The mood stabilizer lamotrigine produces antidepressant behavioral effects in rats: role of brain-derived neurotrophic factor

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Abstract
The anticonvulsant drug lamotrigine has been shown to produce strong antidepressant effects in the treatment of patients with bipolar disorder. However, to date there are few preclinical reports on its behavioral actions in animal models of depression or its underlying molecular mechanisms. The current study investigated the effects of lamotrigine in the forced swimming test and the learned helplessness test. The results demonstrate that both 15 and 30 mg/kg acute treatment of lamotrigine significantly reduced immobility in the forced swimming test without affecting locomotor activity. Sub-chronic twice daily injections of 30 mg/kg lamotrigine robustly decreased escape failures in animals that had developed learned helplessness symptoms. In parallel, the sub-chronic lamotrigine treatment also up-regulated frontal and hippocampal brain-derived neurotrophic factor expression in both naïve and stressed animals and restored the stress-induced down-regulation of brain-derived neurotrophic factor expression. This study provides further evidence for the use of lamotrigine as a novel antidepressant in the treatment of bipolar disorders.

Keywords
antidepressant, brain derived neurotrophic factor, forced swimming test, lamotrigine, learned helplessness

Introduction
Bipolar disorder, otherwise known as manic-depressive illness, is a seriously debilitating and recurring psychiatric disease that affects up to 4% of the worldwide population. Patients suffer from extreme mood swings, alternating between the depressive episode and the manic episode, or experience a mixed state of both. Despite a variety of mood stabilizers available, a common problem with the treatment of the depressive phase is that many medications precipitate the onset of the manic episode or increase the frequencies of manic-depressive cycles (Bourin and Prica, 2007). Thus, it is imperative to develop new antidepressant compounds for bipolar disorders without the mania-precipitating side effects.

Recently, lamotrigine, a potent anticonvulsant and antiepileptic agent, has shown some promise as such a novel antidepressant. It demonstrates clinically antidepressant efficacies against the depressive episode of bipolar disorders and major depressive disorders (Bowden et al., 1999; Calabrese et al., 1999), and it does not trigger mania or mixed states as many conventional antidepressants do (Calabrese et al., 2001). However, conflicting observations have been reported on whether the clinical antidepressant action of lamotrigine could be mimicked in the animal model of depression, namely the forced swimming test (FST) behavior model (Bourin et al., 2005; Consoni et al., 2006; Prica et al., 2008; for a review see Bourin and Prica, 2007). The controversy may stem from the dose employed, technical details of the FST (e.g. cylinder diameter), or even the intrinsic problem of the FST as a depression model. In clinical settings, antidepressant actions are observed only after chronic treatment (weeks to months), whereas the FST is responsive to acute antidepressant treatments, rendering it an incomplete animal model of depression. In the current study, therefore, we utilized another behavioral model, learned helplessness (LH), which requires sub-chronic (5–7 days) administration of a typical antidepressant to ameliorate depressive symptoms. In LH, rats develop severe helplessness and despair symptoms after exposure to inescapable shock, showing significantly elevated escape failures in the active avoidance test (Hajszan et al., 2009). By utilizing a combination of FST and LH, we have more convincingly evaluated the antidepressant actions of lamotrigine in rodent animal models.

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Beside the debate in behavior studies, the molecular and cellular mechanisms underlying the antidepressant effects of lamotrigine remain largely elusive. Lamotrigine has been shown to produce anti-glutamatergic effects (Ketter et al., 2003), a feature shared by some antidepressants and highlighted in the development of novel antidepressants (Machado-Vieira et al., 2009). For example, ketamine, a non-selective glutamate N-methyl-D-aspartic acid receptor antagonist, has emerged as a fast-acting and robust antidepressant (Zarate et al., 2006). Potential downstream targets of those glutamatergic acting agents are neurotrophic factors, such as brain derived neurotrophic factor (BDNF) and nerve growth factor. These neurotrophic factors are positively regulated by a variety of classical antidepressants and are believed to engage in the behavioral actions of those treatments (Duman, 2004). Interestingly, in a pilot study by Chang and colleagues (Chang et al., 2009), the chronic treatment of lamotrigine in rats increased BDNF levels in the frontal cortex. In the current study, we aim to augment this finding to correlate with behavioral models and determine whether sub-chronic treatment of lamotrigine affects BDNF levels in the brain of both naive animals and those subjected to inescapable stress.

