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Motor effects of lamotrigine in naive and dopamine-depleted mice

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Abstract

Lamotrigine (3,5-diamino-6-[2,3-dichlorphenyl]-1,2,4-triazine) has been hypothesised to possess antiparkinsonian activity, by inhibiting the release of glutamate from basal ganglia neurones. This study therefore examined the motor effects of lamotrigine in naive and reserpine-treated mice and its interactions with dopaminergic agonists. In normal mice, lamotrigine (5–80 mg/kg i.p.) decreased spontaneous locomotor activity with high doses ($\geq$ 40 mg/kg) causing moderately severe impairment to posture and gait. In mice treated 24 h beforehand with reserpine (5 mg/kg i.p.), lamotrigine (5–40 mg/kg i.p.) had no effect on akinesia by itself and did not alter the locomotion induced with the selective dopamine D_1 receptor agonist 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrochloride (SKF 38393, 30 mg/kg i.p.). By contrast, motor responses to the dopamine D_2 receptor-selective agonist *N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxyphenyl)ethylamine (RU 24213, 5 mg/kg s.c.) and to the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA, 150 mg/kg i.p. in the presence of benserazide, 100 mg/kg i.p.), were significantly potentiated by 10 and 40 mg/kg i.p. lamotrigine respectively. It is suggested that lamotrigine may enhance the antiakinetic action of L-DOPA in parkinson-like mice by increasing motor responding mediated by dopamine D_2 but not dopamine D_1 receptors. This interaction profile of lamotrigine with dopamine D_1 and D_2 receptor mechanisms is opposite to what one sees with antagonists of glutamate receptors.

Keywords: Locomotion; Reserpine; Lamotrigine; Dopamine; (Mouse)

1. Introduction

Recent interest in the antiparkinsonian potential of glutamate receptor antagonists, stems from the finding that corticostriatal input to the basal ganglia, as well as one of the major executive pathways of the basal ganglia involving the subthalamic nucleus, are probably glutamatergic and hyperactive in Parkinson's disease (Albin et al., 1989). Lesioning the subthalamus, or the internal segment of the globus pallidus to which this nucleus projects (entopeduncular nucleus in rodents), alleviates parkinsonian rigidity and akinesia (Bergman et al., 1990). Similar results have been obtained by infusing antagonists of glutamate *N*-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-isoxazole (AMPA) receptors directly into the subthalamus or globus pallidus of reserpine-treated or 6-hydroxydopamine-lesioned rats (Brotchie et al., 1991; Klockgether and Turski, 1990).

The systemic antiparkinsonian effects of glutamate receptor antagonists, on the other hand, have proved to be more variable, with a pronounced reversal of akinesia being demonstrated by some investigators and not others (reviewed in Starr, 1995a). Part of the problem with administering glutamate receptor antagonists by themselves to dopamine-depleted animals, is that any motor restorative activity is often overshadowed by the appearance of adverse side effects, such as ataxia and postural collapse (Carter, 1994; Ginski and Witkin, 1994). Thus, even when locomotion is stimulated by glutamate receptor blockade in parkinsonian models, the ensuing movements generally lack fluency and coordination. The search is on, therefore, for antagonists of glutamate that are better tolerated and which have a lower propensity to cause these motor disturbances, as an alternative palliative treatment for Parkinson's disease in man.

Another possibility for using glutamate receptor antagonists to ameliorate parkinsonism, is as adjunctive treatment to conventional dopamine precursor therapy with L-3,4-dihydroxyphenylalanine (L-DOPA; for review see Starr, 1995b). Various antagonists of the NMDA- or AMPA-type glutamate receptor, at doses which have little or no effect on motor performance by themselves, have been reported to accentuate the motor response elicited with L-DOPA

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(Kaur et al., 1994; Klockgether and Turski, 1990). The advantage of this approach is that it combines the benefits of both types of treatment, since it enables the glutamate antagonists to be administered at threshold doses which do not disrupt motor function directly, whilst allowing smaller maintenance doses of L-DOPA to be used. This, in turn, could benefit the patient by limiting the neurotoxicity attributed to oxidative stress, and by preventing the onset of response fluctuations normally encountered with L-DOPA in advanced stages of Parkinson's disease (Engber et al., 1994). The precise mechanism by which glutamate receptor antagonism potentiates L-DOPA-induced motor activation remains elusive, but it could involve the accelerated synthesis and release of dopamine presynaptically, or the facilitated action of dopamine at D_1 or D_2 receptors postsynaptically (reviewed by Starr, 1995b).

