Psychopharmacology (2005) 181: 415–436
DOI 10.1007/s00213-005-0020-9

REVIEW

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The potential role of lamotrigine in schizophrenia

Received: 16 November 2004 / Accepted: 29 March 2005 / Published online: 6 July 2005

Abstract *Rationale:* Atypical antipsychotic drugs are the drugs of choice for the treatment of schizophrenia. However, despite advances, no treatments have been established for patients who fail to improve with the most effective of these, clozapine. The inhibition of dopamine transmission through blockade of dopamine D2 receptors is considered to be essential for antipsychotic efficacy, but it is postulated that modulation of glutamate transmission may be equally important. In support of this, symptoms similar to schizophrenia can be induced in healthy volunteers using *N*-methyl-D-aspartate (NMDA) antagonist drugs that are also known to enhance glutamate transmission. Furthermore, lamotrigine, which can modulate glutamate release, may add to or synergise with atypical antipsychotic drugs, some of which may themselves modulate glutamate transmission. *Objectives:* We examine the evidence for the efficacy of lamotrigine. We consider how this fits with a glutamate neuron dysregulation hypothesis of the disorder. We discuss mechanisms by which lamotrigine might influence neuronal activity and glutamate transmission, and possible ways in which the drug might interact with antipsychotic medications. *Results:* Data from four clinical studies support the efficacy of adjunctive lamotrigine in the treatment of schizophrenia. In addition, and consistent with a glutamate neuron dysregulation hypothesis of schizophrenia, lamotrigine can prevent the psychotic symptoms or behavioural disruption induced by NMDA receptor antagonists in healthy volunteers or rodents. *Conclusions:* The efficacy of lamotrigine is most likely explained within the framework of a glutamate neuron dysregulation hypothesis, and may arise primarily through the drugs ability to influence glutamate transmission and neural activity in the cortex. The drug is likely to act through inhibition of voltage-gated sodium channels, though other molecular interactions cannot be ruled out. Lamotrigine may add to or synergise with some atypical antipsychotic drugs acting on glutamate transmission; alternatively, they may act independently on glutamate and dopamine systems to bring about a combined therapeutic effect. We propose new strategies for the treatment of schizophrenia using a combination of anti-dopaminergic and anti-glutamatergic drugs.

Keywords Anticonvulsant · Sodium channels · Glutamate release · Schizophrenia · NMDA antagonist model

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Introduction

Schizophrenia remains a disabling illness characterized in most patients by residual symptoms and recurrent relapse despite recent advances in pharmacological treatment. All antipsychotic agents share in common antagonism of dopamine D2 receptors; the more recent "second-generation" agents additionally share serotonin (5-HT2) receptor antagonism but differ from each other in possessing diverse patterns of activity at other receptors (Schotte et al. 1996; Zhang and Bymaster 1999). Among the newer agents, only clozapine has clearly demonstrated enhanced efficacy in patients refractory to D2 antagonists, although roughly half of patients still fail to respond to clozapine (Kane et al. 1988). No treatments have been established for patients who fail clozapine or are only partially responsive (Barnes et al. 1996).

New pharmacological models of schizophrenia have provided novel pharmacological strategies for the treatment of

the disorder. Of particular interest is a model that posits hypofunction of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor, resulting in dysregulation of cortical neuronal activity and glutamate transmission (Olney and Farber 1995; Goff and Coyle 2001; Krystal et al. 2003). For decades it has been recognized that the potent NMDA channel blocker, phencyclidine (PCP), produces psychotic symptoms in abusers that are remarkably similar to symptoms of schizophrenia (Allen and Young 1978; Bakker and Amini 1961; Javitt and Zukin 1991; Adler et al. 1999); in chronic users, an irreversible psychosis with cognitive impairment has also been described (Rainey and Crowder 1975; Jentsch and Roth 1999). Infusion of ketamine, which also blocks the NMDA channel, also simulates the full range of symptoms of schizophrenia in healthy subjects (Krystal et al. 1994). These symptoms were not attenuated by haloperidol (Krystal et al. 1999a), though haloperidol has been used to treat psychotic symptoms induced by phencyclidine in an emergency-room situation (Giannini et al. 1987). In patients with schizophrenia stabilized on haloperidol, ketamine infusion produces a florid relapse of symptoms (Lahti et al. 1995; Malhotra et al. 1997a). Clozapine is able to blunt these effects (Malhotra et al. 1997a,b).

Glycine agonists and glycine transport inhibitors have been shown to reduce negative symptoms of schizophrenia when added to antipsychotic drugs (Tuominen et al. 2005). These agents enhance NMDA receptor function (Bergeron et al. 1998) through activation of the NMDA glycine allosteric modulatory site (Dannhardt and Kohl 1998). In preclinical studies, glycinergic agents suppress phencyclidine-induced behavioural disruption and glutamate release in rats (Javitt et al. 1999). In clinical trials, the glycine site partial agonist, D-cycloserine, the full agonists, glycine and D-serine, and the glycine transporter I inhibitor, sarcosine, have all demonstrated therapeutic benefit for negative symptoms and, in some studies, benefit for psychotic and cognitive symptoms when added to antipsychotic agents other than clozapine (Heresco-Levy 2000; Tsai et al. 1998, 2004). D-Cycloserine monotherapy significantly improved negative symptoms in a single-blind trial (van Berckel et al. 1996). Thus, these results suggest that hypofunction of NMDA receptors might also occur in schizophrenia and might be involved in the generation of negative symptoms. However, clinical results for the partial agonist D-cycloserine have been mixed, since in other studies D-cyloserine added to antipsychotic drugs was found to worsen positive symptoms (van Berckel et al. 1999), or else have no therapeutic benefit (Goff et al. 2004). Furthermore, the combination of D-cycloserine with clozapine resulted in worsening of negative symptoms (Goff et al. 1999; Heresco-Levy and Javitt 2004) and addition of other glycine site agonists to clozapine did not produce clinical benefit (Evins et al. 2000; Potkin et al. 1999; Tsai et al. 1999). Unlike most other atypical antipsychotic drugs, clozapine may facilitate NMDA receptor activation through inhibition of type 1 glycine transporters (Javitt et al. 2004) or through a dopamine D1-dependent mechanism (Chen and Yang 2002; Ninan and Wang 2003). Changes in serum or brain glutamate concentrations after switching from conventional agents to clozapine or olanzapine have tended to correlate with enhanced efficacy for negative symptoms (Goff et al. 2002; Evins et al. 1997). It is possible that these effects interfere in some way with the modulation of NMDA receptor function by glycinergic drugs. In conclusion, studies with glycinergic agents support the hypothesis for a hypofunction of NMDA receptors in schizophrenia. Furthermore, a number of susceptibility genes for schizophrenia are associated with NMDA receptor signalling (Harrison and Weinberger 2005). However, activation of the glycine modulatory site on the NMDA receptor may not be sufficient to treat the range of symptoms of schizophrenia and may be complicated by adverse interactions with clozapine. Other strategies to address the downstream consequences of NMDA receptor hypofunction should be considered.

NMDA antagonists facilitate the release of dopamine (Miller and Abercrombie 1996; Svensson 2000), both in the limbic system (Carboni et al. 1989; Steinpreis and Salamone 1993; Hertel et al. 1995) and frontal cortex (Deutch et al. 1987; Hondo et al. 1994; Adams and Moghaddam 1998). However, dopamine antagonists do not consistently block the psychotic symptoms induced by NMDA antagonists in humans (Krystal et al. 1999a), and dopamine depletion is unable to prevent NMDA-antagonist-induced behaviour in rats (Carlsson and Carlsson 1989). These observations argue against a primary role for dopamine in the generation of psychotic symptoms by NMDA antagonists. NMDA antagonists also enhance the release of glutamate (Moghaddam et al. 1997) and cause alterations in the firing pattern of cortical pyramidal neurons (Shi and Zhang 2003; Jackson et al. 2004). Thus, it is hypothesized that dysregulation of glutamate transmission may be central to the psychotomimetic effects of NMDA antagonists.

The alteration of neuronal activity and enhanced release of glutamate is suggested to arise through two mechanisms. First, attention has focused on a subgroup of NMDA receptors localized on inhibitory GABAergic interneurons. This follows in part from the finding that phencyclidine and ketamine bind with highest affinity to this subgroup (Grunze et al. 1996). It is postulated that diminished NMDA receptor activity on inhibitory interneurons in the schizophrenic brain results in reduced inhibitory drive at GABA-A receptors on glutamatergic pyramidal neurons (Fig. 1). The disinhibition of pyramidal neurons, leading to a disruption of their normal pattern of firing and synchronization (Shi and Zhang 2003; Jackson et al. 2004), results in increased release of glutamate and activation of non-NMDA receptors (Olney and Farber 1995). Drugs that modulate glutamate release, such as the selective type 2/type 3 metabotropic glutamate receptor (mGluR2/3) agonist, LY354740, can block the effects of PCP in rodents (Adams and Moghaddam 1998; Schoepp and Marek 2002), and produce a dose-dependent suppression of ketamine-induced impairment of working memory by ketamine in human volunteers (Krystal et al. 2005).

Secondly, NMDA antagonists elevate serotonin levels in the prefrontal cortex and hippocampus (Martin et al. 1998). Serotonin, acting at 5-HT2A receptors, in turn can enhance

the release of glutamate (Aghajanian and Marek 1999) (Fig. 1). In support of this mechanism, 5-HT2 antagonists have been shown to reduce behavioural effects of NMDA antagonists in rats (Bakshi and Geyer 1997; Carlsson et al. 1999; Gleason and Shannon 1997). The selective 5-HT2A antagonist, M100907, has been shown to suppress NMDA-antagonist-induced c-*fos* expression (Habara et al. 2001), disruption of paired-pulse inhibition (Varty et al. 1999), impairment in attentional performance (Mirjana et al. 2004), and increased glutamate release (Ceglia et al. 2004).

The results with M100907 and with the mGluR2/3 agonist, LY354740, support the hypothesis that disruption of glutamate transmission is an important downstream consequence of NMDA receptor antagonism that might underlie the psychotomimetic effects of ketamine or phencyclidine. However, the situation is likely to be more complex, since LY354740 did not significantly attenuate ketamine-induced expression of psychosis or negative symptoms in healthy volunteers (Krystal et al. 2005), and M100907 monotherapy was not beneficial in patients with schizophrenia (Talvik-Lotfi et al. 2000; de Paulis 2001). In contrast, combination of 5-HT2a receptor antagonism with D2 receptor blockade appears to be an effective treatment strategy, since most atypical antipsychotic drugs have significant activity at both receptors (Breese et al. 2002; Seeman 2002). At this point, it would seem prudent to hypothesise that schizophrenia involves dysregulation of both glutamate and dopamine transmission.

There is increasing evidence that schizophrenia is associated with a gradual neurodegeneration (Konradi and Heckers 2003; Krystal et al. 2003). We may hypothesise that dysregulation of glutamate release might lead to excitotoxicity and neuronal injury. Chronic administration of NMDA antagonists has been shown to cause neuronal degeneration in posterior cingulate and retrosplenial cortex of rats (Olney and Farber 1995; Farber et al. 2002; Konradi and Heckers 2003). However, it remains to be seen whether the pattern of damage induced by NMDA antagonists reflects that observed in the post-mortem schizophrenic brain.

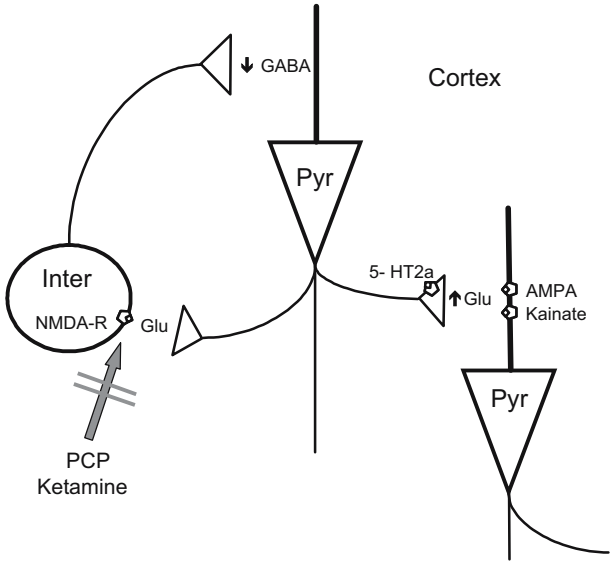

Fig. 1 Hypothesis for glutamate neuron dysregulation induced by NMDA receptor antagonists. Selective block of NMDA receptors on interneurons in the cortex leads to disinhibition of pyramidal neurons leading to altered firing and increased glutamate transmission via non-NMDA glutamate receptors (Olney and Farber 1995). NMDA antagonists may also increase 5-HT release in the cortex. This is proposed to lead to activation of 5-HT2a receptors that further enhance glutamate release (Aghajanian and Marek 1999). *Pyr* Cortical pyramidal neuron, *Inter* inhibitory interneuron

The glutamate neuron dysregulation hypothesis provides a basis from which to propose new pharmacological approaches to the treatment of schizophrenia. In this review, we examine the evidence for the efficacy of lamotrigine in combination with antipsychotic drugs for the treatment of schizophrenia. We consider how this efficacy might relate to glutamate neuron dysregulation, the mechanism by which lamotrigine influences neuronal activity and glutamate transmission, and the possible ways in which the drug might interact with antipsychotic medications. We then consider whether lamotrigine monotherapy would be effective in the treatment of schizophrenia within a framework of dysregulation of glutamate and dopamine transmission in schizophrenia. Based on this, we argue that the treatment of schizophrenia may require a combination of anti-dopaminergic and anti-glutamatergic drugs, at least during the active psychotic phase of the illness.

Clinical and experimental medicine findings with lamotrigine

Lamotrigine is a broad spectrum anticonvulsant (Messenheimer 1995) used also in the treatment of bipolar disorder (Table 1). Its downstream effects on neuronal function include inhibition of glutamate release. Thus, consistent with the glutamate neuron dysregulation hypothesis for schizophrenia, pre-administration of 300 mg of lamotrigine 2 h before ketamine challenge attenuated psychotic, negative, and cognitive effects in a placebo-controlled trial in healthy volunteers (Anand et al. 2000a). Clinical experience also supports a potential therapeutic effect of lamotrigine in schizophrenia (Table 1). Dursun and McIntosh (1999) added lamotrigine (125–250 mg/day) to clozapine in six treatment-resistant schizophrenic patients in a 24-week open-label trial. Lamotrigine was well tolerated and produced a mean 75% reduction in Brief Psychiatric Rating Scale (BPRS) total scores, with maximal improvement occurring in all but one subject between weeks 8 and 16. In subsequent open trials, Dursun and Deakin (2001) found that lamotrigine augmentation of olanzapine, risperidone, and conventional antipsychotics was of considerably less benefit compared with augmentation of clozapine, although the number of patients in this study was small. Tiihonen et al. (2003) conducted a 10-week, double-blind, placebo-controlled, parallel-group trial adding 200 mg of lamotrigine daily to clozapine in 36 treatment-resistant schizophrenic patients. Compared with placebo, lamotrigine significantly reduced ratings of psychosis, but not negative symptoms. The investigators noted that auditory hallucinations were particularly responsive, although only 20% of subjects ac-

Table 1 Clinical evidence for the efficacy of lamotrigine in bipolar disorder and schizophrenia

Indication	Effect	Comments and reference
Long-term treatment of bipolar disorder (manic pole)	Mood stabilization "from above". Delayed the time to intervention for a manic episode. However, lamotrigine significantly less effective than lithium	Combined analysis of two large 18-month prophylaxis studies of patients with bipolar I disorder (Goodwin et al. 2004)
Long-term treatment of bipolar disorder (depressive pole)	Mood stabilization "from below". Delayed the time to intervention for a depressive episode. lamotrigine significantly more effective than lithium	
Schizophrenia	75% reduction in BPRS total scores	A small, 24-week open-label study with six treatment-resistant patients, lamotrigine added to clozapine (Dursun and McIntosh 1999)
	No significant effect on BPRS scores when added to olanzapine or risperidone	Small open-label study, replicated results of Dursun and McIntosh (1999) with clozapine, but very low number of patients in olanzapine or risperidone groups (Dursun and Deakin 2001)
	Significant reduction in psychosis. No improvement in negative symptoms	A 10-week, double-blind, placebo-controlled, parallel-group trial adding 200 mg of lamotrigine daily to clozapine in 36 treatment-resistant schizophrenic patients (Tiihonen et al. 2003)
	Reduction of psychotic in completers. Psychosis improved equally with clozapine and other antipsychotic drugs. No improvement in negative symptoms, but significant improvement in general psychopathology	A double-blind, placebo-controlled, parallel-group trial adding 400 mg of lamotrigine daily to typical or atypical antipsychotics in 38 treatment-resistant schizophrenia patients (Kremer et al. 2004)

counted for most of the therapeutic benefit. Kremer et al. (2004) recently reported improvement of psychotic symptoms with the addition of up to 400 mg of lamotrigine daily to typical or atypical antipsychotics in 38 treatment-resistant schizophrenia patients. Improvement was significant compared with placebo in completers but did not achieve significance in the primary LOCF analysis. Kremer et al. also reported no significant improvement in negative symptoms. Whereas the study by Tiihonen et al. added lamotrigine to clozapine only, Kremer et al. found that psychosis improved equally in patients treated with typical and atypical agents.

