



## Control of air-breathing in fishes: Central and peripheral receptors

Luiz Henrique Florindo<sup>a,b,1</sup>, Vinicius Araújo Armelin<sup>a,1</sup>, David John McKenzie<sup>c,d</sup>,  
Francisco Tadeu Rantin<sup>d,\*</sup>

<sup>a</sup> Department of Zoology and Botany, São Paulo State University (UNESP), Rua Cristóvão Colombo, 2265, São José do Rio Preto, SP, 15054-000, Brazil

<sup>b</sup> Aquaculture Center (CAUNESP), São Paulo State University (UNESP), Rodovia Prof. Paulo Donato Castellane, n/n, Jaboticabal, SP, 14884-900, Brazil

<sup>c</sup> Centre for Marine Biodiversity Exploitation and Conservation, UMR9190 (IRD, Ifremer, UM, CNRS), Université Montpellier, Place Eugène Bataillon cc 093, 34095 Montpellier Cedex 5, France

<sup>d</sup> Department of Physiological Sciences, Federal University of São Carlos (UFSCar), Rodovia Washington Luiz, km 235, São Carlos, SP, 13565-905, Brazil

### ARTICLE INFO

#### Keywords:

Bimodal respiration  
Chemoreception  
Hypercapnia  
Hypercarbia  
Hypoxaemia  
Hypoxia

### ABSTRACT

This review considers the environmental and systemic factors that can stimulate air-breathing responses in fishes with bimodal respiration, and how these may be controlled by peripheral and central chemoreceptors. The systemic factors that stimulate air-breathing in fishes are usually related to conditions that increase the O<sub>2</sub> demand of these animals (e.g. physical exercise, digestion and increased temperature), while the environmental factors are usually related to conditions that impair their capacity to meet this demand (e.g. aquatic/aerial hypoxia, aquatic/aerial hypercarbia, reduced aquatic hydrogenionic potential and environmental pollution). It is now well-established that peripheral chemoreceptors, innervated by cranial nerves, drive increased air-breathing in response to environmental hypoxia and/or hypercarbia. These receptors are, in general, sensitive to O<sub>2</sub> and/or CO<sub>2</sub>/H<sup>+</sup> levels in the blood and/or the environment. Increased air-breathing in response to elevated O<sub>2</sub> demand may also be driven by the peripheral chemoreceptors that monitor O<sub>2</sub> levels in the blood. Very little is known about central chemoreception in air-breathing fishes, the data suggest that central chemosensitivity to CO<sub>2</sub>/H<sup>+</sup> is more prominent in sarcopterygians than in actinopterygians. A great deal remains to be understood about control of air-breathing in fishes, in particular to what extent control systems may show commonalities (or not) among species or groups that have evolved air-breathing independently, and how information from the multiple peripheral (and possibly central) chemoreceptors is integrated to control the balance of aerial and aquatic respiration in these animals.

### 1. Introduction

An adequate supply of O<sub>2</sub> to meet metabolic demands is essential for life of aerobic organisms; any impairment can compromise performance and even be fatal, depending upon the physiological adaptations of the species concerned. Water has a low capacitance for O<sub>2</sub>, containing only a few milligrams per litre, and has low diffusion constants for dissolved gases, such that hypoxia can be a common condition in aquatic environments (Richards et al., 2009). Therefore, organisms that breathe water can often be challenged to meet their demands for O<sub>2</sub> (Carter, 1931; Rahn, 1966; Driedzic and Hochachka, 1978; Kramer and Mehegan, 1981; Kramer and McClure, 1982; Randall, 1982; Kramer, 1987; Diaz and Breitbart, 2009).

