Sensorimotor integration in Complex Regional Pain Syndrome: a transcranial magnetic stimulation study.

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Abstract

There is evidence that patients with Complex Regional Pain Syndrome (CRPS) have altered central sensorimotor processing. Sensory input can influence motor output either through indirect pathways or through direct connections from the sensory to motor cortex. The purpose of this study was to investigate sensorimotor interaction via direct connections in patients with CRPS and to compare the results with normal subjects'.

Direct short-latency sensory-motor interaction was evaluated in eight patients with CRPS1 affecting a hand. Modulation of EMG responses to transcranial magnetic stimulation (TMS) induced by concomitant median nerve stimulation was measured, the so-called, short-latency afferent inhibition (SAI). Results were compared with eight normal subjects who were age and sex matched with the patients. As expected, all the normal subjects' EMG responses to TMS with median nerve stimulation were smaller than responses to TMS alone. In seven of the eight CRPS patients EMG responses to TMS were suppressed when paired with median nerve stimulation. Only one CRPS patient's results showed no suppression of EMG responses. These results suggest that the disease mechanisms of CRPS1 do not typically affect the direct neural circuit between sensory and motor cortex and that normal sensorimotor interaction is occurring via this route.

Introduction

Complex Regional Pain Syndrome (CRPS) is a painful, debilitating condition which may arise following trauma with major nerve damage (Type II) or without it (Type I); spontaneous onset has also been described (Veldman et al., 1993). Peripheral sensory and motor changes have been well documented in CRPS (Stanton-Hicks et al., 1995; Scadding, 1999; Harden, 2001; Stanton-Hicks et al., 2001). In addition more central phenomena such as changes in cortical representation and altered perceptions of the limb and body-schema have also been described (Galer et al., 1995; Rommel et al., 1999; Galer and Jensen, 1999, Juottonen et al., 2002; Maihöfner et al., 2003; McCabe et al, 2003a; Főrderreuther et al., 2004; Lewis et al., 2004). Although the understanding of the pathophysiology of CRPS is still far from being complete, it seems that the condition arises from impairments in both peripheral and central mechanisms via interaction between afferent and efferent signals (Jänig and Baron, 2003).

The breakdown of sensory-motor interaction has been proposed as the mechanism at least partially responsible for development of CRPS (see Harris, 1999; McCabe et al., 2003b; 2005). This is supported by evidence that artificial generation of discordance between sensory input and motor output, via an optokinetic device, induces somaesthetic disturbances in healthy volunteers, whilst the provision of corrective sensory input, using the same device, induces an analgesic response in those with CRPS type 1 (McCabe et al., 2003b; 2005). Sensory inputs interact with the motor cortex through several pathways of varying complexity. The shortest and most direct of them involves monosynaptic connections that pass directly from sensory to motor cortex (Avendano et al., 1992; Widener and Cheney, 1997). The purpose of this study was to evaluate whether impairment in this pathway might be associated with CRPS symptoms.

Sensorimotor interaction can be evaluated by coupling transcranial magnetic stimulation (TMS), a noninvasive method of stimulating the motor cortex, with peripheral nerve stimulation. The size of a muscle twitch (motor evoked potential – MEP) induced by a TMS of the motor cortex is determined by the level of excitability of the stimulated cortex and can be modulated by electrical stimulation of a peripheral nerve innervating the area of the body where the muscle twitch is induced. The actual effect of peripheral nerve stimulation on motor cortex excitability depends on the interstimulus interval (ISI) between the conditioning sensory stimulation and the subsequent test TMS. If the time between stimulation of the peripheral nerve and that of the motor cortex is near the time needed for the peripheral nerve afferent input to reach the cortex an inhibitory effect occurs (Figure 1). This is referred to as short latency afferent inhibition (SAI) (Sailer et al., 2003). It is thought that SAI is produced by cortico-cortical sensorimotor interactions (Tokimura et al., 2000; Abbruzzese et al., 2001).

[Figure 1 near here]

If in CRPS patients there is a breakdown in the sensorimotor interaction taking place within the direct sensorimotor pathway then the inhibitory effect will be smaller than normal. This study was designed to evaluate this hypothesis.

