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Effects of lacosamide and carbamazepine on human motor cortex excitability: A double-blind, placebo-controlled transcranial magnetic stimulation study

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ABSTRACT

Purpose: Lacosamide (LCM) and carbamazepine (CBZ) are antiepileptic drugs both acting on neuronal voltage-gated sodium channels. Patch-clamp studies demonstrated significant differences in how LCM and CBZ affect neuronal membrane excitability. Despite valuable information patch-clamp studies provide, they also comprise some constraints. For example, little is known about effects of LCM on intracortical synaptic excitability. In contrast, transcranial magnetic stimulation (TMS) can describe drug-induced changes at the system level of the human cerebral cortex.
Methods: The present study was designed to explore dose-depended effects of LCM and effects of CBZ on motor cortex excitability with TMS in a randomized, double-blind, placebo-controlled crossover trial in healthy human subjects. Subjects received 600 mg CBZ, 200 mg LCM, 400 mg LCM or placebo preceding TMS measurements.
Results: Compared to placebo, TMS motor thresholds were significantly increased after carbamazepine and lacosamide, with a trend for a dose dependent effect of lacosamide. Both, carbamazepine and lacosamide did not affect TMS parameters of intracortical synaptic excitability.
Conclusions: TMS measurements suggest that lacosamide and carbamazepine predominantly act on neuronal membrane excitability.

1. Introduction

CNS effects of neuroactive substances can be tested non-invasively with transcranial magnetic stimulation (TMS). TMS can measure several functions of cortical excitability, such as axonal membrane excitability of pyramidal tract neurons, and distinct forms of intracortical synaptic excitability.[1] In addition to some in vitro or animal research, TMS can investigate brain functions at a more comprehensive network level. This approach has been used in the past to compare pharmaco-physiologic properties of antiepileptic drugs of known action with newer substances, some with incompletely understood pharmacological mechanisms or multiple modes of action.[2–5]

Here we explored dose-depended effects of lacosamide (LCM) and effects of carbamazepine (CBZ) on motor cortex excitability with TMS in a randomized, double-blind, placebo-controlled crossover trial in young healthy human subjects. It was found in vitro that LCM selectively enhances slow inactivation of voltage-gated sodium channels, and, in contrast to CBZ, does not affect steady-state fast inactivation.[6] This mechanism of LCM to modulate sodium channels leads to normalization of activation thresholds and reduced pathophysiological hyper-responsiveness, without affecting physiological activity.[7] Therefore, it is thought that LCM, compared to CBZ, will be better tolerated by patients while being as or even more effective in controlling seizure activity.

On the basis of the results from nonhuman studies, we hypothesized that the TMS profiles of LCM and CBZ could be divergent. The idea behind this approach is not to use TMS to distinguish between fast and slow sodium channel inactivation, but to search for differential effects of the two drugs on the system level, that studies on the cellular level were unable to detect. CBZ, like other 'classical' sodium channel blockers such as phenytoin, predominantly demonstrated increased TMS motor thresholds indicating reduced neuronal membrane excitability, without developing significant changes of synaptic intracortical inhibition and facilitation.[4,8,9] Because of its novel mode of action it could only be speculated which TMS parameters LCM might affect. More than exclusively affecting neuronal membrane excitability, LCM could possibly also affect inhibitory mechanisms such as short-latency intracortical inhibition[10] or stimulation-induced excitability changes.[11,12] This would be in line with other well-tolerated modern antiepileptic drugs.[2,4,5,13]

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2. Materials and methods

2.1. Subjects

Fifteen healthy young men (mean age 26 ± 0.9 years; age range 19–32 years) gave their written informed consent to participate in the study. Women were not included due to potential medication risks in case of pregnancy. None of the subjects had any neurological or psychiatric disorder, as evaluated by certified medical specialists with experience in neurology (NL and HR). Further contraindications were: cardiac disorders; known hypersensitivity against lacosamide, carbamazepine, azoic dye or tricyclic antidepressants; acute intermittent porphyria; bone marrow disorders; implants in the head; drug or alcohol abuse; intake of any other medication and participation in another clinical trial within the previous 8 weeks. All subjects were consistent right-handers. Experimental procedures were approved by the Ethics Committee of the University of Kiel (Germany) and by the German Federal Institute for Drugs and Medical Devices (Bundesinstitut fuer Arzneimittel und Medizinprodukte, BfArM), and the study was performed according to the ethical standards laid down in the Declaration of Helsinki. The study was supported by a grant from UCB Pharma GmbH in Monheim (Germany), monitored by the Center for clinical studies (Zentrum fuer klinische Studien, ZKS) in Kiel and registered under www.ClinicialTrials.gov (NCT01382017).

