Dyspnea as a Noxious Sensation: Inspiratory Threshold Loading May Trigger Diffuse Noxious Inhibitory Controls in Humans

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Morelot-Panzini, Capucine, Alexandre Demoule, Christian Straus, Marc Zelter, Jean-Philippe Derenne, Jean-Claude Willer, and Thomas Similowski. Dyspnea as a noxious sensation: inspiratory threshold loading may trigger diffuse noxious inhibitory controls in humans. J Neurophysiol 97: 1396–1404, 2007. First published July 26, 2006; doi:10.1152/jn.00116.2006. Dyspnea, a leading respiratory symptom, shares many clinical, physiological, and psychological features with pain. Both activate similar brain areas. The neural mechanisms of dyspnea are less well described than those of pain. The present research tested the hypothesis of common pathways between mechanisms of dyspnea and pain. Both activate similar brain areas. The neural mechanisms of dyspnea are less well described than those of pain. The present research tested the hypothesis of common pathways between the two sensations. Six healthy men (age 30–40 yr) were studied. The spinal nociceptive flexion reflex (RIII) was first established in response to electrical sural stimulation. Dyspnea was then induced by inspiratory threshold loading, forcing the subjects to develop 70% of their maximal inspiratory pressure to inhale. This led to progressive inhibition of the RIII reflex that reached 50% during the fifth minute of loading (P < 0.001), was correlated to the intensity of the self-evaluated respiratory discomfort, and had recovered 5 min after removal of the load. The myotatic H-reflex was not inhibited by inspiratory loading, arguing against postsynaptic alpha motoneuron inhibition. Dyspnea, like pain, thus induced counterirritation, possibly indicating a C-fiber stimulation and activation of diffuse noxious inhibitory descending controls known to project onto spinal dorsal horn wide dynamic range neurons. This confirms the noxious nature of certain types of breathlessness, thus opening new physiological and perhaps therapeutic perspectives.

INTRODUCTION

Dyspnea is a polymorphous respiratory symptom, which may be defined as “the respiratory discomfort occurring for an usual activity level leading normally to no breathing difficulties” (Killian and Campbell 1995). It determines disability and quality of life impairment in many respiratory, cardiac, or neuromuscular disorders. Its neural mechanisms, however, are not fully understood, given the scarcity of human neurophysiological data.

Dyspnea shares many features with pain (Banzett and Moosavi 2001; Comroe 1956). It is a multidimensional experience modulated by various internal and external factors. Its expression depends on culture and language. It is difficult to quantify. These analogies are objectified by common mechanisms. First, animal studies have shown that neurotransmitters involved in pain are also involved in the activation of respiratory afferents during situations that generate respiratory distress (Balzamo et al. 1996; Delpierre et al. 1995; Scardella et al. 1986). In humans, opioids are effective in alleviating certain forms of dyspnea (Jennings et al. 2002). Second, brain regions activated by pain have been shown to receive respiratory afferents (Straus et al. 1997) and to be involved in human respiratory sensations. This is true of the anterior cingulate cortex and the anterior insula (Casey 1999; Hofbauer et al. 2001). Third, several dyspneic stimuli increase limbic and paralimbic activities (Corfield et al. 1995; Evans et al. 2002; Liotti et al. 2001). This activation is partially lateralized to the right anterior insula (Banzett et al. 2000), as in nitroglycerin-induced cluster headache (Hsieh et al. 1996). Inspiratory respiratory loading also strongly activates these regions (Peiffer et al. 2001).

Counterirritation (the popular “pain numbs pain” notion) is a particular feature of pain physiology. The pain sensations elicited by two remote sources of noxious stimuli exert a negative interaction on one another. This depends on diffuse noxious inhibitory controls (DNICs) subserved by a spino–bulbospinal feedback loop that involves the caudal medulla (Ness and Gebhart 1986) and more precisely the subnucleus reticularis dorsalis (Bouhassira et al. 1992). In animals, DNIC activation inhibits the activity of spinal dorsal horn wide dynamic range neurons (Le Bars et al. 1979a,b). In humans, the spinal nociceptive flexion reflex (RIII) is inhibited in an intensity-dependent manner by heterotopic painful stimuli (see review in Skljarevski and Ramadan 2002; Willer et al. 1984). This inhibition occurs in response to nociceptive thermal stimuli (Willer et al. 1989) or to the visceral pain induced by gastric or rectal distension (Bouhassira et al. 1994, 1998). Conversely, counterirritation is not induced by nonnoxious conditioning stimuli. The diffuse noxious inhibitory descending controls are mainly activated by the peripheral stimulation of unmyelinated C-fibers (Bouhassira et al. 1987).

