes of deactivation and desensitization. The diagram depicts the conformational changes in the LBC and the channel gate (for simplicity only two subunits of the tetramer are shown). Upon binding of glutamate (yellow circle), the LBC closes directing a conformational change to the gate, leading to opening of the channel. Upon removal of glutamate from the open state, the channel closes as unbinding occurs (deactivation). With continued presence of glutamate, the dimer between LBCs rearranges and disengages from the gate, permitting closure of the ion channel (desensitization). Electrophysiological evidence indicates that deactivation and desensitization of AMPA receptors occurs on a time scale that permits these processes to govern the size and shape of excitatory postsynaptic currents [30,42]. Modification of the transitions into these states is predicted to facilitate the secondary consequences of AMPA receptor-dependent depolarization, including engagement of voltage-dependent conductances, mobilization of intracellular-signaling cascades and neurotrophin expression, and induction of synaptic plasticity. (C) Using rapid perfusion techniques, the opening of AMPA receptors following application of glutamate can be seen as a fast inward transient current. If glutamate application is brief (e.g., 1 ms), the inward current decays along an exponential time course and reflects unbinding of transmitter or deactivation. If glutamate application is prolonged (e.g., 100 ms), the inward current also decays exponentially, but reflects transition of channels into the desensitized state. Allosteric modulators can affect either deactivation or desensitisation, or both processes, leading to an enhancement of ion flux through the channel.

Allosteric modulators also can be categorized on the basis of their effects on the biophysical processes of deactivation and desensitization (Fig. 1C). For example, aniracetam has been shown to preferentially attenuate deactivation of AMPA receptors, having little effect on receptor desensitization [42]. Conversely, cyclothiazide almost exclusively slows the transition into the desensitized state of the receptor [42]. The functional consequences of compounds that preferentially affect deactivation or desensitization also have been explored. CX516 (which primarily slows deactivation) markedly enhances synaptic responses in hippocampal neurons to single stimuli, whereas cyclothiazide principally increases synaptic inputs in response to high frequency stimulation [43,44]. Compounds that affect both deactivation and desensitization may be predicted to produce the most robust augmentation of synaptic transmission.

An orthogonal classification of allosteric modulators arises from studies showing that compounds can preferentially enhance current flux through flip or flop isoforms of homomeric AMPA receptors. The first description of splice variant-preferring compounds was for cyclothiazide which displays approximately a 50-fold greater potency for enhan-

