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Effects of different forms of dyspnoea on pain perception induced by cold-pressor test

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ABSTRACT

Although dyspnoea has been shown to attenuate pain, whether different forms of dyspnoea exert a similar inhibitory effect on pain has never been tested. We examined the effects of two different forms of dyspnoea, i.e., "air hunger" sensation (AIR HUNGER) and "work/effort" sensation (WORK/EFFORT), on pain induced by a cold-pressor test. Dyspnoea was induced by two different dyspnoea stimuli (i.e., AIR HUNGER and WORK/EFFORT stimuli) and the magnitudes of both sensations were evaluated by using a visual analogue scale (VAS). At equi-dyspneic VAS levels of two different forms of dyspnoea, pain was induced and the unpleasantness of pain was assessed by pain VAS, pain threshold time (PTT) and pain endurance time (PET). Both AIR HUNGER and WORK/EFFORT caused an increase in PTT and an increase in PET or a decrease in maximal pain VAS. Our findings suggest that AIR HUNGER and WORK/EFFORT exert a similar analgesic effect although the WORK/EFFORT-induced analgesia was slightly more effective.

1. Introduction

It has been shown that dyspnoea occasionally evokes analgesia (Nishino et al., 1999, 2008; Morélot-Panzini et al., 2007). The sensation of "air hunger" (AIR HUNGER) and the sensation of "work/effort" (WORK/EFFORT) are two qualitatively different sensations of dyspnoea (Lansing et al., 2000). Whether or not different types of dyspnoea differently interact with pain has not been fully explored. The study of Morélot-Panzini et al. (2007) not only clearly showed that the acute dyspnoea induced by an addition of inspiratory threshold loading, i.e., respiratory WORK/EFFORT, causes inhibition of the spinal nociceptive flexion reflex (RIII reflex) but also speculated that the inhibition of pain reflex might occur through a subcortical mechanism of diffuse noxious inhibitory controls (DNIC) (Le Bars et al., 1979a,b). The DNIC system involves a spinal–medullary–spinal feedback loop in which stimulation of Aδ- or C-fibers plays an important role (Bouhassira et al., 1987). Less is known of how another form of dyspnoea, i.e., AIR HUNGER, might affect pain sensation.

In generation of AIR HUNGER, an increase in activity of chemoreceptors together with a decreased activity of pulmonary stretch receptors plays a major role (Lansing et al., 2000) whereas the role of C-fiber stimulation from chest wall muscles and lungs may be negligible. Assuming that the DNIC might be the main mechanism of dyspnoea-evoked analgesia, AIR HUNGER stimulus would have little or no effect of producing analgesia, compared with the effect of excessive respiratory work or effort (Banzett et al., 2007; Morélot-Panzini et al., 2007). It is well known that human pain sensitivity varies widely between subjects, and several studies (Chen et al., 1989; Birklein et al., 2008; Nishino et al., 2010) showed that there are different groups of normal healthy subjects whose responses to cold pain stimulation can be easily dichotomized (i.e., pain-sensitive and pain-tolerant subjects). Although the differences in pain sensitivity may modulate the dyspnoea-induced analgesia, no information is available as to how the individual differences in pain sensitivity can affect the dyspnoea-induced analgesia. The aim of the present study was to compare the effects of two different forms of dyspnoea on pain perception induced by cold pressure test in pain-sensitive and pain-tolerant subjects.

2. Materials and methods

2.1. Subjects

The study protocol was approved by the Institutional Ethical Committee of Chiba University (Chiba, Japan), which conforms to the standard set by the Declaration of Helsinki (2008) of the World Medical Association. Studies were carried out in 45 young healthy male subjects whose ages ranged from 22 to 30 yr. None had clinical evidence of respiratory, cardiovascular, neurological or neuromuscular disorders. Each subject gave informed consent to the methodology of the study. None was a smoker or was aware of

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the hypothesis tested in the studies. Mean heights and weights of the subjects were 172.4. ± 6.2 cm and 67.6 ± 9.7 kg (mean ± SD).

2.2. Instruments

The subjects were tested in the sitting posture in an air-conditioned, temperature (24–25 °C) controlled room. They breathed through an experimental apparatus containing a face mask, a pneumotachograph, and a one-way valve system. The experimental apparatus had a resistance of 2.5 cm H_2O/l/s and the total apparatus dead space was 140 ml. Ventilatory airflow was measured with the pneumotachograph (HI201, Nihon Kohden, Tokyo, Japan), and tidal volume (V_T) was obtained by electrical integration of the inspired flow signal. Mask pressure (P_{mask}) was measured with a pressure transducer (Transpac IV; Abbott Critical Care Systems, Chicago, IL). End-tidal carbon dioxide tension (P_{ETCO_2}) and end-tidal oxygen partial pressure (P_{ETO_2}) was measured with an infrared CO_2 analyzer and a polarographic O_2 analyzer, respectively (NEC-Sanei-1H21A, Tokyo, Japan) through a port in the face mask.

Skin temperature was measured using a temperature sensor (Mon-a-therm Skin Probe, Tyco Healthcare Group LP, Tokyo, Japan) taped securely on the back of the subject's left foot.

The degrees of pain and dyspnoea were continuously rated by using visual analogue scales (VAS) which consisted of a horizontal 10 cm line with equally spaced markers. The subject could control the position of the knob of the linear potentiometer along this line.

