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REVIEW

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N-Methyl-D-aspartate receptors as a target for improved antipsychotic agents: novel insights and clinical perspectives

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Abstract *Rationale:* Activation of "co-agonist" *N*-methyl-D-aspartate (NMDA) and Glycine$_B$ sites is mandatory for the operation of NMDA receptors, which play an important role in the control of mood, cognition and motor function. *Objectives:* This article outlines the complex regulation of activity at Glycine$_B$/NMDA receptors by multiple classes of endogenous ligand. It also summarizes the evidence that a hypoactivity of Glycine$_B$/NMDA receptors contributes to the pathogenesis of psychotic states, and that drugs which enhance activity at these sites may possess antipsychotic properties. *Results:* Polymorphisms in several genes known to interact with NMDA receptors are related to an altered risk for schizophrenia, and psychotic patients display changes in levels of mRNA encoding NMDA receptors, including the NR1 subunit on which Glycine$_B$ sites are located. Schizophrenia is also associated with an overall decrease in activity of endogenous agonists at Glycine$_B$/NMDA sites, whereas levels of endogenous *antagonists* are elevated. NMDA receptor "open channel blockers," such as phencyclidine, are psychotomimetic in man and in rodents, and antipsychotic agents attenuate certain of their effects. Moreover, mice with genetically invalidated Glycine$_B$/NMDA receptors reveal similar changes in behaviour. Finally, in initial clinical studies, Glycine$_B$ agonists and inhibitors of glycine reuptake have been found to potentiate the ability of "conventional" antipsychotics to improve negative and, albeit modestly, cognitive and positive symptoms. In contrast, therapeutic effects of clozapine are *not* reinforced, likely since clozapine itself enhances activity at NMDA receptors. *Conclusions:* Reduced activity at NMDA receptors is implicated in the aetiology of schizophrenia. Correspondingly, drugs that (directly or indirectly) increase activity at Glycine$_B$ sites may be of use as adjuncts to other classes of antipsychotic agent. However, there is an urgent need for broader clinical evaluation of this possibility, and, to date, there is no evidence that stimulation of Glycine$_B$ sites *alone* improves psychotic states.

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Abbreviations AMPA: DL-α-NH_2-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid · D-AAO: D-amino acid oxidase · DCS: D-Cycloserine · EAAT: excitatory amino acid transporter · GCP: glutamate carboxypeptidase · GlyT: glycine transporter · GRI: glycine reuptake inhibitor · NAAG: *N*-acetyl-aspartate-glutamate · NMDA: *N*-methyl-D-aspartate · mGluR: metabotropic · OCB: open channel blocker · PCP: phencyclidine · SNAT: small neutral amino acid transporter · vGluT: vesicular glutamate transporter

Introduction: glutamatergic transmission and schizophrenia

Though monoaminergic theories of the treatment of schizophrenia have dominated research and drug development for decades, there is increasing interest in non-monoaminergic strategies. Glutamatergic mechanisms are of special pertinence in view of the following: (1) their reciprocal interactions with monoaminergic networks (Schmidt and Kretschmer 1997; Marino and Conn 2002; Trudeau 2004); (2) their crucial role in the control of cognition, mood and motor function, which are disturbed in schizophrenia (Schmidt and Kretschmer 1997; Danysz and Parsons 1998; Paul and Skolnick 2003); (3) evidence that a dysfunction of glutamatergic transmission is implicated in psychotic states (Meador-Woodruff and Healy 2000; Breese et al. 2002; Pralong et al. 2002; Schiffer 2002; Konradi and Heckers 2003); and (4) the rich palette of ionotropic and metabotropic glutamatergic receptors available for therapeutic intervention.

The present article is principally devoted to NMDA receptors or, more precisely, their $Glycine_B$ co-agonist site—also referred to as the "NR1 subunit glycine binding site." This site can be distinguished from $Glycine_A$ receptors which mediate a major mode of inhibitory transmission in the CNS. Detailed reviews of the significance of NMDA receptors to the etiology of schizophrenia have appeared in recent years (Marino and Conn 2002; Millan 2002; Heresco-Levy 2003; Van Berckel 2003). The present paper emphasizes *recent* findings supporting the notion that a functional deficit at NMDA receptors participates in the induction of psychotic states. It also focuses upon novel concepts for clinical compensation of this hypoactivity. For an understanding of such issues, it is indispensable to outline the complex nature of NMDA receptors and their regulation by endogenous ligands.

NMDA receptors: structure and modulatory sites

CNS-localized NMDA receptors are heteromers comprised of various assemblies of (probably two) NR1 subunits together with two or three NR2 subunits (Fig. 1) (Danysz and Parsons 1998; Dingledineet al. 1999; Yamakura and Shimoh 1999; Cull-Candy et al. 2001; Madden 2002; Millan 2002). At least four classes of NR2 subunit are known: A, B, C and D. The contribution of specific NR2 subunits to NMDA receptors is important in determining their functional profiles, desensitisation kinetics, modulation and both the affinity and efficacy of agonists at $Glycine_B$ sites (Vicini et al. 1998; Cull-Candy et al. 2001; Sheinin et al. 2001; Madden 2002; Liu et al. 2004). Certain NMDA receptors contain several types of NR2 subunits or various isoforms of NR1 subunit. Both NR1 and NR2A subunits are distributed throughout the CNS, being concentrated in the hippocampus, thalamus, frontal cortex and other structures implicated in psychotic states and their control (Danysz and Parsons 1998; Goebel and Poosch 1999; Cull-Candy et al. 2001; Millan 2002). These regions are also rich in NR2B subunits, whereas, despite their presence in forebrain structures, NR2C and NR2D subunits are preferentially found in the cerebellum and brainstem/spinal cord, respectively (Goebel and Poosch 1999; Yamakura and Shimoh 1999; Cull-Candy et al. 2001). Integration of developmentally regulated NR3 subunits into NMDA (NR1/NR2) receptors *attenuates* their activity, while construction of NR3/NR1 subunits *only* yield glycine-sensitive—but glutamate-refractory—receptors of low Ca^{2+} permeability (Chatterton et al. 2002). Though such sites may be relevant to abnormal processes in the developing schizophrenic brain (Deutsch et al. 2001; Millan 2002; Lipska 2004), it is not clear whether they exist in the adult. Further, NR3/NR1 heteromers are resistant to psychotomimetic open channel blockers (OCBs) (see below) questioning their relevance to the genesis of psychotic states in adults.

NMDA and $Glycine_B$ recognition sites are located in homologous regions of NR2 and NR1 subunits, respectively (Fig. 1) (Yamakura and Shimoh 1999; Cull-Candy et al. 2001; Moretti et al. 2004). Despite their physical separation, glutamate and $Glycine_B$ binding sites functionally interact (Danysz and Parsons 1998). For example, glycine enhances the affinity and efficacy of glutamate, an action contributing to its ability to delay desensitisation and to increase the duration and frequency of the open state of the channel (Dingledine et al. 1999). Irrespective of subunit composition, all (NR1/NR2) species of NMDA receptor reveal voltage-dependent blockade by Mg^{2+} which binds to (multiple) sites in the ion channel, restricting the flux of Ca^{2+} (Dingledine et al. 1999; Cull-Candy et al. 2001). Neuronal depolarisation relieves the depolarisation block of NMDA receptor-coupled ion channels. A further common feature of NMDA receptors is a binding site recognized by OCBs, such as the pro-psychotic agents, ketamine and phencyclidine (PCP) (Dingledine et al. 1999).

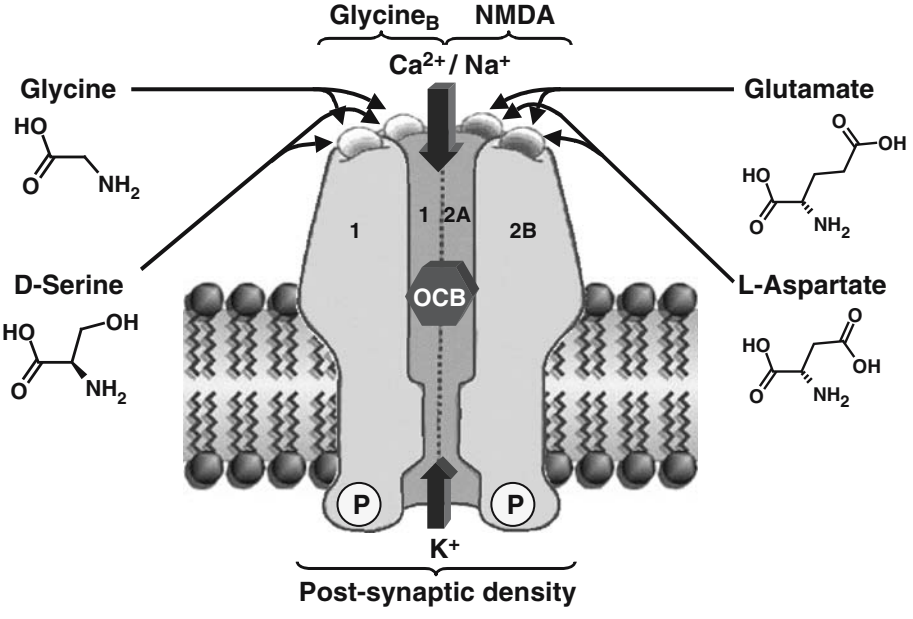

Fig. 1 Schematic illustration of central NMDA receptors bearing co-agonist glutamate and $Glycine_B$ sites. *OCB* Open channel blocker, *P* phosphorylation site(s). Numerous modulatory sites on NR2 subunits responsive to, for example, haloperidol and polyamines, are not indicated for the sake of clarity

NMDA receptors are primarily neuronal but may also be found on astrocytes (Nedergaard et al. 2002; Bezzi et al. 2004). They bear a variety of modulatory sites accessible to intracellular and extracellular mediators such as polyamines, protons, ifenprodil, zinc, glutathione, neurosteroids, ATP and even the antipsychotic haloperidol (Brimecomb et al. 1998; Dingledine et al. 1999; Jang et al. 2004; Kloda et al. 2004; Turecek et al. 2004). Despite their localization on NR2 subunits, modulatory sites can modify the functional status of $Glycine_B$ receptors on NR1 subunits (Yamakura and Shimoh 1999; Cull-Candy et al. 2001). Functional characteristics of NMDA and $Glycine_B$ binding sites can also be modified upon phosphorylation of NR1 or NR2 subunits by protein kinases (Dingledine et al. 1999; Yamakura and Shimoh 1999; Cull-Candy et al. 2001). NMDA receptors interact with diverse postsynaptic proteins incorporated into a "postsynaptic density" (Fig. 1). These proteins regulate the clustering of NMDA receptors in the plasma membrane, modify channel activity and influence their interaction with phosphorylating kinases (Husi et al. 2000; Madden 2002; Iwamoto et al. 2004).

NMDA receptors: multiple endogenous ligands—agonists and antagonists

Perhaps the most surprising feature of NMDA receptors is their responsiveness to a diversity of endogenous ligands, several of which behave as *antagonists* (Figs. 2, 3).

Glycine

Though some glycine may be available to NMDA receptors following "spillover" from glycinergic neurones (Ahmadi et al. 2003), the majority is derived from glial cells (Millan 2002; Miller 2004). Therein, glycine is generated from L-serine via the reversible enzyme, serine hydroxymethyltransferase. Non-released (and recaptured) glycine may be converted back into L-serine, or catabolised (in mitochondria) into inactive metabolites via the poorly characterised multi-enzyme "glycine cleavage system" (Sakata et al. 2001; Millan 2002; Ichinohe et al. 2004). Liberation of glycine from astrocytes is primarily non-vesicular and Ca^{2+}-independent, presumably effected via reversal of glycine transporters upon changes in extracellular levels of glycine and alterations in ion flux (Gadea and Lopez-Colome 2001). Indeed, glial cells possess a high density of glycine-1 transporters (GlyT-1), of which the cerebral distribution tracks the localization of synapses bearing NMDA receptors (Gadea and Lopez-Colome 2001; Chen et al. 2003). These transporters (of which three isoforms have been identified) rapidly take up glycine in a Na^+- and Cl^--dependent fashion and are principally responsible for clearing glycine from the synaptic cleft. In addition, some glycine may be taken up (and released) by small neutral amino acid transporters (SNAT), System A: SNAT 5 on astrocytes and SNAT 1 on neurones (Javitt 2002; MacKenzie and Erickson 2004; Cubelos et al. 2005). A little may also be removed by spatially remote GlyT-2

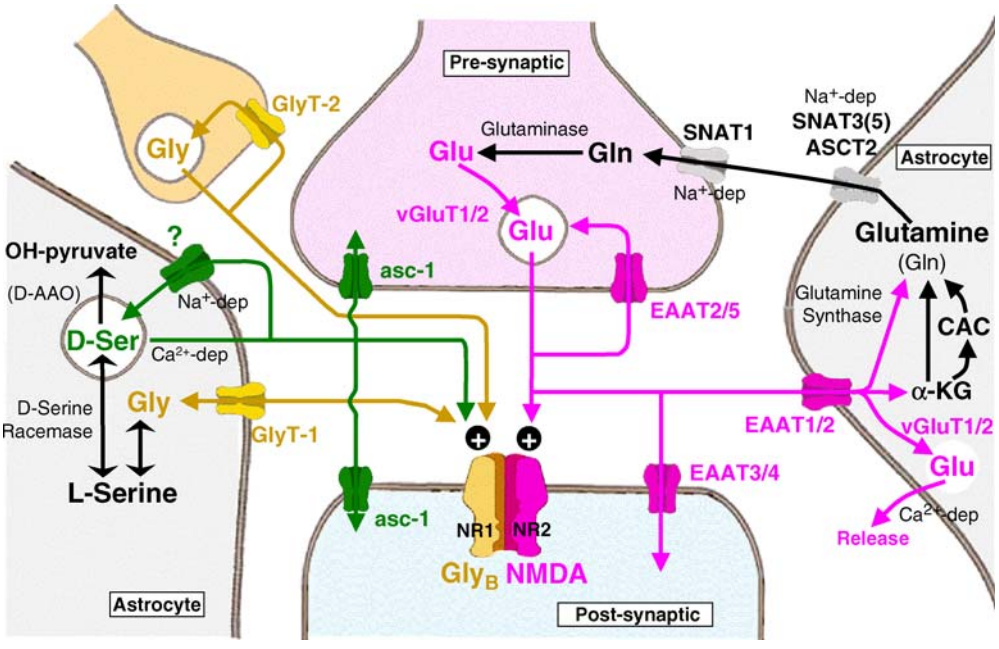

Fig. 2 Generation and synaptic clearance of major endogenous agonists (glutamate, aspartate, glycine, D-serine) at NMDA and $Glycine_B$ recognition sites on NMDA receptors. *GlyT* Glycine transporter, *EAAT* excitatory amino acid transporter, *asc* alanine–serine–cysteine transporter, *SNAT* specific neutral amino acid transporter, *vGluT* vesicular glutamate transporter, *CAC* citric acid cycle, *D-AAO* D-amino acid oxidase, *α-KG* α-keto-glutarate. As discussed in the text, the precise role of multiple glial and neuronal transporters of D-serine remains unclear. Neuronal SNAT 1 also clears glycine. Mechanisms of glutamine efflux are unclear but likely involve reversal of several classes of transporter. Note that the elements illustrated are not necessarily all enriched and co-localized throughout the CNS. For example, the concentration of D-AAO is high in the cerebellum yet low in the forebrain, whereas the GlyT-2 transporter is principally found in the hindbrain and spinal cord

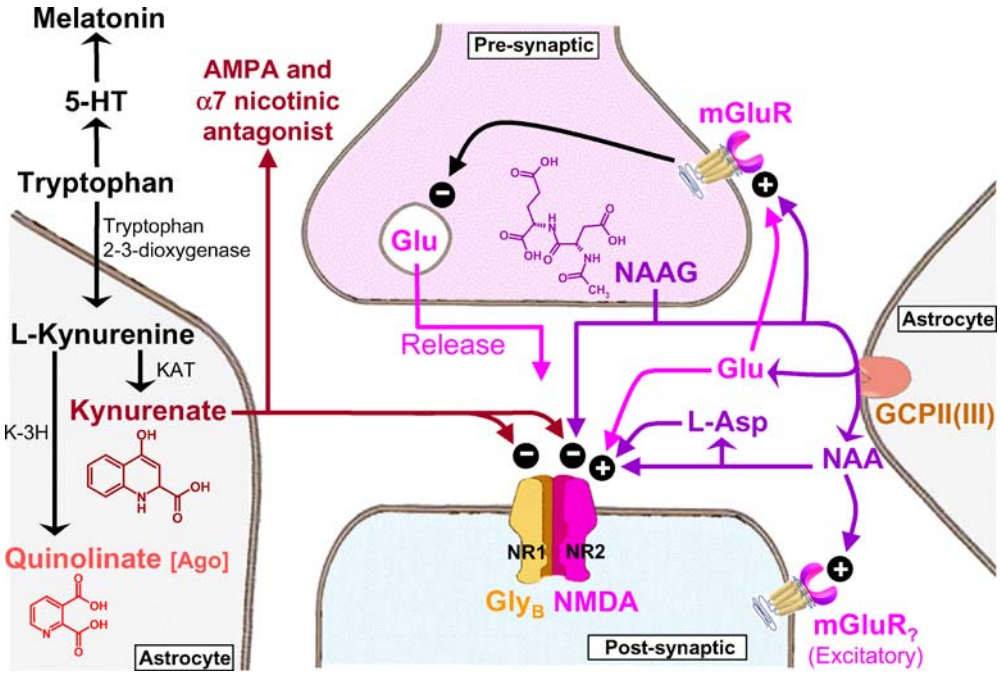

Fig. 3 Generation and synaptic clearance of various endogenous ligands at NMDA and Glycine$_B$ recognition sites on NMDA receptors. *5-HT* Serotonin, *NAAG* *N*-acetyl-aspartate-glutamate, *NAA* *N*-acetyl-aspartate, *GCP* glutamate carboxypeptidase, *KAT* kynurenate amino transferase; *K-3H* kynurenate-3-hydroxylase. Quinolate possesses agonist properties at Glycine$_B$ and NMDA sites. At high concentrations, kynurenate antagonizes AMPA and kainate receptors. It is also a potent antagonist at α_7 nicotinic receptors. Note alternative pathways for transformation of tryptophan into 5-HT/melatonin. Mechanisms for release and clearance of kynurenate are unknown. Several subclasses of inhibitory (Group II and III) metabotropic mGluR receptor are localized on glutamatergic terminals. At high concentrations, the κ-opioid agonist, dynorphin, interacts with NMDA receptors, for example, in hippocampus (Caudle and Dubner 1998; Wollemann and Benyhe 2004), but it is unclear whether its inhibitory effects are relevant to psychotic states. Further, in schizophrenic patients, conflicting data have been documented concerning levels of dynorphin (Heikkilä et al. 1990), and linkage studies have not clearly related the dynorphin gene to schizophrenia (Ventriglia et al. 2002)

transporters on glycinergic neurones. Despite the original assumption that glycine fully occupies Glycine$_B$ sites, GlyT-1 and SNAT transporters are efficient in maintaining locally low and non-saturating levels of glycine (Danysz and Parsons 1998; Haradahira et al. 2003). Accordingly, Glycine$_B$ agonists and drugs blocking GlyT-1—glycine reuptake inhibitors (GRIs)—increase activity at NMDA receptors, providing a basis for potential antipsychotic properties.