Methods

Subjects

Eight adult patients (seven female) with unilateral upper limb CRPS type I were recruited to the study. They were identified from rheumatology clinics and wards at the RNHRD. All subjects met the IASP criteria for CRPS (Stanton-Hicks et al., 1995), had

no contractures, which would compromise the accuracy of the assessment, and were judged as able to tolerate the experimental conditions. CRPS subject's details are given in table 1.

Normal subjects who matched the patients' age, gender and hand dominance were also recruited. These volunteers had no history of CRPS, arthritis or chronic hand pain. Mean (S.D.) age for each group was 45 (13) years.

[Table 1. near here]

The recordings took place at the Burden Neurological Institute (BNI). All participants gave their consent and all procedures were performed in accordance with a protocol approved by the Local Research Ethics Committees at RNHRD and at Frenchay Hospital in Bristol (providing Ethics approval for BNI).

Procedures

Design of the study

For each subject the recordings were conducted in three steps. First, somatosensory evoked potentials (SEP) from the median nerve of the investigated limb were recorded, and the latency of the first cortical component (N20) was determined. Subsequently, the optimal parameters (i.e. site and intensity) for TMS inducing muscle twitches in the representative muscle (abductor pollicis brevis – APB) of the investigated limb were determined. Finally, the recording of electromyographic (EMG) responses to paired peripheral median nerve stimuli (medPS) and TMS was carried out. The median nerve stimulation was set to precede the TMS pulse with an inter-stimulus interval that equalled the latency of the N20 SEP. The test trials with paired stimulation were randomly intermixed with control trials when only TMS pulse was delivered. Six blocks

of eight trials were recorded giving a total of 24 responses to TMS only and 24 responses to paired, TMS + medPS, stimulation.

Median nerve stimulation (medPS)

The median nerve was stimulated over the wrist on the affected side in patients, and on the matching side in control subjects. Square pulse stimuli of 0.2 ms duration were delivered at a frequency of 2Hz via a Digitimer D57A constant current stimulator. Stimulation was at supramaximal intensity for large afferent fibres; sufficient to provoke a visible movement of the thumb.

SEP recording

Standard Ag/AgCl electrodes were attached, according to the IFCN recommended standards, over the brachial plexus (Erb's point) of the limb tested and over the contralateral cortex, 2 cm anterior and 2 cm posterior to the C3/C4 electrode placements of the 10/20 system (Nuwer et al 1994). All electrodes were referenced to Fz. Epochs of 64 ms length were recorded (filter settings: time constant 0.03s low pass filter 700Hz; digitisation rate: 8kHz) with the medPS triggered 1.25 ms into the epoch and 400ms inter-stimulus interval.

EMG Recording

EMG was recorded by 10mm Ag/AgCl electrodes placed in belly-belly montage (20mm inter-electrode distance) over the abductor pollicis brevis (APB) muscle. Impedance was maintained below 5KΩ. The signal was amplified (x1000), band pass filtered (3Hz - 3.9 kHz), digitised (8 KHz), and full wave rectified. Epochs of 128ms length were collected, stored, and analysed off line using in-house software.

Magnetic Stimulation

A Magstim 200 stimulator (maximum output 2.0 T; Magstim Company, Dyfed, UK) with a figure of eight coil was used (outer diameter of each wing 95 mm). The coil was positioned over the head at the optimal site for obtaining a response in the resting contralateral APB muscle; this was judged by threshold and amplitude of the response. The coil was hand held while the weight of the coil and its power cable were counterbalanced by elastic bands suspended from the ceiling overhead. The location was marked on the head with wax pencil and the coil position was checked regularly with reference to the head marks and a spirit level on the coil to ensure that it remained stable throughout the session. The threshold for EMG responses in each muscle was defined as the intensity, (i.e. percentage of maximum stimulator output), required to produce clearly visible responses at the appropriate latency in three out of six sweeps. Threshold was measured in the passive, relaxed condition of the muscle.

For the paired, TMS + medPS, recordings TMS intensity was set to 20% above the threshold and TMS pulses were delivered in blocks of eight stimuli at a rate of 0.2 Hz. The TMS pulses were triggered 44 ms into the recorded EMG epoch.