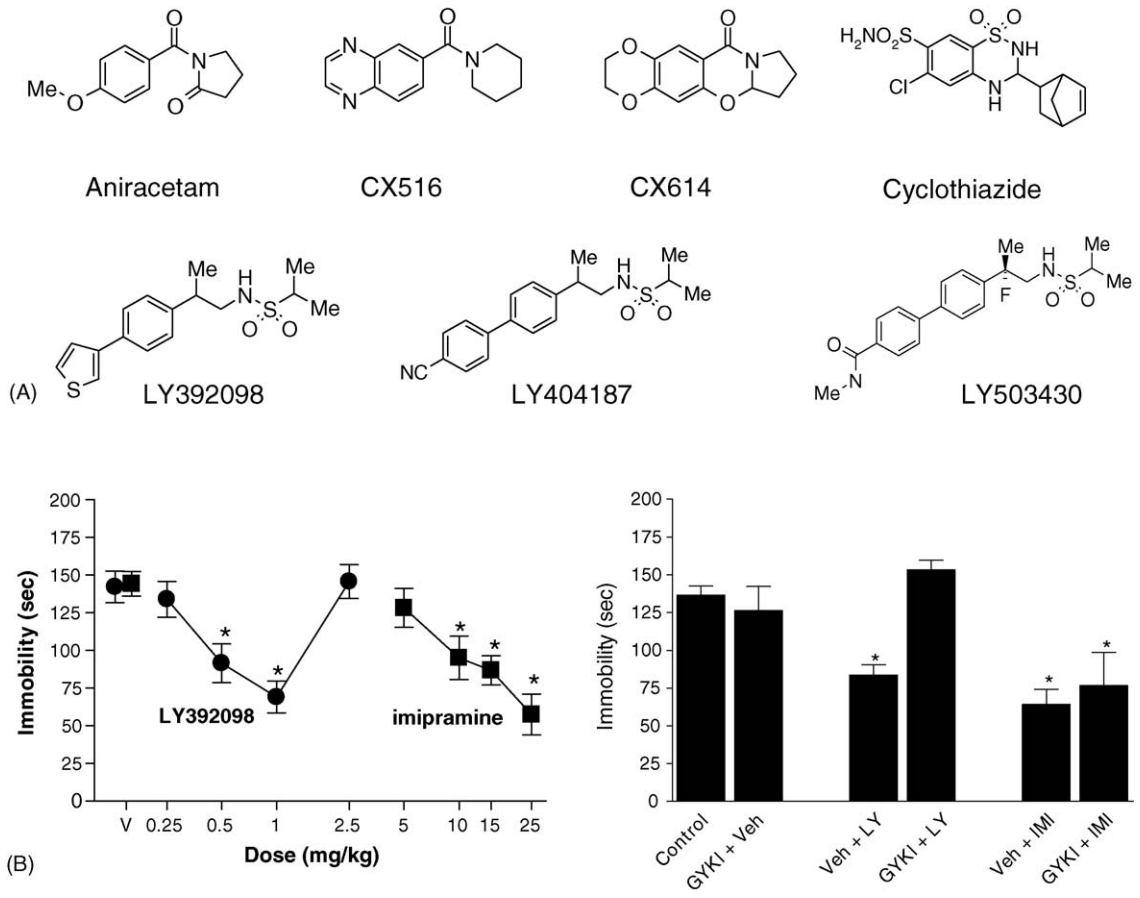

Fig. 2 – (A) Structures of some AMPA receptor potentiators and an illustration of the antidepressant-like effects they can produce. Structures illustrated are the pyrrolidines aniracetam and some cortex pharmaceutical (CX) compounds, the benzothiazide cyclothiazide, and the biarylsulfonamides from Eli Lilly and Company (LY). (B) The potent antidepressant-like effects of LY392098 are shown in comparison with imipramine (data adapted from [104]) (left panel). The right panel illustrates selective blockade of the antidepressant-like effects of LY392098 but not imipramine by the AMPA receptor antagonist GYKI 53655 (data adapted from [117]). * Represents significant differences from the vehicle control group, $p < 0.05$.

cing currents through GLU_{A1} flip receptors compared with GLU_{A1} flop receptors [42,45]. A similar preference for flip splice variants has been reported for LY503430 [46]. In contrast, aniracetam, and the sulfonylamino compound, PEPA, are considerably more potent at flop variants of $GLU_{A1–4}$ homomeric receptors [47,48]. Because flip and flop isoforms are differentially expressed in the CNS [49], compounds with splice variant selectivity may be capable of targeting AMPA receptors expressed in particular brain regions, leading to regional enhancement of glutamatergic synaptic transmission.

The preferential sensitivity of flip and flop receptors to allosteric regulation has focused efforts to elucidate the molecular determinants of these differences in the flip–flop domain. Mutagenic studies have demonstrated that a single residue, serine (S) 750 in GLU_{A1} flip and asparagine (N) 750 in GLU_{A1} flop, governs the greater sensitivity of GLU_{A1} flip to cyclothiazide and aniracetam, respectively [42,47]. This residue also has been shown to contribute to the greater potency of LY404187 for flip splice variants of $GLU_{A1–4}$ receptors (although, unlike for cyclothiazide, it is not the sole determinant) [50]. The critical nature of this residue was further established in crystallography studies of cyclothiazide in the LBC of GLU_{A2} flop containing an N750S mutation. Cyclothiazide was proposed to attenuate desensitization by stabilizing the intradimer interface between two adjacent LBCs, in part through binding to this S residue. In addition, when this GLU_{A2} flop-Ser crystal was superimposed with that of native GLU_{A2} flop containing an Asn at this position, it was observed that tight binding of cyclothiazide would be precluded [29]. Collectively, these results suggest that this single residue is critical for conferring the sensitivity of flip and flop isoforms to allosteric regulation.

5. AMPA receptors regulate growth and neurotrophic factors

It remains unknown what intervening biochemical events bridge the gap between the initial pharmacological response and maximal efficacy of antidepressants. A prevailing hypoth-

