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Coadministration of gabapentin or MK-801 with lamotrigine slows tolerance to its anticonvulsant effects on kindled seizures

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Abstract

The development of tolerance to therapeutic effects of antiepileptic drugs can be a problem in the treatment of epilepsy, bipolar disorder, and pain syndromes. In the present study, acute treatment with the new antiepileptic drug lamotrigine (LTG, 15 mg/kg) markedly suppressed seizure stage and seizure duration in amygdala-kindled rats; but this antiseizure effect was rapidly lost following 4–8 days of repeated treatment. When gabapentin (GBP, 20 mg/kg) was coadministered with LTG, the ability of LTG to suppress seizure stage, seizure duration, and after-discharge (AD) duration was markedly extended. In addition, GBP coadministration with LTG decreased the number of animals that developed LTG-related running fits (Stage 6 seizures) and lengthened the number of days required to develop running fits or complete tolerance. Neither acute nor repeated treatment with MK-801 (0.3 mg/kg), a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, had effects on kindled seizures. However, cotreatment with MK-801 markedly extended the anticonvulsant effects of LTG on the three seizure indices and reduced running fits. These data indicate that cotreatment with either GBP or MK-801 slows tolerance development to the anticonvulsant effects of LTG on kindled seizures. Therapeutic implications of the present study remain to be explored.

Keywords: Tolerance; Lamotrigine; Gabapentin; MK-801; Amygdala kindling

1. Introduction

While the antiepileptic drug lamotrigine (LTG) is demonstrated to be effective in epilepsy, bipolar disorders, and pain syndromes (Backonja, 2000; Botts and Raskind, 1999; De Leon, 2001; Leppik, 1998; Post et al., 2000; Wallace, 2001), the loss of clinical efficacy has been reported in epilepsy and bipolar patients after chronic treatment (Calabrese et al., 2000; Collins et al., 2000; Marson et al., 1997). Some aspects of these breakthrough phenomena may be due to tolerance development to drug's effects (De Leon, 2001; Weiss et al., 1995).

Studies in experimental animals show that repeated treatment with LTG leads to a progressive loss of anticonvulsant effects on amygdala kindled seizures (Krupp et al., 2000; Postma et al., 2000). A similar tolerance phenomenon has also been observed for other anticonvulsant drugs, including carbamazepine (Krupp et al., 2000; Mana et al., 1992; Weiss et al., 1993a,b, 1995), levetiracetam (Löscher and Hönack, 2000), benzodiazepines (Amano et al., 2001; Kalynchuk et al., 1994; Kippin et al., 1998; Mana et al., 1992), ethanol (Kippin et al., 1998), and to a lesser extent, valproate (Mana et al., 1992; Weiss et al., 1993b).

Cross-tolerance, that is the loss of response to a second drug due to tolerance development to the effects of the first agent, has provided some insights into the mechanisms of tolerance. This phenomenon has been observed between some anticonvulsant drugs, including from carbamazepine to valproate and LTG, but not diazepam, and from LTG to carbamazepine, but not valproate (Krupp et al., 2000; Weiss et al., 1993a,b). It has been postulated that cross-tolerance may be associated with similar or overlapping mechanisms

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of a drug's actions, suggesting the potential therapeutic impact of agents with different mechanisms in the face of loss of efficacy via tolerance (Kim et al., 1993; Krupp et al., 2000; Weiss et al., 1993a,b, 1995). This has led to the hypothesis that the anticonvulsant tolerance may be slowed by the combined treatment with the drugs that have different neural mechanisms of actions.

The anticonvulsant effects of LTG are believed to be largely related to inhibition of glutamate release through voltage- and use-dependent blockade of sodium channels (Kuo, 1998) and high-voltage-activated calcium channels (Wang et al., 1998). In addition, central GABAergic system may be involved in the effects of LTG. Acute administration of LTG reduces $GABA_A$ receptor-mediated synaptic transmission in the rat amygdala (Braga et al., 2002), but elevates GABA release in the rat entorhinal cortex (Cunningham and Jones, 2000). Chronic treatment with LTG increases hippocampal GABA levels (Hassel et al., 2001).

Gabapentin (GBP) is a novel anticonvulsant drug. Although its mechanisms of action are still under investigation, the anticonvulsant effects of GBP are thought to partially derive from enhancing nonsynaptic GABA release, accelerating glutamate metabolism, and inhibiting its release (Taylor et al., 1998).