Air is much richer in oxygen and fishes were the first vertebrates to evolve adaptations to breathe air, the fossil record dates to the late

Silurian, ~ 420 million years ago. This predates the conquest of land by the ancestors of tetrapods, which evolved from lobe-finned fishes (Sarcopterygii) that resembled the extant Dipnoi (Panchen, 1980; Little, 1983, 1990; Gordon and Olson, 1994; Long, 1995; Schultze and Trueb, 1991; Amemiya et al., 2013). Aquatic hypoxia or periodic emersion (caused by tidal oscillations or by unfavorable environmental conditions), are considered the two main circumstances that exerted evolutionary pressure for selection of aerial respiration in fishes (Inger, 1957; Johansen, 1970; Graham et al., 1978; Randall et al., 1981; Horn and Gibson, 1988; Sayer and Davenport, 1991; Graham, 1997). However, it is important to emphasize that these were probably not the only selective pressures involved in the evolution of air-breathing, because it is a very diverse adaptation found in over 40 families, such that it seems to have evolved independently on numerous occasions (Randall et al., 1981; Graham, 1997; Hsia et al., 2013). All air-breathing fishes are

\* Corresponding author.

E-mail address: [frantin@ufscar.br](mailto:frantin@ufscar.br) (F.T. Rantin).

<sup>1</sup> These authors have contributed equally to this work (co-first authors).

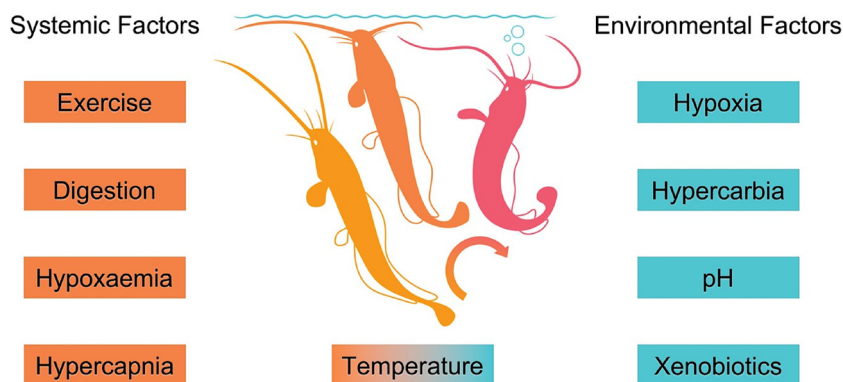


Fig. 1. Systemic and environmental factors with effects on air-breathing behavior in fishes. Note that temperature can be both a systemic factor and an environmental factor. The arrow indicate the chronological order of an air-breathing event.

'bimodal breathers', they possess gills that play a role in gas exchange and they vary in the extent to which they rely on air-breathing to meet their routine  $O_2$  demands, from entirely 'obligate' to entirely 'facultative' (Johansen, 1970; Graham, 1997; Lefevre et al., 2014).

Aquatic surface respiration (ASR) is a common adaptation of unimodal water-breathing fishes, that apparently helps to maintain  $O_2$  uptake and aerobic metabolism during aquatic hypoxia. It consists of rising to the surface to ventilate the gills with the uppermost layer of water in contact with air, where there is constant diffusion of gases from the atmosphere (Kramer and Mehegan, 1981; Kramer and McClure, 1982). This adaptation is a reflex triggered by low  $O_2$  availability and is believed to have led towards the evolution of true air-breathing in fishes (Shingles et al., 2005; Florindo et al., 2006; Chapman and McKenzie, 2009; Richards, 2011). It is postulated that the ASR reflex may have favored the selection of air-breathing based on the following hypotheses: (1) ASR allowed individuals to survive in waters under severe hypoxia; (2) some individuals inadvertently came into contact with the air during ASR (e.g. by inhaling it), which provided conditions for  $O_2$  uptake from the air across vascularized epithelia, making it possible to select them as air-breathing organs (ABO) (Burggren, 1982; Gee and Gee, 1995); and (3) ASR exposes the animals to predation, so individuals with the capacity to gulp and hold air could protect themselves from predators by temporarily returning to the depths, hence further favoring the evolution of adaptations for true aerial respiration (Kramer et al., 1983; Smith and Kramer, 1986; Gee and Gee, 1995; Shingles et al., 2005; Chapman and McKenzie, 2009).

