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Lamotrigine inhibits monoamine uptake in vitro and modulates 5-hydroxytryptamine uptake in rats

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Abstract

Lamotrigine is a novel anticonvulsant drug which also stabilises mood in bipolar illness via an unknown mechanism. We report the concentration-dependent inhibition of 5-hydroxytryptamine (5-HT) uptake in both human platelets and rat brain synaptosomes (IC_{50}s were 240 and 474 μM, respectively) by lamotrigine. Synaptosomal uptake of noradrenaline (IC_{50} 239 μM) and dopamine (IC_{50} 322 μM) was also inhibited. Tetrodotoxin failed to modulate 5-HT uptake suggesting that sodium channel blockade does not mediate the lamotrigine effect. Lithium, sodium valproate, zonisamide, and carbamazepine all possess anti-manic activity but only the latter inhibited 5-HT uptake. The inhibition of the *p*-chloroamphetamine-induced 5-HT syndrome in rats suggests that lamotrigine also inhibits 5-HT uptake in vivo. These effects probably reflect an affinity for biogenic amine transporters. However, at present, it remains uncertain whether, at clinically effective doses, these effects contribute significantly to the efficacy of lamotrigine in bipolar illness.

Keywords: Lamotrigine; 5-HT (hydroxytryptamine, serotonin) uptake; Anticonvulsant; Bipolar disorder

1. Introduction

Li^+ has been the mainstay of treatment for bipolar illness for several decades but in recent years the inadequacy of this therapy for many patients has become increasingly apparent (Silverstone and Romans, 1997). In the search for alternatives, carbamazepine and sodium valproate have emerged as useful adjuncts to lithium (Post et al., 1996). Although these therapies do offer some protection against bipolar depression when used prophylactically, lithium, carbamazepine, and sodium valproate are all relatively ineffective against acute bipolar depression (Kalin, 1996).

Lamotrigine (3,5-diamino-6-(2,3-dichlorphenyl)-1,2,4-triazine; Lamictal) is a new generation broad-spectrum anticonvulsant (Goa et al., 1993) which is believed to mediate its anticonvulsant activity by the use- and voltage-dependent blockade of Na^+ channels (Xie et al., 1995). Preliminary reports indicate that lamotrigine may also be useful in the treatment of bipolar illness with efficacy against depressive breakthroughs and rapid cycling bipolar disorder (Calabrese et al., 1996; Corn et al., 1996; Walden et al., 1996). The 5-hydroxytryptamine (5-HT) system is widely implicated in the pathophysiology of depression (Owens and Nemeroff, 1994) and current antidepressant therapy is largely based upon boosting 5-HT neurotransmission by inhibiting biogenic amine reuptake (Moller and Volz, 1996). We have used rat brain synaptosomes and washed human platelets to test the hypothesis that lamotrigine inhibits biogenic amine uptake in vitro. These in vitro studies are complemented by an examination of the effect of lamotrigine in the *p*-chloroamphetamine-induced 5-HT behavioural syndrome in rats (Tricklebank, 1985; Adell et al., 1989; Hutson and Curzon, 1989). Attenuation of the syndrome is a recognised marker for inhibition of 5-HT uptake in vivo (Fuller, 1980; Fuller and Snoddy, 1986).

2. Materials and methods

2.1. Washed platelets

Whole human blood was obtained from human volunteers and platelets isolated by centrifugation, washed, and

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then resuspended in cold (4°C) HEPES buffer (pH 7.4) consisting of (in mM): HEPES, 5.0; NaCl, 140; KCl, 2.82; KH_2PO_4, 0.75; $NaHCO_3$, 5.5; $CaCl_2$, 1.0; $MgSO_4$, 0.5; glucose, 5.1. Platelet counts were adjusted to about 300 000/μl. A total of 10 μM pargyline was added to inhibit monoamine oxidase activity.