D-Serine

L-Serine can be transformed into D-serine by D-serine racemase (Wolosker et al. 1999; Miller 2004; Xia et al. 2004). Though present in the liver and kidneys, D-serine racemase is enriched in the hippocampus, cortex and other cerebral structures which possess high levels of NMDA receptors (Schell et al. 1995; Wolosker et al. 1999; De Miranda et al. 2000). D-Serine is a high efficacy agonist at Glycine$_B$ sites and, dependent upon subunit composition, may be more efficacious than glycine itself (Danysz and Parsons 1998; Wolosker et al. 1999; Mothet et al. 2000). Like D-serine racemase, D-serine is predominantly found in astrocytes enveloping glutamatergic terminals in forebrain regions (Wolosker et al. 1999; Mothet et al. 2000; Miller 2004; Xia et al. 2004). In fact, levels of D-serine appear to be inversely correlated with those of the glial enzyme, D-amino acid oxidase (D-AAO), which cleaves (deaminates) D-serine into hydroxypyruvate (Wolosker et al. 1999; Urai et al. 2002; Miller 2004). The localization of D-AAO in glial cells implies that they participate in elimination of D-serine from the synaptic cleft. Though the identity of these glial D-serine transporters (which may be Na^+-dependent) is unclear, they are certainly different from GlyT-1 transporters (Ribeiro et al. 2002). Neurones can also take up D-serine (and L-serine) via a Na^+-independent, alanine–serine–cysteine (asc) transporter termed asc-1 found in pyramidal cells of the cortex and hippocampus: it is localized postsynaptically on soma and dendrites, as well as presynaptically on terminals (Nakauchi et al. 2000; Helboe et al. 2003; Matsuo et al. 2004). A further (alanine-insensitive) D-serine transporter has been reported in rat brain, though its nature remains unclear (Javitt et al. 2002; Helboe et al. 2003). Reversal of the glial D-serine transporter may lead to liberation of D-serine (Ribeiro et al. 2002; Miller 2004), but release is principally accomplished (in contrast to glycine) in a vesicular and Ca^{2+}-dependent fashion

(Mothet et al. 2000, in press; Cook et al. 2002; Bezzi et al. 2004; Parpura et al. 2004).

Glutamate

In neurones, glutamate is loaded by vesicular glutamate transporters (vGluT) into vesicles, then released onto postsynaptic NMDA receptors (Danysz and Parsons 1998; Madden 2002; Trudeau 2004). Several classes of Na^+-dependent, excitatory amino acid transporter (EAAT) have been identified. They are localized on postsynaptic neurones, on presynaptic glutamatergic terminals and, most importantly, on glial cells (Danbolt 2001; Nedergaard et al. 2002). The principal circuit for regeneration of glutamate is, then, its recapture by astrocytes and subsequent conversion by glutamine synthase into glutamine, which is also generated from glutamate derived from the citric acid cycle (Marcaggi and Attwell 2004). Glutamine is liberated from astrocytes by multiple Na^+-dependent and Na^+-independent mechanisms, including reversal of the transporters "ASCT2" and a System N subtype of SNAT (Fig. 3) (Deitmer et al. 2003; Dolinska et al. 2004; Kanamori and Ross 2004). The latter *differs* to the "A" class of SNAT on neurones (SNAT 1) which takes up glutamine in a Na^+-dependent fashion (Kanamori and Ross 2004; MacKenzie and Erickson 2004). Completing the cycle, glutamine is transformed by glutaminase into glutamate in neurones. An additional pool of glutamate is provided by glial cells, partly via reversal of EAAT1 (GLAST) and/or EAAT2 (GLT-1). Glutamate is also liberated from astrocytes via gap junction hemichannels (Ye et al. 2003). In addition, astrocytes possess vGluT1 and vGluT2, permitting its release by Ca^{2+}-dependent and exocytotic mechanisms (Nedergaard et al. 2002; Bezzi et al. 2004; Montana et al. 2004; Parpura et al. 2004).

N-Acetyl-aspartate-glutamate

A final source of extracellular glutamate is provided by extracellular cleavage of *N*-acetyl-aspartate-glutamate (NAAG) (Neale et al. 2000; Barinka et al. 2004) via two forms of glutamate carboxypeptidase (GCP) II and III localized on plasma membranes of astrocytes (Berger et al. 1999; Speno et al. 1999; Bacich et al. 2002; Bzdega et al. 2004; Vieira and Devlin 2004). GCP II/III simultaneously generate a further agonist, aspartate, which is also derived from glutamatergic—as well as GABAergic—terminals (Gundersen et al. 2004). Extracellular aspartate is, in fact, generated from NAAG via *N*-acetyl-asparate (Fig. 5), a weak agonist at the NMDA recognition site and an agonist at excitatory metabotropic receptors (Rubin et al. 1995; Yan et al. 2003). Transformation of NAAG into glutamate, *N*-aspartyl-aspartate and asparate shifts the balance to postsynaptic *excitation* since NAAG has *low* intrinsic activity at NMDA receptors sites and behaves as an *antagonist* relative to glycine and D-serine, for example, in the CA1 region of the hippocampus (Grunze et al. 1996; Coyle 1997; Bergeron et al. 2005). Moreover, NAAG is an agonist at presynaptic metabotropic $(mGluR)_3$ receptors inhibitory to glutamate release (Neale et al. 2000; Garrido Sanabria et al. 2004; Olszewski et al. 2004). Thus, a disequilibrium in conversion of NAAG may modify activity at NMDA receptors—and this occurs in psychotic states. Astrocytes do not only cleave NAAG: they also take it up via a proton-coupled di/tripeptide transporter termed "PEPT2" (Fujita et al. 2004; Terada and Inui 2004).

Kynurenate

Kynurenate behaves as an antagonist at the glutamate recognition site and, with greater potency, at $Glycine_B$ sites (Schwarcz and Pellicciari 2002). The ultimate source of kynurenate is tryptophan, and the glial pathway, which results in formation of kynurenate, is an alternative to neuronal generation of serotonin and melatonin (Stone and Darlington 2002). Interestingly, kynurenine also behaves as a weak antagonist at AMPA and kainate sites (Stone and Darlington 2002) and possesses antagonist properties at α_7-nicotinic receptors (Alkondon et al. 2004). Despite these additional actions, blockade of $Glycine_B$ and NMDA sites by kynurenate likely contributes to its influence upon mood, monoaminergic transmission and motor function, including its perturbation of sensory auditory gating, an effect common to many pro-psychotic agents (Erhardt and Engberg 2002; Stone and Darlington 2002; Erhardt et al. 2004). Currently, little is known concerning glial release and recapture of kynurenate. Interestingly, L-kynurenine can be transformed into quinolinate, a weak agonist at $Glycine_B$ and NMDA receptors—which possesses neurotoxic properties (Schwarcz and Pellicciari 2002; Stone and Darlington 2002). Thus, alternative enzymatic conversion of L-kynurenine can alter the balance between endogenous agonists and antagonists at NMDA receptors.

Evidence that a deficit in transmission at NMDA sites is involved in schizophrenia

Pro-psychotic actions of open channel blockers

The OCBs, PCP and ketamine, trigger re-emergence of symptoms in remitted schizophrenia patients and elicit hallucinations and other psychotomimetic effects in normal subjects (Steinpreis 1996; Adler et al. 1999; Millan 2002; Coyle and Tsai 2004). Though their effects are not identical to deficits seen in schizophrenia, they more closely resemble psychotic disorders than those of monoaminergic psychostimulants such as amphetamine, notably as regards cognitive disruption and the induction of thought disorders and negative symptoms (Lahti et al. 2001; Abel et al. 2003; Van Berckel 2003; Morgan et al. 2004). Their actions are variably attenuated by antipsychotics such as haloperidol and clozapine (Malhotra et al. 1997; Lahti et al. 2001;

Oranje et al. 2002, Van Berckel 2003). Neuronal mechanisms underlying the effects of OCBs are many, of which the following should be briefly evoked:

1) Sensitisation of subcortical and cortical dopaminergic pathways (Kegeles et al. 2000, 2002; Balla et al. 2003; Laruelle et al. 2003)
2) Activation of mesolimbic serotonergic pathways and consequent recruitment of corticolimbic populations of 5-HT_{2A} receptors, effected independents of NMDA receptors (Millan et al. 1999; Aghajanian and Marek 2000)
3) Disruption of striatothalamic filtering of sensory input into the cortex (Carlsson et al. 2001)
4) A generalized perturbation of hippocampal function (Tamminga et al. 2003)
5) Disinhibition of cortico-cortical glutamatergic loops (Moghaddam and Jackson 2003)
6) A generalized disruption of cortical activity via desynchronization and reduced efficiency of neural transmission (Jackson et al. 2004)
7) Excessive cholinergic transmission in cortex (Farber 2003)
8) Excitotoxic damage elicited via non-NMDA receptors (Deutsch et al. 2001; Lewis and Levitt 2002; Farber 2003)

One common mechanism underlying these changes may be interruption of a NMDA receptor-mediated, tonic excitation of GABAergic interneurones inhibitory to projection neurones (Carlsson et al. 2001; Farber 2003; Schiffer et al. 2003; Shi and Zhang 2003; de Lima et al. 2004).

Underpinning a role of NMDA receptors in the psychotomimetic effects of PCP and ketamine in man and rodents, they are at least partially mimicked by antagonists at the NMDA recognition site (Lowe et al. 1994; Muir and Lees 1995; Bakshi et al. 1999; Dyker et al. 1999). However, it would be unwise to automatically attribute the full complement of pro-psychotic properties of OCBs to interruption of transmission at NMDA receptors. Thus, selective blockade of NR2B or NR2A subunits alone may not elicit psychosis (Higgins et al. 2003; Spooren et al. 2004). Further, $Glycine_B$ antagonists do not mimic behavioural effects of OCBs in rodents and, at least at modest doses, do not appear to be psychotomimetic in man (Danysz and Parsons 1998; Lees et al. 2001; Beardsley et al. 2002; Millan 2002). It is also worth pointing out that memantine, an "atypical," low affinity OCB with distinctively rapid kinetics, does not elicit psychotic symptoms in man at doses exerting clinically relevant benefit in Alzheimer's disease (Reisberg et al. 2003). Finally, direct interactions of PCP and ketamine with sites other than NMDA receptors (including monoaminergic receptors and transporters, sigma binding sites and ion channels) contribute to their functional and, possibly, pro-psychotic properties (see point 2 above) (Steinpreis 1996; Millan et al. 1999; Kapur and Seeman 2002; Millan 2002; Yu et al. 2002; Van Berckel 2003).

Psychotic-like phenotype of mice possessing genetically modified NMDA receptors

In rodents, PCP, ketamine and other more selective OCBs elicit bizarre behaviours, hyperactivity and cognitive deficits, certain of which are attenuated by antipsychotic agents (Steinpreis 1996; Schmidt and Kretschmer 1997; Millan 2002). Notably, mice in which the functional status of NMDA receptors has been genetically modified show phenotypes bearing comparison to the effects of OCBs. First, "compound" heterozygotic mice bred from two lines possessing point mutations in the NR1 subunit showed a sustained (antipsychotic-resistant) hyperactivity. They also revealed a suppression of hippocampal long-term potentiation which could be rescued by D-serine (Ballard et al. 2002). Second, mice in which the NR1 subunit was substantially "knocked-down" (by 95%) showed motor hyperactivity and stereotypies which were specifically abrogated by clozapine (Mohn et al. 1999). Dopaminergic transmission was not accelerated, but these mice also manifest deficits in sexual and social behaviour, as well as compromised sensory filtering (prepulse inhibition) underpinning a psychosis-like phenotype (Mohn et al. 1999; Duncan et al. 2004b, Miyamoto et al. 2004). Third, homozygotic mice in which the NR2A subunit was deleted revealed learning deficits and a hyperlocomotion which was attenuated by antipsychotics. This increase in locomotor behaviour was possibly related to an overactivity of ascending dopaminergic and serotonergic pathways (Miyamoto et al. 2001). However, this interpretation must be made cautiously since elimination of activity at both NR2A and NR2B receptors is requisite for the induction of hyperlocomotion and a psychotic-like phenotype (Kadotani et al. 1996; Higgins et al. 2003; Spooren et al. 2004). Finally, though of less obvious pertinence to schizophrenia, mice overexpressing NR2B receptors revealed enhanced hippocampal long-term potentiation and improved cognitive performance (Tang et al. 1999).

Alterations in NMDA receptors in schizophrenia

Neurochemical studies of glutamatergic neurotransmission in psychotic patients support the hypothesis that the functional activity of NMDA receptors is perturbed. However, observations have proven surprisingly inconsistent (Table 1) (Millan 2002; Schiffer 2002; Van Berckel 2003; Coyle and Tsai 2004). Reasons underlying disparate data include the following: (1) the influence of treatment with antipsychotics or other drugs—very few studies have controlled for this; (2) disease status at the time of measurement; (3) contrasting findings for measures of mRNA encoding NMDA receptor subunits as compared to radioligand binding studies; (4) age; and (5) differences between cerebral structures. Decreases in NMDA receptor density may reflect reduced function. On the other hand, increases in NMDA receptor density have also been construed as "compensating" (upregulation) for reduced stimulation by endogenous ligands. Though there are data supporting the latter

Table 1 Summary of major alterations in expression (mRNA levels) of NMDA receptor subunits in schizophrenia

	NR1		NR2A	NR2B	NR2C	NR2D
Structure	mRNA	Binding	mRNA	mRNA	mRNA	mRNA
Thalamus	↓	↓	–	↓	↓	–
Cortex[a]	↓/–/↑	↑	↑	↑	–	↑
Hippocampus	↓	?	–	↑	–	–
Substantia Nigra	↑	?	–	–	–	–

↓ = Decrease, ↑ = increase and – = no significant change. "Binding" refers to radioligand studies of $Glycine_B$ sites on the NR1 subunit
[a]Data for cortex are variable and depend on the region investigated (see text)

notion, one must be cautious in adopting such interpretations. Indeed, changes in levels of mRNA encoding NMDA receptor subunits are difficult to interpret in the absence of information on levels of the corresponding protein.

Notwithstanding the above caveats, schizophrenia is accompanied by a broad pattern of alterations in NMDA receptor-related subunits in the thalamus, a structure dysfunctional in schizophrenia (Clinton and Meador-Woodruff 2004a,b). Thus, robust decreases in levels of mRNA encoding NR1 subunits have been reported, together with reduced binding of the $Glycine_B$ radioligand, [^{3}H]MDL105,519 (Ibrahim et al. 2000; Meador-Woodruff et al. 2003; though see Popken and Leggio 2002). The diminished expression of NR1 subunits may be specific to the exon 22 containing isoform, a region of the NR1 subunit which interacts with the postsynaptic density; correspondingly, expression of genes encoding several of these proteins was also modified in the thalamus of schizophrenic patients (Clinton et al. 2003; Meador-Woodruff et al. 2003; Clinton and Meador-Woodruff 2004a,b). Though NR2A and NR2D subunits were unaffected, NR2B and NR2C subunits were diminished, changes paralleled by a reduction in binding of the NR2B subunit radioligand, [^{3}H]ifenprodil; in contrast, binding to NMDA recognition sites and to ion channels was unaffected. Consistent with enhanced glutamate clearance, expression of glial EAAT1/2 was elevated (Ibrahim et al. 2000, but see Clinton and Meador-Woodruff 2004a). Completing the picture of alterations in glutamatergic function, expression of vGluT2 and glutamatinase increased, though these changes suggest *enhanced* glutamate availability (Smith and Haroutunian 2001a,b; Meador-Woodruff et al. 2003).

The thalamus provides a major afferent pathway to the cortex. This projection appears to be overactive in schizophrenia reflecting compromised filtering of sensory information (Carlsson et al. 2001; Clinton and Meador-Woodruff 2004a,b). In fact, findings in the cortex are more variable than for the thalamus. Decreases in NR1 subunits were found in entorhinal and temporal cortex, yet inconsistent decreases, a lack of change or even increases were seen in subterritories of frontal cortex (Meador-Woodruff and Healy 2000; Millan 2002; Van Berckel 2003). Interestingly, in the study of Humphries et al. (1996), the reduced level of mRNA encoding NR1 subunits in temporal cortex was correlated with cognitive decline. Underpinning a relationship of alterations in NR1 subunit expression to cognitive status, reductions have likewise been seen in the frontal and occipital cortex of Alzheimer's patients (Dracheva et al. 2001; Hynd et al. 2004). As compared to NR1 and other subunits, a relative increase of NR2A subunits was seen in frontal and occipital cortex (mRNA), of NR2B subunits in temporal cortex (binding) and of NR2D subunits (mRNA) in prefrontal cortex (Akbarian et al. 1996; Grimwood et al. 1999; Dracheva et al. 2001; Woo et al. 2004). Despite these changes, binding of radioligands to $Glycine_B$ sites was *increased* in several cortical areas; further, no consistent pattern of changes has been seen with radioligands at recognition sites for glutamate (Ishimaru et al. 1994; Grimwood et al. 1999; Millan 2002; Zavitsanou et al. 2002; Van Berckel 2003). Thus, while cortical NMDA receptors are affected in schizophrenia, there is no clear evidence for a reduction in their activity.

Nevertheless, in the hippocampus, which is dysfunctional in schizophrenia (Medoff et al. 2001), decreases in NR1 subunit mRNA were asymmetrically localized to the left half of the brain; this laterality resembles other functional deficits characterising schizophrenia (Gao et al. 2000; Law and Deakin 2001; Crow 2004). A relative increase in NR2B mRNA but no change in NR2A subunits was noted (Harrison et al. 2003). Paralleling decreases in NR1 subunits, a reduction in mRNA encoding vGluT1 was seen: this suggests a reduction in glutamate loading into synapses and in glutamate release (Harrison et al. 2003).

In the striatum, neither studies of NMDA receptor subunit expression nor of radioligand binding have revealed marked changes (Meador-Woodruff and Healy 2000; Millan 2002; van Berckel 2003). Cortical glutamatergic pathways provide a major input to the striatum. They also (together with the bed nucleus of the stria terminalis, subthalamic nucleus and lateral dorsal tegmentum) send glutamatergic afferents to the substantia nigra and ventrotegmental area (Meltzer et al. 1997; Stefensen et al. 1998; Georges and Aston-Jones 2002; Laruelle et al. 2003; Sesack et al. 2003). These glutamatergic inputs, which act via both NMDA and non-NMDA (AMPA) receptors (Mathé et al. 1998; Adell and Artigas 2004), target dopaminergic perikarya and GABAergic neurones (Fig. 4) (Carlsson et al. 2001; Chen et al. 2001; Sesack et al. 2003; Takahata and Moghaddam 2003). Thus, an interesting finding was an increase in levels of NR1 subunits in the substantia nigra in schizophrenia (Mueller et al. 2004), coinciding with the argument that *excessive* activity at NMDA receptors on subcortical dopaminergic cell bodies may contribute to their hypersensitivity/hyperactivity in schizophrenia. Hence, *antagonist* properties at these populations might be favourable to its management (Fig. 4) (Carlsson et al. 2001; Millan 2002; Moghaddam 2003).

Thus, alterations in NR2 subunits in schizophrenic brains vary in an isoform and structure-dependent fashion and require further characterisation. However, observations in the thalamus, hippocampus and cortex coincide with the notion of reduced function at NR1 subunits bearing $Glycine_B$ sites.

