ORIGINAL CONTRIBUTION

Effect of Levetiracetam on Rapid Motor Learning in Humans

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Background: The human motor cortex (M1) has a role in motor learning. Antiepileptic drugs that suppress M1 excitability may affect learning, presumably by inhibiting long-term potentiation. Levetiracetam, a new antiepileptic drug with a unique preclinical profile, also suppresses M1 excitability, but in a way that is different from other antiepileptic drugs. The effect of levetiracetam on motor learning has yet to be addressed.

Objective: To investigate whether levetiracetam alters rapid motor learning in humans.

Methods: We measured pinch force and acceleration and motor excitability before and after 30 minutes of pinch practice at 0.5 Hz in 10 healthy volunteers. Either 3000 mg of levetiracetam or placebo was administered 1 hour before the experiment.

Results: After practice, pinch acceleration was significantly increased with placebo, but not with levetiracetam. All other measures showed no significant change.

Conclusion: Levetiracetam interferes with rapid motor learning; this is consistent with a negative influence on long-term potentiation.

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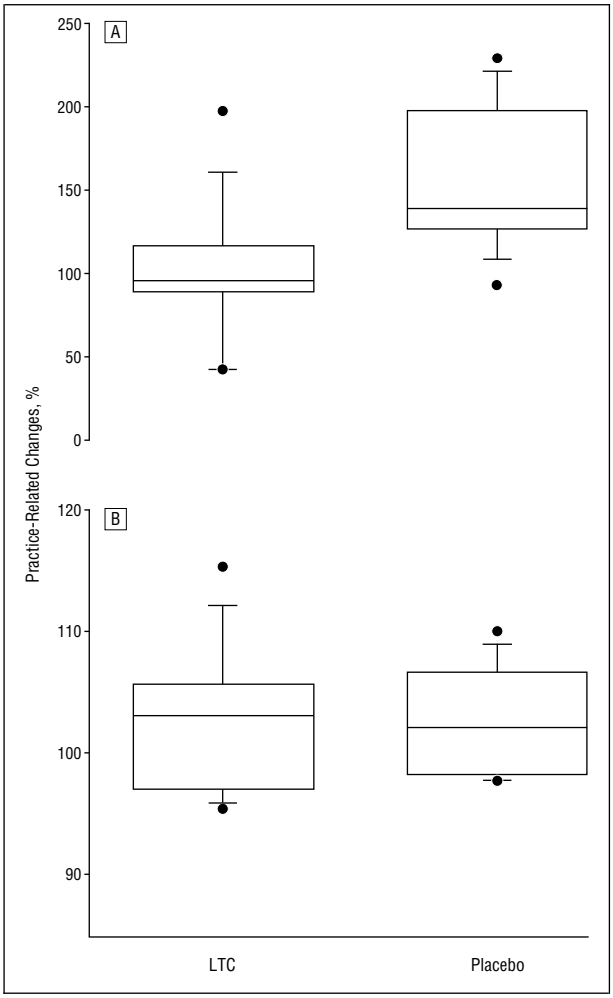
THE HUMAN MOTOR cortex (M1) has a role not only in executing voluntary movement but also in performing more intricate processes such as motor learning.[1] Motor output maps are enlarged during acquisition of new skills.[2,3] In addition to its involvement in motor skill learning that occurs over several days to weeks, M1 can show changes in excitability with relatively short-term training for an hour or less.[4] Rapid motor learning is presumably related to reorganization of M1 that encodes the kinematic details of the practiced movement.[5] In rat brain, repetition of certain movements modifies synaptic efficacy,[6] resulting in long-term potentiation (LTP) that has also been demonstrated in M1.[7] Thus, rapid motor learning may require short-term alterations in synaptic dynamics, such as LTP or a similar process, that contribute to change in M1 excitability.

Long-term potentiation is part of a continuum of types of neural modification, some leading to beneficial alterations such as motor learning and others that may be primarily pathological, such as kindling.[8] Many antiepileptic drugs (AEDs) affect learning and memory, likely through influences on LTP, like their effects on kindling.[9-11] The AEDs affecting γ-aminobutyric acid (GABA) transmission suppress both M1 excitability and plasticity.[12-14] However, lamotrigine, a sodium- and calcium-channel modifier, does not affect practice-related M1 plasticity, which shares the same mechanism as rapid motor learning,[13] although it suppresses M1 excitability.[14] Levetiracetam is a novel AED with an unique preclinical profile.[15] We have previously shown that levetiracetam also suppresses M1 excitability, but differently from other AEDs.[16] To better understand the mechanism of levetiracetam's action, we investigated its effect on M1 plasticity by means of a rapid motor learning paradigm.

