Cortical Neurophysiological Modification after Peripheral Neuronal Sensitization

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Abstract. [Purpose] It is known that peripheral noxious events provoke sensitization of the peripheral and spinal nervous systems and influence neural transmissions to the brain. In this study, we aimed to examine how brain activation is affected when provoked by electrical stimulation and by prior sensitization with peripheral application of a painful agent (capsaicin). [Subjects] Six normal adult volunteers were enrolled in this study. [Methods] Pain intensity of participants was reported using a visual analogue scale (VAS). Utilizing magnetoencephalography (MEG), changes in the brain’s areas and levels of activation were observed by measuring magnetic field alterations. [Results] Locations of equivalent current dipoles (ECDs) changed depending on changes of VAS. The moment (Q) value of the ECDs before the capsaicin cream application was 12.2 ± 6.5 nAm. After applying the capsaicin cream to the left forearm, the Q value increased. The present results suggest that an underlying hyper-responsive condition (neural sensitization) provoked by peripheral capsaicin may cause such changes. Importantly, this study revealed that cortical responses altered in the absence of participant perception of altered pain sensation. [Conclusions] Our findings suggest that alteration of cortical activity may occur when therapeutic electrical stimulations are used after prior pain sensitization.

Key words: Magnetoencephalography, TENS, Sensitization

INTRODUCTION

Effective pain management is extremely important to achieve the best motor function and quality of daily life outcomes in musculoskeletal disorders. Several types of therapeutic electrical stimulation devices have been developed based on neurophysiological and rehabilitation concepts. The most common way electrical stimulation is used to control pain is through transcutaneous electrical nerve stimulation (TENS) and interferential current1, 2). The way in which electrical stimulation, and in particular TENS, functions to control pain has been researched and gate control theory3) and opiate-mediated control theory4) have also been developed.
Recent neurophysiological research highlights the important role of peripheral/spinal neuronal sensitization and plastic changes in the development and maintenance of chronic pain conditions. These changes are known to be provoked by peripheral application of noxious stimulants such as formalin, capsaicin, etc. Baumann reported that cutaneous application of capsaicin induced hyper-responses in unmyelinated small nerve fibers as well as axonal reflex-related neurogenic hyperalgesia. In addition to this peripheral process, alteration of primary afferents induces sensitization of second order spino-thalamic tract (STT) neurons, a major noxious pain pathway, known to have an influence on pain perception.

Following peripheral sensory nerve stimulation, noxious information is conducted to the brain. A previous study demonstrated that after intradermal capsaicin injection in human subjects, a state of hyperalgesia followed with a decreased pain threshold and increased intensity of pain when stimulated above the threshold. These pain events are experienced and recognized in the brain which plays the most important role in the nervous system. In contrast to the peripheral and spinal cord nervous systems, neuronal sensitization and plastic changes in the brain have not been sufficiently investigated. The acute pain phase in particular has been neglected because of central sensory neuronal complexity.

Recently, various aspects of brain activity have been clarified with the development of neuroimaging technology. Magnetoencephalography (MEG) technology enables us to identify the neural transmission pathways and areas of brain activation. In recent MEG research, Inui et al. reported that the first cortical activity evoked by electrical painful stimulation was in the contralateral primary somatosensory cortex (SI) and subsequently bilateral activity was observed in the secondary somatosensory cortex (SII), insular, cingulate cortex and other anatomical areas. However, electrically-provoked cortical activity before and after neuronal sensitization, has not been previously investigated.

Therefore, the purpose of this study was to examine the impact of peripheral nerve sensitization using capsaicin (a noxious irritant) on brain activation provoked by electrical stimulation.

**SUBJECTS AND METHODS**

Six normal adult volunteers (5 males, 1 female, aged 25–43 years, mean age: 30.5 ± 2.7) were enrolled in this study. None of the subjects had significant general medical problems which might affect normal somatosensory perception. All protocols in the study were approved by the Hiroshima University Ethics Committee. All subjects were informed of the purposes of the study and gave their written consent to participation. Prior to the MEG study, plane T2-weighted magnetic resonance (MRI) images were taken to check for non-symptomatic brain lesions.