Despite being a phylogenetically ancient specialization, aerial respiration retains great importance in the natural history of many extant fish species, especially in tropical freshwaters that can become hypoxic due to reduced  $O_2$  capacitance at high temperatures (Rahn, 1966; Kramer et al., 1978; Graham, 1997; Diaz and Breitburg, 2009; Pörtner and Lannig, 2009), a condition that may be intensified by climate global change (Lehtonen, 1996; Diaz, 2001; Diaz and Breitburg, 2009). In addition to its importance in  $O_2$ -poor environments, air-breathing behavior in fishes can also supply  $O_2$  to support aerobic activities such as exercise or digestion, although this has received less research attention than responses to hypoxia (Johansen, 1970; Gee and Graham, 1978; Stevens and Holeyton, 1978; Dejours, 1994; Brauner et al., 1995; Graham, 1997; Seymour et al., 2004, 2007; McKenzie et al., 2012; Lefevre et al., 2014; Blasco et al., 2017).

Fishes possess specialized chemosensitive cells, located in the central and/or peripheral nervous system, capable of monitoring the partial pressure of  $O_2$  ( $P_{O_2}$ ) or  $CO_2$  ( $P_{CO_2}$ ), as well as the hydrogenionic potential (pH), in the blood and/or the environment (internally and/or externally oriented chemoreceptors) (see Hara, 1992; Milsom, 2012 for reviews). These chemoreceptors modulate a wide range of behavioral and physiological adjustments that favor the survival of fishes during situations of hypoxia/hypoxaemia (i.e. reduced levels of  $O_2$  in the

environment or in the body, respectively) and hypercarbia/hypercapnia (i.e. increased levels of  $CO_2$  in the environment or in the body, respectively), and air-breathing behavior is a prime example (Smatresk et al., 1986; McKenzie et al., 1991a; Milsom et al., 2002; Florindo et al., 2004, 2006; Bojink et al., 2010; Lopes et al., 2010; Milsom, 2012; Zeraik et al., 2013; Belão et al., 2015). There are differences in the location, distribution and orientation of these chemoreceptors among species, and their functions may vary depending on the specificity of these cells – such characteristics of fish chemoreceptors and their respective physiological influences have been previously reviewed by Gilmour (2001), Perry and Gilmour (2002), Gilmour and Perry (2006), Milsom (2012), Perry and Abdallah (2012), Porteus et al. (2012) and Zachar and Jonz (2012).

The number of studies on the role of chemoreceptors in controlling air-breathing in fishes is still modest, especially regarding central chemoreceptors. However, peripheral chemoreceptors appear to be more involved in air-breathing modulation than central chemoreceptors, as in many species studied to date the disruption of afferent nervous pathways attenuates or abolishes this behavior in response to aquatic hypoxia or hypercarbia (Hedrick et al., 1991; McKenzie et al., 1991a; Bojink et al., 2010; Lopes et al., 2010; Belão et al., 2015). Thus, given this overall context, this review evaluates current knowledge about systemic and environmental factors that stimulate air-breathing in fishes, and the role of chemoreceptors in the reflex control of this behavior.

## 2. Stimulators of reflex air-breathing responses

Several factors stimulate air-breathing behaviors in fishes, which can be classified as either "systemic" or "environmental" (Fig. 1). Systemic factors are states of the organism that increase  $O_2$  demand for aerobic metabolism, in particular warming, exercise and digestion, which then stimulate overall ventilatory activity. Environmental factors, on the other hand, are external conditions that increase the animals'  $O_2$  demand; challenge respiratory gas exchange, and/or damage the fragile epithelium of the gill lamellae. This includes warming, hypoxia, hypercarbia, pH and pollutants. In species that are obligate air-breathers such factors will alter the intensity of aerial respiration whereas, in facultative air-breathers, such factors can trigger the air-breathing behavior as well as modulate its intensity.

