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Experimental pain in the gingiva and its impact on prefrontal cortical hemodynamics: A functional near-infrared spectroscopy study

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HIGHLIGHTS

- Prefrontal cortex activity was measured after pain stimulation to the gingiva.
- Mild pain was induced to the tissue around the right maxillary central incisor.
- Oxy-Hb in the contralateral prefrontal cortex was reduced upon pain stimulation.
- Oxy-Hb decreased in the superior, middle, and orbital part of frontal gyrus.

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ABSTRACT

Evaluating alterations in brain activity in response to pain stimulus can help understand the mechanisms underlying pain perception. We measured oxygenated hemoglobin (oxy-Hb) levels using functional near-infrared spectroscopy (fNIRS) in order to assess prefrontal cortex activation after inducing a pain stimulus to the gingiva. Twenty-three right-handed, healthy male subjects (mean age: 29.3 ± 3.6 years) were subjected to a mild pain stimulus to the tissue around the right maxillary central incisor. The periodontal pain stimulus (PPS) was elicited from a pocket probe, and a multi-channel fNIRS system with its accompanying 22-channel probes was used for measuring oxy-Hb levels. Mean oxy-Hb levels for each channel were calculated on the basis of values obtained at rest and during the PPS load, for 1 min each. The change in oxy-Hb level was calculated by subtracting oxy-Hb at rest from oxy-Hb levels during PPS load. Oxy-Hb levels in each channel during both conditions were then compared using the paired *t*-test and Bonferroni correction. Pain stimulation caused oxy-Hb levels to decrease in virtually all areas of the prefrontal cortex, particularly, in the superior frontal gyrus, the middle frontal gyrus, and the orbital part of the superior, middle, and inferior frontal gyrus, on the brain side contralateral to the pain load. This measurement could prove beneficial as an index for objective pain evaluation.

1. Introduction

Pain information is transmitted to pain-related brain regions (such as the somatosensory association cortex, the insula, the cingulate gyrus, and the thalamus) via two pathways, namely the pathway that encodes sensory (intensity) and location aspects and the pathway responsible for emotional/cognitive/evaluative features of the pain-eliciting stimulus [1,2]. Affective information pertaining to pain is projected from the amygdala, toward the anterior cingulate gyrus and prefrontal cortex; the resulting perception of discomfort is due to the negative emotion caused by pain [3].

The role of the prefrontal cortex in the pain pathway is unclear with a number of studies reporting conflicting patterns of activity elicited following a painful stimulus. For example, a meta-analysis conducted by Apkarian et al. [1] demonstrated that application of a noxious stimulus to healthy subjects was accompanied by an increase in prefrontal cortex activity. However, other studies conducted on patients suffering from pain after tooth extraction [4], patients with rheumatoid arthritis [5], and even

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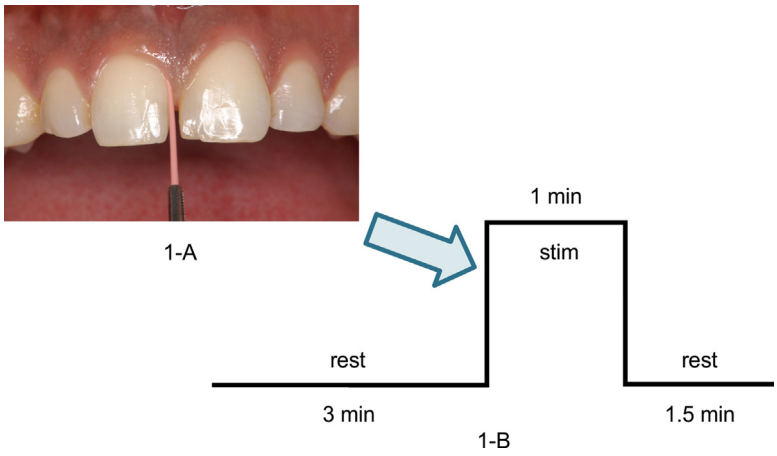

Fig. 1. Experimental pain stimulus and time schedule. Pain stimulation was produced by a pocket probe onto the gingiva of the right maxillary central incisor (1-A). The time schedule of the fNIRS measurements started with a 3-min rest, followed by application of the pain stimulus for 1 min, and a 1.5-min rest (1-B). The pain stimulus was delivered while changing the application site six times in 60 s.

healthy subjects [6] have suggested that pain stimuli causes a decrease in prefrontal cortex activity. Therefore, the relation of chronic and acute pain to activity in the prefrontal cortex remains unknown.

