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Abnormal motor cortex plasticity in juvenile myoclonic epilepsy

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ABSTRACT

Purpose: Abnormal cortical plasticity has been hypothesized to play a crucial role in the pathogenesis of juvenile myoclonic epilepsy (JME). To study the motor cortical plasticity we used paired associative stimulation (PAS). When a repetitive electrical stimulus to the median nerve is paired with a transcranial magnetic stimulus (TMS) pulse over the controlateral motor cortex with at an interstimulus interval (ISI) of 21.5–25 ms, a long term potentiation (LTP)-like synaptic plasticity is induced in the corticospinal system.

Aim of this study was to investigate the motor cortex LTP-like synaptic plasticity by means of PAS in patients with JME.

Methods: Twelve adult patients with JME were compared with 13 healthy subjects of similar age and sex. PAS consisted of 180 electrical stimuli of the right median nerve paired with a single TMS over the hotspot of right abductor pollicis brevis (APB) at an ISI of 25 ms (PAS25). We measured motor evoked potentials (MEPs) before and after each intervention for up to 30 min.

Results: In healthy subjects the PAS25 protocol was followed by a significant increase of the MEP amplitude ($p < 0.001$). On the contrary, in patients with JME, the MEP amplitude did not change.

Conclusion: Defective motor cortex plasticity is likely involved in the pathogenesis of JME.

1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common idiopathic generalized epilepsy (IGE), with a presumed genetic aetiology [1]. Myoclonic jerks, absences and generalized tonic–clonic seizures are the core findings in this syndrome [2]. So far, motor cortex hyperexcitability [3] and abnormal function of fronto-thalamic networks have been involved in the pathophysiology of JME [4–6]. Hyperexcitability of primary visual areas and excessive response of the primary motor cortex to visual inputs would be another important factor [7,8] since the presence of a photoparoxysmal response is common [2].

Abnormal cortical plasticity has been frequently hypothesized to play a crucial role in the pathogenesis of epilepsies [9,10], at least in experimental models of temporal lobe epilepsy [11]. However, considering the clinical context, there are no direct evidences to support this hypothesis, possibly because of experimental difficulties. Transcranial magnetic stimulation (TMS) is a well-established, safe, painless and non-expensive neurophysiologic method for non-invasive measurement of cortical excitability [12]. It also offers a unique opportunity to study cortical plasticity in a non-invasive fashion. In the last few years, a variety of TMS protocols have been developed to probe mechanisms of synaptic plasticity in the intact human brain [13]. Among these, paired associative stimulation (PAS) involves repeated pairing of an electrical stimulus to the median nerve with a later transcranial magnetic stimulus (TMS) over the contralateral motor cortex [14,15]. This induces changes in cortical excitability, whose sign depends on the interval between the median nerve and the TMS stimuli. Intervals of 25 ms (PAS25) have an enhancing effect, whereas intervals of around 10 ms (PAS10) reduce excitability [14–16]. Pharmacological studies suggest that such changes involve temporary modifications in synaptic efficacy, equivalent to long-term potentiation (LTP) and long-term depression (LTD), as described in animal preparations [17].

Aim of the present study was to test the effects of PAS25 in patients with JME compared to healthy controls. We wanted to explore if, in the complex framework of the JME pathophysiology, an abnormal motor cortical plasticity could play a given role.

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2. Materials and methods

2.1. Subjects

We studied 12 consecutive adult patients with JME (10 female, mean age 32.8 years, SD 10.7) referring to the Epilepsy Clinic of the University Department of Neurology, Novara, Italy. Diagnoses were made by two experienced epileptologists not involved in the present study on the basis of the clinical history, seizure type and electroencephalography (EEG) findings according to the established diagnostic criteria [18].

Thirteen normal subjects of similar age and sex acted as controls (10 female, mean age 27.9 years; SD 5.6). They had no family or personal history of neurologic disease or epilepsy. Reportedly, both patients and controls had not been taking neuroactive drugs (alcohol and caffeine included) for 72 h prior to the study, except for the patient antiepileptic treatment. Their general and neurological examinations were normal. All subjects were right-handed based on the Edinburgh Handedness Inventory and gave written informed consent. Experiments were approved by the local Ethics Committee and were performed in accordance with the Declaration of Helsinki.

2.2. Patient features

The clinical features of patients are reported in Table 1. Eight of the 12 patients were classified as photosensitive because they showed a photoparoxysmal response (PPR) to intermittent light stimulation (ILS), which did never entail clinical phenomena. ILS was performed according to the international standards [19]. In general, the clinical course of the patients was favourable, and all of them reported being seizure-free. All patients were on a standard antiepileptic treatment. Valproate, alone or in combination with levetiracetam, was the most frequent choice.

2.3. TMS and EMG recordings

All neurophysiologic studies took place between 2:00 and 6:30 p.m. in a quiet laboratory, at a standard temperature of 22 °C.