Lamotrigine (3,5-diamino-6-[2,3-dichlorphenyl]-1,2,4-triazine) is a potent anticonvulsant agent that is safe for human administration, which probably suppresses the release of glutamate release from neurones by a mechanism that involves the blockade of voltage-gated Na^+ channels (Meldrum and Leach, 1994; Xie et al., 1995). This property prompted initial tests with lamotrigine in a small group of five parkinson sufferers, which seemed to indicate the drug conferred an added clinical benefit when given in conjunction with L-DOPA (Zipp et al., 1993), though this was not later confirmed in a double-blind trial (cited by Löschmann et al., 1995). It also proved to be ineffective in rodents (Löschmann et al., 1995). Mitchell et al. (1995), however, have established the antiparkinsonian utility of drugs which reduce glutamate release, by showing that the κ opiate receptor agonist enadoline, restores moderately robust movements to 6-hydroxydopamine-lesioned monkeys. The purpose of the present study, therefore, was to examine the motor effects of lamotrigine in naive and monoamine-depleted mice, and to investigate the interactive effects of lamotrigine on dopamine-dependent motor behaviours in the reserpine model of parkinsonism.

2. Materials and methods

2.1. Animals and behavioural measurements

Male albino mice (TO strain, A.R. Tuck), weighing 27–35 g, were housed in groups of 25 at 22 ± 1°C, under fluorescent lighting from 07:00 to 17:00 h, and allowed free access to food and water. Experiments were carried out between 10:00 and 17:00 h and each animal was used only once. All procedures were conducted in accordance with the Animals (Scientific Procedures) U.K. Act, 1986.

Lamotrigine (5–80 mg/kg i.p.) was first administered to normal mice to establish an effective dose range. Control animals received vehicle alone (20% v/v dimethylsulphoxide in water, 5 ml/kg i.p. water). After injection, mice were placed singly onto the floor of a Perspex observation box (29 × 26 × 21 cm high), without prior acclimatisation, and locomotor activity monitored every 10 min for 30 min by means of a Radiospares 8960 Microwave Doppler Module, connected to a combined amplifier, timer and LED display. The units were constructed in this laboratory to our own design, and calibrated to detect horizontal movements. The presence of other behaviours was noted by a trained observer, but these were not quantified.

Further experiments were then conducted in mice treated 24 h beforehand with reserpine (5 mg/kg i.p.). Animals were injected with lamotrigine (5–40 mg/kg i.p.), either alone or together with L-DOPA (150 mg/kg i.p.) plus benserazide (100 mg/kg i.p. given 30 min prior to L-DOPA), SKF 38393 (30 mg/kg i.p.) or RU 24213 (5 mg/kg s.c.). Controls received an equivalent volume of vehicle (5 ml/kg i.p.). The mice were then placed individually onto the floor of a Perspex observation box, again without habituation, and their horizontal movements recorded as above.

2.2. Analysis of data

Locomotion was expressed as cumulative 30 min counts. Drug and control treatments were compared by one-factor or two-factor analysis of variance (ANOVA). Post hoc analysis of individual dose points was performed with Scheffé multiple range test (naive mice) or with Dunnett's *t*-test (reserpine-treated mice). Significance was taken as $P < 0.05$.

2.3. Drugs

Reserpine, L-DOPA, benserazide (Sigma), SKF 38393 (Research Biochemicals, Natick, MA, USA), RU 24213 (Roussel) and lamotrigine (Wellcome) were administered in distilled water. The solution of reserpine was aided with one drop glacial acetic acid (British Drug Houses) and that of lamotrigine with dimethylsulphoxide (Sigma), with subsequent dilution with water.