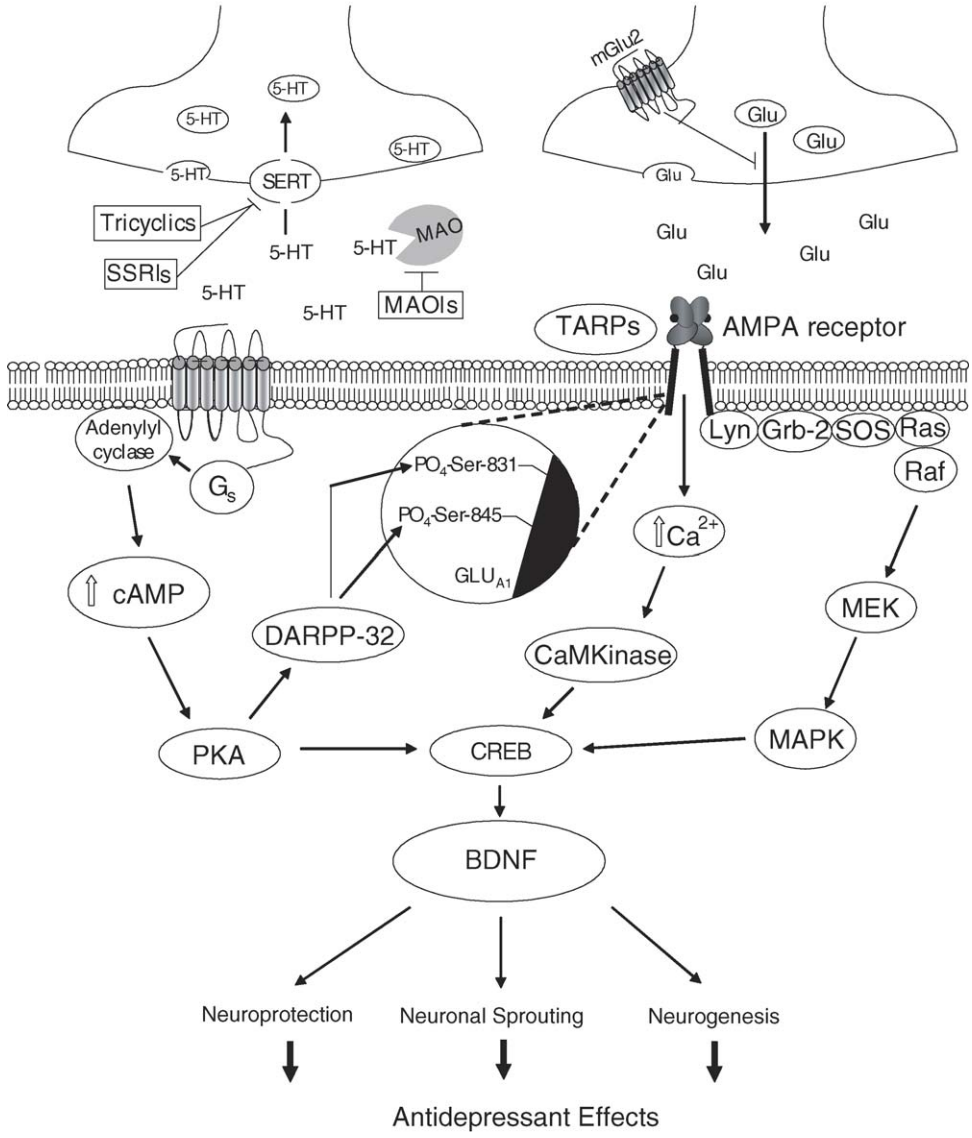

Fig. 3 – A simplified schematic representation of the way in which AMPA receptors may impact depression and the action of antidepressant medications. Traditional antidepressants increase synaptic levels of monoamines such as serotonin or norepinephrine (not shown) either by blocking their enzymatic degradation by monoamine oxidase or by blocking their reuptake through the serotonin transporter or norepinephrine transporter (not shown). This leads to activation of PKA pathways which leads to BDNF induction. Monoamine-increasing antidepressants also may induce BDNF through Ca^{2+}/CaM kinase pathways (e.g., through activation of G_q-coupled receptors; not shown). Blockade of 5-HT uptake by the SSRI antidepressant fluoxetine has been shown to phosphorylate the AMPA receptor subunit GLU_{A1} through the DARPP-32 phosphoprotein pathway. The specific serine phosphorylation of GLU_{A1} in turn amplifies the signaling of AMPA receptors. AMPA receptor activity may result in BDNF induction through both Ca^{2+}-dependent and -independent (MAPK) pathways (see text). Postsynaptic AMPA receptors are activated by glutamate, the release of which is regulated by presynaptic metabotropic glutamate receptors, such as $mGlu_2$, which inhibits glutamate release. The details within these major pathways have not been elaborated in this rendition. Further, other pathways are likely. Activation of PKA for example could induce CREB through MAPK-mediated mechanisms. BDNF: brain-derived neurotrophic factor, CaM Kinase: Ca^{2+}/calmodulin-dependent protein kinase, cAMP: adenosine 3′,5′-cyclic monophosphate, CREB: Ca^{2+}/cAMP response element-binding protein, DARPP-32: dopamine- and cAMP-regulated phosphoprotein of M_r 32,000, Glu: glutamate, Grb-2: growth factor receptor-binding protein 2, G_s: adenylyl cyclase stimulatory G-protein, 5HT: 5-hydroxytryptamine (serotonin), MAO: monoamine oxidase, MAOIs: monoamine oxidase inhibitors, MAPK: mitogen-activated protein kinase, MEK: MAPK kinase, PKA: protein kinase A, SERT: serotonin transporter, SOS: son of sevenless, SSRIs: selective serotonin-uptake inhibitors, TARPs: transmembrane AMPA receptor regulatory proteins, and tricyclics: tricyclic antidepressants.

esis is that increased brain-derived neurotrophic factor (BDNF) expression is a key event [11,16,18] (Fig. 3).

BDNF acts in a host of biological cascades that are initiated through the binding of BDNF to the full-length catalytic TrkB receptor. Cellular survival and differentiation are predominant functions of Trk receptor pathways. These activities are regulated through extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K) and phospholipase Cγ (PLC-γ) pathways (see [51] for a review). BDNF binding induces TrkB dimer formation and autophosphorylation of tyrosine residues in the intracellular domain [52]. In addition, a truncated form of TrkB is also abundant in adult brain [53]. The truncated isoform can modulate the activity of the catalytic form by formation of heterodimers [54] whereby it acts as a negative modulator of BDNF signaling [55].

The TrkB receptor also regulates the activity of ion channels and G-protein-coupled receptors (GCPRs) although little work has yet been done to uncover the extent of these interactions [51]. For example, BDNF acting through TrkB increases the tyrosine phosphorylation of NMDA- and voltage-gated potassium channels [56,57]. Interestingly, whereas it is generally a facilitatory protein, BDNF has also been shown to reduce potassium and AMPA currents [57,58]. As will be discussed below, both AMPA and monoamine receptors regulate BDNF and Trk receptor levels.

The BDNF hypothesis of antidepressant action arose from the initial observation that a variety of antidepressant drugs were able to produce an increase in mRNA encoding BDNF and its receptor, TrkB, in rat hippocampus following chronic treatment [59]. These drugs included tranylcypromine, a monoamine oxidase inhibitor (MAOI), sertraline, a selective serotonin reuptake inhibitor (SSRI), and desmethylimipramine, a tricyclic antidepressant. The expression of BNDF mRNA and/or protein has also been found to be increased following treatment with a phosphodiesterase inhibitor [60,61], electroconvulsive shock [59,62], or chronic exercise [63,64], all of which can be efficacious in the treatment of depression. Based on these convergent data, it has been hypothesized that BDNF induction may be a common mechanism by which these various treatments produce antidepressant efficacy. Additional support for this hypothesis comes from the finding that direct infusion of recombinant BDNF into the central nervous system can produce antidepressant-like effects in rats in both the forced swim test and the "learned helplessness" (inescapable shock) models [11,18]. Additionally, antidepressants were reported to have no behavioral effect in the forced swim test in heterozygous BDNF knockout mice, or in mutant mice expressing a dominant negative isoform of the primary BDNF receptor, TrkB, whereas the antidepressant drugs tested significantly reduced immobility in this assay in wild-type mice [65].

