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Modulation of glutamate receptors: Strategies for the development of novel antidepressants

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Summary. On a biochemical level, conventional antidepressants have been shown to modulate synaptic levels of biogenic amines (i.e., serotonin, norepinephrine, and dopamine), most often by interfering with reuptake processes or inhibiting metabolism. Strategies directed at modulating glutamatergic transmission may overcome the principal limitations (i.e., delayed onset and low efficacy) that appear to be inherent to these conventional agents. In this brief overview, I summarize two glutamate-based approaches to develop novel antidepressants. These distinct and (on a cellular level) seemingly diametric strategies may converge on intracellular pathways that are also impacted upon by chronic treatment with biogenic amine based agents.

Keywords: NMDA antagonists – Depression – Behavioral despair – AMPA – AMPA receptor potentiators

Functional NMDA antagonists as antidepressants: Preclinical and clinical evidence

For the purpose of this overview, functional NMDA antagonists are compounds that reduce transmission at any of the multiple, allosteric regulatory sites on NMDA receptors. Over the past decade, a body of literature has emerged (reviewed in Trullas, 1997; Skolnick, 1999, Petrie et al., 2000) demonstrating that functional NMDA antagonists are active in "behavioral despair" procedures. Behavioral despair procedures such as the forced swim (Porsolt et al., 1977a,b) and tail suspension (Steru et al., 1985) tests, whilst not true animal models of depression, are highly predictive of antidepressant activity in humans (Borsini and Meli, 1988; Porsolt and Lenegre, 1992). Like clinically effective antidepressants, competitive NMDA antagonists (e.g., AP-7, CGP 39551), uncompetitive antagonists (e.g., MK-801, memantine), a polyamine (NR-2B) antagonist (eliprodil), and a glycine partial agonist (ACPC) reduce immobility in these behavioral despair procedures. These data have recently been reviewed (Trullas, 1997; Skolnick, 1999; Petrie et al., 2000), and will not be re-described in detail here. Nonetheless, a recent report based on this literature merits additional comment. Harkin et al. (1999) described the ability of nitric oxide (NO) synthase inhibitors to reduce immobility in the FST (with no concomitant change in motor activity, see below). Further, this antidepressant-like effect was blocked by pretreatment with L-arginine, the substrate for NO synthase. Since an increase in NO production (via activation of NO synthase) is one of the principal downstream events associated with NMDA receptor activation, these findings indicate that an antidepressant-like action may also be produced by interruption of the signaling cascade as well as at the receptor level, thereby increasing the potential number of targets for novel "glutamate-based" antidepressants.

In contrast to a relatively large body of preclinical data, there has been only one report of a study specifically designed to test the hypothesis that NMDA antagonists are antidepressant. Berman et al. (2000) administered either the uncompetitive NMDA antagonist ketamine or saline to patients who were unresponsive to conventional antidepressants. Ketamine (0.5 mg/kg, infused over 40 min) significantly reduced Hamilton Depression (HAM-D) scores within 3 h. The reduction in HAM-D scores continued to emerge over time, and persisted for at least 72 h, the planned duration of this study. At the point the study was terminated, HAM-D scores were reduced (X $\pm$ SD) 14 $\pm$ 10 and 0 $\pm$ 12 points in the ketamine and saline

cohorts, respectively. Whilst intravenous infusion of ketamine is not a practical means of treating depression, this study provides a proof-of-principle consistent with pre-clinical data that NMDA receptor blockade results in an antidepressant action. Since NMDA receptor modulation has a powerful, albeit complex effect on biogenic amine turnover (see Skolnick et al., 2001), it could be argued that the antidepressant-like actions of functional NMDA antagonists result from elevated levels of biogenic amines (e.g., norepinephrine and dopamine). However, the rapid antidepressant action of ketamine described by Berman et al. (2000) indicates that it is the NMDA antagonist properties *per se* that are responsible for these effects since intravenous infusion of biogenic-amine based agents (e.g, an SSRI or tricyclic) will not produce such a rapid improvement in symptoms. The antidepressant-like properties of functional NMDA antagonists led us to test the hypothesis that NMDA receptors would be impacted by chronic treatment with conventional antidepressants.