Since lamotrigine and other anticonvulsant drugs with different mechanisms of action are commonly used in the treatment of psychiatric disorders (Rogawski and Loscher 2004), we briefly consider two other anticonvulsants that, like lamotrigine, are used in the treatment of bipolar disorder. Valproate is the anticonvulsant most frequently prescribed to patients with schizophrenia (Citrome et al. 2000). In a recent double-blind, randomized study of 249 schizophrenic patients admitted for acute exacerbation of symptoms, the combination of valproate added to risperidone or olanzapine produced a more rapid response than antipsychotic monotherapy; however, the difference in response between groups diminished over time and was no longer significant by week 4 of treatment (Citrome et al. 2004; Casey et al. 2003). In contrast, three controlled studies found no therapeutic benefit of valproate adjunctive therapy in chronic, treatment-refractory patients (Ko et al. 1985; Dose et al. 1998; Hesslinger et al. 1999; Basan and Leucht 2004). Another anticonvulsant, carbamazepine, was found to improve symptoms when added to antipsychotic medication in patients with schizophrenia who had EEG abnormalities (Neppe 1983). The combination of carbamazepine with antipsychotic agents is complicated by potential induction by carbamazepine of antipsychotic metabolism (Arana et al. 1986), which would reduce exposure to the antipsychotic agent. The fact that despite this symptoms improved in the study by Neppe (1983) should be taken as further support for the efficacy of carbamazepine in this setting. However, in a placebo-controlled, crossover trial of carbamazepine monotherapy, no improvement in the symptoms of chronic outpatients was observed (Carpenter et al. 1991).

Summary of clinical studies

Thus, clinical data with lamotrigine support the use of drugs that reduce glutamate release as adjunctive treatments for patients with schizophrenia. However, it remains to be seen whether this will be confirmed by larger double-blind placebo-controlled trials. There are insufficient data to conclude whether or not a similar anticonvulsant drug, carbamazepine, may also have adjunctive efficacy in schizophrenia, whereas studies suggest that valproate, an anticonvulsant with a different mechanism of action, does not produce a sustained effect. It is notable that lamotrigine and valproate also have different clinical profiles in the treatment of bipolar disorder (Ketter and Calabrese 2002), whereas they have similar broad-spectrum efficacy in the treatment of epilepsy (Loscher 1999). The glutamate neuron dysregulation model of schizophrenia predicts that facilitation of NMDA receptor function on inhibitory inter-

neurons or inhibition of glutamate release should produce similar therapeutic effects. Whereas evidence now supports the therapeutic benefit of both approaches, the pattern of clinical efficacy has not been consistent. Glycine site agonists predominantly treat negative symptoms (Tuominen et al. 2005), whereas lamotrigine seems to improve only positive symptoms (Tiihonen et al. 2003; Kremer et al. 2004). Evidence for efficacy with glycine site agonists has been strongest when added to conventional antipsychotics and weakest when added to clozapine, whereas the opposite may be true with lamotrigine. The difference between these two approaches is discussed further later on. However, more data are needed from large clinical trials to verify the preliminary observations.

Efficacy of lamotrigine in NMDA antagonist models of psychosis

With the assumption that NMDA antagonists can be used to model schizophrenia in the laboratory, at least at a superficial level, they are increasingly used to investigate the potential efficacy of novel antipsychotic drugs, particularly those that do not rely on dopamine D2 receptor blockade (Krystal et al. 1999b). As discussed earlier, drugs that negatively modulate glutamate transmission, such as 5-HT2a antagonists (Mirjana et al. 2004; Ceglia et al. 2004) and mGluR2/3 agonists (Schoepp and Marek 2002; Carter et al. 2004; Krystal et al. 2005), have already been shown to reduce some NMDA-antagonist-induced symptoms in humans or behavioural or neurochemical effects in rodents. In the following section we review the few studies that have examined the effects of lamotrigine and two other anticonvulsant drugs, carbamazepine and valproate, in NMDA antagonist models (Table 2). The first model, disruption of prepulse inhibition (PPI) by psychotomimetic agents, is used frequently to assess the antipsychotic potential of novel drugs (Geyer et al. 2001). The second model, in which psychotomimetic agents were used to disrupt an operant reversal-learning task, was chosen because it may allow assessment of the effects of the novel agents on cognitive function, which is a symptom domain of particular importance in schizophrenia. The final model, in which NMDA antagonists induce neurodegeneration, intends to provide information about the neuroprotective potential of novel drugs, since this is likely to be an important long-term aim of antipsychotic treatment.

Lamotrigine prevents the disruption of prepulse inhibition by ketamine in mice

Pre-pulse inhibition can be used as a measure of sensorimotor gating, a process by which organisms filter information from the environment (reviewed by Braff and Geyer 1990; Braff et al. 2001). PPI is deficient in certain psychiatric disorders, notably schizophrenia (Braff et al. 1992), Huntington's disease (Braff et al. 2001), and mania (Perry et al. 2001a). Disruption of PPI can be achieved pharmacologically in rodents using NMDA receptor antagonists (Mansbach and Geyer 1989) or drugs that increase dopamine D2 receptor activation, such as *d*-amphetamine (Ralph et al. 1999). These pharmacological disruptions can be prevented by certain antipsychotic drugs and, as a result, the model is frequently used to study or predict the efficacy of novel agents (Bakshi et al. 1994; Varty and Higgins 1995; Swerdlow and Geyer 1998; Geyer et al. 2001).

The ability of lamotrigine to prevent *d*-amphetamine- and ketamine-induced disruption of PPI in 129SvPasIco mice was recently investigated by Brody et al. (2003). Lamotrigine at a dose of 27 mg/kg i.p. prevented disruption of PPI by ketamine, but the drug had no effect on *d*-amphetamine-induced disruption. Lamotrigine alone had no effect on startle magnitude or on PPI itself. In a separate study by the same group, carbamazepine (50 mg/kg i.p.) also prevented disruption of PPI by ketamine, but not amphetamine (Ong et al. personal communication). However, carbamazepine also significantly reduced startle magnitude, which may confound interpretation of the PPI data. In contrast, sodium valproate (400 mg/kg i.p.) did not prevent ketamine or amphetamine-induced disruption of PPI. Valproate did significantly reduce baseline startle magnitude, although it did not affect baseline PPI. These results suggest that anticonvulsant efficacy per se is insufficient to prevent the disruptive effects of ketamine on PPI, but that sodium channel inhibition may be important.

To what extent do these results support the efficacy of lamotrigine in schizophrenia? PPI is robust and ubiquitous across species, including rodents and humans, suggesting that it is a fundamental trait of sensory processing in mammals. PPI deficits have been correlated with positive and negative symptoms of schizophrenia (Perry and Braff 1994; Perry et al. 1999; Weike et al. 2000), in particular thought disorder (Perry et al. 1999). It is hypothesized that impairment in sensorimotor gating may leave patients unable to screen out distracting stimuli (Perry and Braff

Table 2 Preclinical evidence for the efficacy of lamotrigine in psychiatry models

Model	Effect	Comments and reference
Ketamine- or *d*-amphetamine-induced disruption of PPI	Prevention of the disruption by ketamine, but not *d*-amphetamine	Effective at 27 mg/kg i.p. (Brody et al. 2003)
Ketamine- or *d*-amphetamine-induced disruption of reversal learning	Prevention of the disruption by ketamine, but not *d*-amphetamine	Effective at 25 mg/kg i.p. (Idris et al. 2005)
Amphetamine-, chlordiazepoxide-induced locomotor activity	Reduction in the increase in total distance travelled	Effective at 20 mg/kg p.o. (Arban et al. 2005)

1994). There is evidence that the treatment of patients with antipsychotic drugs improves and, in some reports, normalizes PPI (Weike et al. 2000; Kumari et al. 2002), although this has not been confirmed by all studies (Perry et al. 2001b). However, in preclinical studies that used ketamine to disrupt PPI, the efficacy of lamotrigine or carbamazepine confirms only that these drugs are able to inhibit some mechanism downstream of NMDA receptor antagonism, presumably the enhanced release of glutamate. Thus, the degree of similarity between the pathology underlying schizophrenia and the mechanism underlying disruption of rodent behaviour by ketamine is of critical interest, in particular since there is evidence that the effects of NMDA antagonists on PPI in rodents may be qualitatively different in humans. An early study of healthy human volunteers by Karper et al. (1994) did observe a small reduction in PPI with ketamine, but startle magnitude was also altered, which tends to confound analysis of PPI data. Subsequent studies with ketamine in healthy subjects found that the drug either did not alter (van Berckel et al. 1998) or else increased PPI (Duncan et al. 2001; Abel et al. 2003), despite the co-appearance of psychotic symptoms. A possible explanation for the apparent discrepancy may be the difficulty in testing a range of doses and pretreatment times in human volunteer studies; thus it can be difficult to compare results between human and animal studies (discussed by Krystal et al. 2003). Thus, although the PPI deficit induced by ketamine in mice was prevented by pretreatment with lamotrigine or carbamazepine (Brody et al. 2003), it is not necessarily the case that these drugs would reverse an established PPI deficit in patients with schizophrenia. It would be valuable to conduct a clinical study in patients with schizophrenia to investigate the ability of lamotrigine to reverse the deficits in PPI.

Lamotrigine prevents the disruption of a reversal-learning task by PCP in rats

Reversal-learning tasks probe the ability of an individual to adapt to changing stimulus-reward contingencies and depend on the integrity of the ventral prefrontal cortex (Clark et al. 2004). Performance of these tasks is often disrupted in patients with schizophrenia (Mackintosh and Little 1969) and is thought to be a consequence of hypofrontality (Weinberger and Berman 1996). For example, in the Wisconsin card-sorting task, patients with schizophrenia tend to persevere with the initial contingency and find it difficult to adapt when a new contingency is introduced (Deicken et al. 1995). A similar pattern of disruption can be achieved with ketamine in healthy volunteers (Krystal et al. 2000). Reversal learning can also be demonstrated in non-human primates (Smith et al. 1999) and rodents (Jentsch and Taylor 2001; Abdul-Monim et al. 2003). In the latter, performance could be disrupted by administration of PCP or *d*-amphetamine. The ability of lamotrigine to prevent PCP or *d*-amphetamine-induced disruption of reversal learning in rodents was studied by Idris et al. (2005). Lamotrigine (5–20 mg/kg i.p.) dose-dependently reduced the deficit in reversal learning induced by PCP, but did not prevent the deficit induced by *d*-amphetamine. In the same study, the atypical antipsychotic clozapine partially reduced the deficit in reversal learning induced by PCP, but also had no effect against *d*-amphetamine-induced deficits. In a previous study by the same group, the atypical antipsychotic, ziprasidone, prevented PCP-induced disruption of reversal learning, whereas the classical antipsychotic, haloperidol was ineffective (Abdul-Monim et al. 2003). However, haloperidol could prevent disruption induced by *d*-amphetamine (Idris et al. 2005). Sodium valproate at doses up to 200 mg/kg i.p. was unable to reduce the deficit in reversal learning induced by PCP or *d*-amphetamine (Idris et al. personal communication). Carbamazepine has yet to be studied in this model.

These results are similar to those from the PPI model and similar arguments can be applied to their interpretation—specifically, that interaction of lamotrigine with the mechanism by which PCP disrupts reversal learning in the rat does not necessarily predict efficacy of lamotrigine against an established reversal-learning deficit in patients with schizophrenia. However, an advantage of the reversal-learning paradigm over PPI is that disruption by NMDA antagonists does appear to translate from animals to humans (Krystal et al. 2000). Despite this, it remains to be determined whether NMDA-induced disruption of reversal learning and the disruption observed in patients with schizophrenia share a common substrate. Given that reversal-learning tasks have been shown to depend on functioning of the orbitofrontal cortex (reviewed by Clark et al. 2004), an informative way forward might be to use functional imaging techniques in healthy human subjects to examine the effects of ketamine on this brain region during performance of a reversal-learning task and compare these results with studies of reversal learning in patients (Volz et al. 1997; Riehemann et al. 2001). The orbitofrontal cortex may be of particular interest for studying the mechanism of action of lamotrigine because lamotrigine has been shown to increase the BOLD response selectively in this region during application of transcranial magnetic stimulation over the frontal cortex (Li et al. 2004). Finally, as in the case of PPI, a study of the ability of lamotrigine to improve a deficit in reversal learning in patients with schizophrenia would add a great deal to our understanding of the relationship between reversal learning deficits in animal models, human volunteer studies, and patients.

Lamotrigine reduces the number of cortical neurons injured by MK-801 in rats

The predominant view of schizophrenia is that it is caused by a neurodevelopmental dysfunction (Weinberger 1996; Bunney et al. 1997; Miyamoto et al. 2003). However, there is increasing evidence that the disorder is associated with a gradual neurodegenerative decline (Konradi and Heckers 2003; Krystal et al. 2003; Lewis et al. 2003). The neurodegenerative component may be operative at disease onset or may develop only later in the course of the disease.

Neuroimaging studies have provided evidence for both. Brain volume reductions have been reported in regions such as the prefrontal cortex (Lim et al. 1996; reviewed in Bogerts 1999) and hippocampus (reviewed in Weinberger 1999), and similar reductions have been observed in first-onset patients (Vita et al. 1997; Davies et al. 1998; Cahn et al. 2002). Furthermore, longitudinal imaging studies of patients with schizophrenia document gradual morphometric changes with disease progression (DeLisi et al. 1997; Gur et al. 1998; Lieberman et al. 2001, 2005; Mathalon et al. 2001; Wood et al. 2001; Ho et al. 2003). Post-mortem studies of gliosis or apoptotic cell death suggest that gross cell loss does not occur in schizophrenia (Heckers 1997; Falke et al. 2000); however, gliosis may not be apparent if atrophy of the neuropil and synaptic disconnection are the major deficits. Indeed, immunocytochemical and ultrastructural studies found reductions in neuropil, dendritic arborization, synaptic spine density, and white matter density in post-mortem schizophrenia brains (reviewed in Konradi and Heckers 2003; Krystal et al. 2003; Lewis et al. 2003; Jones 2004). Region-specific increases and decreases in glutamate receptor expression (reviewed in Deakin and Simpson 1997) and alterations of white matter connectivity (Buchsbaum et al. 1998; Lim et al. 1999) may also occur. Deficits in cortical connectivity may be close to the root cause of schizophrenia. They may give rise to the aberrant thought processes characteristic of schizophrenia and may also fuel other changes, including further alterations in the neuropil, and altered function of the dopamine system (see later).