There are intimate interrelationships between nociceptive modulation and respiratory control at the brain stem level. For example, the parabrachial complex is a site of intense integration of nociceptive and respiratory information (Jiang et al. 2004) (40% of the neurons in this region that respond to a
noxious stimulus exhibit a phasic respiratory activity) and this area projects to neurons of the subnucleus reticularis dorsalis that activates DNIC (Almeida et al. 2002). In addition, micro-injections of the γ-aminobutyric acid (GABA) antagonist bicucculline into the midline raphe of the ventromedial medulla or into the laterally adjacent reticular nucleus simultaneously suppress the motor withdrawal evoked by noxious tail heat and modulate respiration (Nason and Mason 2004).

Bearing in mind the similarities between dyspnea and pain, the noxious-specific nature of counterirritation and the connections between the control of nociception and respiration, the aim of the present study was to provide neurophysiological arguments for the noxious nature of dyspnea and therefore to gain novel information on the corresponding peripheral neural pathways. We sought to test the hypothesis that a stimulus acutely inducing experimental dyspnea would trigger counter-irritation, and therefore we set out to assess the effects of high inspiratory threshold loads on the RII reflex in humans.

METHODS

Subjects

After approval by the appropriate authority (Comité Consultatif de Protection des Personnes se prêts à la Recherche Biomédicale Pitié-Salpêtrière) six normal Caucasian men participated in the study (age 30–40 yr, body mass index 21.6–28.6 kg/m²). They were free from any past medical history including chronic or recurrent pain of any nature. At the time of the study, they were free from any acute disease and pain of any sort. Women were deliberately excluded to avoid any risk of interference with menstrual pain. The subjects received detailed information and gave written consent. Some had had previous experience of respiratory physiology experiments, but all were naive regarding pain physiology experiments.

Experimental conditions

The subjects were instructed to avoid sleep deprivation during the 48 h before the experiments, to refrain from taking analgesic and antiinflammatory medications and from any consumption of alcohol and psychotropic substances, and to eat lightly on the day of the study. They emptied their bladder immediately before the experimental sessions.

During the study, the subjects sat comfortably on an examination bed with their back and head fully supported. They wore earplugs and headphones through which they listened to a quiet musical piece of their choice, to mask the auditory ambiance of the laboratory. They breathed with a nose clip on, through a mouthpiece connected in series with a saliva trap, a heated pneumotachograph (3700 series, linearity range 0–160 L/min; Hans Rudolph, Kansas City, MO) and a two-way valve (Hans Rudolph 2600 medium). The experimental apparatus had a resistance <1 cmH₂O · L⁻¹ · s⁻¹ and its dead space was 100 mL.

Respiratory measurements and phrenic nerve stimulation

Ventilatory airflow (V') was assessed by connecting the pneumotachograph to a linear differential pressure transducer (±5 cmH₂O, Validyne, Northridge, CA). Tidal volume (Vₜ) was obtained by electrical integration of flow. The determination of inspiratory time (Tᵢ), expiratory time (Tₑ), and total time (Tₑ+Tᵢ) gave access to breathing frequency (1/Tₑ+Tᵢ), mean inspiratory flow (Vₜ/Tᵢ), and duty cycle (Tᵢ/Tₑ+Tᵢ).

End-tidal carbon dioxide tension (PETCO₂) was measured at the expiratory port of the Hans Rudolph valve with an infrared CO₂ analyzer (MacLab, AD Instruments, Castle Hill, Australia).

Esophageal pressure (Pes) and gastric pressure (Pga) were measured with two thin-walled balloon catheters (length 80 mm, internal diameter 1.5 mm; C76080U, Marquat, Boissy-Saint-Léger, France) (Green et al. 2002) and two differential pressure transducers (±150 cmH₂O, DP 15–32, Validyne). Transdiaphragmatic pressure (Pdi) was determined by electronic subtraction of Pes from Pga.

Abdominal displacements were assessed using a mechanical strain gauge mounted on an elastic belt at umbilical level (Nihon Kohden, Tokyo, Japan).

Surface recordings of diaphragm electromyographic activity in response to phrenic nerve stimulation were obtained using skin-taped silver cup electrodes filled with conductive paste and located on the midclavicular line in the lowest accessible intercostal space (Verin et al. 2002).

