Dyspnea (shortness of breath) and pain are well-evolved warnings of important physiological derangements that may require animals to alter their behavior to survive. Dyspnea and pain are also two of the most common symptoms that bring patients to medical care, another potentially adaptive behavior. Chronic dyspnea and pain, however, cause suffering and disability in many millions of patients; they often occur together in individuals. Although there has been great progress in recent decades in understanding the neurophysiology of pain, less is known about the neurophysiology of dyspnea, and even less is known about the interaction of these two symptoms. In the current issue of the Journal of Neurophysiology (p. 1396–1404), Morelot-Panzini and co-workers present a novel and interesting study showing that the presence of experimentally induced dyspnea inhibits a pain reflex. The results provoke us to think about both the commonality of pain and dyspnea pathways and about how they may interact.

For centuries people have applied noxious stimuli in one locale to inhibit the perception of pain in another location. There are several mechanisms through which endogenous analgesia can be elicited by competing noxious or stressful stimuli. Morelot-Panzini and co-workers present evidence showing that such analgesia can be induced using dyspnea (the perception of respiratory discomfort) as the analgesa-eliciting stimulus, rather than pain (Morelot-Panzini et al. 2006). They reason that dyspnea acts as a “counterirritant”, and therefore it is a noxious sensation sharing some common neural pathways with pain. Dyspnea is a leading symptom of cardiopulmonary disease, and afflicts 50% of patients in tertiary care (equal to the symptom burden of pain).

Half a century ago a leading respiratory physiologist advised that “It might be profitable to compare the symptom dyspnea with the symptom pain” (Comroe 1956). Then, as now, the field of pain was further advanced than the field of dyspnea, due both to the number of researchers in the field, and to the added complexity of the physiological stimuli. A number of authors have echoed the pain-dyspnea analogy, but until this century the analogy was based only on the similarity of subjective characteristics. Recent brain imaging studies have shown that very similar cortical regions are activated by the perceptions of dyspnea and pain (Banzett et al. 2000; Evans et al. 2002; Peiffer et al. 2001), providing the first evidence that there is a neurophysiological link between these sensations. The study of Morelot-Panzini et al. takes an entirely different and novel approach to examine the neurophysiological connection between pain and dyspnea. We hope this will provoke other neurophysiologists to enter the fray.

Questions will arise in the reader’s mind about some fundamental concepts and definitions. Pain is understood to be the perception of tissue damage, or impending tissue damage. Pain normally arises from stimulation of “nocioceptors” that signal “noxious” conditions, i.e., those that threaten harm. Dyspnea signals a threat to adequate pulmonary ventilation. Clearly, insufficient oxygen or excess carbon dioxide is a dramatic and immediate threat to tissues throughout the body, a noxious condition. The need for adequate oxygen and acid–base status is so great that the danger signal can be generated by a feed-forward mechanism that triggers the distress during conditions (airway obstruction, increased respiratory work) that predict an impending problem. It is reasonable to infer that survival under these conditions depends on immediate and focused attention to breathing; temporary attention to most threats signaled by pain may be necessary. A burned hand is insigificant during suffocation.

In contrast to pain, which can be produced by stimulation of a single type of receptor in a single location, dyspnea most likely results from “imbalance” between levels of afferent signals that are normally present. For instance, if the cyclic inflation of the lungs (sensed by pulmonary stretch receptors) does not match the motor output of the brain stem respiratory centers (projected rostrally as “corollary discharge”), the unpleasant sensation of air hunger results (reviewed by Banzett and Lansing 1996). Excessive respiratory work or effort expended to cyclically inflate the lungs results in another unpleasant sensation – this latter phenomenon was employed by Morelot-Panzini and colleagues to evoke analgesia using external resistive loading of inspiration. Although most evidence suggests that the perception of dyspnea in this circumstance arises from muscle mechanoreceptors and perception of motor outflow (corollary discharge), the authors speculate that the observed analgesia arises from C-fibers in respiratory muscles or lungs via a subcortical mechanism of diffuse noxious inhibitory control (DNIC). While the effect demonstrated in this study is clear, this specific mechanism remains to be proven –

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there are several alternative endogenous analgesic mechanisms that could be triggered by dyspnea. Pioneering efforts are seldom conclusive; we hope that future experiments from this group and others will define the mechanism, and by doing so advance our understanding of the neural mechanisms underlying dyspnea. One interesting experiment will be the comparison of strength of analgesia produced by an air hunger stimulus to that produced by a respiratory work stimulus. The sensation of air hunger appears to be more unpleasant than the sensation of excessive respiratory work (Lansing et al. 2000) but is not thought to involve C-fiber activation; thus if C fiber-driven DNIC is the analgesic mechanism, then air hunger should be a less potent analgesia-producing stimulus. Conversely, if the dyspnea-evoked analgesia depends on the noxiousness or unpleasantness of the stimulus, air hunger should be a more effective analgesia-producing stimulus. Morélot-Panzini et al. report preliminary observations in their discussion that an “air hunger” type stimulus did not appear to reduce the RIII response to a pain stimulus. These preliminary observations could be followed up with experiments in which the presence and degree of “air hunger” can be confirmed and its analgesic effects compared directly with “work and effort” of known magnitude.

Looking beyond the specifics of this particular phenomenon, the more general question of the nature of interaction between pain and dyspnea (mutual inhibition or facilitation) is important not only because of its physiological interest, but also because these two distressing symptoms frequently co-exist in patients. A published psychophysical study of the interaction of dyspnea and pain at the perceptual level showed that pain produced a small but consistent increase in perceived dyspnea, while dyspnea produced a larger but more variable decrease in pain (Nishino et al. 1999). The study of Morélot-Panzini and colleagues shows that this interaction may occur at the sub-cortical level. Both psychophysical and neurophysiological approaches will be needed to understand the similarities and interactions between these two troubling symptoms that frequently occur together in seriously ill patients.

REFERENCES


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