Progressive changes in cortical connectivity in schizophrenia would also be consistent with dysregulation of glutamate transmission. We can speculate that low doses of NMDA antagonists mimic acutely the cortical disconnectivity of schizophrenia and hence closely reproduce schizophrenic thought processes. Over a longer time course, NMDA antagonists may also mimic in rats some of the neuropathology observed in patients (Farber et al. 2002). In this study, which used the NMDA antagonist MK-801, Farber et al. (2002) found that sodium channel blocking agents, lamotrigine, carbamazepine, phenytoin, riluzole, and TTX all reduced the number of injured cortical neurons. They also found that valproate and other non-sodium channel blocking anticonvulsant drugs, such as gabapentin and felbamate, could also protect neurons. A similar effect has been observed with the mGluR2/3 agonist, LY379268 (Carter et al. 2004). These data suggest that unlike the behavioural disruption seen with NMDA antagonists, a wider range of pharmacological approaches might be effective. One explanation for this may be that the neurotoxicity induced by NMDA antagonists may not follow from the disruption of pyramidal neuron activity, as proposed in the model shown in Fig. 1, but instead may arise through an alternative mechanism unrelated to the psychotomimetic effects of the drugs (cf. Nakki et al. 1996). This suggests that NMDA antagonists may not necessarily model the neurodegenerative process in schizophrenia, which in any case occurs over a much longer time course. There is a need for further study of the nature and time course of the pathology caused by NMDA antagonist drugs, the similarity of the pathology to that observed in patients with schizophrenia, and the reliance of this pathology on altered glutamate transmission. However, even though NMDA antagonists may not accurately model the neurodegeneration associated with schizophrenia, they provide further evidence, in support of other models, for a broad neuroprotective effect of lamotrigine (Ketter et al. 2003; Rogawski and Loscher 2004; and see Table 3), valproate (Li et al. 2002; Gould et al. 2004; Hao et al. 2004; Vajda 2002; Rogawski and Loscher 2004), and possibly carbamazepine (Mai et al. 2002; but also see Nonaka et al. 1998). Thus, these drugs could offer some benefit as neuroprotectants for patients with schizophrenia.

Finally, in relation to augmentation strategies, severity of tardive dyskinesia has been found to correlate with the concentration of excitatory amino acids in CSF of schizo-

Table 3 Preclinical evidence for the efficacy of lamotrigine in neurology models

Model	Effect	Comments and reference
Maximal electroshock test in rat (generalized seizures)	Anticonvulsant	Effective at 10 mg/kg i.p. (Castel-Branco et al. 2003)
Pentylene tetrazole induced myoclonic and tonic–clonic seizures	Anticonvulsant	Effective at 20 mg/kg p.o. (Arban et al. 2005)
Lethargic mouse (absence seizures)	Anticonvulsant	4.8–144 μmol/kg i.p. (Hosford and Wang 1997)
Amygdala kindled seizures in rat (partial seizures)	Anticonvulsant	14 mg/kg p.o. (Stratton et al. 2003)
Development of kindling in the amygdala of rats (epileptogenesis)	Prevented the development of kindling	Effective with a daily dose of 20 mg/kg p.o. (Stratton et al. 2003)
Stimulation induced status epilepticus in rat	Reduced hippocampal cell death	Effective with a daily dose of 12.5 mg/kg p.o. (Halonen et al. 2001)
Circulatory arrest in rat (global cerebral ischemia)	Reduced infarct volume	Effective at 10 mg/kg i.v. (Crumrine et al. 1997)
Common carotid artery occlusion in gerbil (cerebral ischaemia)	Reduced infarct volume	Effective at 50 mg/kg i.p. (Lee et al. 1999) Effective at 50 mg/kg i.v. (Shuaib et al. 1995)
3-nitropropionic acid administration to rat (excitotoxicity)	Reduced neuronal loss	Effective at 10–20 mg/kg i.p. (Lee et al. 1999)

phrenia patients, suggesting that glutamatergic neurotoxicity may contribute to irreversible neurological injury from conventional antipsychotics as well (Goff et al. 1995). Thus, add-on treatment with neuroprotective drugs may be of long-term benefit for patients treated chronically with antipsychotic drugs.

Summary of preclinical studies

The preclinical data reviewed here demonstrate that acute treatment with lamotrigine and carbamazepine, but not sodium valproate, can prevent the disruption of rodent behaviour by NMDA antagonists. Because both of these drugs, but not valproate, are sodium channel inhibitors that can modulate the release of glutamate (see below), these studies add to a growing body of evidence that implicates glutamate transmission and the activity of cortical pyramidal neurons in the behavioural effects of NMDA antagonists. These results are consistent with the hypothesis that glutamate neuron dysregulation generates the psychotic symptoms observed in human subjects given ketamine. In addition to the observable similarity between symptoms induced by ketamine and symptoms of schizophrenia, there is increasing evidence that a disruption of glutamate transmission also occurs in schizophrenia.

The lack of efficacy of valproate in the two behavioural models reviewed above is surprising given that the effects of NMDA antagonists are proposed to arise through reduced activity of GABAergic interneurons (Olney et al. 1999; Krystal et al. 2003) (Fig. 1). Krystal et al. (1998) previously found that the benzodiazepine, lorazepam, was unable to reduce many of the effects of ketamine in healthy volunteers, although the drug did reduce the emotional distress caused by the psychotomimetic. A difficulty with studies involving GABAergic drugs is sedation that can confound interpretation of the results. However, it is recognised that GABA-enhancing strategies may have a place in the acute treatment of psychosis to reduce anxiety (Parepally et al. 2002). The use of valproate in this setting is supported by the clinical data reviewed earlier (Citrome et al. 2004; Casey et al. 2003). In addition, given the positive effects of valproate and other GABA-enhancing drugs vs NMDA-antagonist-induced neurodegeneration (Farber et al. 2002), these drugs may also confer some neuroprotective benefit.

Finally, an important area for further preclinical research will be the study of the effects of lamotrigine and other novel antipsychotic agents given chronically, preferably in models in which behavioural disruption has already been established, e.g. after chronic treatment with NMDA antagonists (e.g. Jentsch et al. 1997; Schwabe et al. 2005). Lamotrigine, given chronically, has been studied in models of relevance to epilepsy with mixed results (Postma et al. 2000; Stratton et al. 2003); other studies, reviewed below, have examined the effects of chronic lamotrigine on amino acid and monoamine levels in rodents (Hassel et al. 2001; Ahmad et al. 2004a,b) and humans (Kuzniecky et al. 2002).

Possible mechanisms of action of lamotrigine in schizophrenia

Sodium channel inhibition

Lamotrigine is thought to bind and stabilize the inactivated state of voltage-gated sodium channels (Kuo 1998; Xie et al. 1995; Liu et al. 2003), thus reducing the ability of a neuron to generate high-frequency trains of action potentials. The affinity of lamotrigine for the inactivated state of the human brain type II sodium channel, based on recombinant cell line studies, is estimated to be in the range 10–30 μM (Xie et al. 1995; Kuo 1998). This concentration range is similar to that in the brains of patients with epilepsy during treatment with lamotrigine (Walker et al. 2000). Use-dependent inhibition of brain sodium channels is thought to be central to the anticonvulsant efficacy of the drug. Similar results have been obtained with carbamazepine (Willow et al. 1995; Kuo 1998); furthermore, in a recent review, Ambrosio et al. (2002) concluded that inhibition of sodium channels is most likely responsible for the anticonvulsant efficacy of carbamazepine. However, other molecular interactions of carbamazepine such as inhibition of NMDA-mediated activity (Cunha et al. 2002 and see below), might contribute to poorer tolerability, limiting its apparent efficacy and use. Valproate, in contrast to lamotrigine and carbamazepine, has only weak effects on fast sodium currents at concentrations up to 1 mM (Johannessen 2000), although it has been shown to inhibit burst firing of neurons at therapeutically relevant concentrations (6–30 μM; McLean and Macdonald 1986). The mechanism in this latter case is suggested to involve inhibition of so-called persistent sodium currents (Taverna et al. 1998).

Lamotrigine does not distinguish between the different subtypes of brain sodium channel (Whitaker et al. 2001) and so will stabilize inactivation of each, thus regulating high-frequency action potential generation at the soma and propagation of these potentials along the axon, and perhaps affecting dendritic integration of high-frequency synaptic input. This is likely to be a highly effective mechanism to limit neuronal activity in some seizure disorders, but it is unclear how this mechanism might confer antipsychotic efficacy without understanding how neurons behave and interact during psychotic episodes in patients with schizophrenia. A reduction in burst firing of cortical neurons (Shi and Zhang 2003; Jackson et al. 2004) but an increase in overall firing (Jackson et al. 2004) was observed in rats after exposure to NMDA antagonists. In the latter study, the firing of individual neurons was less organized, and there was reduced synchronization between neurons. It will be important to investigate how lamotrigine might affect neuronal network activity in the prefrontal cortex in the presence of PCP or other psychotomimetic drugs.

Activation of many G-protein-coupled receptors can lead to phosphorylation of sodium channels, which then alters their function (Cantrell and Catterall 2001). More importantly, in the context of the role of dopamine in schizophrenia, activation of cAMP-dependent protein kinase A can phosphorylate sodium channel alpha subunits, leading

to diminished channel conductance in hippocampal pyramidal neurons and striatal medium spiny neurons (reviewed by Cantrell and Catterall 2001). Activation of dopamine D2 receptors, which inhibit adenylate cyclase and so reduce PKA activation, has been shown to enhance sodium currents in medium spiny neurons projecting to the substantia nigra (Surmeier et al. 1992). Furthermore, dopamine D2 receptor stimulation may enhance the transition of neurons in the striatum from a hyperpolarised "downstate" to a depolarised "upstate" by influencing sodium channel function (Surmeier and Kitai 1997). Thus, the influence of lamotrigine on sodium channel function under these conditions will be an interesting subject for research. The influence of atypical antipsychotic drugs on sodium channel function also merits investigation. In the prefrontal cortex, olanzapine enhanced the firing and excitability of pyramidal neurons after 21 days of treatment (Gronier and Rasmussen 2003). If sodium channels are involved, then compounds like lamotrigine that interact with the channels in a use-dependent manner may be well placed to augment the therapeutic effect of the antipsychotic drug, as suggested by the emerging clinical data.

In conclusion, sodium channels are critical for neuronal activity and transmitter release. In this review, we argue that dysregulation of cortical neuronal activity and glutamate release is central to the effects of psychotomimetic drugs and may contribute to the pathology of schizophrenia. Thus, modulation of neuronal activity and glutamate release via sodium channel inhibition is likely to be central to the ability of lamotrigine and carbamazepine to prevent NMDA-antagonist-induced behavioural disruption in the PPI and reversal-learning models, and may be responsible for the add-on efficacy of these drugs in schizophrenia.

Calcium channel inhibition

Some in vitro effects of lamotrigine persist in the presence of the sodium channel blocker, tetrodotoxin (TTX). Cunningham and Jones (2000) found that inhibition of spontaneous excitatory post-synaptic potentials (EPSPs) in the entorhinal cortex persisted in the presence of tetrodotoxin. Indirect evidence suggests that lamotrigine may inhibit N-type voltage-activated calcium channels (Stefani et al. 1996; Wang et al. 1996a,b; Hainsworth et al. 2001), since the inhibitory effects of the drug on evoked EPSPs were occluded by the selective blocker, ω-conotoxin (Wang et al. 1996a,b). However, lamotrigine did not inhibit N-type calcium channels expressed in a recombinant cell line, which suggests that the drug does not interact directly with the channels (T. Dale, personal communication). In contrast, Hainsworth et al. (2003) found that lamotrigine (10 μM) could inhibit human R-type, but not T-type calcium channels in recombinant cell lines. This may be important to follow up since R-type channels are thought to be involved in the dendritic release of dopamine from neurons in the ventral tegmentum or substantia nigra (Bergquist and Nissbrandt 2003).

High concentrations of carbamazepine (up to 1 mM) have been shown to interact with presynaptic calcium channels (Zhu et al. 2002). Lower concentrations (1–50 μM) appeared to affect postsynaptic calcium entry, either through NMDA receptor channels (Hough et al. 1996) or through inhibition of L-type calcium channels (Ambrosio et al. 2002; but see also Lingamaneni and Hemmings 2003). Furthermore, in a study by Cunha et al. (2002), carbamazepine potently inhibited the NMDA component of the EPSP, an effect thought to be unrelated to its presynaptic inhibitory effects. To our knowledge, valproate has not been shown to interact with voltage-gated calcium channels in the central nervous system (Loscher 2002).

These data suggest that lamotrigine interaction with presynaptic voltage-gated calcium channels may allow control over spontaneous glutamate release and may differentiate the drug from carbamazepine and valproate. Whether this interaction confers adjunctive efficacy in schizophrenia remains to be proven. Calcium channel blockers, such as nifedipine or nilvadipine, which inhibit L-type calcium channels, have been trialed in patients with schizophrenia with mixed success (Suddath et al. 1991; Yamada et al. 1996). However, where positive effects have been seen, it is possible that enzyme induction leading to higher plasma levels of the co-administered antipsychotic might have played a part (Stedman et al. 1991). There is also some evidence that the L-type calcium channel inhibitor, nimodipine, can attenuate ketamine-induced psychotic symptoms in recovering alcoholics (Krupitsky et al. 2001). Investigation of drugs that specifically block N-type calcium channels, such as cilnidipine (Takahara et al. 2004) or ziconotide (Miljanich 2004), would be useful.

Other ion channels

A recent study by Poolos et al. (2002) found that lamotrigine (50–100 μM), but not carbamazepine (50 μM), had a greater inhibitory effect on dendritically evoked neuronal firing compared to firing evoked at the soma of hippocampal pyramidal neurons. They attributed the effect to activation of a hyperpolarisation-activated cation current (Ih), which is predominant in the dendrites of these neurons (Magee et al. 1998). Berger and Luscher (2004) also found an increase in Ih in cortical layer V pyramidal neurons after application of lamotrigine (50–100 μM), although in this case dendritic input to the soma was not attenuated; instead an increase in somatic excitability was observed in the presence of lamotrigine, which the authors attributed to depolarization mediated by the activation of Ih. These finding are intriguing and merit further study. However, close attention to therapeutically relevant concentrations of the sodium channel blockers will be important to assess the clinical relevance of the effects. Indeed, Berger and Luscher conclude that effects of lamotrigine on Ih are likely to be of less significance than effects on sodium channels at therapeutic drug concentrations. In addition, study of the effect of lamotrigine on recombinant hyperpolarisation-

activated cyclic nucleotide-gated (HCN) ion channels, which are thought to contribute to Ih (Robinson and Siegelbaum 2003), would be useful.

