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Cough, pain and dyspnoea: similarities and differences

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Abstract

The three common symptoms, pain, dyspnoea and cough, share some important features. We felt that the analogies to be made among them could be instructive, possibly suggesting new avenues of research. Each of these symptoms can be profoundly uncomfortable, and can profoundly degrade quality of life. The sign, cough, is often given more prominence than the symptom, urge to cough, but both are important to the patient (the former is of more concern to nearby people). Advances in pain research over the last several decades have pointed the way to new studies of dyspnoea; they may serve as a model for the psychophysical study of the perception of urge to cough, as well as providing models for understanding both central and peripheral sensitization of the afferent pathway. We briefly review here the afferent and central pathways and psychophysics of pain, dyspnoea and urge to cough.

Keywords

Cough; pain; dyspnoea; urge to cough; referred pain; psychophysics

1. Introduction

Pain, dyspnoea and cough are very common and troubling symptoms. There are a number of important analogies to be made among these three common symptoms (internal sensations). Each of these symptoms can be profoundly uncomfortable. All three of these symptoms also produce externally observable signs — this is most prominent in the case of cough, where the sign, cough, is often given more prominence than the symptom, urge to cough. This may be true because cough is more easily quantified than urge to cough, or because cough is more disturbing to surrounding people (e.g. in a concert hall) than are withdrawal from pain or laboured breathing. In all cases, we must ask what is it we wish to treat, sign or symptom — what is important to the patient? In all cases treatment to the extent of eliminating the symptom entirely may put the patient at risk, while inadequate treatment may allow a profound decrease in quality of life and ability to work.

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The rapid, near explosive growth in pain research serves as both a scientific and political model for future advances in cough and dyspnoea. The advances in pain research are the result of tireless efforts from a number of individuals, exemplified by the late John Bonica, who worked vigorously at all levels of scientific organization, business, government and the press to advance the quality and quantity of pain research and treatment. As a result, our knowledge of pain has grown dramatically. In the early 1970s, the entire field of pain, like the current fields of cough and dyspnoea, received only a brief mention, if any, in typical medical textbooks. The field of pain research has grown so rapidly that now no one person can grasp all of it; the latest Textbook of Pain condenses it into 1214 pages! This advance in pain research serves as an excellent social-political model, and also as an excellent scientific model that may share many features with cough and dyspnoea. We describe here the physical and experiential similarities of these three disorders with the view to suggesting future research directions.

2. Afferent inputs

Pain, cough and dyspnoea share a common feature; they originate in afferent nervous systems that detect and signal real or impending threats to the organism.

2.1. Affferent nerves and pain

Pain sensations are mediated by a family of nociceptor afferents that can be divided into relatively fast conducting, thinly myelinated A-δ nociceptors and the slower conducting, nonmyelinated C-fibre nociceptors. The evoked sensations are distinct. A-δ nociceptors mediate sensations of pricking mechanical or thermal pain and cold pain that usually are easily localized. In contrast, C-fibres usually mediate sensations of burning heat or deep pressure that are diffuse and poorly localized [1]. Neuropeptides are typically limited to a subset of C-fibre neurones. Both types of pain fibres from the majority of somatic structures enter the dorsal horn of the spinal cord but synapse at different locations.

Pain afferent systems are not static. Injury, inflammation or repeated stimulation can sensitize the pain system at both the peripheral level of nociceptors and at spinal and higher levels [1]. Intrinsic systems that exacerbate pain serve a recuperative function, assisting healing by promoting behaviours that immobilize and protect an injured area. The cough system may also be sensitized at the peripheral and central level. This sensitization may serve an equally important biological function: for instance, healing can be promoted by voluntary pain-related behaviours. However, there are many instances in which excessive or prolonged pain or cough sensitivity seems to serve little purpose, and may even interfere with healing. Such inappropriate sensations are likely targets of therapeutic interventions. For pain, such interventions are usually termed analgesics and include both peripheral and centrally acting agents as well as non-pharmacological interventions. Opioid agents such as morphine are classic analgesics that can be effective for pain, cough and dyspnoea. Opiates, however, are not always effective, and have well known deleterious effects. Specific interventions can also reduce pain by an additional mechanism. Reducing inflammation or muscle spasm, or inhibiting migraine headaches, is not accomplished by an analgesic attenuation of afferent input. Rather, it is caused by reducing the physical conditions that sensitize or activate the afferent system. This mechanism, which lacks a specific term in pain control, may play a more significant role in cough and dyspnoea.