MK-801 is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, which itself is ineffective against completed kindled seizures, although it does block their development. Cotreatment with MK-801 has been reported to block tolerance development to various barbiturates (Khanna et al., 1998), diazepam (File and Fernandes, 1994), and opiates (Trujillo et al., 2001), and potentiate the anticonvulsant potency of valproate (Dziki et al., 1992; Urbanska et al., 1991) in animal models.

Kindling has become a useful model for assessing the efficacy of antiepileptic drugs and the development of tolerance to them (Post and Weiss, 1996; Weiss and Post, 1998). The present study was therefore designed to determine whether the development of tolerance to the anticonvulsant effects of LTG could be slowed by coadministration of GBP or MK 801 in amygdala-kindled rats.

2. Materials and methods

2.1. Animals

Adult male Sprague–Dawley rats, purchased from Taconic Farms (Germantown, NY), were housed two per cage on 12-h light/dark cycle (light on 07:00–19:00 h) at 22 °C with food and water available ad libitum. Animals were allowed to acclimate for at least 1 week prior to surgery until reaching a weight of 300–350 g. All animal use procedures were in accordance with an approved animal study protocol under the guidelines of the National Institute of Health.

2.2. Amygdala kindling

Rats received surgical implantation of a bipolar platinum electrode (Plastics One, Roanoke, VA) in the left amygdala under chloral hydrate (Sigma, 400 mg/kg ip) anesthesia using standard aseptic stereotaxic procedures. The coordinates of electrode placement with reference to interaural zero (Paxinos and Watson, 1986) were 5.7 anterior, 4.5 lateral, and 2.0 ventral (value in mm). After a recovery period of at least 1 week, all rats received kindling stimulation using a constant current stimulator (Frederick Haer, Model 6BP) with stimulus parameter consisting of pulses of 100 Hz, biphasic square waves, with peak-to-peak amplitude of 800 μA and train duration of 0.5 s. Electroencephalographic (EEG) activity was recorded simultaneously from the same electrode using a Grass Instruments Polygraph (Model 7C).

The rats were kindled once daily until they developed major motor seizures (stage ≥ 3). Seizure stages were rated using a modified method (Racine, 1972): behavioral arrest (Stage 1), facial chewing movements (Stage 2), unilateral forelimb clonus (Stage 3), bilateral forelimb clonus and rearing (Stage 4), and with rearing and falling (Stage 5) in addition to wild running fits and bouncing (Stage 6). Afterdischarge (AD) and seizure (if stage ≥ 3) duration were also measured. Fully kindled rats were randomly divided into groups (8–11 animals per group) for drug trials and continued to receive the electrical stimulation daily during drug trials (see below).

2.3. Drugs

LTG (Glaxo Wellcome, Research Triangle Park, NC, USA) was dissolved in a vehicle containing 50% physiological saline, 40% propylene glycol, and 10% ethanol. GBP and MK-801 (RBI, Natick, MA, USA) were dissolved in physiological saline. All drugs were injected intraperitoneally in a volume of 1–2 ml/kg body weight.

2.4. Experimental design

2.4.1. LTG and GBP

Two groups of kindled rats received injections of vehicle ($n=9$) or GBP (20 mg/kg, $n=8$) 2 h before the kindling stimulation, followed by an injection of LTG (15 mg/kg) 1 h before the stimulation. The 2 h time point was chosen because GBP was found to be ineffective or less effective when administered 15 min or 1 h prior to stimulation, respectively (unpublished observations). In addition, De Sarro et al. (1998) found that GBP exerted its maximal anticonvulsant activity at pretreatment times of 2 h, despite the decreasing blood and brain levels of GBP at this time. Rats receiving LTG plus GBP or vehicle were kindled for a maximum of 30 days.

To determine whether GBP alone had anticonvulsant effects at this dosage and time point, two other groups of rat were treated with vehicle ($n=8$) or GBP (20 mg/kg,