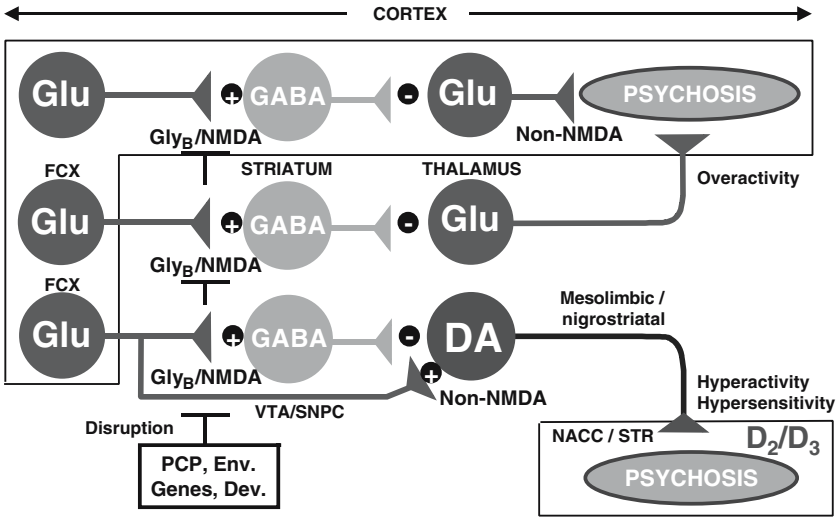

Fig. 4 Overview of the NMDA receptor hypoactivity hypothesis of schizophrenia. *PCP* Phencyclidine, *VTA* ventrotegmental area, *SNPC* substantia nigra pars compacta, *NACC* nucleus accumbens, *GRI* glycine reuptake inhibitor. The organization of pathways is simplified—structures other than the cortex provide glutamatergic input to the striatothalamic filter and to dopaminergic neurons. Reduced activity at NMDA receptors is provoked by genetic, developmental and/or environmental factors (mimicked by PCP). Their hypoactivity leads to a reduction in GABAergic inhibitory tone onto glutamatergic neurons in the thalamus and cortex. Hyperactivity of the latter is implicated in the induction of psychotic states, possibly reflecting an indirect influence (not shown) upon subcortical mesolimbic dopaminergic pathways. The sensitivity and activity of mesolimbic dopaminergic pathways may also be enhanced upon a reduction in activity at NMDA receptors leading to a relief of inhibitory GABAergic tone. Accordingly to this configuration, antipsychotic strategies other than D_2/D_3 receptor blockade may be effective, e.g., recruitment of GlycineB receptors, blockade of certain classes of non-NMDA receptor and a reduction in cortical glutamate release (by lamotrigine or metabotropic agonists)

Despite the need for confirmatory data on levels of *protein* rather than mRNA, this contention is underpinned by studies of their endogenous ligands.

Alterations in endogenous ligands of NMDA receptors in schizophrenia

In certain investigations, evidence for reduced levels of glutamate (and aspartate) was reported in the cortex and hippocampus of schizophrenics, and, in one study, the magnitude of this decrease correlated with the intensity of positive symptoms (Fig. 5) (Tsai et al. 1995; Faustman et al. 1999; see Millan 2002; Théberge et al. 2003). Interestingly, synaptosomal liberation of glutamate was reduced in schizophrenic brain (Sherman et al. 1991). An additional mechanistic basis for a reduction in extracellular glutamate levels was recently provided by an elegant study of Matute et al. (2005). They showed that levels of both the mRNA and the protein for glial EAAT1 are elevated in the frontal cortex of schizophrenics and also that these transporters display a marked (fourfold) increase in functional activity. This

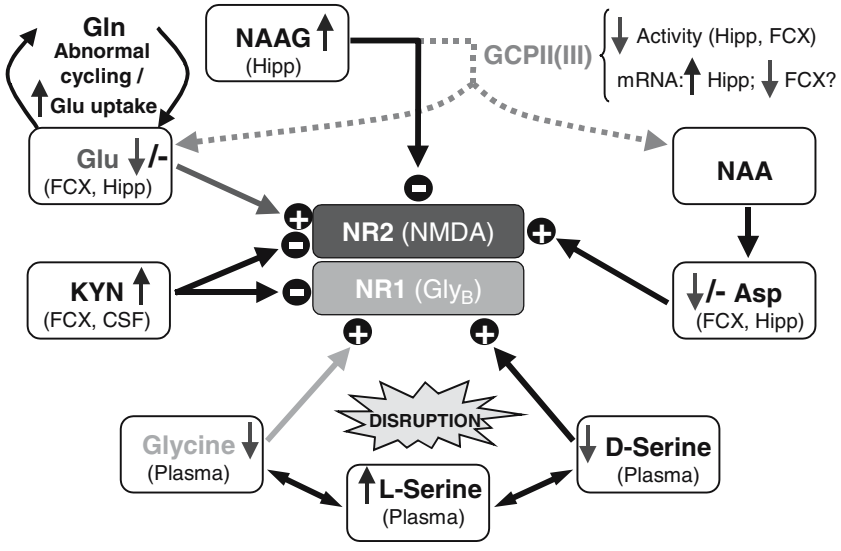

Fig. 5 Alterations in levels of endogenous ligands for NMDA receptors in schizophrenia. *NAAG N*-Acetyl-aspartate-glutamate, *NAA N*-acetyl-aspartate, *GCP* glutamate carboxypeptidase, *KYN* kynurenate, *Gln* glutamine, *FCX* frontal cortex, *Hipp* hippocampus. ↓ = Decrease, ↑ = increase and – = no significant change. For details of glutamate–glutamine cycling, see text

change appears to be specific inasmuch as levels of glial EAAT2 are reduced (Ohnuma et al. 2000). In the hippocampus, lower levels of glutamate may, on the other hand, be attributable to reduced numbers of glutamatergic terminals or to a decreased density of glial vGluT1 (Harrison et al. 2003). However, several studies have not found evidence for reduced glutamate levels in schizophrenia (see Millan 2002; Van der Heijden et al. 2004). Further, studies of the glutamate–glutamine cycle have revealed a complex pattern of changes not invariably consistent with reduced generation of glutamate. Thus, glutamine levels have been found (by the same group) to be either increased or decreased in cingulate cortex (Théberge et al. 2002, 2003), whereas both glutamine and glutamate were elevated in prodromic adolescents (Tibbo et al. 2004). Levels of glutamine synthase were reduced (consistent with elevated glutamate levels). On the other hand, higher levels of glutamate dehydrogenase suggest more rapid cleavage of glutamate to α-keto-glutarate, whereas elevated levels of glutamate acid decarboxylase indicate more rapid conversion to GABA (Gluck et al. 2002; Burbaeva et al. 2003). From these findings, it cannot be asserted with confidence that there is a generalized reduction in glutamate availability to cortical NMDA receptors in schizophrenia. Moreover, in the thalamus, increases in levels of glutamine, glutaminase, vGluT2 and EAAT1/2 might reflect *greater* rather than lesser availability of glutamate (Théberge et al. 2002, 2003; Meador-Woodruff et al. 2003). In any case, there is an interpretational challenge inasmuch as the relationship between changes in glutamate levels and specific populations of glutamatergic receptor—NMDA or other—remains unknown. Accordingly, changes in levels of other endogenous ligands may afford more direct information concerning the functional status of NMDA receptors.

As pointed out above, NAAG is cleaved by an astrocyte-localized GCP II/III into glutamate and aspartate. Tsai et al. (1995) reported higher levels of NAAG in frontal cortex and hippocampus, together with a decrease in the enzymatic activity of GCP II, that is, a shift in equilibrium from higher efficacy ligands (glutamate/aspartate) to a low efficacy ligand (NAAG) at NMDA receptors. However, contrary to expectations, levels of mRNA for GCP II were increased in the CA3 region of the hippocampus—though preliminary data indicate a reduction of mRNA for GLP II in frontal cortex (Hakak et al. 2001; Ghose et al. 2004).

Though it has long been accepted that glycine–serine metabolism is perturbed in schizophrenia, data showing reduced availability of glycine and D-serine to central NMDA receptors have proven difficult to obtain (Kumashiro et al. 1995; Millan 2002; Hashimoto et al. 2003; Sumiyoshi et al. 2004). However, Hashimoto et al. (2003) recently found that concentrations of D-serine in plasma are markedly reduced in psychotic patients. Levels of L-serine and of total serine were actually higher, an observation corroborated by Sumiyoshi et al. (2004). These (and other) authors also reported a decrease in circulating levels of glycine which was correlated with the severity of negative symptoms (Ermilov et al. 2004). These data likely reflect decreases in central availability of D-serine and glycine, but it would obviously be desirable to reproduce such findings at the cerebral level. In this light, it is of note that elevations in levels of the endogenous antagonist, kynurenate, were observed in the cortex and cerebrospinal fluid (Erhardt et al. 2001; Schwarcz et al. 2001).

Finally, the positive modulator of NMDA receptors, glutathione, interacts with an allosteric site—probably the same one as zinc—and decreases in its levels in schizophrenia were interpreted as contributing to reduced activity at these sites (Do et al. 2000).

To summarize (Fig. 5), these findings are globally in line with reduced stimulation of NMDA receptors in schizophrenia. However, data for glutamate are ambivalent. Further, the extent to which changes in plasma and cerebrospinal fluid levels of ligands for $Glycine_B$ and NMDA recognition sites reflect changes at the synaptic level remains unclear since local concentrations are tightly controlled by neuronal and astrocytic mechanisms of uptake and degradation (Figs. 2, 3).

Susceptibility genes for proteins which interact with NMDA receptors

Despite the high heritability of schizophrenia, the existence of multiple susceptibility genes of modest effect has hindered their identification (Collier 2003; Fukumaki and Shibata 2003; Harrison and Owen 2003; Elkin et al. 2004). Indeed, with the possible exception of NR2B subunits (Ohtsuki et al. 2001; Di Maria et al. 2004), no associations between genes expressing NMDA receptor subunits and schizophrenia have been found—despite positive reports for mGluR receptors and AMPA subunits (Schiffer 2002; Williams et al. 2002; Fukumaki and Shibata 2003). Nevertheless, polymorphisms in the promoter regions of NR1, NR2A and NR2B subunits may be associated with reduced NMDA receptor function and increased risk of schizophrenia (Miyatake et al. 2002; Itokawa et al. 2003; Lipsky and Goldman 2003). Further, several studies have pinpointed polymorphisms in genes which interact with NMDA receptors (Schiffer 2002; Harrison and Owen 2003).

Thus, linkage has been found between chromosome 8p and schizophrenia, and several markers in the neuroregulin (NRL1) gene located in this region comprise a haplotype associated with increased risk for schizophrenia (Stefansson et al. 2002, 2004; Williams et al. 2003; Yang et al. 2003). Further, "subtle" changes in expression patterns of three NRL1 isoforms were seen in schizophrenic brains (Hashimoto et al. 2004; Law et al. 2004). NRL1 is localized to vesicles in neuronal terminals containing glutamate. Following release, the NRL1 "ectodomain" binds to the receptor ErbB4 which co-localizes with NMDA receptors within the common postsynaptic density (Garcia et al. 2000; Dracheva et al. 2001; Moghaddam 2003; Stefansson et al. 2004). Accordingly, NRL1 enhances expression of NMDA receptors and increases their activity by promoting tyrosine kinase-mediated phosphorylation (Buonnano and Fischbach 2001). Support for functional interrelationships between NRL1 and NMDA receptors relevant to schizo-

phrenia was acquired in mice with mutant NRL1 genes. These animals displayed a reduced density of NMDA receptors and a motor hyperactivity reduced by clozapine (Gerlai et al. 2000; Stefansson et al. 2002, 2004). Further, mice lacking the gene for ErbB4 displayed cognitive deficits (Golub et al. 2004). In another region of the 8p chromosome close to the NRL1 gene, a further polymorphism associated with schizophrenia was found by Gerber et al. (2003). The gene encodes the catalytic unit of calcineurin which controls both activity at NMDA receptors and synaptic plasticity (Krupp et al. 2002; Hedou and Mansuy 2003). By analogy to NRL1, mice lacking calcineurin display behavioural abnormalities resembling schizophrenia (Miyakawa et al. 2003). Dysbindin may also be located in the postsynaptic density of NMDA receptors, and linkage to schizophrenia was reported in several studies (Vaillend et al. 1999; Schiffer 2002; Straub et al. 2002; Schwab et al. 2003). Interestingly, its levels are reduced in the cortex of schizophrenics (Weickert et al. 2004).

An association of the gene encoding D-AAO with schizophrenia was demonstrated by Chumakov et al. (2002), together with a polymorphism for a primate-specific gene, G72, which interacts with, and possible activates, D-AAO. These findings were recently corroborated by Korostishevsky et al. (2004). Collectively, the data are consistent with an overactivity of D-AAO in schizophrenia and, correspondingly, lower levels of D-serine.

Finally, the gene encoding GCP II was detected near a translocation breakpoint region related to increased risk for schizophrenia (Semple et al. 2001).

The above findings have been enthusiastically embraced by many commentators. However, it remains to be shown that such polymorphisms (alone or collectively) are associated with changes in the functional status of NMDA receptors likely to precipitate psychotic states.

Antipsychotic properties of drugs increasing activity at NMDA receptors

Agonists, partial agonists, GRIs: interpretational challenges

Numerous, chemically diverse antagonists at Glycine$_B$ sites have been synthetized, including the kynurenate analogue, 5,7-dichlorokynurenic acid, and the selective agent, L701,324 (Fig. 6). In contrast, reflecting limited scope for modification of the structure of glycine, it has proven difficult to design novel agonists at Glycine$_B$ sites (Bräuner-Osborne et al. 2000; Millan 2002). Despite extensive metabolism both peripherally and centrally, and its poor penetration of the blood–brain barrier, systemic administration of glycine increases brain levels of glycine in rodents and man (D'Souza et al. 2000; Javitt et al. 2004a). D-Serine is also highly metabolised but shows superior penetration into the CNS, allowing for the use of lower doses (Hashimoto and Chiba 2004). A further advantage vs glycine is low affinity for Glycine$_A$ receptors, though nephrotoxicity limits its utility in rats. As regards synthetic ligands, all *selective* Glycine$_B$ agonists possess lower efficacy than glycine and D-serine at Glycine$_B$ sites, for example, the cyclic agents, S18841 and D-cycloserine (DCS) (Fig. 6) (Danysz and Parsons 1998; Cordi et al. 1999; Millan 2002).

Knowledge of the precise degree of "resting" Glycine$_B$ receptor stimulation by endogenous ligands is critical for interpretation of the effects of exogenous ligands. Indeed, DCS and other partial agonists can, in principle, either activate or block Glycine$_B$ sites. Unfortunately, few studies have attempted to resolve this issue in showing that their actions are either blocked (if due to agonist properties) by selective antagonists or mimicked (if due to antagonist properties) (Millan 2002). Further compounding interpretation of the effects of partial agonists, their actions are *less*

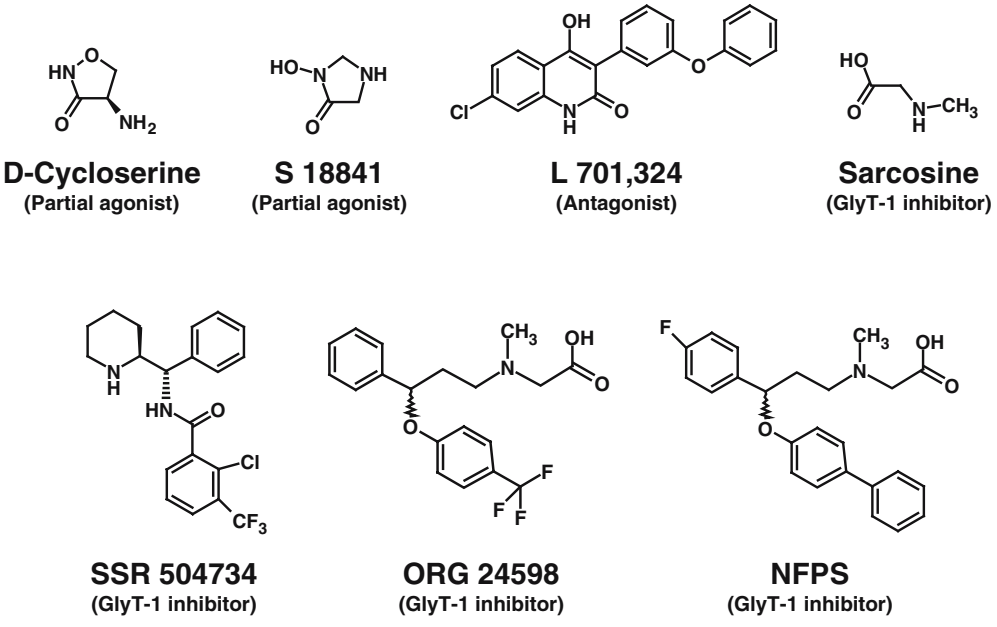

Fig. 6 Chemical structures of synthetic ligands at Glycine$_B$ receptors and glycine transporters. *NFPS* *N*-[3-(4′-Fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine, *ORG 24598* *R*-(−)-*N*-methyl-*N*-[3-[(4-trifluoromethyl)phenoxy]-3-phenyl-propyl]glycine, *SSR 504,734* (2-chloro-*N*-[(*S*)-phenyl[(2*S*)]-piperidin-2-yl]methyl)-3-trifluoromethyl benzamide. NFPS is also known as ALX-5407

pronounced at high vs low doses (Danysz and Parsons 1998). It is difficult to attribute biphasic dose–response curves to partial agonist properties since agonist effects should, on the contrary, be apparent at *high* low doses. Alternative explanations include the following: (1) high potency agonist actions at NMDA receptor subtypes *differing* to subtypes blocked at higher concentrations; (2) high dose interactions with "allosteric" sites or postsynaptic proteins negatively coupled to NMDA receptors; and (3) induction of NMDA receptor internalisation at high concentrations (Nong et al. 2003). Finally, DCS may exert actions independently of NMDA receptors (Rouaud and Billard 2003).

The amino acid and GRI, sarcosine, have been clinically evaluated in schizophrenia (see below; Tsai et al. 2004a,b), and several novel GRIs have been described, including ORG 24598 (Harsing et al. 2003), NFPS (Kinney et al. 2003) and SSR 504,374 (Depoortere et al. 2004) (Fig. 6). The major difficulty in interpreting their actions is a lack of knowledge concerning the significance of glycine vs D-serine at $Glycine_B$ sites implicated in psychotic states.

Actions of $Glycine_B$ receptor ligands and GRIs in models of antipsychotic properties

Glycine displays little effect in classical models of antipsychotic activity, such as blockade of the actions of hallucinogens and of psychostimulants (Table 2) (Javitt et al. 1997; Javitt 2002; Millan 2002). The awkward question arises of whether this poor activity suggests a lack of clinical antipsychotic properties. Alternatively, such models may be inappropriate to studies of $Glycine_B$ receptor ligands lacking, in contrast to conventional antipsychotics, antagonist properties at dopaminergic and serotonergic receptors. The latter position is underpinned by positive effects of glycine in two other models of schizophrenia. The first is neonatal lesions of the ventral hippocampus in rats. This developmental model is characterised by "psychosis-like" behaviours in adults and reduced release of glutamate in the hippocampus and frontal cortex (Schroeder et al. 1999; Lipska 2004). The second is chronic treatment with PCP which enhances the responsiveness of cortical and subcortical dopaminergic pathways to amphetamine.

