



# The sensing of respiratory gases in fish: Mechanisms and signalling pathways



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## ABSTRACT

Chemoreception in fish is critical for sensing changes in the chemical composition of the external and internal environments and is often the first step in a cascade of events leading to cardiorespiratory and metabolic adjustments. Of paramount importance is the ability to sense changes in the levels of the three respiratory gases, oxygen (O<sub>2</sub>), carbon dioxide (CO<sub>2</sub>) and ammonia (NH<sub>3</sub>). In this review, we discuss the role of piscine neuroepithelial cells (NEC), putative peripheral chemoreceptors, as tri-modal sensors of O<sub>2</sub>, CO<sub>2</sub> and NH<sub>3</sub>. Where possible, we elaborate on the signalling pathways linking NEC stimulation to afferent responses, the potential role of neurotransmitters in activating downstream neuronal pathways and the impact of altered levels of the respiratory gases on NEC structure and function. Although serotonin, the major neurotransmitter contained within NECs, is presumed to be the principal agent eliciting the reflex responses to altered levels of the respiratory gases, there is accumulating evidence for the involvement of “gasmitters”, a class of gaseous neurotransmitters which includes nitric oxide (NO), carbon monoxide (CO) and hydrogen sulphide (H<sub>2</sub>S). Recent data suggest that CO inhibits and H<sub>2</sub>S stimulates NEC activity whereas NO can either be inhibitory or stimulatory depending on developmental age.

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## 1. Introduction

Fish possess well-developed reflexes to regulate cardiorespiratory function in the face of environmental change, in particular when confronted with altered levels of one or more of the three respiratory gases, oxygen (O<sub>2</sub>), carbon dioxide (CO<sub>2</sub>) or ammonia (NH<sub>3</sub>). The levels of these gases, while typically constant in open, well-mixed pristine natural environments, can vary markedly both temporally and spatially in natural and aquaculture settings. The most common causes for altered gas levels include crowding, diurnal cycling of photosynthesis and respiration, surface ice formation, and increasing atmospheric CO<sub>2</sub> (Diaz, 2001; Diaz and Breitburg, 2009; Diaz and Rosenberg, 2008). To minimize the deleterious consequences associated with decreased O<sub>2</sub> (hypoxia), increasing CO<sub>2</sub> (hypercapnia) and elevated ammonia (high environmental ammonia; HEA) on physiological function, fish exhibit an orchestrated series of responses often aimed at maximising gas transfer across the gill and transport within the blood (Perry and Gilmour, 2010; Perry and Wood, 1989; Randall and Daxboeck, 1970). Fish can respond to these stimuli within seconds and once

initiated, the responses can persist for the duration of the stimulus, be attenuated, or disappear despite the continued presence of the initial stimulus. Arguably, the most common response of fish to hypoxia, hypercapnia or HEA is hyperventilation, an increase in the volume of water flowing over the gills, resulting from increases in breathing frequency and/or ventilatory stroke volume (Hughes, 1973; Randall and Shelton, 1963). The aim of this paper is not to comprehensively review the cardiorespiratory reflexes accompanying changes in ambient gas composition but rather to focus on recent developments surrounding the specific mechanisms whereby, fish sense respiratory gases, a process known as chemoreception. For a thorough account of the cardiorespiratory reflexes associated with hypoxia and hypercapnia, the reader is referred to the paper (this volume) by Bursleson (2015) and other detailed review articles (Bushnell and Jones, 1992; Butler and Metcalfe, 1988; Farrell, 1993; Farrell and Jones, 1992; Fritsche and Nilsson, 1992; Gilmour and Perry, 2007; Olson, 1998; Perry et al., 2009a; Perry and Gilmour, 1999, 2010; Randall, 1982; Taylor, 1992). In addition, a number of previous reviews have covered aspects of chemoreception in fish (Bursleson, 2009; Bursleson et al., 1992; Gilmour, 2001; Gilmour and Perry, 2007; Jones and Milsom, 1982; Jonz and Nurse, 2006; Milsom, 1995, 2012; Milsom et al., 1999; Perry et al., 2009b; Porteus et al., 2012; Shelton et al., 1986).

