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Short communication

Analgesic effects of dyspnoea: "Air hunger" does not inhibit the spinal nociception reflex in humans

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ABSTRACT

Dyspnoea has distinct sensory modalities, including air hunger and the sensation of excessive breathing "work/effort". Both have analgesic properties. In the case of work/effort, spinal mechanisms have been documented (inhibitory effect on the spinal nociceptive flexor reflex, RIII). This mechanism involves C-fibres. As C-fibres are unlikely to play a major role in air hunger, we hypothesised that inducing this type of dyspnoea would not result in RIII inhibition. Eight healthy volunteers were exposed to a hypercapnic hyperoxic gas mixture (5% CO_2 and 95% O_2) and asked to voluntarily fight the corresponding ventilatory reflex response by reducing tidal volume below its spontaneous level. Ventilatory variables and dyspnoea intensity (ordinal scale) were measured. Electromyography of the biceps femoris was used to record the amplitude of RIII in response to painful electrical sural nerve stimulation. Air hunger failed to inhibit the RIII reflex. We conclude that the mechanisms of air hunger induced analgesia do not include a spinal contribution and are therefore mostly central.

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1. Introduction

Dyspnoea, like pain, has distinct sensory modalities (Parshall et al., 2012), with "air hunger" and excessive breathing "work/effort" being prominent. Air hunger mostly occurs in response to hypoxia or hypercapnia and work/effort in response to respiratory muscle load-capacity imbalance (Simon et al., 1989). Air hunger and work/effort involve distinct mechanisms (Parshall et al., 2012). Air hunger is thought to primarily arise from chemoreceptor stimulation and a corollary discharge from the brainstem to the sensory cortex. Work/effort is thought to arise from thoracic afferents and a corollary discharge of suprapontine origin.

Both air "hunger" and "work/effort" have been shown to interact with pain and have analgesic properties (Nishino et al., 2008; Yashiro et al., 2011).[1] Indeed, Nishino et al. (2008) showed that

exposing normal individuals of the male gender to a combination of hypercapnia and an elastic load significantly raised the pain thermal threshold. Yashiro et al. (2011) induced both "air hunger" and "work "effort" in normal individuals and tested the effects on pain provoked by a cold-pressor test. They observed that both dyspnoeic modalities resulted in increased pain threshold, pain maximal intensity and pain tolerance time. The antinociceptive effects of dyspnoea can result from the release of endogenous opioids in response to stress (Gamble and Milne, 1990; Gronroos and Pertovaara, 1994) or from "competition" at the level of central brain networks shared by dyspnoea and pain (von Leupoldt et al., 2009). They can also involve spinal mechanisms, as follows.

Experimental "work/effort" induced by inspiratory threshold loading (ITL) inhibits the spinal nociceptive flexor reflex (RIII) (Morelot-Panzini et al., 2007). RIII inhibition in response to a heterotopic stimulus attests to the involvement of C and/or A∂ fibres (Bouhassira et al., 1987), the corresponding afferent message activating descending diffuse noxious inhibitory controls (DNICs) that interfere with the spinal transmission of noxious messages (Le Bars and Villanueva, 1988). Because, in the above study by Morelot-Panzini et al. (2007), the ITL paradigm involved strenuous inspiratory efforts, we postulated that respiratory muscle C-fibres were responsible for dyspnoea and the activation of DNICs (Morelot-Panzini et al., 2007). Be this postulate true or not, our

[1] Of note, Gronroos and Pertovaara (1994) observed that acute hypercapnia elevated the heat and ischaemic pain thresholds but not the mechanical and electric pain ones. In this study, respiratory sensations were not evaluated.

observations indicate that the perceptual attenuation of pain during inspiratory loading experiments (Nishino et al., 2008; Yashiro et al., 2011) proceeds at least in part from spinal mechanisms. Whether or not this is also the case for air hunger is unknown.

The present study was therefore specifically designed to test the effects of air hunger on spinal pain transmission mechanisms. To do so, we considered the analgesic effects of air hunger granted from a perceptual point of view (effects hence not re-tested psychophysiologically in this study), and focused on the RIII reflex taken as a "pathophysiological outcome". Because current concepts about the pathophysiology of air hunger do not make a contribution of C-fibre likely, we hypothesised that inducing experimental air hunger without inspiratory muscle loading would not result in RIII inhibition.

2. Materials and methods

The methods used here derive from those previously described (Morelot-Panzini et al., 2007).

2.1. Subjects and ethics

Eight healthy subjects were studied (5 men, 3 women; age: 26–40 years). Their medical history was unremarkable and they were pain-free on the days of the experiments. The study complied with the Declaration of Helsinki and was approved by the appropriate French ethics committee. Participants received detailed information about the methods used but were not initially informed about the research hypothesis (this information was provided *post hoc*). All subjects provided written consent to participate.