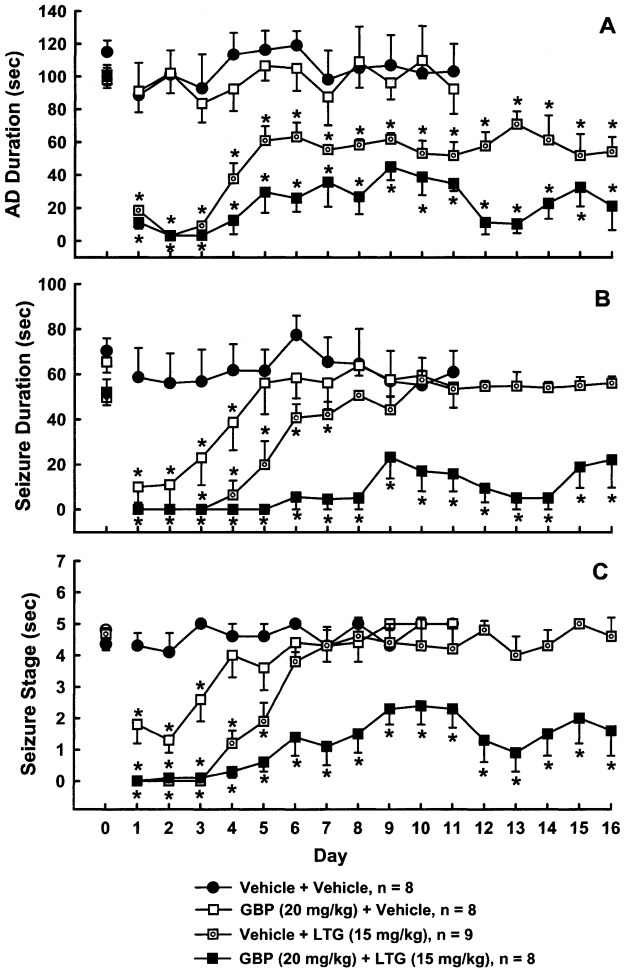

Fig. 1. Coadministration of GBP (20 mg/kg) with LTG (15 mg/kg) slows the development of tolerance in terms of AD duration (A), seizure duration (B), and seizure stage (C) in amygdala-kindled rats. GBP and LTG or corresponding vehicles were administered intraperitoneally 2 and 1 h before the kindling stimulation, respectively. Data are expressed as mean ± S.E.M. ($n = 8$ or 9). Day 0 indicates predrug values. * $P < .05$: vs. day-matched vehicle controls, analyzed using two-way ANOVA, followed by Student's t test.

$n = 8$) 2 h before the stimulation. Both groups also received the LTG vehicle 1 h before the stimulation. These animals were stimulated for 11 days.

2.4.2. LTG and MK-801

As above, two groups of kindled rats were treated with LTG (15 mg/kg) 1 h before the kindling stimulation, and then received injections of vehicle ($n = 11$) or MK-801 (0.3 mg/kg, $n = 11$) 30 min before the stimulation. Both groups were kindled for a maximum of 9 days.

Although previous work in our own laboratory (Weiss et al., 1993a) and others (File and Fernandes, 1994; Khanna et al., 1998; Trujillo et al., 2001) did not indicate that MK-801 was anticonvulsant on fully kindled seizures at this dosage and time point, to be certain, we administered two other groups of rats with MK-801 (0.3 mg/kg, $n = 7$) or vehicle ($n = 7$) 30 min prior to stimulation for a total of 5 days of electrical stimulation. Both groups also received the LTG vehicle 1 h before stimulation.

For each study, the animals received vehicle or drug injection and electrical stimulation once daily, and the criterion used to assess tolerance was the occurrence of three seizures (each stage ≥ 3) in a period of four consecutive stimulations. Those rats experiencing severe running fits on two or more occasions were eliminated from the study.

2.5. Data analysis

Data were expressed as mean ± S.E.M. In those animals that could not continue to the end of drug trials due to running fits ($n = 2$) or electrode failures ($n = 4$), the three seizure indices of the last day were carried forward. Two-way analysis of variance (ANOVA) was used to analyze Drug × Day interaction on seizure stage, AD, and seizure duration. One-way ANOVA was used to analyze drug's effects on the number of days required to develop complete tolerance. Student's t test was used to further analyze differences between groups. The criterion for statistical significance was $P \leq .05$.