Materials and methods

Animals

Male Sprague–Dawley rats (Beijing Laboratory Animal Center) weighing 175–200 g were pair-housed and maintained under standard conditions with a 12-h light/dark cycle and ad libitum access to food and water. Behavioral testing was performed from 10:00 to 17:00 concurrent with stated housing conditions. The experiments were carried out in accordance with guidelines of the Beijing Laboratory Animal Center and the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23).

Drug design

Lamotrigine (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in a mixture of 0.5% carboxymethylcellulose, 0.4% Tween 80, 0.9% benzyl acid and saline, which served as the control vehicle in all behavioral and molecular assays. Animals were randomly assigned into different experimental groups, receiving 0 (vehicle), 15 or 30 mg/kg acute administration of lamotrigine in the FST and locomotor activity test (LMA). The doses used were based on previous studies (Bourin et al., 2005; Consoni et al., 2006; Prica et al., 2008). All drugs were administered intraperitoneally (i.p.) at 1.0 ml/kg. After an initial screen by those two tests, only 30 mg/kg dose was chosen for sub-chronic twice daily treatment in the LH and brain BDNF level assay.

Forced swimming test

Animals were subjected to two FSTs (a 15-min first swim test and a 10-min second swim test) separated by 24 h as described in previous studies (Greene et al., 2009). A single injection of lamotrigine or vehicle was administered 1 h before the second test session. For the FST, a rat was placed in a Plexiglas cylinder (65 cm in height, 30 cm in diameter) filled with 25 °C water to a height of 45 cm. After the test, animals were dried under a lamp for 30 min. The water was changed and the cylinder was rinsed with clean water after each swim. All FST experiments were filmed by a camcorder and only the first 5 min of the second swim was scored offline by an experienced rater blind to the experimental design for immobility, swimming and climbing at a 5-s interval (Greene et al., 2009; Hunsberger et al., 2007; Warner-Schmidt and Duman, 2007). Immobility was defined as floating or remaining motionless without leaning against the wall of the cylinder. Swimming was defined as movements throughout the swim cylinder and climbing as upward movements of forepaws along the cylinder walls.

Locomotor activity

The LMA test was conducted as described in previous studies (Zhao et al., 2009). Briefly stated, the test arena (100 cm × 100 cm × 50 cm) was divided into 25 squares of identical size by black lines. The arena was illuminated with dim overhead lights. Each rat was placed into the center of the arena and allowed to explore for 5 min. Locomotor activity was assessed by the following two indices: travel distance measured by the number of crossings, and the number of rearing up events with both front paws elevated from the floor. Similar to the FST, a single injection of lamotrigine or vehicle was administered 1 h before the LMA.

Learned helplessness

A standard LH paradigm was used as described in previous studies (Hajszan et al., 2009). Testing was conducted in commercial shuttle boxes (Med Associates, St. Albans, Vermont, USA) divided into two equal compartments by a central barrier. A computer-operated guillotine door built into the central barrier allowed passage between compartments. Inescapable footshock (IES) was administered at one side of the shuttle box with the guillotine door closed (60 footshocks, 0.85 mA intensity, 15 s average duration, 60 s average inter-shock interval). This intensity of IES presentation has been shown to be effective in inducing helpless behavior in rats (Hajszan et al., 2009). Non-stressed control animals were exposed to the chambers but did not receive footshock (NS treatment). Helpless behavior was evaluated by analyzing rats’ performance in an active escape paradigm. Active avoidance testing consisted of 30 trials of escapable footshock (0.65 mA intensity, 35 s maximum duration, 90 s average inter-trial interval) with the guillotine door open. Each trial used a fixed-ratio 1 schedule, during which one shuttle crossing by rats terminated the shock. Shock was terminated automatically if rats did not escape after 35 s. A computer automatically recorded the number of escape failures. Lamotrigine (30 mg/kg) or vehicle administration started a day after the IES or NS and continued for seven days, twice daily. The active avoidance test was conducted 24 h after the last drug treatment.

