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Modulation of Calcium and Potassium Currents by Lamotrigine

Key Words
Lamotrigine
Calcium
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Valproate
Verapamil
Epilepsy
Bipolar disorder

Abstract
Actions of the new antiepileptic drug lamotrigine (LTG) were characterized using extracellular and whole cell patch clamp recordings from rat CA1 and CA3 pyramidal cells in vitro. The results suggest that LTG, beside its previously described effect on the fast sodium inward current, also modulates – presumably voltage-gated – calcium currents and the transient potassium outward current I_D. These may be effective mechanisms to inhibit pathological excitation in epilepsy and may be of potential benefit in treating underlying cellular disturbances in bipolar disorder.

Introduction

Lamotrigine (LTG; 3,5-diamino-6-(2,3 dichlorphenyl)-1,2,4-triazine) is a clinically useful antiepileptic drug, mainly administered as an add-on medication to other anticonvulsants in therapy resistant epilepsy [1]. Due to reported efficacy in single case observations [2–4] it is also gaining increasing interest as a potential mood stabilizer in psychiatry. Similar to other antiepileptic drugs, e.g. carbamazepine (CBZ) and phenytoin, a blockade of voltage-dependent sodium channels [5] mainly in their inactivated state [6] has been demonstrated so far. Furthermore, LTG exerts cell-protective effects by decreasing glutamate release in the striatum [7]. Beside a high sodium influx and elevated glutamate release, an increase of the intracellular calcium concentration has been suggested as an underlying disturbance both in epilepsies and bipolar disorder [8]. Based on this rationale, calcium antagonists have been tested partially successfully for the treatment of bipolar disorder, both in manic and depressed episodes [9]. Another approach to limit hyperexcitability is a modulation of potassium currents. Recently, the important impact of potassium-dependent repolarization for age-specific epilepsies has been demonstrated [10]. The fast transient potassium outward current (I_A) counteracts depolarization of a neuron. So far, an increase of this current has been demonstrated for valproate [11] and CBZ [12].

Most antiepileptic drugs which act on the level of ion channels do not exert just one specific blockade. For example, both valproate and CBZ show actions on voltage-gated sodium, calcium and potassium channels [12–15]. All of these excitation-limiting effects may be of potential value in treating both epilepsies and bipolar disorder. Our electrophysiological in vitro experiments were designed to test whether LTG is also capable of modulating calcium and potassium currents in hippocampal neurons beside its known action on sodium channels.

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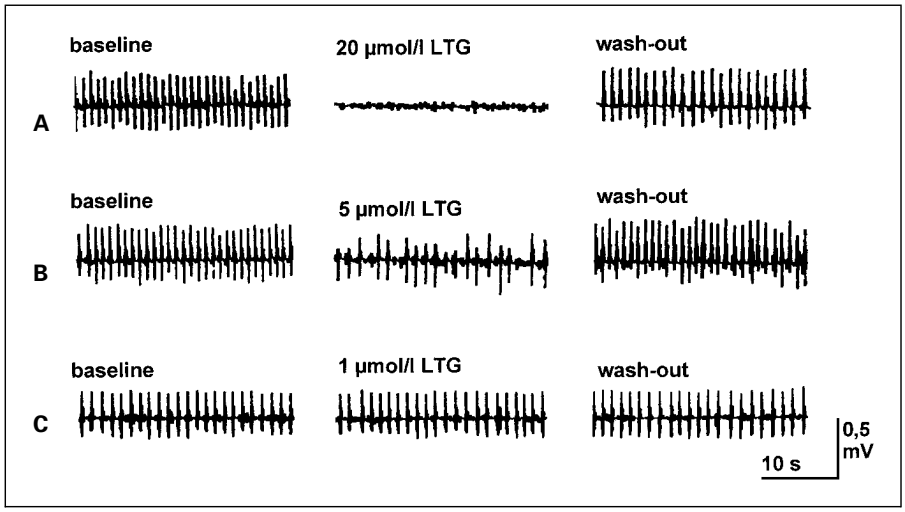

Fig. 1. LTG reduces extracellular field potentials induced by omission of Mg^{2+} from the extracellular bath solution. Recordings before (baseline), 30 min during and 60 min after (wash-out) the superfusion with 20 µmol/l (**A**), 5 µmol/l (**B**) and 1 µmol/l LTG (**C**).