METHODS

Ten healthy, right-handed volunteers (age, 22 to 43 years; 5 women and 5 men) participated in this study. All gave written informed consent. The experiment was approved by the institutional review board of the National Institute of Neurological Disorders and Stroke, Bethesda, Md.

Maximum pinch force of the left thumb and index finger was determined by means of a pinch gauge (Jamar; Sammons Preston, Inc, Bolingbrook, Ill). Volunteers were instructed to use only their thumb and index finger for the pinch force measurements. Maximum forces for 5 maximum voluntary contractions were measured each time, and average pinch force of 5 trials was calculated.



Boxplot representation of practice-related changes in pinch acceleration (A) and pinch force (B). Pinch acceleration was significantly increased with placebo, but not after levetiracetam (LTC), while pinch force was not increased in either condition. Outliers are marked by dots, horizontal lines indicate the median, boxes show the middle half of the data, and limit lines represent the range of the data.

Acceleration of each thumb flexion was measured by a miniature triaxial accelerometer (model 8791A250; Kistler Instrument Corp, Amherst, NY), firmly affixed to the proximal phalanx of the thumb with tape. The signal was amplified by a powered signal conditioner (Type 5134 power supply/coupler; Kistler Instrument Corp). Two-dimensional acceleration (x- and y-axis representing the proximal-distal and up-down directions, respectively, of the thumb movement) was measured simultaneously. The peak accelerations of 12 pinch movements were measured each time and average acceleration was calculated.

Motor evoked potentials (MEPs) of the flexor pollicis brevis (FPB) and abductor digiti minimi muscles of the left hand were recorded by means of silver–silver chloride surface electromyography (EMG) electrodes placed over these muscles in a belly-tendon montage. The EMG amplitude was amplified by means of a conventional EMG machine (Counterpoint; Dantec Electronics, Skovlunde, Denmark), with bandpass between 10 and 2000 Hz. The signal was digitized at a frequency of 5 kHz and fed into a laboratory computer for further off-line analysis. Transcranial magnetic stimulation (TMS) was delivered through a figure-of-8–shaped coil (each loop measures 70 mm in diameter) connected to a magnetic stimulator (Magstim 200; The Magstim Company Ltd, Whitland, Wales), and placed flat on the scalp over the right M1. The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline. With a slightly suprathreshold stimulus intensity, the stimulating coil was moved over the right hemisphere to determine the optimal position for eliciting MEPs of maximal amplitudes in the FPB. The optimal position of the coil was then marked on the scalp with a pen to ensure coil placement throughout the experiment. The TMS triggering and data acquisition were controlled with a LabVIEW program (National Instruments, Austin, Tex).[17]

Resting motor threshold (RMT) was determined to the nearest 1% of the maximum stimulator output and was defined as the minimal stimulus intensity required to produce an MEP of more than 50 μV in at least 5 of 10 consecutive trials. The MEP amplitudes were measured peak to peak. Recruitment curve of MEP amplitudes at stimulation intensities of 110%, 120%, 130%, and 140% RMT were measured. The TMS stimuli were delivered randomly between 5 and 7 seconds apart, with 15 stimuli for each stimulation intensity beginning with the lowest intensity, that is, 110% RMT.

Supramaximal electrical stimulation of the median and ulnar nerves at the wrist was used to assess spinal and peripheral motor excitability. While muscles were relaxed, the peak-to-peak amplitude and persistence of F waves (average, 20 trials) and compound muscle action potential (CMAP; maximum, 3 trials) were determined. The sum of CMAPs after median and ulnar nerve stimulation was used for the FPB.