2.2. Synaptosomes

Adult male Lister hooded rat cortex (5-HT and noradrenaline uptake) or striatum (dopamine uptake) was dissected out, homogenised in 0.32 M sucrose solution, and synaptosomes isolated by centrifugation before being gently suspended in cold (4°C) pre-gassed (5% CO_2, 95% O_2) Krebs solution containing (in mM): NaCl, 115; KCl, 4.97; KH_2PO_4, 1.2; $NaHCO_3$, 5.5; $CaCl_2$, 1.0; $MgSO_4$, 1.22; glucose, 11.1; pargyline, 0.01. The protein concentration of the crude synaptosomal preparation, as determined by the method of Bradford (1976) with bovine serum albumin as a standard, was in the range of 0.2–0.5 mg/ml. Killing of animals conformed with Home Office regulations as outlined in the Animals (Scientific Procedures) Act, 1986.

2.3. Biogenic amine uptake

Test compounds (10 μl volumes) were added to 800 μl aliquots of either [^{3}H]5-HT (final concentration 20 nM unless otherwise stated), [^{3}H]noradrenaline (50 nM), or [^{3}H]dopamine (20 nM). Uptake was initiated by the addition of 190 μl of either the platelet or synaptosome preparation and incubated for 10 min at 37°C. Uptake was terminated by rapid filtration through pre-wet Whatman GF/B filter paper followed by three washes of ice-cold buffer using a Brandel Harvester. The radioactivity of the filter discs was assessed by liquid scintillation counting. Non-specific uptake was determined, and subsequently subtracted from all other counts, by adding 100 μM 'cold' monoamine to the reaction buffer. Data points represent the mean ± S.E.M. of at least four different assays. Within assays, determinations were performed in triplicate and expressed as a percentage of within-assay controls (also performed in triplicate). IC_{50}s were generated by calculating the geometric mean (number (n) and 95% confidence interval (CI_{95}) indicated in parentheses) of values estimated by fitting a sigmoidal model of the following form using a non-linear curve fit based on the algorithm of Marquardt (1963) for each test compound in each individual assay (not shown) with the assumption that uptake would be depressed to non-specific levels at infinitely high concentrations:

$$y = \frac{(a-d)}{1+(x/c)^b} + d$$

where, y = raw counts; x = concentration of compound; a = lower asymptote; d = upper asymptote; b = Hill slope; $c = IC_{50}$.

2.4. 5-HT behavioural syndrome

This was induced in adult male Lister hooded rats by administering (i.p.) a standard submaximal dose (10 mg/kg) of *p*-chloroamphetamine. Beginning 30 min later, animals were assessed for the presence (score 1) or absence (score 0) of the following characteristic components of the 5-HT behavioural syndrome (Tricklebank, 1985): tremor, forepaw treading, head weaving, and hind limb abduction, at 10 min intervals for 1 h. The total score for each animal was therefore in the range of 0–6 for each of the four components of the syndrome; the medians and interquartile ranges were calculated. Vehicle, the selective 5-HT reuptake inhibitor fluoxetine (3 and 10 mg/kg), or lamotrigine (20 mg/kg) were administered (i.p.), respectively, 30, 30, or 90 min before the *p*-chloroamphetamine. Modulation of the syndrome was deemed significant when $P < 0.05$ (tested using an unpaired non-parametric two-sided Mann–Whitney *U*-test).

2.5. Materials

Lamotrigine was synthesised by Glaxo Wellcome. [^{3}H]5-HT, [^{3}H]noradrenaline and [^{3}H]dopamine from were obtained from Amersham, UK; GBR-12909 dihydrochlo-