3. Results

3.1. Motor effects of lamotrigine in normal mice

Thirty minutes locomotor scores for control mice averaged 2218 ± 322 ($n = 7$). Lamotrigine decreased locomotor activity (main effect $F(5,41) = 5.53$, $P = 0.0007$ by ANOVA), causing a significant hypokinesia at 40 and 80 mg/kg ($P < 0.01$ by Scheffé test; Fig. 1). At low doses (5–20 mg/kg) lamotrigine-treated mice appeared normal, exhibiting species-typical sniffing and grooming and fluent locomotion. Beginning at 40 mg/kg, lamotrigine induced signs of muscle relaxation, characterised by flattening of the body. At 80 mg/kg, the mice exhibited more extensive

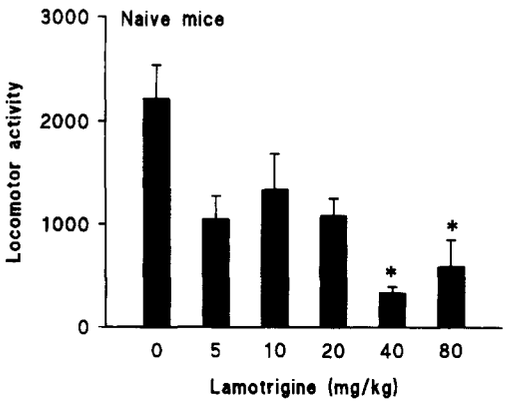

Fig. 1. Locomotor depressant effect of lamotrigine in normal mice. Mice were injected with lamotrigine or distilled water (5 ml/kg) and placed individually onto the floor of a Perspex observation box without prior acclimatisation. Horizontal movements were measured every 10 min using a Radiospares 8960 Microwave Doppler module. Results are mean cumulative 30 min motor scores ± S.E.M. of at least 6 determinations. * $P < 0.01$ versus controls by Scheffé test.

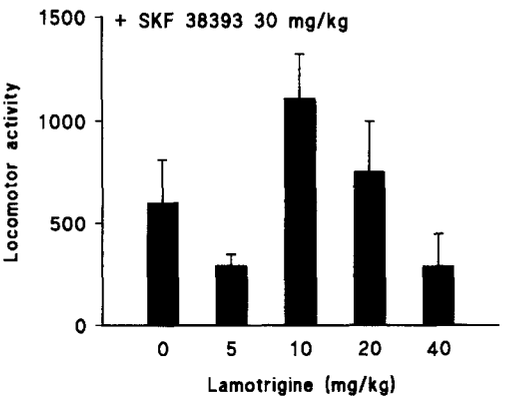

Fig. 3. Lack of effect of lamotrigine on SKF 38393-induced locomotion in 24 h reserpine-treated mice. Experiments were performed as in Fig. 2, except that lamotrigine and SKF 38393 (30 mg/kg i.p.) were coadministered. Results are mean cumulative 30 min motor scores ± S.E.M. of at least 6 determinations.

postural collapse with loss of righting reflex, leading us to discontinue this dose in subsequent experiments.

3.2. Motor effects of lamotrigine in 24 h reserpine-treated mice

Cumulative 30 min locomotor scores for control mice were 5.8 ± 2.5 ($n = 6$; Fig. 2), but there were no signs of other species-typical activities. Lamotrigine, 5–40 mg/kg, appeared to induce some behavioural arousal, including sniffing and grooming, but forward movements were slow and stilted and failed to reach statistical significance (main effect $F(4,40) = 2.47$, $P = 0.062$ by ANOVA).

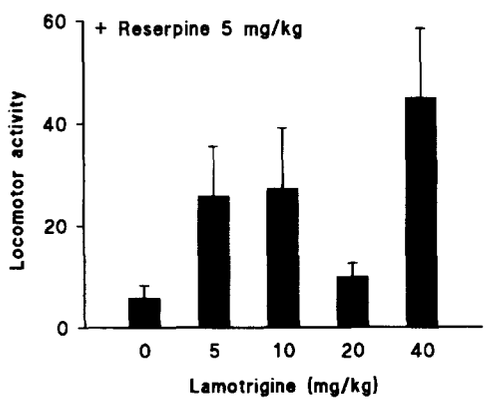

Fig. 2. Lack of effect of lamotrigine on reserpine-induced akinesia. Mice were injected with reserpine (5 mg/kg i.p.), then 24 h later with lamotrigine, and their motor activity recorded immediately as described in Fig. 1. Results are mean cumulative 30 min motor scores ± S.E.M. for at least 6 determinations.

3.3. Effects of lamotrigine on SKF 38393-induced locomotion in 24 h reserpine-treated mice

In accordance with earlier studies, a high dose of the dopamine D_1 receptor-selective agonist SKF 38393, 30 mg/kg i.p., reinstated fluent and well-coordinated forward walking, rearing, sniffing and grooming that lasted > 2 h. Cumulative 30 min motor counts were 603 ± 209 (main effect $F(1,22) = 26.15$, $P = 0.0001$ by ANOVA; Fig. 3). Co-administration of lamotrigine, 5–40 mg/kg, did not significantly affect the animals' locomotor response to SKF 38393 (interaction term $F(4,83) = 1.62$, $P = 0.18$), except that some muscle relaxation was evident at the highest dose.