After surface EMG electrodes were placed, each volunteer was instructed to perform pinch practice for 1 to 2 minutes to become familiar with the experimental setup. Either a single oral dose of 3000 mg of levetiracetam or placebo was then administered in a double-blind fashion. One hour later, pinch force and acceleration and motor excitability were measured (prepractice measure). Then, pinch practice with a metronome set at 0.5 Hz was performed for 30 minutes. The measures were repeated after practice (postpractice measure). The administration order of levetiracetam and placebo was randomly assigned. Intervals between 2 experimental sessions were between 72 hours and 2 weeks. For the pinch practice, subjects were asked to make a brisk pinch of short duration after each beat of the metronome and then to completely relax the left hand until the next beat. Continuous visual and auditory EMG feedback was given to ensure an EMG burst of less than 300 milliseconds.

Data are expressed as mean±SEM. The different measures were analyzed separately. The postpractice measures of pinch force and acceleration were expressed as a percentage of prepractice values. Peak-to-peak amplitudes of MEPs and F waves were related to CMAP and expressed as a percentage of CMAP. Statistical analysis used the nonparametric Mann-Whitney test to compare 2 groups, either between levetiracetam and placebo or between prepractice and postpractice values. $P<.05$ was regarded as significant.

RESULTS

All volunteers tolerated the experiment with no serious side effects or complications, except for mild drowsiness and dizziness in 4 individuals when they took levetiracetam. With placebo, 30-minute pinch practice significantly increased pinch acceleration (152%±14%), but this change was not observed after levetiracetam (101%±14%). In contrast, pinch force was not increased in either condition (103%±2.0% under levetiracetam and 103%±1.4% under placebo) (**Figure**).

The **Table** shows TMS, F wave, and CMAP measurements. The MEP amplitudes tended to be reduced

Practice-Related Changes in Motor Excitability Measures*

	Flexor Pollicis Brevis Muscle				Abductor Digiti Minimi Muscle			
	Levetiracetam		Placebo		Levetiracetam		Placebo	
Measures	Pre	Post	Pre	Post	Pre	Post	Pre	Post
RMT	42 ± 3.4	42 ± 3.1	42 ± 3.3	41 ± 3.2	. . .	. . .	. . .	. . .
Recruitment curve, % CMAP								
110% RMT	1.7 ± 0.4	1.2 ± 0.2	2.9 ± 0.9	2.2 ± 0.6	3.5 ± 1.2	2.7 ± 1.0	3.7 ± 0.7	3.1 ± 0.5
120% RMT	4.6 ± 0.9	3.5 ± 0.7	6.3 ± 2.0	5.7 ± 1.3	6.2 ± 1.8	5.8 ± 1.7	6.4 ± 1.1	7.0 ± 1.5
130% RMT	7.0 ± 1.7	5.9 ± 1.9†	8.6 ± 2.1	9.3 ± 2.0	9.5 ± 2.7	9.1 ± 2.4	12.1 ± 2.3	10.5 ± 2.1
140% RMT	7.9 ± 1.8‡	8.5 ± 2.4‡	11.1 ± 2.5	12.5 ± 3.0	13.1 ± 3.5	13.6 ± 2.9	14.7 ± 2.7	13.6 ± 2.9
F wave								
Amplitude, % CMAP	0.62 ± 0.15	0.77 ± 0.30	0.68 ± 0.24	0.81 ± 0.27	1.33 ± 0.37	1.28 ± 0.37	1.55 ± 0.38	1.51 ± 0.32
Presence, %	47 ± 4	48 ± 9	41 ± 9	52 ± 5	74 ± 6	66 ± 8	80 ± 6	84 ± 4
CMAP, mV	24.3 ± 2.0	25.4 ± 1.8	26.3 ± 1.5	26.7 ± 1.5	14.8 ± 1.2	14.6 ± 1.2	15.7 ± 1.6	15.5 ± 1.5

*All values are expressed as mean ± SEM. Pre indicates prepractice; post, postpractice; RMT, resting motor threshold; and CMAP, compound muscle action potential.
†$P<.05$ compared with placebo-treated state.
‡$P<.01$ compared with placebo-treated state.

under levetiracetam compared with placebo, in both prepractice and postpractice measures, particularly at stimulation intensities of 130% and 140% RMT. Mean MEP amplitudes of FPB (at 130% and 140% RMT) under levetiracetam were 63% to 81% of those under placebo. However, MEP amplitudes were not changed significantly after pinch practice in either condition in both the FPB and abductor digiti minimi muscles. There were no differences in RMT, F-wave amplitudes and persistence, and CMAP between levetiracetam- and placebo-treated states. In addition, these were unchanged after pinch practice. There were no significant differences in practice-related changes of pinch acceleration, force, and TMS measurements between volunteers with and without side effects.

