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Lamotrigine treatment reverses depressive-like behavior and alters BDNF levels in the brains of maternally deprived adult rats

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ABSTRACT

Lamotrigine is an anticonvulsant and has an antiglutamatergic action, which may contribute to its antidepressant effects, since glutamate has been linked to depression. The purpose of the present study was to investigate the behavioral and molecular effects of lamotrigine treatment in maternally deprived rats. To this aim, deprived and non-deprived male rats were treated with lamotrigine (20 mg/kg) once a day for 14 days during their adult phase. Their behavior was then assessed in the forced swimming and open field tests. In addition to this, the BDNF and NGF levels were assessed in the prefrontal cortex, hippocampus and amygdala. In the course of this study we demonstrated that maternally deprived rats treated with saline and lamotrigine showed an increase in their immobility time and a decrease in the climbing and swimming times when compared with non-deprived rats treated with saline alone. Treatment with lamotrigine reversed the increase in the immobility time in the deprived rats. The BDNF levels were decreased in the amygdala in deprived rats treated with saline, and treatment with lamotrigine reversed this decrease. The NGF levels were decreased in the hippocampus in deprived rats treated with saline, but treatment with lamotrigine did not reverse this decrease. In conclusion, lamotrigine showed antidepressant effects in the forced swimming test, and it presented positive effects on the BDNF protein levels in the amygdala of maternally deprived rats.

1. Introduction

Depression is one of the most prevalent and costly psychopathologies and is globally accepted as a leading cause of morbidity and mortality (Pacher and Ungvari, 2001). There are many symptoms that are included in major depression, but the more frequent symptoms are: depressed mood, anhedonia, irritability, difficulties in concentrating, and abnormalities in appetite and sleep (Nestler et al., 2002).

Preclinical studies have provided direct evidence that early life stress leads to a heightened responsiveness to stress and alterations in the hypothalamic–pituitary–adrenal system throughout the lifespan (Heim and Nemeroff, 2001). Among the paradigms used to study early adverse life events, long maternal separation in rodents mimics the early life neglect/loss of parents in humans and has been presented as one of the most potent natural stressors during development. Maternal separation has been developed to examine the consequences of early adverse experiences on behavior and neurobiology. This model has been described as a model of vulnerability to drug dependence, anxiety, stress-induced illness and depression (Hall, 1998; Francis et al., 1999).

The treatment of depression is based on the monoaminergic system. Classic antidepressants act on the modulation of this system by inhibiting the reuptake of neurotransmitters, increasing their concentrations in the synaptic cleft (Schmidt et al., 2008). The major shortcomings in treating these disorders with antidepressants are that the therapeutic response develops slowly (over 3–4 wks), there are often side effects and there are a significant percentage (30%) of non-responders (Wong and Licinio, 2001). Thus, it is necessary to identify and develop alternative therapeutic options for the treatment of major depression.

Lamotrigine is an anticonvulsant belonging to the class of inhibitors that act on the sodium channels. It is one of the most widely used drugs in bipolar disorder and is widely used to control the depressive symptoms associated with bipolar disorder (Calabrese et al., 2003). Also, its effectiveness in the treatment of depression was highlighted in a randomized, double blind study (Thomas et al., 2010). The anticonvulsant action of lamotrigine is facilitated by reducing the neuronal excitability through the inhibition of the sodium channels, preventing their return

Abbreviations: BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate.

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to a resting state and thus decreasing the number of potential actions. This effect on the sodium channels results in a decreased release of glutamate (Waldmeier et al., 1996), which is involved in the pathogenesis of depression. The effect of lamotrigine on the 5-HT1A receptors in healthy human males is measured using body temperature and plasma cortisol as an index of 5-HT1A receptor function (Shiah et al., 1998). In vitro, using human platelets and rat brain synaptosomes, lamotrigine inhibits the uptake of 5-HT, dopamine and noredrenaline in a manner that appeared to be independent of any effect on the sodium channels (Southam et al., 1998). Lamotrigine does not exhibit a high affinity in binding to the following neurotransmitter receptors: adenosine A1 and A2; adrenergic α1, α2, and β; dopamine D1 and D2; γ-aminobutyric acid (GABA) A and B; histamine H1; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT2 (Leach et al., 1991).

The antiglutamatergic action of lamotrigine may also contribute to its antidepressant effect (Ketter and Wang, 2003), since glutamate has been linked to depression (Tokita et al., 2011), and that glutamate receptor antagonists like N-methyl-aspartate (NMDA) have shown antidepressant-like effects in animal models of depression (Réus et al., 2010, 2011a).

