Neural network dysfunction in bipolar depression: clues from the efficacy of lamotrigine

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Introduction

An understanding of the mechanisms of action of clinically effective mood-stabilizing drugs provides a basis on which to form hypotheses concerning the underlying pathology of bipolar disorder. This approach has been taken with lithium and valproic acid, yielding the hypothesis that a dysfunction of neuroplasticity and cellular resilience may be a central component of the disorder [1,2], with a range of molecular targets identified [3,4]. In contrast, although the mechanism of action of lamotrigine in both bipolar disorder [5,6] and schizophrenia [7] has been considered, relatively little progress has been made beyond a classification of its efficacy with respect to other anti-epileptic drugs [8]. Indeed, since lamotrigine differs markedly from valproic acid and other anticonvulsant drugs in its efficacy in bipolar disorder [9], and it differs from other anti-epileptic drugs [8], it is unclear why inhibition of these channels might confer antidepressant efficacy. In healthy volunteers, we found that lamotrigine had a facilitatory effect on the BOLD (blood-oxygen-level-dependent) response to TMS (transcranial magnetic stimulation) of the prefrontal cortex. This effect was in contrast with an inhibitory effect of lamotrigine when TMS was applied over the motor cortex. In a follow-up study, a similar prefrontal specific facilitatory effect was observed in a larger cohort of healthy subjects, whereas valproic acid inhibited motor and prefrontal cortical TMS-induced BOLD response. In vitro, we found that lamotrigine (3–10 μM) enhanced the power of gamma frequency network oscillations induced by kainic acid in the rat hippocampus, an effect that was not observed with valproic acid (100 μM). These data suggest that lamotrigine has a positive effect on corticolimbic network function that may differentiate it from other mood stabilizers. The results are also consistent with the notion of corticolimbic network dysfunction in bipolar disorder.

Efficacy of lamotrigine in bipolar disorder

The first large placebo-controlled open-label study of lamotrigine in 195 patients with bipolar I disorder with symptoms of depression reported a significant reduction in HAM-D (Hamilton Depression Rating Scale) and MADRS (Montgomery–Åsberg Depression Rating Scale) scores compared with placebo [10]. Results of subsequent double-blind trials in bipolar depression were mixed, although a recent meta-analysis of these studies concluded that there was evidence for consistent efficacy of lamotrigine that was most marked in the most severely symptomatic patients [11]. In two 18-month mood-prophylaxis trials, lamotrigine significantly delayed the recurrence of mood episodes, with particular efficacy in preventing episodes of depression [12]. Prevention of episodes of depression was also observed in antidepressant efficacy may provide a valuable approach to understanding the illness. The present brief review sets out some of the studies conducted with lamotrigine in rodents, healthy human volunteers and patients with bipolar disorder. Data suggest that the drug has a positive effect on corticolimbic network function, which is consistent with a hypothesis for abnormal activity of these circuits in bipolar depression.

Key words: bipolar depression, functional magnetic resonance imaging (fMRI), gamma oscillation, lamotrigine, transcranial magnetic stimulation (TMS).

Abbreviations used: AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; BOLD, blood-oxygen-level-dependent; ERK, extracellular-signal-regulated kinase; fMRI, functional magnetic resonance imaging; GluR, glutamate receptor; GSK3, glycogen synthase kinase 3; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; TMS, transcranial magnetic stimulation.