Table 2 Actions of $Glycine_B$ agonists and glycine reuptake inhibitors (GRIs) in experimental models of antipsychotic properties

	Ventral hippocampal lesion		Chronic PCP	Acute PCP		Acute Amph	
	↑ Amph LA	↓ PPI	Amph. ↑ DA rel	↑ LA	↑ DA rel	↑ LA	↑ DA rel
Glycine/ D-serine	Yes	Yes	Yes	Yes	Yes	IA	IA
GRI	?	Yes	Yes	Yes	?	IA	IA

Yes = attenuated, ? = unknown and IA = inactive
LA Locomotor activity, *PPI* prepulse inhibition, *DA rel* DA release, *PCP* phencyclidine. See text for details

This phenomenon is seen both in rodents and in man and resembles psychotic states (Breier et al. 1997; Kegeles et al. 2000; Balla et al. 2001a,b; Javitt et al. 2004a). In the former model, glycine blocked increases in locomotor behaviour elicited by novelty and amphetamine (Kato et al. 2001). Further, it normalized the disruption of sensory motor gating—decreased prepulse inhibition—displayed by these animals (Le Pen et al. 2003). In the model of chronic PCP administration, long-term administration of glycine attenuated the enhanced ability of amphetamine to provoke central release of dopamine (Javitt et al. 2004a). The effects of glycine in these procedures presumably reflect its ability to normalize sustained deficits in activity at NMDA receptors. However, observations that glycine reduces the locomotor hyperactivity and subcortical dopamine release evoked by *acute* administration of OCBs are less easy to explain (Toth and Lajtha 1986; Javitt et al. 1997, 1999, 2000; Millan et al. 1999; Millan 2002).

Central administration of D-serine likewise blocked acute motor actions of PCP, an action expressed stereospecifically inasmuch as L-serine was ineffective. Further, the action of D-serine was prevented by 7-chlorokynurenate (Tanii et al. 1994). D-Serine also prevented disruption of learning by PCP (Campbell et al. 1999). When administered during the vulnerable postnatal period, PCP profoundly disrupts synaptogenesis leading to cognitive deficits in adult rats: chronic treatment with D-serine reversed the compromised spatial working memory shown by rats exposed to PCP (Andersen and Pouzet 2004). This neurodevelopmental model resembles neonatal hippocampal lesions (*vide supra*) and may relate to the disruption of declarative memory seen in psychotic patients (Perry et al. 2000).

Though DCS does not itself enhance prepulse inhibition in adult rats, it reversed its disruption by microinjection of $Glycine_B$ antagonists into the nucleus accumbens (Kretschmer and Koch 1998; Geyer et al. 2001). This suggests, in line with a broad pattern of procognitive properties in rodents (Andersen et al. 2002; Jones et al. 2004; Stouffer et al. 2004), that partial agonists might improve deficits in cognitive-attentional function shown by psychotic patients. Unfortunately, actions of partial agonists have not as yet been described in protocols of chronic PCP administration and neonatal hippocampal lesions. By analogy to glycine and D-serine, DCS reduces the induction of hyperlocomotion and limbic release of dopamine by PCP. However, it remains to be proven that such effects reflect agonist actions at $Glycine_B$ sites since they were *mimicked* by $Glycine_B$ antagonists (Millan 2002) which actually show antipsychotic actions in certain models (see Millan et al. 2000). Though at first sight paradoxical, these findings are compatible with a model depicted in Fig. 4 which permits both a direct excitatory and an indirect (GABA-mediated) inhibitory influence of NMDA receptors on dopaminergic perikarya (Carlsson et al. 2001; Moghaddam 2003). By analogy to glycine, DCS exerts little influence upon the actions of amphetamine and hallucinogens (Przegalinski et al. 1999; Javitt 2002; see Millan 2002). Finally, of direct relevance to adjunctive use in man, co-administration of DCS with other partial agonists enhances actions of

haloperidol against both amphetamine and PCP in rodents (Millan et al. 2000, unpublished observations).

There is a striking concordance in the actions of GRIs as compared to those of glycine in several experimental models (Table 2). Thus, NFPS mimicked glycine in preventing the sensitisation of amphetamine-induced dopamine release elicited by chronic administration of PCP (Javitt et al. 2004a). In a separate study, a further GRI, ORG 24598, mimicked glycine in preventing sensory motor (gating) deficits in rats sustaining neonatal lesions of the hippocampus (Le Pen 2003). Further, several GRIs abrogated acute PCP-induced hyperlocomotion with potencies correlating to their affinities at GlyT-1 sites (Javitt and Frusciante 1997; Javitt et al. 1999; Harsing et al. 2003). GRIs also reversed PCP-elicited changes in EEG power spectra in conscious rats (Harsing et al. 2003) and elicited cerebral patterns of c-*fos* expression similar to those seen with clozapine (Kinney et al. 2003). By contrast, GRIs show little activity in psychostimulant (amphetamine) models of antipsychotic activity, mimicking the weak activity of glycine. Indicative of improved cognitive function, GRIs enhanced hippocampal long-term potentiation and enhanced prepulse inhibition (Kinney et al. 2003). Finally, in line with these findings, in heterozygous mice with genetically inactivated GlyT-1 transporters, mnesic performance was improved and sensory motor gating was less perturbed by exposure to amphetamine (Tsai et al. 2004b).

Glycine and DCS were recently shown to suppress the vacuous oral movements provoked by long-term administration of haloperidol to rats (Shoham et al. 2004). This effect may reflect agonist actions at NMDA receptor sites incorporating NR2A subunits (Blanchet et al. 1999). Though surprising (Schmidt and Kretschmer 1997; Kretschmer 1998; Andreassen et al. 2003), this finding is paralleled by clinical findings outlined below.

To summarize, $Glycine_B$ agonists and GRIs present a coherent pattern of data overall consistent with antipsychotic properties in rodent models. However, such actions are generally seen *alone*. By contrast, as discussed below, their effects alone in schizophrenia have not been evaluated, rather their facilitatory influence upon the actions of antipsychotic drugs. In distinction to agonists, data indicating antipsychotic effects of the partial agonist, DCS, in rodents are not compelling, and it is unclear whether its potentiation of the actions of conventional antipsychotics reflects an increase in activity at NMDA sites.

Actions of $Glycine_B$ receptor ligands and GRIs in schizophrenic patients

Doses of glycine of up to 0.8 g/kg/day (generally 40–60 g) safely achieve increases in cerebrospinal fluid levels of glycine, and about a dozen studies of nearly 200 patients have described the effects of glycine as an adjunct to antipsychotic treatment (Heresco-Levy 2000, 2003; Millan 2002; Heresco-Levy and Javitt 2004; Tuominen et al. 2005). Several trials (usually over 6 weeks) were placebo-controlled and double blind, and glycine was shown not to influence serum levels of antipsychotics (Leiderman et al. 1996; Javitt et al. 2001). As summarized in Table 3 and discussed in the above citations, addition of glycine to haloperidol and other conventional neuroleptics achieves a dose-dependent decrease in primary negative symptoms and more modest but significant improvements of cognitive and positive symptoms. Notably, these effects were seen in otherwise treatment-resistant patients, and the effectiveness of glycine was inversely proportional to pretreatment levels of glycine in serum. Moreover, there was no exacerbation of the extrapyramidal side effects of antipsychotics, rather a tendency for improvement (Rosse et al. 1989; Heresco-Levy et al. 1999). Importantly, similar findings were documented for the newer antipsychotics, olanzapine and risperidone: adjunctive glycine (0.8 mg/kg/day) improved negative and, less markedly, cognitive and positive symptoms in treatment-refractory subjects, while also ameliorating tardive dyskinesia (Heresco-Levy et al. 2004). Intriguingly, glycine is not generally effective in patients receiving clozapine (Potkin et al. 1999; Evins et al. 2000; Millan 2002; Heresco-Levy 2003; though see Heresco-Levy and Javitt 2004). One simple explanation would be that clozapine is uniquely effective against negative symptoms ("ceiling effect"). However, a more likely explanation is that clozapine itself enhances activity at NMDA receptor sites (see below).

Underpinning the above findings, in a 6-week study, association of D-serine (30 mg/kg/day, ca. 2 g in total) with conventional neuroleptics improved negative and, less markedly, positive and cognitive symptoms, without worsening side effects (Tsai et al. 1998). Likewise, by analogy to glycine, D-serine did not enhance the efficacy of clozapine (Tsai et al. 1999).

Mimicking its less robust effects (alone) than glycine in experimental models, the partial agonist, DCS, shows less marked improvements when given in association with antipsychotic agents to patients. Dose–response studies in subjects receiving conventional antipsychotics have shown that low doses (ca. 30 mg/day) are ineffective, high doses aggravate positive symptoms and only an intermediate dose of ca. 50 mg/day provides a reduction in negative symptoms in otherwise treatment-resistant patients without a

Table 3 Antipsychotic actions of drugs activating $Glycine_B$ sites in association with haloperidol and other antipsychotic agents

	Agonist		PAG	GRI
Drug	Glycine	D-serine	DCS	Sarcosine
Dose/day	40–80 g	2 g	50 mg	2 g
Positive symptoms	–/↓	↓	–/↓	↓
Deficit symptoms	↓↓	↓↓	↓	↓↓
Cognitive symptoms	↓	↓	↓	↓
Extrapyramidal side effects	↓	–	–	–

↓ = Improvement, – = no clear change. The table summarizes data obtained with "conventional" antipsychotics such as haloperidol, as well as the newer agents, risperidone and olanzapine

PAG Partial agonist, *GRI* glycine reuptake inhibitor, *DCS*D-cycloserine

significant improvement in positive or cognitive symptoms (Goff et al. 1999; Van Berckel 2003; Javitt 2002; see Millan 2002; Heresco-Levy 2003). As with glycine treatment, low levels of serum glycine were predictive of a good response to DCS (Heresco-Levy et al. 1998). Comparable findings of a modest improvement in negative symptoms were obtained with patients on risperidone or olanzapine (Evins et al. 2002; Heresco-Levy et al. 2002). DCS actually worsened negative symptoms when given in association with clozapine (Goff et al. 1996; Goff et al. 1999; Javitt 2002). Recently, in a retrospective analysis of a 5-year period of parallel investigations, Heresco-Levy and Javitt (2004) underpinned this impression of less robust effects of DCS as compared to those of glycine. In a meta-analysis, Tuominen et al. (2005) came to a similar conclusion, and Duncan et al. (2004a) recently obtained negative results with adjunctive DCS in patients showing mainly negative symptoms. The lack of a clear improvement in cognitive symptoms with DCS is, perhaps, surprising in view of the procognitive actions of partial agonists in rodents. On the other hand, it may be relevant that the influence of DCS upon mnemonic function in patients with dementia was not sufficiently robust to justify pursuing clinical trials (Johannesen and Myhrer 2002; Jones et al. 2004).

Despite essentially anecdotal reports of pro and/or antipsychotic effects of very high (tuberculostatic) doses of DCS (up to 3,000 mg/day) in non-psychotic subjects (see Millan 2002; Heresco-Levy 2003), no controlled trials of its effects alone in schizophrenia have been undertaken. Similarly, effects of glycine and D-serine alone remain to be elucidated. Results of such studies would be important for several reasons: (1) according to the NMDA receptor hypoactivity hypothesis, they should be effective alone; (2) most studies of antipsychotic actions in rodents have been undertaken with $Glycine_B$ agonists *alone*; and (3) should $Glycine_B$ agonists display clinically relevant antipsychotic effect alone, this would vastly improve perspectives for the development of novel therapeutic agents of this class (see below).

By analogy to $Glycine_B$ receptor ligands, potential antipsychotic actions of GRIs alone remain to be examined. However, sarcosine exerted clinical effects remarkably similar to those of glycine and D-serine in a 6-week double-blind study of patients under treatment with conventional antipsychotics including, principally, risperidone (Tsai et al. 2004a). That is, sarcosine, which was well tolerated, achieved improvement in negative and, less markedly, positive and cognitive symptoms. Though sarcosine dehydrogenase can demethylate sarcosine to glycine, it is unlikely to be acting as a "prodrug" since active doses of sarcosine (2 g/day) are far lower than those of glycine (40–80 g) needed for efficacy.

Influence of antipsychotics upon NMDA receptors: possible role in their actions

Administration (generally chronic) of antipsychotics elicits a complex, drug, time, receptor-subunit and tissue-dependent influence upon glutamatergic pathways and NMDA receptors (Bardgett et al. 1993; Fitzgerald et al. 1995; Ossowska et al. 1999; Millan 2002; Gemperle et al. 2003; Heresco-Levy 2003; Tarazi et al. 2003). Interesting differences have emerged between clozapine and haloperidol. These agents preferentially enhance glutamate levels and activity at NMDA receptors in cortex vs striatum, respectively (Yamamoto et al. 1994; Arvanov et al. 1997; Hayashi et al. 1999; Rodriguez and Pickel 1999).

Clozapine-induced increases in NMDA receptor activity in cortex involve several mechanisms depicted in Fig. 7. Clozapine reduces uptake of glutamate in cortex by decreasing glial expression of EAAT1 and neuronal expression of EAAT3 (See and Lynch 1996; Chen and Yang 2002; Millan 2002; Melone et al. 2003; Schmidt et al. 2003). Extracellular levels of glutamate may also be raised by inhibition of GABAergic interneurones and, upon chronic administration, by a diminution in the activity of GCP II (Squires and Saederup 1998; Michel and Trudeau 2000; Flores and Coyle 2003). Interestingly, patients receiving clozapine—and olanzapine—show higher plasma levels of glutamate (Evins et al. 1997; Goff et al. 2002), and a recent imaging study suggested that clozapine increases occupation of thalamic NMDA receptors by glutamate (Bressan et al. 2003). Elevations in glutamate levels will directly recruit NMDA receptors and indirectly enhance their activity via activation of AMPA receptors, though clozapine does not affect AMPA sites per se (Gemperle et al. 2003). AMPA receptor recruitment of astrocytes will also induce release of D-serine. In parallel, clozapine may enhance glycine levels by inhibiting SNAT 1 sites for neuronal uptake of glycine (Javitt et al. 2004b; Schwieler et al. 2004) and GlyT-1 sites for glial reuptake of glycine (Williams et al. 2004). Direct agonist actions of clozapine at $Glycine_B$ sites were speculated to attenuate actions of kynurenate, but there is no direct evidence for this (Schwieler and Erhardt 2003; Schwieler et al. 2004). Independently of glutamate and glycine, clozapine enhances the functional activity of NMDA receptors via their phosphorylation by protein kinase A (possibly dopamine and D_1 receptor mediated) (Leveque et al. 2000; Chen and Yang 2002; Tseng and O'Donnell 2004), protein kinase C and calmodulin II (Hayashi et al. 1999; Seamans et al. 2000; Jardemark et al. 2003; Ninan et al. 2003a; Gonzalez and Robinson 2004; Naudon et al. 2004). Finally, *N*-desmethylclozapine, a major metabolite of clozapine, is an agonist at M_1 receptors which allosterically facilitate activity at NMDA receptors (Sur et al. 2003; Weiner et al. 2004). The preferential enhancement by clozapine of NMDA receptor-mediated transmission in frontal cortex is associated with enhanced long-term potentiation and may be related to its beneficial influence upon negative symptoms (Gemperle et al. 2003; Serretti et al. 2004). It may also explain the inability of $Glycine_B$ agonists to improve clinical effects of clozapine.

Haloperidol more markedly increases striatal levels of glutamate than clozapine (Bardgett et al. 1993; Yamamoto et al. 1994; see Millan 2002). Its actions are exerted by several mechanisms including blockade of D_2 and, perhaps, D_4 receptors inhibitory to glutamate release (Berger et al. 2001; Cepeda et al. 2001; Rivera et al. 2002; Centonze et al.

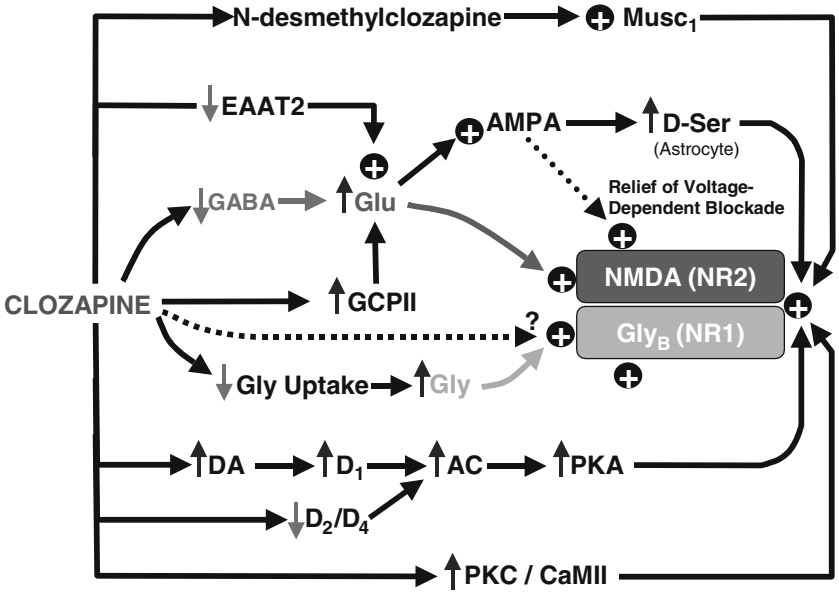

Fig. 7 Overview of multiple mechanisms implicated in the facilitatory influence of clozapine at NMDA receptors in cortex. *DA* Dopamine, *GCP* glutamate carboxypeptidase, *AC* adenylyl cyclase, *EAAT* excitatory amino acid transporter, *GlyT* glycine transporter, *Musc* muscarinic receptor, *PKA* protein kinase A, *PKC* protein kinase C, *CaMII* calmodulin II. It is unclear how clozapine recruits PKC and CaMII. Its influence upon EAAT2 and GCPII is only seen upon long-term administration in vivo. The suggestion that clozapine may directly (and allosterically) engage $Glycine_B$ site remains speculative. Note that (1) many of these potential mechanisms would benefit from confirmation; (2) they have been documented under a variety of conditions using a diversity of techniques; and (3) mechanisms shown are expressed in the cortex or other specific brain regions but not necessarily throughout the CNS

2004; Gan et al. 2004) and reduced striatal expression of EAAT2 (De Souza et al. 1999; Schneider et al. 1998; Schmidt et al. 2003). Haloperidol may also enhance NMDA receptor function by inducing striatal expression of NR1 subunits (Fitzgerald et al. 1995). In vitro, it enhances activity at NMDA receptors by increasing protein kinase A-mediated phosphorylation of NR1 subunits: this action may reflect both blockade of D_2 receptors (inhibitory to protein kinase A) and increased DA release leading to activation of co-localized D_1 sites (facilitatory to protein kinase A) (Leveque et al. 2000; Liu et al. 2004). Though haloperidol interacts with NR2B and GlyT-1 sites, its potency is probably too low to be of relevance in vivo (Ilyin et al. 1996; Brimecombe et al. 1998; Lee and Rajakumar 2003; Williams et al. 2004, Yanahashi et al. 2004). Sustained reinforcement of glutamatergic transmission in the striatum may be excitotoxic (Leveque et al. 2000; Millan 2002) and contribute to the long-term onset of tardive dyskinesia with haloperidol. Nevertheless, long-term administration of glycine *attenuated* extrapyramidal motor effect of haloperidol in man and in rodents countering this possibility (Heresco-Levy 2003; Shoham et al. 2004).

Certain studies suggest that the influence of antipsychotics upon NMDA receptors is even more complex and may also involve inhibitory effects (Levine et al. 2003; Ninan et al. 2003b). Nevertheless, the general pattern of data clearly supports the above-described facilitatory influence of clozapine in the cortex and of haloperidol in striatum. In future work, it will be important to further analyse the functional consequences of their actions in additional brain regions and at specific constellations of NMDA receptor subunits. It will also be interesting to characterise the influence of other, mechanistically novel, antipsychotics upon activity at NMDA receptors.