There are also published data suggesting an interaction between lamotrigine and voltage-gated potassium channels. Grunze et al. (1998) and Zona et al. (2002) reported that lamotrigine (100–500 μM) could increase a transient potassium current in hippocampus and cortex, respectively, although effects were small and required high drug concentrations. In a recent study, lamotrigine, again at relatively high concentrations (100–300 μM), was shown to inhibit the A-type potassium current in a hippocampal cell line, H19-7 (Huang et al. 2004). Zona et al. (1990) previously showed that carbamazepine can also augment a transient potassium current in cortical neurons, although valproate does not (Zona and Avoli 1990). In contrast, Walden et al. (1993) reported an enhancement of late potassium currents by valproate in neurons of the snail. Studies using recombinant systems with mammalian channels will be required to investigate these interactions further, but given the high concentrations of lamotrigine and carbamazepine required to obtain effects, it seems unlikely that they contribute to the therapeutic efficacy of the drug.

Glutamate release

Lamotrigine has been shown to reduce glutamate transmission evoked by electrical stimulation in vitro. Wang et al. (1996a,b) showed that low concentrations of lamotrigine (10 μM) could inhibit EPSPs evoked in the basolateral amygdala. Calabresi et al. (1996, 1999) reported inhibition of EPSPs in cortex (IC_{50} ~60 μM) and striatum (IC_{50} 27 μM). However, higher concentrations of lamotrigine were required to produce robust inhibition in the hippocampus (32% inhibition with 100 μM; Langosch et al. 2000). In contrast, Xie et al. (1995) saw no effect of lamotrigine (50 μM) in hippocampal slices. Where inhibition of the EPSP has been observed, a presynaptic site of action was assumed, since lamotrigine had no effect on responses produced by direct application of glutamate receptor agonists. Furthermore, paired-pulse facilitation of the electrically evoked EPSP was increased by lamotrigine, a classic sign of presynaptic inhibition (Manabe et al. 1993; Sanchez-Prieto et al. 1996). The discrepancy between findings may be in part due to the different brain regions studied, but may also arise from differences in stimulation parameters. Waldmeier et al. (1995) studied [^{3}H]glutamate release from cortical slices evoked either by electrical stimulation or the sodium channel opener, veratridine. The sodium channel blocker, tetrodotoxin, could inhibit both, but was at least tenfold less potent against electrical than veratridine-induced release. Similarly, lamotrigine was more potent at inhibiting glutamate release evoked by veratridine (IC_{50} ~31 μM; Waldmeier et al. 1995) but was unable to inhibit release from cortical synaptosomes evoked by depolarization with potassium chloride (Lingamaneni and Hemmings 1999). In a recent in vivo study, Ahmad et al. (2004a) reported that lamotrigine, at therapeutically relevant concentrations, could inhibit an increase in extracellular glutamate induced by veratridine applied via a microdialysis probe to the hippocampus. The inhibitory effect of lamotrigine increased with chronic dosing (21 days), although this could be explained by increases in plasma and brain concentrations of the drug over the first few days of dosing. Perhaps of more relevance to schizophrenia, Idris et al. (2004) found that lamotrigine could prevent the increase in tissue levels of glutamate in the frontal cortex induced by acute treatment of rats with PCP. Thus, the method used to stimulate release can affect modulation by sodium channels blockers, and this may be relevant when considering the efficacy of sodium channel blockers in relation to the neuronal activity that might underlie symptoms of schizophrenia.

In addition to evoked glutamate release, lamotrigine has also been shown to inhibit spontaneous release through a mechanism that may not depend on sodium channels. Cunningham and Jones (2000) recorded spontaneous excitatory postsynaptic currents from neurons of the entorhinal cortex and showed that lamotrigine (50 μM) could inhibit the frequency of these events, even in the presence of tetrodotoxin. Von Wegerer et al. (1997) also examined spontaneous events in hippocampal slices bathed in a low-magnesium solution. Under these conditions, spontaneous, presumed calcium-mediated extracellular field potentials were recorded and shown to be inhibited by low concentrations of lamotrigine (minimum effective concentration, 2 μM). The relevance of spontaneous glutamate release in vitro to in vivo neuronal function is not known, although spontaneous excitatory transmission could be important in setting the signal-to-noise level in a circuit or in setting inhibitory tone through background activation of interneurons. Thus, the observation that lamotrigine may modulate spontaneous glutamatergic events merits further investigation.

Carbamazepine can also inhibit glutamate transmission in vitro via a presynaptic mechanism, although high concentrations are required. Cunha et al. (2002) found that the drug inhibited EPSPs and attenuated the presynaptic fibre volley in the hippocampus (EC_{50} 263 μM). Carbamazepine has also been shown to inhibit glutamate release evoked by electrical stimulation of striatal slices (IC_{50} >100 μM; Waldmeier et al. 1995). In contrast to the two sodium channel blockers, sodium valproate has been shown to increase basal glutamate release in cortical slices (Dixon and Hokin 1997), although the drug concentration required (0.5–2 mM) was above that required for clinical efficacy. Chronic treatment with valproate has also been shown to up-regulate expression of the glutamate transporter, GLT-1 (Ueda and Willmore 2000), although this effect is unlikely to contribute to the acute effects of the drug in the animal models reviewed earlier.

Thus, lamotrigine and, to some extent, carbamazepine can inhibit glutamate transmission with potency dependent on stimulation parameters. Interaction with brain sodium channels is likely to contribute to inhibition of stimulated, although perhaps not spontaneous, glutamate transmission.

GABA release

Recent preclinical, post-mortem, and genetic data point to abnormalities in GABA neurotransmission, as well as glutamate, in schizophrenia (Benes 2000; Lewis 2000). The increase in glutamate release after treatment with PCP and ketamine is thought to be secondary to a reduction in tonic GABAergic inhibition of pyramidal neurons (Olney et al. 1999). Paulson et al. (2003) have shown that 18-day treatment of rats with MK-801 increases the cortical expression of the GABA transporter, GAT-3. Idris et al. (2004) found that acute treatment with PCP resulted in a significant decrease in tissue levels of GABA in the frontal and cingulate cortex, the same areas where increases in glutamate levels were observed. Therefore, enhancement of tonic GABA transmission might be an alternative mechanism by which drugs can prevent the psychotomimetic effects of NMDA antagonists. There is mixed evidence that lamotrigine can enhance GABA levels. Cunningham and Jones (2000) found that lamotrigine increased spontaneous GA BA-mediated synaptic events in the entorhinal cortex. Whereas Braga et al. (2002) showed that lamotrigine could inhibit spontaneous inhibitory postsynaptic currents recorded from neurons of the basolateral amygdala (significant inhibition at 10 μM). Chronic treatment with lamotrigine increased GABA levels in the hippocampus (Hassel et al. 2001), although no change in GABA was noted in cortical areas. Four weeks of treatment with lamotrigine resulted in an increase in GABA in the occipital cortex of healthy human volunteers measured by magnetic resonance spectroscopy (Kuzniecky et al. 2002). In contrast to these studies of spontaneous GABA release or measurement of tissue levels, Ahmad et al. (2004a) found that lamotrigine could inhibit veratridine-induced GABA release in the hippocampus in vivo; they also showed that this effect persisted after 21 days of treatment with lamotrigine. Further studies should compare the temporal and region-specific changes induced by lamotrigine on both tonic and phasic GABA release.

Carbamazepine has been shown to inhibit GABA release evoked by veratridine or electrical stimulation (Waldmeier et al. 1995), a result that mirrors the drug's effect on glutamate release. To our knowledge, there are no reports of an enhancement of GABA release by carbamazepine, although there are some data to suggest that carbamazepine might enhance GABA-A mediated responses via interaction with an allosteric site on the receptor (Granger et al. 1995), and changes in GABA-B receptor density have been observed after treatment with both carbamazepine and valproate (Motohashi et al. 1989; Motohashi 1992). Effects of valproate on GABAergic transmission have been extensively explored (Loscher 1999; Johannessen 2000). Significant increases in whole-brain GABA levels have been observed in rats after valproate at 200 mg/kg (Loscher et al. 1985). The mechanism through which valproate enhances GABA levels remains to be confirmed, although inhibition of the enzyme succinate semialdehyde dehydrogenase is considered a likely candidate (Johannessen 2000).

Whatever the molecular mechanism by which valproate and lamotrigine enhance GABA levels, the lack of efficacy of valproate in either the NMDA models or in patients with schizophrenia would suggest that enhancing GABA is not sufficient to confer therapeutic benefit.

Monoamine release

Lamotrigine has been shown to interact with 5-HT, noradrenaline, and dopamine uptake transporters, but only at high, non-therapeutic concentrations (Table 4). In vitro studies also found an inhibitory action of lamotrigine on monoamine oxidase MAO-A and MAO-B activities in rat brain homogenates (E. Southam, personal communication). The inhibition was concentration dependent and reversible. K_i values were determined as 15 μM (MAO-A) and 18 μM (MAO-B). Similar effects of lamotrigine on MAO-A activity were seen with human liver preparations. However, these in vitro observations were not matched by evidence of ex-vivo MAO inhibition or altered monoamine disposition in vivo. Thus, after the administration of lamotrigine to rats, there was no (MAO-A) or minimal (MAO-B) reduction in brain MAO activities when assayed ex vivo. Furthermore, in vivo brain microdialysis failed to detect alterations in extracellular hippocampal or frontal cortex monoamine concentrations (reviewed in Xie and Hagan 1998). In the same study, lamotrigine had no effect on tyramine-induced hypertension in rats or 5-hydroxytryptophan (5-HTP)-induced head shaking in mice, providing strong evidence that the drug does not perturb monoamine metabolism in vivo. The absence of observable effects of lamotrigine on monoamine disposition in vivo may be explained by the competitive and highly reversible nature of the interaction of lamotrigine with MAO isoforms, such that it is competed out by endogenous ligand.

In a recent study by Ahmad et al. (2004b), acute treatment with lamotrigine (10–20 mg/kg) decreased extracellular dopamine and 5-HT levels in dialysate from the ventral hippocampus of freely moving rats, but without affecting metabolite levels. Chronic treatment produced an increase in dopamine and 5-HT levels after 2 days, but these had returned to baseline by day 21. In conclusion, lamotrigine does not appear to have a direct effect on monoamine levels but could influence these indirectly through other mechanisms.

Interactions with antipsychotic drugs

The clinical data currently support the add-on efficacy of lamotrigine in combination with antipsychotic drugs. There is some very preliminary indication that efficacy may be apparent only in combination with clozapine (Dursun and Deakin 2001), although a larger study found equal efficacy with other atypical antipsychotic drugs (Kremer et al. 2004). Notwithstanding the possibility, based on the preclinical evidence, that lamotrigine may be an effective antipsychotic drug when given as monotherapy (discussed later), it is important to consider how the drug might interact with typical and atypical antipsychotic drugs.

Table 4 The pharmacology of lamotrigine

Molecular target	Preparation	Concentration	Reference
Human type IIa sodium channel	Recombinant channels in a HEK293 cell line	Estimated K_i 12 μM for the inactivated state of the channel	Xie et al. 1995
N-type Ca^{2+} channels	Recombinant channels in a HEK293 cell line	<50% block at 1 mM	GlaxoSmithKline, data on file
T-type Ca^{2+} channels	Endogenous channels in a TT cell line	<50% block at 1 mM	
NMDA receptor	Binding vs CNQX, CGS, or TCHP	IC_{50}>100 μM	
5-HT transporter	Inhibition of 5HT uptake in human platelets	IC_{50} 240 μM	Southam et al. 1998
Noradrenaline transporter	Inhibition of noradrenaline uptake in rat cortical synaptosomes	IC_{50} 239 μM	
Dopamine transporter	Inhibition of dopamine uptake in rat cortical synaptosomes	IC_{50} 322 μM	
MAO-A	Rat brain homogenate	Ki 9 μM	E. Southam, personal communication
	Human liver microsomes	IC_{50} 22 μM	
	Rat brain synaptosomes	IC_{50} 200 μM	
MAO-B	Rat brain homogenate	K_i 26 μM	
	Rat brain synaptosomes	IC_{50} 50 μM	
Dihydrofolate reductase activity		IC_{50} 118 μM	GlaxoSmithKline, data on file
5-HT3 receptor	Binding assay	IC_{50} 18 μM	
Adenosine a1, a2	Binding assay	IC_{50} >100 μM	
Adrenergic a1, a2, b			
Dopamine D1, D2			
GABA-A, B			
Histamine H1			
Opioid kappa, sigma			
ACh muscarinic			
Serotonin 5-HT2			

There are three scenarios: First, lamotrigine might enhance exposure to the antipsychotic medication. Second, lamotrigine may reduce some of the side effects associated with antipsychotic drugs, and so improve tolerability, compliance, and apparent efficacy of the antipsychotic. Finally, lamotrigine might augment the efficacy of the antipsychotic medication through a synergistic or additive mechanism.

Considering the first scenario, lamotrigine is not known to inhibit any of the cytochrome P-450 enzymes (GlaxoSmithKline, data on file) responsible for metabolism of the major atypical antipsychotic drugs. Thus, lamotrigine would not be predicted to increase exposure to any of these drugs. A formal drug interaction study in healthy subjects has been carried out with lamotrigine and olanzapine (Ascher et al. 2004). The study found that plasma levels of olanzapine at steady state were comparable when the drug was administered with lamotrigine or with placebo. In contrast, plasma levels of lamotrigine were lower when the drug was administered with olanzapine compared with placebo. There has been one case report of increased exposure to clozapine in the presence of lamotrigine (Kossen et al. 2001); however, no change was observed in a larger study carried out by Tiihonen et al. (2003). Although the effects of lamotrigine on the pharmacokinetics of clozapine was not a main objective of this clinical study, trough concentrations of clozapine obtained after 14 weeks of treatment with lamotrigine (200 mg for the last 4 weeks) do not indicate a significant drug interaction. Evaluation of antipsychotic exposures should be included in all future studies of the efficacy of add-on lamotrigine, but for now, pharmacokinetic interaction would not seem to provide an explanation for efficacy.

The second scenario, that lamotrigine might reduce the side-effect burden of the antipsychotic treatment, is harder to address with the limited clinical date available so far. An examination of the incidence of extrapyramidal side effects in patients given lamotrigine in addition to their antipsychotic drug may be worthwhile, since there are hints that lamotrigine has some benefit in the treatment of Parkinson's disease (Zipp et al. 1995), although significant improvements in motor function have not been observed (Zipp et al. 1995; Shinotoh et al. 1997). An open-label study in patients diagnosed with Alzheimer's disease showed some treatment improvement in depressed mood, word recognition, and naming with lamotrigine treatment (Tekin et al. 1998), and lamotrigine may have a beneficial effect on cognition in patients with epilepsy (Aldenkamp and Baker 2001). Furthermore, healthy volunteers on low

doses of lamotrigine showed improvement on measures of cognitive activation and alertness (Aldenkamp et al. 2002).

In the final scenario, lamotrigine and antipsychotic drugs may act through the same biochemical mechanism or pathway. Dopamine is central to the mechanism of action of antipsychotic drugs, since antipsychotic efficacy closely correlates with antagonist activity at the dopamine D2 receptor (Creese et al. 1976). This also holds for the atypical antipsychotic drugs, and the correlation between D2 receptor occupancy and antipsychotic efficacy has been verified using non-invasive imaging (Nordstrom et al. 1993; Kapur et al. 1999), with an occupancy in excess of 65% necessary for efficacy (Seeman 2002). However, lamotrigine does not bind to dopamine receptors, nor does it affect the availability or release of dopamine in vivo (Table 4). It remains to be seen whether interaction with R-type calcium channels, observed in a recombinant cell line (Hainsworth et al. 2003), might confer some effect on dopamine neuron activity (Bergquist and Nissbrandt 2003). Furthermore, it would be useful to study the impact of use-dependent sodium channel inhibition on the firing of dopamine neurons after treatment with NMDA antagonists. Thus, there is reason to suspect that lamotrigine might interact directly with the dopamine system, although experimental data are lacking. Given that D2 receptor occupancy appears to be a critical parameter in the efficacy and side-effect potential of antipsychotic drugs, it might be valuable to examine this parameter in the presence and absence of lamotrigine.