3. Results

3.1. Effects of coadministration of LTG with GBP

Compared to vehicle controls, acute LTG treatment at a dose of 15 mg/kg (Day 1) strikingly suppressed seizure stage, AD, and seizure duration (Fig. 1), but these anticonvulsant actions were gradually attenuated with increasing days of treatment. Following 6–8 days of repeated LTG treatment, seizure stage and seizure duration had completely

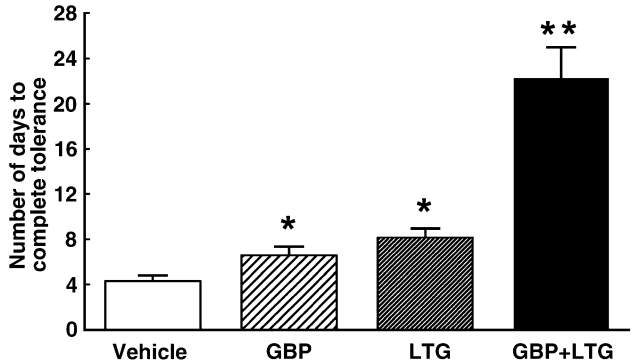

Fig. 2. The effects of coadministration of GBP (20 mg/kg) with LTG (15 mg/kg) on number of days required to develop the complete tolerance, defined as three seizures (stage ≥ 3) occurred in a period of four consecutive stimulations. GBP and LTG or corresponding vehicles were given intraperitoneally 2 and 1 h before the kindling stimulation, respectively. Data are expressed as mean ± S.E.M. ($n = 8–9$). * $P < .05$, ** $P < .001$: vs. vehicle controls, analyzed with one-way ANOVA, followed by Student's t test.

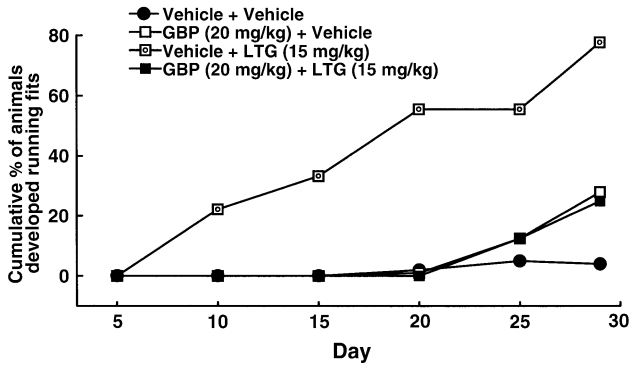

Fig. 3. The effects of coadministration of GBP (20 mg/kg) with LTG (15 mg/kg) on cumulative percentage of rats that developed running fits (stage 6 seizure). GBP and LTG or corresponding vehicles were administered intraperitoneally 2 and 1 h before the kindling stimulation, respectively. The number of rats that developed running fits was recorded daily.

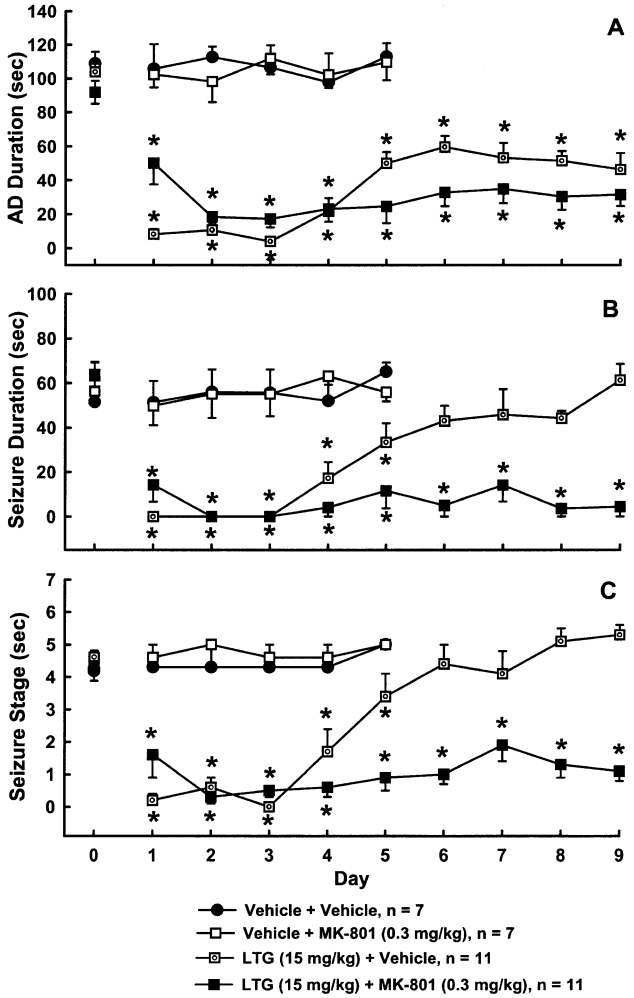

Fig. 4. Coadministration of MK-801 (0.3 mg/kg) with LTG (15 mg/kg) slows the development of the anticonvulsant tolerance in terms of AD duration (A), seizure duration (B) and seizure stage (C) in amygdala-kindled rats. LTG and MK-801 or corresponding vehicles were administered intraperitoneally 60 and 30 min before the kindling stimulation, respectively. Data are expressed as mean ± S.E.M. ($n = 7$ or 11). Day 0 indicates predrug values. * $P < .05$: vs. day-matched vehicle controls, analyzed using two-way ANOVA, followed by Student's t test.