Open questions and future perspectives

Multiple targets for antipsychotic modulation of activity at NMDA receptors

The above discussion highlights many potential strategies for modulating the functional status of NMDA receptors. First, it may be possible to develop more effective direct agonists at $Glycine_B$ sites. In this regard, efforts should be made to target specific subpopulations of NMDA receptors implicated in the induction of psychotic states, for example, those on GABAergic interneurones inhibitory to cortical glutamatergic pathways and to dopaminergic cell bodies. This may be feasible if such populations incorporate specific isoforms of NR1 subunits or specific assemblies of NR2 subunits modulating the ligand-binding profile of $Glycine_B$ sites on NR1 subunits. Supporting this possibility, several drugs have been developed which interact with discrete classes of NR2 subunit (Danysz and Parsons 1998; Dingledine et al. 1999; Yamakura and Shimoh 1999; Madden 2002, Feng et al. 2004). Second, alternative targets on NMDA receptors would be modulatory sites recognizing, for example, neurosteroids, polyamines or glutathione (Dingledine et al. 1999). Third, it may ultimately be possible to alter the function of NMDA sites via actions at NRL1, dysbindin or other postsynaptic pro-

teins. Fourth, a novel possibility for indirect modulation of NMDA sites would be to target receptors which control the release of D-serine, glycine and glutamate from astrocytes (Bezzi and Volterra 2001). Fifth, drugs which affect reuptake, synthesis and/or degradation of D-serine, kynurenate and NAAG are an intriguing possibility. However, several questions remain. For example, inasmuch as D-serine and glycine are interconverted in glial cells, modification of the availability of one will inevitably affect the other. There would be little point in enhancing levels of D-serine if this indirectly results in a compensatory reduction in levels of glycine. Further, modification of the availability of kynurenate may indirectly influence serotonergic and cholinergic transmission with uncertain consequences for psychotic states (Stone and Darlington 2002; Alkondon et al. 2004).

Which endogenous ligands control activity at NMDA receptors?

A major question is whether $Glycine_B$ sites are tonically saturated. There is now a consensus that they are not—and functional actions of glycine, D-serine and GRIs in animals and man bear testimony to this (Danysz and Parsons 1998; Javitt 2002; Millan 2002; Haradahira et al. 2003). However, many therapeutically relevant uncertainties remain, notably, the degree of occupation of specific populations: in defined brain regions, in psychotic patients exposed or not to antipsychotics and in normal subjects exposed to stress or illicit drugs. Irrespective of the overall degree of occupation of $Glycine_B$ sites, a fundamental and related question is the participation of various endogenous ligands. For example, what is the relative importance of glycine as compared to D-serine in psychotic patients, and what is the contribution of these endogenous agonists as compared to the antagonist kynurenate? This issue is of far more than academic interest. Indeed, it underpins all current efforts to develop novel drugs for treating schizophrenia via $Glycine_B$ sites. For example, GRIs and/or D-AAO inhibitors will only display antipsychotic activity if glycine and/or D-serine, respectively, are genuinely ligands of NMDA receptors involved in the induction and control of psychotic states. Analogous arguments apply to agents which reduce the synthesis of kynurenate.

Significance of NMDA receptors in relation to AMPA and metabotropic receptors

The significance of glutamatergic mechanisms to schizophrenia and its treatment is not limited to NMDA receptors and extends to their AMPA, kainate and metabotropic counterparts. The interrelationship between these sites is beyond the scope of the present review. However, two intriguing aspects of *contrasting* implications should be briefly mentioned. First, AMPA and kainate receptors rapidly enhance activity at NMDA receptors by neuronal depolarisation, which relieves their Mg^{2+} block. In addition, AMPA receptors enhance release of D-serine from astrocytes, thereby indirectly enhancing activity of NMDA sites in a slower and more sustained fashion (Schell et al. 1995; Nedergaard et al. 2002). Whether such actions are relevant to the proposed use of AMPAkines for the improvement of cognitive dysfunction in schizophrenia would be of interest to determine (Johnson et al. 1999; Goff et al. 2001; Marenco et al. 2002). Second, the paradox of why PCP and other OCBs act psychotomimetically yet *enhance* glutamate release may be explicable by glutamatergic loops separated by intervening GABAergic interneurones (see above) (Fig. 4). PCP may then mimic schizophrenia by blocking NMDA input onto GABAergic neurones. This leads to an increase in downstream glutamate release onto AMPA and other classes of glutamatergic receptor mediating pro-psychotic effects. One implication of this hypothesis is that drugs reducing glutamate release, such as lamotrigine (Anand et al. 2000; Hosak and Libiger 2002; Tiihonen et al. 2003) or presynaptic metabotropic receptor agonists (Moghaddam 2002; Schoepp and Marek 2002; Winter et al. 2003), may be useful antipsychotic agents—though they might exacerbate hypoactivity at certain populations of NMDA sites. Alternatively, antagonists at AMPA receptors may be of interest as antipsychotic agents (Mathé et al. 1998; Johnson et al. 1999; Sebban et al. 2002; Takahata and Moghaddam 2003), though this notion is diametrically opposed to the above-mentioned use of AMPAkines as cognitive enhancers.

Clinical efficacy of NMDA receptor modulators alone

There is currently no evidence that enhancing activity at $Glycine_B$ sites is itself sufficient for antipsychotic activity. Results of clinical trials addressing this issue will be critical since a lack of therapeutic efficacy alone implies the need for adjunctive utilization of $Glycine_B$ agonists, GRIs and other classes of agent. This is hard to envisage on a broad scale and would complicate development of novel agents. One alternative strategy would be to combine within a single molecule (direct or indirect) modulatory activity at $Glycine_B$ sites and D_2/D_3 dopamine receptor antagonism. Such a "multitarget" approach would fit well with the multifactorial origins of schizophrenia. For both selective and multitarget agents at $Glycine_B$ sites, it would be desirable to focus on the influence upon cognitive symptoms in view of their importance to the overall outcome of treatment and the major role of NMDA receptors in mnemonic processes (Kane et al. 2003).

Confirmation of the role of $Glycine_B$ sites in the actions of $Glycine_B$ agonists and GRIs

The convergent effects of glycine, D-serine and GRIs in experimental models of antipsychotic activity and in psychotic patients support the notion of a common mode of action: enhanced activity at $Glycine_B$ sites on NMDA receptors. Nevertheless, no formal proof is available from clinical investigations, and there have been few rigorous tests of this assumption in rodent studies. In principle, their

actions should be prevented by selective $Glycine_B$ receptor antagonists. Further, assuming actions at common sites, in the presence of $Glycine_B$ agonists at doses sufficient to saturate $Glycine_B$ sites, GRIs should exert no further effect. Reciprocally, assuming that glycine is a critical endogenous ligand, in the presence of GRIs, direct $Glycine_B$ agonists should exert no further actions. Such studies remain to be performed. This is important since it is difficult to exclude additional central actions of these agents. For example, a dose of glycine sufficient to evoke substantial elevations in its levels in the brain is likely to influence cerebral concentrations of interrelated modulators—including D-serine. Thus, in future work, it will be necessary to more rigorously underpin the $Glycine_B$ hypothesis of antipsychotic activity with appropriate pharmacological controls.

Conclusions

In conclusion, there is a compelling body of experimental and clinical data implicating NMDA receptors in the pathogenesis and, potentially, treatment of schizophrenia. Further, several mechanisms are available for countering the hypoactivity of NMDA receptors which is thought to participate in psychotic states. However, two fundamental questions remain. First, which is the most appropriate therapeutic strategy (for example, direct agonists, modulators of glycine reuptake and/or modulators of D-serine availability)? Second, will drugs, which selectively modulate activity at $Glycine_B$ sites, be therapeutically effective alone? If so, this would transform the landscape of drug discovery in schizophrenia. On the other hand, they may only be useful as adjunctive agents. Rather than selective drugs, multitarget drugs interacting with $Glycine_B$ receptors as well as D_2/D_3 receptors (or other complementary sites) may represent novel and improved antipsychotics. This remains to be seen. In any case, in view of evidence that AMPA, kainate and metabotropic receptors are also involved in the etiology of schizophrenia, one may be reasonably optimistic as regards the future utility of glutamatergic strategies for the control of this devastating disorder.

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References

Abel KM, Allin MPG, Hemsley DR, Geyer MA (2003) Low dose ketamine increases prepulse inhibition in healthy men. Neuropharmacology 44:729–737

Adell A, Artigas F (2004) The somatodentritic release of dopamine in the ventral tegmental area and its regulation by afferent transmitter systems. Neurosci Biobehav Res 28:415–431

Adler CM, Malhotra AK, Elman I, Goldberg T, Egan M, Pickar D, Breier A (1999) Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. Am J Psychiatry 156:1646–1649

Aghajanian GK, Marek GJ (2000) Serotonin model of schizophrenia: emerging role of glutamate mechanisms. Brain Res Interactive 31:302–312

Ahmadi S, Muth-Selbach U, Lauterbach A, Lipfert P, Neuhuber WL, Zeilhofer HU (2003) Facilitation of spinal NMDA receptor currents by spillover of synaptically released glycine. Science 300:2094–2097

Akbarian S, Sucher NJ, Bradley D, Tafazzoli A, Trinh D, Hetrick WP, Potkin SG, Sandman CA, Bunney WE, Jones EG (1996) Selective alterations in gene expression for NMDA receptor subunits in prefrontal cortex of schizophrenia. J Neurosci 16:19–30

Alkondon M, Pereira EF, Yu P, Arruda EZ, Almeida LE, Guidetti P, Fawcett WP, Sapko MT, Randall WR, Schwarcz R, Tagle DA, Albuquerque EX (2004) Targeted deletion of the kynurenine aminotransferase ii gene reveals a critical role of endogenous kynurenic acid in the regulation of synaptic transmission via $alpha_7$ nicotinic receptors in the hippocampus. J Neurosci 24: 4635–4648

Anand A, Charney D, Oren DA, Berman RM, Hu XS, Cappiello A, Krystal JH (2000) Attenuation of the neuropsychiatric effects of ketamine with lamotrigine. Arch Gen Psychiatry 57:270–276

Andersen JD, Pouzet B (2004) Spatial memory deficits induced by perinatal treatment of rats with PCP and reversal effect of D-serine. Neuropsychopharmacology 29:1080–1090

Andersen JM, Lindberg V, Myhrer T (2002) Effects of scopolamine and D-cycloserine on non-spatial reference memory in rats. Behav Brain Res 129:211–216

Andreassen OA, Waage J, Finsen B, Jorgensen HA (2003) Memantine attenuates the increase in striatal preproenkephalin mRNA expression and development of haloperidol induced persistent oral dyskinesias in rats. Brain Res 994:188–192

Arvanov VL, Liang X, Schwartz J, Grossman S, Wang RY (1997) Clozapine and haloperidol modulate NMDA- and non-NMDA receptor-mediated neurotransmission in rat prefrontal cortical neurons in vitro. J Pharmacol Exp Ther 283:226–234

Bacich DJ, Ramadan E, O'Keefe DS, Bukhari N, Wegorzewska I, Ojeifo O, Olszewski R, Wrenn CC, Bzdega T, Wroblewska B, Heston WD, Neale JH (2002) Deletion of the glutamate carboxypeptidase II gene in mice reveals a second enzyme activity that hydrolyzes *N*-acetylaspartylglutamate. J Neurochem 83:20–29

Bakshi VP, Tricklebank M, Neijt HC, Lehmann-Masten V, Geyer MA (1999) Disruption of prepulse inhibition and increases in locomotor activity by competitive *N*-methyl-aspartate receptor antagonists in rats. J Pharmacol Exp Ther 288:643–652

Balla A, Hashim A, Burch S, Javitt DC, Lajtha A, Sershen H (2001a) Phencyclidine-induced dysregulation of dopamine response to amphetamine in prefrontal cortex and striatum. Neurochem Res 26:1001–1006

Balla A, Koneru R, Smiley J, Sershen H, Javitt DC (2001b) Continuous phencyclidine treatment induces schizophrenia-like hyperreactivity of striatal dopamine release. Neuropsychopharmacology 25:157–164

Balla A, Sershen H, Serra M, Koneru R, Javitt DC (2003) Subchronic continuous phencyclidine administration potentiates amphetamine-induced frontal cortex dopamine release. Neuropsychopharmacology 28:34–44

Ballard TM, Pauly-Evers M, Higgins GA, Ouagazzal AM, Mutel V, Borroni E, Kemp JA, Bluethmann H, Kew JNC (2002) Severe impairment of NMDA receptor function in mice carrying targeted point mutations in the glycine binding site results in drug-resistant nonhabituating hyperactivity. J Neurosci 22:6713–6723

Bardgett ME, Wrona CT, Newcomer JW, Csernansky JG (1993) Subcortical excitatory amino acid levels after acute and subchronic administration of typical and atypical neuroleptics. Eur J Pharmacol 230:245–250

Barinka C, Sacha P, Sklenar J, Man P, Bezouska K, Slusher BS, Konvalinka J (2004) Identification of *N*-glycosylation sites on glutamate carboxypeptidase II necessary for proteolytic activity. Protein Sci 13:1627–1635

Beardsley PM, Ratti E, Balster RL, Willetts J, Trist D (2002) The selective glycine antagonist gavestinel lacks phencyclidine-like behavioural effects. Behav Pharmacol 13:583–592

Berger MA, Defagot MC, Villar MJ, Antonelli MC (2001) D_4 and metabotropic glutamate receptors in cerebral cortex and striatum in rat brain. Neurochem Res 26:345–352

Berger UV, Luthi-Carter R, Passani LA, Elkabes S, Black I, Konradi C, Coyle JT (1999) Glutamate carboxypeptidase II is expressed by astrocytes in the adult rat nervous system. J Comp Neurol 415:52–64

Bergeron R, Coyle JT, Tsai G, Greene RW (2005) NAAG reduces NMDA receptor current in CAI hippocampal pyramidal neurons of acute slices and dissociated neurons. Neuropsychopharmacology 30:7–16

Bezzi P, Volterra A (2001) A neuron-glia signalling network in the active brain. Curr Opin Neurobiol 11:387–394

Bezzi P, Gundersen V, Galbete JL, Seifert G, Steinhäusser C, Pilati E, Volterra A (2004) Astrocytes contain a vesicular compartment that is competent for regulated exocytosis of glutamate. Nat Neurosci 7:613–620

Blanchet PJ, Konitsiotis S, Whittemore ER, Zhou ZL, Woodward RM, Chase TN (1999) Differing effects of NMDA receptor subtype selective antagonists on dyskinesia in levodopa treated 1-methyl-4-phenyl-tetrahydropyridine monkeys. J Pharmacol Exp Ther 290:1034–1040

Bräuner-Osborne H, Egebjerg J, Nielsen E, Madsen U, Krogsgaard-Larsen P (2000) Ligands for glutamate receptors: design and therapeutic prospects. J Med Chem 43:2609–2645

Breese GR, Knapp DJ, Moy SS (2002) Integrative role for serotonergic and glutamatergic mechanisms in actions of NMDA antagonists: relationships to antipsychotic drug actions on NMDA antagonist responsiveness. Neurosci Biobehav Rev 26:441–455

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A (1997) Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel position emission tomography method. Proc Natl Acad Sci U S A 94:2569–2574

Bressan RA, Erlandsson K, Mulligan RS, Gunn RN, Cunningham VJ, Owens J, Ell PJ, Pilowsky LS (2003) Evaluation of NMDA receptors in vivo in schizophrenic patients with [^{123}I]CNS 1261 and SPET. Ann NY Acad Sci 1003:364–367

Brimecombe JC, Gallagher MJ, Lynch DR, Aizenman E (1998) An NR2B point mutation affecting haloperidol and CP101,606 sensitivity of single recombinant NMDA receptors. J Pharmacol Exp Ther 286:627–634

Burbaeva GS, Boksha IS, Turishcheva MS, Vorobyeva EA, Savushkina OK, Tereshkina EB (2003) Glutamine synthetase and glutamate dehydrogenase in the prefrontal cortex of patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 27:675–680

Buonanno A, Fischbach GD (2001) Neuregulin and ErbB receptor signalling pathways in the nervous system. Curr Opin Neurobiol 11:287–296

Bzdega P, Crowe SL, Ramadan ER, Sciarretta KH, Olszewski RT, Ojeifo OA, Rafalski VA, Wroblewska B, Neale JH (2004) The cloning and characterization of a second brain enzyme with NAAG peptidase activity. J Neurochem 89:627–635

Campbell CM, Butelman ER, Woods JH (1999) Effects of (+)-HA-966, CGS-19755, phencyclidine, and dizocilpine on repeated acquisition of response chains in pigeons: systemic manipulation of central glycine sites. J Pharmacol Exp Ther 289:521–527

Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML (2001) Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. Annu Rev Pharmacol Toxicol 41:237–260

Caudle RM, Dubner R (1998) Ifenprodil blocks the excitatory effects of the opioid peptide dynorphin 1–17 on NMDA receptor-mediated currents in the CA3 region of the guinea pig hippocampus. Neuropeptides 32:87–95

Centonze D, Usiello A, Costa C, Picconi B, Erbs E, Bernardi G, Borrelli E, Calabresi P (2004) Chronic haloperidol promotes corticostriatal long-term potentiation by targeting dopamine D_{2L} receptors. J Neurosci 24:8214–8222

Cepeda C, Hurst RS, Altemus KL, Flores-Hernandez J, Calvert CR, Jokel ES, Grandy DK, Low MJ, Rubinstein M, Ariano MA, Levine MS (2001) Facilitated glutamatergic transmission in striatum of D_2 receptor-deficient mice. J Neurophysiol 85:659–670

Chatterton JE, Awobuluyi M, Premkumar LS, Takahashi H, Talantova M, Shin Y, Cul J, Tu S, Sevarino KA, Nakanishi N, Tong G, Lipton SA, Zhang D (2002) Excitatory glycine receptors containing the NR3 family of NMDA receptor subunits. Nature 413:793–798

Chen L, Yang CR (2002) Interaction of dopamine D_1 and NMDA receptors mediates acute clozapine potentiation of glutamate EPSPs in rat prefrontal cortex. J Neurophysiol 87:2324–2336

Chen LW, Wei LC, Lang B, Ju G, Chan YS (2001) Differential expression of AMPA receptor subunits in dopamine neurons of the rat brain: a double immunocytochemical study. Neuroscience 106:149–160

Chen L, Muhlhauser M, Yang CR (2003) Glycine transporter-1 blockade potentiates NMDA-mediated responses in rat prefrontal cortical neurons in vitro and in vivo. J Neurophysiol 89:691–703

Chumakov I, Blumenfeld M, Guerassimenko O, Cavarec L, Palicio M, Cohen D (2002) Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc Natl Acad Sci U S A 99:13675–13680

Clinton SM, Meador-Woodruff JH (2004a) Abnormalities of the NMDA receptor and associated intracellular molecules in the thalamus in schizophrenia and bipolar disorder. Neuropsychopharmacology 29:1353–1362

Clinton SM, Meador-Woodruff JH (2004b) Thalamic dysfunction in schizophrenia: neurochemical, neuropathological, and in vivo imaging abnormalities. Schizophr Res 69:237–253

Clinton SM, Haroutunian V, Davis KL, Meador-Woodruff JH (2003) Altered transcript expression of NMDA receptor-associated postsynaptic proteins in the thalamus of subjects with schizophrenia. Am J Psychiatry 160:1100–1109

Collier DA (2003) The genetics of schizophrenia: glutamate not dopamine? Eur J Pharmacol 480:177–184