The MEG recordings were performed using a 204-channel whole-head magnetometer (Neuromag System TM: Neuromag Ltd, Finland). The electrical stimulation was performed with a felt chip type bipolar stimulator (NM-420S, Nihonkohden, Tokyo, Japan). Electrical stimulation was applied with the cathode placed proximal to the anode located at the site of capsaicin cream application. A square wave of 0.2 ms in duration and 5 mA in intensity was delivered at a rate of 2/s. Preliminary tests using a similar stimulus without prior application of capsaicin cream did not cause pain (In a prior trial, when capsaicin cream was not applied, this stimulus intensity did not cause pain: details described below). The 1% capsaicin cream was made by mixing 500 mg capsaicin powder, 0.8 mg 95% ethyl alcohol, and 49.5 g hydrophilic ointment, and 0.5 g of the cream was applied to the dorsal side of the left forearm (Fig. 1). The MEG was performed with subjects fully awake with eyes closed in sitting positions. Three separate 50-second recordings were taken, once prior to, and twice following cream application. At rest with eyes closed, and in fully awake sitting positions, the recordings were performed three times for a period of 50 seconds each, once prior to and twice following cream application. At rest with eyes closed, and in fully awake sitting positions, the recordings were performed three times for a period of 50 seconds each, once prior to and twice following application of the capsaicin cream. Following application, pain intensity of participants was obtained using a continuous visual analogue scale (VAS). The second and third MEGs were performed when VAS reached 2 and 4 respectively. That is to say, when the VAS reached a value of 2 (herein condition A), a second MEG recording was conducted. Similarly, when the VAS recorded a value of 4 (herein condition B), a third MEG recording was conducted.

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Responses were sampled at 300 Hz, and band-pass filtered within 0.1–25 Hz. The MEG was measured 100 times and then averaged. The moment (Q) of the equivalent current dipoles (ECDs), peak latency (PL), and the estimated sites of the ECDs on the right cerebral hemisphere were located by using the standard MEG analysis tool. The goodness of fit (GOF) for the sites, the latencies and the Q of the ECDs used were more than 70%. The locations of the ECDs were identified by overlapping the axes that fit between the axes of the coordinate system derived from the MEG and MRI recordings.

Regarding the statistically significant differences in Q for the serial changes in pain, a one-way analysis of variance (repeated measure one-way ANOVA) was used for comparing Q values. The post hoc test with Dunnett’s t-test followed the repeated measure ANOVA, and SPSS13.0J was used for making data comparisons between the three groups (control, conditions A and B). The \( \chi^2 \) test was used to determine the relationship between serial changes of VAS and serial site changes of ECDs. P values less than 0.05 were considered significant.

**RESULTS**

The time required for the capsaicin cream to induce hyperalgesia on the dorsal side of the forearm to reach the designated VAS pain levels was on average 5 minutes (3 to 5 minutes) for condition A and 10 minutes (8 to 12 minutes) for condition B. After capsaicin application, no participant reported increased subjective pain intensity due to electrical stimulation.

The average peak latency of the ECDs at the time of each measured pain level in the six subjects was 84.0 ± 32.4 (51–141) ms in control, 117.0 ± 25.5 (87–143) ms under condition A, and 104.8 ± 25.7 (74–140) ms under condition B (Table 1).

The Q of the ECDs before the capsaicin cream application was 12.2 ± 6.5 nAm. After applying the capsaicin cream to the left forearm, the Q value at the time of condition A was 18.8 ± 14.0 nAm. At the time of condition B, Q increased to 21.2 ± 15.1 nAm (Table 2).

The estimated sites of the ECDs prior to the capsaicin application were located in the SI (n=4) and premotor cortex (n=2). At the timing of condition A, the ECDs were located in the premotor cortex (n=5) and SI (n=1). At the timing of condition B, ECDs were located in the premotor cortex (n=3), SI (n=2) and posterior parietal cortex (n=1) (Table 2).

Trends in ECD fluctuations with regard to changes in VAS were of two types. In one type (n=3) the ECDs under control conditions were located in the SI, changing to the premotor cortex or posterior parietal cortex depending on changes in VAS. A second type (n=3) displayed ECDs in the premotor cortex or SI under control conditions and did not alter with changes in VAS (Table 1).

**Case 1**

For Subject 2, as seen in Fig. 2, the SI reacted prior to the capsaicin cream application to the dorsal side of the left forearm. However, the ECDs were located in the premotor cortex under condition A and condition B. As the subjectively expressed pain increased, the Q values also displayed a tendency to...
This study demonstrated that cortical neuronal responses, provoked by constant non-painful electrical stimuli, changed after capsaicin-induced painful sensitization. One possible explanation for this is that afferent neuronal signals from peripheral nerves may have been influenced by the sensitization of the central and peripheral nervous systems. Capsaicin produces continuous pain through stimulation of C fibers and sensitization of dorsal horn cells. This sensitization causes an expansion of the receptive field and an increase in tactile sensitivity. The conduction system within the spine and brain related to other stimuli (e.g. tactile sense etc.) is also known to be slightly affected\(^{10,11}\).