Further support of a BDNF theory and its relevance to human depression comes from a study by Shimizu et al. [66], in which serum BDNF levels were found to be significantly lower in antidepressant-naive patients with major depressive disorder than in either normal control subjects or antidepressant-treated patients with major depressive disorder. A significant negative correlation between serum BDNF and scores on the Hamilton rating scale for depression was observed in this study. A downregulation in message and protein expression of the full-length but not the truncated isoform of TrkB has been observed in frontal cortex and hippocampus of suicide patients [67]; this effect was not associated with antidepressant medication. However, it is important to note that the reduced TrkB receptors were also observed in patients with non-depressed psychiatric diagnoses.

BDNF is known to have neurotrophic and neuroprotective effects (e.g., [68–70]), and there is evidence that BDNF can promote neurogenesis (see [18]). Therefore, the BDNF hypothesis of antidepressant action also has conceptual validity in that depression is correlated with reduced gray matter volume in a number of brain regions, including the hippocampus [71–73]. This reduction in volume may be a result of decreased neuronal arborization, as well as decreased cell number (see [74] for review). Atrophy of hippocampal neurons can also be experimentally induced in animals by chronic stress [75,76], which is believed to play a role in the etiology of depression [77]. Stress can damage neurons through at least two mechanisms: (1) unregulated or oversecretion of toxic glucocorticoids and (2) reduction in neurotrophic factors. Additionally, reductions in BDNF mRNA have been reported in the hippocampus of rats exposed to experimental stress [59,78,79]. It is thus hypothesized that the neurotrophic and neurogenic effects of BDNF may produce antidepressant effects by reversing the morphological deficits associated with depression.

There is evidence linking the effects of antidepressants to neurogenesis. Neurogenesis in the hippocampal formation has been shown to be increased by antidepressant drugs and electroconvulsive shock, and decreased by stress (see [11,18] for review). More recently, disruption of neurogenesis in the hippocampus by X-ray treatment was found to prevent the behavioral effects of antidepressants in the novelty-suppressed feeding and chronic unpredictable stress models in mice [12]. The neurogenic effects of antidepressants have been postulated to be mediated by BDNF [80].

Like traditional (clinically validated) antidepressants, AMPA receptor potentiators have been shown to increase BDNF expression (see Table 1 for summary). The AMPA receptor potentiator LY451646 has also been reported to increase progenitor cell proliferation in adult rat hippocampus [81]. Rats treated for 21 days with LY451646 showed a 45% increase in the number of cells labeled with bromodeoxyuridine (BrdU), a marker of mitosis. The upregulation of BrdU labeling appeared as an increase in the number of cells arranged in clusters, implying that this effect resulted from single progenitor cells giving rise to clonal populations of immature daughter cells. Although previous studies using antidepressant drugs have shown that a large portion of proliferating cells differentiate into neurons after treatment (e.g., [82]), the phenotype of BrdU-labeled cells was not determined after LY451646 treatment, so it cannot be definitively concluded that these cells differentiated to neurons. Additionally, it is unknown whether LY451646 treatment may have affected the survival of new cells rather than (or in addition to) the generation of new cells per se.

A model for the induction of BDNF expression by antidepressants is given in Fig. 3. Traditional antidepressants are thought to induce BDNF expression by activating the

Table 1 – Effects of AMPA receptor potentiators on BDNF expression, neurogenesis, and antidepressant-like effects

Preparation or model	Compound	Effect	Reference
BDNF formation and neurogenesis			
Rat entorhinal/hippocampal slices	CX546 and CX614	Increased mRNA for BDNF and trkB	[115]
Rat hippocampus	CX546	Increased BDNF mRNA	[115]
Primary cortical neurons	LY392098	Increased mRNA for BDNF and trkB Increased BDNF protein	[83]
Rat hippocampus	LY451646	Increased mRNA for BDNF and trkB Increased BDNF protein	[116]
Rat hippocampus	LY451646	Increased cell proliferation	[81]
Antidepressant-like behavioral effects			
Forced-swim — mouse	LY392098	Decreased immobility	[104,117]
Forced-swim — rat	LY392098	Decreased immobility	[117]
Tail-suspension — mouse	LY392098	Decreased immobility	[117]
Tail-suspension — mouse	LY451646 LY404817	Decreased immobility	[118]
Forced-swim — mouse	LY451646 LY404817	Decreased immobility	[118]
Submissive behavior — rat	CX516 CX691 CX731	Decreased submissive behaviors	[105]
Interactions with monoamine antidepressants — mouse	LY392098	Facilitation of antidepressant-like effects of conventional antidepressants	[104]