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Abstract

One strategy to understand bipolar disorder is to study the mechanism of action of mood-stabilizing drugs, such as valproic acid and lithium. This approach has implicated a number of intracellular signalling elements, such as GSK3β (glycogen synthase kinase 3β), ERK (extracellular-signal-regulated kinase)/MAPK (mitogen-activated protein kinase) or protein kinase C. However, lamotrigine does not seem to modulate any of these targets, which is intriguing given that its profile in the clinic differs from that of valproic acid or lithium, with greater efficacy to prevent episodes of depression than mania. The primary target of lamotrigine is the voltage-gated sodium channel, but it is unclear why inhibition of these channels might confer antidepressant efficacy. In healthy volunteers, we found that lamotrigine had a facilitatory effect on the BOLD (blood-oxygen-level-dependent) response to TMS (transcranial magnetic stimulation) of the prefrontal cortex. This effect was in contrast with an inhibitory effect of lamotrigine when TMS was applied over the motor cortex. In a follow-up study, a similar prefrontal specific facilitatory effect was observed in a larger cohort of healthy subjects, whereas valproic acid inhibited motor and prefrontal cortical TMS-induced BOLD response. In vitro, we found that lamotrigine (3–10 μM) enhanced the power of gamma frequency network oscillations induced by kainic acid in the rat hippocampus, an effect that was not observed with valproic acid (100 μM). These data suggest that lamotrigine has a positive effect on corticolimbic network function that may differentiate it from other mood stabilizers. The results are also consistent with the notion of corticolimbic network dysfunction in bipolar disorder.

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a study of patients with rapid cycling bipolar disorder [13]. In contrast with other anticonvulsant drugs, the efficacy of lamotrigine in treating mania is less well established, with efficacy noted in just two small double-blind studies [14]. Overall, the clinical profile of lamotrigine, compared with other mood-stabilizing drugs, such as lithium and valproic acid, suggests that it is most effective in the prevention or amelioration of depressive symptoms [15,16].

Lamotrigine exerts a positive effect on the activity of corticolimbic circuits in healthy human volunteers and patients with bipolar disorder

The well-established anticonvulsant efficacy of lamotrigine is presumed to arise through a reduction of neural excitability owing to the drug’s effects on voltage-gated sodium and perhaps calcium channels [17]; however, it is unclear why such a mechanism should confer efficacy against the depressive pole of bipolar disorder. In order to understand better the efficacy of lamotrigine, the effects of the drug on neural activity in different brain areas was assessed in healthy human volunteers using a combination of TMS (transcranial magnetic stimulation) to activate specific cortical circuits, and fMRI (functional magnetic resonance imaging) to monitor the response. As expected from previous studies using TMS [18,19], a 325 mg dose of lamotrigine increased the stimulus required to activate the abductor digit minimi muscle following stimulation of the motor cortex. Furthermore, in the presence of the drug, a significant reduction in TMS-induced activation of motor cortical circuits underneath the stimulator coil was observed [20]. The reduction in BOLD (blood-oxygen-level-dependent) response was consistent with reduced excitability of the motor cortex, and in line with the effects of a sodium channel blocker [21]. In the second part of their study, Li et al. [20] applied TMS to the prefrontal cortex, evoking a reproducible BOLD response in corticolimbic brain areas. However, in contrast with motor cortex TMS, the BOLD response evoked in the hippocampus and orbital frontal gyrus following stimulation of prefrontal cortex was significantly and counterintuitively increased after subjects received lamotrigine. In a follow-up study conducted with 30 subjects, an increase in activation of corticolimbic brain areas following TMS over prefrontal cortex was confirmed when subjects received lamotrigine. In contrast, a diffuse reduction in BOLD response to TMS across corticolimbic regions was observed when subjects received a therapeutically relevant dose of valproic acid [22].

A complimentary approach was taken in 12 patients with bipolar I disorder. Haldane et al. [23] hypothesized that lamotrigine might facilitate the function of neural circuits involved in the processing of emotional stimuli. Consequently, they monitored brain activation during a face-recognition task conducted before and after 12 weeks of monotherapy with lamotrigine (200 mg/day). They also examined brain activation during a working memory, ‘N-back’ task. A meta-analysis of clinical data indicates that, unlike some other anticonvulsant drugs, lamotrigine does not have a detrimental effect on cognition and may, in fact, be beneficial [24]. The imaging study found that brain activation during the N-back task was increased in superior and medial frontal cortex after lamotrigine monotherapy [23]. During the presentation of angry faces, greater activation of frontal brain regions was observed after lamotrigine monotherapy compared with baseline. The regions that were most activated by lamotrigine were those previously associated with the performance of emotional face recognition tasks in healthy individuals (discussed in [23]).