### 2.1. Systemic factors

The  $O_2$  demands of fishes increase considerably during physical exercise, and this leads to an increase in air-breathing frequency in all species studied to date (Smatresk, 1988; Lefevre et al., 2014). Although this response would be expected in obligate air-breathers, it also occurs in all facultative species that have been studied, namely *Amia calva*,

*Cliarus gariepinus*, *Gymnotus carapo*, *Hoplosternum littorale*, *Lepisosteus oculatus*, *Megalops cyprinoides*, *Neoceratodus forsteri*, and *Pangasianodon hypophthalmus* (Grigg, 1965; Gee and Graham, 1978; Farmer and Jackson, 1998; Seymour et al., 2004, 2007; McKenzie et al., 2012; Lefevre et al., 2013; Blasco et al., 2017). Food consumption also causes a transient increase in metabolic rate and O<sub>2</sub> demand, which can be extremely pronounced in some ectotherms (Secor, 2009; McCue, 2006). There is evidence that obligate air-breathing fishes increase aerial respiration when feeding in normoxic water, but this phenomenon is also expected to occur in facultative air-breathing fishes (Pandian and Vivekanandan, 1976; Lefevre et al., 2012).

An increase in temperature is a combined systemic/environmental factor that stimulates air-breathing behavior in fishes because it increases the demand for O<sub>2</sub> in the tissues and requires increased O<sub>2</sub> delivery (Johansen et al., 1970; Rahn et al., 1971; Horn and Riggs, 1973; Gee, 1980; Graham and Baird, 1982; Glass et al., 1986; Johnston and Dunn, 1987; McMahon and Burggren, 1987; Smatresk, 1988; Clarke and Johnston, 1999; Geiger et al., 2000; Silva et al., 2017). Indeed, warming also lowers O<sub>2</sub> solubility in water, which reduces aquatic P<sub>O2</sub> and additionally contributes to stimulate air-breathing behavior (Rahn, 1966; Johansen et al., 1970; Graham and Baird, 1982; McMahon and Burggren, 1987). Nevertheless, Gee (1980), Glass et al. (1986) and Geiger et al. (2000) performed experiments in which water temperature was manipulated without affecting its P<sub>O2</sub> levels (normoxia preserved by bubbling pure O<sub>2</sub> in the water when necessary), and observed an increase in air-breathing frequency associated with temperature elevation in *Channa argus*, *Megalops atlanticus* and *Umbra limi*—demonstrating that the stimulatory influence of temperature on this behavior is not a mere consequence of aquatic hypoxia.

The mechanisms by which air-breathing is stimulated by increased O<sub>2</sub> demand are not fully understood (Lefevre et al., 2014, 2016). The increase in air-breathing frequency could supplement aquatic gas exchange, because many bimodal breathing fishes have reduced gill surface areas, with lower O<sub>2</sub> extraction capacity than unimodal water-breathing species (Eduardo et al., 1979; Lomholt and Johansen, 1979; Graham, 1983; Rantin et al., 1992; Fernandes and Rantin, 1994; Fernandes et al., 1994; Graham, 1997; Oliveira et al., 2004; Belão et al., 2011). This argument cannot, however, explain why some bimodal breathing fishes can sustain similar aerobic scopes by aquatic respiration alone, if they are denied access to air during forced exercise (McKenzie et al., 2012; Lefevre et al., 2014, 2016).

The response may in fact be an inescapable chemoreflex, driven by internal chemoreceptors that monitor blood O<sub>2</sub> levels (Lefevre et al., 2014; McKenzie et al., 2016). It has been suggested that the spontaneous aperiodic episodes of air-breathing that are observed in many facultative air-breathing fishes in normoxia, when external O<sub>2</sub> chemoreceptors should be quiescent, are driven by the internal chemoreceptors: as blood O<sub>2</sub> levels fall after an air-breath, this eventually stimulates another breath (Shelton et al., 1986; Smatresk, 1988). There is some indirect evidence for this 'internal' respiratory drive because, in the spiny catfish *C. gariepinus*, individuals with higher intrinsic metabolic rates and O<sub>2</sub> demands spontaneously breathed more air in normoxia (McKenzie et al., 2016). When fishes exercise at increasing intensity, this progressively depletes venous blood of O<sub>2</sub> (Stevens and Randall, 1967; Farrell and Clutterham, 2003). In bimodal breathing fishes, this venous hypoxaemia may cause inescapable chemoreflexive stimulation of air-breathing, that increases with intensity as they exercise harder (McKenzie et al., 2012; Lefevre et al., 2014). This is an area that deserves further investigation.

