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The respiratory cycle modulates brain potentials, sympathetic activity, and subjective pain sensation induced by noxious stimulation

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ABSTRACT

To test the hypothesis that a respiratory cycle influences pain processing, we conducted an experimental pain study in 10 healthy volunteers. Intraepidermal electrical stimulation (IES) with a concentric bipolar needle electrode was applied to the hand dorsum at pain perceptual threshold or four times the perceptual threshold to produce first pain during expiration or inspiration either of which was determined by the abrupt change in an exhaled CO_2 level. IES-evoked potentials (IESEPs), sympathetic skin response (SSR), digital plethysmogram (DPG), and subjective pain intensity rating scale were simultaneously recorded. With either stimulus intensity, IES during expiration produced weaker pain feeling compared to IES during inspiration. The mean amplitude of N200/P400 in IESEPs and that of SSR were smaller when IES was applied during expiration. The magnitude of DPG wave gradually decreased after IES, but a decrease in the magnitude of DPG wave was less evident when IES was delivered during expiration. Regardless of stimulus timing or stimulus intensity, pain perception was always concomitant with appearance of IESEPs and SSR, and changes in DPG. Our findings suggest that pain processing fluctuates during normal breathing and that pain is gated within the central nervous system during expiration.

1. Introduction

There is growing evidence that pain can be relieved by slow deep breathing in the settings of the nursing (Miller & Perry, 1990) or in experimental pain research (Chalaye et al., 2009; Zautra et al., 2010). Zen meditation, accompanied with extremely slow breathing, also has similar beneficial effects on the perception of pain (Grant et al., 2011; Zeidan et al., 2011). All the previous experimental pain studies on respiratory modulation, however, did not investigate whether analgesic effects during slow breathing would change between inspiratory phase (IP) and expiratory phase (EP). As to a relationship between pain processing and the cardiac cycle, the magnitude of pain-related brain potentials is changed across the cardiac cycle and tends to be smaller during systole where reflex parasympathetic activation occurs (Edwards et al., 2008). The pending issue is whether pain perception and pain-related responses of the brain or the autonomic nervous system are changed during a respiratory cycle in normal breath. We hypothesize that pain processing is modulated by a respiratory cycle and that pain will be decreased during EP compared to IP in slow breathing as well as normal breath, since the Lamaze method of childbirth preparation involving exercises and breathing control recommends to keep EP longer for relieving pain during parturition without drugs (Michaels, 2010).

The mechanism of pain processing has been studied by analyzing subjective pain intensity scores and physiological measures such as brain potentials and autonomic functions following noxious stimulation that induces the whole range from modest to strong pain. However, pain-related brain potentials such as laser evoked potentials are modulated by the level of attentiveness (Garcia-Larrea et al., 1997) or stimulus-related factors such as saliency (Iannetti et al., 2008); therefore, it is still debated as to whether the vertex "N2–P2" potential in laser evoked potentials reflects the distinctive response in central pain processing or rather attentional or orienting response that often appears regardless of sensory modality (Garcia-Larrea et al., 1997; Baumgärtner & Treede, 2009; Iannetti et al., 2008; Lee et al., 2009; Mouraux & Iannetti, 2008, 2009; Mouraux et al., 2011; Truini et al., 2004, 2007). We assume that if the subject's attentiveness is kept constant and stimulus-related

Abbreviations: EP, expiratory phase; IP, inspiratory phase; IES, intraepidermal stimulation; IESEPs, intraepidermal electrical stimulus-evoked potentials; DPG, digital plethysmogram; SSR, sympathetic skin response.

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factors are fairly controlled, feeble noxious stimulation at the pain perceptual threshold of the subject will minimize the attentional or orienting aspects of the pain-evoked response and, thereby, allow us to analyze physiological measures such as evoked potentials closely related to pain processing *proper*. Thus, using intraepidermal stimulation technique (IES) with a concentric bipolar needle electrode (Inui et al., 2002; Inui and Kakigi, 2012; Mouraux et al., 2010; Otsuru et al., 2009), we investigated whether brain potentials, sympathetic activity, and subjective pain intensity ratings are changed during IP or EP in normal breath either of which was precisely determined by monitoring an exhaled CO_2 level. We set two stimulation intensity, the perceptual threshold and four times as large as the perceptual threshold, to confirm whether respiratory modulation of pain processing consistently occurs with either stimulus intensity.

2. Methods

2.1. Subjects

Ten male paid-volunteers took part in the experiments. All were healthy university students and identified as right-handed, based on the Edinburgh questionnaire (Oldfield, 1971). The mean age was 19.6 ± 0.2 years (mean ± standard error (SE); range, 19–21 years), and the mean height was 172.9 ± 1.2 cm (mean ± SE; range, 167–178 cm). All of the participants provided written informed consent in accordance with the Declaration of Helsinki and the guidelines approved by the Ethical Committee of Aomori University of Health and Welfare.

