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Antidepressant-like effect of lamotrigine in the mouse forced swimming test: Evidence for the involvement of the noradrenergic system

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Abstract

Lamotrigine is an anticonvulsant drug that is also effective in the treatment of mood disorders, especially bipolar disorder. However, few studies have been conducted in animal models of depression to evaluate its mechanism of action. The present study investigated the effect of lamotrigine in the forced swimming test in mice and the involvement of the noradrenergic system in this effect. Lamotrigine (20–30 mg/kg, i.p.) decreased the immobility time in the forced swimming test and the number of crossings in the open-field test. In addition, the pretreatment of mice with the inhibitor of the enzyme tyrosine hydroxylase, α-methyl-*p*-tyrosine (100 or 250 mg/kg), prevented the antidepressant-like effect of lamotrigine (30 mg/kg, i.p.) in the forced swimming test. Besides that, the pretreatment of mice with prazosin (1 mg/kg, i.p., an α_1-adrenoceptor antagonist) or yohimbine (1 mg/kg, i.p., an α_2-adrenoceptor antagonist) also prevented the anti-immobility effect of lamotrigine (30 mg/kg, i.p.). Moreover, the administration of subeffective doses of phenylephrine (5 mg/kg, i.p., an α_1-adrenoceptor agonist) or clonidine (0.06 mg/kg, i.p., an α_2-adrenoceptor agonist) was able to potentiate the action of a subeffective dose of lamotrigine (10 mg/kg, i.p.) in the forced swimming test. Thus, the present study suggests that the antidepressant-like effect of lamotrigine in the forced swimming test is related to the noradrenergic system, likely due to an activation of α_1- and α_2-postsynaptic adrenoceptors.

Keywords: Lamotrigine; Noradrenergic system; Forced swimming test; Antidepressant

1. Introduction

Lamotrigine [3,5-diamino-6(2,3-dichlorophenyl)-1,2,4-triazine] is an anticonvulsant agent used primarily in the treatment of generalized and partial seizures (Kwan and Brodie, 2001; Bazil, 2002). The best characterized actions of lamotrigine are associated with the inhibition of voltage gated sodium channels, inhibition of the release of excitatory amino acids such as glutamate and aspartate, and calcium-channel blockade, mechanisms that are believed to mediate its seizure suppressing activity (Cheung et al., 1992; Xie et al., 1995; Cunningham and Jones, 2000).

In common with other anticonvulsant drugs, including sodium valproate and carbamazepine, lamotrigine exhibits mood-stabilizing properties (Bowden, 1998; Post et al., 1998). A series of randomized trials have shown that lamotrigine was effective for the treatment of patients with bipolar I disorder who were currently experiencing an episode of major depression (Calabrese et al., 1999a). In addition, it has a low potential for inducing the switch to mania, a risk that is often associated with the use of conventional antidepressants (Calabrese et al., 1999b, 2001). Interestingly, several studies have suggested that lamotrigine might have antidepressant properties in unipolar depression (Frye et al., 2000; Barbee and Jamhour, 2002; Rocha and Hara, 2003) and may accelerate the onset of action when given in combination with typical antidepressants such as fluoxetine and paroxetine (Normann et al., 2002; Barbosa et al., 2003). Southam et al.

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(1998) reported that the synaptosomal uptake of serotonin, noradrenaline and dopamine in rat brain was inhibited by lamotrigine, suggesting that its efficacy against bipolar depression could be a consequence of the inhibition of monoamines reuptake.

Recently, some preclinical work with mice (Bourin et al., 2005) and rats (Consoni et al., 2006) have reported that lamotrigine exhibits antidepressant-like effects in the forced swimming test, a widely used model for assessing pharmacological antidepressant activity (Cryan et al., 2002). These effects seem to be mediated through an interaction with the serotonergic (Bourin et al., 2005; Consoni et al., 2006) and noradrenergic systems (Consoni et al., 2006). The suggestion that the effect of lamotrigine is due to an interaction with the noradrenergic system was given by the finding that it produced a similar result in the modified forced swimming test in rats as compared to the one produced by nortriptyline, a noradrenaline reuptake inhibitor (Consoni et al., 2006).