2.2. Afferent nerves and cough

At the level of the primary afferent nerves, pain and cough pathways are remarkably analogous. Sensations such as referred pain and allodynia also find similarities in various cough disorders. As with pain, cough can be evoked in experimental animals by stimulation of nociceptive C-fibres as well as by faster conducting Aδ-fibres [2]. The majority of cough afferents travel in

the vagus nerve. Just as the quality of painful sensations may depend on whether C-fibres or Aδ-fibres are activated, it is likely that the quality of the sensation of the urge to cough depends on the type of afferent nerve being stimulated. For example, the violent immediate cough evoked by spritzing tartaric acid on the human larynx is likely due to stimulation of Aδ-fibres [3]. In guinea pigs Aδ-fibres that evoke cough are strongly activated by acidic solutions and are situated in the larynx, trachea and main bronchi. These fibres do not respond to chemicals that stimulate C-fibres such as capsaicin and bradykinin. The cough-evoking Aδ-fibers in large airways respond to punctate mechanical stimulation, anosmotic solutions and acids [2]. In some studies these Aδ-fibres that can lead to cough are referred to as "irritant receptors". Cough evoked by the Aδ-fires in the large airways can be evoked even in anaesthetized animals [4].

Several stimulants known to selectively stimulate nociceptive C-fibres but not A fibres in the airways (e.g. capsaicin, bradykinin) also evoke cough in laboratory animals and humans [5]. Inflammatory conditions can lead to changes in their electrical excitability as well phenotypic changes caused by changes in gene transcription rates [6]. The C-fibre-evoked cough, however, is very sensitive to general anaesthesia, and low levels of the C-fibre stimulation evoke urge to cough sensations that are similar to an irritating itch.

2.2.1. Referred pain and referred cough—It has long been known that pain can be perceived at sites distant from the site of injury and afferent nerve stimulation. This phenomenon is termed referred pain. This is especially common with visceral pain disorders [7]. In these cases it is hypothesized that the visceral nociceptive nerves converge on dorsal horn neurones that also receive specific somatosensory input from other sites in the body. For example a nociceptive fibre in the heart may interact with neurones in the dorsal horn that are normally involved with conveying painful sensations in the left arm. When these cardiac C-fibres are stimulated by inflammation or hypoxia, transmitters are released from the central terminals at these synapses such that pain is now diffusely sensed in the left arm.

2.2.2. Central sensitization—Like the primary afferent nerves involved in pain, the vagal C-fibres and cough-evoking tracheal Aδ-fibres are not static. The transmitters released from converging nociceptors may also lead to long-lasting changes in the secondary neurones leading to a synaptic sensitization ("central sensitization") [8]. This can lead to pain being evoked even by an ordinarily non-painful stimulus, such as lightly brushing the arm; this phenomenon is termed allodynia. Among the mechanisms that may underlie allodynia is central sensitization of afferent pain pathways caused by converging nociceptor input; this has been well described in many experimental systems [9,10].

It now appears that there is a similar convergence of nociceptive vagal C-fibre afferent nerves onto secondary neurones involved in cough [11]. Moreover, even in the absence of convergence in the strict sense, the peptides released from the vagal C-fibres (e.g. neurokinins and calcitonin gene-related peptide) may modulate the efficacy of large numbers of nearby synapses. This could lead to conditions where C-fibre stimulation sensitizes the cough pathways to the extent that even non-tussive stimuli evoke urge to cough sensations analogous to allodynia. This could also lead to "referred cough" sensations analogous to the referred pain discussed above. Mechanically probing the larynx, trachea or large bronchi causes an immediate and violent cough. By contrast, mechanically probing the lungs, nose or oesophagus does not evoke cough. Stimulating nociceptors in the lungs or oesophagus can, however, lead to cough [12,13], and in humans oesophageal reflux is one of the most common causes of chronic cough [14]. A likely explanation is the process of central sensitization. In other words, stimulating C-fibre terminals in the oesophagus (or lungs) causes the release of transmitters and peptides in the brainstem that then sensitize the cough reflex pathway originating in the laryngeal and tracheal receptors [12]. If this is the case one might suspect that inflammation in the lungs or oesophagus could lead to referred sensations of irritation in the throat. Try as one might to clear the throat

or scratch that itch, the sensation rapidly returns. Why? We suggest that it is because the seat of the problem is elsewhere, and the sensation is referred from the distant site. The cough evoked by stimulating the wall of the external acoustic meatus of the ear (Arnold's reflex) may be another example of a referred cough reflex [15]. By analogy the photic-sneeze reflex is an example in which the optic sensory nerve stimulation somehow leads to nasal urge to sneeze sensations, presumably by centrally sensitizing the nasal trigeminal sneeze pathway [16].