Clozapine and other atypical antipsychotic drugs also have significant affinity for other receptors, notably dopamine D1, D4, noradrenergic alpha-1, 5-HT2a, 5-HT2c, and muscarinic M1, which may be responsible for increased efficacy (Coward 1992; Seeman 1992) or lower incidence of extrapyramidal symptoms (EPS) (Duncan et al. 1999; Seeman 2002). Lamotrigine does not bind to any of these receptors nor does it influence the availability or release of noradrenaline or 5-HT (Table 4).

Since we have argued that the efficacy of lamotrigine arises through inhibition of glutamate release, it is appropriate to consider whether antipsychotic drugs also affect glutamatergic transmission (reviewed in Heresco-Levy 2003). As mentioned earlier, most atypical antipsychotic drugs are antagonists of 5-HT2a receptors (Seeman 2002). Activation of these receptors within the cortex can enhance the release of glutamate (Aghajanian and Marek 1999). Unfortunately there is no direct evidence that the combination of lamotrigine with a selective 5-HT2a receptor antagonist produces an additive or synergistic inhibition of glutamate release, but it would be valuable to carry out such a study. Lamotrigine could in theory augment inhibition of glutamate release mediated by blockade of 5-HT2a receptors by atypical antipsychotic drugs. However, clozapine has actually been shown to increase levels of glutamate in the cortex (Daly and Moghaddam 1993; Yamamoto and Cooperman 1994). This observation is difficult to reconcile with the efficacy of lamotrigine in combination with Clozapine. Further study of the effects of these two drugs on glutamate release is warranted.

Clozapine may differentiate from other atypical antipsychotic drugs in other ways and perhaps should be considered separately from the other drugs in add-on trials with lamotrigine. Clozapine has been shown to enhance the excitatory response of cortical pyramidal neurons to application of NMDA (Arvanov et al. 1997). This enhancement may involve activation of dopamine D1 receptors, since it was absent in dopamine-depleted slices and could be blocked by the D1-selective antagonist, SCH23390 (Chen and Yang 2002; Ninan and Wang 2003). D1 receptor activation by other drugs has also been shown to promote NMDA receptor function (Morari et al. 1994; Dunah and Standaert 2001; Flores-Hernandez et al. 2002). Clozapine has significant affinity for dopamine D1 receptors, although it is still unclear whether the drug acts as an agonist or antagonist (Tauscher et al. 2004). A downstream consequence of D1 receptor activation leading to NMDA receptor facilitation appears to be inhibition of sodium and N-type calcium currents (Fienberg et al. 1998), so it is conceivable that lamotrigine might augment the impact of D1 receptor activation through such a mechanism. Reduced activation of cortical D1 receptors has been linked to negative and cognitive symptoms of schizophrenia (Davis et al. 1991; reviewed in Laruelle et al. 2003). Alternatively or in addition, clozapine may facilitate NMDA receptor activation through inhibition of type 1 glycine transporters (GlyT-1) (Javitt et al. 2004). However, this is unlikely to be a site of synergism between clozapine and lamotrigine, since the latter does not interact with this transporter (H. Herdon, personal communication). In contrast, these effects of clozapine on NMDA receptor function may be relevant to the worsening of symptoms when in combination with D-cycloserine (Goff et al. 1999; Heresco-Levy and Javitt 2004). Clinical data for clozapine and glycinergic agents suggest that negative symptoms of schizophrenia may be closely linked to NMDA receptor function; the absence of a compelling direct effect of lamotrigine on NMDA receptor function might be consistent with the absence of clinical effect of the drug on negative symptoms. However, this should be revisited as soon as further clinical data for lamotrigine are available.

Interactions between lamotrigine and antipsychotic drugs at a systems level

In the previous section we discussed how lamotrigine and antipsychotic drugs might interact within specific neurochemical systems. However, it is equally possible that the drugs work on different systems and their effects combine at a higher level to influence symptoms of schizophrenia. We can propose that lamotrigine regulates the firing of pyramidal neurons and the release of glutamate, whereas the antipsychotic drugs have their principal effect on dopamine transmission. The interaction between glutamate and dopamine in the schizophrenic brain has been a subject of significant discussion (Laruelle et al. 2003; Kapur 2003; Lisman and Otmakhova 2001). Dopamine is proposed to have a facilitatory rather than causal role in the generation

of the symptoms of schizophrenia (Laruelle and Abi-Dargham 1999; Lisman and Otmakhova 2001; Kapur 2003). In support of this, *d*-amphetamine induces a form of psychosis in volunteers (Griffith et al. 1972; Angrist and Gershon 1970), but the symptoms are not considered to be fully similar to those of the schizophrenic patient. On the other hand, the drug can exacerbate positive symptoms in patients with schizophrenia (Lieberman et al. 1987). Furthermore, unlike NMDA receptor antagonists, treatment with *d*-amphetamine does not seem to induce negative symptoms, but may improve these symptoms in some patients (Angrist et al. 1982; van Kammen and Boronow 1988). Laruelle and Abi-Dargham (1999) and Kapur (2003) have described dopamine as the "wind of the psychotic fire", increasing the salience of abnormal thoughts or hallucinations. Lisman and Otmakhova (2001) suggest that dopaminergic activity signals novelty, perhaps again increasing the impact of aberrant cortical activity on conscious thought. A consequence of this view is that psychosis is only temporarily subdued by dopamine-blocking drugs (Kapur 2003), which seems to be borne out by the frequent observation that identical symptoms remerge if the antipsychotic medication is withdrawn. Glutamate neuron dysregulation, on the other hand, may lie closer to the root cause of schizophrenia and may be responsible for the aberrant thought processes characteristic of the disorder. This view is supported by the acute psychotomimetic effects of ketamine in humans. The recent studies by Shi and Zhang (2003) or Jackson et al. (2004) show how altered glutamate transmission induced by PCP may be associated with disorganized firing of pyramidal neurons in the cortex. We postulate that this disorganization may mimic that induced by aberrant cortical connectivity in the schizophrenic brain. Thus, glutamatergic dysregulation (or disorganized neuronal activity) in combination with altered dopamine transmission may generate the recognizable symptoms of schizophrenia. The model may explain some of the observations from human volunteer studies with lamotrigine and ketamine. Lamotrigine, acting on the glutamate system, prevents the aberrant thoughts and hallucinations experienced by healthy subjects given ketamine (Anand et al. 2000a), but leaves intact or perhaps even enhances the feelings of euphoria that are likely associated with increased dopamine release (Anand et al. 2000b). In contrast, antipsychotic drugs, acting mainly on the dopaminergic component of ketamine's effect, produce only a modest reduction of the symptoms induced in human volunteers (Malhotra et al. 1997b; Lahti et al. 2001) or else are ineffective (Krystal et al. 1999b). Similarly, antipsychotic drugs are relatively ineffective against behavioural disruption induced by NMDA antagonists in preclinical species (Duncan et al. 2000; Abdul-Monim et al. 2003; Idris et al. 2005).

Although NMDA antagonists may recreate acutely the neurophysiological and neurochemical conditions necessary for the emergence of psychotic symptoms, the situation in schizophrenia is likely to be more complex. It will be important to study the efficacy of drugs like lamotrigine in monotherapy to determine whether an anti-glutamatergic treatment strategy would be effective alone. However, for the following reasons it is likely that efficacy would not be seen with lamotrigine monotherapy, but combination with anti-dopaminergic medications may be essential, at least during the active psychotic phase of the illness. Very briefly, schizophrenia is widely considered to be a developmental disorder that appears during adolescence (Keshavan and Hogarty 1999) and that is preceded by a prodromal phase (Yung and McGorry 1996). This phase is proposed to include or else cause dysregulation of cortical neural activity and glutamate transmission. For example, neurodegeneration may already have taken place by first onset of psychotic symptoms (Vita et al. 1997; Davies et al. 1998; Thompson et al. 2001; Cahn et al. 2002). Multiple lines of evidence suggest that alterations in glutamate transmission can impact the dopamine system. Cortical glutamatergic efferents exert significant control over the firing pattern of mesolimbic and mesocortical dopamine neurons (Tong et al. 1995; Overton and Clark 1997; Takahata and Moghaddam 2000). Furthermore, PCP has been shown to increase the firing of dopamine neurons in the ventral tegmental area (VTA) of anaesthetized rats (French 1994; reviewed by Svensson 2000). Takahata and Moghaddam (2003) also recently showed that the motoric effects of PCP in rats could be prevented by local inhibition of AMPA glutamate receptors in the VTA. Thus, the impact of glutamate on dopamine neuron activity may be sufficient to facilitate the emergence of psychotic symptoms (Grace 1991). Furthermore, since dopamine exerts significant control over glutamate transmission in cortical and limbic brain areas, a disrupted dopamine system may well cause

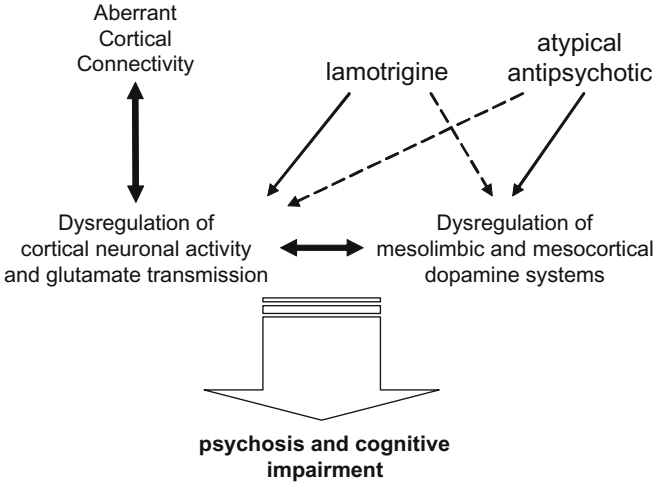

Fig. 2 A combination of dysregulation of glutamate and dopamine systems may contribute to the expression of psychosis and the symptoms of schizophrenia. Aberrant cortical connectivity is postulated to cause alterations of glutamatergic transmission; this in turn may lead to alterations in the dopamine system. A vicious cycle of altered glutamate and dopamine transmission drives further degenerative alterations in cortical connectivity. The principal site of action of lamotrigine is postulated to be on cortical neuronal activity and glutamate transmission; the drug may also influence the dopamine system directly, but there is currently no strong evidence for this. In contrast, atypical antipsychotic drugs are presumed to have their major effect through control of dopamine receptor activation; however, they may also influence the glutamate system through other receptor interactions

further dysregulation of glutamate transmission and alterations in cortical function, creating a vicious cycle of glutamate–dopamine interactions (Laruelle et al. 2003) (Fig. 2).

Although speculative, this framework does allow predictions to made about how schizophrenia might be treated. First, as soon as a patient presents with symptoms of schizophrenia, treatment with anti-dopaminergic drugs will be necessary. However, since antipsychotic treatment does not address the underlying glutamatergic dysfunction, except perhaps through some mild modulatory effects mediated by D1 or 5-HT2a receptors, cessation of treatment would inevitably lead to the re-emergence of symptoms. Secondly, drugs designed to reduce glutamate release may not be sufficient to correct the glutamatergic dysregulation arising from the combination of aberrant cortical connectivity and secondary alterations of dopaminergic transmission. Reducing glutamate transmission may also not be sufficient to reset the dopamine system back to its normal state, given the complex homeostatic mechanisms involved. Consequently, the model suggests that both anti-dopaminergic and anti-glutamatergic drugs should be combined in the early treatment of schizophrenia. However, as soon as symptoms have been controlled, it may be possible to withdraw the patient from anti-dopaminergic agents and maintain only the glutamate-reducing drug, to control the underlying dysfunction and to provide prophylaxis against the re-emergence of a permissive dopaminergic state.

Conclusions

There is increasing evidence from clinical studies that lamotrigine can augment the efficacy of antipsychotic drugs in the treatment of schizophrenia. The efficacy of lamotrigine may be explained within a glutamate neuron dysregulation hypothesis of schizophrenia and may arise primarily through the drug's ability to influence glutamate transmission and neural activity in the cortex. However, clinical data so far contrasts with other glutamate-related approaches, such as activation of the glycine site on NMDA receptors, since the improvement with lamotrigine appears to be mainly in positive symptoms. At a molecular level, lamotrigine most likely acts through inhibition of voltage-dependent sodium channels, although other molecular interactions, e.g. with N-type or R-type calcium channels, cannot be ruled out. These effects of lamotrigine may add to or synergize with effects of some atypical antipsychotic drugs acting on glutamate transmission via inhibition or 5-HT2a receptors, activation of dopamine D1 receptors, or inhibition of glycine uptake. However, we also propose that lamotrigine (modulating glutamate transmission) and antipsychotic drugs (modulating dopamine transmission) may act at two different points on a cycle of pathophysiology that underlies the symptoms of schizophrenia (Fig. 2). Based on this model, we propose new strategies for the treatment of schizophrenia using a combination of anti-dopaminergic and anti-glutamatergic drugs.

Acknowledgements The authors thank Mrs. Barbara Wilson, Drs. Dan Javitt, Gary Evoniuk, Dr. Jo Neill and Prof. Mark Geyer for helpful discussion. We would also like to thank the reviewers for their many valuable comments, suggestions, and encouragement.