Cook SP, Galve-Roperh I, del Pozo AM, Rodriguez-Crespo I (2002) Direct calcium binding results in activation of brain serine racemase. J Biol Chem 277:27782–27792

Cordi A, Lacoste JM, Audinot V, Millan MJ (1999) Design, synthesis and structure–activity relationships of novel strychnine-insensitive glycine receptor ligands. Bioorg Med Chem Lett 9:1409–1414

Coyle JT (1997) The nagging question of the function of *N*-acetylaspartylglutamate. Neurobiol Dis 4:231–238

Coyle JT, Tsai G (2004) NMDA receptor function, neuroplasticity, and the pathophysiology of schizophrenia. Int Rev Neurobiol 59:491–515

Crow TJ (2004) Cerebral asymmetry and the lateralization of language: core deficits in schizophrenia as pointers to the gene. Curr Opin Psychiatry 17:97–106

Cubelos B, Gonzalez-Gonzalez IM, Gimenez C, Zafra F (2005) Amino acid transporter SNATs localizes to glial cells in the rat brain. Glia 49:230–244

Cull-Candy S, Brickley S, Farrant M (2001) NMDA receptor subunits: diversity, development and disease. Curr Opin Neurobiol 11:327–335

Danbolt NC (2001) Glutamate uptake. Prog Neurobiol 65:1–105

Danysz W, Parsons CG (1998) Glycine and NMDA receptors: physiological significance and possible therapeutic applications. Pharmacol Rev 50:597–664

Deitmer JW, Broer A, Broer S (2003) Glutamine efflux from astrocytes is mediated by multiple pathways. J Neurochem 87:127–135

De Lima AD, Opitz T, Voigt T (2004) Irreversible loss of subpopulation of cortical interneurons in the absence of a glutamatergic network. Eur J Neurosci 19:2931–2943

De Miranda J, Santoro A, Engelender S, Wolosker H (2000) Human serine racemase: molecular cloning, genomic organization and functional analysis. Gene 256:183–188

Depoortere R, Decobert M, Cudennec A, Claustre Y, Terranova J, Françon D, Alonso R, Simiand J, Perrault G, Griebel G, Soubrié P, Scatton B (2004) SSR504734, a selective and reversible inhibitor of the glycine transporter type 1 (GLYT1): III) effects in tests predictive of antipsychotic activity. Int J Neuropsychopharmacol 7:S433

De Souza IEJ, McBean GJ, Meredith GE (1999) Chronic haloperidol treatment impairs glutamate transport in the rat striatum. Eur J Pharmacol 382:139–142

Deutsch SI, Rosse RB, Schwartz BL, Mastropaolo J (2001) A revised excitotoxic hypothesis of schizophrenia: therapeutic implications. Clin Neuropharmacol 24:43–49

Di Maria E, Gulli R, Begni S, De Luca A, Bignotti S, Pasini A, Bellone E, Pizzuti A, Dallapiccola B, Novelli G, Ajmar F, Gennarelli M, Mandich P (2004) Variations in the NMDA receptor subunit 2B gene (GRIN2B) and schizophrenia: a case-control study. Am J Med Genet 128B:27–29

Dingledine R, Borges K, Bowie D, Traynelis SF (1999) The glutamate receptor ion channels. Pharmacol Rev 51:7–61

Do KQ, Trabesinger AH, Kirsten-Krüger M, Lauer CJ, Dydak U, Hell D, Holsboer F, Boesiger P, Cuénod M (2000) Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. Eur J Neurosci 12:3721–3728

Dolinska M, Zablocka B, Sonnewald U, Albrecht J (2004) Glutamine uptake and expression of mRNA's of glutamine transporting proteins in mouse cerebellar and cerebral cortical astrocytes and neurons. Neurochem Int 44:75–89

Dracheva S, Marras SA, Elhaken SL, Kramer FR, Davis KL, Haroutunian V (2001) *N*-Methyl-D-aspartic acid receptor expression in the dorsolateral prefrontal cortex of elderly patients with schizophrenia. Am J Psychiatry 158:1400–1410

D'Souza DC, Gil R, Cassello K, Morrissey K, Abi-Saab D, White J, Sturwold R, Bennett A, Karper LP, Zuzarte E, Charney DS, Krystal JH (2000) IV Glycine and oral D-cycloserine effects on plasma and CSF amino acids in healthy humans. Biol Psychiatry 47:450–462

Duncan EJ, Szilagyi S, Schwartz MP, Bugarski-Kirola D, Kunzova A, Negi S, Stephanides M, Efferen TR, Angrist B, Peselow E, Corwin J, Gonzenbach S, Rotrosen JP (2004a) Effects of D-cycloserine on negative symptoms in schizophrenia. Schizophr Res 71:239–248

Duncan GE, Moy SS, Perez A, Eddy DM, Zinzow WM, Lieberman JA, Snouwaert JN, Koller BH (2004b) Deficits in sensorimotor gating and tests of social behavior in a genetic model of reduced NMDA receptor function. Behav Brain Res 153:507–519

Dyker AG, Edwards KR, Fayad PB, Hormes JT, Lees KR (1999) Safety and tolerability of aptiganel hydrochloride in patients with acute ischemic stroke. Stroke 30:2038–2042

Elkin A, Kalidindi S, McGuffin P (2004) Have schizophrenia genes been found? Curr Opin Psychiatry 17:107–113

Erhardt S, Engberg G (2002) Increased phasic activity of dopaminergic neurones in the rat ventral tegmental area following pharmacologically elevated levels of endogenous kynurenic acid. Acta Physiol Scand 175:45–53

Erhardt S, Blennow K, Nordin C, Skogh E, Lindström LH, Engberg G (2001) Kynurenic acid levels are elevated in cerebro spinal fluid of patients with schizophrenia. Neurosci Lett 313:96–98

Erhardt S, Schwieler L, Emanuelsson C, Geyer M (2004) Endogenous kynurenic acid disrupts prepulse inhibition. Biol Psychiatry 56:255–260

Ermilov M, Kremer I, Blanaru M, Bloch B, Neeman G, Javitt D, Heresco-Levy U (2004) Glutamatergic neurotransmission-associated amino acids: plasma levels and relation to symptoms. Int J Psychopharmacol 7:S285

Evins AE, Amico E, Shih V, Goff DC (1997) Clozapine treatment increases serum glutamate and aspartate compared to conventional neuroleptics. J Neural Transm 104:761–766

Evins AE, Fitzgerald SM, Wine L, Rosselli R, Goff DC (2000) Placebo-controlled trial of glycine added to clozapine in schizophrenia. Am J Psychiatry 157:826–828

Evins AE, Amico E, Posever TA, Toker R, Goff DC (2002) D-Cycloserine added to risperidone in primary negative symptoms of schizophrenia. Schizophr Res 56:19–23

Farber NB (2003) The NMDA receptor hypofunction model of psychosis. Ann NY Acad Sci 1003:119–130

Faustman WO, Bardgett M, Faull KF, Pfefferbaum A, Csernansky JG (1999) Cerebrospinal fluid glutamate inversely correlates with positive symptom severity in unmedicated male schizophrenic/schizoaffective patients. Biol Psychiatry 45:68–75

Feng B, Tse HW, Skifter DA, Morley R, Jane DE, Monaghan DT (2004) Structure–activity analysis of a novel NR2C/NR2D-preferring NMDA receptor antagonist: 1-(phenanthrene-2-carbonyl)piperazine-2,3-dicarboxylic acid. Br J Pharmacol 141: 508–516

Fitzgerald LW, Deutsch AY, Gassic G, Heinemann SE, Nestler EJ (1995) Regulation of cortical and subcortical glutamate receptor subunit expression by antipsychotic. Drugs J Neurosci 95: 2453–2461

Flores C, Coyle JT (2003) Regulation of glutamate carboxypeptidase II function in corticolimbic regions of rat brain by phencyclidine, haloperidol, and clozapine. Neuropsychopharmacology 28:1227–1234

Fujita T, Kishida T, Wada M, Okada N, Yamamoto A, Leibach FH, Ganapathy V (2004) Functional characterization of brain peptide transporter in rat cortex: identification of high-affinity type H+/peptide transporter PEPT2. Brain Res 997:52–61

Fukumaki Y, Shibata H (2003) Glutamate receptor genes as candidates for schizophrenia susceptibility. Drug Dev Res 60:137–151

Gadea A, Lopez-Colomé AM (2001) Glial transporters for glutamate, glycine, and GABA III. Glycine transporters. J Neurosci Res 64:218–222

Gan L, Falzone TL, Zhang K, Rubinstein M, Baldessarini RJ, Tarazi FI (2004) Enhanced expression of dopamine D_1 and glutamate NMDA receptors in dopamine D_4 receptor knockout mice. J Mol Neurosci 22:167–178

Gao XM, Sakai K, Roberts RC, Conley RR, Dean B, Tamminga CA (2000) Ionotropic glutamate receptors and expression of NMDA receptor subunits in subregions of human hippocampus: effects of schizophrenia. Am J Psychiatry 157:1141–1149

Garcia RA, Vasudevan K, Buonanno A (2000) The neuregulin receptor ErbB-4 interacts with PDZ-containing proteins at neuronal synapses. Proc Natl Acad Sci U S A 97:3596–3601

Garrido Sanabria ER, Wozniak KM, Slusher BS, Keller A (2004) GCP II (NAALADase) inhibition suppresses mossy fiber-CA3 synaptic neurotransmission by a presynaptic mechanism. J Neurophysiol 91:182–193

Gemperle AY, Enz A, Pozza MF, Lüthi A, Olpe HR (2003) Effects of clozapine, haloperidol and iloperidone on neurotransmission and synaptic plasticity in prefrontal cortex and their accumulation in brain tissue: an in vitro study. Neuroscience 117:681–695

Georges F, Aston-Jones G (2002) Activation of ventral tegmental area cells by the bed nucleus of the stria terminalis: a novel excitatory amino acid input to midbrain dopamine neurons. J Neurosci 22:5173–5187

Gerber DJ, Hall D, Miyakawa T, Demars S, Gogos JA, Karayiorgou M, Tonegawa S (2003) Evidence for association of schizophrenia with variation in the 8p21.3 gene PPP3CC encoding calcineurin gamma subunit. Proc Natl Acad Sci U S A 100: 8993–8998

Gerlai R, Pisacane P, Erickson S (2000) Heregulin, but not ErbB2 or ErbB3, heterozygous mutant mice exhibit hyperactivity in multiple behavioural tasks. Behav Brain Res 109:219–227

Geyer MA, Kreba-Thomson K, Braff DL, Swerdlow NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology 156:117–154

Ghose S, Weickert CS, Colvin SM, Coyle JT, Herman MM, Hyde TM, Kleinman JE (2004) Glutamate carboxypeptidase II gene expression in the human frontal and temporal lobe in schizophrenia. Neuropsychopharmacology 29:117–125

Gluck MR, Thomas RG, Haroutunian V (2002) Implications of altered glutamate and GABA metabolism in the dorsolateral prefrontal cortex of aged schizophrenic patients. Am J Psychiatry 159:1165–1173

Goebel DJ, Poosch MS (1999) NMDA receptor subunit gene expression in the rat brain: a quantitative analysis of endogenous mRNA levels of NR1, NR2A, NR2B, NR2C, NR2D and NR3A. Brain Res Mol Brain Res 69:164–170

Goff DC, Tsai G, Monoach DS, Flood J, Darby DG, Coyle JT (1996) D-Cycloserine added to clozapine for patients with schizophrenia. Am J Psychiatry 153:1628–1630

Goff DC, Tsai G, Levitt J, Amico E, Monoach D, Schoenfeld DA, Hayden DL, McCarley R, Coyle JT (1999) A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. Arch Gen Psychiatry 56:21–27

Goff DC, Leahy L, Berman I, Posever T, Herz L, Leon AC, Johnson SA, Lynch G (2001) A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. J Clin Psychopharmacol 21:484–487

Goff DC, Hennen J, Lyoo IK, Tsai G, Wald LL, Evins AE, Yurgelun-Todd DA, Renshaw PF (2002) Modulation of brain and serum glutamatergic concentrations following a switch from conventional neuroleptics to olanzapine. Biol Psychiatry 51:493–497

Golub MS, Germann SL, Lloyd KC (2004) Behavioral characteristics of a nervous system-specific erbB4 knock-out mouse. Behav Brain Res 153:159–170

Gonzalez MI, Robinson MB (2004) Protein kinase C-dependent remodelling of glutamate transporter function. Mol Interv 4:48–58

Grimwood S, Slater P, Deakin JFW (1999) NR2B-containing NMDA receptors are up-regulated in temporal cortex in schizophrenia. NeuroReport 10:461–465

Grunze HC, Rainnie DG, Hasselmo ME, Barkai E, Hearn EF, McCarley RW, Greene RW (1996) NMDA-dependent modulation of CA1 local circuit inhibition. J Neurosci 16:2034–2043

Gundersen V, Talgoy Holten A, Strom-Mathisen J (2004) GABAergic synapses in hippocampus exocytose aspartate on to NMDA receptors: quantitative immunogold evidence for co-transmission. Mol Cell Neurosci 26:156–165

Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, Haroutunian V, Fienberg AA (2001) Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci U S A 98:4746–4751

Haradahira T, Okauchi T, Maeda J, Zhang MR, Nishikawa T, Konn Suzuki K, Suhara T (2003) Effects of endogenous agonists, glycine and D-serine, on in vivo specific binding of [^{11}C]L-703,717, a PET radioligand for the glycine-binding site of NMDA receptors. Synapse 50:130–136

Harrison PJ, Owen MJ (2003) Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 361: 417–419

Harrison PJ, Law AJ, Eastwood SL (2003) Glutamate receptors and transporters in the hippocampus in schizophrenia. Ann NY Acad Sci 1003:94–101

Harsing LG, Gacsalyi I, Szabo G, Schmidt E, Sziray N, Sebban C, Tesolin-Decros B, Matyus P, Egyed A, Spedding M, Levay G (2003) The glycine transporter-1 inhibitors NFPS and Org 24461: a pharmacological study. Pharmacol Biochem Behav 74:811–825

Hashimoto A, Chiba Y (2004) Effect of systemic administration of D-serine on the levels of D- and L-serine in several brain areas and periphery of rat. Eur J Pharmacol 495:153–158

Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, Nakazato M, Kumakiri C, Okada S, Hasegawa H, Imai K, Iyo M (2003) Decreased serum levels of D-serine in patients with schizophrenia. Arch Gen Psychiatry 60:572–576

Hashimoto R, Straub RE, Weickert CS, Hyde TM, Kleinman JE, Weinberger DR (2004) Expression analysis of neuregulin-$_1$ in the dorsolateral prefrontal cortex in schizophrenia. Mol Psychiatry 9:299–307

Hayashi T, Su TP, Kagaya A, Nishida A, Shimizu M, Yamawaki S (1999) Neuroleptics with differential affinities at dopamine D_2 receptors and sigma receptors affect differently the NMDA-induced increase in intracellular calcium concentration: involvement of protein kinase. Synapse 31:20–28

Hedou G, Mansuy IM (2003) Inducible molecular switches for the study of long-term potentiation. Philos Trans R Soc Lond B Biol Sci 358:797–804

Heikkilä L, Rimon R, Terenius L (1990) Dynorphin A and substance P in the cerebrospinal fluid of schizophrenic patients. Psychiatry Res 34:229–236

Helboe L, Egebjerg J, Moller M, Thomsen C (2003) Distribution and pharmacology of alanine–serine–cysteine transporter 1 (asc-1) in rodent brain. Eur J Neurosci 18:2227–2238

Heresco-Levy U (2000) NMDA receptor-based treatment approaches in schizophrenia: the first decade. Int J Neuropsychopharmacol 3:243–258

Heresco-Levy U (2003) Glutamatergic neurotransmission modulation and the mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 27:1113–1123

Heresco-Levy U, Javitt DC (2004) Comparative effects of glycine and D-cycloserine on persistent negative symptoms in schizophrenia: a retrospective analysis. Schizophr Res 66:89–96

Heresco-Levy U, Javitt DC, Ermilov M, Mordel C, Silipo G, Shimoni J (1998) Double-blind, placebo-controlled, crossover trial of D-cycloserine adjuvant therapy for treatment-resistant schizophrenia. Int J Neuropsychopharmacol 1:131–136

Heresco-Levy U, Javitt DC, Ermilov M, Mordel C, Silipo G, Lichtenstein M (1999) Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Arch Gen Psychiatry 56:29–36

Heresco-Levy U, Ermilov M, Shimoni J, Shapira B, Silipo G, Javitt DC (2002) Placebo-controlled trial of D-cycloserine added to conventional neuroleptics, olanzapine, or risperidone in schizophrenia. Am J Psychiatry 159:480–482

Heresco-Levy U, Ermilov M, Lichtenberg P, Bar G, Javitt DC (2004) High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia. Biol Psychiatry 55:165–171

Higgins GA, Ballard TM, Huwyler J, Kemp JA, Gill R (2003) Evaluation of the NR2B-selective NMDA receptor antagonist Ro 63-1908 on rodent behaviour: evidence for an involvement of NR2B NMDA receptors in response inhibition. Neuropharmacology 44:324–341

Hosak L, Libiger J (2002) Antiepileptic drugs in schizophrenia: a review. Eur Psychiatry 17:371–378

Humphries CR, Mortimer A, Hirsch SR (1996) NMDA receptor RNA correlation with antemortem cognitive impairment in schizophrenia. NeuroReport 7:2051–2055

Husi H, Ward MA, Choudhary IS, Blackstock WP, Grant SGN (2000) Proteomic analysis of NMDA receptor-adhesion protein signaling complexes. Nat Neurosci 3:661–669

Hynd MR, Scott HL, Dodd PR (2004) Selective loss of NMDA receptor NR_1 subunit isoforms in Alzheimer's disease. J Neurochem 89:240–247

Ibrahim HM, Hogg AJ, Healy DJ, Harountunian V, Davis KL, Meador-Woodruff JH (2000) Ionotropic glutamate receptor binding and subunit mRNA expression in thalamic nuclei in schizophrenia. Am J Psychiatry 157:1811–1823

Ichinohe A, Kure S, Mikawa S, Ueki T, Kojima K, Fujiwara K, Linuma K (2004) Glycine cleavage system in neurogenic regions. Eur J Neurosci 19:2365–2370

Ilyin VI, Whittemore ER, Guastella J, Weber E, Woodward RM (1996) Subtype-selective inhibition of NMDA receptors by haloperidol. Mol Pharmacol 50:1541–1550

Ishimaru M, Kurumaji A, Toru M (1994) Increases in strychnine-insensitive glycine binding sites in cerebral cortex of chronic schizophrenics: evidence for glutamate hypothesis. Biol Psychiatry 35:84–95

Itokawa MK, Yamada K, Yoshitsugu K (2003) A microsatellite repeat in the promoter of the NMDA receptor 2A subunit (GRIN2A) gene suppresses transcriptional activity and correlates with chronic outcome in schizophrenia. Pharmacogenetics 13:271–278

Iwamoto T, Yamada Y, Hori K, Watanabe Y, Sobue K, Inui M (2004) Differential modulation of NR1–NR2A and NR1–NR2B subtypes of NMDA receptor by PDZ domain-containing proteins. J Neurochem 89:100–108

Jackson ME, Homayoun H, Moghaddam B (2004) NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex. Proc Natl Acad Sci U S A 101:8467–8472

Jang MK, Mierke DF, Russek SJ, Farb DH (2004) A steroid modulatory domain on NR2B controls NMDA receptor proton sensitivity. Proc Natl Acad Sci U S A 101:8198–8203