BDNF protein detection

For molecular assays, rats underwent the same IES or NS procedures and subsequent 7-day twice-daily administration...
(30 mg/kg lamotrigine or vehicle) as their counterparts in the active avoidance test. One day after the last drug injection, instead of the active avoidance test, brains of these rats were removed and both halves of the frontal cortex and the hippocampal tissue were dissected for protein assays. Tissues were kept on dry ice and stored at −80°C. After homogenizing by sonication, the BDNF protein level of each sample was quantified by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) following the manufacturer’s protocol. BDNF protein level was normalized to the total protein level determined by BCA analysis (Pierce Chemical, Rockford, IL, USA). Results were expressed as pictogram of BDNF protein/milligram of total protein.

**Statistical analysis**

All analyses were performed using SPSS 13.0 software and data were reported as mean ± S.E.M. One-way analysis of variance (ANOVA) and subsequent Fisher’s post hoc test were used to examine group differences in the FST and the LMA. Two-way ANOVA with drug treatment (lamotrigine and vehicle) and stress (IES and NS) as variables were used to examine active avoidance performance and brain BDNF levels. The level of statistical significance was set at $p < 0.05$.

**Results**

**Acute lamotrigine treatment reduces immobility in the FST**

A single injection of lamotrigine produced a strong antidepressant effect in the FST (Figure 1). Lamotrigine significantly reduced immobility ($F(2, 15) = 53.43, p < 0.001$); increased swimming ($F(2, 15) = 5.03, p < 0.05$); and climbing behavior ($F(2, 15) = 43.99, p < 0.001$). Post hoc analysis indicated that lamotrigine treatment produced a significant reduction of immobility, $p < 0.001$ for both 15 and 30 mg/kg, with 30 mg/kg resulting in bigger effects. Only 30 mg/kg but not 15 mg/kg lamotrigine administration significantly increased swimming behavior, $p < 0.01$, while climbing behavior was significantly enhanced, $p < 0.001$, for both 15 and 30 mg/kg lamotrigine treatments.

Importantly, acute lamotrigine treatment had no effect on locomotor activity tested at the same time point as FST (Table 1). The effect of lamotrigine on neither the number of crossings nor rearings was significant ($F(2, 15) = 0.10, p = 0.90, F(2, 15) = 0.26, p = 0.77$), indicating that the reduction of immobility observed in the FST after lamotrigine treatment was not due to locomotor hyperactivity.

**Sub-chronic lamotrigine treatment reduces escape failures in LH**

Sub-chronic treatment of lamotrigine produced a robust antidepressant effect in the LH (Figure 2). The interaction between the drug treatment and the stress condition was significant ($F(1, 28) = 19.34, p < 0.001$). The effects of the drug treatment and the stress condition were also significant ($F(1, 28) = 16.58, p < 0.001; F(1, 28) = 39.32, p < 0.001$). Further analysis showed that in animals with vehicle administration, those receiving initial IES treatment showed

*Table 1. Effects of lamotrigine on locomotor activity ($n = 6$)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of crossings</th>
<th>Number of rearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>66.67 ± 5.81</td>
<td>14.17 ± 2.06</td>
</tr>
<tr>
<td>Lam 15 mg/kg</td>
<td>63.50 ± 10.03</td>
<td>13.00 ± 2.98</td>
</tr>
<tr>
<td>Lam 30 mg/kg</td>
<td>61.17 ± 9.19</td>
<td>15.50 ± 1.35</td>
</tr>
</tbody>
</table>

Results are expressed as means ± S.E.M.
significantly elevated escape failures \((F(1, 14) = 71.21, p < 0.001)\), indicating IES successfully caused learned helplessness symptoms. In animals with lamotrigine treatment, no performance difference emerged between IES and NS animals \((F(1, 14) = 1.46, p = 0.27)\). Furthermore, in IES-treated animals, lamotrigine injection significantly reduced escape failures when compared with vehicle administration \((F(1, 14) = 26.02, p < 0.001)\), indicating sub-chronic treatment of lamotrigine produced a strong antidepressant effect in animals that had developed learned helplessness; in NS animals, there was no difference between the two drug groups \((F(1, 14) = 0.09, p = 0.77)\).