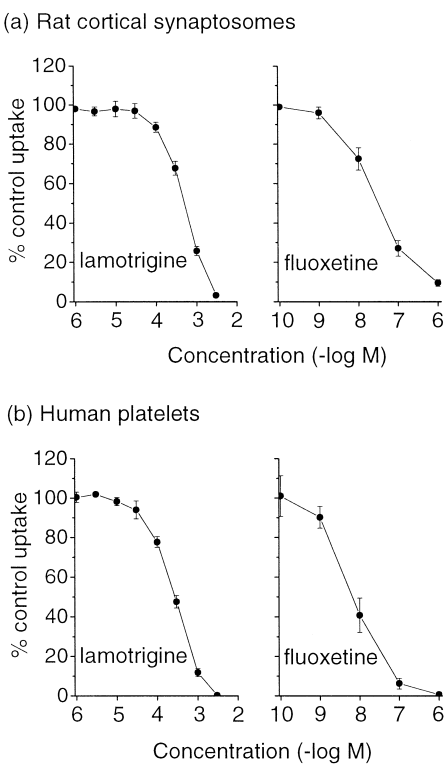

Fig. 1. Lamotrigine inhibits 5-HT uptake in rat and human tissues. Concentration–inhibition curves for lamotrigine and fluoxetine on 5-HT uptake in (a) rat cortical synaptosomes and (b) human platelets.

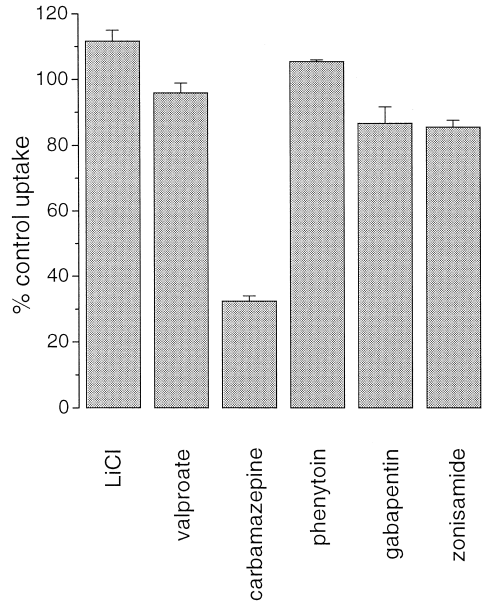

Fig. 2. Effect of a 1 mM concentration of LiCl, sodium valproate, carbamazepine, phenytoin, gabapentin and zonisamide on 5-HT uptake in rat cortical synaptosomes.

ride and nomifensine maleate from Research Biochemicals; fluoxetine hydrochloride from Tocris Cookson, UK and the remaining chemicals from Sigma.

3. Results

3.1. Lamotrigine inhibits 5-HT uptake in rat and human tissues in vitro

Lamotrigine inhibited 5-HT uptake by both rat cortical synaptosomes (Fig. 1a) and human platelets (Fig. 1b) in a concentration-dependent manner with IC_{50}s of 474 μM ($n = 6$, CI_{95} 380 to 589 μM) and 240 μM ($n = 4$, CI_{95} 114 to 502 μM), respectively. At the highest concentration tested (3 mM) 5-HT uptake was effectively abolished. As a positive control, the selective 5-HT reuptake inhibitor fluoxetine was also shown to inhibit 5-HT uptake with IC_{50}s of 22 ($n = 4$, CI_{95} 13 to 39 nM) and 7.3 nM ($n = 4$, CI_{95} 3.8 to 14.2 nM) in synaptosomes (Fig. 1a) and platelets (Fig. 1b), respectively.

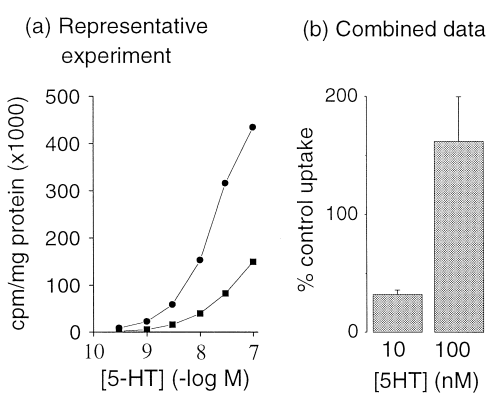

Fig. 3. Inhibition of 5-HT uptake by lamotrigine is at least partially reversible by increasing substrate concentrations. (a) Substrate concentration response curves for 5-HT uptake by rat cortical synaptosomes in the absence (control) and presence of 1 mM lamotrigine—representative experiment. (b) The reduction in 5-HT uptake by rat cortical synaptosomes from control (substrate concentration = 10 nM) levels by 1 mM lamotrigine is reversed by a 10-fold increase in substrate concentration.