Chronic treatment with conventional antidepressants: effects on NMDA receptors

The hypothesis that chronic antidepressant treatment would impact NMDA receptors was initially explored using radioligand binding techniques (Nowak et al., 1993). Following chronic administration of imipramine (15 mg/kg, i.p. for two weeks) to mice, significant changes were detected in radioligand binding to NMDA receptors in cerebral cortex (but not other brain regions such as hippocampus and striatum). These changes included a reduction (~36%) in basal [^{3}H]MK-801 binding, a ~2.5-fold reduction in the potency of glycine to inhibit [^{3}H]5,7-dichlorokynurenic acid binding, and a reduction (~28%) in the proportion of high affinity glycine sites inhibiting [^{3}H]CGP 39655 binding. Similar effects were not manifested in mice administered a single dose of imipramine. These findings led to additional studies to determine if other antidepressants also altered radioligand binding to NMDA receptors. In these studies, mice were treated for two weeks with antidepressants drawn from every principal therapeutic "class" (e.g., tricyclics, MAOIs, SSRIs, "atypicals") as well as electroconvulsive shock. These regimens produced significant reductions in the potency of glycine to inhibit [^{3}H]5,7-dichlorokynurenic acid binding to strychnine-insensitive glycine receptors and/or a reduction in the proportion of high affinity glycine sites allosterically inhibiting the binding of [^{3}H]CGP 39655 to glutamate recognition sites. There was no obvious relationship between either the magnitude of antidepressant-induced change in these two neurochemical parameters or the clinical potency of the antidepressant and the magnitude of change in either parameter. The former point is perhaps best illustrated by citalopram, which reduces the affinity of glycine to inhibit [^{3}H]5,7-dichlorokynurenic acid binding by ~2-fold (the smallest effect produced by any of the antidepressant studied), but essentially abolishes the high affinity component of glycine displaceable [^{3}H]CGP 39653 binding. Because these were "one dose, one time point" studies (that is, neither doses nor regimen lengths were optimized), it may be argued that it would not be possible to evince clear cut relationships from this neurochemical snapshot. Certainly, the demonstration that these neurochemical changes emerge over time and that a two week dosing regimen is not optimum for imipramine reinforce this notion (Paul et al., 1994). Nonetheless, the striking discordance in these neurochemical measures produced by citalopram indicates that antidepressant treatments may be producing multiple changes in NMDA receptors. Several other neurochemical findings are consistent with this hypothesis. Thus, a two week regimen of imipramine to rats produced a significant reduction in the number of [^{3}H]CGP 39653 binding sites in cortex (Paul et al., 1993), an effect not observed in mice (Nowak et al., 1993). Further, chronic treatment with several (e.g., desipramine, amytryptyline**)** but not all of the antidepressants reduced the basal binding of [^{3}H]5,7-dichlorokynurenic acid to mouse cerebral cortex.

Because subunit composition defines the physiological and pharmacological properties of NMDA receptors (e.g., Wafford et al., 1993; Laurie and Seeburg, 1994; Harvey and Skolnick 1999), it was hypothesized that antidepressant-induced changes in radioligand binding to NMDA receptors reflected changes in NMDA receptor composition. This hypothesis was initially explored by determining if antidepressants induced changes in the mRNAs encoding specific NMDA receptor subunits. *In situ* hybridization (Boyer et al., 1998) of brain slices from mice chronically treated with either imipramine or citalopram revealed widespread, and, in some instances, rather dramatic changes in the expression of specific subunits encoding NMDA receptor subunits. Using a pan probe to detect