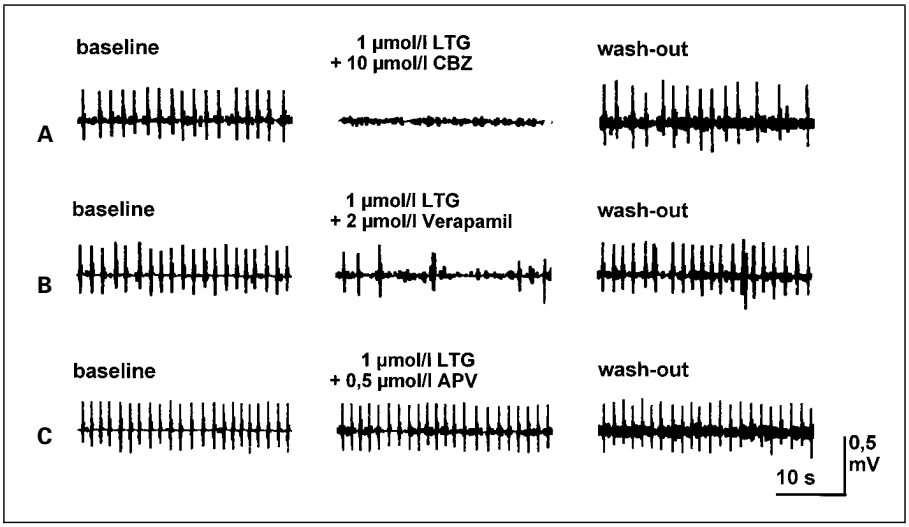

Fig. 2. Effects of combinations of subthreshold concentrations of LTG with subthreshold concentrations with CBZ (**A**), VERA (**B**) and 5-aminophosphonovalerate (APV; **C**).

Methods

Extracellular Recordings

Extracellular recordings of spontaneous, rhythmic excitatory field potential (EFP) bursts in low Mg^{2+} artificial cerebrospinal fluid (ACSF) are a convenient method to screen substances for calcium antagonistic properties. Several investigations have shown that calcium currents essentially contribute to the generation of these EFPs [16, 17]. Reduction or omission of Mg^{2+} induces EFPs by increasing the transmembraneous calcium flux into the cell. Hitherto, suppression of EFPs indicates calcium antagonistic properties of a substance (for details of this rationale, see [17]).

Our experiments [18] were performed in hippocampal slices of guinea pigs (weight 350–550 g, both genders). After removing the brain under ether anesthesia, transverse hippocampal slices of 350–500 µ*M* were cut. The ionic composition of the ACSF during pre-incubation of the slices for 1 h was (in mmol/l): NaCl 124, KCl 4, $CaCl_2$ 0.75, KH_2PO_4 1.24, $MgCl_2$ 1.3, $NaHCO_3$ 26, and glucose 10. Slices were kept at 28 ºC and equilibrated with 5% CO in O_2 (pH 7.35–7.4) throughout the preincubation and recording period. After placing a slice in the recording chamber and switching to ACSF without Mg^{2+}, spontaneous EFPs developed in the hippocampal CA3 and CA1 area. To increase epileptic activity, potassium concentration was elevated from 4 to 8 mmol/l in some recordings. Recordings were made with borosilicate electrodes containing 2 mmol/l NaCl. The signals were amplified by a conventional microelectrode amplifier from NPI electronics, stored on an oscilloscope and plotted on a chart recorder. Results are given as mean ± SE.

Intracellular Recordings

In order to characterize the effect of LTG on the early transient potassium outward current, we performed whole cell patch clamp and voltage clamp recordings from CA 1 pyramidal neurons in a hippocampal slice preparation from Long-Evans rats (20–30 days, both genders).