Jardemark KE, Ninan I, Liang X, Wang RY (2003) Protein kinase C is involved in clozapine's facilitation of NMDA- and electrically evoked responses in pyramidal cells of the medial prefrontal cortex. Neuroscience 118:501–512

Javitt DC (2002) Glycine modulators in schizophrenia. Curr Opin Investig Drugs 3:1067–1072

Javitt DC, Frusciante M (1997) Glycyldodecylamide, a phencyclidine behavioral antagonist, blocks cortical glycine uptake: implications for schizophrenia and substance abuse. Psychopharmacology 129:96–98

Javitt DC, Sershen H, Hashim A, Lajtha A (1997) Reversal of phencyclidine-induced hyperactivity by glycine and the glycine uptake inhibitor glycyldodecylamide. Neuropsychopharmacology 17:202–204

Javitt DC, Balla A, Sershen H, Lajtha A (1999) Reversal of phencyclidine-induced effects by glycine and glycine transport inhibitors. Biol Psychiatry 45:668–679

Javitt DC, Sershen H, Hashim A, Lajtha A (2000) Inhibition of striatal dopamine release by glycine and glycyldodecylamide. Brain Res Bull 52:213–216

Javitt DC, Silipo G, Cienfuegos A, Shelley AM, Bark N, Park M, Lindenmayer JP, Suckow R, Zukin SR (2001) Adjunctive high-dose glycine in the treatment of schizophrenia. Int J Neuropsychopharmacol 4:385–391

Javitt DC, Balla A, Sershen H (2002) A novel alanine-insensitive D-serine transporter in rat brain synaptosomal membranes. Brain Res 941:146–149

Javitt DC, Balla A, Burch S, Suckow R, Xie S, Sershen H (2004a) Reversal of phencyclidine-induced dopaminergic dysregulation by NMDA receptor/glycine-site agonists. Neuropsychopharmacology 29:300–307

Javitt DC, Duncan L, Balla A, Sershen H (2004b) Inhibition of system A-mediated glycine transport in cortical synaptosomes by therapeutic concentrations of clozapine: implications for mechanisms of action. Mol Psychiatry, in press

Johannesen TS, Myhrer T (2002) Impaired visual memory in rats reared in isolation is reversed by D-cycloserine in the adult rat. Eur J Pharmacol 437:73–77

Jones R, Laake K, Oeksengaard AR (2004) D-Cycloserine for Alzheimer's disease (Cochrane review). In: The Cochrane Library, Issue 2. Wiley, Chichester, UK

Johnson SA, Luu NT, Herbst TA, Knapp R, Lutz D, Arai A, Rogergs GA, Lynch G (1999) Synergistic interactions between ampakines and antipsychotic drugs. J Pharmacol Exp Ther 289:392–397

Kadotani H, Hirano T, Masugi M, Nakamura K, Nakao K, Katsuki M, Nakanishi S (1996) Motor discoordination results from combined gene disruption of the NMDA receptor NR2A and NR2C subunits, but not from single disruption of the NR2A or NR2C subunit. J Neurosci 16:7859–7867

Kanamori K, Ross BD (2004) Quantitative demonstration of extracellular glutamine concentrations in rat brain, and its elevation in vivo by system A transporter inhibitor, alpha-(methylamino) isobutyrate. J Neurochem 90:203–210

Kane JM, Krystal J, Correll CU (2003) Treatment models and designs for intervention research during the psychotic prodrome. Schizophr Bull 29:747–756

Kapur S, Seeman P (2002) NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D_2 and serotonin 5-HT_2 receptors—implications for models of schizophrenia. Mol Psychiatry 7:837–844

Kato K, Shishido T, Ono M, Shishido K, Kobayashi M, Niwa S (2001) Glycine reduces novelty- and methamphetamine-induced locomotor activity in neonatal ventral hippocampal damaged rats. Neuropsychopharmacolgy 24:330–332

Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, Van Heertum RL, Cooper TB, Carlsson A, Laruelle M (2000) Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. Biol Psychiatry 48:627–640

Kegeles LS, Martinez D, Kochan LD, Hwang DR, Huang Y, Mawlawi O, Suckow RF, Van Heertum DR, Laruelle M (2002) NMDA antagonist effects on striatal dopamine release: positron emission tomography studies in humans. Synapse 43:19–29

Kinney GG, Sur C, Burno M, Mallorga PJ, Williams JB, Figueros DJ, Wittmann M, Lemaire W, Conn PJ (2003) The glycine transporter type 1 inhibitor *N*-[3-(4′-fluorophenyl)-3-(4″-phenylphnoxy)propyl]sarcosine potentiates NMDA receptor-mediated responses in vivo and produces an antipsychotic profile in rodent behavior. J Neurosci 23:7586–7591

Kloda A, Clements JD, Lewis RJ, Adams DJ (2004) Adenosine triphosphate acts as both a competitive antagonist and a positive allosteric modulator at recombinant NMDA receptors. Mol Pharmacol 65:1386–1396

Konradi C, Heckers S (2003) Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment. Pharmacol Ther 97:153–179

Korostishevsky M, Kaganovich M, Cholostoy A, Ashkenazi M, Ratner Y, Dehary D, Bernstein J, Bening-Abu-Shach U, Ben-Asher E, Lancet D, Ritsner M, Navon R (2004) Is the G72/G30 locus associated with schizophrenia? Single nucleotide polymorphisms, haplotypes, and gene expression analysis. Biol Psychiatry 56:169–176

Kretschmer BD (1998) Ligands of the NMDA receptor-associated glycine recognition site and motor behavior. Amino Acids 14: 227–234

Kretschmer BD, Koch M (1998) The ventral pallidum mediates disruption of prepulse inhibition of the acoustic startle response induced by dopamine agonists, but not by NMDA antagonists. Brain Res 798:204–210

Krupp JJ, Vissel B, Thomas CG, Heinemann SF, Westbrook GL (2002) Calcineurin acts via the C-terminus of NR2A to modulate desensitisation of NMDA receptors. Neuropharmacology 42:593–602

Kumashiro S, Hashimoto A, Nishikawa T (1995) Free D-serine in post-mortem brains and spinal cords of individuals with and without neuropsychiatric diseases. Brain Res 681:117–125

Lahti AC, Weiler MA, Michaelidis T, Parwani A, Tamminga CA (2001) Effects of ketamine in normal and schizophrenic volunteers. Neuropsychopharmacology 25:455–467

Laruelle M, Kegeles LS, Abi-Dargham A (2003) Glutamate, dopamine, and schizophrenia from pathophysiology to treatment. Ann NY Acad Sci 1003:138–158

Law AJ, Deakin JFW (2001) Asymmetrical reduction of hippocampal NMDAR1 glutamate receptor mRNA in the psychoses. NeuroReport 12:2971–2974

Law AJ, Weickert S, Hyde TM, Kleinman JE, Harrison PJ (2004) Neuregulin-1 (NRG-1) mRNA and protein in the adult human brain. Neuroscience 127:125–136

Lee J, Rajakumar N (2003) Role of NR2B-containing NMDA receptors in haloperidol-induced c-FOS in striatum and nucleus accumbens. Neuroscience 122:739–745

Lees KR, Lavelle JF, Cunha L, Diener HC, Sanders EACM, Tack P, Wester P (2001) Glycine antagonist (GV150526) in acute stroke a multicentre, double-blind placebo-controlled phase II trial. Cerebrovasc Dis 11:20–29

Leiderman E, Zylberman I, Zukin SR, Cooper TB, Javitt DC (1996) Preliminary investigation of high-dose oral glycine on serum levels and negative symptoms in schizophrenia: an open-label trial. Biol Psychiatry 39:213–215

Le Pen G, Kew J, Alberati D, Borroni E, Heitz MP, Moreau JL (2003) Prepulse inhibition deficits of the startle reflex in neonatal ventral hippocampal-lesioned rats: reversal by glycine and glycine transporter inhibitor. Biol Psychiatry 54:1162–1170

Leveque JC, Macias W, Rajadhyaksha A, Carlson RR, Barczak A, Kang S, Li XM, Coyle JT, Huganir RL, Heckers S, Konradi C (2000) Intracellular modulation of NMDA receptor function by antipsychotic drugs. J Neurosci 20:4011–4020

Levine JB, Martin G, Wilson A, Treistman SN (2003) Clozapine inhibits isolated NMDA receptors expressed in *Xenopus* oocytes in a subunit specific manner. Neurosci Lett 346:125–128

Lewis DA, Levitt P (2002) Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci 25:409–432

Lipska BK (2004) Using animal models to test a neurodevelopmental hypothesis of schizophrenia. J Psychiatry Neurosci 29: 282

Lipsky RH, Goldman D (2003) Genomics and variation of ionotropic glutamate receptors. Ann NY Acad Sci 1003:22–35

Liu L, Wong TP, Pozza MF, Lingenhoehl K, Wang Y, Sheng M, Auberson YP, Wang YT (2004) Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. Science 304:1021–1024

Lowe DA, Emre M, Frey P, Kelly PH, Malanowski J, McAllister KH, Neijt HC, Rudeberg C, Urwyler S, White TG (1994) The pharmacology of SDZ EAA 494, a competitive NMDA antagonist. Neurochem Lett 25:583–600

Mackenzie S, Erickson JD (2004) Sodium-coupled neutral amino acid (system N/A) transporters of the SLC38 gene family. Pflugers Arch 447:784–795

Madden DR (2002) The structure and function of glutamate receptor ion channels. Nat Rev Neurosci 3:91–101

Malhotra AK, Adler CM, Kennison SD, Elman I, Pickar D, Breier A (1997) Clozapine blunts NMDA antagonist-induced psychosis: a study with ketamine. Biol Psychiatry 42:664–668

Marcaggi P, Attwell D (2004) Role of glial amino acid transporters in synaptic transmission and brain energetics. Glia 47:217–225

Marenco S, Egan MF, Goldberg TE, Knable MB, McClure RK, Winterer G, Weinberger DR (2002) Preliminary experience with an ampakine (CX516) as a single agent for the treatment of schizophrenia: a case series. Schizophr Res 57:221–226

Marino MJ, Conn PJ (2002) Direct and indirect modulation of the NMDA receptor: potential for the development of novel antipsychotic therapies. Curr Drug Targets 1:1–16

Mathé JM, Nomikos GG, Schilström B, Svensson TH (1998) Non-NMDA excitatory amino acid receptors in the ventral tegmental area mediate systemic dizocilpine (MK-801) induced hyperlocomotion and dopamine release in the nucleus accumbens. J Neurosci Res 51:583–592

Matsuo H, Kanai Y, Tokunaga M, Nakata T, Chairoungdua A, Ihimine H, Tsukada S, Ooigawa H, Nawashiro H, Kobayashi Y, Fukuda J, Endou H (2004) High affinity D- and L-serine transporter Asc-1: cloning and dendritic localization in the rat cerebral and cerebellar cortices. Neurosci Lett 358:123–126

Matute C, Melone M, Vallejo-Illarramendi A, Conti F (2005) Increased expression of the astrocytic glutamate transporter GLT-1 in the prefrontal cortex of schizophrenia. Glia 49:451–455

Meador-Woodruff JH, Healy DJ (2000) Glutamate receptor expression in schizophrenia brain. Brain Res Interactive 31:288–294

Meador-Woodruff JH, Clinton SM, Beneyto M, McCullumsmith RE (2003) Molecular abnormalities of the glutamate synapse in the thalamus in schizophrenia. Ann NY Acad Sci 1003:75–93

Medoff DR, Holcomb HH, Lahti AC, Tamminga CA (2001) Probing the human hippocampus using rCBF: contrasts in schizophrenia. Hippocampus 11:543–550

Melone M, Gragina L, Conti F (2003) Clozapine-induced reduction of glutamate transport in the frontal cortex is not mediated by GLAST and EAAC1. Mol Psychiatry 8:12–13

Meltzer LT, Christoffersen CL, Serpa KA (1997) Modulation of dopamine neuronal activity by glutamate receptor subtypes. Neurosci Biobehav Rev 21:511–518

Michel FJ, Trudeau LE (2000) Clozapine inhibits synaptic transmission at GABAergic synapses established ventral tegmental area neurones in culture. Neuropharmacology 39:1536–1543

Millan MJ (2002) NMDA receptor-coupled $Glycine_B$ receptors in the pathogenesis and treatment of schizophrenia: a critical review. Curr Drug Targets 1:191–213

Millan MJ, Brocco M, Gobert A, Joly F, Bervoets K, Rivet JM, Newman-Tancredi A, Audinot V, Maurel S (1999) Contrasting mechanisms of action and sensitivity to antipsychotics of phencyclidine *versus* amphetamine: importance of nucleus accumbens 5-HT_{2A} site for PCP-induced locomotion in the rat. Eur J Neurosci 11:4419–4432

Millan MJ, Audinot V, Dekeyne A, Brocco M, Lestage P, Gobert A, Lacoste JM, Cordi A (2000) S18841, a novel, imidazolinone partial agonist at $Glycine_B$ receptors of potential utility for the treatment of psychotic disorders. Int J Psychopharmacol 3:S133

Miller RF (2004) D-Serine as a glial modulator of nerve cells. Glia 47:275–283

Miyakawa T, Leiter LM, Gerber DJ, Gainetdinov RR, Sotnikova TD, Zeng H, Caron MG, Tonegawa S (2003) Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. Proc Natl Acad Sci U S A 100:8987–8992

Miyamoto Y, Yamada K, Noda Y, Mori H, Mishina M, Nabeshima T (2001) Hyperfunction of dopaminergic and serotonergic neuronal systems in mice lacking the NMDA receptors ε_1 subunit. J Neurosci 21:750–757

Miyamoto S, Snouwaert JN, Koller BH, Moy SS, Lieberman JA, Duncan GE (2004) Amphetamine-induced fos is reduced in limbic cortical regions but not in the caudate or accumbens in a genetic model of NMDA receptor hypofunction. Neuropsychopharmacology:1–9

Miyatake R, Furukawa A, Suwaki H (2002) Identification of a novel variant of the human NR2B gene promoter regions and its possible association with schizophrenia. Mol Psychiatry 7:1101–1106

Moghaddam B (2002) Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. Biol Psychiatry 51:775–787

Moghaddam B (2003) Bringing order to the glutamate chaos in schizophrenia. Neuron 40:881–884

Moghaddam B, Jackson ME (2003) Glutamatergic animal models of schizophrenia. Ann NY Acad Sci 1003:131–137

Mohn AR, Gainetdinov RR, Caron MG, Koller BH (1999) Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. Cell 98:427–436

Montana V, Ni Y, Sunjura V, Hua X, Parpura V (2004) Vesicular glutamate transporter-dependent glutamate release from astrocytes. J Neurosci 24:2633–2642

Moretti L, Pentikäinen OT, Settimo L, Johnson MS (2004) Model structures of the NMDA receptor subunit NR_1 explain the molecular recognition of agonist and antagonist ligands. J Struct Biol 145:205–215

Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV (2004) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 29:208–218

Mothet JP, Parent AT, Wolosker H, Brady RO, Linden DJ, Ferris CD, Rogawski MA, Snyder SH (2000) D-Serine is an endogenous ligand for the glycine site of the NMDA receptor. Proc Natl Acad Sci U S A 97:4926–4931

Mueller HT, Haroutunian V, Davis KL, Meador-Woodruff JH (2004) Expression of the ionotropic glutamate receptor subunits and NMDA receptor-associated intracellular proteins in the substantia nigra in schizophrenia. Mol Brain Res 121:60–69

Muir KW, Lees KR (1995) Clinical experience with excitatory amino acid antagonist drugs. Stroke 26:503–513

Nakauchi J, Matsuo H, Kim DK, Goto A, Chairoungdua A, Cha SH, Inatomi J, Shiokawa Y, Yamaguchi K, Saito I, Endou H, Kanai Y (2000) Cloning and characterization of a human brain Na^+-independent transporter for small neutral amino acids that transports D-serine with high affinity. Neurosci Lett 287:231–235

Naudon L, Moreau I, Vaillend C, Jay TM (2004) Prefrontal cortex neurons express both dopamine D_1 and NMDA-R1 receptors—a double immunofluorescence study. FENS FORUM, 414

Neale JH, Bzdega T, Wroblewska B (2000) *N*-Acetylaspartyl-glutamate: most abundant peptide neurotransmitter in mammalian central nervous system. J Neurochem 75:443–452

Nedergaard M, Takano T, Hansen AJ (2002) Beyond the role of glutamate as a neurotransmitter. Nat Rev Neurosci 3:748–755

Ninan I, Jardemark KE, Liang X, Wang RY (2003a) Calcium/calmodulin-dependent kinase II is involved in the facilitating effect of clozapine on NMDA- and electrically evoked responses in the medial prefrontal cortical pyramidal cells. Synapse 47: 285–294

Ninan I, Jardemark KE, Wang RY (2003b) Olanzapine and clozapine but not haloperidol reverse subchronic phencyclidine-induced functional hyperactivity of NMDA receptors in pyramidal cells of the rat medial prefrontal cortex. Neuropharmacology 44:462–472

Nong YI, Huang YQ, Ju W, Kalia LV, Ahmadian G, Wang YT, Salter MW (2003) Glycine binding primes NMDA receptor internalisation. Nature 422:302–307

Ohnuma T, Tessler G, Arai H, Faull RL, McKenna PJ, Emson PC (2000) Gene expression of metabotropic glutamate receptor 5 and excitatory amino acid transporter 2 in the schizophrenic hippocampus. Brain Res Mol Brain Res 85:24–31

Ohtsuki T, Sakurai K, Dou H, Toru M, Yamakawa-Kobayashi K, Arinami T (2001) Mutation analysis of the NMDAR2B (GRIN2B) gene in schizophrenia. Mol Psychiatry 6:211–216

Olszewski RT, Bukhari N, Zhou J, Kozikowski AP, Wroblewski JT, Shamimi-Noori S, Wroblewska B, Bzdega T, Vicini S, Barton FB, Neale JH (2004) NAAG peptidase inhibition reduces locomotor activity and some stereotypes in the PCP model of schizophrenia via group II mGluR. J Neurochem 89:876–885

Oranje B, Gispen-de Wied CC, Verbaten MN, Kahn RS (2002) Modulating sensory gating in healthy volunteers: the effects of ketamine and haloperidol. Biol Psychiatry 52:557–895

Ossowska K, Pietraszek M, Wardas J, Nowak G, Wolfarth S (1999) Chronic haloperidol and clozapine administration increases the number of cortical NMDA receptors in rats. Naunyn-Schmiedeberg's Arch Pharmacol 359:280–287

Parpura V, Scemes E, Spray DC (2004) Mechanisms of glutamate release from astrocytes: gap junction "hemichannels", purinergic receptors and exocytotic release. Neurochem Int 45:259–264

Paul IA, Skolnick P (2003) Glutamate and depression clinical and preclinical studies. Ann NY Acad Sci 1003:250–272

Perry W, Light GA, Davis H, Braff DL (2000) Schizophrenia patients demonstrate a dissociation on declarative and non-declarative memory tests. Schizophr Res 46:167–174

Popken GJ, Leggio MG (2002) Expression of mRNAs related to the GABAergic and glutamatergic neurotransmitter systems in the human thalamus: normal and schizophrenic. Thalamus Relat Syst 1:349–369

Potkin SG, Jin Y, Bunney BG, Costa J, Gulasekaram B (1999) Effect of clozapine and adjunctive high-dose glycine in treatment-resistant schizophrenia. Am J Psychiatry 156:145–147