The precise molecular mechanisms responsible for the antidepressant action of lamotrigine are still not fully understood. However, evidence suggests that a variety of intracellular pathways and signal transduction cascades are involved in both the pathophysiology and treatment of depression (Coyle and Duman, 2003; Duman, 1998; Duman et al., 1997; Vaidya et al., 2007). Many antidepressant drugs acutely increase monoamine levels, but the requirement for chronic treatment has led to the hypothesis that long-term adaptations are necessary for the therapeutic actions of these treatments (Duman et al., 1994). Several studies have pointed to the role of brain-derived-neurotrophic factor (BDNF) and the nerve growth factor (NGF) in major depression. Decreased levels of BDNF and NGF have been shown in animal models of depression and humans with depression (Karege et al., 2005). Conversely, administration of antidepressant drugs increases BDNF and NGF expression (Nibuya et al., 1995).

Studies linking the effects of lamotrigine on behavior and neurotrophin levels in the brain tissue of maternally deprived rats have not been characterized. So, the present study was aimed to investigate the behavioral and physiological effects of the administration of lamotrigine on maternal deprivation in rats. The behavioral effects were evaluated in the open field test and forced swimming tests. Additionally, BDNF and NGF protein levels were assessed in the prefrontal cortex, hippocampus and amygdala.

2. Material and methods

2.1. Animals

Pregnant female Wistar rats (age of 3 months, weight of 250–280 g) were obtained from the UNESC (Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil) breeding colony. All animals were maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.). The environment temperature (±22 °C) was kept constant. Pregnant females were individually housed with sawdust bedding and ad libitum access to food and water. Litters were culled to eight pups per dam, four males and four females. The day of delivery was marked as day zero, and on post natal day 1 (PND-1) a maternal deprivation protocol was applied to 50% of the male pups from days 1–10 after birth; the other males were used as controls. The animals were weaned at the age of 21 days, and housed in regular cages, with 5 animals to a cage. Females were donated to the UNESC colony for other research purposes. The males were used in the present experiments. There were two experimental groups: (1) control (non-deprived), which received no treatment whatsoever; (2) deprived, which were submitted to maternal deprivation as described. All experimental procedures involving animals were performed in accordance with the NIH Guide for the Care and Usage of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care and with approval by local Ethics Committee under protocol number 01/2011.

2.2. Maternal deprivation protocol

Pregnant Female Wistar rats were maintained in individual cages until the delivery day. Deprivation was carried out for 180 min a day from PND-01 to PND-10 according to previous studies (Réus et al., 2001b; Mello, 2009). The deprivation protocol consisted of: removing the mother from the residence cage and taking her to another room. Pups were maintained in their home cages (grouped in the nest in the presence of maternal odor). We prefer this maternal deprivation protocol because it does not require manipulation of the pups (Mello, 2009; Kosten et al., 2007). At the end of each daily deprivation session, the mothers were returned to their home cages; this procedure was carried out during the light part of the cycle, between 8:00 a.m. and 2:00 p.m. Control rats remained in their resident cages together with their mothers throughout. Only after PND-11 were the cages cleaned normally again, according to the standard laboratory routine. On PND-21 the animals were weaned, and the males were maintained in groups of 4, in 50×25×40 cm plastic cages with a stainless steel lid, having food and water available ad libitum, as per all the other animals in our animal housing facility.

2.3. Drugs and treatment

Lamotrigine was obtained from Sigma (Brazil) and a dose of 20 mg/kg was injected intraperitoneally once a day over 14 days, after the animals had reached the age of 3 months. The dose was based on previous studies (Kaster et al., 2007). The treatments were administrated in a volume of 1 ml/kg. Lamotrigine was diluted in a saline solution (NaCl 0.9% w/v) and control groups received saline solution alone. Adult animals were randomly divided into deprived and non-deprived groups before the start of treatment. To develop this study we employed 60 animals (n = 15 each) separated in four groups, as follows: (1) non-deprived + saline; (2) non-deprived + lamotrigine; (3) deprived + saline; (4) deprived + lamotrigine. The behavior of the animals was evaluated 1 h after the administration of the each injection.