Harvesting of slices was done as described above. Slices were placed in a recording chamber continuously superfused with ACSF containing (in mmol/l): NaCl 124, KCl 3.75, KH_2PO_4 1.25, $MgCl_2$ 1.3, $CaCl_2$ 2.5, $NaHCO_3$ 26, glucose 10. The ACSF was bubbled with 95% O_2/5% CO_2 and maintained at 30 ± 2 °C throughout the recordings. The recordings were obtained with borosilicate glass electrodes (resistance 4–6 MΩ) filled with (in mmol/l): K-citrate 120, $CaCl_2$ 1, $MgCl_2$ 3, MaATP 2, NaGTP 2, EGTA 3 and HEPES 40 (modified from Blanton et al. [19]). In voltage-clamp recordings, tetrodotoxin (TTX) 0.6 µmol/lwas added to the ACSF and in two experiments, tetraethylammonium chloride (TEA) 10 mmol/l was also added. LTG was dissolved in 0.3% DMSO (final concentration), which, in control experiments, had no effect on the electrophysiological properties, and was administered systemically with the ACSF. Both voltage clamp and current clamp recordings, using a bridge circuit, were made with an Axoclamp 2A amplifier (Axon Instruments, Burlingame, Calif., USA). Data were collected standardized at baseline, after a 30-min wash-in period of LTG and after a 30-min wash-out. Results are given in percent of change ± SE.

Experiments were only conducted on cells with a resting membrane potential of 58 mV and above (range in all cells considered for experiments 58–65 mV), their input resistance was between 50 and 100 MΩ. These parameters were monitored for stability at the beginning and after a 30-min wash-out at the end of the experiment.

Differences in the species used and the composition of the ACSF are explained by the fact that extra- and intracellular recordings were conducted independently in two different laboratories. Drugs used were supplied from Sigma except for LTG (Glaxo-Wellcome, England) and CBZ (Desitin Arzneimittel GmbH, Germany).

Results

Extracellular Recordings

After switching the slice to a zero Mg^{2+} solution typical EFPs developed spontaneously within a few minutes (fig. 1, baseline) resembling the extracellular correlate of intracellular paroxysmal depolarization shifts [13, 14, 20]. The discharge rate of EFP in 8 mmol/l K^+ in the ACSF was in the range of 21–88/min (n = 19) with no difference between the CA3 and CA1 region of the hippocampal slice [16].

When LTG 10 µmol/l was added, EFP were reduced both in amplitude and frequency up to a total suppression after 20–40 min. Typical experiments with 20, 5 and 1 µmol/l LTG are depicted in figure 1. A similar decline of EFP rates as with 20 µmol/l LTG was observed in prior experiments where CBZ (50 µmol/l) or verapamil (VERA, 20 µmol/l) was added to the ACSF (cf. Walden et al. [13]). The effect of LTG on low-Mg^{2+}-induced EFP showed dose-dependency with an EFP rate reduction for 5 µmol/l LTG to 0.22 ± 0.24 (n = 5) and to 0.51 ± 0.08 (n = 6) for 2 µmol/l LTG. Following withdrawal of LTG from the ACSF, the baseline EFP rates were fully restored within 56–82/min.

