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Defective interhemispheric inhibition in drug-treated focal epilepsies

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ABSTRACT

Background: Focal epilepsies (FEs) arise from a lateralized network, while in generalized epilepsies (GEs) there is a bilateral involvement from the outset. Intuitively, the corpus callosum is the anatomical substrate for interhemispheric spread.
Objective: We used transcranial magnetic stimulation (TMS) to explore whether there are any physiological differences in the corpus callosum of drug-treated patients with FE and those with genetic GE (GGE), compared to healthy subjects (HS).
Methods: TMS was used to measure the interhemispheric inhibition (IHI) from right-to-left primary motor cortex (M1) and viceversa in 16 patients with FE, 17 patients with GGE and 17 HS. A conditioning stimulus (CS) was given to one M1 10 and 50 ms before a test stimulus delivered to the contralateral M1. Motor evoked potentials (MEPs) were analysed both as a function of the side of stimulation and of the epileptic focus (left-right).
Results: In HS, IHI was reproducible with suppression of MEPs at ISIs of 10 and 50 ms. Similar effects occurred in GGE patients. FE patients behaved differently, since IHI was significantly reduced bilaterally. When FE patients were stratified according to the side of their epileptic focus, the long-ISI IHI (=50 ms) appeared to be defective only when the CS was applied over the "focal" hemisphere.
Conclusions: FE patients had a defective inhibitory response of contralateral M1 to inputs travelling from the "focal" hemisphere that was residual to the drug action. Whilst IHI changes would not be crucial for the GGE pathophysiology, they may represent one key factor for the contralateral spread of focal discharges, and seizure generalization.

1. Introduction

Epilepsy is a common neurological disorder characterized by an enduring predisposition to generate epileptic seizures [1]. Its pathophysiology is complex and largely related to hyperexcitable neural networks resulting from the imbalance between excitatory and inhibitory circuits [2]. The classical dichotomy in focal (FE) and generalized epilepsy (GE) reflects the origin of the epileptic discharge, whether it arises in a lateralized network or it rapidly involves bilateral structures.

Abnormalities in both excitatory and inhibitory neural circuits not only affect the seizure focus, but may also involve distant areas such as the primary motor cortex (M1) [3–5]. White-matter bundles connecting distant cortical areas are the likely anatomical substrate of seizure propagation [6]. Of these, the corpus callosum represents the largest commissure connecting the two hemispheres [7]. Its major role in seizure propagation is suggested by the efficacy of the palliative corpus callosotomy procedure in severe drug-resistant epilepsies [8]. Previous neuroimaging and anatomical studies have explored the role of corpus callosum in interhemispheric propagation [9,10]. However, its physiological role in FE and GE is still a matter of debate [6,11]. Changes in cortical excitability in the hemisphere ipsilateral and contralateral to the seizure focus (i.e. "focal" and "non-focal" hemisphere respectively) may well be a background factor for the propagation of the epileptic discharge, and may distinguish FE from GE [12]. A second

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factor may be an exaggerated interhemispheric transmission/defective inhibition through the corpus callosum. Interhemispheric inhibition (IHI) by means of paired pulse transcranial magnetic stimulation (TMS) was first described by Ferbert et al. [13]. This paradigm employs a standard single TMS stimulus over the hand area of M1 that evokes a test motor evoked potential (MEP) in a muscle of interest. This stimulus can be preceded at different intervals by a conditioning stimulus (CS) over the hand area of the opposite hemisphere [14]. The CS changes the amplitude of the test MEP at critical intervals with an "inter-hemispheric" inhibition with a latency of 6–50 ms [13,15–17]. IHI is mediated by transcallosal fibers since the effects were absent in patients with no corpus callosum [18]. This method was subsequently validated by several studies in the normal subject [17,19,20] and patients with different neurological abnormalities [11,21–24], including one describing the changes between the M1s following the removal of the epileptic focus in FE [11].

The present study was designed to examine the excitability of bilateral M1-to-M1 interhemispheric connections in patients with FE and genetic GE (GGE) compared to healthy subjects (HS). In principle, we hypothesized that IHI would be defective in FE patients, particularly that the "focal" hemisphere would respond excessively to inputs from the "non-focal hemisphere".

2. Materials and methods

All neurophysiologic studies took place between 2:00 and 6.30 p.m. in a quiet room, at a standard temperature of 22 °C.