**Sub-chronic lamotrigine treatment up-regulates frontal and hippocampal BDNF expression level**

Sub-chronic treatment of lamotrigine significantly elevated frontal and hippocampal BDNF protein expression levels in both naive and IES-treated animals (Figure 3). The frontal and hippocampal BDNF levels exhibited a similar response pattern. The results showed that the interaction between drug treatment and stress condition was significant in both frontal cortex \((F(1, 20) = 4.70, p < 0.05)\) and hippocampus \((F(1, 20) = 7.00, p < 0.05)\). The effects of drug treatment and stress condition were also significant in both frontal cortex \((F(1, 20) = 38.89, p < 0.001)\) and hippocampus \((F(1, 20) = 40.75, p < 0.001)\) and hippocampus \((F(1, 20) = 31.76, p < 0.001)\). Further analysis showed that in vehicle-treated animals, those that received IES treatment showed significantly lower BDNF expression levels as compared with the NS control group in both frontal cortex \((F(1, 10) = 37.81, p < 0.001)\) and hippocampus \((F(1, 10) = 28.12, p < 0.001)\), indicating that inescapable shock down-regulated frontal and hippocampal BDNF expression levels. Interestingly, sub-chronic administration of lamotrigine markedly increased frontal and hippocampal BDNF expression levels in stressed animals \((F(1, 10) = 39.59, p < 0.001; F(1, 10) = 38.42, p < 0.001)\). Lamotrigine treatment also significantly increased frontal and hippocampal BDNF levels in non-stressed naive animals \((F(1, 10) = 7.47, p < 0.05; F(1, 10) = 7.44, p < 0.05)\). The difference in BDNF expression between IES and NS animals under lamotrigine treatment was only marginally significant (the frontal cortex \((F(1, 10) = 4.68, p = 0.061)\); the hippocampus \((F(1, 10) = 4.77, p = 0.055)\), possibly due to the relatively small sample size. Importantly, lamotrigine treatment completely normalized stress down-regulated frontal and hippocampal BDNF levels to the basal level, as shown in vehicle-treated non-stressed control groups \((t(10) = 0.49, p = 0.63; t(10) = 0.57, p = 0.58)\), indicating that BDNF may be an important target in lamotrigine’s role as an antidepressant.

**Discussion**

The current study provides further evidence that the mood stabilizer lamotrigine produces robust antidepressant effects in rodent models of depression. In support of previous studies (Bourin et al., 2005; Consoni et al., 2006; Prica et al., 2008), both the 15 and 30 mg/kg acute treatment of lamotrigine significantly reduced immobility in the FST without affecting locomotor activity. Furthermore, sub-chronic twice daily but not acute (see supplementary materials) injections of 30 mg/kg lamotrigine robustly decreased escape failures in animals that were subjected to inescapable shock and had developed learned helplessness behavior. Finally, sub-chronic but not acute (see supplementary materials) treatment of lamotrigine up-regulated frontal and hippocampal BDNF expression levels in both naive and stressed animals and, more importantly, restored stress-induced down-regulation of BDNF to the basal level of vehicle-treated non-stressed control animals, indicating that neurotrophic factors may be important for the antidepressant actions of lamotrigine.

There has been some controversy about whether lamotrigine produces antidepressant effects in rodents (Ali et al., 2003; Bourin et al., 2005; Consoni et al., 2006; Prica et al., 2008).