## 2.2. Environmental factors

Fishes with facultative aerial respiration (both Actinopterygii and Sarcopterygii) typically shift from gill ventilation to air-breathing as O<sub>2</sub> levels in water fall. This transition has been described in numerous species, namely *A. calva*, *Anabas testudineus*, *Ancistrus chagresi*, *C.*

*gariepinus*, *Erpetoichthys calabaricus*, *Heteropneustes fossilis*, *Hoplerthrinus unitaeniatus*, *H. littorale*, *Hypostomus plecostomus*, *Hypostomus regani*, *L. oculatus*, *Lepisosteus osseus*, *M. atlanticus*, *M. cyprinoides*, *N. forsteri*, *P. hypophthalmus*, *Rhinelepis strigosa* and *Synbranchus marmoratus*. The response is based on a chemoreflex, capable of providing sufficient O<sub>2</sub> to maintain aerobic metabolism during aquatic hypoxia, and the transition from water to air-breathing can be elicited either by external or internal [if environmental hypoxia induces hypoxaemia] O<sub>2</sub> chemoreceptors (Hughes and Singh, 1970; Johansen et al., 1970; Hughes and Singh, 1971; Gee and Graham, 1978; Graham and Baird, 1982; Smatresk and Cameron, 1982; Graham and Baird, 1984; Pettit and Beitinger, 1985; Smatresk, 1986; Fritsche et al., 1993; Takasusuki, 1994; Brauner et al., 1995; Mattias et al., 1998; Geiger et al., 2000; Kind et al., 2002; Seymour et al., 2004; Affonso and Rantin, 2005; McKenzie et al., 2007; Lopes et al., 2010; Belão et al., 2011; Lefevre et al., 2011; Belão et al., 2015; Thomsen et al., 2017). It is interesting that, regarding obligate air-breathing fishes, this response varies among actinopterygians (e.g. *Electrophorus electricus* exhibits no change in air-breathing frequency during aquatic hypoxia while *Trichogaster trichopterus* exhibits an increase) (Burggren, 1979; Johansen et al., 1968) but not among sarcopterygians (aquatic hypoxia does not change air-breathing frequency in *Lepidosiren paradoxa*, *Protopterus aethiopicus* and *Protopterus dolloi*) (Johansen and Lenfant, 1968; Sanchez et al., 2001a; Perry et al., 2005a). It is conceivable that obligate sarcopterygians do not possess externally oriented O<sub>2</sub> chemoreceptors in the gills (Lahiri et al., 1970; Perry et al., 2005a; Silva et al., 2017). However, the actinopterygian and sarcopterygian species just cited, as well as the obligate air-breathing teleosts *C. argus* and *Monopterus albus*, show an increase in air-breathing frequency when exposed to aerial hypoxia, which may have been triggered by hypoxaemia through internally oriented chemoreceptors or by external chemoreceptors that monitor the P<sub>O2</sub> of air in the ABO (Johansen et al., 1968; Johansen and Lenfant, 1968; Lomholt and Johansen, 1974; Burggren, 1979; Glass et al., 1986; Sanchez et al., 2001a; Zaccone et al., 2003, 2006; Perry et al., 2005a; Silva et al., 2011, 2017). Nonetheless, the facultative sarcopterygian *N. forsteri* did not exhibit this response after the injection of nitrogen into the lung (Johansen et al., 1967).