COMMENT

According to our previous results,[16] after oral administration, the suppressive effect of levetiracetam on M1 excitability is stable for at least 6 hours and should return to baseline after 48 hours. Thus, its effect on motor learning is presumably stable throughout the present experiment and should not affect the next experiment that followed at least 72 hours later. Pinch force increment may persist after pinch practice,[4] but we found no carryover effect from previous practice on all measures. In addition, randomized administration order of drug and placebo should minimize the differences in any carryover effect between the 2 groups. Although levetiracetam and placebo were administered in double-blind fashion, it might not have been blinded in the 4 subjects who experienced side effects. Thus, we compared the data from this subset of subjects with the others and found that the side effects, ie, possible recognition of drug and placebo, did not affect our results.

This study demonstrates the suppressive effect of levetiracetam on rapid motor learning measured by pinch acceleration. With placebo, as previously described,[4] volunteers showed a significant increase in pinch acceleration after a 30-minute practice, supporting pinch practice as a reproducible method to assess rapid motor learning. However, this increase was not observed in the levetiracetam-treated state. We failed to reproduce other changes such as increased pinch force and increased MEP amplitude observed in previous studies. This discrepancy is presumably due to a different protocol for pinch practice. We used a 30-minute pinch training at 0.5 Hz to complete the experiment while the plasma level of levetiracetam was relatively stable. In contrast, practice lasted for 60 minutes or was at 1 Hz in previous studies.[4,5,13] Animal experiments have demonstrated that different populations of M1 cells are involved in coding static force and dynamic movement variables, and that M1 is more related to controlling the dynamic component, such as movement direction and speed, than static force.[18] Therefore, pinch acceleration is likely a more sensitive measure of M1 plasticity than static pinch force.

Transcranial magnetic stimulation was performed to measure practice-related changes in M1 excitability in both levetiracetam- and placebo-treated states. The F waves and CMAPs measured spinal and peripheral nerve excitability, respectively. Consistent with results from our previous study,[16] MEP amplitudes were suppressed in the tested muscles with levetiracetam, compared with the placebo-treated state, although this difference attained statistical significance only in the FPB at a stimulation intensity of 130% RMT. After pinch practice, no significant changes were observed in RMT, recruitment curves of MEP amplitudes, and F waves and CMAPs in both levetiracetam- and placebo-treated states. These findings are inconsistent with previous observations showing significant increase in MEP amplitudes,[4] presumably due to the difference in practice duration. The present results suggest that enhanced M1 excitability is not a prerequisite for rapid motor learning, but may be a parallel phenomenon induced by repetitive motor practice. During pinch practice, reorganization of cortical networks may precede excitability enhancement.

Short-term repetitive pinch training induces strengthening of intracortical neuronal ensembles generating outputs in favor of the trained movement,[13] which may lead

to increased pinch acceleration. This rapid and long-lasting reorganization may arise by unmasking horizontal excitatory connections within M1 that were previously hidden by coactivated local inhibitory neurons.[19] This change can be persistently strengthened by LTP acting through horizontal excitatory connections.[6] Pharmacologic manipulations that alter the effectiveness of intrinsic connections, ie, GABAergic and glutamatergic interneurons, affect the short-term plasticity of M1 by influencing LTP.[13,19] Although levetiracetam's action is not the result of any interaction with known mechanisms involved in inhibitory and excitatory neurotransmission,[20] its suppressive action on M1 excitability may disturb the rapid motor learning process, presumably by influencing LTP.

In this study, a usual daily dose of levetiracetam was administered as a single dose to achieve sufficient effect. This dose, although its safety has been approved in our previous study as well as in others,[16,21] may induce much higher plasma levels of levetiracetam than does the current therapeutic regimen. The frequency of side effects, albeit mild and transient, was also higher than previously reported.[22] Thus, the present results cannot be directly applied to most patients receiving long-term treatment, but can provide insights about the action of levetiracetam.

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