2.2. Experimental conditions

The subjects were instructed to avoid sleep deprivation and to refrain from taking analgesics, anti-inflammatory medications, alcohol and psychotropic substances 48 h before the experiments. During the experiments, the subjects were seated comfortably in an examination bed with their backs and heads fully supported. They wore earplugs and headphones through which they listened to quiet classical music to mask the auditory ambiance of the laboratory.

2.3. Respiratory measurements

During the CO_2 stimulation sessions (see Section 2.6), the subjects breathed through an airtight facial mask connected in series to a pneumotachograph (MLT 1000L series, linearity range 0–1000 l/min AD Instrument, Castle Hill, Australia) connected to a linear differential pressure transducer (± 5 cm H_2O, Validyne, Northridge, CA). The experimental apparatus had a resistance of 0.02 cm $H_2O\,l^{-1}\,s^{-1}$ and a dead space of 350 ml. Tidal volume (V_T), breathing frequency (f_R), and ventilation (V'_E) were derived from the flow signal. An infrared CO_2 gas analyser (IR1505, Servomex, Plaine Saint Denis, France) was used to measure end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$).

2.4. Dyspnoea

Dyspnoea was measured once a minute during the experimental sessions. Subjects were asked to rate the intensity of their "breathing difficulty" (in French "*difficulté à respirer*", "*gêne respiratoire*") on an ordinal scale from 0 ("no difficulty") to 9 ("intolerable difficulty"). At the end of each experimental session, the subjects were asked to choose the most appropriate item in the

descriptor list proposed by Simon et al. (1989) (French version validated in Morelot-Panzini et al., 2007).

2.5. Reflex responses

The nociceptive flexor reflex was described according to the previously published method (Morelot-Panzini et al., 2007) (see details in Fig. 1a). The Hoffmann (H) reflex and the direct motor responses were also studied according to the previously published method (Morelot-Panzini et al., 2007). This was done to assess α-motoneuron excitability and rule out depression of the efferent pathway of the reflex in the event of RIII inhibition.

2.6. Air hunger inducing protocol

The experimental sequence is summarised in Fig. 1b. Hypercapnic stimulation was performed by connecting a Douglas bag containing a mixture of 95% O_2 and 5% CO_2 to the inspiratory limb of a one-way valve placed after the pneumotachograph. All subjects were first submitted to a "habituation" challenge to avoid any discovery effect on the day of the actual experiments. Subjects were also trained to perform voluntary V_T reduction with visual feedback from the V_T trace. Several days after the habituation challenge and training, the effects of CO_2 stimulation alone ("CO_2") on the RIII reflex were studied. The 95% O_2 and 5% CO_2 mixture was administered over 5 min, followed by a room-air breathing recovery period. The hypercapnic mixture was then readministered and the subjects were then asked to voluntarily fight their automatic response to CO_2 (Chonan et al., 1987) ("CO_2-V_T"). Using visual feedback, they were required to target a V_T of about two-thirds of the V_T recorded during the first CO_2 exposure. Respiratory frequency was not controlled. The effects of CO_2 on the H reflex were evaluated on separate days

2.7. Statistical analysis

Statistical analysis was performed with Prism® software (GraphPad Software Inc., San Diego, CA). All data sets presented a normal distribution according to the Shapiro–Wilk test and data are therefore summarised as mean $\pm$ SD. All variables were averaged minute-by-minute throughout the experiments. Data acquired during the 5 min immediately preceding dyspnoea induction were averaged to compute the baseline value and all "per minute" values were expressed as a percentage of this baseline value. The effects of the CO_2 conditioning stimulation over time were assessed using analysis of variance for repeated measures on minute-by-minute data with a two-by-two protected least square difference test. Differences were considered significant when the risk of a type I error was less than 5% ($P < 0.05$).

3. Results

Hyperoxic hypercapnia alone elicited moderate breathing difficulty ratings that increased dramatically with V_T-restriction (0% of full scale during baseline, $28.1 \pm 8.4\%$ of full scale during the 5th minute of the CO_2 period, $70.6 \pm 1.8\%$ of full scale during 5th minute of the CO_2-V_T period; $F = 223$, $P < 0.0001$). During the CO_2-V_T period, all ratings were greater than 60% of full scale after 2 min (Fig. 2). The subjects consistently chose air hunger as the main descriptor of their breathing difficulty.

V'_E increased significantly after administration of the hypercapnic gas mixture alone, and then decreased significantly during voluntary V_T reduction (Fig. 2). $P_{ET}CO_2$ increased from 42.1 ± 1.8 mmHg at the 5th minute of baseline, to 47.5 ± 1.7 mmHg at the 5th minute of CO_2, to 51.6 ± 2.2 mmHg at the 5th minute of