References

Abdul-Monim Z, Reynolds GP, Neill JC (2003) The atypical antipsychotic ziprasidone, but not haloperidol, improves PCP-induced cognitive deficits in a reversal learning task in the rat. J Psychopharmacol 17:57–66

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

Adams B, Moghaddam B (1998) Corticolimbic dopamine neurotransmission is temporally dissociated from the cognitive and locomotor effects of phencyclidine. J Neurosci 18:5545–5554

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 (1999) Serotonin, via 5-HT2A receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. Brain Res 825:161–171

Ahmad S, Fowler LJ, Whitton PS (2004a) Effects of acute and chronic lamotrigine treatment on basal and stimulated extracellular amino acids in the hippocampus of freely moving rats. Brain Res 1029:41–47

Ahmad S, Fowler LJ, Whitton PS (2004b) Effect of acute and chronic lamotrigine on basal and stimulated extracellular 5-hydroxytryptamine and dopamine in the hippocampus of the freely moving rat. Br J Pharmacol 142:136–142

Aldenkamp AP, Baker G (2001) A systematic review of the effects of lamotrigine on cognitive function and quality of life. Epilepsy Behav 2:85–91

Aldenkamp AP, Arends J, Bootsma HP, Diepman L, Hulsman J, Lambrechts D, Leenen L, Majoie M, Schellekens A, de Vocht J (2002) Randomized double-blind parallel-group study comparing cognitive effects of a low-dose lamotrigine with valproate and placebo in healthy volunteers. Epilepsia 43:19–26

Allen RM, Young SJ (1978) Phencyclidine-induced psychosis. Am J Psychiatry 135:1081–1084

Ambrosio AF, Soares-Da-Silva P, Carvalho CM, Carvalho AP (2002) Mechanisms of action of carbamazepine and its derivatives, oxcarbazepine, BIA 2-093, and BIA 2-024. Neurochem Res 27:121–130

Anand A, Charney D, Oren D, Berman R, Hu X, Cappiello A, Krystal J (2000a) Attenuation of the neuropsychiatric effects of ketamine with lamotrigine. Arch Gen Psychiatry 57:270–276

Anand A, Charney D, Oren D, Berman R, Hu X, Cappiello A, Krystal J (2000b) Potentiation of mood elevating effects of ketamine by lamotrigine: support for the mood elevating effect of inhibition of glutamatergic transmission. XXII CINP Congress, abstract P16.024

Angrist BM, Gershon S (1970) The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. Biol Psychiatry 2:95–107

Angrist B, Peselow E, Rubinstein M, Corwin J, Rotrosen J (1982) Partial improvement in negative schizophrenic symptoms after amphetamine. Psychopharmacology 78:128–130

Arana GW, Goff DC, Friedman H, Ornsteen M, Greenblatt DJ, Black B, Shader RI (1986) Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? Am J Psychiatry 143:650–651

Arban R, Maraia G, Brackenborough K, Winyard L, Wilson A, Gerrard P, Large C (2005) Evaluation of the effects of lamotrigine, valproate and carbamazepine in a rodent model of mania. Behav Brain Res 158:123–132

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

Ascher JA, Sidhu J, Job S, Theis J (2004) A pharmacokinetic interaction study of lamotrigine and olanzapine. Am Psychiatr Assoc Annu Meet New Res Abstr 155:Abs No NR415

Bakker CB, Amini FB (1961) Observations on the psychotomimetic effects of Sernyl. Compr Psychiatry 2:269–280

Bakshi VP, Geyer MA (1997) Reversal of phencyclidine-induced deficits in prepulse inhibition by prazosin, an alpha-1 adrenergic antagonist. J Pharmacol Exp Ther 283:666–674

Bakshi VP, Swerdlow NR, Geyer MA (1994) Clozapine antagonizes phencyclidine-induced deficits in sensorimotor gating of the startle response. J Pharmacol Exp Ther 271:787–794

Barnes TR, McEvedy CJ, Nelson HE (1996) Management of treatment resistant schizophrenia unresponsive to clozapine. Br J Psychiatr Suppl 31:31–40

Basan A, Leucht S (2004) Valproate for schizophrenia. Cochrane Database Syst Rev 1:CD004028

Benes FM (2000) Emerging principles of altered neural circuitry in schizophrenia. Brain Res Brain Res Rev 31:251–269

Berger T, Luscher H-R (2004) Associative somatodendritic interaction in layer V pyramidal neurons is not affected by the antiepileptic drug lamotrigine. Eur J Neurosci 20:1688–1693

Bergeron R, Meyer T, Coyle J, Greene R (1998) Modulation of *N*-methyl-D-aspartate receptor function by glycine transport. Proc Natl Acad Sci U S A 95:15730–15734

Bergquist F, Nissbrandt H (2003) Influence of R-type (Cav2.3) and t-type (Cav3.1-3.3) antagonists on nigral somatodendritic dopamine release measured by microdialysis. Neuroscience 120: 757–764

Bogerts B (1999) The neuropathology of schizophrenic diseases: historical aspects and present knowledge. Eur Arch Psychiatry Clin Neurosci 249(Suppl 4):2–13

Braff DL, Geyer MA (1990) Sensorimotor gating and schizophrenia: human and animal model studies. Arch Gen Psychiatry 47:181–188

Braff DL, Grillon C, Geyer MA (1992) Gating and habituation of the startle reflex in schizophrenic patients. Arch Gen Psychiatry 49:206–215

Braff DL, Geyer MA, Swerdlow NR (2001) Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156:234–258

Braga MFM, Aroniadou-Anderjaska V, Post RM, Li H (2002) Lamotrigine reduces spontaneous and evoked GABAa receptor-mediated synaptic transmission in the basolateral amygdala: implications for its effects in siezure and affective disorders. Neuropharmacology 42:522–529

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

Brody SA, Geyer, MA, Large CH (2003) Lamotrigine reverses ketamine but not amphetamine-induced deficits in prepulse inhibition in mice. Psychopharmacology 169:240–246

Buchsbaum MS, Tang CY, Peled S, Gudbjartsson H, Lu D, Hazlett EA, Downhill J, Haznedar M, Fallon JH, Atlas SW (1998) MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. NeuroReport 9:425–430

Bunney BG, Potkin SG, Bunney WE (1997) Neuropathological studies of brain tissue in schizophrenia. J Psychiatr Res 31:159–173

Cahn W, Pol HE, Lems EB, van Haren NE, Schnack HG, van der Linden JA, Schothorst PF, van Engeland H, Kahn RS (2002) Related Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry 59:1002–1010

Calabresi P, Siniscalchi A, Pisani A, Stefani A, Mercuri NB, Bernardi G (1996) A field potential analysis on the effects of lamotrigine, GP 47779, and felbamate in neocortical slices. Neurology 47:557–562

Calabresi P, Centonze D, Marfia GA, Pisani A, Bernardi G (1999) An in vitro electrophysiological study on the effects of phenytoin, lamotrigine and gabapentin on striatal neurons. Br J Pharmacol 126:689–696

Cantrell AR, Catterall WA (2001) Neuromodulation of Na+ channels: an unexpected form of cellular plasticity. Nat Rev Neurosci 2:397–407

Carboni E, Imperato A, Perezzani L, Di Chiara G (1989) Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. Neuroscience 28:653–661

Carlsson M, Carlsson A (1989) The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice. J Neural Transm 75:221–226

Carlsson ML, Martin P, Nilsson M, Sorensen SM, Carlsson A, Waters S, Waters N (1999) The 5-HT2A receptor antagonist M100907 is more effective in counteracting NMDA antagonist- than dopamine agonist-induced hyperactivity in mice. J Neural Transm 106:123–129

Carpenter WT, Kurz R, Kirkpatrick B, Hanlon TE, Summerfelt AT, Buchanan RW, Waltrip RW, Breier A (1991) Carbamazepine maintenance treatment in outpatient schizophrenics. Arch Gen Psychiatry 48:69–72

Carter K, Dickerson J, Schoepp DD, Reilly M, Herring N, Williams J, Sallee FR, Sharp JW, Sharp FR (2004) The mGlu2/3 receptor agonist LY379268 injected into cortex or thalamus decreases neuronal injury in retrosplenial cortex produced by NMDA receptor antagonist MK-801: possible implications for psychosis. Neuropharmacology 47:1135–1145

Casey DE, Daniel DG, Wassef AA, Tracy KA, Wozniak P, Sommerville KW (2003) Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 28:182–192

Castel-Branco M, Lebre V, Falcao A, Figueiredo I, Caramona M (2003) Relationship between plasma and brain levels and the anticonvulsant effect of lamotrigine in rats. Eur J Pharmacol 482:163–168

Ceglia I, Carli M, Baviera M, Renoldi G, Calcagno E, Invernizzi RW (2004) The 5-HT receptor antagonist M100,907 prevents extracellular glutamate rising in response to NMDA receptor blockade in the mPFC. J Neurochem 91:189–199

Chen L, Yang CR (2002) Interaction of dopamine D1 and NMDA receptors mediates acute clozapine potentiation of glutamate EPSPs in rat prefrontal cortex. J Neurophysiol 87:2324–2336

Citrome L, Levine J, Allingham B (2000) Changes in use of valproate and other mood stabilizers for patients with schizophrenia from 1994 to 1998. Psychiatr Serv 51:634–638

Citrome L, Casey DE, Daniel DG, Wozniak P, Kochan LD, Tracy KA (2004) Adjunctive divalproex and hostility among patients with schizophrenia receiving olanzapine or risperidone. Psychiatr Serv 55:290–294

Clark L, Cools R, Robbins TW (2004) The neuropsychology of ventral prefrontal cortex: decision-making and reversal learning. Brain Cogn 55:41–53

Coward DM (1992) General pharmacology of clozapine. Br J Psychiatr Suppl 17:5–11

Creese I, Burt DR, Snyder SH (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 192:481–483

Crumrine RC, Bergstrand K, Cooper AT, Faison WL, Cooper BR (1997) Lamotrigine protects hippocampal CA1 neurons from ischemic damage after cardiac arrest. Stroke 28:2230–2236

Cunha RA, Coelho JE, Costenla AR, Lopes LV, Parada A, de Mendonça A, Sebastião AM, Ribeiro JA (2002) Effects of carbamazepine and novel 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide derivatives on synaptic transmission in rat hippocampal slices. Pharmacol Toxicol 90:208–213

Cunningham MO, Jones RS (2000) The anticonvulsant, lamotrigine decreases spontaneous glutamate release but increases spontaneous GABA release in the rat entorhinal cortex in vitro. Neuropharmacology 39:2139–2146

Daly DA, Moghaddam B (1993) Action of clozapine and haloperidol on extracellular levels of excitatory amino acids in the prefrontal cortex and striatum of conscious rats. Neurosci Lett 152:61–64

Dannhardt G, Kohl BK (1998) The glycine site on the NMDA receptor: structure–activity relationships and possible therapeutic applications. Curr Med Chem 5:253–263

Davies N, Russell A, Jones P, Murray RM (1998) Which characteristics of schizophrenia predate psychosis? J Psychiatr Res 32:121–131

Davis KL, Kahn RS, Ko G, Davidson M (1991) Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 148:1474–1486

Deakin JF, Simpson MD (1997) A two-process theory of schizophrenia: evidence from studies in post-mortem brain. J Psychiatr Res 31:277–295

Deicken RF, Merrin EL, Floyd TC, Weiner MW (1995) Correlation between left frontal phospholipids and Wisconsin Card Sort Test performance in schizophrenia. Schizophr Res 14:177–181

DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R (1997) Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res 74:129–140

de Paulis T (2001) M-100907 (Aventis). Curr Opin Investig Drugs 2:123–132

Deutch AY, Tam SY, Freeman AS, Bowers MB Jr, Roth RH (1987) Mesolimbic and mesocortical dopamine activation induced by phencyclidine: contrasting pattern to striatal response. Eur J Pharmacol 134:257–264

Dixon JF, Hokin LE (1997) The antibipolar drug valproate mimics lithium in stimulating glutamate release and inositol 1,4,5-trisphosphate accumulation in brain cortex slices but not accumulation of inositol monophosphates and bisphosphates. Proc Natl Acad Sci U S A 94:4757–4760

Dose M, Hellweg R, Yassouridis A, Theison M, Emrich HM (1998) Combined treatment of schizophrenic psychoses with haloperidol and valproate. Pharmacopsychiatry 31:122–125

Dunah AW, Standaert DG (2001) Dopamine D1 receptor-dependent trafficking of striatal NMDA glutamate receptors to the postsynaptic membrane. J Neurosci 21:5546–5558

Duncan GE, Zom S, Lieberman JA (1999) Mechanisms of typical and atypical antipsychotic drug action in relation to dopamine and NMDA receptor hypofunction hypotheses of schizophrenia. Mol Psychiatry 4:418–428

Duncan GE, Miyamoto S, Leipzig JN, Lieberman JA (2000) Comparison of the effects of clozapine, risperidone, and olanzapine on ketamine-induced alterations in regional brain metabolism. J Pharmacol Exp Ther 293:8–14

Duncan EJ, Madonick SH, Parwani A, Angrist B, Rajan R, Chakravorty S, Efferen TR, Szilagyi S, Stephanides M, Chappell PB, Gonzenbach S, Ko GN, Rotrosen JP (2001) Clinical and sensorimotor gating effects of ketamine in normals. Neuropsychopharmacology 25:72–83

Dursun SM, Deakin JF (2001) Augmenting antipsychotic treatment with lamotrigine or topiramate in patients with treatment-resistant schizophrenia: a naturalistic case–series outcome study. J Psychopharmacol 15:297–301

Dursun SM, McIntosh D (1999) Clozapine plus lamotrigine in treatment-resistant schizophrenia (letter). Arch Gen Psychiatry 56:950

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

Evins A, Fitzgerald S, Wine L, Roselli R, Goff D (2000) A placebo controlled trial of glycine added to clozapine In schizophrenia. Am J Psychiatry 157:826–828

Falke E, Han LY, Arnold SE (2000) Absence of neurodegeneration in the thalamus and caudate of elderly patients with schizophrenia. Psychiatry Res 93:103–110

Farber NB, Jiang XP, Heinkel C, Nemmers B (2002) Antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity. Mol Psychiatry 7:726–733

Fienberg AA, Hiroi N, Mermelstein PG, Song W, Snyder GL, Nishi A, Cheramy A, O'Callaghan JP, Miller DB, Cole DG, Corbett R, Haile CN, Cooper DC, Onn SP, Grace AA, Ouimet CC, White FJ, Hyman SE, Surmeier DJ, Girault J, Nestler EJ, Greengard P (1998) DARPP-32: regulator of the efficacy of dopaminergic neurotransmission. Science 281:838–842

Flores-Hernandez J, Cepeda C, Hernandez-Echeagaray E, Calvert CR, Jokel ES, Fienberg AA, Greengard P, Levine MS (2002) Dopamine enhancement of NMDA currents in dissociated medium-sized striatal neurons: role of D1 receptors and DARPP-32. J Neurophysiol 88:3010–3020

French ED (1994) Phencyclidine and the midbrain dopamine system: electrophysiology and behavior. Neurotoxicol Teratol 16:355–362

Geyer MA, Krebs-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

Giannini AJ, Loiselle RH, DiMarzio LR, Giannini MC (1987) Augmentation of haloperidol by ascorbic acid in phencyclidine intoxication. Am J Psychiatry 144:1207–1209

Gleason S, Shannon H (1997) Blockade of phencyclidine-induced hyperlocomotion by olanzapine, clozapine and serotonin receptor subtype selective antagonists in mice. Psychopharmacology 129:79–84

Goff DC, Coyle JT (2001) The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 158:1367–1377

Goff DC, Tsai G, Beal MF, Coyle JT (1995) Tardive dyskinesia and substrates of energy metabolism in CSF. Am J Psychiatry 152:1730–1736

Goff D, Henderson D, Evins A, Amico E (1999) A placebo-controlled crossover trial of D-cycloserine added to clozapine in patients with schizophrenia. Biol Psychiatry 45:512–514

Goff DC, Hennen J, Tsai G, Evins AE, Yurgelun-Todd D, Renshaw P (2002) Modulation of brain and serum glutamatergic concentrations following a switch from conventional neuroleptics to clozapine. Biol Psychiatry 51:493–497

Goff DC, Herz L, Posever T, Shih V, Tsai G, Henderson DC, Freudenreich O, Evins AE, Yovel I, Zhang H, Schoenfeld D (2004) A six-month, placebo-controlled trial of D-cycloserine co-administered with conventional antipsychotics in schizophrenia patients. Psychopharmacology, Oct 21:Epub ahead of print

Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Greene P, Leadbetter R (2004) A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 65:432–441

Gould TD, Quiroz JA, Singh J, Zarate CA, Manji HK (2004) Emerging experimental therapeutics for bipolar disorder: insights from the molecular and cellular actions of current mood stabilizers. Mol Psychiatry 9:734–755

Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41:1–24

Granger P, Biton B, Faure C, Vige X, Depoortere H, Graham D, Langer SZ, Scatton B, Avenet P (1995) Modulation of the gamma-aminobutyric acid type A receptor by the antiepileptic drugs carbamazepine and phenytoin. Mol Pharmacol 47:1189–1196

Griffith JD, Cavanaugh J, Held J, Oates JA (1972) Dextroamphetamine. Evaluation of psychomimetic properties in man. Arch Gen Psychiatry 26:97–100

Gronier BS, Rasmussen K (2003) Electrophysiological effects of acute and chronic olanzapine and fluoxetine in the rat prefrontal cortex. Neurosci Lett 349:196–200

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

Grunze H, von Wegerer J, Greene RW, Walden J (1998) Modulation of calcium and potassium currents by lamotrigine. Neuropsychobiology 38:131–138

Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC (1998) A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psychiatry 55:145–152

Habara T, Hamamura T, Miki M, Ohashi K, Kuroda S (2001) M100907, a selective 5-HT(2A) receptor antagonist, attenuates phencyclidine-induced Fos expression in discrete regions of rat brain. Eur J Pharmacol 417:189–194

Hainsworth AH, Spadoni F, Lavaroni F, Bernardi G, Stefani A (2001) Effects of extracellular pH on the interaction of sipatrigine and lamotrigine with high-voltage-activated (HVA) calcium channels in dissociated neurones of rat cortex. Neuropharmacology 40:784–791

Hainsworth AH, McNaughton NC, Pereverzev A, Schneider T, Randall AD (2003) Actions of sipatrigine, 202W92 and lamotrigine on R-type and T-type Ca2+ channel currents. Eur J Pharmacol 467:77–80

Halonen T, Nissinen J, Pitkanen A (2001) Effect of lamotrigine treatment on status epilepticus-induced neuronal damage and memory impairment in rat. Epilepsy Res 46:205–223

Harrison PJ, Weinberger DR (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 10:40–68

Hao Y, Creson T, Zhang L, Li P, Du F, Yuan P, Gould TD, Manji HK, Chen G (2004) Mood stabilizer valproate promotes ERK pathway-dependent cortical neuronal growth and neurogenesis. J Neurosci 24:6590–6599

Hassel B, Tauboll E, Gjerstad L (2001) Chronic lamotrigine treatment increases rat hippocampal GABA shunt activity and elevates cerebral taurine levels. Epilepsy Res 43:153–163

Heckers S (1997) Neuropathology of schizophrenia: cortex, thalamus, basal ganglia, and neurotransmitter-specific projection systems. Schizophr Bull 23:403–421

Heresco-Levy U (2000) *N*-Methyl-D-aspartate (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

Hertel P, Mathe JM, Nomikos GG, Iurlo M, Mathe AA, Svensson TH (1995) Effects of *d*-amphetamine and phencyclidine on behavior and extracellular concentrations of neurotensin and dopamine in the ventral striatum and the medial prefrontal cortex of the rat. Behav Brain Res 72:103–114

Hesslinger B, Normann C, Langosch JM, Klose P, Berger M, Walden J (1999) Effects of carbamazepine and valproate on haloperidol plasma levels and on psychopathologic outcome in schizophrenic patients. J Clin Psychopharmacol 19:310–315

Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M (2003) Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry 60:585–594

Hondo H, Yonezawa Y, Nakahara T, Nakamura K, Hirano M, Uchimura H, Tashiro N (1994) Effect of phencyclidine on dopamine release in the rat prefrontal cortex; an in vivo microdialysis study. Brain Res 633:337–342

Hosford DA, Wang Y (1997) Utility of the lethargic (lh/lh) mouse model of absence seizures in predicting the effects of lamotrigine, vigabatrin, tiagabine, gabapentin, and topiramate against human absence seizures. Epilepsia 38:408–414

Hough CJ, Irwin RP, Gao XM, Rogawski MA, Chuang DM (1996) Carbamazepine inhibition of *N*-methyl-D-aspartate-evoked calcium influx in rat cerebellar granule cells. J Pharmacol Exp Ther 276:143–149

Huang CW, Huang CC, Liu YC, Wu SN (2004) Inhibitory effect of lamotrigine on A-type potassium current in hippocampal neuron-derived H19-7 cells. Epilepsia 45:729–736

Idris NF, Repeto P, Neill JC, Large CH (2005) Investigation of the effects of lamotrigine and clozapine in improving reversal-learning impairments induced by acute phencyclidine and *d*-amphetamine in the rat. Psychopharmacology 179:336–348

Idris NF, Repeto P, Neill JC, Large CH (2005) Investigation of the effects of lamotrigine and clozapine to improve reversal learning impairments induced by acute PCP and D-amphetamine in the rat. Psychopharmacology. Epub ahead of print

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

Javitt D, Zukin S (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148:1301–1308

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

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

Jentsch J, Roth R (1999) The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 20: 201–225

Jentsch JD, Taylor JR (2001) Impaired inhibition of conditioned responses produced by subchronic administration of phencyclidine to rats. Neuropsychopharmacology 24:66–74

Jentsch JD, Anh Tran, Dung Lee, Youngren, KD, Roth, RH (1997) Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilisation and impairs prefrontal cortical-dependent cognition in the rat. Neuropsychopharmacology 17:92–99

Johannessen CU (2000) Mechanisms of action of valproate: a commentatory. Neurochem Int 37:103–110

Jones LB (2004) Loss of spines and neuropil. Int Rev Neurobiol 59:1–18

Kane J, Honigfeld G, Singer J, Meltzer H (1988) Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796

Kapur S (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160:13–23

Kapur S, Zipursky RB, Remington G (1999) Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. Am J Psychiatry 156:286–293

Karper LP, Grillon C, Morrissey K, Abi-Saab D, Morgan CA, Charney DS, Krystal JH (1994) The effect of ketamine on the acoustic startle response. Soc Neurosci Abstr 20:482

Keshavan MS, Hogarty GE (1999) Brain maturational processes and delayed onset in schizophrenia. Dev Psychopathol 11:525–543

Ketter TA, Calabrese JR (2002) Stabilization of mood from below baseline versus above baseline in bipolar disorder: a new nomenclature. J Clin Psychiatry 63:146–151

Ketter TA, Manji HK, Post RM (2003) Potential mechanisms of action of lamotrigine in the treatment of bipolar disorders. J Clin Psychopharmacol 23:484–495

Ko GN, Korpi ER, Freed WJ, Zalcman SJ, Bigelow LB (1985) Effect of valproic acid on behavior and plasma amino acid concentrations in chronic schizophrenic patients. Biol Psychiatry 20:199–228

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

Kossen M, Selten JP, Kahn RS (2001) Elevated clozapine plasma level with lamotrigine. Am J Psychiatry 158:1930

Kremer I, Vass A, Gorelik I, Bar G, Blanaru M, Javitt DC, Heresco-Levy U (2004) Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. Biol Psychiatry 56:441–444

Krupitsky EM, Burakov AM, Romanova TN, Grinenko NI, Grinenko AY, Fletcher J, Petrakis IL, Krystal JH (2001) Attenuation of ketamine effects by nimodipine pretreatment in recovering ethanol dependent men: psychopharmacologic implications of the interaction of NMDA and L-type calcium channel antagonists. Neuropsychopharmacology 25:936–947

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MBJ, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Krystal JH, Karper LP, Bennett A, D'Souza DC, Abi-Dargham A, Morrissey K, Abi-Saab D, Bremner JD, Bowers MB Jr, Suckow RF, Stetson P, Heninger GR, Charney DS (1998) Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. Psychopharmacology 135:213–229

Krystal JH, Belger A, D'Souza DC, Anand A, Charney DS, Aghajanian GK, Moghaddam B (1999a) Therapeutic implications of the hyperglutamatergic effects of NMDA antagonists. Neuropsychopharmacology 22:S143–S157

Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D, Cassello K, Bowers MB Jr, Vegso S, Heninger GR, Charney DS (1999b) Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl) 145:193–204

Krystal JH, Bennett A, Abi-Saab D, Belger A, Karper LP, D'Souza DC, Lipschitz D, Abi-Dargham A, Charney DS (2000) Dissociation of ketamine effects on rule acquisition and rule implementation: possible relevance to NMDA receptor contributions to executive cognitive functions. Biol Psychiatry 47:137–143

Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R (2003) NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology 169:215–233

Krystal JH, Abi-Saab W, Perry E, D'Souza DC, Liu N, Gueorguieva R, McDougall L, Hunsberger T, Belger A, Levine L, Breier A (2005) Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology Aug 10. Epub

Kumari V, Soni W, Sharma T (2002) Prepulse inhibition of the startle response in risperidone-treated patients: comparison with typical antipsychotics. Schizophr Res 55:139–146

Kuo C-C (1998) A common anticonvulsant binding site for phenytoin, carbamazepine, and lamotrigine in neuron neuronal Na+ channels. Mol Pharm 54:712–721

Kuzniecky R, Ho S, Pan J, Martin R, Gilliam F, Faught E, Hetherington H (2002) Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults. Neurology 58: 368–372

Lahti AC, Koffel B, LaPorte D, Tamminga CA (1995) Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13:9–19

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

Langosch JM, Zhou XY, Frick A, Grunze H, Walden J (2000) Effects of lamotrigine on field potentials and long-term potentiation in guinea pig hippocampal slices. Epilepsia 41:1102–1106

Laruelle M, Abi-Dargham A (1999) Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. J Psychopharmacol 13:358–371

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

Lee YS, Yoon BW, Roh JK (1999) Neuroprotective effects of lamotrigine enhanced by flunarizine in gerbil global ischemia. Neurosci Lett 265:215–217

Lewis DA (2000) GABAergic local circuit neurons and prefrontal cortical dysfunction in schizophrenia. Brain Res Brain Res Rev 31:270–276

Lewis DA, Glantz LA, Pierri JN, Sweet RA (2003) Altered cortical glutamate neurotransmission in schizophrenia: evidence from morphological studies of pyramidal neurons. Ann NY Acad Sci 1003:102–112

Li X, Bijur GN, Jope RS (2002) Glycogen synthase kinase-3beta, mood stabilizers, and neuroprotection. Bipolar Disord 4:137–144

Li X, Teneback CC, Nahas Z, Kozel FA, Large C, Cohn J, Bohning DE, George MS (2004) Interleaved transcranial magnetic stimulation/functional MRI confirms that lamotrigine inhibits cortical excitability in healthy young men. Neuropsychopharmacology 29:1395–1407

Lieberman JA, Kane JM, Alvir J (1987) Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology 91:415–433

Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, Bilder R (2001) Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry 49:487–499

Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, Tohen M; HGDH Study Group (2005) Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62:361–370

Lim KO, Sullivan EV, Zipursky RB, Pfefferbaum A (1996) Cortical gray matter volume deficits in schizophrenia: a replication. Schizophr Res 20:157–164

Lim KO, Hedehus M, Moseley M, de Crespigny A, Sullivan EV, Pfefferbaum A (1999) Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. Arch Gen Psychiatry 56:367–374

Lingamaneni R, Hemmings HC Jr (1999) Effects of anticonvulsants on veratridine- and KCl-evoked glutamate release from rat cortical synaptosomes. Neurosci Lett 276:127–130

Lisman JE, Otmakhova NA (2001) Storage, recall, and novelty detection of sequences by the hippocampus: elaborating on the SOCRATIC model to account for normal and aberrant effects of dopamine. Hippocampus 11:551–568

Liu G, Yarov-Yarovoy V, Nobbs M, Clare JJ, Scheuer T, Catterall WA (2003) Differential interactions of lamotrigine and related drugs with transmembrane segment IVS6 of voltage-gated sodium channels. Neuropharmacology 44:413–422

Loscher W (1999) Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. Prog Neurobiol 58:31–59

Loscher W (2002) Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. CNS Drugs 16:669–694

Loscher W, Vetter M, Bohme G, Stoltenburg-Didinger G (1985) In vivo effects of anticonvulsant drugs on nerve terminal (synaptosomal) GABA levels in 11 brain regions of the rat. J Neural Transm 63:157–167

Mackintosh NJ, Little L (1969) Selective attention and response strategies as factors in serial reversal learning. Can J Psychol 23:335–346

Magee J, Hoffman D, Colbert C, Johnston D (1998) Electrical and calcium signaling in dendrites of hippocampal pyramidal neurons. Annu Rev Physiol 60:327–346

Mai L, Jope RS, Li X (2002) BDNF-mediated signal transduction is modulated by GSK3beta and mood stabilizing agents. J Neurochem 82:75–83

Malhotra A, Pinals D, Adler C, Elman I, Clifton A, Pickar D, Breier A (1997a) Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology 17:141–150

Malhotra A, Adler C, Kennison S, Elman I, Pickar D, Breier A (1997b) Clozapine blunts *N*-methyl-D-aspartate antagonist-induced psychosis: a study with ketamine. Biol Psychiatry 42:664–668

Manabe T, Wyllie DJ, Perkel DJ, Nicoll RA (1993) Modulation of synaptic transmission and long-term potentiation: effects on paired pulse facilitation and EPSC variance in the CA1 region of the hippocampus. J Neurophysiol 70:1451–1459

Mansbach RS, Geyer MA (1989) Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. Neuropsychopharmacology 2:299–308

Martin P, Carlsson ML, Hjorth S (1998) Systemic PCP treatment elevates brain extracellular 5-HT: a microdialysis study in awake rats. NeuroReport 9:2985–2988

Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A (2001) Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 58:148–157

McLean MJ, Macdonald RL (1986) Sodium valproate, but not ethosuximide, produces use- and voltage-dependent limitation of high frequency repetitive firing of action potentials of mouse central neurons in cell culture. J Pharmacol Exp Ther 237:1001–1011

Messenheimer JA (1995) Lamotrigine. Epilepsia 36(Suppl 2):S87–S94

Miljanich GP (2004) Ziconotide: neuronal calcium channel blocker for treating severe chronic pain. Curr Med Chem 11:3029–3040

Miller DW, Abercrombie ED (1996) Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. Brain Res Bull 40:57–62

Mirjana C, Baviera M, Invernizzi RW, Balducci C (2004) The serotonin 5-HT2A receptors antagonist M100907 prevents impairment in attentional performance by NMDA receptor blockade in the rat prefrontal cortex. Neuropsychopharmacology 29:1637–1647

Miyamoto S, LaMantia AS, Duncan GE, Sullivan P, Gilmore JH, Lieberman JA (2003) Recent advances in the neurobiology of schizophrenia. Mol Interv 3:27–39

Moghaddam B, Adams B, Verma A, Daly D (1997) Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with prefrontal cortex. J Neurosci 17:2921–2927

Morari M, O'Connor WT, Ungerstedt U, Fuxe K (1994) Dopamine D1 and D2 receptor antagonism differentially modulates stimulation of striatal neurotransmitter levels by *N*-methyl-D-aspartic acid. Eur J Pharmacol 256:23–30

Motohashi N (1992) GABA receptor alterations after chronic lithium administration. Comparison with carbamazepine and sodium valproate. Prog Neuropsychopharmacol Biol Psychiatry 16: 571–579

Motohashi N, Ikawa K, Kariya T (1989) GABAB receptors are up-regulated by chronic treatment with lithium or carbamazepine. GABA hypothesis of affective disorders? Eur J Pharmacol 166:95–99

Nakki R, Sharp FR, Sagar SM, Honkaniemi J (1996) Effects of phencyclidine on immediate early gene expression in the brain. J Neurosci Res 45:13–27

Neppe VM (1983) Carbamazepine as adjunctive treatment in non-epileptic chronic inpatients with EEG temporal lobe abnormalities. J Clin Psychiatry 44:326–331

Ninan I, Wang RY (2003) Modulation of the ability of clozapine to facilitate NMDA- and electrically evoked responses in pyramidal cells of the rat medial prefrontal cortex by dopamine: pharmacological evidence. Eur J Neurosci 17:1306–1312

Nonaka S, Katsube N, Chuang DM (1998) Lithium protects rat cerebellar granule cells against apoptosis induced by anticonvulsants, phenytoin and carbamazepine. J Pharmacol Exp Ther 286:539–547

Nordstrom A-L, Farde L, Wiesel F-A, Forslund K, Pauli S, Halldin C, Uppfeldt G (1993) Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects. Biol Psychiatry 33:227–235

Olney JW, Farber NB (1995) Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 52:998–1007

Olney JW, Newcomer JW, Farber NB (1999) NMDA receptor hypofunction model of schizophrenia. J Psychiatr Res 33:523–533