transcription factor Ca^{2+}/cAMP response element-binding protein (CREB) through protein kinase A (PKA) and Ca^{2+}/calmodulin-dependent protein kinase (CaM kinase) signal transduction pathways (reviewed in [10,18]). AMPA receptor potentiators may also induce BDNF by activating CaM kinase signal transduction pathways. In addition, AMPA receptors have been reported to be linked to BDNF induction through a Ca^{2+}-independent mitogen-activated protein kinase (MAPK) pathway. Hayashi et al. [8] found that Lyn, a member of the Src family of protein tyrosine kinases, is physically associated with AMPA receptor subunits, and can be activated by AMPA receptor activation. Lyn activation was independent of Ca^{2+} flux or neuronal firing, and led to MAPK activation and an increase in BDNF mRNA. Legutko et al. [83] reported that the AMPA receptor potentiator LY392098 increased BDNF mRNA expression in rat cortical neurons, and that this upregulation had both a Ca^{2+}-dependent component and a Ca^{2+}-independent, nimodipine-insensitive component, which appeared to be mediated by a MAPK pathway. A model for the induction of BDNF by AMPA receptor potentiators is also included in Fig. 3.

It should be noted that although BDNF/neurotrophic hypotheses of antidepressant action have a large body of supporting evidence (cf. [18]), they remain controversial as data have also been reported that are inconsistent with the idea that BDNF induction is critical for the activity of antidepressants. For instance, in apparent contradiction to the report by Nibuya et al. [59], other studies have reported either no change [15,84], or a decrease [14,84] in BDNF levels in rat hippocampus following treatment with fluoxetine [14,15,84] or other antidepressant drugs [84], although differences in BDNF exon expression, brain region specificity and time course for induction have yet to be fully understood (cf., [15,84]).

Another piece of evidence against a BDNF hypothesis comes from CREB mutant mice. As noted above, the transcription factor CREB is believed to mediate the induction of BDNF by antidepressant drugs. Conti et al. [13] found that desmethylimipramine did not upregulate BDNF in $CREB^{\alpha\Delta}$ mice, whereas it did increase BDNF mRNA in wild-type animals. However, desmethylimipramine reduced immobility in the forced swim and tail suspension tests in both wild-type and mutant mice. This would seem to dissociate the induction of BDNF from the behavioral responses to antidepressants in rodents. However, differential actions of CREB in distinct CNS loci (e.g., hippocampus versus nucleus accumbens) could be a contributing factor to these results, raising cautions in overinterpretation [85].

6. AMPA receptor alterations in mood disorders

If AMPA receptors are involved in mood disorders, it might be expected that AMPA receptors would be modified in patients with these disorders. A major source of such data comes from the brains of suicide victims. Although studies have not been exhaustive, increased AMPA receptor binding in the striatum of suicide victims has been reported (Table 2). However, other studies have reported decreases in AMPA receptor-related transduction pathways in depressed suicide patients. For example, p44/42 MAPK activity was decreased in prefrontal cortex and hippocampus but not cerebellum of suicide brains with concomitant decreases in mRNA and protein levels of ERK1 and ERK2. MAPK2 and ERK1/2 phosphatase were increased in these regions. The study controlled for age and post-mortem interval with brains from subjects without psychiatric diagnoses [86]. As discussed above, the MAPK

Table 2 – Modulation of AMPA receptors in mood disorders, by stress, and by drugs used to treat depression and bipolar disorder

Preparation	Stressor or disease	Effect on AMPA receptors	Reference
Mood disorders			
Human brain	Suicide victims	Increased [^{3}H]AMPA binding in caudate	[119]
Human brain	Suicide victims	Increased [^{3}H]CNQX binding in caudate	[120]
Human brain	Bipolar disorder	Decreased expression of GLU_{A1} mRNA	[121]
Human brain	Suicide patients — schizophrenia	CN, NA — greater [^{3}H]CNQX binding in suicide vs. non-suicide patients	[122]
Human brain	Bipolar disorder	No change in AMPA receptor binding	[123]
Stress			
Rat dentate granule cells	Chronic mild stress	No change in GLU_{A1} or GLU_{A2}	[124]
Rat dentate granule cells	Chronic mild stress	Increased amplitude of AMPA activation to corticosterone in cells from stressed but not control rats	[125]
Rat hippocampus	Acute restraint	Increased AMPA binding	[92]
Rat hippocampus	Acute social stress	Decreased AMPA binding	[126]
Rat hippocampus	Single restraint episode	Decrease in GLU_{A1} in CA1 and CA3	[127]
Rat hippocampus	Chronic restraint stress	Increased GLU_{A1} mRNA	[128]
Rat brain slice	Acute restraint	DG, CA3, CA4 — GLU_{A2} flip mRNA increased EC — GLU_{A1} flip and GLU_{A2} flip mRNA increased	[129]
Rat brain slice	Chronic restraint	CA1 — GLU_{A1} flip mRNA slightly decreased EC — GLU_{A1} flip, GLU_{A2} flip, and GLU_{A1} flop mRNA increased	[129]
Rat hippocampus	Acute or chronic restraint	No change in AMPA receptor mRNA expression	[130]
Antidepressants and mood stabilizers			
Rat hippocampus	Chronic desmethylimipramine or paroxetine	Increased expression of GLU_{A1} and $GLU_{A2/3}$	[131]
Rat hippocampal synaptosomes	Chronic lithium or valporate in vivo	Decreased GLU_{A1} expression	[132]
Rat hippocampal synaptosomes	Chronic lithium or valporate in vivo	Decreased GLU_{A1} expression Decreased GLU_{A1} phosphorylation at GLU_{A1}p845	[133]
Rat hippocampal synaptosomes	Chronic imipramine in vivo	Increased expression of GLU_{A1}	[133]
Rat frontal cortex	Chronic imipramine or citalopram	Decreased amplitude of field potentials from layer II/III	[134]
Rat hippocampus??	Repeated ECS	Increased GLU_{A1} mRNA	[114]
Rat hippocampus	Repeated ECS	Increased levels of NARP protein	[33]
Mouse striatum, hippocampus, striatum, and cortex	Acute and chronic fluoxetine	Increased phosphorylation of GLU_{A1} — acute distinct from chronic	[94]