All respiratory signals were fed into a Nihon Kohden Neuropack Sigma (Tokyo, Japan) device (10-kHz sampling rate, 20-Hz to 5-kHz bandwidth). They were stored in an Apple Macintosh computer for subsequent analysis (PowerLab, AD Instruments).

With the aim of detecting the putative occurrence of diaphragm or rib cage muscle fatigue, phrenic nerve stimulation was performed through cervical magnetic stimulation (Magstim 200 stimulator, Whitland, Dyfed, UK; doughnut-shaped 90-mm coil, maximum output 2.5 Tesla placed over the spinous process of the sixth cervical vertebra) (Green et al. 2002; Similowski et al. 1989). The supramaximal nature of electromyographic response to phrenic stimulation was verified with a recruitment curve. All stimuli were delivered at end-expiration, under relaxation conditions, and after potentiation by a brief maximal inspiratory effort. The pressure responses to cervical magnetic stimulation were considered valid only when they corresponded to maximal compound motor action potentials.

Assessment of reflex responses

NOCICEPTIVE FLEXION REFLEX (RII REFLEX) (SKJAREVSKI AND RAMADAN 2002). The electromyographic activity of the right biceps femoris muscle was recorded with a pair of surface electrodes placed 2 cm apart on the skin overlaying the muscle mass, after careful skin abrasion (PLS 32–21, Notocord Systems, Croissy sur Seine, France; 2-kHz sampling rate, 20- to 1,000-Hz bandwidth). Another pair of electrodes was used to deliver nociceptive stimuli to the sural nerve within its retromalleolar path. These stimuli consisted of trains of five rectangular electrical shocks of 1-ms duration delivered over 20 ms, 10 times per minute, with a constant-current stimulator. The RII reflex was identified as a multiphasic response 90–180 ms after each stimulation. This response was full-wave rectified and integrated within a 90-ms time window beginning 90 ms after the stimulus. The nociceptive threshold was determined by tentative recruitment and derecruitment sequences. The intensity of nerve stimulation was then adjusted to 20% above the threshold and kept constant.

EXTENSOR HOFFMANN REFLEX (H-REFLEX) (WILLER ET AL. 1987). The posterior tibial nerve was stimulated at the popliteal fossa while the electromyographic H-reflex and the motor (M) response were recorded from the ipsilateral soleus through a pair of surface electrodes fixed on the abraded and degreased skin overlaying the muscle. Time windows of 3–22 and 30–45 ms were defined for the analysis of the M and H responses, respectively. A recruitment–derecruitment procedure was followed to identify the stimulation intensity determining an H response equal to 50% of its maximal value (Hmax/2). This stimulus intensity was then kept constant.

Induction and evaluation of experimental dyspnea

Acute dyspnea was induced by connecting an inspiratory threshold loading device to the inspiratory limb of the breathing valve (7–61 cmH₂O, Threshold Inspiratory Muscle Trainer Nr 730, Health Scan, Cedar Grove, NJ). The spring of the device was adjusted to force the
subject to produce 70% of his previously determined maximal inspiratory esophageal pressure (PES,max) at each inspiration. This load was maintained for 5 min. Every minute, the subjects rated the intensity of “respiratory discomfort” on an ordinal scale graded from 0 (“no discomfort”) to 9 (“intolerable discomfort”). After the experiment, the subjects were asked to describe their respiratory sensations by choosing one or several descriptors among the list proposed by Simon et al. (1989) after translation of this list into French (see APPENDIX).

Experimental procedures

PRELIMINARY EXPERIMENTS. The stability of the RIII reflex over time and the influence of possible confounders were tested in three subjects. First the RIII reflex was recorded during 60-min sessions without any intervention. We never observed RIII fluctuations in excess of 15% of the baseline value. This was the case with the subjects free of respiratory equipment or equipped with the two transnasal catheters and breathing through the study apparatus. Cervical magnetic stimulation did not visibly interfere with the RIII amplitude.

PROTOCOL. Two experimental sessions were performed a week apart, in random order. One aimed at describing the effects of inspiratory threshold loading on RIII reflex amplitude. The other session studied these effects on H-reflex amplitude. Fig. 1 summarizes the corresponding experimental sequences.