Data analysis

The rectified EMG recordings were inspected sweep by sweep for EMG responses (motor evoked potentials – MEPs). The criterion for the presence of an EMG response to TMS was a peak occurring at normal latency for the APB. The peak had to be more than three times the mean level of background EMG, and larger than other peaks in the background. For each subject, all responses were superimposed and a time window for analysis was visually determined to include all single MEPs. Then for each single MEP the mean amplitude over the determined was measured as an index of MEP size. The

distribution of MEP sizes was assessed by Kolmogorov-Smirnov test. Since some of the data sets did not follow the normal distribution, non-parametric Mann Witney U test was used. For each subject, the MEPs with and without medPS conditioning were compared, and the MEP size suppression index was calculated as: *(mean TMS&medPS – mean TMS only) / mean TMS only*, and expressed as a percentage.

[table 2 near here]

Results

The latency of N20 was within normal limits for all subjects and ranged between 18 and 22ms. As expected, all the normal subjects' EMG responses to TMS were suppressed when preceded by median nerve stimulation (see table 2). The difference in EMG response amplitudes between TMS alone and TMS&medPS was statistically significant (p<0.05) in six out of eight subjects. Similarly, the suppression of the EMG response was present in seven but significant in six of the eight CRPS patients. It is of note that one CRSP patient (patient 5) did not show any suppression of EMG response amplitudes with median nerve stimulation. This subject was much younger than the others and had CRPS for only six months. There was no significant difference between CRPS and normal subjects in mean MEP sizes in the TMS only condition.

Discussion

Suppression of EMG responses to TMS was significant in all but one of the CRPS patients. The results for CRSP patients were in no way different than for normal control subjects. These results suggest that the disease mechanisms of CRPS1 do not typically

affect the direct neural circuit between sensory and motor cortex and that normal sensorimotor interaction is occurring via this route.

The existence of a deficient response of motor cortex inhibition mechanisms to sensory stimuli in CRPS1 was suggested by the results of an earlier magnetoencephalographic (MEG) study which showed altered response of the motor cortex idling rhythm (20-Hz) following tactile stimuli in 6 patients with CRPS1 (Juottonen et al. 2002). The 20-Hz rhythm is considered to reflect the level of motor cortex inhibition and normally displays a typical pattern of suppression and subsequent rebound following somatosensory stimulation (Salmelin and Hari, 1994). Juottonen et al. (2002) found considerable increase in suppression of this rhythm as well as a significant reduction in subsequent rebound in CRPS patients compared to healthy controls. However, a recent TMS study investigating cortico-cortical connections within the motor cortex of 12 CRPS1 patients found that in those with upper limb CRPS the motor cortex contralateral to the affected limb displayed reduced inhibition and increased excitability on its own (Eisenberg et al., 2005). This would suggest that findings of Juottonen at al. (2002) may not be caused by impaired sensory-motor interactions but instead are due to intrinsically deficient inhibition within the motor cortex. Our findings of essentially normal short latency afferent inhibition in CRPS patients demonstrate that intrinsic weakness of motor cortex inhibition may not play a decisive role in sensory-motor interactions and that the explanation for the findings of Juottonen at al. (2002) has to be looked for elsewhere. In addition, the findings of Eisenberg et al. (2005) were similar to those demonstrated in patients who did not have CRPS, but whose wrists were immobilised for prolonged periods in splints after wrist fracture (Zanette et al., 2004). Self-imposed immobilisation of the affected limb is a common feature in CRPS due either to the high levels of pain or neglect-like phenomena. Thus, increased excitability

and reduced inhibition found by Eisenberg et al (2005) may well not be related to the basic physiological mechanisms of CRPS but represent a secondary changes due to immobility and could be even due to a paucity of inhibitory sensory inputs due to immobilisation.