2.2. Experimental design

The study was performed in a double-blind placebo-controlled cross-over design. All fifteen subjects participated in four drug conditions, separated by at least 1 week. Uniform capsules, containing 200 mg LCM, 100 mg LCM, 300 mg CBZ or placebo, were orally administered 12 and 2 h before TMS measurements (Fig. 1). This procedure has been used previously,[2,14] since serum concentrations and CNS effects can be expected to peak by the time of TMS measurements.[15,16] The order of drug conditions was pseudorandomized and balanced between subjects, and subjects and examiners were both blinded for them. TMS experiments were all performed on the left primary motor cortex (M1) and at identical times during morning hours with the subjects comfortably seated in a reclining chair with head and arm rests. Surface EMG from the right first dorsal interosseus muscle (FDI) was recorded through two Ag–AgCl surface electrodes placed over the muscle belly and the tendon. Raw signals were amplified, band-pass filtered (3 Hz–2 kHz) and sampled at 5 kHz by a PC attached to a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, UK) controlled by Signal Software (Cambridge Electronic Design, version 4.08). Muscle relaxation was controlled by auditory and visual feedback. Single- and paired pulse TMS was performed by using a Magstim figure-eight-shaped 70-mm coil connected to Magstim Bistim[2] setup (Magstim Co., Dyfed, UK). The TMS coil was held over the left M1 with the handle pointing posterior and lateral. The induced electrical field of this coil positioning is optimal for a transsynaptic activation of the corticospinal system.[17] The optimal site for eliciting motor-evoked potentials (MEPs) in the resting right FDI was marked with a skin marker to ensure that the coil was constantly held correct during the experiment.

2.3. TMS measurements of cortical excitability

In each experimental session we measured the individual resting motor threshold (RMT), active motor threshold (AMT), the intensity to evoke MEP of ~1-mV peak-to-peak amplitude (SI1mV), short-interval intracortical inhibition/intracortical facilitation (SICI/ICF), recruitment curves (REC) and cortical silent periods (CSP).

Stimulus intensities (in percentage of maximal stimulator output) of TMS were determined at the beginning of each experiment. SI1mV was determined with single-pulse TMS first. RMT was determined using the maximum likelihood threshold hunting procedure[18] when the first dorsal interosseus muscle was completely relaxed. For AMT we used the lowest TMS intensity at which 50% of the stimuli elicited reliable MEP of approximately 200 μV in amplitude in the tonically contracting FDI.[19] For SICI/ICF two magnetic stimuli were given through the same stimulating coil in random order at 0.25 Hz.[10] The intensity of the conditioning stimulus was set to 90% AMT and the test-stimulus intensity to SI1mV. For SICI we used interstimulus intervals (ISI) of 2 ms and 4 ms, and for ICF ISIs of 9 ms and 12 ms. The control condition (test pulse alone) was applied 40 times, and each of the conditioning-test stimuli 20 times. The mean peak-to-peak amplitude of the conditioned MEP at each ISI was expressed as a percentage of the mean peak-to-peak size of the unconditioned test pulse. Mean SICI was defined as the mean percentage inhibition at ISIs of 2 and 4 ms, whereas mean ICF was defined as the mean facilitation at ISIs of 9 and 12 ms. Recruitment curves were measured with ten increasing stimulus intensities (90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, and 180% of RMT), each with 8 pulses. A mean was calculated for each intensity. At the end of each session, 10 pulses with SI1mV and 10 pulses with 120% RMT were applied under tonic contraction of the right first dorsal interosseus muscle. Out of these recordings CSPs were calculated in rectified and averaged EMG traces with a prestimulus period of 100 ms. We measured the CSP (in ms) from the TMS stimulus artefact to the point where the EMG signal reached the amplitude of the mean prestimulus EMG activity again for more than 5 ms.

2.4. Data analyses

The measures motor thresholds, SICI/ICF, recruitment and CSP were analyzed with separate analyses of variance (ANOVAs) for

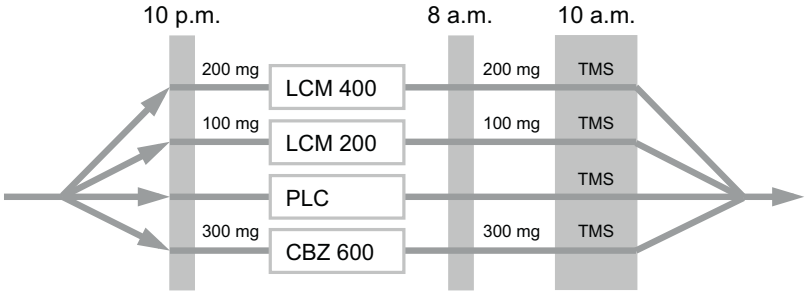

Fig. 1. Experimental design. Fifteen healthy volunteers received 200 mg or 400 mg lacosamide (LCM200, LCM400), 600 mg carbamazepine (CBZ600) or placebo (PLC) in a double-blind cross-over design. Half of the dose was taken 12 h and half of it 2 h before motor cortical excitability was examined with transcranial magnetic stimulation (TMS).