CONTROL EXPERIMENTS. A third session was performed 1 wk later in three subjects. Inspiratory threshold loading was replaced by 1) 20 min of unloaded breathing during which the subjects were asked to evaluate their degree of respiratory discomfort every 2 min; 2) 5 min of concentration on a mental arithmetic task (count down from 300 by steps of three as fast as possible and repeat); 3) 5-min “washout.”

Data management

Respiratory variables were averaged over 1-min epochs, every 5 min during unloaded breathing and every minute during loaded breathing.

RIII and H-reflex data were averaged minute by minute throughout the experiment. A baseline value was computed by averaging all the data gathered during the 5 min immediately before inspiratory loading. All values were expressed as percentages of this baseline value.

Statistical analysis

All analyses were performed using Statview 5.0 (Abacus Concept, San Francisco, CA), Medcalc 8.0 (Medcalc, Brussels, Belgium), or Statistix 8.0 (Statistix, Tallahassee, FL).

FIG. 1. Flow chart of the successive steps of an experiment. See text for details. (1) “reflex” arrow corresponds to either a RIII recruitment–derecruitment sequence to determine threshold stimulation intensity or to an H recruitment–derecruitment sequence to determine the stimulation intensity required to obtain Hmax/2, followed by a stabilization period of 10 min and then a new recruitment–derecruitment procedure. (2) Conditioning stimulus could be inspiratory threshold loading for 5 min, or a control session consisting of 20 min of unloaded breathing followed by 5 min of concentration on a simple mental arithmetic exercise and by 5 min of “washout.

Normality was tested using the Shapiro-Wilk test, according to the result of which subsequent parametric or nonparametric tests were chosen. The effects of inspiratory loading and other conditioning procedures over time on respiratory pattern data, intensity of dyspnea, and RIII and H-reflexes were assessed using either an ANOVA for repeated measures followed by Fisher’s protected least-square difference test (normal data sets) or the Kruskal-Wallis nonparametric ANOVA (nonnormal data sets). The effects of inspiratory loading on the pressure responses to phrenic nerve stimulation were tested with a bilateral single-group Student’s t-test. For the respiratory variables found to exhibit statistically significant changes during the loading period, statistical associations between their changes and the changes in RIII amplitude with Spearman’s rank correlation coefficient.

Differences were considered significant when the probability of a type I error was <.05.

RESULTS

Control experiments

The minute-by-minute grading of respiratory discomfort in the absence of any respiratory loading and the mental arithmetic task were not associated with fluctuations of RIII reflex in excess of 10% of the baseline value. There was also no change in tidal volume, breathing frequency, T1/Tp, Vt/Tp, and PETCO2. The responses to cervical magnetic stimulation were identical at the beginning and at the end of the control sequence, both in conditions of relaxation and of potentiation.

Inspiratory threshold loading

DYSPNEA. Inspiratory threshold loading elicited dyspnea in all subjects. Respiratory discomfort was very intense from the outset, graded 6–8 after the first minute of loading. This was significantly higher than at baseline (P < 0.0001). Intensity of the dyspneic sensation increased in a cumulative fashion over time (Fig. 2). During the third, fourth, and fifth minutes of loading, the intensity of dyspnea was significantly greater than that during the first minute (P < 0.001). Dyspnea suddenly and completely disappeared within 1 min after load withdrawal. This pattern was similar during the two loading sessions.

Among the list of 19 descriptors proposed by Simon et al. (1989), each subject chose three (n = 2) to four (n = 4) items, a total of seven items being mentioned. In all cases, the main descriptor of the dyspneic sensation belonged to the “work” cluster (Simon et al. 1989) (Table 1). The next most frequent cluster was the “concentration” one, mentioned by five subjects. The “suffocating” cluster appeared twice and the “hunger” cluster never appeared.

NOCEPCITIVE RIII REFLEX. In five subjects, inspiratory threshold loading was associated with inhibition of RIII response, which was visible by the second minute and reached the P < 0.05 threshold for significance at the third minute. It stayed diminished during the entire loading time (Figs. 2 and 3). During the fifth minute, RIII reflex amplitude was 50 ± 12% of its baseline value (P < 0.001).

After load withdrawal, five subjects exhibited a clear increase in RIII amplitude. In one case, inhibition became apparent only at this moment. Overall, the RIII reflex amplitude remained significantly lower than baseline during the first 3 min after load withdrawal (Fig. 2).
H-REFLEX. A slight increase in H-reflex amplitude was observed from the third minute of inspiratory loading, the P < 0.05 threshold for significance being reached at the fourth minute. This increase persisted during the first 3 min of recovery (Fig. 2).