Aquatic hypercarbia can increase the frequency of aerial respiration in several species of fish with obligatory or facultative air-breathing, such as *A. chagresi*, *E. calabaricus*, *H. unitaeniatus*, *H. plecostomus*, *L. paradoxa*, *N. forsteri*, *P. aethiopicus*, *P. dolloi*, *S. marmoratus* and *T. trichopterus* (Johansen, 1966; Johansen et al., 1967; Johansen and Lenfant, 1968; Burggren, 1979; Graham and Baird, 1982; Pettit and Beitinger, 1985; Smatresk, 1988; Sanchez and Glass, 2001; Sanchez et al., 2005; Perry et al., 2008; Bojink et al., 2010), although there are species where water CO<sub>2</sub> does not influence air-breathing behavior (e.g. *E. electricus*, *M. albus* and *P. hypophthalmus*) (Johansen et al., 1968; Lomholt and Johansen, 1974; Thomsen et al., 2017). As CO<sub>2</sub> is much more soluble in water than O<sub>2</sub> (Rahn, 1966) bimodal breathing fishes, including obligate air-breathing species with reduced gills, eliminate large amounts of metabolic CO<sub>2</sub> through water breathing (Lenfant et al., 1966; Johansen and Lenfant, 1967; Babiker, 1979; Perry et al., 2005b; Perry and Gilmour, 2006). However, hypercarbia decreases or even reverses the CO<sub>2</sub> concentration gradient between water and blood, leading to an increase in plasma P<sub>CO2</sub>. The accumulation of CO<sub>2</sub> can then produce a respiratory acidosis that hinders blood O<sub>2</sub> transport through Bohr and Root effects, potentially challenging O<sub>2</sub> supply (Perry and Kinkead, 1989; Randall et al., 2014). In bimodal breathers, the accumulation of CO<sub>2</sub> may be alleviated by direct elimination of this gas to the atmosphere (Lefevre et al., 2016). This could explain why air-breathing reflexes can be triggered by internal and/or external chemoreceptors sensitive to CO<sub>2</sub>/H<sup>+</sup> (Bojink et al., 2010; Milsom, 2012). Nonetheless, in *A. calva*, infusions of NH<sub>4</sub>HCO<sub>3</sub> into the dorsal aorta caused large increases in plasma P<sub>CO2</sub> and stimulated gill ventilation, but had no effect on air-breathing, indicating that aerial respiration is not stimulated by internal CO<sub>2</sub> in this species (McKenzie et al., 1991b).