Overton PG, Clark D (1997) Burst firing in midbrain dopaminergic neurons. Brain Res Brain Res Rev 25:312–334

Parepally H, Chakravorty S, Levine J, Brar JS, Patel AM, Baird JW, Chalasani L, Delaney JA, Atzert R, Chengappa KN (2002) The use of concomitant medications in psychiatric inpatients treated with either olanzapine or other antipsychotic agents: a naturalistic study at a state psychiatric hospital. Prog Neuropsychopharmacol Biol Psychiatry 26:437–440

Paulson L, Martin P, Persson A, Nilsson CL, Ljung E, Westman-Brinkmalm A, Eriksson PS, Blennow K, Davidsson P (2003) Comparative genome- and proteome analysis of cerebral cortex from MK-801-treated rats. J Neurosci Res 71:526–533

Perry W, Braff DL (1994) Information-processing deficits and thought disorder in schizophrenia. Am J Psychiatry 151:363–367

Perry W, Geyer MA, Braff DL (1999) Sensorimotor gating and thought disturbance measured in close temporal proximity in schizophrenic patients. Arch Gen Psychiatry 56:277–281

Perry W, Minassian A, Feifel D, Braff DL (2001a) Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. Biol Psychiatry 50:418–424

Perry W, Heaton RK, Potterat E, Roebuck T, Minassian A, Braff DL (2001b) Working memory in schizophrenia: transient "online" storage versus executive functioning. Schizophr Bull 27:157–176

Poolos NP, Migliore M, Johnston D (2002) Pharmacological upregulation of h-channels reduces the excitability of pyramidal neuron dendrites. Nat Neurosci 5:767–774

Postma T, Krupp E, Li XL, Post RM, Weiss SR (2000) Lamotrigine treatment during amygdala-kindled seizure development fails to inhibit seizures and diminishes subsequent anticonvulsant efficacy. Epilepsia 41:1514–1521

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

Rainey JMJ, Crowder MK (1975) Prolonged psychosis attributable to phencyclidine: a report of three cases. Am J Psychiatry 132:1076–1078

Ralph RJ, Varty GB, Kelly MA, Wang YM, Caron MG, Rubinstein M, Grandy DK, Low MJ, Geyer MA (1999) The dopamine D2, but not D3 or D4, receptor subtype is essential for the disruption of prepulse inhibition produced by amphetamine in mice. J Neurosci 19:4627–4633

Riehemann S, Volz HP, Stutzer P, Smesny S, Gaser C, Sauer H (2001) Hypofrontality in neuroleptic-naive schizophrenic patients during the Wisconsin Card Sorting Test—a fMRI study. Eur Arch Psychiatry Clin Neurosci 251:66–71

Robinson RB, Siegelbaum SA (2003) Hyperpolarization-activated cation currents: from molecules to physiological function. Annu Rev Physiol 65:453–480

Rogawski MA, Loscher W (2004) The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Nat Med 10:685–692

Sanchez-Prieto J, Budd DC, Herrero I, Vazquez E, Nicholls DG (1996) Presynaptic receptors and the control of glutamate exocytosis. Trends Neurosci 19:235–239

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

Schotte A, Janssen P, Gommeren W, Luyten W, Vangompel P, Lesage A, Deloore K, Leysen J (1996) Risperidone compared with new and reference antipsychotic drugs—in vitro and in vivo receptor binding. Psychopharmacology 124:57–73

Schwabe K, Brosda J, Wegener N, Koch M (2005) Clozapine enhances disruption of prepulse inhibition after sub-chronic dizocilpine- or phencyclidine-treatment in Wistar rats. Pharmacol Biochem Behav 80:213–219

Seeman P (1992) Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. Neuropsychopharmacology 7:261–284

Seeman P (2002) Atypical antipsychotics: mechanism of action. Can J Psychiatry 47:27–38

Shinotoh H, Vingerhoets FJ, Lee CS, Uitti RJ, Schulzer M, Calne DB, Tsui J (1997) Lamotrigine trial in idiopathic parkinsonism: a double-blind, placebo-controlled, crossover study. Neurology 48:1282–1285

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

Shuaib A, Mahmood RH, Wishart T, Kanthan R, Murabit MA, Ijaz S, Miyashita H, Howlett W (1995) Neuroprotective effects of lamotrigine in global ischemia in gerbils. A histological, in vivo microdialysis and behavioral study. Brain Res 702:199–206

Smith AG, Neill JC, Costall B (1999) The dopamine D3/D2 receptor agonist 7-OH-DPAT induces cognitive impairment in the common marmoset. Pharmacol Biochem Behav 63:201–211

Southam E, Kirkby D, Higgins GA, Hagan RM (1998) Lamotrigine inhibits monoamine uptake in vitro and modulates 5-hydroxytryptamine uptake in rats. Eur J Pharmacol 358:19–24

Stedman TJ, Whiteford HA, Eyles D, Welham JL, Pond SM (1991) Effects of nifedipine on psychosis and tardive dyskinesia in schizophrenic patients. J Clin Psychopharmacol 11:43–47

Stefani A, Spadoni F, Siniscalchi A, Bernardi G (1996) Lamotrigine inhibits Ca2+ currents in cortical neurons: functional implications. Eur J Pharmacol 307:113–116

Steinpreis RE, Salamone JD (1993) The role of nucleus accumbens dopamine in the neurochemical and behavioral effects of phencyclidine: a microdialysis and behavioral study. Brain Res 612:263–270

Stratton SC, Large CH, Cox B, Davies G, Hagan RM (2003) Effects of lamotrigine and levetiracetam on seizure development in a rat amygdala kindling model. Epilepsy Res 53:95–106

Suddath RL, Straw GM, Freed WJ, Bigelow LB, Kirch DG, Wyatt RJ (1991) A clinical trial of nifedipine in schizophrenia and tardive dyskinesia. Pharmacol Biochem Behav 39:743–745

Surmeier DJ, Kitai ST (1997) State-dependent regulation of neuronal excitability by dopamine. Nihon Shinkei Seishin Yakurigaku Zasshi 17:105–110

Surmeier DJ, Eberwine J, Wilson CJ, Stefani A, Kitai ST (1992) Dopamine receptor subtypes co-localise in rat striatonigral neurons. Proc Natl Acad Sci U S A 89:10178–10182

Svensson TH (2000) Dysfunctional brain dopamine systems induced by psychotomimetic NMDA-receptor antagonists and the effects of antipsychotic drugs. Brain Res Brain Res Rev 31:320–329

Swerdlow NR, Geyer MA (1998) Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. Schizophr Bull 24:285–301

Takahara A, Konda T, Enomoto A, Kondo N (2004) Neuroprotective effects of a dual L/N-type Ca(2+) channel blocker cilnidipine in the rat focal brain ischemia model. Biol Pharm Bull 27:1388–1391

Takahata R, Moghaddam B (2000) Target-specific glutamatergic regulation of dopamine neurons in the ventral tegmental area. J Neurochem 75:1775–1778

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

Talvik-Lotfi M, Nyberg S, Nordstrom AL, Ito H, Halldin C, Brunner F, Farde L (2000) High 5HT2A receptor occupancy in M100907-treated schizophrenic patients. Psychopharmacology 148:400–403

Tauscher J, Hussain T, Agid O, Verhoeff NP, Wilson AA, Houle S, Remington G, Zipursky RB, Kapur S (2004) Equivalent occupancy of dopamine D1 and D2 receptors with clozapine: differentiation from other atypical antipsychotics. Am J Psychiatry 161:1620–1625

Taverna S, Mantegazza M, Franceschetti S, Avanzini G (1998) Valproate selectively reduces the persistent fraction of Na+ current in neocortical neurons. Epilepsy Res 32:304–308

Tekin S, Aykut-Bingol C, Tanridag T, Aktan S (1998) Antiglutamatergic therapy in Alzheimer's disease—effects of lamotrigine. J Neural Transm 105:295–303

Tiihonen J, Hallikainen T, Ryynanen 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

Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R, Toga AW, Rapoport JL (2001) Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proc Natl Acad Sci U S A 98:11650–11655

Tong ZY, Overton PG, Clark D (1995) Chronic administration of (+)-amphetamine alters the reactivity of midbrain dopaminergic neurons to prefrontal cortex stimulation in the rat. Brain Res 674:63–74

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

Tsai G, Yang P, Chung L-C, Tsai I-C, Tsai C-W, Coyle J (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, Lange N (2004) Glycine transporter I inhibitor, *N*-methylglycine (sarcosine), added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 55:452–456

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

Ueda Y, Willmore LJ (2000) Molecular regulation of glutamate and GABA transporter proteins by valproic acid in rat hippocampus during epileptogenesis. Exp Brain Res 133:334–339

Vajda FJ (2002) Valproate and neuroprotection. J Clin Neurosci 9:508–514

van Berckel BN, Hijman R, van der Linden JA, Westenberg HG, van Ree JM, Kahn RS (1996) Efficacy and tolerance of D-cycloserine in drug-free schizophrenic patients. Biol Psychiatry 40:1298–1300

van Berckel BN, Oranje B, van Ree JM, Verbaten MN, Kahn RS (1998) The effects of low dose ketamine on sensory gating, neuroendocrine secretion and behavior in healthy human subjects. Psychopharmacology 137:271–281

van Berckel BN, Evenblij CN, van Loon BJ, Maas MF, van der Geld MA, Wynne HJ, van Ree JM, Kahn RS (1999) D-Cycloserine increases positive symptoms in chronic schizophrenic patients when administered in addition to antipsychotics: a double-blind, parallel, placebo-controlled study. Neuropsychopharmacology 21:203–210

van Kammen DP, Boronow JJ (1988) Dextro-amphetamine diminishes negative symptoms in schizophrenia. Int Clin Psychopharmacol 3:111–121

Varty GB, Higgins GA (1995) Examination of drug-induced and isolation-induced disruptions of prepulse inhibition as models to screen antipsychotic drugs. Psychopharmacology 122:15–26

Varty GB, Bakshi VP, Geyer MA (1999) M100907, a serotonin 5HT2A receptor antagonist and putative antipsychotic, blocks dizocilpine-induced prepulse inhibition deficits in Sprague–Dawley and Wistar rats. Neuropsychopharmacology 20:311–321

Vita A, Dieci M, Giobbio GM, Tenconi F, Invernizzi G (1997) Time course of cerebral ventricular enlargement in schizophrenia supports the hypothesis of its neurodevelopmental nature. Schizophr Res 23:25–30

Volz HP, Gaser C, Hager F, Rzanny R, Mentzel HJ, Kreitschmann-Andermahr I, Kaiser WA, Sauer H (1997) Brain activation during cognitive stimulation with the Wisconsin Card Sorting Test—a functional MRI study on healthy volunteers and schizophrenics. Psychiatry Res 75:145–157

von Wegerer J, Hesslinger B, Berger M, Walden J (1997) A calcium antagonistic effect of the new antiepileptic drug lamotrigine. Eur Neuropsychopharmcol 7:77–81

Walden J, Altrup U, Reith H, Speckmann EJ (1993) Effects of valproate on early and late potassium currents of single neurons. Eur Neuropsychopharmacol 3:137–141

Waldmeier PC, Baumann PA, Wicki P, Feldtrauer J-J, Stierlin C, Schmutz M (1995) Similar potency of carbamazepine, oxcarbazepine, and lamotrigine in inhibiting the release of glutamate and other neurotransmitters. Neurology 45:1907–1913

Walker MC, Tong X, Perry H, Alavijeh MS, Patsalos PN (2000) Comparison of serum, cerebrospinal fluid and brain extracellular fluid pharmacokinetics of lamotrigine. Br J Pharmacol 130:242–248

Wang SJ, Huang CC, Hsu KS, Tsai JJ, Gean PW (1996a) Presynaptic inhibition of excitatory neurotransmission by lamotrigine in the rat amygdalar neurons. Synapse 24:248–255

Wang SJ, Huang CC, Hsu KS, Tsai JJ, Gean PW (1996b) Inhibition of N-type calcium currents by lamotrigine in rat amygdalar neurones. NeuroReport 7:3037–3040

Weike AI, Bauer U, Hamm AO (2000) Effective neuroleptic medication removes prepulse inhibition deficits in schizophrenia patients. Biol Psychiatry 47:61–70

Weinberger DR (1996) On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia. Neuropsychopharmacology 14(3 Suppl):1S–11S

Weinberger DR (1999) Cell biology of the hippocampal formation in schizophrenia. Biol Psychiatry 45:395–402

Weinberger DR, Berman KF (1996) Prefrontal function in schizophrenia: confounds and controversies. Philos Trans R Soc Lond B Biol Sci 351:1495–1503

Whitaker WR, Faull RL, Waldvogel HJ, Plumpton CJ, Emson PC, Clare JJ (2001) Comparative distribution of voltage-gated sodium channel proteins in human brain. Mol Brain Res 88:37–53

Willow M, Gonoi T, Catterall WA (1995) Voltage clamp analysis of the inhibitory actions of diphenylhydantoin and carbamazepine on voltage-sensitive sodium channels in neuroblastoma cells. Mol Pharmacol 27:549–558

Wood SJ, Velakoulis D, Smith DJ, Bond D, Stuart GW, McGorry PD, Brewer WJ, Bridle N, Eritaia J, Desmond P, Singh B, Copolov D, Pantelis C (2001) A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. Schizophr Res 52:37–46

Xie X, Hagan RM (1998) Cellular and molecular actions of lamotrigine: possible mechanisms of efficacy in bipolar disorder. Neuropsychobiology 38:119–130

Xie X, Lancaster B, Peakman T, Garthwaite J (1995) Interaction of the antiepileptic drug lamotrigine with recombinant rat brain type IIA Na+ channels and with native Na+ channels in rat hippocampal neurones. Pflügers Arch 430:437–446

Yamada K, Kanba S, Ashikari I, Ohnishi K, Yagi G, Asai M (1996) Nilvadipine is effective for chronic schizophrenia in a double-blind placebo-controlled study. J Clin Psychopharmacol 16:437–439

Yamamoto BK, Cooperman MA (1994) Differential effects of chronic antipsychotic drug treatment on extracellular glutamate and dopamine concentrations. J Neurosci 14:4159–4166

Yung AR, McGorry PD (1996) The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull 22:353–370

Zhang W, Bymaster FP (1999) The in vivo effects of olanzapine and other antipsychotic agents on receptor occupancy and antagonism of dopamine D1, D2, D3, 5HT2A and muscarinic receptors. Psychopharmacology (Berl) 141:267–278

Zhu G, Okada M, Murakami T, Kawata Y, Kamata A, Kaneko S (2002) Interaction between carbamazepine, zonisamide and voltage-sensitive Ca2+ channel on acetylcholine release in rat frontal cortex. Epilepsy Res 49:49–60

Zipp F, Burklin F, Stecker K, Baas H, Fischer PA (1995) Lamotrigine in Parkinson's disease—a double blind study. J Neural Transm Parkinsons Dis Dement Sect 10:199–206

Zona C, Avoli M (1990) Effects induced by the antiepileptic drug valproic acid upon the ionic currents recorded in rat neocortical neurons in cell culture. Exp Brain Res 81:313–317

Zona C, Tancredi V, Palma E, Pirrone GC, Avoli M (1990) Potassium currents in rat cortical neurons in culture are enhanced by the antiepileptic drug carbamazepine. Can J Physiol Pharmacol 68:545–547

Zona C, Tancredi V, Longone P, D'Arcangelo G, D'Antuono M, Manfredi M, Avoli M (2002) Neocortical potassium currents are enhanced by the antiepileptic drug lamotrigine. Epilepsia 43:685–690