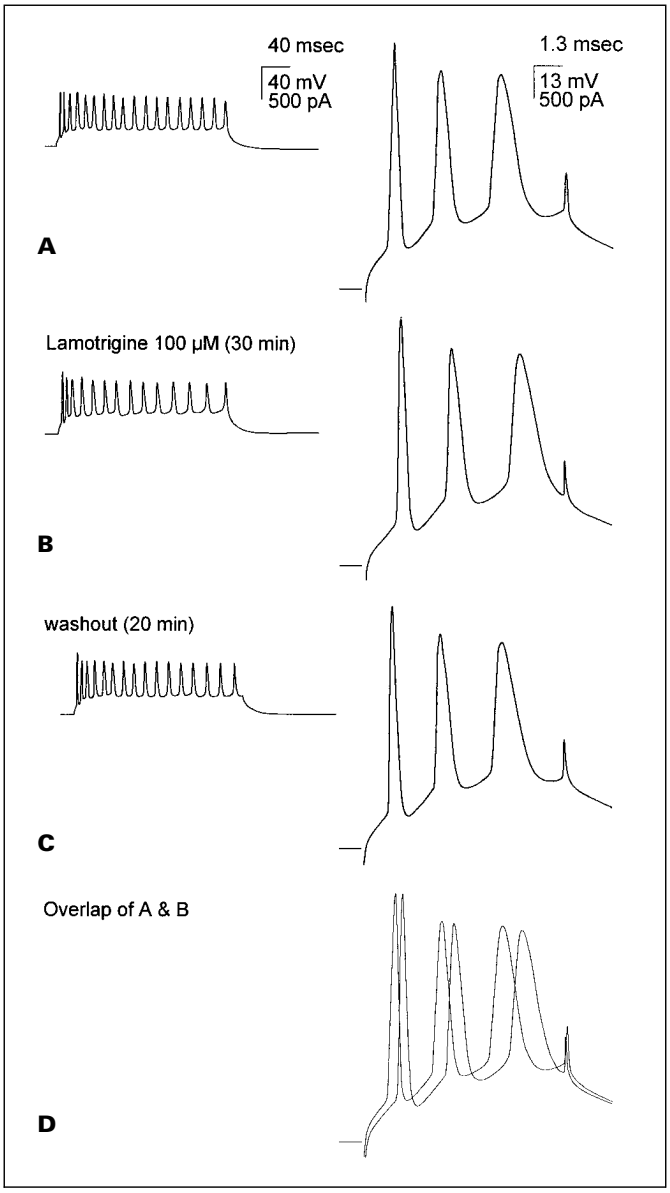

Fig. 3. 100 µ*M* LTG reduces neuronal excitability in a whole cell patch clamp recording of a pyramidal CA1 neurone. Left trace: Response to 150 pA current input, duration 250 ms, holding potential –60 mV. Right trace: Response to 850 pA current input, duration 10 ms, holding potential –60 mV. **A** Baseline. **B** After 30-min LTG (100 µ*M*). **C** After 30-min wash-out. **D** Overlap of **A** and **B**, right traces.

With 1 µmol/l LTG, no effect on the EFP rate could be observed. This concentration of 1 µmol/l of LTG was considered as a subthreshold concentration (fig. 1C). Similar, subthreshold concentrations evaluated in earlier experiments were 2 µmol/l for VERA and 10 µmol/l for CBZ [13, 14]. To investigate the additive effects of LTG