**Figure 3.** Effects of sub-chronic lamotrigine treatment (twice daily for 7 days) on frontal and hippocampal BDNF protein expression levels. Results are expressed as mean ± S.E.M. * p < 0.05; ** * p < 0.001, as compared with vehicle treated controls. n = 6 for each drug treatment group, including 30 mg/kg dose of lamotrigine and vehicle.
Ali and colleagues (2003) reported that neither acute nor chronic oral administration of lamotrigine (dose range: 1–5 mg/kg) reduced immobility in mice in the FST. Nonetheless, a few recent studies by different groups all concluded that lamotrigine reduces immobility in the FST. The dose range that produces significant antidepressant actions in the FST is between 10 and 32 mg/kg (Bourin et al., 2005; Consoni et al., 2006; Prica et al., 2008). In the current study, we further confirm that acute injection of lamotrigine at doses of 15 and 30 mg/kg in rats produces a significant reduction of immobility in the FST, lending additional credence to lamotrigine’s antidepressant effects. We should note that even at the higher dose (30 mg/kg), lamotrigine treatment did not result in any significant changes in locomotor activity, indicating that this compound was well tolerated and the reduction of immobility observed in the FST was not due to locomotor abnormality.

Consistent with previous findings (Prica et al., 2008), the current FST results showed that a low dose of lamotrigine increased the climbing behavior, while a high dose reduced immobility by enhancing both climbing and swimming behavior. In the revised FST paradigm, climbing behavior is mediated by noradrenergic neurotransmissions while swimming behavior is modulated by serotonergic neurotransmissions (Lucki, 1997). For example, desipramine, a tricyclic antidepressant (TCA) that selectively inhibits the reuptake of norepinephrine, reduces immobility and increases climbing behavior in FST, whereas fluoxetine, a selective serotonin reuptake inhibitor (SSRI), reduces immobility but only increases swimming behavior in the same test (Cryan et al., 2002). Lamotrigine might engage in both noradrenergic and serotonergic systems to mediate behavior in the FST. This hypothesis has been supported partially by the fact that lamotrigine functions as a non-selective inhibitor of monoamine neurotransmitters, including serotonin, norepinephrine and dopamine, in rat synaptoneurosomes (Southam et al., 1998).

We should again note that the dose of lamotrigine treatment plays an important role in its regulation on monoamineergic systems. Studies in human patients have indicated that when given at relatively low dose (100 mg per day for seven days), lamotrigine does not exert its mood-alleviating actions via the serotonin system (Shiah et al., 1998). However, at higher doses (400 mg per day) lamotrigine produced marked female genital disorder, a well-known side effect of SSRIs (Erfurth et al., 1998). At moderate doses (300 mg per day) lamotrigine treatment improved depressive mood in patients with Alzheimer’s disease (Tekin et al., 1998). Comparable to the dose of 250 mg per day in humans, sub-chronic treatment (5 mg/kg for seven days) of lamotrigine in rats significantly down-regulated 5-HT1A-receptor mediated adenylcyclase responses in the frontal cortex (Vinod and Subhash, 2002). A recent study by Bourin and colleagues (2005) also reported that the reduction of immobility in the FST by sub-active doses of lamotrigine (2 and 4 mg/kg) could be enhanced by a variety of serotonin 1A receptor targeting agents.

Although the FST serves as a useful model to screen antidepressant efficacies of new compounds, it fails to mimic the clinical reality that antidepressants usually take chronic treatment to cause behavioral changes. Thus in the current study we also utilized the LH paradigm, a rodent depression model with excellent validities and, more importantly, only responsive to sub-chronic or chronic antidepressant treatment. After receiving inescapable shocks, animals develop a variety of physiological and behavioral changes that mirror depressive symptoms in humans, such as elevated corticosterone levels and loss of appetite (Schmidt and Duman, 2007). The LH paradigm is sensitive to a variety of antidepressant treatments, including TCAs, such as imipramine, and SSRIs, such as fluoxetine. In our study the IES stress produced severe LH behavior in rats. In LH animals, the elevated escape failures were significantly ameliorated by 7-day sub-chronic treatment of lamotrigine. In the non-stressed control group, lamotrigine did not result in any significant behavioral changes. Put together, sub-chronic treatment of lamotrigine produces a strong antidepressant effect in the LH model.