the mouse homologue (ξ) of rat NMDAR-1, modest reductions (<20%) were observed in several brain regions. Certainly, the use of a pan probe may mask more robust changes in the expression of specific splice variants. However, examination of the mouse homologues ($\varepsilon_{1,2.3}$) of rat NMDAR2A-C revealed changes that appeared antidepressant-specific (with the caveat that this was a one dose, one time point study), more restricted from a neuroanatomical perspective than the changes seen in the ξ subunit, and in some instances, quite robust. For example both antidepressants reduced levels of mRNA encoding the ε_2 subunit in amygdala by ~40%, but did not alter levels of this transcript in thalamus and striatum. In contrast, citalopram reduced ε1 mRNA levels by 25–30% in striatum, thalamus and amygdala, whilst imipramine produced a significant reduction in levels of this transcript only in amygdala (~20%). Similar antidepressant and region specific reductions in mRNA levels were observed in hippocampal and cortical substructures (Boyer et al., 1998; reviewed in Skolnick, 1999). Of particular note is that these antidepressant-induced changes in NMDA receptor mRNA levels were unidirectional – that is, when significant, these changes were uniformly reductions. The widespread changes in expression of mRNA encoding NMDA receptor subunits is in marked contrast to the antidepressant-induced changes in radioligand binding, which appear restricted to cortex (e.g., Nowak et al., 1993, 1996). Whilst it could be argued that antidepressant-induced changes in radioligand binding to NMDA receptors are unrelated to the observed changes in mRNA levels encoding specific NR2 subunits, the more likely explanation is that the alterations in transcript levels detected by *in situ* hybridization would likely be muted or masked in the pooled tissue preparations used in radioligand binding studies.

These antidepressant-induced changes in both radioligand binding and mRNA expression would, at face value, appear consistent with a reduction in NMDA receptor function. Both *in vitro* and *in vivo* findings are consistent with this hypothesis. Thus, in cultured cerebellar granule neurons, BDNF or basic FGF-induced reductions in NMDAR-2A and 2C mRNA expression result in a concomitant reduction in NMDA-induced Ca^{++} entry (Brandoli et al., 1998). The reductions in NMDAR-2A and 2C mRNA expression in this *in vitro* study were comparable to those noted in in several brain regions following chronic treatment with citalopram and/or imipramine (Boyer et al., 1998). Perhaps more compelling evidence for a reduction in NMDA receptor function is the report of Popik et al. (2000) that chronic antidepressant treatment dampens the anxiolytic-like actions of functional NMDA antagonists acting at the glycine site but *not* benzodiazepines in the elevated plus maze.

AMPA receptor potentiators: Antidepressant-like actions in models of behavioral despair

AMPA receptors mediate the majority of fast excitatory transmission in the central nervous system (reviewed in Bettler and Mulle, 1994). By dint of neuronal depolarization, AMPA receptor activation can relieve the voltage-dependent Mg^{++} block of NMDA receptors, permitting glutamate and glycine to activate the latter family of ligand-gated ion channels (reviewed in Malenka and Nicoll, 1999). On a cellular basis, it could be predicted that AMPA receptor activation would tend to blunt or abolish, rather than mimic, the action of NMDA antagonists. Based on the pre-clinical and clinical data indicating that NMDA antagonists have antidepressant-like effects, there is a face value inconsistency in the hypothesis that AMPA receptor potentiators will share these actions. Nonetheless, there may be common functional endpoints that link these apparently disparate mechanisms. The emergence of a body of evidence during the past five years indicating that brain derived neurotrophic factor (BDNF) is a pivotal downstream mediator of antidepressant action (reviewed in Altar et al., 1999; Duman et al., 1997; Skolnick et al., 2001) provided the impetus to pursue this hypothesis. In view of: 1) a decade old literature that AMPA receptor activation can produce a robust increase in the expression of mRNA encoding BDNF (e.g., Zafra et al., 1990) and 2) the availability of potent, brain penetrating AMPA receptor potentiators (Ornstein et al., 2000), we examined the effects of representatives from this class of molecule (biarylpropylsulfonamides) in behavioral despair models (Li et al., 2001).