VENTILATORY AND PRESSURE-GENERATION PATTERNS. On initiation of inspiratory threshold loading during the “RIII” experimental sequence, minute ventilation immediately increased (P < 0.001 after the first minute), tidal volume, V_{T}/T_{I}, Pes, and Pdi also significantly increased on loading (P < 0.001 in all cases), whereas T_{F}/T_{T} decreased (P = 0.018), as did the contribution of the diaphragm to the inspiratory effort (Pga/Pdi from 0.51 ± 0.14 to 0.28 ± 0.2, P = 0.002). There was no statistically significant change in breathing frequency, which slowed in some subjects and remained stable in others, and in PetCO_{2} (Fig. 4).

### Table 1. Descriptors chosen by the subjects to depict the respiratory discomfort felt during inspiratory threshold loading

<table>
<thead>
<tr>
<th>Descriptor of the Respiratory Sensation</th>
<th>Number of Subjects Using This Descriptor</th>
<th>Number of Subjects Considering This Descriptor as the Main One</th>
</tr>
</thead>
<tbody>
<tr>
<td>My breathing requires effort*</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>My breathing requires more work*</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>My breathing requires more concentration</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>My breathing is heavy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>My breathing is shallow</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>I feel that I am being smothered**</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I feel that I am suffocating**</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I feel out of breath</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*This descriptor belongs to the “work” cluster defined by Simon et al. (1989). ** This descriptor belongs to the “suffocating” cluster defined by Simon et al. (1989).

During the subsequent period of sustained loading, all the above variables remained stable until disconnection from the load, except T_{F}/T_{T}, which exhibited a statistically significant decrease over time (Fig. 4). The patterns of change in V_{T}/T_{I} and T_{F}/T_{T} are in line with previous descriptions (Eastwood et al. 1994).

During the “H” experimental sequence, similar patterns of change were observed, a given subject behaving in the same manner on both occasions irrespective of the order of occurrence.

![FIG. 2. Evolution over time of the dyspneic sensation (top panel, values from 0 to 9 on the ordinal scale), surface of the RIII reflex (middle panel, in % of baseline), and amplitude of the H-reflex (bottom panel in % of baseline) during inspiratory threshold loading. Each vertical bar represents 1 min. First 5 bars correspond to 5 min of steady state before loading; the 5 black bars represent the first 5 min of recovery (see text for details). One SD is depicted over each bar. Symbol * denotes a significant difference as compared with baseline (P < 0.05). Of note, RIII data and H data were gathered from 2 separate experiments, which produced identical patterns in terms of dyspnea. For the sake of simplicity, the “dyspnea” panel corresponds to the data gathered during the RIII experiments only.](http://jn.physiology.org/)

![FIG. 3. Evolution over time of RIII reflex surface during inspiratory threshold loading in the 6 subjects after ensemble averaging (left column) and in one representative individual (right column). First line of panels corresponds to baseline (average of the responses to the stimulations delivered during the 5th minute after the stabilization of these responses). Second line of panels corresponds to the average of the responses to the stimulations delivered during the 1st minute after the application of the inspiratory threshold load. Third line of panels corresponds to the average of the responses to the stimulations delivered during the 5th minute spent under inspiratory threshold loading. Inhibition is clearly visible. Last line of panels corresponds to the average of the responses to the stimulations delivered during the 5th minute after the withdrawal of the inspiratory load. Recovery is clearly visible.](http://jn.physiology.org/)
correlated with TI/TT (rho 0.0026 to 0.653, 95% confidence interval 0.382 to 0.774 to 0.068, 95% confidence interval 0.642 to 0.068, 95% confidence interval 0.270, 95% confidence interval 0.039), and there was a negative correlation between dyspnea intensity and TI/Tt (rho = -0.418, 95% confidence interval -0.642 to -0.068, 95% confidence interval 0.024). There was no significant correlation between RIII amplitude during loading and any of VT, F, V'f, Pes, Pdi, Pes/Pdi, V'/Tt, or PETCO2.

DIAPHRAGM FATIGUE. Inspiratory threshold loading did not decrease the twitch Pdi response to cervical magnetic stimulation and did not alter the corresponding Pes/Pdi ratio (Table 2). This strongly suggests that the loading period did not induce diaphragmatic fatigue or rib cage muscle fatigue (Similowski et al. 1998). Potentiated Pdi twitches were significantly greater (P = 0.0041) after loading than before, suggesting the reinforcement of potentiation by the loading protocol.

