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Riluzole does not have an acute effect on motor thresholds and the intracortical excitability in amyotrophic lateral sclerosis

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Abstract Intracortical excitability in amyotrophic lateral sclerosis (ALS) is impaired. The effectiveness of the glutamate antagonist riluzole (Rilutek®, Rhône-Poulenc Rorer) in ALS has been shown in clinical studies. In healthy subjects it modifies intracortical excitability in a frequently used double-stimulus paradigm of transcranial magnetic stimulation (TMS). Under riluzole intracortical inhibition is enhanced in healthy individuals, although not always significantly, whereas intracortical facilitation has been described as reduced [10, 11]. We wanted to find out whether riluzole affects and potentially rebalances impaired intracortical excitability in ALS. We, therefore, enrolled 13 patients with clinically and electromyographically confirmed ALS into this study. Five patients had to be excluded because motor thresholds were too high to get reliable motor evoked potentials (MEPs). In the remaining 8 patients, mean age was 59.9 ± 11.9 years (± standard deviation) and mean symptom duration 9.6 ± 2.5 months. Intracortical excitability was assessed before and 1.5 hours after the first intake of a loading dose of 100 mg of riluzole using a conventional paired-pulse TMS paradigm with interstimulus intervals (ISI) ranging from 1–30 ms and intensities adjusted to yield MEPs of 1.0 mV for test pulses and of 90% active motor threshold for conditioning pulses. Patients' baseline results were compared to those of 9 age-matched, healthy control subjects. Before drug intake, motor thresholds did not differ between groups, but there was significantly less intracortical inhibition in the ALS patient group. Riluzole intake did not significantly alter motor thresholds or intracortical excitability in the ALS patients. We conclude that riluzole does not immediately influence intracortical excitability in ALS. Our results are in contrast to the findings of Stefan et al (1998) [14] where a partial normalization of intracortical inhibition in ALS was observed after at least 5 days of drug intake. The difference between that study and our result may indicate a delayed onset of riluzole's influence on intracortical excitability.

Key words Amyotrophic lateral sclerosis · Transcranial magnetic stimulation · Intracortical excitability · Riluzole

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive degeneration of motor neurons at all levels of the central nervous system (spinal, brain stem, and cortex). The cause of ALS is unknown; it occurs sporadically in the vast majority of cases (sporadic ALS), although in 5–10% of patients a hereditary component is likely to be involved (familial ALS)

[1]. A number of pathophysiological mechanisms for the cause of ALS have been proposed, e.g. increased and toxic activity of the excitatory neurotransmitter glutamate [13, 16, 15]. Neurophysiological studies in ALS have provided evidence of a decreased intracortical inhibition [17, 19, 5], whereas intracortical facilitation, motor thresholds and the duration of the cortical silent period were normal [19].

Riluzole (Rilutek®, Rhône-Poulenc Rorer) modulates cortical and spinal neurotransmission by a number of mechanisms, including the inhibition of presynaptic release of the excitatory transmitters glutamate and aspartate [12], the non-competitive block of glutamate receptors [2] and the inactivation of voltage-dependent sodium channels [6]. Its effectiveness in ALS has been shown in clinical studies [3, 9].

In the light of the impaired intracortical excitability in ALS and the slowing of disease progression by riluzole, the question arises whether riluzole affects and possibly normalizes the intracortical excitability in ALS. Indeed, studies in healthy control groups have shown an association between riluzole activity and intracortical excitability [10, 11]. In one of these studies [10], a single dose of 150 mg riluzole caused a significant reduction of intracortical facilitation and a non-significant enhancement of intracortical inhibition, whereas motor thresholds and silent periods remained unchanged. Another study [11] yielded similar findings of a significant reduction of intracortical facilitation and a significant increase of intracortical inhibition following riluzole intake over 7 days. Based on these findings we wanted to test the influence of riluzole on motor thresholds and intracortical excitability in newly diagnosed ALS patients.