In a previous MEG study, Inui et al. stimulated A\(\delta\) fibers using an original intradermal electrical stimulation method, and the somatosensory magnetic field was evoked in the SI at a long latency, averaging 93.9 to 160.8 ms\(^9\). Kakigi et al. reported that in the spinal cord, faster pain signals in A\(\delta\) peripheral nerve fibers are conducted faster and slower pain signals in C fibers are conducted slower. Although the stimulation used in our study could not specifically provoke pain-conducting fibers, the relatively longer latency observed suggests that the slower conducting fibers may have contributed to the recorded ECDs in our present study\(^{12}\).

We measured ECDs to evaluate the sites and strength of the source of the brain’s magnetic field and observed that there were two types of change in estimated ECDs sites. One type changed from SI in the control to the premotor cortex after induced hyperalgesia. The second type of response was characterized by no observed shift to premotor cortex activation after induced hyperalgesia. Anatomically, it is known that SI responds to direct nociceptive stimulation and not to pain anticipation. The premotor cortex receives input from the cingulate cortex, a part of the limbic system, which is also believed to control the prefrontal cortex and is involved in activation of autonomic nerves. It is also suggested that these domains have a close relationship with the pain sensation system, as studies on patients with pain have recorded activity in these sites. A shift in the activated ECDs sites to the premotor cortex and supplementary motor area (SMA) following induced hyperalgesia in this study also indicates a relationship between the premotor cortex and pain sensation\(^{13,14}\).

| Table 1. | Serial changes of the PL of the ECDs at each pain level in the six subjects |
|-----------------|-----------------|-----------------|
| Control | VAS 2 | VAS 4 |
| Subject 1 | 141 (PC) | 143 (PC) | 140 (PC) |
| 2 | 89 (SI) | 134 (PC) | 98 (PC) |
| 3 | 55 (SI) | 109 (PC) | 119 (SI) |
| 4 | 79 (PC) | 87 (PC) | 79 (PC) |
| 5 | 51 (SI) | 140 (PC) | 119 (PPC) |
| 6 | 89 (SI) | 89 (SI) | 74 (SI) |

Mean ± SD of PL (ms) 84 ± 32.4 117 ± 25.5 104.8 ± 25.7

| Table 2. | Comparison of the mean values of Q at each pain level and serial changes in the estimated position of the ECDs according to the changing VAS in the six subjects |
|-----------------|-----------------|-----------------|
| Q of ECDs | Subject 1 | Control | VAS 2 | VAS 4 |
| Subject 2 | 11 | 15.8 | 19.1 |
| 3 | 8.2 | 10.5 | 11.9 |
| 4 | 17.5 | 17.5 | 18.8 |
| 5 | 8.6 | 9.6 | 11.2 |
| 6 | 22.6 | 46.8 | 51.2 |

Mean ± SD of PL (ms) 12.2 ± 6.5 18.8 ± 14 21.2 ± 15.1

SI: Primary somatosensory cortex.
PC: Premotor cortex.
PPC: Posterior parietal cortex.

Several studies have focused on the relationship between Q values and hyperalgesia\(^{15}\). These studies showed that when the intensity of pain stimulation was gradually increased, a correlation between VAS levels of pain and the Q value of the ECDs was obtained, with Q increasing in SI and SII. Although the intensity of stimulation was not altered...
in our study, the Q value increased accompanied by a change in VAS, suggesting that an underlying hyper-responsive condition (neural sensitization), provoked by peripheral capsaicin, may cause such changes in Q.

The present study revealed that cortical responses altered even though participants did not mention nor experience additional painful sensory feeling evoked by electrical stimuli. Since the present study did not show analgesic effects, we could make no conclusions regarding the cortical neurophysiological mechanisms involved in TENS or interferential current. However, our findings suggest that some alteration of cortical activity might occur with these therapeutic electrical stimulations.

Fig. 2. Located positions of the ECDs in the coronal view of the MRI and three-dimensional image of the brain in Subject 2. The ECDs were located in the SI in the control and PC in VAS 2 and 4. L: Left, R: Right, A: Anterior, P: Posterior.

REFERENCES