2.4. Open-field test

This apparatus consists of a 45×60 cm brown plywood arena surrounded by 50 cm high wooden walls and containing a frontal glass wall. The floor of the open field was divided into nine rectangles (15×20 cm each) via black lines. Animals were gently placed on the left rear quadrant, and left to explore the arena. On the 12th day of chronic treatment, the rats were exposed to the open-field apparatus. The number of horizontal (crossings) and vertical (rearings) activities performed by each rat during the 5 min observation period were counted by an expert observer, in order to assess any possible effects on spontaneous locomotor activity.

2.5. Forced swimming test

The forced swimming test was conducted according to previous reports (Detke et al., 1995; Garcia et al., 2008a, 2008b; Porsolt et al., 1977). The test involves two individual exposures to a cylindrical tank filled with water, in which the rats cannot touch the bottom of the tank or escape. The tank is made of transparent Plexiglas, 80 cm tall, 30 cm in diameter, and filled with water (22–23 °C) to a depth of 40 cm. On the 13th day of chronic treatment with lamotrigine, 1 h after the administration of the drug treatment, the rats were individually placed in the cylinder containing water for 15 min (pre-test session). On the 14th day, the rats received the last intraperitoneal

drug treatment, and after 1 h, they were again subjected to the forced swimming test for a 5 min session (test session) and the immobility, climbing and swimming time of the rats were recorded in seconds. After the conclusion of the behavioral tests, all rats were killed by decapitation, and the skulls were immediately removed. The prefrontal cortex, hippocampus and amygdala were quickly isolated by hand dissection using a magnifying glass and a thin brush, the dissection being based on the histological distinctions described by Paxinos and Watson (1986).

2.6. Neurotrophins measurement

The BDNF and NGF levels in the prefrontal cortex, hippocampus and amygdala were measured by sandwich-ELISA, according to the manufacturer's instructions (Chemicon, USA for BDNF and Millipore, USA & Canada for NGF). Briefly, the rat's prefrontal cortex, hippocampus and amygdala were homogenized in a phosphate buffer solution (PBS) with a protease inhibitor cocktail (Sigma). Microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:2 in sample diluent with the standard curve ranging from 7.8 to 500 pg/ml of BNDF and NGF. The plates were then washed with sample diluent and a monoclonal anti-BNDF for a total of four times, and an anti-NGF rabbit antibody (diluted 1:1000 in sample diluent) was added to each well and incubated for 3 h at room temperature. After washing, a peroxidase conjugated anti-rabbit antibody (diluted 1:1000) was added to each well and incubated at room temperature for 1 h. After the addition of the streptavidin–enzyme, substrate and stop solutions, the amount of each neurotrophin was determined by absorbance at 450 nm. The standard curve demonstrates a direct relationship between Optical Density (OD) and the concentration. Total protein was measured utilizing Lowry's method using bovine serum albumin as a standard, as previously described by Lowry et al. (1951).

2.7. Statistical analysis

All data is presented as mean ± S.E.M. Differences among experimental groups in the forced swimming and open field tests, and in the assessment of BDNF and NGF levels were determined by one-way ANOVA, followed by the Tukey *post-hoc* test when ANOVA was significant; p values < 0.05 were considered to be statistical significant.

3. Results

The effects of the administration of lamotrigine on immobility, climbing and swimming times are illustrated in Fig. 1A. In deprived rats treated with saline we observed an increase in the immobility time ($p<0.001$; Fig. 1A) and a decrease in the climbing and swimming time ($p<0.001$; Fig. 1A), compared with non-deprived rats treated with saline. The treatment with lamotrigine reversed the increase in the immobility time ($p<0.001$; Fig. 1A) in deprived rats. The non-deprived groups did not differ significantly. Interestingly, in the open-field test, the treatment with lamotrigine did not modify the number of crossings ($p=0.78$; Fig. 1B) and rearings ($p=0.51$; Fig. 1B) in any of the groups.

The effects of the administration of lamotrigine on BDNF and NGF levels in the rat's prefrontal cortex, hippocampus and amygdala are shown in Fig. 2. The BDNF levels were decreased in the amygdala ($p<0.021$; Fig. 2A) in deprived rats treated with saline, and treatment with lamotrigine changed this decrease. In the prefrontal cortex ($p=0.97$; Fig. 2A) and hippocampus ($p=0.233$; Fig. 2A), treatment with lamotrigine in rats did not alter the BDNF protein levels. The NGF levels were decreased in the hippocampus ($p<0.05$; Fig. 2B) in deprived rats treated with saline, but treatment with lamotrigine did not alter this decrease. However, NGF protein levels did not alter in the prefrontal cortex ($p=0.192$; Fig. 2B) or the amygdala ($p=0.32$; Fig. 2B).