3.2. Effect of some standard anticonvulsants and lithium on 5-HT uptake

Carbamazepine (1 mM) was found consistently to reduce control 5-HT uptake into rat cortical synaptosomes whereas LiCl, sodium valproate, phenytoin, gabapentin, and zonisamide exhibited little or no inhibitory activity at this concentration (Fig. 2). Similarly, 5-HT uptake by human platelets incubated in the presence of 1 mM carbamazepine was reduced to 29 ± 8.7% of control values

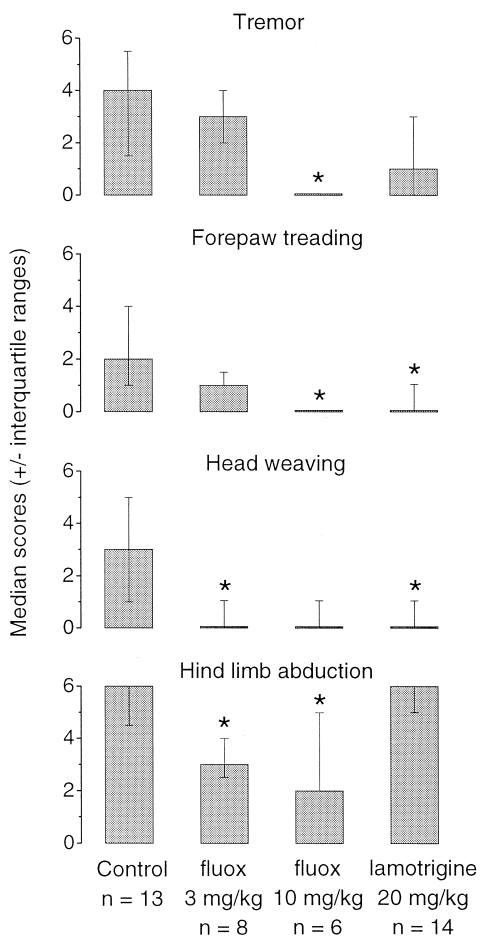

Fig. 4. Effect of lamotrigine and fluoxetine (fluox) on the tremor, forepaw treading, head weaving and hind limb abduction components of the *p*-chloroamphetamine-induced 5-HT behavioural syndrome in rats. ∗ $P <$ 0.05.

whereas uptake in the presence of 1 mM sodium valproate or phenytoin was unchanged (108 ± 3.8%, and 83 ± 7.6% of control values, respectively).

3.3. Effect of tetrodotoxin on 5-HT uptake

In order to determine if the inhibition of 5-HT uptake by lamotrigine may have been a consequence of its well characterised activity at Na^+ channels, we investigated the effect on 5-HT uptake of incubating synaptosomes with the standard Na^+ channel blocker tetrodotoxin (1 μM). 5-HT uptake in the presence of tetrodotoxin was 107 ± 2.6% of control demonstrating that transport of this monoamine is not directly linked to Na^+ channel activity.

3.4. Effect of increasing substrate concentration on inhibition of 5-HT by lamotrigine

The representative experiment illustrated in Fig. 3a demonstrates that 5-HT uptake by rat cortical synaptosomes was found to be dependent upon the concentration of substrate both in the presence and absence of 1 mM lamotrigine. Thus, the reduction in the uptake of label caused by 1 mM lamotrigine incubated in the presence of 10 nM 5-HT was reversed by increasing the substrate concentration 10-fold (Fig. 3b). It was not clear from the range of substrate concentrations used in this study whether the inhibitory effect of lamotrigine was fully reversible.