TABLE 2. Effects of 5-min inspiratory threshold loading on pressure responses to cervical magnetic stimulation during the “RIII” experimental sequence

<table>
<thead>
<tr>
<th>Kind of Twitch</th>
<th>Before Loading</th>
<th>After Loading</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxed Pdi, cmH2O</td>
<td>26.94 ± 14.09</td>
<td>28.55 ± 10.01</td>
<td>0.28</td>
</tr>
<tr>
<td>Relaxed Pes/Pdi</td>
<td>0.642 ± 0.03</td>
<td>0.624 ± 0.05</td>
<td>0.642</td>
</tr>
<tr>
<td>Potentiated Pdi, cmH2O</td>
<td>29.98 ± 13.21</td>
<td>34.92 ± 15.91</td>
<td>0.0041**</td>
</tr>
<tr>
<td>Potentiated Pes/Pdi</td>
<td>0.631 ± 0.09</td>
<td>0.634 ± 0.07</td>
<td>0.916</td>
</tr>
</tbody>
</table>

Values are percentages (of baseline values) ± SE. Pdi, transdiaphragmatic pressure; Pes, esophageal pressure. *Student’s paired t-test; **significant difference but suggestive of potentiation rather than fatigue.

DISCUSSION

This study shows that breathing against a high inspiratory threshold load is associated with inhibition of the RIII nociceptive flexion reflex, with a statistical link between dyspnea intensity and magnitude of RIII inhibition. This is probably the expression of counterirritation as reported with experimental somatic and visceral pains. Because counterirritation is specific to pain (Roby-Brami et al. 1987), our observations suggest that the particular form of dyspnea induced by inspiratory threshold loading is of a noxious nature and shares important neural features with pain.

Methodological considerations

POPULATION SIZE. Our study population is small in size, mainly because of the extremely demanding and unpleasant nature of the experiments for the subjects. In spite of this, we did detect highly statistically significant differences in our main outcome (the amplitude of the RIII reflex), which is reassuring concerning the reality of our observations.

LOAD AND RESPIRATORY SENSATION. We chose inspiratory threshold loading to induce a rapid and intense dyspnea through a predetermined and mandatory level of inspiratory effort. This alleviated the need for visual feedback, which could possibly interfere with the RIII reflex (Willer et al. 1979). Also to minimize attentional influences (Skiljarevski and Ramadan 2002; Willer et al. 1979), we did not ask the subjects to describe their respiratory sensations during loading. Posthoc, they reported an “increased sense of breathing effort” (Table 1). Therefore we cannot generalize our results to “dyspnea” in the broadest sense.

INTRUSIVE SOURCES OF RIII INHIBITION. We took care to rule out the contribution of possibly noxious stimuli inherent to the experimental setup (transnasal catheters, prolonged stay in sitting posture, nose clip, mouthpiece) that could have induced counterirritation. The focusing of attention on respiration that inevitably occurred during loaded breathing (as illustrated by the frequent choice of the item “my breathing requires more effort” among the dyspnea descriptors proposed to the subjects) could have been a source of RIII inhibition. To minimize attentional influences (Skljarevski and Ramadan 2002), we did not ask the subjects to concentrate on a mental arithmetic task. This is at variance with previously published observations (Willer et al. 1979). Also to minimize attentional influences (Skljarevski and Ramadan 2002; Willer et al. 1979), we did not ask the subjects to concentrate on a mental arithmetic task. This is at variance with previously published observations (Willer et al. 1979),
possibly because of differences in the study population [naive subjects in our study vs. trained ones in the study by Willer et al. (1979)]. It is also possible that the unavoidable degree of stress generated by the experimental setup somehow cancelled the effects of attention (Willer et al. 1979). It could be argued that the mental arithmetic task that we asked our subjects to perform was not an adequate control. Indeed, during loaded breathing, the subjects were forced to concentrate on their respiration to ward off suffocation, whereas the mental arithmetic task was not associated with negative feedback. In another set of subjects (data not shown), we induced dyspnea of the “air hunger” type by administering a CO₂-enriched gas mixture and studied the corresponding effects on the RIII reflex. Preliminary results show that no RIII inhibition occurred, thus possibly accounting for differences between the “air hunger” and the “sense of excessive effort” types of respiratory sensation in terms of the interaction with pain.