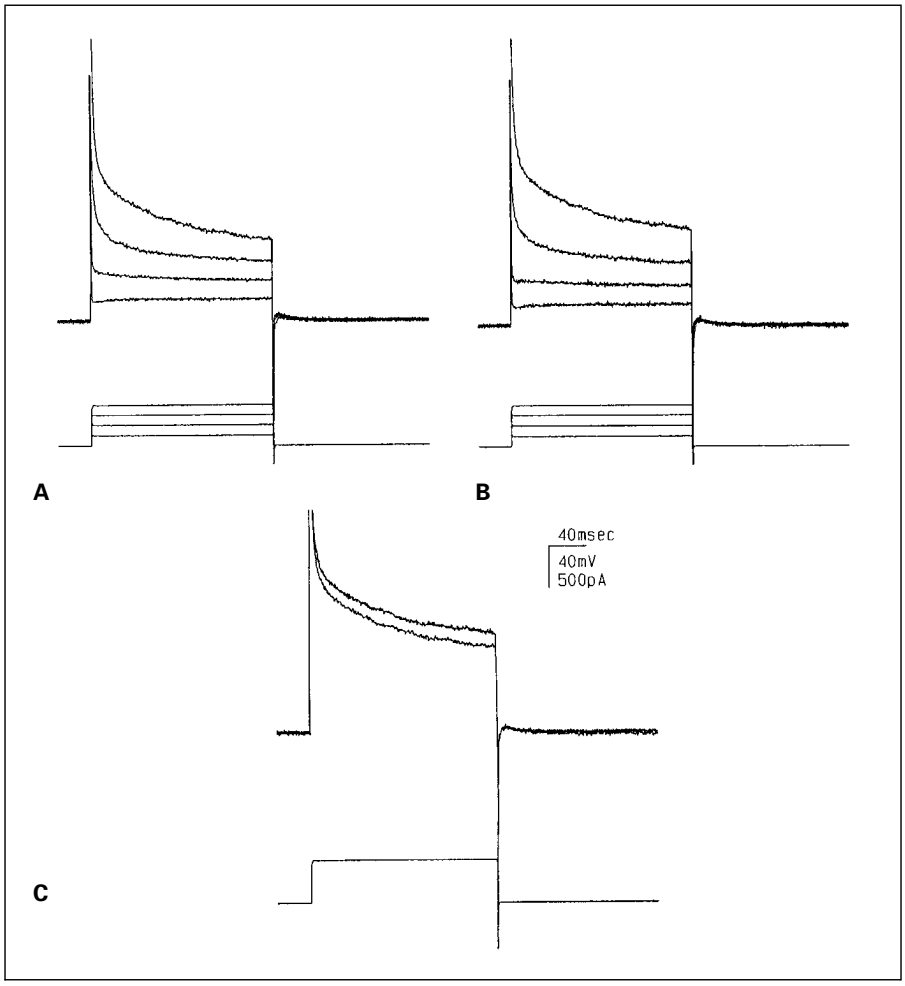

Fig. 4. Voltage clamp recordings, 100 μ*M* LTG, TTX 0.6 μ*M*, HP –80 mV. **A** Baseline response to depolarizing voltage steps of 10–40 mV. **B** After 30-min LTG. **C** Overlap of **A** and **B**, response to a +40 mV step.

with CBZ and VERA, the subthreshold concentration of 1 μmol/l LTG was administered either with the subthreshold concentration of 10 μmol/l CBZ or the subthreshold concentration of 2 μmol/l VERA. These combinations reduced the EFP rate to 0.62 ± 0.32 ($n = 8$) for LTG with CBZ (fig. 2A) and to 0.34 ± 0.14 ($n = 6$) for LTG with VERA (fig. 2B).

Since removal of the magnesium block of the postsynaptic NMDA receptor is one mechanism involved in the generation of low-Mg^{2+}-induced field potential changes [17] the effect of the NMDA antagonist 5-aminophosphonovalerate (APV) on the EFP repetition rate was tested. APV reduced the frequency of occurrence of EFP in a dose-dependent manner. The subthreshold concentration of APV without effects on the EFP rate turned out to be 0.5 μmol/l. However, combining subthreshold concentration of 1 μmol/l LTG with the subthreshold concentration of 0.5 μmol/l APV was without effect ($n = 4$; fig. 2C), making the NMDA receptor unlikely as the primary site of action for LTG.

Intracellular Recordings

Bridge Mode Recordings. A depolarizing current was injected through the recording electrode (150–950 pA, 250 ms), starting from a holding potential of –60 mV, eliciting a high-frequency train of action potentials (AP). LTG (25 μmol/l, administered systemically with the ACSF for 30 min, $n = 7$) neither effected input resistance, nor AP threshold and AP duration. Maximal spiking frequency at 150 pA was reduced by $-36 \pm 27\%$ (range $-67 \rightarrow 0\%$, $p \leq 0.025$, Mann-Whitney test). Although LTG had no effect on the AP amplitude of the first spike, it caused a nonsignificant trend of reversibly decreasing the AP amplitude of the second spike ($-5 \pm 6\%$). These findings can be explained with the previously described inhibition of fast sodium channels [4, 5, 10]. In 5/7 cells,

an increase of the latency from current input to AP threshold of the first spike (Δ_{tc-tAP}) was observed ($21 \pm 16\%$, range $42 \rightarrow 0\%$). All of these changes were only partially reversible within 30-min wash-out.

Increasing the concentration, LTG (100 μmol/l, $n = 6$) diminished the first AP amplitude by $13 \pm 11\%$ ($p \leq 0.025$), and reduced the AP frequency for given current steps ($-43 \pm 20\%$ at 350 pA, $-42 \pm 9\%$ at 150 pA, both significant at $p \leq 0.025$). Further analysis showed that this was caused by a reversible increase of the interspike interval with unchanged AP duration. Δ_{tc-tAP} was also increased by $55 \pm 37\%$ ($p \leq 0.025$) at 150 pA (fig. 3). This observation was backed up by 2 further recordings from a holding potential of –75 mV showing a clear-cut increase of Δ_{tc-tAP}.