CA1: hippocampal region, CA3: hippocampal region, CA4: hippocampal region, CN: caudate nucleus, DG: dentate gyrus, EC: entorhinal cortex, ECS: electroconvulsive seizures, NA: nucleus accumbens, and NARP: neuronal activity-regulated pentraxin.

pathway has been demonstrated to play a role in the generation of BDNF by an AMPA receptor potentiator. However, BDNF itself may exert its effects through a MAPK-signaling pathway [87–89], making it difficult to interpret the specific relevance of this data to AMPA receptors.

Assessments of glutamate levels have been determined by proton magnetic resonance-imaging methods in patients with major depression, where it has been reported that glutamate levels are significantly increased [3]. At the same time, however, these patients exhibited decreased GABA levels. These observations taken in the occipital cortex, point to an increased excitatory tone in this brain area in depressed individuals. Future studies will have to focus on brain areas of greater relevance to depression.

Stressful life events can markedly impact biochemistry and behavior and have been postulated to be important precursors of psychiatric illness including the mood disorders (cf., [11,90]. As already noted above, the BDNF hypothesis of depression suggests that stress-induced neural atrophy is a causative factor in depression. Although not extensively studied and a consistent picture has yet to emerge, AMPA receptors have been shown to participate in the regulation of these processes. Some of the data addressing a role for AMPA receptors in controlling the reactive milieu under stress is summarized in Table 2. Increases, decreases and no effect have been reported in AMPA receptor affinity, number, or message. These seeming inconsistencies could be a function of the differences in stressors and the duration of stress application. A decrease in AMPA receptor number or function is consistent with

observations of decreased memory and LTP in rats exposed to stress (cf., [91]). However, these data are not easy to reconcile with the observations of increased AMPA receptor number or function [92]. Moreover, it is not clear how to interpret these changes with respect to function. Do changes in AMPA receptors occur as a result of a compensatory process directed at dampening neural damage from stress? Thus, AMPA receptor increases could result in increases in BDNF production that would help to thwart the danger from reduced trophic support. As with neurochemical markers such as dopamine, stress complexly alters the configuration of AMPA receptors in the central nervous system. More detailed and parametric investigations will be needed to define the conditions under which AMPA receptor isoforms are modified by stress in order to better appreciate the role that these processes may play in depression and antidepressant drug action.

7. AMPA receptors are affected by drugs used to treat depression and bipolar disorder

There have been only a limited number of investigations in this area (Table 2). Drugs used to treat bipolar disorder and regulate mania have been shown to downregulate AMPA receptor function. With conventional antidepressants, the data accumulated to date is generally consistent with the idea that chronic treatment with antidepressants upregulates the function of AMPA receptors.

Recent data have indicated that antidepressants may upregulate AMPA receptor function by altering the level of phosphorylation of individual amino acid residues comprising AMPA receptor subunits. Since it was determined that serotonin produces effects through the dopamine- and cAMP-regulated phosphoprotein of M_r 32,000 (DARPP-32)-signaling pathway [93], the possibility that antidepressants that increase the synaptic availability of serotonin would also be functioning through AMPA receptor pathways was investigated. Both in vitro and in vivo data confirmed this hypothesis [94]. Acute or repeated dosing with fluoxetine changed the phosphorylation state of GLU_{A1} to one that favors increased channel conductance. The mechanisms underlying the phosphorylation of specific residues of GLU_{A1} are suggested to be as follows and are outlined in Fig. 3. Fluoxetine increases the concentration of serotonin at the synapse by blocking the uptake of serotonin into the presynaptic neuron. Binding of serotonin to specific serotonin receptors changes the phosphorylation state of DARPP-32. Depending upon the phosphorylation state of DARPP-32, this protein can act as either a phosphatase inhibitor or a kinase inhibitor and is thus in a position to regulate signal transduction cascades. Thr^{34}-DARPP-32 phosphorylation is increased through the protein kinase A site and Thr^{75}-DARPP-32 phosphorylation is decreased through the cyclin-dependent kinase 5 site, both of these changes being driven through serotonin binding to 5-HT_4 and 5-HT_6 receptors. Activation of 5-HT_2 receptors, on the other hand, increases the phosphorylation state of Ser^{137}-DARPP-32 through the casein kinase-1 site [93]. Through the serotonin-mediated changes in the phosphorylation state of DARPP-32, the GLU_{A1} subunit of the AMPA receptor is selectively phosphorylated. Whereas acute treatment with fluoxetine increases the phosphorylation of GLU_{A1} at Ser^{831} and Ser^{845}, repeated dosing for 19 days with fluoxetine selectively increases the phosphorylation of GLU_{A1} at Ser^{845}. Additional support for the role of DARPP-32 in this process was derived from experiments with mice deficient in the DARPP-32 phosphoprotein. In these mice, GLU_{A1} phosphorylation was reduced and the potency of fluoxetine for evoking antidepressant-like behavioral effects was significantly decreased [94].