When, during these experiments, the subjects were asked to voluntarily fight the CO₂-induced hyperpnea, they experienced severe dyspnea of the “air hunger” type and their concentration on breathing was by definition extremely intense. Yet there was still no RIII inhibition. All in all, we are therefore confident that a focusing of attention on respiration during loaded breathing was not the source of RIII inhibition in our subjects. Of note, the time dynamics of the RIII reflex inhibition by a mental task differs radically from the dynamics that we observed (onset within seconds vs. 2 min in our subjects, quasi-complete inhibition, immediate recovery without aftereffect) (Willer et al. 1979).

Possible pathways of the RIII inhibition by inspiratory threshold loading

Loading inspiration can change the motor drive to leg muscles (Fontanari et al. 1996) and their proprioceptive reflex (Balzamo et al. 1997). In our subjects, the H-reflex was not depressed by the same stimulus that provoked the depression of the RIII reflex (Fig. 2). This argues against postsynaptic alpha motoneuron inhibition.

In view of the known spinal integration of noxious and respiratory inputs (e.g., Qin et al. 2002), one possible mechanism to explain our findings could be competition at the level of spinal interneurons. Of note, our subjects experienced a progressively increasing dyspneic sensation, whereas the inspiratory stimulus remained constant, despite the absence of progressive muscle fatigue (Fig. 2). This resembles temporal summation and could be interpreted as the perceptual correlate of wind-up in spinal wide dynamic range neurons (Craig 2003), and further fuels the dyspnea–pain analogy. Another possible mechanism to explain our results would be the activation by the respiratory stimulus of supraspinal diffuse noxious inhibitory descending controls. These controls are observed, in animals, by a spino–bulbospinal loop, relaying in the subnucleus reticularis dorsalis and inhibiting dorsal horn interneurons. In humans, the loop is thought to be identical (Dansiger et al. 1996; De Broucker et al. 1990; Roby-Brami et al. 1987). Our data do not bring proof of one mechanism or the other. Such proof could derive from replicating our experiments in patients with compete spinal cord transection. Indeed, the supraspinal origin of the counterirritation phenomenon has been inferred in man because RIII inhibition lacks in tetraplegic patients subjected to heterotopic noxious stimulation (Roby-Brami et al. 1987). If inspiratory threshold loading does not induce RIII inhibition in tetraplegic patients, then a spinal mechanism for our observations will be improbable.

At the present stage, we favor the hypothesis of an activation of the diffuse noxious inhibitory controls for several reasons.

First, as mentioned in the introduction, nociceptive modulation and respiratory control are intimately interrelated at the brain stem level, and there are arguments for respiratory influences on the subnucleus reticularis dorsalis nucleus (Almeida et al. 2002; Ezure 2004; Jiang et al. 2004; Nason and Mason 2004).

Second, the activation of diffuse noxious inhibitory controls depends almost exclusively on stimulation of C-fibers (Bouhassira et al. 1987; Cadden and Morrison 1991) and C-fibers abound in the lung, airway, and respiratory muscles. For example, the phrenic nerve in humans contains unmyelinated afferents (Duron 1981); carries noxious information (Scawn et al. 2001); and projects to the cingulated gyrus (Straus et al. 1997), an area that is deeply involved in respiratory sensations (Peiffer et al. 2001). It seems safe to speculate that the inspiratory loading protocol to which our subjects were submitted induced C-fiber stimulation, either at the bronchopulmonary level through the intense intrathoracic pressures that were developed or within respiratory muscles through the major increase in their tension (see, e.g., Hertel et al. 1976; see also Hill 2000 on C-fiber activation by diaphragm loading and fatigue; Kaufman and Rybicki 1987 on the activation of group III and group IV muscle afferents independently of fatigue; Sinoway et al. 1989). In this regard, our observations could be regarded as providing a plausible link between C-fibers and the type of dyspnea that is induced by mechanical inspiratory loading.

Third, inspiratory loading influenced the RIII reflex in a manner closely analogous to gastric or rectal distension (Bouhassira et al. 1994, 1998), themselves considered to be sources of activation of the diffuse noxious inhibitory controls. Of note, because of the already extremely unpleasant experimental paradigm we did not study the same subjects with inspiratory loading induced dyspnea and digestive pains, and thus there is a need for caution here. However, as during previously published gastric distension experiments (Bouhassira et al. 1994), we reassuringly found a statistically significant inverse correlation between the intensity of the noxious sensation and the magnitude of the RIII reflex (rho = −0.574, 95% confidence interval −0.774 to −0.270, P = 0.002). RIII inhibition and recovery seem less marked with inspiratory loading than with gastric distension. This could be attributable either to differences in the dynamic characteristics of the receptors activated (Bouhassira et al. 1998), or to particularities of the form of dyspnea generated, or to the mere fact that there was no intensity-matched pain control in our subjects.