**Table 1**  
Systemic and environmental factors and its effects on air-breathing behavior in various species of fish.

Species	Physical Exercise	Digestion	Increased Temperature	Aquatic Hypoxia	Aerial Hypoxia	Aquatic Hypercarbia	Aerial Hypercarbia	Reduced Environmental pH	Contaminants (H <sub>2</sub> S)
<b>FACULTATIVE</b>									
<i>Amblyops</i>	+ <sup>30</sup>		+ <sup>9, 12</sup>	+ <sup>9</sup>				+ <sup>26</sup>	
<i>Anabas testudineus</i> (A)				+ <sup>8</sup>					
<i>Ancistrus chagresi</i> (A)		+ <sup>19</sup>		+ <sup>19</sup>		+ <sup>19</sup>			
<i>Clarias gariepinus</i> (A)	+ <sup>52</sup>			+ <sup>45, 51</sup>			+ <sup>16</sup>		
<i>Epiplatys calabaricus</i> (A)				+ <sup>22</sup>		+ <sup>22</sup>			
<i>Gymnotus carapo</i> (A)	+ <sup>49</sup>								
<i>Heteromystes fossilis</i> (A)				+ <sup>10</sup>					
<i>Hoplosternum littorale</i> (A)	+ <sup>15</sup>			+ <sup>40, 44</sup>		+ <sup>43</sup>			
<i>Hypostomus plecostomus</i> (A)				+ <sup>15, 29, 37</sup>				+ <sup>29</sup>	+ <sup>29, 37</sup>
<i>Hypostomus regani</i> (A)	+ <sup>30</sup>			+ <sup>19</sup>		+ <sup>19</sup>			
<i>Lepisosteus oculatus</i> (A)		+ <sup>11</sup>		+ <sup>31</sup>	+ <sup>20</sup>		nc <sup>20</sup>		
<i>Lepisosteus osseus</i> (A)		+ <sup>32</sup>		+ <sup>20</sup>					
<i>Megalops atlanticus</i> (A)	+ <sup>36, 41</sup>			+ <sup>24</sup>					
<i>Megalops cyprinoides</i> (A)			+ <sup>25</sup>	+ <sup>32</sup>					
<i>Missurnus anguillicaudatus</i> (A)	+ <sup>2</sup>			+ <sup>36</sup>					
<i>Neoceratodus forsteri</i> (S)	+ <sup>50</sup>			+ <sup>27, 35</sup>	nc <sup>5</sup>	+ <sup>5</sup>			
<i>Pangasianodon hypophthalmus</i> (A)				+ <sup>46, 54</sup>		nc <sup>54</sup>			
<i>Rhinelepis strigosa</i> (A)				+ <sup>28</sup>		+ <sup>3</sup>			
<i>Synbranchius marmoratus</i> (A)		+ <sup>18</sup>		+ <sup>21 / nc<sup>3</sup></sup>					
<i>Umbra limi</i> (A)		+ <sup>23</sup>			+ <sup>23</sup>				
<b>OBLIGATORY</b>									
<i>Chaanna argus</i> (A)		+ <sup>14, 48</sup>							
<i>Chaanna striata</i> (A)									
<i>Electrophorus electricus</i> (A)				nc <sup>7</sup>	+ <sup>7</sup>	nc <sup>7</sup>	+ <sup>7</sup>		
<i>Lepidostiren paradoxus</i> (S)		+ <sup>53</sup>		nc <sup>34</sup>	+ <sup>34, 47, 53</sup>	+ <sup>33, 38</sup>	nc <sup>33</sup> / + <sup>38</sup>		
<i>Monopterus albus</i> (A)				+ <sup>13</sup>	+ <sup>13</sup>	nc <sup>13</sup>			
<i>Protopterus aethiopicus</i> (S)				nc <sup>6</sup>	+ <sup>6</sup>	+ <sup>6</sup>	+ <sup>1 / -4</sup>		
<i>Protopterus annectens</i> (S)						+ <sup>16</sup>	+ <sup>4 / nc<sup>42</sup></sup>		
<i>Protopterus dollot</i> (S)				nc <sup>39</sup>	+ <sup>39</sup>	+ <sup>42</sup>	+ <sup>17</sup>		
<i>Trichogaster trichopterus</i> (A)				+ <sup>17</sup>	+ <sup>17</sup>	+ <sup>17</sup>	+ <sup>17</sup>		

Note: (A) Actinopterygii; (S) Sarcopterygii; (H<sub>2</sub>S) Hydrogen sulfide; (+) Stimulation; (-) Inhibition; (nc) No change; (blank) No data available.

References: <sup>1</sup> Smith (1930); <sup>2</sup> Grigg (1965); <sup>3</sup> Johansen (1966); <sup>4</sup> Jesse et al. (1967); <sup>5</sup> Johansen et al. (1967); <sup>6</sup> Johansen and Lenfant (1968); <sup>7</sup> Johansen et al. (1968); <sup>8</sup> Hughes and Singh (1970); <sup>9</sup> Johansen et al. (1970); <sup>10</sup> Hughes and Singh (1971); <sup>11</sup> Rahm et al. (1971); <sup>12</sup> Horn and Riggs (1973); <sup>13</sup> Lombolt and Johansen (1974); <sup>14</sup> Pandian and Vivekanandan (1976); <sup>15</sup> Gee and Graham (1978); <sup>16</sup> Babiker (1979); <sup>17</sup> Burggren (1979); <sup>18</sup> Gee (1980); <sup>19</sup> Graham and Baird (1982); <sup>20</sup> Smatresk and Cameron (1982); <sup>21</sup> Graham and Baird (1984); <sup>22</sup> Pettit and Beiting (1985); <sup>23</sup> Glass et al. (1986); <sup>24</sup> Smatresk (1986); <sup>25</sup> McMahon and Burggren (1987); <sup>26</sup> McKenzie et al. (1991b); <sup>27</sup> Fritsche et al. (1993); <sup>28</sup> Takasuki (1994); <sup>29</sup> Brauner et al. (1995); <sup>30</sup> Farmer and Jackson (1998); <sup>31</sup> Mattias et al. (1998); <sup>32</sup> Geiger et al. (2000); <sup>33</sup> Sanchez and Glass (2001); <sup>34</sup> Sanchez et al. (2001a); <sup>35</sup> Kind et al. (2002); <sup>36</sup> Seymour et al. (2004); <sup>37</sup> Alfonso and Rantin (2005); <sup>38</sup> Sanchez et al. (2005); <sup>39</sup> Perry et al. (2005a); <sup>40</sup> McKenzie et al. (2007); <sup>41</sup> Seymour et al. (2007); <sup>42</sup> Perry et al. (2008); <sup>43</sup> Bojlink et al. (2010); <sup>44</sup> Lopes et al. (2010); <sup>45</sup> Belão et al. (2011); <sup>46</sup> Lefevre et al. (2011); <sup>47</sup> Silva et al. (2011); <sup>48</sup> Lefevre et al. (2012); <sup>49</sup> McKenzie et al. (2012); <sup>50</sup> McKenzie et al. (2013); <sup>51</sup> Belão et al. (2015); <sup>52</sup> Blasco et al. (2017); <sup>53</sup> Silva et al. (2017); <sup>54</sup> Thomsen et al. (2017).



