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Vagal afferent nerves with the properties of nociceptors

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ABSTRACT

Vagal afferent nerves are essential for optimal neural regulation of visceral organs, but are not often considered important for their defense. However, there are well-defined subsets of vagal afferent nerves that have activation properties indicative of specialization to detect potentially harmful stimuli (nociceptors). This is clearly exemplified by the vagal bronchopulmonary C-fibers that are quiescent in healthy lungs but are readily activated by noxious chemicals and inflammatory molecules. Vagal afferent nerves with similar activation properties have been also identified in the esophagus and probably exist in other visceral tissues. In addition, these putative vagal nociceptors often initiate defensive reflexes, can be sensitized, and have the capacity to induce central sensitization. This set of properties is a characteristic of nociceptors in somatic tissues.

1. Introduction

The term nociceptor is commonly used to imply that the nerve in question initiates pain, although this assumption is not always validated. To our knowledge there is no conclusive evidence that the vagal primary afferent nerves initiate pain. This function seems to be reserved for a subset of afferent nerves originating in the spinal dorsal root ganglia. Vagal inputs likely integrate with the inputs from the spinal pathways in the central nervous system to modulate perception of pain. However, this potential role hardly qualifies vagus nerves as pain pathways. Thus, if the common usage of term nociceptor is followed, it is at present difficult to argue that any particular subset of vagal nerve fibers should be labeled as nociceptors.

In this text we evaluate the question whether there are vagal afferent nerves that specialize on the detection of stimuli associated with impeding or actual tissue damage and initiate responses aimed to prevent or limit tissue damage. We review the evidence that there are well-characterized examples of vagal afferent nerves with the properties that typically characterize certain types of somatosensory nociceptors. While the nomenclature of these vagal nerves continues to be debated, we argue that there are practical advantages in conceptualizing these vagal afferent nerves as nociceptors.

In the Integrated Action of the Nervous System, Sherrington discussed specific types of sensory nerve fibers in the skin that, "Instead of but one kind of stimulus being their adequate excitant, they may be regarded as adapted to a whole group of excitants, a group of excitants which has in relations to the organism one feature common to all its components, namely a nocuous character" (Sherrington, 1906). Sherrington argued that such nerve fibres… "under selective adaptation, attach to the skin a so-to-say specific sense of its own injuries" and termed this special type of afferent nerve nociceptor. In contrast, in modern literature the term nociceptor is generally used to refer to the nerves that mediate pain. Thus, it appears that compared to Sherrington's original description, the defining property of the nociceptor has shrunk from the nature of its activators to a single specific consequence of its activation (pain). This complicates the discussion of the afferent nerves that fit the Sherrington's characterization of the nociceptors, but whose role in pain has not been established. Such nerves include large numbers of vagal afferent nerve fibers innervating the viscera.

Vagal afferent nerves are traditionally thought of as the afferent pathways that detect physiologic information from the viscera while a subset of the spinal afferent nerves is implicated in detection of "noxious" visceral information (Blackshaw et al., 2007; Grundy, 2002). Indeed, there is extensive evidence of the well-defined vagal afferent nerve fibers specialized to detect stimuli associated with physiological activity of visceral tissues (reviewed elsewhere in this issue). The examples include the vagal low threshold mechanosensitive nerve terminals in the lungs ("stretch receptors") and in the esophagus (tension mechano-receptors), and the vagal afferent nerves specialized to detect nutrients. On the other hand, a subset of vagal afferent nerves has sensory transduction properties allowing for selective detection of stimuli associated with tissue inflammation and damage. For the purpose of this discussion we will term these nerves "putative vagal nociceptors" referring to the Sherrington's original definition above. In the instances when a commonly accepted term is available to denote a specific group of putative vagal nociceptors (such as bronchopulmonary C-fibers) this term will be preferred.