LY392098, the prototypic biarylpropylsulfonamide described by Ornstein et al. (2000), manifests an antidepressant-like action in both mice and rats, significantly reducing the duration of immobility in the forced swim test (Fig. 1). The minimum effective dose was 0.5 mg/kg (i.p.) in both species when administered 1 hour prior to testing (Li et al., 2001). In mice, statistically significant reductions in immobility were detected within 30 minutes after administration of

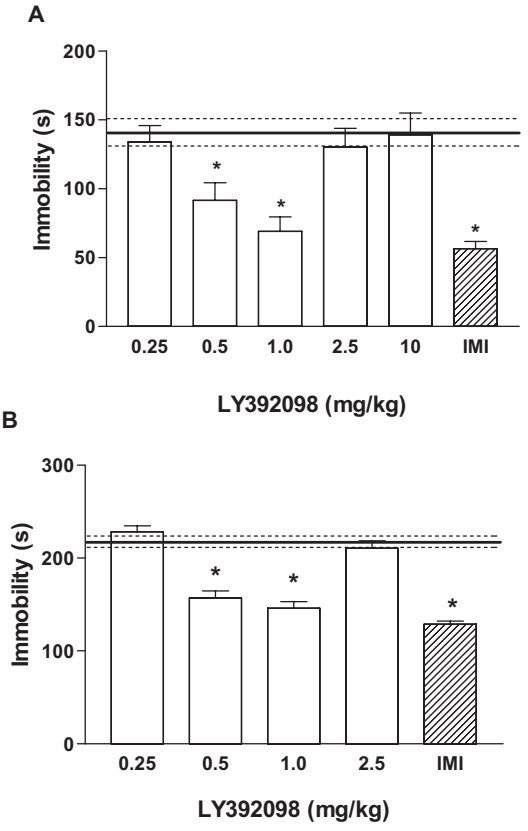

Fig. 1. LY392098 reduces immobility in the forced swim test. **A** Data obtained in mice. **B** Data obtained in rats. LY 392098 or vehicle were administered intraperitoneally as fully described in Li et al. (2001). The horizontal solid line bracketed by dashed lines represents the X ± SEM immobility (in s) of vehicle treated animals. Imipramine (15 mg/kg, i.p. injected 15 min prior to testing) was administered as a positive comparator. Values represent X ± SEM of 5–13 animals. * $P \leq 0.05$, compared to vehicle treated animals (Dunnett's test)

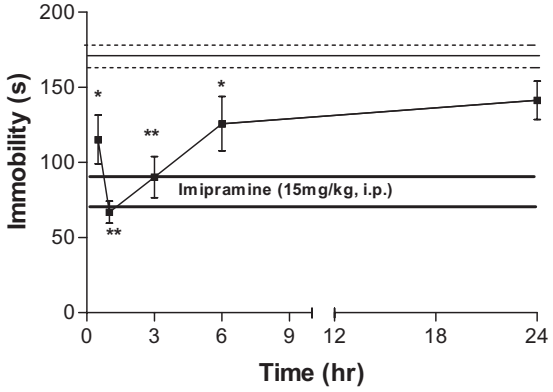

Fig. 2. LY392098: duration of action in the forced swim test. Mice were tested 0.5–24 h after administration of LY392098 (1 mg/kg, i.p.). The horizontal solid line bracketed by dashed lines represents the X ± SEM immobility (in s) of vehicle treated animals. The immobility of mice injected with a standard dose of imipramine (15 mg/kg, i.p. administered 15 min prior to testing) was 81.8 ± 9.6 s. Values represent SEM of 6–12 animals. * $P \leq 0.05$, ** $p \leq 0.01$ * $P \leq 0.05$, compared to vehicle treated animals (Dunnett's test). These data are from Li et al. (2001)

LY392098 (1 mg/kg), and sustained for at least 6 hours, with the maximum reduction in immobility comparable to that produced by a standard dose of imipramine (15 mg/kg, i.p.) administered 15 minutes prior to testing (Fig. 2).