Pralong E, Magistretti P, Stoop R (2002) Cellular perspectives on the glutamate–monoamine interactions in limbic lobe structures and their relevance for some psychiatric disorders. Prog Neurobiol 67:173–202

Przegalinski E, Siwanowicz J, Chojnacka-Wojcik E (1999) Lack of effect of a $Glycine_B$ receptor partial agonist on amphetamine-induced sensitisation in mice. Pol J Pharmacol 51:385–390

Reisberg B, Doody R, Stöffler A (2003) Memantine in moderate to severe Alzheimer's disease. N Engl J Med 348:1333–1341

Ribeiro CS, Reis M, Panizzutti R, de Miranda J, Wolosker H (2002) Glial transport of the neuromodulator D-serine. Brain Res 929: 202–209

Rivera A, Cuellar B, Giron FJ, Grandy DK, de la Calle A, Moratalla R (2002) Dopamine D_4 receptors are heterogeneously distributed in the striosomes/matrix compartment of the striatum. J Neurochem 80:219–229

Rodriguez JJ, Pickel VM (1999) Enhancement of NMDA immunoreactivity in residual dendritic spines in the caudate–putamen nucleus after chronic haloperidol administration. Synapse 33: 289–303

Rosse RB, Theut SK, Banay-Schwartz M, Leighton M, Scarcella E, Cohen CG, Deutsch SI (1989) Glycine adjuvant therapy to conventional neuroleptic treatment in schizophrenia an open-label, pilot study. Clin Neuropharmacol 12:416–424

Rouaud T, Billard JM (2003) D-Cycloserine facilitates synaptic plasticity but impairs glutamate neurotransmission in rat hippocampus slices. Br J Pharmacol 140:1051–1056

Rubin Y, La Placa MC, Smith DH, Thibault LE, Lenkinski RE (1995) The effect of *N*-acetylaspartate on the intracellular free calcium concentration in NTera2-neurons. Neurosci Lett 198:209–212

Sakata Y, Owada Y, Sato K, Kojima K, Hisanaga K, Shinka T, Suzuki Y, Aoki Y, Satoh J, Kondo H, Matsubara Y, Kure S (2001) Structure and expression of the glycine cleavage system in rat central nervous system. Mol Brain Res 94:119–130

Schell MJ, Molliver ME, Snyder SH (1995) D-Serine, an endogenous synaptic modulator: localization to astrocytes and glutamate-stimulated release. Proc Natl Acad Sci U S A 92:3948–3952

Schiffer HH (2002) Glutamate receptor genes. Mol Neurobiol 25: 191–212

Schiffer WK, Logan J, Dewey SL (2003) Positron emission tomography studies of potential mechanisms underlying phencyclidine-induced alterations in striatal dopamine. Neuropsychopharmacology 28:2192–2198

Schmidt WJ, Kretschmer BD (1997) Behavioural pharmacology of glutamate receptors in the basal ganglia. Neurosci Biobehav Rev 21:381–392

Schmidt A, Zink M, Petroianu G, May B, Braus DF, Henn FA (2003) Decreased gene expression of glial and neuronal glutamate transporters after chronic antipsychotic treatment in rat brain. Neurosci Lett 347:81–84

Schneider J, Wade T, Lidsky T (1998) Chronic neuroleptic treatment alters expression of glial glutamate transporter GLT-1 Mma in the striatum. NeuroReport 9:133–136

Schoepp DD, Marek GJ (2002) Preclinical pharmacology of mGlu2/3 receptor agonists: novel agents for schizophrenia? Curr Drug Targets CNS Neurol Disord 1:215–225

Schroeder H, Greekseh G, Beeker A, Bogerts B, Hoellt V (1999) Alterations of the dopaminergic and glutamatergic neurotransmission in adult rats with postnatal ibotenic acid hippocampus lesion. Psychopharmacology 145:61–66

Schwab SG, Knapp M, Mondabon S, Hallmayer J, Borrmann-Hassenbach M, Albus M, Lere B, Rietschel M, Trixler M, Maier W, Wildenauer DB (2003) Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. Am J Hum Genet 72:185–190

Schwarcz R, Pellicciari R (2002) Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. J Pharmacol Exp Ther 303:1–10

Schwarcz R, Rassoulpour A, Wu HQ, Medoff D, Tamminga CA, Roberts RC (2001) Increased cortical kynurenate content in schizophrenia. Biol Psychiatry 50:521–530

Schwieler L, Erhardt S (2003) Inhibitory action of clozapine on rat ventral tegmental area dopamine neurons following increased levels of endogenous kynurenic acid. Neuropsychopharmacology 28:1770–1777

Schwieler L, Engberg G, Erhardt S (2004) Clozapine modulates midbrain dopamine neuron firing via interaction with the NMDA receptor complex. Synapse 52:114–122

Seamans JK, Durstewitz D, Christie BR, Stevens CF, Sejnowski TJ (2000) Dopamine D_1/D_5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons. Proc Natl Acad Sci U S A 98:301–306

Sebban C, Tesolin-Decros B, Ciprian-Ollivier J, Perret L, Spedding M (2002) Effects of phencyclidine (PCP) and MK 801 on the EEGq in the prefrontal cortex of conscious rats; antagonism by clozapine, and antagonists of AMPA-, α_1- and 5-HT_{2A}-receptors. Br J Pharmacol 135:65–78

See RE, Lynch AM (1996) Duration-dependent increase in striatal glutamate following prolonged fluphenazine administration in rats. Eur J Pharmacol 302:279–282

Semple CAM, Devon RS, Le Hellard S, Porteous DJ (2001) Identification of genes from a schizophrenia-linked translocation breakpoint region. Genomics 73:123–126

Serretti A, De Ronchi D, Lorenzi C, Barardi D (2004) New antipsychotics and schizophrenia: a review on efficacy and side effects. Curr Med Chem 11:343–358

Sesack SR, Carr DB, Omelchenko N, Pinto A (2003) Anatomical substrates for glutamate–dopamine interactions. Ann NY Acad Sci 1003:36–52

Sheinin A, Shavit S, Benveniste M (2001) Subunit specificity and mechanism of action of NMDA partial agonist D-cycloserine. Neuropharmacology 41:151–158

Sherman AD, Davidson AT, Baruah S, Hegwood TS, Waziri B (1991) Evidence of glutamatergic deficiency in schizophrenia. Neurosci Lett 121:77–80

Shi WX, Zhang XX (2003) Dendritic glutamate-induced bursting in the prefrontal cortex: further characterization and effects of phencyclidine. J Pharmacol Exp Ther 305:680–687

Shoham S, Mazeh H, Javitt DC, Heresco-Levy U (2004) Glycine and D-cycloserine attenuate vacuous chewing movements in a rat model of tardive dyskinesia. Brain Res 1004:142–147

Smith RE, Haroutunian V (2001a) Expression of excitatory amino acid transporter transcripts in the thalamus of subjects with schizophrenia. Am J Psychiatry 158:1393–1399

Smith RE, Haroutunian V (2001b) Vesicular glutamate transporter transcript expression in the thalamus in schizophrenia. NeuroReport 12:1–3

Speno HS, Luthi-Carter R, Macias WL, Valentine SL, Joshi ART, Coyle JT (1999) Site-directed mutagenesis of predicted active site residues in glutamate carboxypeptidase II. Mol Pharmacol 55:179–185

Spooren W, Mombereau C, Maco M, Gill R, Kemp JA, Ozmen L, Nakanishi S, Higgins GA (2004) Pharmacological and genetic evidence indicates that combined inhibition of NR2A and NR2B subunit containing NMDA receptors is required to disrupt prepulse inhibition. Psychopharmacology 175:99–105

Squires RF, Saederup E (1998) Clozapine and several other antipsychotic/antidepressant drugs preferentially block the same core fraction of $GABA_{(A)}$ receptors. Neurochem Res 23:1283–1290

Stefansson H, Sigurdsson E, Steinhorsdottir V, Bjornsdottir S, Sigmundsson T, Stefansson K (2002) $Neuregulin_1$ and susceptibility to schizophrenia. Am J Hum Genet 71:877–892

Stefansson H, Setinthorsdottir V, Thorgeirsson TE, Gulcher JR, Stefansson K (2004) $Neuregulin_1$ and schizophrenia. Ann Med 36:62–71

Stefensen SC, Svingos AL, Pickel VM, Henriksen SJ (1998) Electrophysiological characterization of GABAergic neurons in ventral tegmental area. J Neurosci 18:8003–8015

Steinpreis RE (1996) The behavioural and neurochemical effects of phencyclidine in humans and animals: some implications for modelling psychosis. Behav Brain Res 74:45–55

Stone TW, Darlington LG (2002) Endogenous kynurenines as targets for drug discovery and development. Nat Rev Drug Discov 1:609–620

Stouffer EM, Petri HL, Devan BD (2004) Effect of D-serine on a delayed match-to-place task for the water maze. Behav Brain Res 152:447–452

Straub RE, Jiang Y, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C, Wormley B, Sadek H, Kadambi B, Cesare AJ, Gibberman A, Wang X, O'Neill FA, Walsh D, Kendler KS (2002) Genetic variation in 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am J Hum Genet 71:337–348

Sumiyoshi T, Anil AE, Jin D, Jayathilake K, Lee M, Meltzer HY (2004) Plasma glycine and serine levels in schizophrenia compared to normal controls and major depression: relation to negative symptoms. Int J Neuropharmacol 7:1–8

Sur C, Mallorga PJ, Wittmann M, Jacobson MA, Pascarella D, Williams JB, Brandish PE, Pettibone DJ, Scolnick EM, Conn PJ (2003) *N*-Desmethylclozapine, a novel allosteric agonist at $muscarinic_1$ receptor potentiates NMDA receptor activity. Proc Natl Acad Sci U S A 100:13674–13679

Takahata R, Moghaddam B (2003) Activation of glutamate neurotransmission in the prefrontal cortex sustains the motoric and dopaminergic effects of phencyclidine. Neuropsychopharmacology 28:1117–1124

Tamminga CA, Lahti AC, Mefoff DR, Gao XM, Holcomg HH (2003) Evaluating glutamatergic transmission in schizophrenia. Ann NY Acad Sci 1003:113–118

Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, Liu G, Tsien JZ (1999) Genetic enhancement of learning and memory in mice. Nature 401:63–69

Tanii Y, Nishikawa T, Hashimoto A, Takahashi K (1994) Stereoselective antagonism by enantiomers of alanine and serine of phencyclidine-induced hyperactivity, stereotypy and ataxia in the rat. J Pharmacol Exp Ther 269:1040–1048

Tarazi FI, Baldessarini RJ, Kula NS, Zhang H (2003) Long-term effects of olanzapine, risperidone, and quetiapine on ionotropic glutamate receptor types: implications for antipsychotic drug treatment. J Pharmacol Exp Ther 306:1145–1151

Terada T, Inui K (2004) Peptide transporters: structure, function, regulation and application for drug delivery. Curr Drug Metab 5:85–94

Théberge J, Bartha R, Drost DJ, Menon RS, Malla A, Takhar J, Neufeld RW, Rogers J, Pavlosky W, Schaefer B, Densmore M, Al-Semaan Y, Williamson PC (2002) Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. Am J Psychiatry 159: 1944–1946

Théberge J, Al-Semann Y, Williamson PC, Menon RS, Neufeld RWJ, Rajakumar N, Schaefer B, Densmore M, Drost DJ (2003) Glutamate and glutamine in the anterior cingulate and thalamus of medicated patients with chronic schizophrenia and healthy comparison subjects measured with 4.0-T proton MRS. Am J Psychiatry 160:2231–2233

Tibbo P, Hanstock C, Valiakalayil A, Allen P (2004) 3-T proton MRS investigation of glutamate and glutamine in adolescents at high genetic risk for schizophrenia. Am J Psychiatry 161:1116–1118

Tiihonen J, Hallikainen T, Ryynänen OP, Repo-Tiihonen E, Kotilainen I, Eronen M, Toivonen P, Wahlbeck K, Putkonen A (2003) Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. Biol Psychiatry 54:1241–1248

Toth E, Lajtha A (1986) Antagonism of phencyclidine induced hyperactivity by glycine in mice. Neurochem Res 11:393–400

Trudeau LE (2004) Glutamate co-transmission as an emerging concept in monoamine neuron function. Rev Psychiatr Neurosci 29:296–310

Tsai G, Passani LA, Slusher BS, Carter R, Baer L, Kleinman JE, Coyle JT (1995) Abnormal excitatory neurotransmitter metabolism in schizophrenic brain. Arch Gen Psychiatry 52:829–836

Tsai G, Yang P, Chung LC, Lange N, Coyle JT (1998) D-Serine added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 44:1081–1089

Tsai GE, Yang P, Chung LC, Tsai IC, Tsai CW, Coyle JT (1999) D-Serine added to clozapine for the treatment of schizophrenia. Am J Psychiatry 156:1822–1825

Tsai G, Lane HY, Yang P, Chong MY, Lang N (2004a) Glycine transporter I inhibitor, *N*-methylglycine (sarcosine), added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 55:452–456

Tsai G, Ralph-Williams RJ, Martina M, Bergeron R, Berger-Sweeney J, Dunham KS, Jiang Z, Caine SB, Coyle JT (2004b) Gene knockout of glycine transporter 1: characterization of the behavioral phenotype. Proc Natl Acad Sci U S A 101:8485–8490

Tseng KY, O'Donnell P (2004) Dopamine–glutamate interactions controlling prefrontal cortical pyramidal cell excitability involve multiple signalling mechanisms. J Neurosci 24:5131–5139

Tuominen HJ, Tiihonen J, Wahlbeck K (2005) Glutamatergic drugs for schizophrenia: a systematic review and meta-analysis. Schizophr Res 72:225–234

Turecek R, Vlcek K, Petrovic M, Horak M, Vlachova V, Vyklicky L (2004) Intracellular spermine decreases open probability of NMDA receptors. Neuroscience 125:879–887

Urai Y, Jinnouchi O, Kwak KT, Suzue A, Nagahiro S, Fukui K (2002) Gene expression of D-amino acid oxidase in cultured rat astrocytes regional and cell type specific expression. Neurosci Lett 324:101–104

Vaillend C, Ungerer A, Billard JM (1999) Facilitated NMDA receptor-mediated synaptic plasticity in the hippocampal CA1 area of dystrophin-deficient mice. Synapse 33:59–70

Van Berckel BNM (2003) Glutamate and schizophrenia. Curr Neuropharmacol 1:351–370

Van der Heijden FMMA, Tuinier S, Fekkes D, Sijben AES, Kahn RS, Verhoenven WMA (2004) Atypical antipsychotics and the relevance of glutamate and serotonin. Eur Neuropsychopharmacol 14:259–265

Ventriglia M, Bocchi Chiavetto L, Bonvicini C, Tura GB, Bignotti S, Racagni G, Gennarelli M (2002) Allelic variation in the human prodynorphin gene promoter and schizophrenia. Neuropsychobiology 46:17–21

Vicini S, Wang JF, Li JH, Zhu WJ, Wang YH, Luo JH, Wolfe BB, Grayson DR (1998) Functional and pharmacological differences between recombinant NMDA receptors. J Neurophysiol 79:555–566

Vieira AR, Devlin AM (2004) Glutamate carboxipeptidase II (GCPII) His475Tyr polymorphism and association studies. Am J Med Gen 130A:329–330

Weickert CS, Straub RE, McClintock BW, Matsumoto M, Hashimoto R, Hyde TM, Herman MM, Weinberger DR, Kleinman JE (2004) Human dysbindin (DTNBP1) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. Arch Gen Psychiatry 61:544–555

Weiner DM, Meltzer HY, Veinbergs I, Donohue EM, Spalding TA, Smith TT, Mohell N, Harvey SC, Lameh J, Nash N, Vanover KE, Olsson R, Jayathilake K, Lee M, Levey AI, Hacksell U, Burstein ES, Davis RE, Brann MR (2004) The role of M_1 muscarinic receptor agonism of *N*-desmethylclozapine in the unique clinical effects of clozapine. Psychopharmacology 177: 207–216

Williams NM, Bowen T, Spurlock G, Norton N, Williams HJ, Hoogendoom B, Owen MJ, O'Donovan MC (2002) Determination of the genomic structure and mutation screening in schizophrenic individuals for five subunits of the NMDA glutamate receptor. Mol Psychiatry 7:508–514

Williams NM, Preece A, Spurlock G, Norton N, Williams HJ, Zammit S, O'Donovan MD, Owen MJ (2003) Support for genetic variation in neuregulin$_1$ and susceptibility to schizophrenia. Mol Psychiatry 8:485–487

Williams JB, Mallorga PJ, Conn PJ, Pettibone DJ, Sur C (2004) Effects of typical and atypical antipsychotics on human glycine transporters. Schizophr Res 71:103–112

Winter JC, Eckler JR, Rabin RA (2003) Serotonergic/glutamatergic interactions: the effects of mGlu (2/3) receptor ligands in rats trained with LSD and PCP as discriminative stimuli. Psychopharmacology 172:233–240

Wollemann M, Benyhe S (2004) Non-opioid actions of opioid peptides. Life Sci 75:257–270

Wolosker H, Blackshaw S, Snyder SH (1999) Serine racemase: a glial enzyme synthesizing D-serine to regulate glutamate–*N*-methyl-D-aspartate neurotransmission. Proc Natl Acad Sci U S A 96:13409–13414

Woo TUW, Walsh JP, Benes FM (2004) Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the *N*-methyl-D-aspartate receptor subunit NR_{2A} in the anterior cingulate cortex in schizophrenia and bipolar disorder. Arch Gen Psychiatry 61:649–657

Xia M, Liu Y, Figueroa DJ, Chiu CS, Wei N, Lawlor AM, Lu P, Sur C, Koblan KS, Connolly TM (2004) Characterization and localization of a human serine racemase. Mol Brain Res 125:96–104

Yamakura T, Shimoh K (1999) Subunit- and site-specific pharmacology of the NMDA receptor channel. Prog Neurobiol 59:279–298

Yamamoto BK, Pehek EA, Meltzer HY (1994) Brain region effects of clozapine on amino acid and monoamine transmission. J Clin Psychiatry 55:8–14

Yan HD, Ishihara K, Serikawa T, Sasa M (2003) Activation by *N*-acetyl-L-aspartate of acutely dissociated hippocampal neurons in rats via metabotropic glutamate receptors. Epilepsia 44:1153–1159

Yanahashi S, Hashimoto K, Hattori K, Yuasa S, Iyo M (2004) Role of NMDA receptor subtypes in the induction of catalepsy and increase in Fos protein expression after administration of haloperidol. Brain Res 1011:84–93

Yang JZ, Si TM, Ruan Y, Ling YS, Han YH, Wang XL, Zhou M, Zhang HY, Kong QM, Liu C, Zhang DR, Yu YQ, Liu SZ, Ju GZ, Shu L, Ma DL, Zhang D (2003) Association study of neuregulin$_1$ gene with schizophrenia. Mol Psychiatry 8:706–709

Ye ZC, Wyeth MS, Baltan-Tekkok S, Ransom BR (2003) Functional hemichannels in astrocytes: a novel mechanism of glutamate release. J Neurosci 23:3588–3596

Yu B, Wang C, Liu L, Johnson KM, Gallagher JP (2002) Adaptation to chronic PCP results in hyperfunctional NMDA and hypofunctional $GABA_A$ synaptic receptors. Neuroscience 113:1–10

Zavitsanou K, Ward PB, Huang XF (2002) Selective alterations in ionotropic glutamate receptors in the anterior cingulate cortex in schizophrenia. Neuropsychopharmacology 27:826–833