The TMS/fMRI studies described above [20] provide evidence for contrasting effects of lamotrigine on prefrontal and motor circuits that could be relevant to the drug’s efficacy in bipolar depression and epilepsy respectively. To our knowledge studies of the effects of lamotrigine on the excitability of individual neurons in motor compared with prefrontal cortex have not yet been conducted, so we cannot rule out a difference in sensitivity of neural elements within the two regions. Studies using TMS combined with EEG (electroencephalography) have shown that motor and prefrontal cortices differ significantly in their baseline reactivity to TMS [25], raising the possibility that the differences observed with lamotrigine could be a consequence of the difference in relative activation by stimuli of similar intensity. However, the qualitatively similar effect of lamotrigine on the tasks used by Haldane et al. [23] to activate the prefrontal cortex suggests that the facilitation of activation by the drug is of physiological relevance.

Lamotrigine exerts a positive effect on neural network activity in rodents in vitro

In order to shed further light on the facilitatory effect of lamotrigine on corticolimbic activity, we investigated the actions of the drug on activity of the hippocampus in vitro. We reasoned that it would be important to study the effects of the drug, not on individual neurons, as has been done in the past [17], but on the neural network during periods of ‘physiological’ activity.

We examined the effects of lamotrigine on oscillatory field potentials in the CA3 region of the hippocampus evoked by low concentrations of kainic acid [26]. Network oscillations evoked in this way occur at frequencies in the gamma-band (20–80 Hz), and are thought to mimic physiological network activity in the hippocampus underlying memory encoding and retrieval [27]. Lamotrigine significantly enhanced the power of kainate-induced gamma oscillations in the hippocampus at concentrations consistent with its therapeutic range (3–10 μM), whereas valproic acid at a relevant therapeutic concentration of 100 μM had no effect (C.H. Large, M. Rosato-Siri, A. Casagrande and A. Ugolini, unpublished work). Higher concentrations of lamotrigine (100 μM) produced a decrease in network activity. These preliminary results provide an intriguing insight into the counterintuitive facilitatory effects of lamotrigine observed in healthy volunteers and patients with bipolar disorder. Furthermore, the results highlight the importance of studying networks of neurons, where ensemble activity may unmask drug effects that
Interactions of lamotrigine with molecular targets implicated in bipolar disorder

The serine/threonine kinase, GSK3 (glycogen synthase kinase 3) is a central component in the Wnt and PI3K (phosphoinositide 3-kinase)/Akt intracellular signalling pathways, which play a critical role in multiple cellular processes, such as metabolism, proliferation, differentiation, synaptogenesis, apoptosis and cellular plasticity/resilience. Lithium inhibits GSK3 directly, and indirectly by increasing the phosphorylation of Akt, which phosphorylates Ser\(^\text{\text{ε}}\) and ε in rat hippocampus and frontal cortex [37,38], although this does not appear to be a direct effect on PKC. Attenuation of PKC activity has been suggested to contribute to the anti-manic effects of lithium and valproic acid; a hypothesis that is supported by the apparent anti-manic efficacy of tamoxifen (a non-steroidal anti-oestrogen known to inhibit PKC at high concentrations) [39,40]. Perhaps in line with the mostly antidepressant efficacy of lamotrigine in bipolar disorder, there are no reports of effects of the drug on PKC activity.

Lithium and valproic acid have been shown to activate the ERK (extracellular-signal-regulated kinase) MAPK (mitogen-activated protein kinase) signalling cascade in cell lines and primary neurons as well as in the rat prefrontal cortex and hippocampus [41,42], with consequent behavioural changes that mimic anti-manic effects. Furthermore, lithium was shown to reverse an increase in locomotor activity produced by the ERK/MAPK inhibitor, SL327 [41]. Lamotrigine had no effect on ERK/MAPK phosphorylation in rat primary cortical neurons [43].