The effects of LY392098 in the forced swim test were biphasic in both rats and mice, with immobility times returning to values obtained in saline treated mice at doses ≥2.5 mg/kg. However, even at doses up to 20-fold higher than the minimum effective dose, LY392098 did not increase immobility times above those seen in saline treated mice (Li et al., 2001). LY392098 also produced a dose dependent reduction in immobility in the tail suspension test, with a minimum effective dose of 5 mg/kg (i.p.). There was no indication of a biphasic dose response curve in the tail suspension test at doses of LY392098 as high as 20 mg/kg. Based on measurement of brain levels of LY392098 in the mouse strains used in these studies, it was concluded that pharmacodynamic rather than pharmacokinetic factors were responsible for differences in the shapes of the dose response curves in these behavioral despair measures (Li et al., 2001; Bai et al., 2001). The ability of a noncompetitive AMPA antagonist (LY300168, also known as GYKI53655) to block the effects of LY392098 (but not imipramine) in the forced swim tests provides prima facie evidence that AMPA receptor activation is required for this antidepressant-like action of LY392098 in the forced swim test (Li et al., 2001; Skolnick et al., 2001). In sum, LY392098 is active in two behavioral despair measures that are frequently employed to detect antidepressants. The ability of an AMPA receptor antagonist to block LY392098-mediated reductions in immobility indicates that this antidepressant-like action is AMPA receptor mediated. Further, the effects of LY392098 in behavioral despair models are shared by other, structurally related AMPA receptor potentiators such as LY451646 (Bai et al., 2001), indicating these effects are common to other brain penetrant molecules that can activate the same subset of AMPA receptor potentiators as LY392098.

These data indicate that AMPA receptor activation is required for the antidepressant-like actions of LY392098 (Li et al., 2001). Further, this and other

biarylpropylsulfonamides produce very robust increases in BNDF expression in neuron culture (Legutko et al., 2001) as well as *in vivo* (M. Mackowiak, personal communication). Nonetheless, a causal link between an increase in BDNF expression and an antidepressant-like action has not been established. Certainly, AMPA receptor activation can produce multiple effects, including an alteration in the synaptic levels of biogenic amines. For example, AMPA receptor potentiators such as cyclothiazide and S18986-1 have been reported to selectively enhance AMPA receptor-mediated increases in norepinephrine release from hippocampal and cortical slices (Desai et al., 1994; Lockhart et al., 2000). Further, AMPA receptor stimulation increases dialysate concentrations of both dopamine and serotonin in multiple brain regions (Maione et al., 1995; Tao et al., 1997). These findings, taken together with the activity of many agents that increase synaptic concentrations of biogenic amines in behavioral despair procedures (Porsolt and Lenegre, 1992), prompted us to perform microdialysis studies in rats administered LY392098. Biogenic amine levels were measured in prefrontal cortex, a region responding to conventional antidepressants with an increase in extracellular biogenic amines (e.g., Jordan et al., 1994). A dose of LY392098 producing the maximum reduction in immobility in the forced swim test (1 mg/kg) produced no increase in dialysate levels of norepinephrine, dopamine, or serotonin whilst standard doses of fluoxetine produced dose and time related changes in these transmitters (Skolnick et al., 2001). Clearly, further studies examining the effects of such AMPA receptor potentiators on biogenic-amine levels in other brain regions are in order. However, these data indicate the antidepressant-like actions of LY392098 may be independent of increases in synaptic concentrations of biogenic amines. These data are also consistent with the views of Porsolt and Lenegre (1992) that the forced swim and tail suspension tests are capable of detecting agents that do not directly block the uptake and/or metabolism of biogenic amines because these behavioral despair procedures are not based on mechanistic preconceptions.

An additional issue that merits discussion is the temporal relationship between changes in BDNF expression and the antidepressant-like actions of LY392098. Thus, the rapid onset of action of LY392098 in behavioral despair procedures (Fig. 2) would appear to preclude significant increases in BDNF expression. However, it has been reported that under certain circumstances, BDNF expression can be induced as an immediate early gene response (Lauterborn et al., 1996), and changes in brain mRNA levels are detectable within 30 minutes of a behavioral manipulation (Hall et al., 2000). Studies measuring BDNF expression following AMPA receptor activation *in vivo* (M. Mackowiak, personal communication) as well as studies using transgenic animals with abnormal BDNF expression (Lyons et al., 1999) will be important in establishing a causal link between this neurotrophin and the antidepressant-like actions of LY392098 (and related compounds).