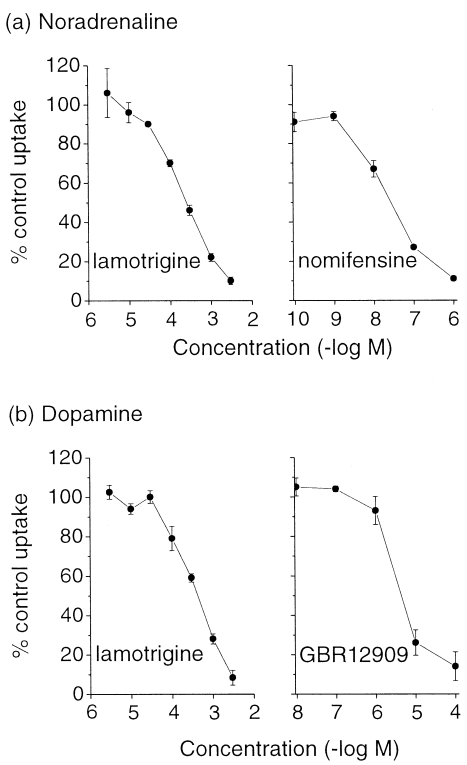

Fig. 5. Lamotrigine inhibits the uptake of noradrenaline and dopamine. Concentration–inhibition curves for (a) lamotrigine and nomifensine on noradrenaline uptake in rat cortical synaptosomes and (b) lamotrigine and GBR12909 on dopamine uptake in rat striatal synaptosomes.

3.5. Lamotrigine inhibits certain components of the p-chloroamphetamine-induced behavioural syndrome in rats

p-Chloroamphetamine induced the tremor, forepaw treading, head weaving, and hind limb abduction components of the 5-HT syndrome in rats; in its absence, none was observed. Lamotrigine (20 mg/kg) significantly reduced the median scores for forepaw treading and head weaving and non-significantly reduced tremor (Fig. 4). The selective 5-HT reuptake inhibitor fluoxetine (3 or 10 mg/kg) significantly reduced the severity of all four components of the syndrome.

3.6. Lamotrigine inhibits noradrenaline and dopamine uptake

Noradrenaline uptake by rat cortical synaptosomes was inhibited by lamotrigine in a concentration-dependent manner (Fig. 5a, IC_{50} 239 μM, $n = 4$, CI_{95} 215 to 266 μM). As a positive control, nomifensine also inhibited noradrenaline uptake (Fig. 5a, IC_{50} 22 nM, $n = 4$, CI_{95} 20 to 23 μM). Similarly, lamotrigine and the standard blocker of dopamine transport GBR12909 inhibited uptake by rat striatal synaptosomes (Fig. 5b), with IC_{50}s of 322 μM ($n = 4$, CI_{95} 209 to 526 μM) and 5.4 μM ($n = 4$, CI_{95} 3.0 to 9.6 μM), respectively.

4. Discussion

These data indicate that lamotrigine is an inhibitor of 5-HT uptake in both human and rat tissues in vitro. Although the active concentration range (IC_{50}s 200–500 μM) was four orders of magnitude greater than the selective 5-HT uptake inhibitor fluoxetine, it does correspond well with that observed for the inhibition of Na^+ currents in Chinese hamster ovary cells transfected with human type IIA Na^+ channels (Xie et al., 1995). The inability of tetrodotoxin to modulate 5-HT uptake suggests that Na^+ channel blockade is unlikely to mediate the effects of lamotrigine on 5-HT uptake. Furthermore, the dependence of 5-HT uptake on substrate concentration in the presence of 1 mM lamotrigine argues against a non-specific effect. Thus, the inhibition of 5-HT uptake most likely reflects an affinity for the compound at the carrier molecule targeted by the selective 5-HT reuptake inhibitor antidepressants (Moller and Volz, 1996). The attenuation of the *p*-chloroamphetamine-induced behavioural syndrome is consistent with the inhibition of the 5-HT transporter in vivo (see below). The inhibition of synaptosomal noradrenaline and dopamine uptake with broadly similar potencies to that of 5-HT inhibition demonstrates a lack of selectivity between biogenic amine transporters.