Voltage Clamp Recordings. These effects were a hint pointing towards a modulation of the fast transient potassium outward current. Accordingly, voltage clamp analysis was performed in 8 neurons after addition of TTX (0.6 μmol/l). From a holding potential of –80 mV, depolarizing voltage steps from 10 to 40 mV were conducted. 6/8 neurons showed an increase of a transient outward current, activated instantly and lasting for more than 200 ms, observed with a step command of +40 mV in the presence of 100 μmol/l LTG (fig. 4). Again, this increase was only partially reversible within a 30-min wash-out period. To exclude an effect of DMSO by itself, three cells were recorded under similar conditions, adding only 0.3% DMSO. No changes were observed under this condition.

To ensure that this finding was not due to an increase of the delayed rectifier, we added TEA 10 mmol/l together with TTX at baseline ($n = 2$ neurons). As a result, we obtained a similar increase of the early current component which was again only partially reversible after a 30-min wash-out (fig. 5).

Analysis of all 8 neurons (fig. 6A) showed that this early current consists of an instantly activating and rapidly declining component (fig. 6B) and a second component, activated within a short delay and lasting for more than 150 ms (fig. 6C). This appears characteristic for I_A and I_D, respectively [21]. These currents are closely related and co-existing fast transient potassium outward currents which are, in contrast to the delayed rectifier, not sensitive to TEA. Averaging over all 8 neurons and extrapolating to $t = 0$ showed an increase of current in LTG by 193 pA for the early component made of both I_A and I_D. Subtracting the extrapolated I_D component at $t = 0$, based on the current between 50 and 150 ms after I_A inactivation, reveals that the current increase caused by LTG is almost exclusively due to an enhancement of I_D (fig. 6D). At this point, it remains undetermined whether this is a true increase or a shift of its steady state inactivation function, which still has to be further characterized.

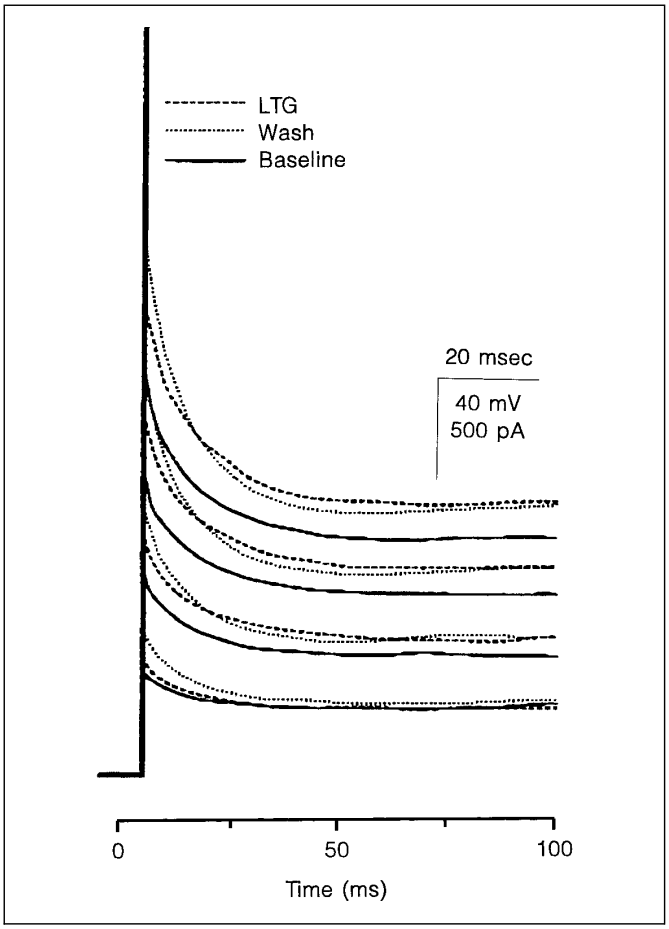

Fig. 5. Voltage clamp recordings, 100 μ*M* LTG, TTX 0.6 μ*M*, TEA 10 mM, HP –80 mV. Magnification of the early components (t from 0 to 100 ms) shows again the increase of the fast, non-TEA-sensitive transient outward current. Solid line = baseline; large dots = LTG for 20 min; small dots = after a 30-min wash-out.