Methods

We investigated 13 patients with newly diagnosed ALS who had never received any specific treatment for this disease (Table 1). Diagnosis was confirmed by at least two board-certified neurologists (CDR & WB) after a thorough clinical and electomyographical examination in which patients fulfilled the standardized El Escorial criteria [4]. The severity of symptoms was scored using an ALS severity scale [7] (ALSSS) measuring the ability of speech, swallowing, walking and hand motor function, 10 points for each measure indicate normal performance. Since in 5 patients the motor thresholds were found to be too high to elicit reliable motor evoked potentials (MEPs), only 8 patients entered the study protocol (mean age, 59.9 years; range, 37–76 years). Of the 8 patients included, 5 had clinical signs of the bulbar type of ALS (mainly dysarthria and swallowing difficulties), while 3 patients had upper limb weakness and wasting of hand muscles without bulbar affection. Patients were tested before and 90 minutes after taking a loading dose of 100 mg riluzole. For baseline comparison we investigated 9 untreated and age-matched volunteers (mean age, 53.4 years, range 41–73 years) who had no history of any neurological or unstable medical disease and were normal on a routine examination. The protocol was approved by the local ethics committee, and written informed consent was obtained from all subjects prior to entry into the study.

During the investigations the subjects were seated in a reclining chair with the arms and the neck comfortably supported. In patients with hand muscle wasting, we investigated the more affected side, and the predominant hand in the other patients. We delivered transcranial magnetic stimulation (TMS) over the contralateral motor cortex, and stimuli were generated by two Magstim 200 stimulators connected via a bistimulation module (The Magstim Company, Dyfed, UK). In this set-up, each stimulator yields a maximum magnetic field of 2.0 tesla. Stimuli were delivered via a figure-eight coil in which each wing had an outer diameter of 7 cm. The coil was placed over the optimal cortical representation of the abductor *digiti minimi* muscle of the investigated hand. This had been determined in preliminary trials by moving the coil in the sagittal and, subsequently, in the frontal axis in approximately 0.3 cm steps. The coil was held in the optimal position, i.e. tangentially to the skull with the handle pointing backwards at about 45° laterally, and the coil position was frequently controlled and corrected if necessary. We recorded MEPs from the abductor digiti

Table 1 Clinical characteristics of ALS patients

Patient	Symptom duration (months)	Age (years)	Sex	RMT (%)	ALSSS (points)
1	12	68	M	45	36
2	9	51	F	52	31
3	7	68	M	55	34
4	12	61	M	49	36
5	10	59	M	40	32
6	12	76	M	41	27
7	7	59	F	77	32
8	7	37	F	46	17
9	23	61	M	> 100	13
10	84	67	M	> 100	28
11	51	36	M	> 100	36
12	5	44	M	> 100	19
13	9	60	F	> 100	35
Average ± SD					
(1–8 patients)	9.6 ± 2.5	59.9 ± 11.9		50.6 ± 11.8	28.9 ± 7.8
(all patients)	20.7 ± 23.6	57.3 ± 12.8		*	30.6 ± 6.2

ALS = amyotrophic lateral sclerosis, RMT = resting motor threshold, SD = standard deviation; M = male; F = female
ALSSS = amyotrophic lateral sclerosis severity scale (maximal score = 40 indicating normal function)
Symptom duration = Time since onset of symptoms
* The mean threshold of all subjects could not be determined as the RMT for patients 9-13 could not be specified

minimi muscle of the investigated hand by two silver-silver chloride electrodes in a belly-tendon montage. MEPs were recorded by a digital device at a sampling rate of 5000 Hz (Synamps, Neuroscan Inc., Herndon, VA, USA), filtered at 10 Hz and 5 kHz and stored for off-line analysis of amplitudes.