Studies examining brain activity caused by painful stimuli mainly employ positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques; however, both of these approaches require the use of constraints on the head and body, making it difficult to conduct measurements in various postures [7]. In contrast, functional near-infrared spectroscopy (fNIRS) requires relatively less constraints and allows for measurements in different postures and during various movements [8]. Therefore, fNIRS can be used to measure brain activity in the posture in which pain is experience the pain and also in the standing or sitting positions.

Thus far, most studies on brain activity during pain have been performed by using fMRI, and by loading the extremities with thermal or mechanical stimuli. Similarly, fMRI has been used to examine brain activity evoked by pain in the oral cavity through loading electric [9–11] or thermal stimuli onto teeth [12]. For most people, pain in the oral cavity involves both the teeth and the oral mucosa. However, brain activity at the time of loading the pain stimulus to the oral mucosa has not yet been studied. Assessing brain activation during pain perception in the oral mucosa, such as in the gingiva, is important for understanding the mechanisms of pain in the oral cavity. Moreover, evaluating how the pain responds to pain might help to establish indicators that allow for objective evaluation of pain. In this study, we examined altered oxy-Hb levels in the prefrontal cortex during experimental loading of a pain stimulus to the gingiva using fNIRS.

2. Methods

2.1. Participants

Participants were recruited via an announcement addressed to faculty members and students affiliated with Aichi Gakuin University School of Dentistry. Previous studies have suggested that sex-related hormones could be confounding in the relationship between pain and the analgesic response [13]. Consequently, only men were selected as participants in this study. Twenty-three right-handed, healthy males (mean ± S.D. age: 29.3 ± 3.6 years) gave their consent after receiving explanations on the major points of the study. Written informed consent was obtained from all subjects. All procedures were approved by the Ethics Committee at Aichi Gakuin University School of Dentistry (authorization number: 163).

2.2. Experimental pain stimulus

The experimental pain stimulus was applied via a probe [14] typically used for measuring periodontal pockets. In consideration of safety, accessory points for root canal filling (GUTTA PERCHA POINTS Accessory: GC Corporation, Tokyo, Japan) were used to deliver the periodontal pain stimulus (PPS). For the PPS, an accessory point was inserted in the labial gingival sulcus of the right maxillary central incisor, six times in 60 s while changing the site of insertion each time (Fig. 1). Normally, a sensation of stinging pain is felt upon application of an accessory point. Therefore, the intensity of the pain caused by the PPS was evaluated using the Visual Analogue Scale (VAS; range: 0–100 mm) [15], and results showed VAS level of 27 ± 6 mm (mean ± S.D.), which is indicative of a mild pain stimulus [16].

2.3. fNIRS and measurement items

In order to measure changes in oxy-Hb level, we employed a multi-channel fNIRS system (ETG-4000: Hitachi Medical Corporation, Tokyo, Japan) using two wavelengths of near-infrared light (695 and 830 nm), as well as the accompanying 22-channel probe. The measurement probe that we used had an array of 3 × 11 optical fibers, and the distance between the light-emitting unit and the detector unit was 3 cm. fNIRS measurement sometimes results in Hb changes because of factors unrelated to brain activity, such as poor optical fiber contact caused by bodily movement or changes in blood flow associated with muscle activity. In the current study, fNIRS measurements were restricted to the prefrontal cortex; therefore, artifacts related to blood influx to the temporal muscle most likely did not affect our data. However, it is unclear whether artifacts are uncontaminated. Therefore, we obtained data using a 52-channel probe instead of the 22-channel probe, and no artifacts were observed in the oxy-Hb waveforms obtained using this measurement. The probe targeting the prefrontal cortex was placed in such a way that the array at its bottom coincided with the line of T3-Fpz-T4 (international 10–20 system reference points) [17].

Measurements were obtained during all of the following time points: 3-min rest period, PPS load for 1 min, and 1.5-min post-PPS rest (Fig. 1). Fig. 2 shows a graph of average oxy-Hb levels