2.2. Electrophysiological measures

We recorded EEG from 35 scalp sites and a polygram such as electrooculogram (EOG), EKG, digital plethysmogram (DPG), sympathetic skin response (SSR), an exhaled CO_2 level and thorax or finger movement using a 64 channel Electroencephalograph (EEG-1200 Neurofax, Nihon Kohden Corp., Tokyo, Japan). For EEG recording, a 31 channel Electrocap (E1-L/M, Electro-Cap International, Inc., Ohio, USA) was used to obtain potentials from the following positions on the scalp according to the International 10/20 system: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, FPz, FCz, CPz, Oz, FC3, FC4, CP3, CP4, TP7, TP8, FT7, and FT8. Additional surface electrodes were positioned at F9, F10, TP9, TP10, A1 (left earlobe), and A2 (right earlobe), and the ground electrode, on the forehead. The left earlobe (A1) electrode served as a reference. The scalp or earlobe electrode impedance was kept below 5 kΩ. In addition to EEG, ocular movements and eye blinks were recorded using two additional surface electrodes placed at the upper-left and lower-right sides of the left eye. Using a pulse oximeter (OLV-3100, Oxypal Neo, Nihon Kohden Corp., Tokyo, Japan) with a finger probe (TL-201 T, Nihon Kohden Corp., Tokyo, Japan), the DPG was obtained from left index finger and transferred to an EEG-1200 Neurofax. Using an expiratory carbon dioxide gas monitor (OLG-2800, Nihon Kohden Corp., Tokyo, Japan) with a carbon dioxide (CO_2) sensor kit (TG-920P, Nihon Kohden Corp.) including a CO_2 sensor (TG-121T, Nihon Kohden Corp.) and a nasal adapter (YG-121T, Nihon Kohden Corp.), an exhaled CO_2 level was continuously monitored. The analog signal from the expiratory carbon dioxide gas monitor was transferred to an EEG-1200 Neurofax and an electromyograph MEB-4308 (Nihon Kohden Corp., Tokyo, Japan) with which we could give an electric pulse for nerve stimulation or a trigger pulse to drive another peripheral nerve stimulator at a given time: when an exhaled CO_2 level abruptly exceeded 20 mmHg indicating an early phase of expiration (expiratory phase, EP) or when it abruptly fell below 20 mmHg indicating an early phase of inspiration (inspiratory phase, IP). For SSR recording, we used standard surface EEG disk electrodes (8 mm diameter, argentum surface, H503A, Nihon Kohden Corp.), applied with commercial electrode paste (Eelefix, Nihon Kohden Corp.) to the palm and the dorsum of the left hand. The thorax movement was recorded using a thorax movement sensor kit (TR-111A, Nihon Kohden Corp., Tokyo, Japan). To record the subjective evaluation of pain intensity in each stimulation, the extension movement of right index or middle finger from a resting position also was detected using an apparatus that comprises two digital laser sensors, aligned parallel (LV-H62, Keyence Corp., Osaka, Japan). All data imported to an EEG-1200 Neurofax were digitized with a sampling rate of 1 kHz. For EEG data, the time constant was 0.3 s and the cut-off frequency of a low-pass filter, 120 Hz at −3 dB. For recording of SSR and thorax or finger movement, the time constant was set at 2.0 s and the cutoff frequency of a low-pass filter, 15 Hz at −3 dB.

2.3. Intraepidermal electrical stimulation with a concentric bipolar needle electrode

For nociceptive stimulation, we used an intraepidermal electrical stimulation (IES) method with a concentric bipolar needle electrode that was developed for the selective stimulation of cutaneous A-delta fibers (Inui et al., 2006). We used a disposable, stainless steel concentric bipolar needle electrode for IES (NM-990W, Nihon Kohden Corp., Tokyo, Japan). The anode is an outer ring of 0.1 mm in height, 1.4 mm outside diameter and 0.1 mm in thickness, and the cathode is an inner needle of 0.2 mm in length that stuck out from the outer ring surface by 0.1 mm, providing a stimulation area of 1.54 mm^2 that is narrower than a one-tenth of a stimulation area in a planar concentric bipolar electrode (19.6 mm^2) (see Kaube et al., 2000; de Tommaso et al., 2011; Perchet et al., 2012). By pressing the electrode against the skin gently, the needle tip was inserted in the epidermis and superficial part of the dermis where nociceptors are located, while the outer ring was attached onto the skin surface (for details, see Inui et al., 2006). In the present study, the electrode was put on the dorsum of the left hand, between the first and second metacarpal bones. To precisely determine subject's pinprick sensation threshold, we used a newly developed peripheral nerve stimulator for the exclusive use of IES (PNS-7000, Nihon Kohden Corp., Tokyo, Japan) that allows us to control a pulse intensity at a 0.01 mA unit and provides a distinct shape of the pulse with a different rise, plateau or fall time at a 0.1 ms step. To obtain cutaneous A-delta fiber activation selectively, we used a triple trapezoid pulse of 0.2-ms rise, 1.5-ms plateau and 0.5-ms fall time with an interval of 20 ms. Prior to EEG recordings, we determined the minimum intensity producing a feeble pain, referred to as the perceptual threshold, in each subject by increasing the current intensity stepwise by a 0.01 mA unit until a subject feels a pain. We confirmed that the level of the perceptual threshold was reproducible by repeating threshold determination in each subject. Also, since the stimulus intensity of >1 mA may recruit unwanted activation of large-diameter A beta fibers (Legrain & Mouraux, 2013), we assured ourselves that the stimulus intensity at four times the perceptual threshold in each subject would be <1 mA. The stimulus intensity was unchanged during recording session. It was set at the perceptual threshold or at four times the perceptual threshold producing a definite pain sensation in each subject. In order to avoid giving stimulus frequently during EEG recording session, we controlled on–off of IES by manually interrupting transmission of a trigger pulse from an electromyograph MEB-4308, by which we monitored an exhaled CO_2 level, to the PNS-7000 stimulator.

2.4. Experimental procedures

The subject sat relaxed in a comfortable reclining chair in a quiet room that was air-conditioned and electrically shielded: the

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