Motor thresholds were determined by stepwise reductions of the stimulus intensity of single TMS delivered over the optimal representation of the abductor digiti minimi muscle of the investigated hand. The resting motor threshold was defined as the intensity at which none out of 10 consecutive MEPs were larger than 50 μV while the investigated muscle was at rest. Muscle relaxation was monitored by visual and auditory feedback. The highest intensity at which MEPs did not exceed baseline activity and did not cause a silent period during voluntary abduction of the small finger was set as active motor threshold. In addition, a test pulse intensity was determined that yielded a MEP amplitude of about 1.0 mV.

The intracortical excitability was assessed by delivering single test pulses and paired pulses. The latter consisted of a subthreshold conditioning stimulus (90% active motor threshold) followed by a test pulse after interstimulus intervals (ISIs) of 1, 2, 3, 4, 5, 6, 7, 8, 10, 15, 20 or 30 ms. Four blocks were tested; in each of them, three ISIs and single test pulses were each tested 12 times in a random order. We made an off-line measurement of MEP peak-to-peak amplitudes, and the MEPs elicited by the paired stimuli of each block were expressed as a percentage of the MEP induced by the single test pulses of that block.

Statistical analysis

We used two-tailed, unpaired t-tests to compare the motor thresholds of controls with those of ALS patients before drug intake, and a repeated-measures analysis of variance (ANOVA) to compare the intracortical excitability of control subjects to that of patients before drug intake. For the latter analysis we pooled the ISIs known to yield intracortical inhibition (1–2 ms) and those known to yield intracortical facilitation (ISIs 10–15 ms).

To detect an effect of drug intake we compared the motor thresholds of ALS patients before drug intake to their thresholds after drug intake (two-tailed, paired t-tests). Similarly, we compared the intracortical excitability of patients before drug intake to that after drug intake (repeated-measures ANOVA, ISI 1–2 ms and ISI 10–15 ms pooled).

For ANOVAs we indicated the result of the F-test, the degrees of freedom and the P-value, and conditional on a significant main effect, we performed post-hoc analyses using t-tests. For correlation analyses we calculated Pearson's correlation coefficient and indicated values higher than +0.7 or lower than –0.7.

Results

Motor thresholds

The mean values for resting motor threshold (active motor threshold) were 49.0 ± 4.8% (35.0 ± 2.5%) in the control group compared to 50.6 ± 11.8% (41.7 ± 10.6%) in the ALS patient group before riluzole intake; the differences were not significant (t-tests). After drug intake, the thresholds of ALS patients were 48.6 ± 10.5% (39.4 ± 10.1%) and were not significantly lower than at baseline (t-tests).

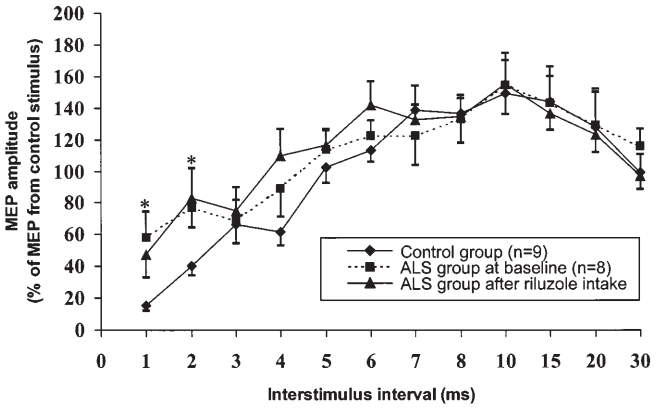

Fig. 1 Intracortical excitability. Mean values and standard errors of 8 ALS patients and 9 control subjects. Note that there is less intracortical inhibition in the patient group before and after riluzole intake than in normal controls. * = significant difference between group between controls and ALS patients before riluzole intake (unpaired t-tests)

Intracortical excitability

We found a reduced intracortical inhibition in ALS patients before riluzole intake compared to the control group (Fig. 1, effect of group for the ISI 1–2 ms, $F[1,15] = 8.4$, $P < 0.01$). ISIs of 1 ms and 2 ms yielded significant differences between controls and baseline results for ALS (post-hoc, unpaired t-test, $P < 0.05$). In contrast, the intracortical facilitation did not differ between ALS before drug intake and controls. In patients, the intake of riluzole did not significantly affect either intracortical inhibition (ISI 1–2 ms) or intracortical facilitation (ISI 10–15 ms, Fig. 1).