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The classically described somatosensory nociceptor in the skin is an unmyelinated afferent nerve fiber (C-fiber) that is polymodal, i.e. responsive to various physical stimuli in an intensity range associated with impending or actual tissue damage as well as to noxious chemical stimuli including endogenous molecules produced in tissue injury and inflammation (Julius and Basbaum, 2001). The C-fiber nociceptor is relatively unresponsive to innocuous stimulation thus displaying little activity in a healthy uninjured skin not exposed to noxious factors. Typical phenomena observed in C-fiber somatosensory nociceptors are peripheral and central sensitization. Peripheral sensitization denotes an increase of the primary afferent nerve sensitivity and is typically initiated by inflammatory mediators. Central sensitization is the capacity of nociceptors to induce an increase in the synaptic efficacy on the second order sensory neurons. Central sensitization in the somatosensory system results in reduced threshold for pain, an amplification of pain responses and a spread of pain hypersensitivity to non-injured areas. The consequences of C-fiber nociceptor activation are nocifensive reflexes and a major sensation attributed to the skin C-fiber nociceptors is pain.

Similar to somatosensory nociceptors, certain vagal afferent nerves are selectively responsive to noxious stimuli, initiate defensive reflexes and contribute to warning sensations, and can be sensitized and have capacity to induce central sensitization. It should be kept in mind that the definition of noxious stimuli may be context dependent. For example, certain mechanical force may be considered noxious in some tissue, and innocuous in another more distensible tissue. It should be also noted that even though vagal nociceptors and somatosensory nociceptors in the skin share certain fundamental properties this does not imply that they are identical in all aspects. It has been long appreciated that the nociceptors in the skin (and likely elsewhere in somatic tissues) can be divided into distinct classes with certain class-specific properties. Similarly, as discussed below, the putative vagal nociceptors can be segregated into distinct subtypes, but the basis of the subdivision may differ between vagal and somatosensory nociceptors.

2. Putative vagal nociceptive nerve fibers in the lungs

Vagal afferent nerves innervating the mammalian lungs can be divided into two general categories: the A-fiber mechanosensors sensitive to lung distention (also termed pulmonary stretch receptors) and bronchopulmonary C-fibers (Canning et al., 2006). In addition, several other types of vagal afferent nerve fibers can be found in the respiratory system such as myelinated fibers innervating the neuroepithelial bodies (Adriaensen et al., 2006) and the touch-sensitive A-fibers in the large conducting airways (Riccio et al., 1996). The unmyelinated fibers (C-fibers) comprise majority (>75%) of the afferent nerve fibers innervating the lungs (Agostoni et al., 1957). Vagal C-fibers innervate all compartments of the lungs from the large conducting airways to alveoli (Coleridge and Coleridge, 1984; Lee and Pissari, 2001). General anatomical and functional properties of the bronchopulmonary C-fibers are reasonably similar in all species in which these nerves have been studied including mouse, rat, guinea pig, rabbit, cat, dogs and monkey (reviewed in (Canning and Chou, 2009)). Anatomically, the vagal C-fibers in the airway have been described as extensively branched nerve fibers that form dense plexus (Baluk et al., 1992; Watanabe et al., 2005). Thus the vagal C-fibers in the respiratory mucosa structurally resemble C-fiber nociceptors in the skin. A proportion of the vagal C-fibers in all species contain neuropeptides such as substance P, neurokinin A and calcitonin gene related peptide, although the neuropeptides are more commonly found in the C-fibers of some rodents.

The primary function of the respiratory system is gas exchange. This function critically depends on airway patency and functional integrity of the alveolar membrane. Hypoxia resulting from a serious limitation to alveolar gas exchange is an imminent danger to the organism. Given a relatively delicate biology of the airway epithelium and alveolar membrane, and the fact that they come to extensive contact with the components of outside environment (inhaled air) it is relatively straightforward to identify exogenous noxious factors with the potential to compromise lung function. Examples of such noxious factors are sulfur dioxide, acids, cigarette smoke, ozone, acrolein, ammonia and particulate matter. Similarly, inflammation in the lungs can limit alveolar gas exchange through a number of mechanisms deteriorating ventilation–perfusion ratio such as edema, infiltration and impaired mucociliary transport. Thus, and similar to the situation elsewhere in the body, inflammatory mediators signal the presence of noxious factors in the lungs.