Respiratory pattern and RIII inhibition

Interferences between hypercapnia and pain perception were previously suggested (Gamble and Milne 1990; Gronroos and Pertovaara 1994). PET CO₂ did not increase in our subjects and, if anything, it tended to slightly decrease (Fig. 4). Even if PET CO₂ misinterpreted P a CO₂ during the 5-min loading period in the absence of steady state, it is most unlikely that our
subjects developed hypercapnia. It can thus not be plausibly involved in our observations.

Fatigue is known to activate diaphragmatic C-fibers (Hill 2000). Had it been present in our subjects, this would have provided a strong argument for the implication of C-fibers (and thus of the diffuse noxious inhibitory controls). The lack of change in phrenic nerve stimulation-induced respiratory pressures made low-frequency fatigue of inspiratory muscle unlikely (Table 2), but this does not rule out changes at the muscle level. As already mentioned, nonfatiguing muscle contraction can activate C-fibers. In spite of the absence of inspiratory muscle fatigue, the intensity of dyspnea increased over time during inspiratory loading and this was correlated with both the decrease in RIII amplitude and the decrease in T/T that occurred during the loading period. Whether there is a causative relationship of any sort to explain these observations is not known. Indeed, the changes in the three variables (dyspnea intensity, RIII, T/T) could very well be postulated to be three different expressions of, for example, an increasingly intense C-fiber stimulation, which would activate the diffuse noxious inhibitory controls and modify the output of the respiratory central pattern generator. Such a hypothesis would fit with the previously mentioned data reported by Nason and Mason (2004) (see INTRODUCTION). It must be noted in this regard that the respiratory neurons of the pre-Botzinger complex are characterized by the coexpression of neurokinin-1 receptors and mu-opioid receptors (Gray et al. 1999).

Summary and perspectives

Our results, attesting to the noxious nature of a stimulus responsible for a form of acute dyspnea, bring new elements to the neurophysiological understanding of dyspnea in humans and complement existing neuroimaging data demonstrating common or close brain projections for pain and dyspnea.

Important questions remain. Whether dyspnea is related to the visceral or somatic type of pain has to be elucidated. As visceral pain, certain forms of dyspnea activate the amygdala but do not activate the primary somatosensory cortex (Evans et al. 2002; Lu et al. 2004; Peyron et al. 2000), whereas somatic pain does not activate the amygdala and does activate the primary sensorimotor cortex (Peyron et al. 2000). Yet the respiratory muscles, possibly implicated in our results, are ontogenetically more somatic than visceral. The implication of C-fibers in the RIII reflex inhibition during inspiratory threshold loading must be ascertained and their exact nature clarified. This could provide a rationale to studies of dyspnea alleviation by substances interacting with C-fibers. Whether other types of dyspneic sensory experiences also qualify as noxious must be determined. In this regard, RIII reflex studies could better delineate the similitudes and dissimilitudes between the “air hunger” and the “increased sense of effort” types of respiratory sensations.

APPENDIX

English-to-French translation of the 19 items proposed by Simon et al. (1989) to describe the distinguishable sensations of breathlessness that can be experimentally induced in normal volunteers

The translations were obtained as follows:

- English-to-French translation by two respiratory physicians working separately (versions 1a and 1b)
- Discussion between these two physicians until agreement on a common sentence (version 2)
- Reverse translation by a native English speaker with professional skills in medical edition but unaware of the original list of items
- Comparison of the original list with the list produced by the reverse translation
- In the case of complete agreement, the French “version 2” was kept
- In the case of disagreement, discussion between the two original physicians and a third one until agreement on a final sentence (version 3)
- Version 2 was also kept in the case of disagreement according to French usage. For example, item 4 “I feel a hunger for more air” led to “J’ai soif de plus d’air” as version 2; the reverse translation came back as “I am thirsty for air,” but version 2 was kept as “J’ai soif de plus d’air” because this conforms to usage.
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DISCLOSURE

The study did not benefit from industry-sponsored grants and did not involve any conflict of interest.

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