Brain Dynamics of Scalp Evoked Potentials and Current Source Densities to Repetitive (5-pulse Train) Painful Stimulation of Skin and Muscle: Central Correlate of Temporal Summation

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Summary: Temporal summation is a potent central somatosensory mechanism and may be a major mechanism involved in e.g. neuropathic pain. This study assessed the long-latency somatosensory evoked potentials (SEPs) in response to trains of repeated painful electrical stimulation of human skin and muscle in order to investigate the cerebral representation of temporal summation. Forty series of stimuli were delivered at stimulus intensities corresponding to moderate pain levels in 20 young men. Each series consisted of a five-burst-pulses (1 ms) train delivered at 2 Hz, known to activate temporal summation, i.e. increased pain intensity during the series of stimuli. Grand mean averaged waveforms (31 ch. EEG) were obtained in response to the skin and muscle stimulation. In the "train" SEPs, the wave morphology was characterized by four peak components after the first stimulus (100 to 450 ms) and by three components after the fifth stimulus (2100-2145 ms). The latency was significantly prolonged for muscle stimulation only. The 3D topographic maps at the peak activation time (100, 140, 250, and 450 ms) showed clear reduction in the amplitudes and their spatial extent (P4/P100-Fc2/N100, P0z/P140-Fc2/N140, Cz/P250, Cz/N460) between the first and the fifth stimulus. The current source density (CSD) topology exhibited markedly differential patterns changing from the first to the fifth stimulus. For the skin stimulation, the fifth stimulus was associated with a distinct emergence of the frontal negativity source at Fc2 right frontal cortex. This was consistent across the 100, 140, 250, and 450 peak components but was not even visible in the first stimulus. In the muscle, the fifth stimulus was associated with a marked reduction of the frontal positivity at contralateral F4 site in the early stages at 100 and 140 ms, and with a total disappearance of positive source at Cz. In summary, this study demonstrated a clear temporal summation of psychophysical ratings, reduction of the peak amplitudes in the last of the first stimuli, dissociation from simple amplitude increase of the cerebral responses to pain, and a concurrent transformation of the CSD patterns. This change in "rapid cortical dynamics" of short-term plasticity could be an important mechanism for wind-up and pain processing in the brain.

Keywords: Painful stimulation; Sensitization; Psychophysics; SEP waves; Dynamic SEP topography; Dipoles.

Introduction

Temporal summation is defined as a psychophysical or physiological augmentation when a fast repetition of a stimulus causes increased pain perception and/or associ-
be an important parameter in central hyper-excitability and hyper-algesia.

Recently, the clinical relevance of temporal summation has been studied. Petersen-Felix et al. (1995) studied the effects of isoflurane on repeated electrical nociceptive stimuli, and found that the 2-4-fold higher isoflurane concentrations (1.00-1.50 volume% end-tidal) were required to depress repetitive stimuli compared with single stimulus. The NMDA-antagonist (Ketamine) (Arendt-Nielsen et al. 1995) has so far been the most potent drug to inhibit central summation. The inhibition of central temporal summation has also been examined after extradural anesthesia (Curatolo et al. 1995) which is unable to block temporal summation of repeated electrical stimuli while spinal anesthesia (Curatolo et al. 1997) could inhibit it. These studies suggest that repetitive stimuli are more sensitive than the traditional single stimulation in differentiating the potency of spinal anesthetics. It furthermore demonstrates the importance of this summation mechanism. So far the interpretation has been that summation is a predominant spinal action. The possible cerebral correlate is unknown.

Based on the psychophysical evidence from human studies, the process of temporal summation might involve spinal as well as cerebral mechanisms. The cerebral hypothesis of temporal summation has been strengthened by a recent study in animals (Gozariu et al. 1997). In intact rats, the temporal summation effects of cerebral excitability after noxious stimulation could be counteracted by a proposed supra-spinal inhibitory mechanism. The present study was aimed at investigating the cerebral representation of responses to temporal summation using long-latency somatosensory evoked potentials (SEPs) to repetitive painful skin and muscle stimulation. We predicted that if temporal summation occurred corresponding changes in cerebral dynamics should be identifiable. We applied the advanced spline surface Laplacian analyses of the current source densities (CSDs) in the SEPs. Surface Laplacian analyses have been used recently in defining the cerebral activation in brain maturation (Srinivasan 1999), movement (van Burik and Pfurtscheller 1999), cognitive function (Gevins 1996; Shibata et al. 1999; Tenke et al. 1998), drug action (Dimpfel et al. 1996), and general cortical imaging (Nunez et al. 1994). Surface Laplacian analyses can effectively estimate skull current density or cortical current source densities. The cortical current density is the result of physical spatial low-pass filtering of scalp potentials, accentuation of the radial dipoles, devoid of volume conduction effect or reference bias, and emphasis on the shallow local current sources. No prior surface Laplacian estimate of the SEPs in painful stimulation has been reported. Using analyses of the scalp potential dynamics and the associated patterning of current source densities, the main goal of the study was to isolate and identify the dynamics of the SEPs in relation to temporal summation during painful skin and muscle stimulation.

Materials and Methods

Subjects

Twenty healthy men (mean age: 25.7, standard deviation: 5.2 years) participated in this study. Informed consents were obtained in accordance with the Helsinki Declaration. The subjects were first familiarized with the electrical stimulation and were extensively trained in the use of the psychophysical ratings. During the experiments the subjects were seated in a quiet room in a reclined armchair and were asked to keep their eyes open.

Electrical stimulation and subjective pain ratings: An electrical constant current stimulator (Aalborg University, Denmark) was used to generate square-wave pulses. The stimulus consisted of a train of five 1-ms pulses repeated at 2 Hz. The hairy skin overlying the left brachioradialis muscle 5 cm below the left elbow was stimulated with the two surface (7 mm diameter) electrodes (13LO202, Dantec, Denmark). Alternatively, the muscle was stimulated by two disposable 20-mm long sensory needle electrodes (13R27, 28G, Dantec, Denmark) with an uninsulated 3 mm tip. The muscle electrodes were inserted into the muscle 10 mm apart (Svensson et al. 1997).

After five ascending and descending trials at 1 mA steps, the stimulus intensity was adjusted to a moderate pain sensation which was anchored as 6 on a 0-10 point scale (Chen et al. 1998). The train of stimuli consisted of five single pulses, spaced 500 ms apart (2 Hz). A single train of stimuli caused five corresponding sensations and five evoked responses in the EEG, which could be identified in the average of the 40 trains. Forty repeated trains of stimuli at the same stimulus intensity were presented to the subjects for recording of SEPs. The subjects had a 10-min break between the recordings of SEPs from the skin and from the muscle. Immediately after each train of stimuli, the subjects were asked to rate the first and the fifth stimulus. The corresponding intensities were: 0 = no pain, 1 = slight intense, 2 = mild intense, 3 = moderate intense, 4 = slight pain (pain threshold), 5 = mild pain, 6 = moderate pain, 7 = moderate-strong pain, 8 = strong pain, 9 = severe pain, 10 = nearly unbearable pain.

EEG Recordings

The SEPs were recorded from 32 surface electrodes (including one electro-oculogram, EOG) mounted on the scalp using a standard EEG-cap (ECI, Dayton, USA) and referenced to linked ears (A1/A2). The sites and labels of...