Vagal bronchopulmonary C-fibers are stimulated by a wide range of exogenous noxious stimuli including those mentioned above, as well as by endogenous inflammatory mediators. The receptors responsible for the activation have been identified for a number of these noxious stimuli. Available data indicate that certain members of the TRP ion channel family, namely TRPV1 and TRPA1, play a prominent role in the activation of bronchopulmonary C-fibers by noxious stimuli. The selective TRPV1 agonist capsaicin has long been used to stimulate the vagal bronchopulmonary C-fibers for the study of respiratory reflexes and in electrophysiological experiments. Indeed, a majority of the bronchopulmonary C-fibers in all species are activated by capsaicin (Lee and Pissari, 2001; Lee et al., 2003). TRPV1 directly mediates or contribute to sensory transduction of acid, certain lipid mediators such 12-lipoxygenase products and anandamide, bradykinin and others (Clapham et al., 2005). More recently, TRPA1 has been shown to mediate robust activation in the vagal bronchopulmonary C-fibers (Nassenstein et al., 2008; Taylor-Clark et al., 2009b). TRPA1 has attracted much attention in the pain field (Jordt et al., 2004; Story et al., 2003). Due to an atypical mechanism of TRPA1 activation that involves covalent modification of specific cysteine residues, TRPA1 confers sensitivity to a long list of reactive electrophilic compounds (Hinman et al., 2006; Macpherson et al., 2007). Some examples of the exogenous noxious chemicals relevant for the lung include environmental pollutants acrolein, toluene diisocyanate, and presumably ozone and nitrogen oxides (Taylor-Clark et al., 2009b). Endogenous TRPA1 activators can be produced by oxidative stress (nitrated fatty acids, 4-hydroxynonenal, 4-oxononenal) or during prostaglandin metabolism (i.e. the PGD_2 metabolite 15-deoxy-Δ(12,14)-prostaglandin J_2) (Andersson et al., 2008; Bessac and Jordt, 2008; Taylor-Clark et al., 2009a, 2008a,b). Thus, combined expression of TRPV1 and TRPA1 channels makes vagal C-fibers in the lungs wide range chemosensors for noxious chemicals. In addition, other specific receptors such as the adenosine A_1 and A_{2A} receptors and nicotinic receptors can mediate activation of the vagal C-fibers (Chuaychoo et al., 2006; Kou et al., 1989).

In contrast to their robust activation by noxious stimuli, the vagal bronchopulmonary C-fibers are rather quiescent in the healthy uninjured lungs. A recent quantitative analysis of data from >20 studies in 5 species (rats, guinea pig, rabbits, cats and dogs) (reviewed in Canning) documents that the bronchopulmonary C-fibers are either silent or display a low level of irregular activity during normal breathing. This is consistent with their mechanosensitive properties. Typically, high levels of lung inflation (deemed non-physiologic) are required to induce meaningful action potential discharge in the naive unsensitized vagal bronchopulmonary C-fibers (Fig. 1D–E). The low resting activity of the vagal C-fibers also implies that these fibers are not effectively stimulated by chemicals comprising the physiological milieu in the environment of their nerve terminals.

The activation properties of vagal bronchopulmonary C-fibers are in stark contrast with the activation profile of the non-nociceptive vagal A-fiber mechanosensors in the lungs (reviewed in (Canning et al., 2006)). The majority of the lung mechanosensors display regular discharge in phase with the cyclic lung distention during eupneic breathing (Fig. 1)(Lee et al., 2003; Bergren, 1997). Unlike