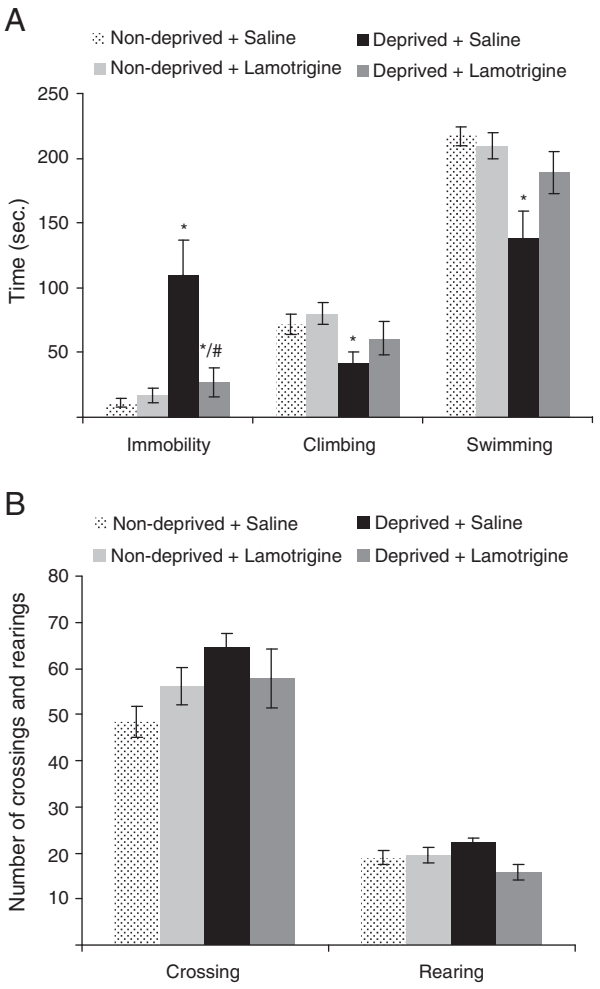

Fig. 1. The effects of the administration of lamotrigine on an animal model of depression on the immobility time, climbing time and swimming time (1A) of rats subjected to the forced swimming test and on the number of crossings and rearings (1B) of rats subjected to the open field test. Bars represent means ± S.E.M. ($n=15–18$). *$p<0.05$ vs. non-deprived + saline; and #$p<0.05$ vs. deprived + saline according to one-way ANOVA followed by Tukey *post-hoc* test.

4. Discussion

Several animal models of depression have been developed. They include models in which the “depressive behavior” is the result of genetic selection or manipulation, or via environmental stressors during development or in adulthood. Maternal deprivation has been developed to study the effects of early adverse experiences on behavior and neurobiology. In particular, maternal separation has been proposed to represent a potential animal model of major depression. During postnatal development, maternal separation induces a response characterized by reduced activity and other depressive-related behaviors (Hennessy et al., 2001). For instance, in adult male rats that have experienced maternal separation, antidepressants can normalize anxiety-like behavior and endocrine stress. Our results showed that in animals deprived, but not treated, we obtained an increase of immobility in the forced swimming test and administration of lamotrigine could reverse this effect. Our results also showed a decrease in the climbing times and swimming times in rats that were maternally deprived but not treated. These effects in the forced swimming test were also demonstrated in other studies which were interpreted accordingly as a depression-like behavior (Aisa et al., 2007; El Khoury et al., 2006; Réus et al., 2001b).