The results of our study and those of Juottonen et al. (2002) leaves the question of where in the central nervous system does sensorimotor integration breakdown in CRPS. Most probably it occurs within other more indirect pathways e.g. via the basal ganglia and/or second and third order somatosensory cortical areas. In this study only direct short-latency sensory-motor interactions at the level of the cortex were evaluated. Investigation of changes in long latency afferent inhibition might provide a part of the response to this question. Long latency afferent inhibition is a consistent inhibition that can be recorded at longer ISIs, between 100 and 200 ms and it is thought to involve indirect pathways such as the basal ganglia or cortical association areas (Abbruzzese et al., 2001; Chen et al., 1999; Sailer et al., 2003). This will have to be a subject of another study.

In this study, for eliciting SAI, we used a subject specific single ISI that was equal to the subjects N20 peak latency. In studies in which a range of ISIs have been used there has been some disagreement about the optimal ISI for producing maximal SAI. Kessler et al (2005) found maximal SAI at ISIs equal to both N20 latency and to N20+2ms. However Tokimura et al. (2000) found the largest SAIs at ISIs that were four seconds longer than the N20 peak latency. In all these studies, the SAI for ISIs equal to N20 latency was typically detectable even if not maximum. This explains our findings in healthy controls where for two subjects SAIs, although quite clearly present (35.3 and 34.4%), were not significant. However, this raises a question why we have chosen the N20 latency ISI in the first place.

The choice of the ISI was determined by the specificities of the patients we studied. The patients with CRPS, by the very nature of their condition, find it very difficult to tolerate any sensory stimuli applied to the affected limb. The median nerve stimuli used in this study were no exception. Thus, we had to limit the duration of testing and total number of median nerve stimulations to the necessary minimum. Effectively, this meant to reduce the TMS&medPS to only a single ISI. However, as we know the ISI value for bringing about the maximal SAI varied between 0 and 4 sec + N20 latency in previous studies (Tokimura et al. 2000; Kessler et al 2005). Therefore, it typically requires testing across a range of ISIs to determine exactly the ISI that causes the larges SAI for a particular subject. Obviously, this approach would inevitably prolong the experiment and would require delivery of larger number of median nerve stimuli. Thus, it was considered unsuitable for our patients. On the other hand, N20 latency is an independent physiological variable, specific to a particular subject, and essentially independent from this study and its hypothesis. Therefore, the choice of an ISI equal to N20 latency seemed physiologically the "safest" option, the least open to doubts. Had we taken, for example, N20+2ms the questions might be why not +1, +3 or +4, and so on. Of course, had we found the inhibition absent or considerably weaker in patients, that testing of SAI at longer ISIs would be necessary. However, given that we have found essentially normal SAI in patients the issue is not of any practical relevance – even with ISIs that may does not produce maximal inhibition the CRPS patients had essentially normal results.

The results of one CRPS subject (5) were different from the rest. The anomalous result could not be explained by any errors in determining the timing of the arrival of the afferent input to the motor cortex. This patient had a clear N20 somatosensory evoked potential from which to establish the interval needed between median nerve stimulation

and TMS. Using the latency of N20 as the ISI worked for the other participants – patients and normal subjects. There were two differences noted in her presentation that might explain the difference in results. She was much younger, and she had CRPS for only six months duration. Further studies including patients in early and late stages of the condition are needed to determine whether the pathophysiology of CRPS might change with disease duration and to see if there is a subset of patients in whom the direct connections are involved. It also remains to be seen whether any breakdown in sensory motor interaction is a consequence of or contributing factor to pain in CRPS.

Acknowledgements

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Legends

Figure 1. Inhibition of EMG responses to TMS of motor cortex by single electrical stimuli to the median nerve at the wrist in a relaxed subject.

This example shows the average of 24 responses EMG responses evoked in the thumb muscle, abductor pollicis brevis, by TMS over the motor cortex in a healthy subject (top line) and the average of 24 responses when conditioned by a median nerve stimulus given 18 ms earlier (bottom trace). The sharp spikes 1 and 2 are artifacts in the EMG at the time of median nerve stimulus and TMS respectively. Onset latency of the EMG response to TMS are 24.6 ms (i.e. after the artifact spike 2). The large peaks immediately after the median nerve stimulation (spike 1) on the bottom trace are the immediate motor response, which are visible as muscle twitch.