2.3. Induction of dyspnoea and pain

While the subject was breathing through the respiratory circuit in which an extra dead space of 300 ml was incorporated, dyspnoea was induced by two different dyspnoea stimuli, i.e., (1) relative hypopnea against the increased respiratory dead space and (2) hyperpnea against inspiratory-flow-resistive loading. The unpleasant sensation felt during relative hypopnea was designated AIR HUNGER and the subject was asked to rate the magnitude of this sensation by using a 10-cm visual analogue scales (air hunger VAS). The numerical value of zero indicated "no discomfort at all", 100 indicated a sensation that was "intolerable discomfort". During the experiments the subject was asked to breathe at fixed rate of 15/min set by a metronome while the subject's tidal breath was displayed as a line on the oscilloscope.

The AIR HUNGER stimulus was started by maintaining or gradually decreasing the tidal volume until the target air hunger VAS reached the approximate value of 70. Once the target value of air hunger VAS was attained, the subject was asked to keep this level of tidal volume as a new tidal volume target while the new target line for tidal volume was drawn on the screen of oscilloscope.

During hyperpnea stimulus, flow resistive loading was imposed by placing plastic tube resistors (3.5 mm in diameter and 10 cm in length with a resistance of 60 cm H_2O/l/s at a flow rate of 0.5 l/s) in inspiratory limb of the one-way valve system. Each subject was asked to sense the effort or work he was expending with his breathing muscles to inflate his chest. The sensation felt during hyperpnea was designated WORK/EFFORT and the subject was asked how hard it is to breathe and to rate the intensity of this sensation by using a 10-cm visual analogue scale (work/effort VAS). The numerical value of zero indicated "felt none", 100 indicated a sensation that was "maximum imaginable". In order to differentiate clearly this sensation of WORK/EFFORT from the above-mentioned AIR HUNGER sensation, the concepts of AIR HUNGER and WORK/EFFORT were explained according to the standard script employed in previous studies (Moosavi et al., 2000; Lansing et al., 2000). We also commented that in contrast to AIR HUNGER, the sensation you were feeling during hyperpnea against the flow-resistive loading might not be necessarily uncomfortable. The subject was asked to gradually increase his tidal volume against resistive loading until the target work/effort VAS reached the approximate value of 70, and when the target value of work/effort VAS was obtained, the subject was asked to maintain this level of tidal volume as a new target tidal volume. After the initiation of dyspnoea stimuli, it took usually 3–5 min for breathing patterns and VAS values to stabilize.

Pain was induced by a cold-pressor test. The left foot of each subject was immersed up to the malleolus of ankle in the iced water container (Foot Bub Jet MCR-3600, ALINCO Co., Tokyo, Japan). Local skin adaptation was prevented by stirring and bubbling the ice water (0–1 °C). The subject was asked to keep his foot in the ice water as long as possible, or to the cut-off limit of 2 min was reached. During the immersion of the left foot in the iced cold water, the subject was asked to concentrate his attention on pain sensation and to rate continuously the unpleasantness of pain by using a 10-cm visual analogue scale (pain VAS). The numerical value of zero indicated "no discomfort at all", 100 indicated a sensation that was "intolerable discomfort". The continuous pain VAS ratings were conducted by manipulating the linear potentiometer.

Immediately after the completion of cold water test run, all the subjects put their feet into the warm water box (38 °C).

2.4. Experimental protocol

The subjects were given a short training period to accustom them to the use of the VAS both for pain and dyspnoea. During this training period, the subjects were screened for cold pain tolerance by immersing their hands into the iced water. If the subjects retracted their hands immediately or claimed excruciating pain, they were pain-sensitive candidates ($n = 25$), and if they reported only light to moderate pain during a 1-min of the immersion of their hands in the ice-water, they were pain-tolerant candidates ($n = 20$).

After the screening test, the subjects started to breathe through the respiratory circuit with or without the extra dead space. The distal limb of experimental apparatus was connected to a T-Piece system supplied with 100% oxygen (2–3 l/min).

When a stable test condition was obtained, in each subject the cold pressor test was performed under three test conditions, i.e., control, AIR HUNGER, and WORK/EFFORT, in a randomized order with an interval of 10–15 min. During the control condition, the subject was asked to breathe through the respiratory circuit without the extra dead space at the fixed rate of 15/min but no target tidal volume was given. During the AIR HUNGER and WORK/EFFORT runs, the subject was asked to maintain the target tidal volume at the fixed respiratory rate of 15/min while breathing through the respiratory circuit with the extra dead space.

2.5. Data analysis

Pain threshold time (PTT) was defined as the time from immersion of the foot in the ice water to the onset of pain sensation. Pain endurance time (PET) was the duration from the ice water immersion of subject's foot until the withdrawal of the foot. The subjects who withdrew their feet before the cut-off time was designated "pain-sensitive". PET was measured in pain-sensitive subjects. When the subject reaches the cut-off time of 2 min, the subject was designated "pain-tolerant" and the maximal value of pain VAS before the cut-off time was obtained.

A sample size calculation was based on the results of our previous study (Nishino et al., 2010) in which the mean values of PTT were 12.2 ± 5.8 s (mean ± SD) in pain-tolerant group. A minimum difference in PTT means of 6 s was considered necessary. Thus for a two-side, 0.05 level of significance test with at least 80% power, the