2.1. Subjects

We studied a total of 33 adult patients with epilepsy referred to the Epilepsy Clinic of the University Department of Neurology, Novara, Italy. Sixteen had FE (10 women, mean age 36.4 years ± 9.3) and 17 had GGE (11 women, mean age 34.2 years ± 12.5). Seventeen normal subjects of similar age and sex acted as controls (11 women, mean age 30.1 years ± 7.9). They had no family or personal history of neurologic disease or epilepsy. Apart from the regular antiepileptic medication taken by the patients, both patients and controls had not been on neuroactive drugs (alcohol and caffeine included) for 72 h prior to the study. Their general and neurological examinations were normal. All subjects were right-handed based on the Edinburgh Handedness Inventory. They gave written informed consent to the experimental procedures, which were approved by the local Ethics Committee and were performed in accordance with the Declaration of Helsinki.

2.2. Patient features

These are reported in Table 1. Thirteen of the 16 patients with FE had temporal lobe epilepsy (TLE) and 3 frontal lobe epilepsy (FLE). Magnetic resonance imaging (MRI) revealed a brain lesion in 12 out of the 16 patients (Table 1). No abnormalities of the corpus callosum have been detected. On the basis of ictal Video-EEG recordings, 8 out of the 16 patients had a definite left epileptic focus, whilst the remaining 8 were diagnosed with a right focus. Nine were seizure-free and the remainder had only focal seizures without secondary generalization in the last one year of observation. Eight patients have experienced secondary generalization in the past, 7 became seizure-free and 1 had residual focal motor seizures. All of them were taking one or multiple antiepileptic drugs (AEDs); carbamazepine and levetiracetam were the most commonly used drugs.

In the GGE group, the most common subtypes were juvenile myoclonic epilepsy (JME) (6/17 patients), epilepsy with tonic-clonic seizures (TCE) (6/17 patients) and juvenile absence epilepsy (JAE) (4/17 patients). One patient had eyelid myoclonia with absences (EMA). All of them were seizure-free on AEDs, the most common of which were valproate and lamotrigine.

2.3. TMS

For paired-TMS we used two high-power Magstim 200^2 machines (Magstim, Whitland, UK). The magnetic stimulus had a nearly monophasic pulse configuration with a rise time of ~100 μs, decaying back to zero over ~0.8 ms [25]. The stimulators were connected to a figure-of-eight coil (outer winding diameter 70 mm).

2.4. Test stimuli

Motor evoked potentials (MEPs) were recorded from the left and right first dorsal interosseous (FDI) muscles [13,26], using 9 mm-diameter Ag-AgCl surface cup electrodes, in a typical belly-tendon montage. Responses were amplified by a CED 1402 isolated amplifier (CED, Cambridge, UK). Filters were 20 Hz – 3 kHz, and the sampling rate was 10 kHz. The signal was recorded by a PC using Signal software ver. 4.08 (Cambridge Electronic Devices, Cambridge, UK). The test coil was placed tangentially to the scalp at a 45° angle to the midline, to induce a posterior-anterior (PA) current flow across the central sulcus (Fig. 1C). The hand motor area of the left and right M1 was defined as the point where stimulation consistently evoked the largest MEP. We defined the resting motor threshold (rMT) as the lowest intensity that evoked 5 small responses (~50 μV) in the relaxed FDI muscle in a series of 10 stimuli [27]. The intensity of the test stimulus (TS) was finally adjusted to evoke a MEP of ~1 mV peak-to-peak amplitude in the relaxed FDI.

2.5. Interhemispheric inhibition

Interhemispheric inhibition (IHI) was measured with a paired-pulse paradigm previously described [13,28] both from left-to-right (LtoR) and from right-to-left (RtoL) M1s in a randomized order (Fig. 1C). Coils were positioned at an angle of 45° from the midline with the handles pointing backward and laterally. The coils were adjusted over both hemispheres to the *hotspot* of the contralateral FDI and the positions were marked on the scalp so that the angle and coil position was the same throughout the investigation [11]. In all patients, the coil position was not limited by the shape of the skull.

A CS was given to one hemisphere 10 (short latency IHI, SIHI) or 50 ms (long latency IHI, LIHI) before a TS delivered to the other side. The TS and the CS were adjusted to produce a MEP with a peak-to-peak amplitude of ~1 mV (CS_{1mV}; TS_{1mV}) [29]. There were two randomized blocks, i.e. IHI from right-to-left and viceversa. Each block had three conditions that were randomized within the block. Condition 1: TS alone (MEP test). Condition 2 and 3: the same as condition 1, except that the TS was preceded by a CS with an ISI of 10 or 50 ms (conditioned MEP). Fifteen trials for each condition were recorded (total of 45 trials) in random order for each subject with a 5 s (±20%) intertrial interval. The responses to each single trial were stored on a PC and analysed offline at the end of the experiment. For each condition, we calculated the average of the single trial peak-to-peak MEP amplitude. The conditioned MEP was expressed as a percentage of the MEP test size.

2.6. Data analysis

All data were expressed as mean ± standard error of the mean (SEM). The normality of the dataset was proved using the