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In this review, our intent is to highlight the more recent developments pertaining to chemoreception in fishes including the role of neuroepithelial cells (NECs) as tri-modal sensors of O<sub>2</sub>, CO<sub>2</sub> and NH<sub>3</sub>, the signalling pathways linking NEC stimulation to afferent responses, the potential role of neurotransmitters in activating downstream neuronal pathways and the impact of altered levels of the respiratory gases on NEC function. Additionally, we focus on the emerging roles of the gaseous neurotransmitters (nitric oxide carbon monoxide and hydrogen sulphide) in facilitating or modulating chemoreception in fishes.

## 2. Peripheral chemoreceptors in fish

### 2.1. Neuroepithelial cells

In water breathing fishes, peripheral chemoreceptors are predominantly, if not exclusively responsible for initiating the cardiorespiratory responses to changes in the levels of respiratory gases. Although direct data exist for only three species, neuroepithelial cells (NECs) are generally considered to be the chemoreceptors for O<sub>2</sub> and CO<sub>2</sub> in zebrafish *Danio rerio* (Jonz et al., 2004; Qin et al., 2010), O<sub>2</sub> in catfish *Ictalurus punctatus* (Burlleson et al., 2006) and NH<sub>3</sub> in trout (*Oncorhynchus mykiss*) (Zhang et al., 2011). NECs were first described in fish and elasmobranchs by Dunel-Erb et al. (1982). They discussed their findings with reference to the morphology of the NECs that had been previously described in the walls of the respiratory tract of mammals. Their work was central in triggering over 30 years of research on NECs and their chemoreceptive properties in aquatic vertebrates. In all adult fish species studied to date, the NECs are located primarily in the distal half of the gill filament and in some species (e.g. goldfish (*Carassius auratus* and zebrafish) can also be found scattered on the respiratory lamellae (Dunel-Erb et al., 1982; Bailly et al., 1989; Jonz and Nurse, 2003; Coolidge et al., 2008; Tzaneva and Perry, 2010). Within the gill filament epithelium NECs are located in close proximity to the efferent filament artery (eFA; the blood vessel that exits the gill filament) and thus on the leading edge of the filament incident to the inspired water current flowing over the gills (Hughes, 1966; Hughes and Morgan, 1973). This location makes them ideal candidates for sensing changes in the levels of respiratory gases both from the external environment (inspired water) and the blood exiting the gill (Jonz and Nurse, 2003). Lamellar NECs are smaller and appear more spherical than filament NECs (Jonz and Nurse, 2003). They are typically exposed to the external environment making them suitable for sensing external changes in respiratory gases (Jonz and Nurse, 2003; Tzaneva and Perry, 2010).

NECs are derived from a diffuse group of cells originating in the neural crest and are primarily characterized by dense-cored vesicles (DCV) 80–100 nm in diameter (Pearse, 1969; Dunel-Erb et al., 1982). They can be identified by serotonin immunoreactivity which is typical for the DCV (Bailly et al., 1992; Coolidge et al., 2008; Jonz and Nurse, 2003; Porteus et al., 2013; Saltys et al., 2006; Tzaneva and Perry, 2010; Regan et al., 2011). The NECs of water-breathing vertebrates share similar characteristics with type I (glomus) cells of the mammalian carotid body and the neuroepithelial bodies (NEBs) of air-breathing (including mammals) vertebrates (Van et al., 1999; Zaccone et al., 1989). The demonstration that NECs isolated from zebrafish (Jonz et al., 2004) and channel catfish (Burlleson et al., 2006) gill respond to hypoxia by membrane depolarization via background K<sup>+</sup> channels provided the first compelling direct evidence for their role in O<sub>2</sub> chemoreception. The cellular response of gill filament NECs to hypoxia closely resembled the O<sub>2</sub> sensitive background K<sup>+</sup> currents identified in type I cells of the carotid body (Gonzalez et al., 1994). In contrast to the glomus cells of the carotid body, branchial NECs are able to sense

both internal (blood) and external (water) changes in respiratory gases. The carotid body is designed to monitor internal changes in respiratory gases exclusively (Milsom and Burlleson, 2007). Furthermore, a variety of neurotransmitters including serotonin (5-HT), catecholamines (CA) and acetylcholine (ACh) are co-localised in the glomus cells of the carotid body; the NECs apparently contain a single neurotransmitter, 5-HT.