3.4. Effects of lamotrigine on RU 24213-induced locomotion in 24 h reserpine-treated mice

As noted previously, the dopamine D_2 receptor-selective agonist RU 24213, 5 mg/kg s.c., elicited a head-down, hunched posture, sniffing directed at the floor and a ponderous forward locomotion lasting 30–40 min. Cumulative 30 min locomotor scores averaged 701 ± 133 (main effect $F(1,29) = 113.3$, $P = 0.0001$ by ANOVA; Fig. 4). Lamotrigine potentiated the locomotor response to RU 24213 in a curvilinear fashion (interaction term $F(4,87) = 7.13$, $P = 0.0001$ by ANOVA), with a significant increase occurring at 10 mg/kg lamotrigine ($P < 0.01$ by Dunnett's test), but not at lower or higher doses (Fig. 4). At 40 mg/kg lamotrigine, there were once again signs of postural difficulties.

3.5. Effects of lamotrigine on locomotion induced by L-DOPA plus benserazide in 24 h reserpine-treated mice

Motor recovery was evident 30 min after injecting mice with 150 mg/kg i.p. L-DOPA (60 min after benserazide,

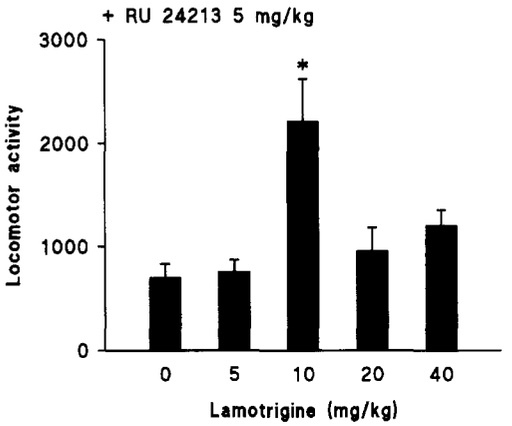

Fig. 4. Potentiation of RU 24213-induced locomotion by lamotrigine in 24 h reserpine-treated rats. Experiments details as for Fig. 4, except that lamotrigine was coadministered with RU 24213 (5 mg/kg s.c.). Results are mean 30 min cumulative motor scores ± S.E.M. of al least 6 determinations. * $P < 0.01$ versus controls by Dunnett's test.

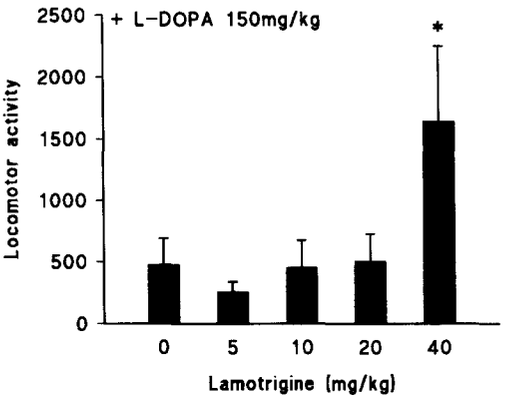

Fig. 5. Potentiation of locomotion induced by L-DOPA by lamotrigine in 24 h reserpine-treated rats. Experimental details as for Fig. 4, except that benserazide (100 mg/kg i.p.) was injected, followed 30 min later by L-DOPA (150 mg/kg i.p.) and lamotrigine. Results are mean 30 min cumulative motor scores ± S.E.M. of at least 6 determinations. * $P < 0.05$ by Scheffé test.

100 mg/kg i.p.), and consisted of slow forward walking, together with sniffing, occasional rearing and grooming and some latent ataxia. Locomotor scores for 30 min were 476 ± 212 (main effect $F(1,14) = 26.4$, $P = 0.0001$ by ANOVA; Fig. 5). Lamotrigine did not modify the L-DOPA response at 5–20 mg/kg, but there was a significant increase in L-DOPA-induced locomotion at 40 mg/kg (interaction term $F(4,84) = 3.0$, $P = 0.022$ by ANOVA; Fig. 5). Movements were fluent and although there was a slight flattening of posture initially, this later disappeared. With this drug combination, mice became very active and stereotyped, displaying perseverative rearing, sniffing, grooming and occasionally licking.