Discussion

In the experiments presented here it was found that the new antiepileptic drug LTG reduced dose-dependently the repetition rate of extracellular field potentials in the low-magnesium model of epilepsy. The addition of subthreshold concentrations of LTG and the organic calcium antagonist VERA or the antiepileptic drug CBZ, respectively, also led to a reduction of the frequency of

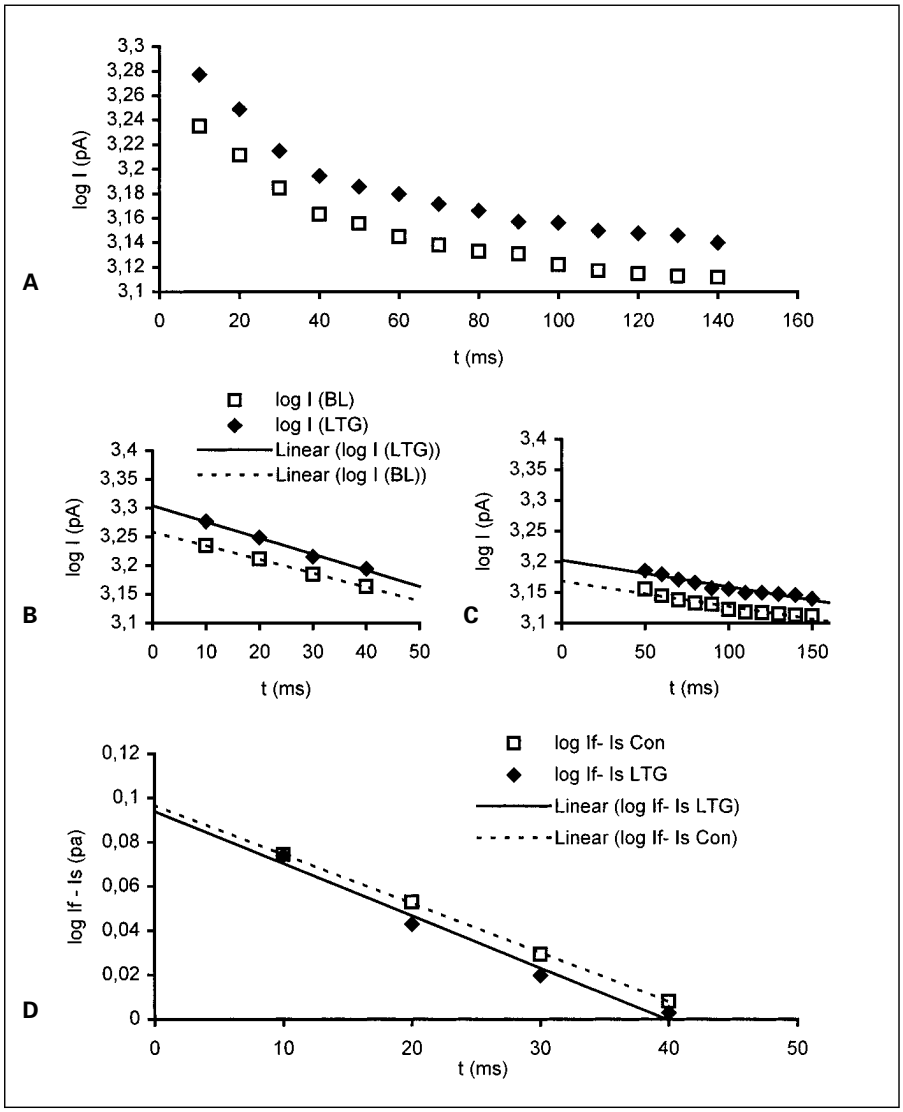

Fig. 6. A Plots of log I (pA) – t (ms) for the mean current of all 4 neurons in response to a +30 mV step (–80→–50 mV). I(BL) = Control before LTG application; I(LTG) = after 30 min application of 100 μ*M* LTG. **B** Linear regression for the interval 10–40 ms to extrapolate for the I_A component at t = 0. **C** Linear regression for the interval 50–150 ms to extrapolate for the I_D component at t = 0. **D** Subtraction of the slow component I_D from the fast component I_A both for LTG and control reveals that there is no significant contribution of I_A. The overall increase of current is almost exclusively due to an increase of I_D.