In larval zebrafish the NECs are found exclusively on the skin prior to gill development (Coccimiglio and Jonz, 2012); their numbers gradually decline as the gill forms and ultimately the gill becomes the principal location of NECs. The NECs first appear on gill filament primordia at 5 dpf (days post fertilization) and are innervated by 7 dpf (Jonz and Nurse, 2005) yet physical responses to hypoxia are observed in zebrafish as early as 2 dpf and hyperventilatory responses are clearly evident at 4 dpf (Coccimiglio and Jonz, 2012; Jonz and Nurse, 2005). Thus, on this basis and other indirect data, it was suggested that the skin NECs act as early O<sub>2</sub> chemoreceptors prior to maturation of the gill (Coccimiglio and Jonz, 2012). We must emphasize that although it is largely assumed based on *in vitro* studies and indirect correlative data from intact fish that the NECs are functioning *in vivo* as O<sub>2</sub> chemoreceptors both in adult and larval zebrafish, there is little, if any, direct evidence to support this view. The absence of direct *in vivo* data, in part, reflects the technical limitations associated with conducting electrophysiological recordings on NECs *in situ* and the absence of a viable loss-of-function model whereby NEC development is prevented.

Recent evidence suggests that the NECs are also a site of CO<sub>2</sub> detection in fish based on recent studies using zebrafish (Abdallah et al., 2012; Abdallah et al., 2014; Perry and Abdallah, 2012; Qin et al., 2010). Raised ambient CO<sub>2</sub> levels result in inhibition of background K<sup>+</sup> currents and subsequent membrane depolarization, a response comparable to that of type I cells of the carotid body when faced with high CO<sub>2</sub> levels (Buckler and Vaughan-Jones, 1994). Thus, in addition to being the putative peripheral O<sub>2</sub> chemoreceptors in fish, there is emerging evidence that the NECs also serve as CO<sub>2</sub> sensors giving them a bimodal sensory function resembling that of the carotid body Type 1 cells. In addition, there is accruing evidence that fish NECs are the mediators of the hyperventilatory responses associated with HEA (Zhang et al., 2011, 2014). Recent developments related to specific features of O<sub>2</sub>, CO<sub>2</sub> and NH<sub>3</sub> sensing will be discussed in greater detail below.

### 2.2. Potential neurotransmitters involved in chemoreception

The gills, and presumably the NECs, receive innervation from the IX and X cranial nerves also referred to as the “branchial” nerves (Nilsson, 1984; Sundin and Nilsson, 2002). The majority of reports on NEC innervation are derived from studies on trout, goldfish, and zebrafish. The filament NECs of all three species appear to be innervated by nerve processes originating from the filament base (Bailly et al., 1992; Jonz and Nurse, 2003; Tzaneva and Perry, 2010). Lamellar NECs of zebrafish and goldfish are also in proximity of nerve fibers that emanate from the nerve bundle located between the central venous sinus (CVS) and the eFA (Jonz and Nurse, 2003; Tzaneva and Perry, 2010). Being in close proximity to nerve fibers suggests that chemoreception *via* NECs may be through the release of neurotransmitters onto afferent nerve fibers. Recently, it was proposed that in adult fish, serotonergic NECs act as the primary O<sub>2</sub> sensors presumably secreting serotonin onto a primary afferent neuron or acting in a paracrine manner by releasing serotonin directly onto neighboring vascular muscle cells (Porteus et al., 2013). The same authors demonstrated that although zebrafish NECs do not appear to contain acetylcholine or catecholamines, there are nearby cholinergic nerve fibres suggesting a possible role for acetylcholine in chemoreception via relay neurons (Porteus et al., 2013). A potential role for serotonin

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