returned to vehicle-treated levels (Fig. 1B and C), and AD duration approximately to half of the vehicle-treated values (Fig. 1A). The initial effects of GBP (20 mg/kg) on seizure stage and seizure duration was similar to LTG, but the two seizure indices returned to vehicle–control levels even more rapidly (4–5 days) than with LTG (Fig. 1B and C). GBP treatment had no effect on AD duration (Fig. 1A).

When LTG and GBP were coadministered, a marked suppression of seizure stage, AD, and seizure duration remained throughout Day 16 of the study. Fig. 1 illustrates the effects of coadministration of GBP with LTG on amygdala-kindled seizures. Two-way ANOVA analysis revealed a significant drug × day interactions on AD duration [$F(3, 45) = 4.05$, $P < .001$], seizure duration [$F(3,45) = 6.39$, $P < .001$], and seizure stage [$F(3,45) = 5.08$, $P < .001$]. Combined treatment with LTG and GBP significantly increased the number of days (22.3 days) required to achieve the tolerance criterion as compared to animals treated with GBP (6.6 days) and LTG (8.2 days) monotherapy [$F(3, 29) = 260.92$, $P < .001$] (Fig. 2).

On LTG, 78% of the animals developed running fits by Day 30 of repeated treatment, while only 25% of the LTG animals cotreated with GBP showed running fits (Fig. 3).

3.2. Effects of coadministration of LTG with MK-801

Fig. 4 shows the effects of acute and repeated MK-801 cotreatment with LTG against amygdala-kindled seizures. Two-way ANOVA analysis revealed a significant drug × day interaction on AD duration [$F(3,24) = 3.45$, $P < .001$], seizure duration [$F(3,24) = 5.94$, $P < .001$], and seizure stage [$F(3,24) = 7.72$, $P < .001$]. Administration of MK-801 (0.3 mg/kg) alone, acutely or chronically, did not affect any of the kindled seizure indices. The time course for the effects of acute and repeated LTG treatment alone was similar to that seen in previously (Fig. 1), i.e., LTG-induced tolerance to the effects on seizure duration and

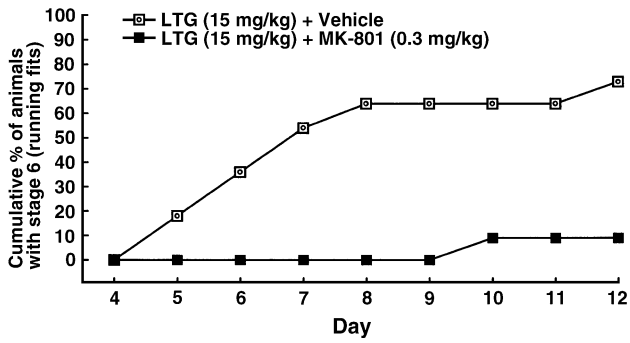

Fig. 5. The effects of cotreatment with LTG (15 mg/kg) and MK-801 (0.3 mg/kg) on cumulative percentage of rats that developed running fits (stage 6 seizures). LTG and MK-801 or corresponding vehicles were administered intraperitoneally 60 and 30 min before the kindling stimulation, respectively. The number of rats that developed running fits was recorded daily. Note: No animals that developed running fits in groups treated with vehicle + vehicle and vehicle + MK-801, respectively.

seizure stage developed in the first 6 days of repeated treatment. Cotreatment of MK-801 with LTG, however, produced a significantly more extended reduction of seizure stage, AD, and seizure duration than with LTG alone. Combined treatment with the two drugs also remarkably lessened cumulative percentage of animals that developed running fits in comparison with LTG-treated animals (Fig. 5).

4. Discussion

The principal finding of the present study is that the development of tolerance to the anticonvulsant effects of LTG in amygdala-kindled rats is slowed by coadministration with two drugs with very different properties and putative mechanisms of action. GBP by itself showed some evidence of efficacy that was rapidly attenuated, while MK-801 alone had no effects on any of the seizure indices.