Glutamate-based strategies for novel antidepressants: convergence with intracellular pathways impacted by traditional antidepressants

A comprehensive discussion of the pathways impacted by both conventional antidepressants and glutamate-based approaches is beyond the scope of this overview (for a more comprehensive review, see Skolnick et al., 2001). In this contribution, two distinct and, at a cellular level, seemingly diametric approaches have been described that produce antidepressant-like actions in models of behavioral despair. Whilst AMPA receptor activation can lead to NMDA receptor activation, *in vivo* electrophysiological studies with LY392098 (and structurally related compounds) have shown that a marked activation of AMPA receptors can be produced in the absence of significant NMDA receptor activation (Vandergriff et al., 2001). At face value, these findings indicate that the antidepressant-like actions of AMPA receptor potentiators and NMDA antagonists are compatible from a cellular standpoint.

Both NMDA antagonists and agents that increase the expression of BDNF (exemplified here by AMPA receptor potentiators such as LY392098 [Legutko et al., 2001] and biogenic-amine based antidepressants [Nibuya et al., 1995; Russo-Neustadt et al., 1999]) may be viewed, in a broad sense, as neuroprotective agents. Thus, the ability of NMDA antagonists to protect neurons from a variety of insults (reviewed in Lipton and Rosenberg, 1994), including stress-induced damage to the hippocampal formation (Gould and Tanapat, 1999), has been well described. The observation that BDNF is able to block glucocorticoid-induced cell death in hippocampal neurons (Nitta et al., 1999) as well as protect and maintain serotonergic and dopaminergic neurons from a variety of insults

(Mamounas et al., 1995, 2000; Altar et al., 1994; Frim et al., 1994) may contribute to maintaining appropriate levels of synaptic transmission in the face of stress-induced insults.

This functional convergence of NMDA antagonists and agents that increase BDNF expression may extend beyond neuroprotection to neurogenesis. Thus, in addition to its well described neuroprotective effects, Cameron et al. (1998) reported that within 4 h of MK-801 administration, [^{3}H]thymidine incorporation was increased ~3-fold near the border of the hilus and granule cell layer of the hippocampus. Malberg et al. (2000) recently reported an increase in the number of bromodeoxyuridine labeled neurons in rat hippocampus following chronic (but not acute) electroconvulsive shock (10 days) or fluoxetine (14 days). Whilst the temporal pattern between antidepressant-induced increases in BDNF expression (e.g., Nibuya et al., 1995) and bromodeoxyuridine labeled neurons described in the Malberg et al. (2000) study is quite similar, a *causal* link has not been established. These studies do not address either the relevance of presumptive increases in neurogenesis to an antidepressant action in man, or if neurogenesis is a necessary and/or sufficient condition for a therapeutic response. Nonetheless, the Cameron et al. (1998) study is intriguing in light of the rapid improvement (within hours) of severely depressed patients after ketamine (like MK-801, an uncompetitive NMDA antagonist) infusion (Berman et al., 2000).

Other recent studies indicate conventional antidepressants and other strategies directed at elevating BDNF share a common cellular target, the NMDA receptor (Skolnick et al., 2001). Thus, Brandoli et al. (1998) demonstrated that incubating cerebellar granule cell neurons with BDNF resulted in significant reductions in the expression of NMDAR-2A and -2C (corresponding to ε1 and ε3 in mice). As discussed earlier in this overview, this BDNF-induced reduction in NMDA receptor subunit mRNA and protein was sufficient to effect a significant reduction in NMDA-evoked increases in $[Ca^{+2}]_I$, which can be viewed as *prima facie* evidence of a reduction in NMDA receptor function. Quantitatively similar reductions (up to ~40%) in mRNA encoding ε1–3 (corresponding to the rat NMDAR2A, -2B, and -2C) can be effected by chronic antidepressant (sixteen days of imipramine and citalopram) in several regions of mouse brain (Boyer et al. 1998). These data have led us to propose glutamate-based strategies to develop novel agents that may ultimately target a reduction in function at NMDA receptors. Well-controlled clinical studies will determine if such strategies result in a more rapid onset of action or greater efficacy than conventional antidepressants.

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