Several experimental and clinical studies indicate that the noradrenergic system is widely implicated in the pathophysiology of depression (Frazer, 2000; Nutt, 2006). Drugs affecting the noradrenergic neurotransmission, such as those that inhibit noradrenaline reuptake at nerve terminals, or its metabolism (monoamine oxidase inhibitors), are effective in depression. Also, early studies have shown that the depletion of monoamines with reserpine leads to depressogenic effects in individuals already vulnerable to affective illness (Goodwin and Bunney, 1971).

Taking into account that only few studies have been conducted with lamotrigine in animal models to clarify its mechanism of antidepressant action, the present work aimed to extend literature data by further investigating the involvement of the noradrenergic system in the antidepressant-like effect of lamotrigine in the forced swimming test in mice.

2. Materials and methods

2.1. Animals

Female Swiss mice (30–40 g) were maintained at 22–27 °C with free access to water and food, under a 12:12 h light:dark cycle (lights on at 7:00 h). Twenty mice were housed per cage. The cages were placed in the experimental room 24 h before the test for acclimatization. All manipulations were carried out between 9:00 and 17:00 h, with each animal used only once. All procedures in this study were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize animal suffering and the number of animals used.

2.2. Drugs and treatment

The following drugs were used: clonidine, lamotrigine, α-methyl-*p*-tyrosine, phenylephrine, prazosin, yohimbine (Sigma Chemical Co, USA). Lamotrigine and α-methyl-*p*-tyrosine were dissolved in saline with 10% Tween 80, whereas all the other drugs were dissolved in isotonic saline solution (NaCl 0.9%) immediately before use. Appropriate vehicle-treated groups were also assessed simultaneously. All drugs were administered by intraperitoneal (i.p.) route, in a volume of 10 ml/kg body weight.

To test the hypothesis that the antidepressant-like effect of lamotrigine is mediated through an interaction with the noradrenergic system, animals were pretreated with α-methyl-*p*-tyrosine (100 mg/kg or 250 mg/kg, an inhibitor of the enzyme tyrosine hydroxylase) 4 h before the administration of lamotrigine (30 mg/kg, i.p.). After 30 min the animals were tested in the forced swimming test or in the open-field test.

In a separate series of experiments, the animals were pretreated with prazosin (1 mg/kg, i.p., an α_1-adrenoceptor antagonist) or yohimbine (1 mg/kg, i.p., an α_2-adrenoceptor antagonist) 30 min before the administration of lamotrigine (30 mg/kg, i.p.) and submitted to the forced swimming test 30 min later.

Alternatively, animals were pretreated with subeffective doses of phenylephrine (5 mg/kg, i.p., an α_1-adrenoceptor agonist) or clonidine (0.06 mg/kg, i.p., an α_2-adrenoceptor agonist) 20 min before the administration of lamotrigine (30 mg/kg, i.p), and 30 min later the forced swimming test and the open-field test were carried out.

Doses and administration schedule were chosen on the basis of experiments previously performed in our laboratory and the literature data confirm the selectivity and efficacy of the above-mentioned treatments at the concentrations used (Asakura et al., 1994; Bourin et al., 1996; Zomkowski et al., 2002; Mantovani et al., 2006; Machado et al., 2007).

2.3. Forced swimming test

Mice were individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25 ± 1 °C; the total duration of immobility was recorded during the last 4 min of the 6-min period. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. A decrease in the duration of immobility is indicative of an antidepressant-like effect (Porsolt et al., 1977).

2.4. Open-field test

The ambulatory behavior was assessed in an open-field test as described previously (Rodrigues et al., 1996). The apparatus consisted of a wooden box measuring 40 × 60 × 50 cm. The floor of the arena was divided into 12 equal squares. The number of squares crossed with all paws (crossing) was counted in a 6-min session.

2.5. Statistical analysis

All experimental results are given as the mean ± S.E.M. Comparisons between experimental and control groups were performed by one-way or two-way ANOVA followed by