GBP slowed tolerance development to LTG at doses (20 mg/kg) that were ineffective on AD duration (Fig. 1). This result is consistent with De Sarro et al.'s (1998) study, showing that GBP at dose of 2.5 mg/kg did not significantly affect the occurrence of audiogenic seizures in DBA/2 mice, but potentiated the antiseizure activity of several anticonvulsants, including LTG.

When given alone, MK-801 at the dose (0.3 mg/kg) chosen did not show the antiseizure effects in either acute or repeated treatment. However, when MK-801 at the same dose was coadministered with LTG, the persistence of LTG's anticonvulsant effects was markedly extended (Fig. 4). A number of studies have found that MK-801 at low dose (0.0025–0.3 mg/kg) did not possess anticonvulsant effects, but blocked tolerance development to various barbiturates (Khanna et al., 1998), diazepam (File and Fernandes, 1994), and opiates (Trujillo et al., 2001). However, MK-801 at moderate to high doses (0.25–4 mg/kg) has shown anticonvulsant effects on kindled seizures (Gilbert, 1988; McNamara et al., 1988; Sato et al., 1988; Young et al., 1989). Cotreatment of valproate with MK-801 at low dose has been reported to increase the anticonvulsant potency of valproate against kindled (Dziki et al., 1992; Löscher and Hönack, 1991) and electroshock seizures in mice (Urbanska et al., 1991), suggesting that MK-801's ability to slow LTG tolerance development may be not simply an additive effect of two anticonvulsant agents.

Little is known about the mechanism accounting for tolerance development to the anticonvulsant effects of LTG. Since the anticonvulsant effects of LTG are believed to be largely attributed to inhibition of glutamate release and facilitation of GABA activity (Braga et al., 2002; Kuo, 1998), it seems that LTG tolerance mainly associate with changes in central GABAergic and glutamatergic systems, in which LTG's inhibition of glutamate release and/or its facilitation of GABA activity may be increasingly weakened with repeated LTG treatment. These changes eventually result in a loss of seizure-induced adaptations related to the anticonvulsant effects of LTG (Weiss et al., 1995). This also could account for the greater number of LTG tolerant animals that developed running fits (Figs. 3 and 5).

Based on this putative mechanism of LTG tolerance, there seems to be two possibilities by which coadministration of GBP could slow LTG tolerance. GBP may have the ability to prevent attenuation of GABA receptor activity by elevating the concentration and probably the rate of synthesis of nonsynaptic GABA in brain tissues (Gotz et al., 1993; Leach et al., 1997; Taylor et al., 1998). Another possibility is that GBP may reduce glutamatergic transmission by accelerating glutamate metabolism and inhibiting its release (Taylor et al., 1998).

LTG has been reported to inhibit ketamine-induced hyperglutamatergic effects in humans (Anand et al., 2000). Coadministration with MK-801, a noncompetitive NMDA receptor antagonist, may also suppress glutamatergic activity via blockade of the NMDA receptors. Therefore, both GBP and MK-801 appear to reduce ratio of excitatory to the inhibitory neurotransmission, and then lead to the extended efficacy of LTG against kindled seizures.

The present study may have implications for clinical therapeutics, although this remains to be directly demonstrated. It has been reported that a discontinuance rate due to a lack of efficacy is as high as 24% with LTG and 58% with GBP in the treatment of epilepsy (Collins et al., 2000). The relapse rate in the treatment of bipolar disorder with LTG is over 50% (Calabrese et al., 1998, 2000). To what extent some of these relapses are related to loss of efficacy via tolerance development is not known. Thus, whether coadministration of GBP could extend the therapeutic efficacy of LTG clinically deserves to be explored in the future studies. GBP is only effective in partial seizures (Bazil and Pedley, 1998), and its effectiveness is questionable in mania (Pande et al., 2000) and in monotherapy of refractory bipolar illness (Frye et al., 2000).

In summary, repeated treatment with the anticonvulsant drug LTG is rapidly associated with the development of tolerance to its anticonvulsant effects against amygdala-kindled seizures. This tolerance is slowed by coadministration with GBP, another anticonvulsant drug, or MK-801, a noncompetitive NMDA receptor antagonist. The slowing of tolerance development to LTG by cotreatment with either GBP or MK-801 may be associated with their GABAergic and glutamatergic mechanisms, respectively. The potential relevance of the present results to clinical therapeutics in the treatment of epilepsy and affective disorders remains to be explored.

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