There is evidence that the changes in GLU_{A1} phosphorylation induced by fluoxetine result in activation of AMPA ion channel conductance. Thus, phosphorylation of Ser^{845} by PKA augments the peak current amplitude generated by homomeric GLU_{A1} receptor channels [95]. Likewise, AMPA receptor currents can also be potentiated by CaM kinase II or protein kinase C, which increase the phosphorylation of Ser^{831} [96]. The ratio of phosphorylation states of Ser^{831} and Ser^{845} has been shown to regulate synaptic plasticity [97]; alteration of this ratio, as occurs upon chronic dosing with fluoxetine, might represent a mechanism underlying antidepressant efficacy.

Based upon these results with fluoxetine and the data discussed previously on the involvement of AMPA receptors in mood disorders, it is tempting to speculate that AMPA receptor potentiation via GLU_{A1} phosphorylation could be a general process through which antidepressant effects are generated. There are to our knowledge, however, no data on the effects of other known antidepressants on this process. However, two compounds have been investigated that display antidepressant-like effects in rodent models. A melanin-concentrating hormone antagonist was shown to have antidepressant-like activity in the forced swim test and to increase Ser^{845} phosphorylation of GLU_{A1} in explants of the nucleus accumbens shell of mice [98]. Likewise, the metabotropic glutamate group II ($mGlu_{2/3}$) antagonists LY341495 and MGS0039 produced antidepressant-like activity in rat and mouse models [99]. Importantly, these in vivo effects were blocked by the AMPA receptor antagonist NBQX, implying that the antidepressant-like activity of these compounds is driven through increased AMPA receptor activity generated by the blockade of $mGlu_{2/3}$ receptors [100]. Related to these effects is the observation that, as with AMPA receptor potentiators, MGS0039 increases cell proliferation in mouse hippocampus upon chronic administration in vivo [101]. In contrast, the acute effects of imipramine in the forced swim test were not modified by an AMPA receptor antagonist (Fig. 2).

8. Antidepressant-like behavioral effects of AMPA receptor potentiators

Animal models of depression, like other models of psychiatric disease, are imperfect. Nonetheless, for a broad range of compounds, structures, and mechanisms, the forced swim test predicts the efficacy of compounds to treat depression in humans [102–104]. In the forced swim test and tail suspension tests, both models of ''behavioral despair'', several AMPA receptor potentiators have demonstrated efficacy comparable to that of SSRI and tricyclic antidepressants (Fig. 2, Table 1).

Importantly, the activity of LY392098 in this assay has been demonstrated to be due to AMPA receptor facilitation and not some ancillary activity this compound may be producing. Fig. 2 shows that the decrease in immobility in the forced swim test in mice is prevented by an AMPA receptor antagonist; in contrast, the activity of the tricyclic antidepressant imipramine was not. Antidepressant-like efficacy has also been observed for pyrrolidine-based AMPA receptor potentiators. In this study, the AMPA receptor potentiators piracetam, aniracetam, CX516 (BDP 12), CX691, and CX731, like the SSRI antidepressant fluoxetine, decreased the amount of submissive behavior of rats in a dominant/submissive interaction when given chronically [105]. Interestingly, the onset of action of the antidepressant-like effects of the AMPA receptor potentiators was faster under these conditions than that of fluoxetine. Thus, based on the preclinical models, AMPA receptor potentiators of two structural classes have demonstrated antidepressant-like efficacy in mice and rats and under acute and longer term treatment regimens.

AMPA receptor potentiators also produced synergistic effects when combined with clinically effective antidepressants. In the mouse forced swim test, an ineffective dose of the AMPA receptor potentiator LY392098 significantly augmented the potency of several other antidepressant compounds: SSRIs (fluoxetine and citalopram), a norepinephrine uptake inhibitor (nisoxetine) a mixed norepinephrine/serotonin uptake blocker (duloxetine), a tricyclic antidepressant (imipramine), and a phosphodiesterase 4 inhibitor (rolipram). Similarly, ineffective doses of the traditional antidepressants potentiated the antidepressant-like effects of LY392098 [104]. These observations of synergy are consistent with the idea that AMPA receptor potentiators produce their antidepressant-like effects through a mechanism that, although distinct, ultimately converges upon a common final pathway. Since AMPA receptor potentiators such as LY393098 do not directly impact monoamine levels in cortex (cf., [6]), then, were a common mechanism to be postulated, it could involve a downstream event such as BDNF induction. Another mechanism for this synergy could be the impact that monoaminergically based antidepressants have upon AMPA receptor function as discussed above (see also Fig. 3).

An AMPA receptor potentiator has been studied for its effect on cerebral glucose utilization and c-fos activation in rat brain. LY404187 increased these measures of neural activation in 28 out of the 52 brain areas evaluated [106]. Brain structures involved in cognition and depression such as rostral neocortical areas and the hippocampus, dorsal raphe nucleus, and locus coeruleus were among these.

