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Insights into the evolution of polymodal chemoreceptors

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ABSTRACT

Respiratory chemoreceptors in vertebrates are specialized cells that detect chemical changes in the environment or arterial blood supply and initiate autonomic responses, such as hyperventilation or changes in heart rate, to improve O_2 uptake and delivery to tissues. These chemoreceptors are sensitive to changes in O_2, CO_2 and/or H^+. In fish and mammals, respiratory chemoreceptors may be additionally sensitive to ammonia, hypoglycemia, and numerous other stimuli. Thus, chemoreceptors that affect respiration respond to different types of stimuli (or modalities) and are considered to be "polymodal". This review discusses the polymodal nature of respiratory chemoreceptors in vertebrates with a particular emphasis on chemoreceptors of the carotid body and pulmonary epithelium in mammals, and on neuroepithelial cells in water- and air-breathing fish. A major goal will be to examine the evidence for putative polymodal chemoreceptors in fish within the context of studies on mammalian models, for which polymodal chemoreceptors are well described, in order to improve our understanding of the evolution of polymodal chemoreceptors in vertebrates, and to aid in future studies that aim to identify putative receptors in air- and water-breathing fish.

1. Introduction

A polymodal receptor is a specialized cell that may become activated by multiple forms of sensory stimuli. Polymodal receptors were first characterized in the sensing of painful or noxious stimuli, e.g. chemical, mechanical or thermal (Bessou and Perl, 1969; Kumazawa, 1996). Such polymodal receptors that mediate sensing of chemical irritation or tissue damage, called nociceptors, are well established in visceral and somatic tissues in vertebrates, and transmit information to the central nervous system to evoke pain sensation (Gebhart, 1996; Kumazawa, 1996; Perl, 1996). In addition to the sensing of pain by nociceptors, other sensory receptors may be polymodal, such as chemoreceptors responsible for initiating autonomic reflexes, like hyperventilation. These receptors are sensitive to changes in levels of respiratory gases (e.g. O_2 and CO_2), H^+ and other stimuli.

In this review, the morphological and functional studies that have defined the polymodal nature of respiratory chemoreceptors within specialized organs in mammalian and aquatic vertebrates will be discussed. A major goal of this paper will be to use a comparative approach to examine the evidence for putative polymodal chemoreceptors in water- and air-breathing fish within the context of studies on mammalian models, for which polymodal chemoreceptors are well described. Such an analysis may improve our understanding of the evolution of polymodal chemoreceptors in vertebrates, and aid in future studies to identify putative polymodal receptors in air- and water-breathing fish—species for which relatively little is known about the chemoreceptor control of breathing.

2. Polymodal chemoreceptors in mammals

2.1. Carotid body

The carotid body is the principal, peripheral organ that controls breathing in mammals, where a decrease in arterial partial pressure of O_2 (P_{O2}) evokes reflex hyperventilation. The carotid body is a paired structure that resides within the neck, at the bifurcation of the common carotid arteries, where they give rise to the internal and external carotids (González et al., 1994; Kumar and Prabhakar, 2012). The size of the organ is variable and is dependent upon the size of the animal—-approximately 750 μm in length in rat (Hess, 1975) and 2–3 mm in human (Heath et al., 1970). The primary chemosensory unit of the carotid body is the type I (or glomus) cell (Fig. 1A). Type I cells occur in clusters associated with sensory nerve terminals of the carotid sinus nerve, which is compose primarily of fibres of the glossopharyngeal nerve with some contribution from the vagus (González et al., 1994). To date, the type I cell is the most well-described polymodal chemoreceptor that mediates respiratory reflexes in vertebrates, and will therefore be discussed first.