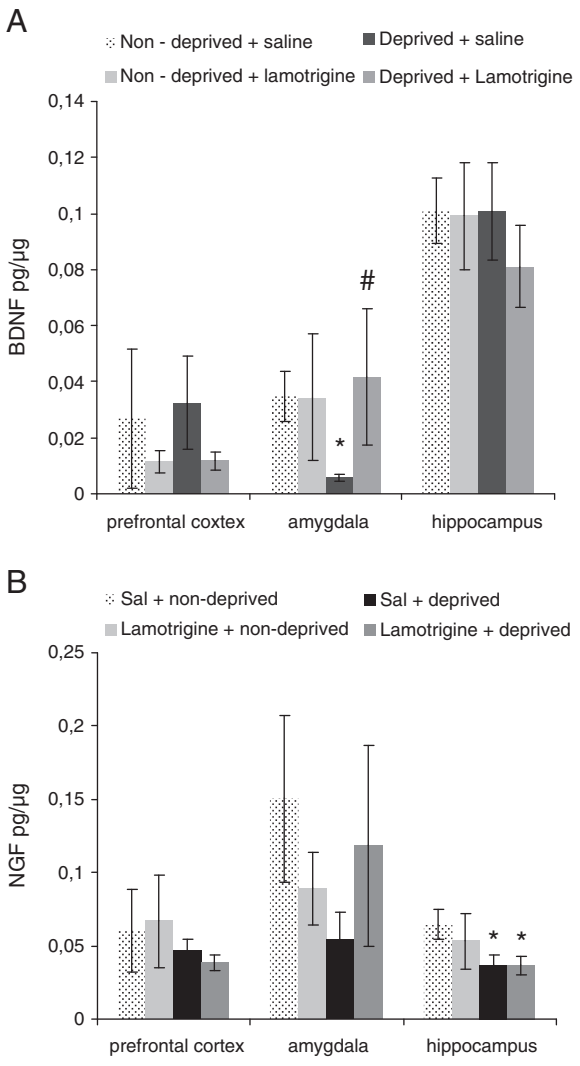

Fig. 2. The effects of the administration of lamotrigine on animal model of depression on the BDNF protein levels (2A) and NGF protein levels (2B) in the prefrontal cortex, hippocampus and amygdala. Bars represent means ± S.E.M. (n = 10). *p<0.05 *vs.* non-deprived + saline; and #p<0.05 vs. deprived + saline according to one-way ANOVA followed by Tukey *post-hoc* test.

The anticonvulsant drug lamotrigine has been shown to produce antidepressant effects in patients with bipolar disorder (Li et al., 2010), but it is already known that lamotrigine presents some antidepressant-like effects. Lamotrigine has demonstrated moderate antidepressant efficacy in the treatment of bipolar and major depressive disorders (Bowden et al., 1999; Calabrese et al., 2001; Calabrese et al., 1999; Goodwin et al., 2008; Vigo and Baldessarini, 2009) without significant side-effects, such as the precipitation of mania (Hu et al., 2010). Our findings show that lamotrigine has reversed the increase in the immobility time in untreated deprived rats, an effect that was also present in a previous study, in which lamotrigine decreased the immobility time in the forced swimming test (Li et al., 2010). The forced swimming test is a measure of the animal's response to chronic antidepressant treatments. These findings emphasize the important antidepressant effect of lamotrigine.

Major depression is associated with reduced volumes in the hippocampus and prefrontal cortex, whereas antidepressant treatments promote several forms of neuronal plasticity, including neurogenesis, synaptogenesis and neuronal maturation in the hippocampus (Karege et al., 2002). Several neurotrophic factors are associated with depression or antidepressant action. An emerging hypothesis proposes that in addition to changes in neurochemical balance, problems in information processing within specific neural networks may play a critical role in the pathophysiology of depression (Chen et al., 2001). Regulation of intracellular messenger cascades mediates the ability of neuronal systems to adapt in response to pharmacological and environmental stimuli. Antidepressants can recover plasticity within intracellular signal transduction pathways (Duman et al., 1997; Vaidya et al., 2007), suggesting that synaptic plasticity improvement is a crucial event underlying antidepressant efficacy.

Recent findings suggest that neurotrophin function might be altered in depression. For example, decreased serum levels of brain-derived neurotrophic factor in patients with major depression (Rao and Rapoport, 2009) and an increased BDNF immunoreactivity in hippocampal BDNF in the postmortem brain of patients treated with antidepressants drugs (Duman, 2004) have been observed.

A potential target of lamotrigine in the brain is the arachidonic acid signaling cascade. Chronic administration of lamotrigine markedly down-regulates arachidonic acid signaling (Garrido et al., 2003). This signaling pathway has been implicated in interfering with transcription of neuronal survival factors, and its down-regulation enhances the expression of BDNF and other neurotrophic factors in the brain (Lindsay, 1994). Studies of neurotrophic factors, particularly BDNF, have been of particular interest and have lead to the neurotrophic hypothesis of depression (Chang et al., 2009). BDNF is the most abundant neurotrophic factor, it promotes the growth and development of immature neurons and enhances the survival and function of adult neurons (Chung et al., 2009).