While acute lamotrigine treatment might produce antidepressant actions through regulations of the monoamine system, sub-chronic treatment of lamotrigine might engage in a variety of other neurotransmission systems. According to the neurotrophic hypothesis of depression, stress and depression may result in a deficiency of neurotrophic factors that finally leads to pathological damages of several key brain regions such as the frontal cortex and hippocampus, and antidepressants function by reversing such neurotrophic-factor deficiencies (Duman, 2004). Various stress procedures decreases BDNF levels in the frontal cortex and hippocampus, whereas chronic treatment of almost all classes of antidepressants increases BDNF in those regions of interest (for a review see Nestler et al., 2002). In animals subjected to inescapable stress, the frontal and hippocampal BDNF expression levels were significantly reduced and could be alleviated by chronic treatment of fluoxetine, imipramine and rolipram (Itoh et al., 2004; Song et al., 2006). Given that both bipolar disorder and major depressive disorder (MDD) patients have a reduced hippocampal expression of BDNF and other neurotrophic factors (Dwivedi et al., 2003; Knable et al., 2004), increasing BDNF expression might be a common pathway for antidepressants to exert therapeutic actions. In the current study we demonstrated that in IES-treated animals both frontal and hippocampal BDNF protein levels were significantly lowered as compared with the non-stressed control group, and sub-chronic administration of lamotrigine restores BDNF protein expression in parallel to improvements in behavioral performance. In line with a previous report (Chang et al., 2009), sub-chronic lamotrigine treatment also increases brain BDNF expression level in experimentally naive animals.

A potential mechanism for lamotrigine to increase BDNF is via the arachidonic acid signaling cascade. Chronic or sub-chronic administration of mood stabilizers including lamotrigine and lithium has been shown to down-regulate arachidonic acid signaling in the brain (Rao et al., 2008). This signaling pathway is implicated in cell death and the interference in transcription of neuronal survival factors, whereas its down-regulation actually enhances the brain expression of BDNF and other neurotrophic factors (Garrido et al., 2003; Tang et al., 1996). Interestingly, in the current study it only took 7-day sub-chronic administration of lamotrigine to up-regulate hippocampal and frontal BDNF.
protein expression, a faster onset of changes as compared with the previous report (Chang et al., 2009). The differences in doses (30 versus 10 mg/kg) and treatment route (twice daily i.p. injection versus oral administration) might explain the discrepancies. We should also note that lamotrigine increases BDNF levels much faster than do traditional antidepressants such as fluoxetine and imipramine, which take at least 3–4 weeks to reveal any significant BDNF enhancement, indicating that lamotrigine could serve as a fast-acting anti-depressant drug.

In summary, the current study showed that acute lamotrigine treatment decreased immobility in rat FST and for the first time demonstrated its antidepressant efficacies using the LH model, which requires long-term drug treatment. Sub-chronic treatment of lamotrigine also up-regulated frontal and hippocampal BDNF expression levels in both naïve and stressed animals, and restores the stress-induced down-regulation of BDNF expression. The current study provides substantial evidence supporting the use of lamotrigine as a novel antidepressant for bipolar disorder and MDD, and highlights a potential role of the neurotrophic factor BDNF in mediating its behavioral action.

Ongoing and future studies will further characterize the antidepressant effects of lamotrigine. Rodent models that are responsive to chronic antidepressant treatments and thus hold better face validities will be used to examine if lamotrigine has any fast-acting therapeutic effects. Such models include chronic unpredictable stress and the novelty-suppressed feeding test, which respectively mimic the anhedonia symptoms of depression and anxiety-like behavior (Schmidt and Duman, 2007). The role of BDNF can be examined by both pharmacological and genetic approaches. Selective inhibitors for BDNF-TrkB signaling cascade and heterozygous BDNF knock-out mice will be utilized to see if the blockade of this pathway can abolish the antidepressant actions of lamotrigine. Finally, the interaction between lamotrigine and monoamineergic systems can be investigated by co-administration of lamotrigine and various selective serotonin/dopamine agonists and antagonists in different rodent models of depression. Altogether those approaches will provide a better overarching perspective for the use of lamotrigine as a novel antidepressant treatment.

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