The sensory nature of the carotid body was first appreciated by the anatomical and histological work of De Castro in 1926, and its role as a

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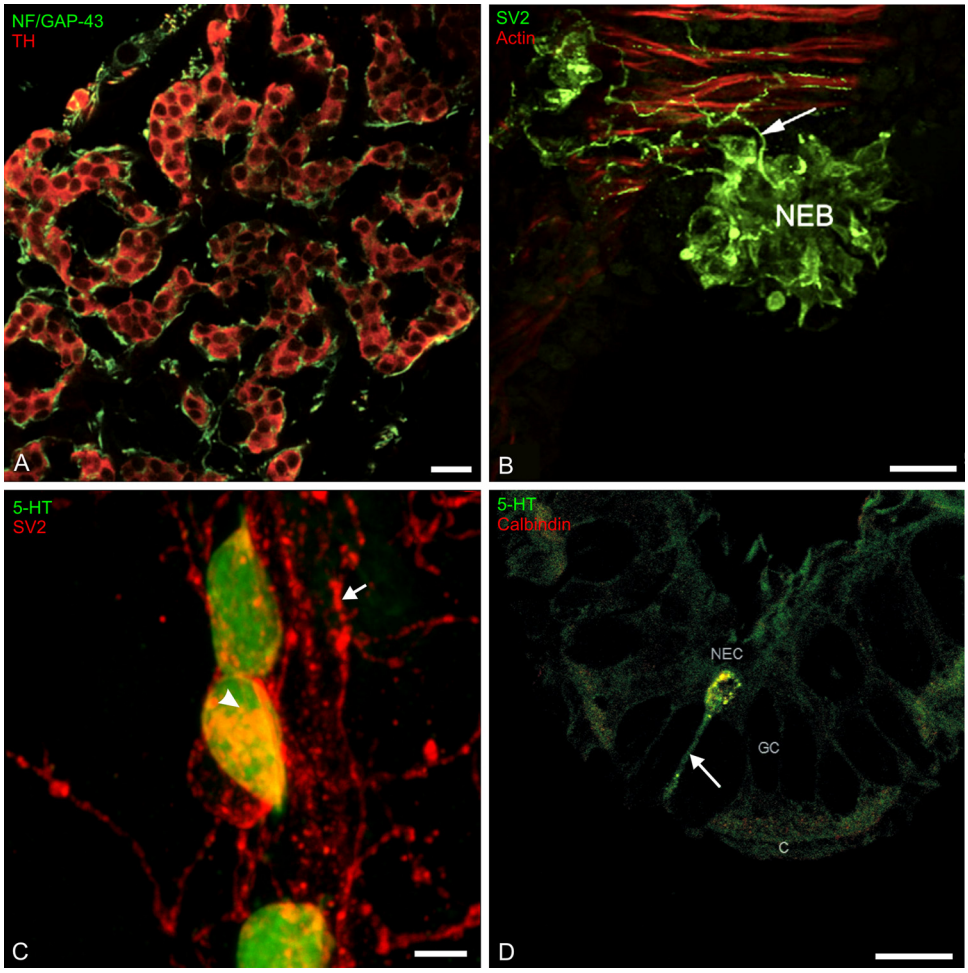

Fig. 1. Confocal immunofluorescence imaging of polymodal chemoreceptors in vertebrates. (A) Innervation of type I (glomus) cells in a section from 2-week-old rat carotid body immunolabelled with antibodies against neurofilament (NF)/GAP-43 (green) to label sensory nerve fibres and terminals, and tyrosine hydroxylase (TH, red) to label type I cells. Scale bar = 20 µm. Reprinted from Nurse (2010) with permission. (B) Neuroepithelial body (NEB) and its innervation in neonatal mouse lung. The section was immunolabelled for synaptic vesicle glycoprotein 2 (SV2, green) and actin (red) to identify smooth muscle. The fine subepithelial nerve branch entering the base of the NEB is indicated by an arrow. Scale bar = 20 µm. Reprinted from Cutz et al. (2013) with permission. (C) Neuroepithelial cells (NECs) of the zebrafish gill filament in a whole-mount preparation labelled with antibodies against serotonin (5-HT, green) and SV2 (red). Anti-SV2 labelled nerve fibres in the gill filaments (arrow) and cytoplasmic secretory vesicles in NECs (arrowhead). Scale bar 5 = µm. (D) NEC with process (arrow) in the mucociliated epithelium of the respiratory gas bladder of *L. oculatus*. Immunofluorescence labelling for calbindin D28k (red and yellow) and 5-HT (green). GC, goblet cell; C, ciliated cell. Scale bar = 10 µm. Reprinted from Jonz et al. (2015) with permission (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