In addition to lamotrigine, we tested several standard anticonvulsant drugs (carbamazepine, sodium valproate, phenytoin, gabapentin, and zonisamide) and Li^+ for an

effect on 5-HT uptake. In vivo microdialysis has revealed that anticonvulsant doses of carbamazepine increase extracellular 5-HT levels in the hippocampi of genetically epilepsy prone and outbred rats (Yan et al., 1992; Kaneko et al., 1993; Dailey et al., 1997a,b), a finding reflected in the concentration-dependent inhibition of 5-HT uptake seen in vitro in the present studies. In contrast, in the present studies we could find no evidence of sodium valproate or zonisamide, which are also reported to raise extracellular 5-HT levels in the rat brain (Whitton and Fowler, 1991; Biggs et al., 1992; Okada et al., 1992; Kaneko et al., 1993), modulating 5-HT uptake in vitro. Since lithium, carbamazepine, sodium valproate, and zonisamide all possess anti-manic activity in bipolar patients (Post et al., 1996) and yet only carbamazepine inhibited 5-HT uptake, there appeared to be no correlation between these two phenomena. Lamotrigine differs from existing therapies for bipolar illness in that acute administration is effective against both the manic and depressive phases of the disorder (Calabrese et al., 1996; Corn et al., 1996). It is, therefore, tempting to speculate that the efficacy of acutely administered lamotrigine against bipolar depression is a consequence of the inhibition of reuptake of biogenic amines. However, the relatively poor control of acute bipolar depression offered by carbamazepine, which inhibited 5-HT uptake with a similar potency to lamotrigine, suggests that there must be other contributing factors.

Na^+/K^+ ATPase-dependent transport is responsible for removing 5-HT from the extracellular space and for delivering *p*-chloroamphetamine into serotinergic nerve terminals (Fuller, 1980) from where it causes the Ca^{2+}-independent release of 5-HT from non-vesicular pools (Kuhn et al., 1985). In the short-term, there is a strong temporal correlation between elevations in extracellular 5-HT concentrations and the development of the *p*-chloroamphetamine-induced behavioural syndrome (Hutson and Curzon, 1989) which is believed to be mediated by 5-HT receptor activation (Tricklebank, 1985). In the longer term, *p*-chloroamphetamine eventually results in the depletion of brain 5-HT concentrations (Fuller, 1980). In vivo, inhibition of the 5-HT transporter prevents the accumulation of *p*-chloroamphetamine in nerve terminals and thereby prevents the chain of events which culminate in the 5-HT behavioural syndrome. Prior administration of lamotrigine was observed to abolish the forepaw treading and head weaving components of the *p*-chloroamphetamine-induced 5-HT syndrome and to ameliorate the tremor. Apart from hind limb abduction remaining unaffected, the pattern and extent of the behavioural effects of 20 mg/kg lamotrigine were broadly comparable to those of fluoxetine (3 and 10 mg/kg), suggesting that the inhibition of the 5-HT transporter observed in rat and human tissues in vitro also occurred in vivo. The concentration of lamotrigine employed in these studies was high but within the range used to inhibit seizures in rats (Miller et al., 1986; Wheatley and Miller, 1989; O'Donnell and Miller, 1991). It remains unclear, however, whether clinically effective doses of lamotrigine will be sufficient to modulate 5-HT uptake in the brains of patients and thereby contribute to the psychotropic effects of the drug.

Finally, Dailey et al. (1996) have proposed that 5-HT may contribute to the mechanism(s) of action of some anticonvulsant drugs, including carbamazepine. The brains of genetically epilepsy prone rats have widespread deficits in 5-HT concentrations due to a reduction in $V_{(max)}$ of 5-HT uptake (Statnick et al., 1996). Carbamazepine and the selective inhibitors of 5-HT uptake fluoxetine and sertraline all produce dose-dependent reductions in the intensity of audiogenic seizures which correlate with increased extracellular 5-HT concentrations (Dailey et al., 1992; Yan et al., 1994, 1995). This raises the possibility that inhibition of 5-HT uptake may contribute to the anticonvulsant action of lamotrigine.

5. Conclusions

These data demonstrate that lamotrigine inhibits 5-HT uptake in both rat and human tissues in vitro and modulates the *p*-chloroamphetamine-induced 5-HT behavioural syndrome in rats. Uptake inhibition is non-selective since noradrenaline and dopamine uptake is also inhibited in vitro. These effects probably reflect affinity for lamotrigine at biogenic amine carriers. However, it remains unclear whether at clinically effective doses these effects contribute to the efficacy of lamotrigine in bipolar illness.

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