Besides this effect, lamotrigine has an important role in the regulation of signaling cascades. Consistent with another study (Bowden et al., 1999; Chung et al., 2009), chronic treatment of lamotrigine significantly increased frontal and hippocampal BDNF protein levels in rats, but in contrast to our findings, it demonstrated that the chronic administration of lamotrigine reversed the decrease in BDNF levels only in the amygdala of deprived rats. We cannot explain this discrepancy, but could be related to the type of animal model and duration of treatment. Consistent with our findings, another study showed an increase in the expression of BDNF and its receptor, tyrosine kinase receptor B, in the amygdala after neonatal maternal separation or maternal deprivation (Petrovich et al., 2005). In a previous study (Réus et al., 2011b) we showed that maternal deprivation did not alter the levels of BDNF in the hippocampus and pre-frontal cortex, but increased their levels in amygdala. The amygdala, which is involved in fear and anxiety, plays a role in feeding behavior and reward processing (Levi-Montalcini, 1987; Paton et al., 2006). Thus, it is possible that the change in behavior may be related to differences in levels of BDNF in the amygdala.

NGF was the first trophic factor to be discovered as a target to regulate the survival and maturation of neurons (Cirulli et al., 1998) and a series of in-depth experiments has been created to the study how the mother-infant relationship might affect the NGF in the CNS of neonatal rats. Our results showed a decrease in NGF levels in the hippocampus of animals that were maternally deprived, but not treated. Contrarily to these findings, other studies have shown an increase in NGF expression in the hippocampus, cerebral cortex and hypothalamus in a model of depression (Cirulli et al., 2000; Cirulli et al., 1998). In addition to this, early maternal separation increased the NGF levels in the dorsal and ventral hippocampus (Faure et al., 2006), suggesting that this elevation reflects a compensatory mechanism. However, we have previously shown in a similar study, that maternal deprivation reduced the NGF levels in the hippocampus.

Treatment with lamotrigine did not reverse the levels of NGF protein in the hippocampus of deprived rats. Furthermore, another study has shown that chronic administration of the antidepressant escitalopram decreased the right cortical NGF levels in chronically stressed rats even under the untreated control conditions (Schulte-

Herbrüggen et al., 2009). In rats, treatment with the antidepressant mood stabilizer lithium at various dosages increased NGF level in the hippocampus, amygdala, frontal cortex, and limbic forebrain, whereas NGF in the striatum, midbrain, and hypothalamus remained unchanged (Hellweg et al., 2002). In a mouse model of induced learned helplessness, after the administration of a defined series of foot shocks, stress treatment led to a transient NGF decrease in the frontal cortex after a period of 6 h that was absent in the control mice (Schulte-Herbrüggen et al., 2006). A similar observation was made in rats after threatening treatment with or without painful stimuli, which was followed by a significant reduction of NGF protein in the amygdala and the frontal cortex after a period of 2 h (von Richthofen et al., 2003). In both studies, NGF returned to control levels after a stress-dependent decrease. In addition to this, our studies showed no significant effects in the prefrontal cortex of deprived rats treated with saline, but showed a trend toward decreased levels of NGF in the amygdala in the same group, as already shown in a previous study (Réus et al., 2001b) and that the maternal deprivation reduced the levels of NGF in the amygdala and did not significantly alter levels in the pre-frontal cortex of rats.

Lamotrigine has anticonvulsant action by reducing neuronal excitability through the inhibition of sodium channel voltage dependents in the inactivated state, preventing their return to a resting state and consequently decreasing the number of action potentials. This effect on the sodium channels results in decreased glutamate release (Leach et al., 1986; Waldmeier et al., 1996). In fact, electrophysiological studies in the amygdala (Wang et al., 2002) and in the striatum (Calabrese et al., 1999) showed that lamotrigine reduced excitatory post-synaptic potential mediated by glutamate, an effect reversed when exogenous glutamate was applied, findings consistent with the proposal that lamotrigine had an inhibitory action on glutamate release. Glutamate is involved in the pathogenesis and treatment of depression. Antagonists of NMDA receptors, such as ketamine and memantine presented antidepressant-like effects in rats, and increased the BDNF levels in the hippocampus (Garcia et al., 2008a; Réus et al., 2010, 2011a).

5. Conclusion

In conclusion, treatment with lamotrigine showed antidepressant effects in the forced swimming test and reversed the decrease in BDNF levels in the amygdala of maternally deprived rats. The antidepressant effects of lamotrigine may be related, at least in part, by its action on BDNF in the amygdala of deprived rats. It is important to note that lamotrigine also acts on other pathways involved with depression, such as the glutamatergic and serotoninergic systems. With this in mind, more studies are necessary to clarify the molecular means by which lamotrigine presents its behavior effects.

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