4. Discussion

The present results disclose a sedative action of high doses of lamotrigine (40–80 mg/kg) in naive mice, resulting in hypokinesia, but fail to reveal an antiakinetic action of lamotrigine administered alone to mice whose brain monoamines have been depleted with the Rauwolfia alkaloid reserpine. These findings correspond closely to those of Löschmann et al. (1995), who recently reported a lack of motor stimulant activity with lamotrigine in intact, reserpine-treated or 6-hydroxydopamine-lesioned Wistar rats. The two studies differ, however, in the way in which lamotrigine was observed to interact with dopaminergic drug treatments. Löschmann et al. (1995) found that lamotrigine did not alter the responsiveness of reserpine-treated or 6-hydroxydopamine-hemilesioned rats to the mixed dopamine D_1/D_2 receptor agonist apomorphine, or to the selective dopamine D_2 receptor agonist lisuride, leading the authors to conclude that lamotrigine would have no beneficial effect on the symptomatology of human parkinson patients. In our hands, lamotrigine was unable to modify the locomotor stimulant actions of the selective dopamine D_1 receptor agonist SKF 38393, but significantly potentiated the animals' response to the selective dopamine D_2 receptor agonist RU 24213, and to the dopamine precursor L-DOPA. On the basis of the present findings, therefore, we would endorse the apparent lack of antiparkinsonian efficacy of lamotrigine when employed as monotherapy, but suggest it may be premature to disregard the potential of this compound to augment the effectiveness of dopamine replacement therapy. Our data are in line with the early promise shown by lamotrigine/L-DOPA mixtures in a handful of parkinsonian patients (Zipp et al., 1993), but which apparently was not fulfilled in a subsequent double-blind trial (see Löschmann et al., 1995). Reasons for lamotrigine's inefficacy in man may become apparent when full details of this later trial are published.

In some respects the behavioural profile described for lamotrigine in these and earlier experiments, resembles what one sees when glutamate transmission is blocked with glutamate receptor antagonists. The sedative and myorelaxant actions of competitive and channel-blocking NMDA receptor antagonists, and to a lesser extent of glycine and polyamine site NMDA receptor antagonists, or of AMPA receptor blockers (Carter, 1994; Ginski and Witkin, 1994), were plain to see in naive mice treated with lamotrigine. Postural abnormalities including hind limb abduction, flattening of the body and ataxia, were also evident with lamotrigine, although these only became pronounced at the higher doses (≥ 40 mg/kg). At these elevated dose levels of lamotrigine, myorelaxation was sufficient to interfere with the ambulation of the animals, causing a 'dragging' of the hindquarters reminiscent of dizocilpine and *R*-(*E*)-2-amino-4-methyl-5-phosphono-3-pentanoate (CGP 40116), two of the most debilitating NMDA receptor antagonists in this regard (Carter, 1994; Starr, 1995a). This was only partly true of lamotrigine

administered to monoamine-depleted mice. Thus, whilst the horizontal movements reinstated by RU 24213 were potentiated at the expense of fluency, the motor response to L-DOPA was intensified by lamotrigine without undergoing appreciable deterioration, possibly because lamotrigine interacts with these dopaminergic agents in different ways. Whatever the reason, these findings indicate that lamotrigine may be both safe and effective when used as an adjuvant to L-DOPA, and indeed the brief report of its use in parkinsonian patients did not suggest otherwise (Zipp et al., 1993).

The differential manner in which lamotrigine interacted with D_1 and D_2 receptor-selective dopamine agonists, was opposite to that observed with glutamate receptor antagonists. Generally speaking, it is common to find that inhibiting NMDA or AMPA receptors accentuates both L-DOPA- and SKF 38393-induced locomotion, but has a more complex effect upon dopamine D_2 receptor-dependent locomotion, which may be facilitated, attenuated or remain unchanged by such cotreatment (Goodwin et al., 1992; Morelli et al., 1992; Starr, 1995a; Starr and Starr, 1994a). An increase in dopamine D_1 receptor-mediated motor responding would undoubtably contribute to the enhanced sensitivity of the parkinsonian animal to L-DOPA, although this is not likely to be the only mechanism by which the antiparkinsonian action of L-DOPA is augmented (Starr, 1995a, b). An increase in the biotransformation of L-DOPA into dopamine is a further possibility (Biggs et al., 1996; Hadjiconstantinou et al., 1995). In the present study, however, we found that a high dose of lamotrigine (40 mg/kg) increased the antiakinetic action of L-DOPA, but not that of SKF 38393 (Figs. 3 and 5), making it unlikely that a strengthening of dopamine D_1 receptor expression was a factor in the potentiation of the L-DOPA response by lamotrigine.