9. A role for AMPA receptors in mood disorders

An emerging set of data converges on the possibility that AMPA receptors play a key role in the treatment, and possibly the etiology, of mood disorders. The primary evidence is as follows: (1) AMPA receptor potentiators increase BDNF levels in relevant brain areas, (2) AMPA receptor poteniators increase cell proliferation in the hippocampus in vivo, (3) AMPA receptor potentiators are effective in acute and chronic models of antidepressant activity, (4) AMPA receptor potentiators and conventional antidepressants demonstrate mutual synergy in animal models, and (5) fluoxetine as well as some putative antidepressant agents activate AMPA receptors. An overall summary of the data is presented in simplified schematic form in Fig. 3. Evident in this depiction of the data are the connections linking AMPA receptors to two major pathways of potential relevance to depression: the monoamine pathway and the BDNF pathway. Such interconnections allow for highly regulated control of these substrates.

A number of questions have already been raised throughout this commentary. In addition, the following points could provide a framework for further thought and experimentation. Can functional potentiation of GLU_{A1} be demonstrated (e.g., electrophysiologically) after chronic fluoxetine dosing in vivo? Do antidepressants other than fluoxetine phosphorylate GLU_{A1}? What are the specific monoamine receptors and their subtypes (e.g., 5-HT_{2a}) that operate to change the phosphorylation state of $GLU_{A1}1$? Is there phosphorylation of analogous sites on other AMPA receptor subunits that is relevant to antidepressant activity? What is the role of specific metabotropic receptors in the process of AMPA receptor activation? What is the role played by the proteins regulating AMPA receptor trafficking or scaffolding in antidepressant response? In this regard, the specific localization of the γ-8 scaffolding protein in hippocampus, a site of neurogenesis with antidepressants and AMPA potentiators, is particularly intriguing.

AMPA receptors are ubiquitous and in the brain and serve many different functions. Accordingly, AMPA receptors display differential distribution throughout the brain both in terms of subunit and splice variant (flip/flop) expression (cf., [107,108] and Section 4). Currently it is not understood which AMPA receptor subunits or splice variants are the most relevant to depression, or in which brain loci AMPA receptor modulation most impacts mood. Recent crystallographic studies have increased our understanding of the topographical structure of AMPA receptors and the manner in which potentiators interact with AMPA receptor subunits at the dimer–dimer interface [109]. This will likely facilitate the identification of compounds, which show greater subunit and/or splice variant selectivity. Therefore, identification of which AMPA receptor subunits and splice variants can be best exploited for the clinical treatment of depression is a key area for future research.

In addition to serotonin, other systems also appear to play a role in mood disorders. GABAergic, dopaminergic, and noradrenergic neurotransmission have all been implicated among others (cf., [19,110]). The hypothalamic-pituitary axis is also affected in the mood disorders and under stress. The way in which these systems impact and are impacted by AMPA receptors with regard to mood disorders is not known.

The evidence suggests that conventionally used antidepressant agents such as fluoxetine may have a mechanism of action that is driven through AMPA receptor potentiation. These data are important as they point to a potentially novel mechanism through which antidepressants produce their beneficial clinical outcome. It is critical to understand whether this is a general phenomenon of all effective antidepressants since the data thus far has been limited to fluoxetine. Although an answer is not essential for an appreciation of

the veracity of a role for AMPA receptors in depression, the question of whether there a final common pathway through which antidepressants engender clinical relief is still unanswered? The fact that the acute effects of imipramine in the forced swim test are not altered by an AMPA receptor antagonist (Fig. 2), suggests that independent pathways may be in operation; however, the effects of chronic fluoxetine in this behavioral test have not been assessed for a potential AMPA receptor-mediated component as suggested by the data of Svenningsson et al. [94] discussed above.

The evidence suggests that AMPA receptor potentiators could function as antidepressants in humans. However, there are weaknesses in the logic of the data upon which this suggestion rests. First, increases in BDNF may not be directly related to antidepressant activity. Second, neurogenesis may not be directly related to antidepressant activity (cf., [111]). Third, the antidepressant models used to study AMPA receptor potentiators are not homologous to human depression (cf., [103]) and thus may not predict accurately the clinical outcome of novel mechanisms. Also, as noted earlier, NMDA receptor blockade has been clinically validated as a mechanism for antidepressant response. That AMPA receptor potentiators should also produce antidepressant effects therefore seems counterintuitive, since AMPA receptor potentiation facilitates NMDA receptor function (however, see [112] for a potential unification of these mechanisms based upon the common effect of promoting neurogenesis). Also, from a systems view, the overall picture of the human depressed brain is one of increased metabolic activity where effective antidepressant medication has been shown to dampen this excitatory tone [113]. Although not all brain areas are affected in this manner either by depression or by antidepressant treatments, the data raise some questions regarding the idea that AMPA receptor potentiation could be a treatment entity. New data are necessary to address these and a host of other unanswered questions. In the meantime, the convergence of data both from AMPA receptor potentiator molecules and conventional antidepressants, biochemically, neurochemically, and behaviorally, indicates that experimental attention to the role of AMPA receptors in mood disorders is warranted. The current data also indicate that convergent biochemical pathways involving serotonergic and glutamatergic neurotransmission will be a fruitful area for further investigation.

The holy grail for the treatment of depression is rapid efficacy with minimal side effects. Electroconvulsive therapy and the more toxic MAO inhibitors, for example, are often more efficacious than other antidepressants such as the SSRIs (cf., [19,114]). Does this have anything to do with their impingement and amplification of AMPA receptor signaling? The data discussed in this commentary provide a beginning rationale for considering AMPA receptors as a key part of the antidepressant machinery. Understanding these processes in greater detail will enable the discovery of improved treatments for the crippling and prevalent disorders of mood.

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