occurrence of zero-Mg^{2+}-induced field potentials. The zero-Mg^{2+} model is thought to cause epileptiform discharges due to increased transmembraneous calcium ion fluxes and it is blocked by organic calcium channel inhibitors, e.g. VERA [13, 16, 22]. In concentrations as used in the present investigation, VERA specifically blocks L-type calcium channels, but fails to alter other membrane currents nor affects glutamatergic or GABAergic neurotransmission [23–26]. Thus, LTG may beside its action on voltage-dependent sodium channels [5, 6] also modulate neuronal L-type calcium channels. This is of special interest because calcium antagonistic actions are discussed in treatment strategies of epilepsies [27] as well as in affective disorders [28].

Clinical effects of LTG require steady state plasma concentrations of about 4–16 μmol/l. However, some patients with epilepsy may need concentrations up to 40 μmol/l [29]. Because 55% of the total LTG in humans is bound to plasma proteins, the free concentration range is estimated between 2 and 20 μmol/l which corresponds to the concentrations used in the extracellular experiments. In intracellular experiments, higher concentrations (100 μmol/l) were used to obtain more pronounced differences of currents; however, the same direction, but not magnitude, of effects on potassium currents was also observed in clinically relevant concentrations of 25 μmol/l. In this regard, most concentrations used in this in vitro model correspond to therapeutic plasma levels of LTG.

These extracellular experiments do not differentiate between the types of calcium channels which may be blocked by LTG and the possibility cannot be ruled out that modulations of second messenger systems impinging on calcium channel phosphorylation may be involved. Moreover, the reports in the literature are controversial. Whereas Lees and Leach [30] describe the inhibitory effects of 100 μmol/l LTG on presumptive calcium currents in cultured cortical rat neurons, Lang and Wang [31] found no significant effect on L-type and T-type currents in whole cell clamped pituitary cell lines. For amygdala neurons, however, there are also recent reports on the effects of LTG on N-type calcium channels [32]. The additive effect of subthreshold concentrations of VERA and LTG in our experiments, however, also makes action via L-type calcium channels likely. Although presynaptic effects of LTG on NMDA channels have been described [33], actions through modulation of postsynaptic NMDA channels by LTG appear less likely, as it shows no additive effects in subthreshold concentrations with APV. Furthermore, it has been shown previously that LTG does not to exert actions on NMDA stimulated formation of cyclic GMP [5].

Intracellular recordings focused on another mechanism of limiting excitation, which is strengthening the fast potassium outward current. Our whole cell and voltage clamp experiments in hippocampal CA1 neurons suggest that LTG is a positive modulator of these currents. This is a property of LTG which was previously described for the inorganic substance zinc [34] and, for I_A, from two other antiepileptic drugs: valproate, tested in snail neurons [11] and CBZ, tested in neocortical cell cultures from rats [12], whereas, to our knowledge, positive modulators of I_D have not been described yet.

In conclusion, our experiments show effects of LTG in a calcium-dependent model of epilepsy in extracellular recordings and on fast potassium outward currents in patch clamp recordings. This indicates that the therapeutic efficacy of this drug does not only result from its action on voltage-dependent sodium channels with the consequence of a decreased glutamate release, but also from other modulating effects on ion channels. With respect to calcium, this is of interest, since (a) a disturbed calcium ion homeostasis is discussed in the pathophysiology of affective disorders [8]; (b) the use of calcium antagonistic drugs is considered in the therapy of epilepsy [28], and (c) clinical studies with organic calcium antagonists have shown therapeutic effects both in mania and depression [35–38]. With respect to the modulation of potassium currents by LTG, similar results have been reported for valproate [11] and CBZ [12]; the implication of this finding for the pathophysiology and treatment of epilepsies or bipolar disorder, however, still has to be determined.

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