Inositol phospholipids play a major role in receptor-mediated signal transduction and are implicated in a diverse range of cellular processes, such as enzyme activation, cytoskeletal changes, endocytosis, exocytosis, ion channel activation and production of various second messengers [44]. One of the key enzymes in the pathway, inositol monophosphatase is inhibited directly by lithium at concentrations similar to those achieved clinically in the treatment of bipolar disorder [45,46], leading to a decrease in intracellular \(\text{myo-inositol}\) levels. Furthermore, lithium and valproic acid, as well as carbamazepine, have a common effect to increase the growth cone area of dorsal root ganglia neurons in culture, an effect that was reversed by addition of \(\text{myo-inositol}\) [35]. Lamotrigine has not been shown to influence inositol levels in the rodent brain [47], although its effects on this pathway remain to be fully investigated.

Finally, lithium and valproic acid have been shown to reduce plasma membrane expression of GluR (glutamate receptor) 1 and 2 AMPA (\(\alpha\)-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptor subunits in the hippocampus [48]. In addition, both drugs induced a decrease in GluR1 phosphorylation at a specific PKA (protein kinase A) site known to facilitate AMPA receptor insertion and opening of its ion channel. In contrast, lamotrigine, and some antidepressant drugs, have been shown to increase phosphorylation and/or synaptic levels of GluR1 and enhance surface/synaptic GluR1 and GluR2 in cultured hippocampal neurons [49]. These findings suggest a possible molecular mechanism by which the drug might enhance neural activity in corticolimbic networks.

Conclusions

The combination of results from rodent brain slices, healthy human volunteers and patients with bipolar disorder indicate a consistent facilitatory effect of lamotrigine on corticolimbic circuits, an effect that was not observed with therapeutic levels of sodium valproate. Given the clinical differences between these two drugs in the treatment of bipolar disorder, we can speculate that the facilitatory effect of lamotrigine on prefrontal cortical circuits may underlie the drug’s efficacy against the depressed pole of the illness. This hypothesis suggests that improved treatments for bipolar depression might be achieved by targeted facilitation of corticolimbic function.

With this in mind, we suggest that lamotrigine’s facilitatory effects are likely to be mediated by interaction with voltage-gated sodium channels, rather than through targets, such as GSK3β, ERK/MAPK or PKC, which have been linked to the efficacy of other mood stabilizers. Furthermore, positive effects of lamotrigine on AMPA receptor expression, possibly as a secondary consequence of interaction with sodium channels, should be investigated further; particularly in the light of data suggesting that the long-lasting antidepressant effects of the NMDA (\(N\)-methyl-D-aspartate) receptor antagonist, ketamine might be mediated by downstream activation of AMPA receptors [50].

The studies by Haldane et al. [23] described in the present review focus on the role of the prefrontal cortex in emotional processing, which is clearly abnormal in patients with bipolar disorder. However, the prefrontal cortex is also critical for reward processing, which has also been shown to be disrupted in patients with bipolar disorder [51]. It is interesting to note that lamotrigine has been shown to reduce alcohol consumption in a rodent model of craving [52], an effect that we speculate might also derive from the drug’s effects on corticolimbic circuits. It may therefore be valuable to combine these two areas of research, in particular given the very high proportion of bipolar patients that abuse recreational drugs.
In conclusion, the studies described in the present review highlight the value of exploring the effects of psychoactive drugs on neural circuits. Furthermore, they demonstrate the importance of evoking physiological or pathophysiological activity against which to study drug action. In the case of bipolar disorder, which is characterized by a range of symptom domains that includes dysfunctional mood and reward processing, approaches that focus on the activity of areas such as the orbitofrontal cortex, hippocampus and ventral striatum will be important. In addition, an understanding of the contrasting effects of lamotrigine on motor circuits compared with corticobulbar circuits may also help to highlight improved therapeutic targets for bipolar disorder.

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