2.3. Afferent nerves and dyspnoea

The afferent pathways for dyspnoea are more complex, reflecting the fact that there are actually several different uncomfortable breathing sensations that are classed as dyspnoea [reviewed in 17,18]. These sensations can be varied separately, and have different afferent pathways [e.g. 19,20]. The sense of excessive respiratory work is thought to arise both from receptors in the respiratory pump muscles themselves, and from awareness of cortical motor drive sent to the pump muscles [e.g. 21,22]. The sense of air hunger is thought to arise from any reflex drive to breathe, such as arterial chemoreceptors sensing hypercapnia and hypoxia [23]; the pathway is most likely through brainstem respiratory motor centres. Air hunger is ameliorated by tidal expansion of the lungs, mainly sensed by pulmonary stretch receptors; thus air hunger may be viewed as a result of the balance between respiratory drive and tidal expansion [24,25]. The chest tightness of asthma seems to arise from receptors in the lungs, stimulated either by chemical mediators or by the change in mechanical environment. This latter form of dyspnoea is thus most closely related to cough in its afferent source. Indeed, there is a variant of asthma whose main symptom is urge to cough; thus some pulmonary or airway sensory receptors may be common to tightness and cough.

3. Psychophysics

Studies of perception of urge to cough, pain, and dyspnoea share problems of measurement [26]. While mediated by a protective neural system that can be partly assessed through focussed and more generalized methods, all three of these methods are ultimately 'internal feeling' states that are most appropriately assessed by an individual's verbal description of their own experience. The experience is characterized by both sensory qualities and by affective/emotional properties that motivate behaviours to reduce the aversive aspect of the experience. In the case of pain and dyspnoea, the discomfort of many biologists with "subjective reports" has fueled a search for "objective" behavioural or physiological measures that avoid perceived problems with self report. Reflexes, evoked cortical potentials and now functional neuroimaging have been pursued as objective measures of pain and dyspnoea that are 'uncontaminated' by attitudes, biases and the host of other variables that can alter descriptions of experience. However, the objective measure may be a chimera: such physiological outcome measures are currently validated by comparing them to self-report; each measure can be shown to be dissociated from self-report in response to specific interventions. Furthermore, in the end, it is the subjective sensation that the patient cares most about.

To date, research on the mechanisms and treatment of the symptoms of pain, urge to cough and dyspnoea has relied mainly on methods that use 'subjective' report as the dependent variable. These subjective responses are measured using methods of psychophysics, which classically are described as measuring the relationship between sensory perception and the properties of a physical stimulus. Psychophysical measures have long been used to characterize pain and respiratory sensations, but we have found only one published psychophysical study of the urge to cough [27; but see also 28 in this Special Issue]. This study revealed two basic findings: first, there is a graded perceptual intensity of urge to cough that is systematically related to the concentration of irritant substance (capsaicin). Second, urge to cough is perceived at lower stimulus intensity than needed to evoke the cough reflex (although it was not reported

whether subjects were attempting to suppress cough, which might have affected this relationship).

Future studies may apply many of the methods used in the measurement of pain and dyspnoea perception to expand these basic findings in cough. Such studies may address the current differences found between sophisticated measures of cough behaviour and subjective measures. Clearly, the same physical event of coughing or dyspnoea can be accompanied by distressing sensation in one situation yet be barely noticeable in another. Future psychophysical studies promise to shed new light on the perceptual dimensions of the urge to cough, the ability to discriminate between stimulus-induced sensations, properties over time such as summation and habituation, sensitivity to treatment interventions and, most importantly, the affective dimension of cough distress and the relevant mechanisms that modulate unpleasantness independently of the intensity of the urge to cough or of the cough itself.

In the case of cough and dyspnoea we must be careful in thinking about what the source of unpleasantness is — cough may be pleasant if it relieves the urge to cough, which is clearly unpleasant (just as scratching an itch may be pleasant). Likewise, increased breathing may be pleasant if it relieves the unpleasant urge to breath (air hunger).

As biologists, we may also ask what selective advantage perception of these symptoms has: i.e. why is it is necessary to build and maintain the cortical structures necessary for perception when reflex mechanisms are available to deal with the biological problem? In the case of cough, we imagine that the perception of urge to cough, which precedes cough itself [27], may allow the animal time to activate inhibitory descending pathways to suppress cough in situations ranging from basic survival to social embarrassment (for instance hiding from a predator or avoiding embarrassment in a concert hall). This perception also allows control over a voluntary cough, which in certain situations may be preferable to a reflexive cough. In the case of dyspnoea, we postulate that perception allows the animal to use complex behaviours when mere motor drive to respiratory muscles is not an appropriate solution to the problem (e.g. the case of urge to breathe in a submerged diving animal). In the case of pain, suppression of normal pain reactions is sometimes required to allow the animal to pursue more important tasks; this has been quantified in animal behaviour experiments [29,30].

4. Summary

The field of pain science is clearly ahead of both dyspnoea and cough sciences. The field of dyspnoea science has shown that it is possible to apply some of the concepts and methods used by pain scientists to a complex respiratory event. It is our hope that the neurophysiological and psychophysical approaches used to understand pain and dyspnoea can be modified to help discoveries about the perception of urge to cough, and the function of afferent and central pathways of cough.

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