Subjects sat comfortably in a chair with both arms resting on a pillow placed on their lap. Motor-evoked potentials (MEPs) were recorded from the abductor pollicis brevis (APB) muscle using 9 mm-diameter Ag–AgCl surface-cup electrodes, in a typical belly-tendon montage. Data were collected, amplified (gain, 1000×), and filtered (20 Hz to 3 kHz) through a CED 1902 isolated amplifier (CED, Cambridge, UK) that fed signals to an A/D converter (CED Micro 1401 Mk II). The sampling rate was 10 kHz. The signal was then recorded by a PC using Signal software ver. 4.08 (Cambridge Electronic Devices, Cambridge, UK).

Table 1
Main clinical features of patients.

Patient #	Age	Sex	Current treatment (mg/die)	Photosensitivity
1	26	F	400 LTG	Yes
2	48	F	1300 VPA + 1000 LEV	Yes
3	22	F	100 LTG	Yes
4	49	F	800 VPA	No
5	45	F	800 VPA	No
6	25	M	900 VPA	No
7	42	F	1000 VPA + 100 PB	Yes
8	24	F	400 LTG	Yes
9	28	M	300 VPA	Yes
10	26	F	1000 LEV	Yes
11	38	F	115 PB	Yes
12	21	F	800 VPA	No

JME: juvenile myoclonic epilepsy; LEV: levetiracetam; LTG: lamotrigine; PB: phenobarbital; VPA: valproic acid.

TMS was delivered through a Magstim 200^2 stimulator (Magstim) every 4.5–5.5 s. A figure-of-eight coil (outer winding diameter 70 mm) was held tangentially on the scalp at an angle of 45 deg to the midsagittal plane with the handle pointing laterally and posteriorly. Stimuli were applied to the motor cortex representation of the right APB. The motor hot spot was defined as the point where a magnetic stimulus of constant, slightly suprathreshold intensity consistently elicited an MEP of the highest amplitude. Motor cortex excitability was measured as the peak-to-peak amplitude of the MEP generated by single pulse TMS.

2.4. Paired associative stimulation (PAS)

PAS consisted of 180 electrical stimuli of the right median nerve at the wrist paired with a single TMS shock over the hotspot of right APB muscle at a rate of 0.2 Hz [14,20]. Electrical stimulation (square wave pulse; stimulus duration, 0.2 ms) was applied at an intensity of three times the perceptual threshold using a constant current generator (Digitimer, Welwyn Garden City, UK). TMS was applied at an intensity required to elicit a 1 mV MEP (SI_{1mV}). The effects of PAS given with an interstimulus interval of 25 ms between peripheral and TMS stimuli were tested (PAS25). Subjects were instructed to look at their stimulated hand and count the peripheral electrical stimuli they perceived. The MEPs evoked in the APB were displayed online during the intervention to control for the correct coil position and stored for off-line analysis.

2.5. Experimental procedures

The resting motor threshold (RMT) and MEP size were measured. RMT was defined as the lowest intensity that evoked a response of about 50 μV in the relaxed APB in at least 5 of 10 consecutive trials [21]. The stimulus intensity was changed in steps of 1% of the maximum stimulator output (MSO). Thirty MEPs were recorded with a stimulus intensity of SI_{1mV} before (baseline) and for up to 30 min (T0, T15 and T30) after PAS25. SI_{1mV} was kept constant throughout the experiment. The mean peak-to-peak amplitude was calculated for the data obtained before and after PAS in each single subject.

2.6. Data analysis

The baseline physiological parameters are given in Table 2. The between-group comparability of these variables was tested by a Student's paired *t* test (two-tailed).

MEP amplitudes at each time point were averaged and normalized to baseline. Then they entered a two-way repeated measures (rm) ANOVA with factors "GROUP" (patients, controls) and "TIME" (T0, T15 and T30). In order to evaluate the effects of PAS in each group, a one-way ANOVA was employed with a main factor of "TIME" (baseline, T0, T15 and T30), using absolute MEP values in each experimental session. The Greenhouse–Geisser correction

Table 2
Physiological data (mean ± SEM).

	HS	JME	Differences among groups
#	13	12	
Age	27.9 ± 1.5	32.8 ± 3.1	n.s.
Sex (female)	10	10	n.s.
RMT (%)	40.2 ± 1.0	44.7 ± 2.5	n.s.
PsT (mA)	2.2 ± 0.2	2.6 ± 0.2	n.s.
SI_{1mV} (%)	51.8 ± 2.5	55.3 ± 3.2	n.s.
Baseline MEP (mV)	0.94 ± 0.07	1.08 ± 0.08	n.s.

HS: healthy subjects; JME: juvenile myoclonic epilepsy patients; MEP: motor evoked potential; psT: peripheral sensory threshold; RMT: resting motor threshold; SI_{1mV}: intensity required to elicit a 1 mV MEP; n.s.: non-significant.