chemosensory structure that controlled respiratory reflexes was established a year later by Heymans (for a historic account, see Kumar and Prabhakar, 2012). Direct evidence that carotid body type I cells were chemosensitive was first provided during the 1980s, when it was shown that reduction of P_{O2} in enzymatically-dissociated type I cells induced inhibition of K^+ channels, membrane depolarization, and elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$; Acker and Pietruschka, 1984; Pietruschka, 1985; López-Barneo et al., 1988; López-López et al., 1989). The O_2-sensitive K^+ channels were later identified as two-pore-domain acid-sensitive TASK-like background channels, which are open at resting membrane potential, and the inhibition of which represents a critical early step in hypoxic chemotransduction (Buckler, 1997; Buckler et al., 2000; Buckler, 2015). Activation of type I cells by hypoxia produces Ca^{2+}-dependent release of neurotransmitters that act upon afferent terminals of the carotid sinus nerve. Acetylcholine (ACh) and adenosine triphosphate (ATP) are thought to be the primary, excitatory transmitters involved in conveying the hypoxic stimulus to afferent fibres, while other neurochemicals, such as dopamine, γ-aminobutyric acid (GABA), serotonin (5-hydroxytryptamine, 5-HT) and nitric oxide act as modulators in the carotid body (Nurse, 2010).

The mechanism(s) through which hypoxia is sensed by type I cells has been hotly debated for decades (Kumar and Prabhakar, 2012). The widely-accepted "membrane hypothesis" implicates K^+ channels of the plasma membrane as critical components of initiating membrane depolarization in response to hypoxia, which subsequently leads to activation of voltage-gated Ca^{2+} channels and Ca^{2+}-dependent neurotransmitter release. Upstream components of the O_2-sensing pathway may include effects upon the mitochondrion, the involvement of reactive oxygen species, adenosine monophosphate (AMP)-activated protein kinase, or gaseous neurotransmitters, such as hydrogen sulphide (H_2S) (Evans, 2006; Kumar and Prabhakar, 2012; Prabhakar and Peers, 2014). A recent study demonstrated that, in transgenic mice lacking functional mitochondrial complex I, the hyperventilatory response to hypoxia was abolished; and while carotid body structure and biochemistry remained normal, responses of dispersed type I cells to decreased P_{O2} were absent in transgenic mice (Fernández-Agüera et al., 2015). These observations suggest that acute O_2 sensing by chemoreceptors of the carotid body depends on mitochondrial function at complex I. However, given the evidence of multiple putative O_2 sensors in type I cells, and the sensitivity of the carotid body to a wide range of P_{O2} (~80–20 mmHg), the "chemosome hypothesis" was put forward to suggest that an ensemble of multiple O_2 sensors, each with different sensitivity to O_2, might work together to contribute to the rapidity and broad range of responses within the carotid body (Prabhakar, 2006).

In addition to sensing decreased arterial P_{O2}, type I cells may be activated by other blood-borne stimuli, such as increased CO_2 or H^+, as during hypercapnia or respiratory acidosis. Experiments conducted *in vivo* in normoxic cat demonstrated that, at constant arterial pH, elevated arterial P_{CO2} increased discharge frequency in single carotid body afferent fibres; and decreased arterial pH, at constant P_{CO2}, had the same effect (Biscoe et al., 1970). Isolated type I cells in rat responded to hypercapnia and acidosis with membrane depolarization and increased $[Ca^{2+}]_i$ via membrane ion channels (Buckler and Vaughan-Jones, 1993, 1994). The sensing of CO_2 by type I cells appears to be mediated by intracellular acidification catalyzed by the enzyme, carbonic anhydrase (CA), and can be reduced by CA inhibitors, such as acetazolamide (Buckler et al., 1991; Kumar and Prabhakar, 2012). CA has been localized to carotid body type I cells (Ridderstrale and Hanson, 1984).