Side-effects of riluzole

None of the ALS patients reported any side-effects after the loading dose of riluzole.

Correlation analyses

We did not find a high correlation between the symptom duration, motor thresholds or the test stimulus intensity (expressed in % of resting motor threshold). Also, the degree of intracortical inhibition at ISI 1 ms and ISI 2 ms did not correlate significantly with symptom duration or ALSSS score.

Attempt to retest patients
after longer duration of riluzole intake

Given the lack of immediate efficacy of riluzole on intracortical inhibition we tried to investigate the patients a third time. Two patients agreed to participate in this additional investigation, both had been continuously treated with riluzole 50 mg bid. In subject 8, resting and active thresholds had increased four months after the initial tests (resting motor threshold: 46% of maximal stimulator output at baseline vs 54% at time of retest, active motor threshold: 40% vs 34%), and intracortical inhibition was weakened (pool of ISIs 1-4 ms, 43.3% vs 70.8%). In subject 4, the resting motor thresholds had increased from 49% at baseline to more than 100% after 5 months, so that the intracortical excitability could not be tested any more.

Discussion

Our baseline results show that in ALS patients before riluzole intake motor thresholds are normal and the intracortical inhibition abnormally weak. The normal motor thresholds are consistent with previous studies [19]. Motor thresholds are thought to reflect the excitability of the corticospinal tract, they are altered by drugs that affect central nervous system membrane potentials, but not by drugs influencing neuronal synaptical transmission [18]. Hence, we conclude that membrane potentials in the corticospinal tract of ALS patients are normal. The weakened intracortical inhibition in ALS is consistent with other reports [17, 19, 5]. This inhibition is thought to reflect the activity of intracortical interneurons, since it is absent with transcranial electrical stimulation acting primarily on the pyramidal tract neurons and their axons [8]. It is presumably mediated by synaptical transmission, since it is modulated by GABAergic and glutamatergic drugs [18, 10, 11]. We conclude that the synaptical transmission of inhibitory cortical circuits is impaired in ALS.

The results in ALS patients 1.5 hours after riluzole intake do not indicate any change in motor thresholds or intracortical excitability as compared to baseline. The lack of change for motor thresholds is consistent with the studies in healthy subjects [10, 11], we conclude that riluzole has no acute effect on membrane potentials in ALS. However, the lack of change in intracortical inhibition is unexpected in view of the data in normal controls [10, 11]. However, since intracortical inhibition in healthy subjects was only slightly enhanced 2 hours after riluzole intake [10] and significantly enhanced after 7 days of riluzole intake only [11], this may indicate a progressive onset of the effect of riluzole on intracortical inhibition. In a preliminary report by Stefan and co-workers [14] motor thresholds in 4 of 8 ALS patients studied allowed the determination of intracortical excitability before and 5 days after riluzole intake of 50 mg bid. In these patients, intracortical inhibition was less pronounced than in normal controls but was significantly enhanced and, therefore, partially normalized following riluzole intake. The major difference between this study and our data is the time of neurophysiological testing after riluzole intake (≥ 5 days versus 1.5 hours, respectively). We, therefore, hypothesize that a beneficial effect of riluzole on intracortical inhibition may only become evident after several days (> 1.5 hours but ≤ 5 days). However, another major difference between our data and that of Stefan is the baseline intracortical inhibition which was much weaker in their ALS patients than in our study. Further study is warranted to confirm this possible beneficial effect of riluzole on the intracortical inhibition in ALS; however, the results of the patient retested after 4 months of riluzole intake suggest that the disease progression may hide possible long-term influences of riluzole on intracortical excitability.

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