Interestingly, lamotrigine also enhanced the motor stimulation induced by RU 24213 (Fig. 4), but as this occurred with a lower amount of lamotrigine (10 mg/kg) than that required to potentiate L-DOPA, we cannot be sure if an increase in dopamine D_2 receptor activity contributes to the greater effectiveness of the dopamine precursor in the presence of lamotrigine. This observation contrasts with the lack of effect that lamotrigine had on locomotion evoked with the mixed dopamine D_1/D_2 agonist apomorphine, or with the dopamine D_2 receptor-selective agonist lisuride (Löschmann et al., 1995), but this does not necessarily mean the two studies are at variance. The motorgenic actions of different dopamine D_2 agonists are influenced in different ways by impairing glutamate transmission, as indicated by our previous finding that RU 24213 is strongly antagonised, whilst lisuride is unaffected by coadministration of dizocilpine in reserpine-treated mice (Goodwin et al., 1992). Subtle differences in the pharmacological profiles of these compounds, possibly unrelated to their dopamine D_2 receptor efficacy, may therefore determine whether their antiparkinsonian properties are affected adversely or beneficially by glutamate receptor blockade. We have similarly noticed that apomorphine's interactions with NMDA receptor antagonists are complex and unpredictable (Starr and Starr, 1993), and so the same may be true of this compound's interactions with lamotrigine.

Interestingly, although we have never observed a preferential pattern of dopaminergic $D_2 > D_1$ activation with antagonists of glutamate receptors, it is identical to the interaction that occurs between the α_2-adrenoceptor partial agonist clonidine and dopaminergic behaviour i.e. accentuation of motor responses to L-DOPA and dopamine D_2 receptor agonists, but no effect on those to dopamine D_1 receptor agonists (Rubinstein et al., 1989; Starr and Starr, 1994b). Like lamotrigine, clonidine also has the capacity to inhibit the release of excitatory amino acids presynaptically (Kamisaki et al., 1992). It may be the general rule, therefore, that presynaptic blockade of glutamate release is associated with enhanced responding at dopamine D_2 receptors, whilst postsynaptic blockade of glutamate receptors results in an exaggerated response at dopamine D_1 receptors.

Intracerebral microdialysis and microinjection are now being used in an effort to uncover the site(s) and mechanism(s) of action of glutamate receptor antagonists in the parkinsonian brain, with the substantia nigra pars reticulata being viewed as a key target. In the reserpine-treated rat, we have discovered that the NMDA receptor-ion channel blocker dizocilpine and the competitive NMDA receptor antagonist CGP 40116 infused into this nucleus, markedly increase the rate of bioconversion of L-DOPA into dopamine in dialysis experiments (Biggs et al., 1996), and that this is matched by a parallel increase in the animals' motor activity in stereotaxic intranigral injection experiments (Kaur and Starr, unpublished data). Thus far, we have only investigated lamotrigine behaviourally, but it is worth noting that focal injections of lamotrigine delivered into the substantia nigra pars reticulata of 24 h reserpine-treated rats failed to reverse the associated akinesia (Kaur and Starr, unpublished data), reinforcing the view that lamotrigine has a profile of action which differs from that of conventional NMDA receptor antagonists. Our own experience with lamotrigine is based largely upon its effects in reserpine-treated rodents, where the widespread depletion of brain monoamines is less discrete than occurs with the neuropathology of human idiopathic Parkinson's disease. It is therefore essential to repeat these studies in 6-hydroxydopamine- or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates, where the selective disruption of nigrostriatal dopamine function is held to be a more realistic model of human parkinsonism.

In summary, the present data indicate that presynaptic inhibition of glutamate release by lamotrigine does not have the same behavioural consequences as occluding postsynaptic glutamate receptors. Both classes of compound cause hypokinesia and postural derangements in

normal mice, and facilitation of L-DOPA-induced motor stimulation in monoamine-depleted animals. Lamotrigine may do this partly by enhancing dopamine $D_2 > D_1$ receptor expression, whereas the reverse is largely true of NMDA or AMPA receptor blockade.

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