Several studies demonstrated that aerial hypercarbia can also increase air-breathing frequency in some air-breathing fishes, such as *C. gariepinus*, *E. electricus*, *L. paradoxa*, *P. aethiopicus*, *Protopterus annectens* and *T. trichopterus* (Smith, 1930; Johansen et al., 1968; Delaney et al., 1974, 1976; Delaney et al., 1977; Babiker, 1979; Burggren, 1979; Smatresk, 1988; Sanchez et al., 2005), while other studies showed that it can lead to a decrease (*P. aethiopicus* and *P. dolloi*) (Jesse et al., 1967), or even no changes (in *L. oculatus*, *L. paradoxa* and *P. dolloi*) (Smatresk and Cameron, 1982; Sanchez and Glass, 2001; Perry et al., 2008). Although many of these air-breathing responses may reveal direct chemosensitivity to CO<sub>2</sub>, some of them may be an indirect effect of reductions in blood O<sub>2</sub> levels consequent to a respiratory acidosis. Also, the divergent responses may be explained by interspecific differences in the existence, orientation and function of O<sub>2</sub> and CO<sub>2</sub>/H<sup>+</sup> chemoreceptors, or by differences in CO<sub>2</sub> diffusivity at the gills and ABO of these species. The divergent results may also reflect differences in the CO<sub>2</sub> concentrations to which the animals were submitted, or even interspecific variation in the thresholds for CO<sub>2</sub> concentrations in water or air that stimulate air-breathing.

The pH of water influences several physiological processes in fishes, including respiratory gas exchange and the excretion of nitrogenous wastes (Wilkie and Wood, 1991, 1996; Saha et al., 2002). Water pH is inversely proportional to water P<sub>CO<sub>2</sub></sub>, and a reduction in environmental pH may lead to a respiratory acidosis that compromises O<sub>2</sub> uptake in these animals (Perry and Kinkead, 1989; Perry et al., 1989; Lin and Randall, 1990; Wilkie and Wood, 1996). Therefore, to avoid this effect, fishes with aerial respiration show an increase in the frequency of this behavior when in contact with water with reduced pH (Brauner et al., 1995). In *A. calva*, infusions of HCl into the dorsal aorta caused significant declines in blood pH and O<sub>2</sub> content and elicited air-breathing responses. When, however, the animals were held in hyperoxic water, the infusions only caused a decline in pH and there were no air-breathing responses. This was taken to indicate that there was no direct sensitivity of aerial respiration to plasma pH in that species (McKenzie et al., 1991b). Due to the intrinsic relationship between pH and CO<sub>2</sub> concentration in water, it can also be difficult to separate responses to pH from those to P<sub>CO<sub>2</sub></sub>. Brauner et al. (1995) found, however, that an increase in air-breathing frequency in *H. littorale* was a direct consequence of elevated water acidity and not of higher aquatic P<sub>CO<sub>2</sub></sub>. Furthermore, despite the possible influence of pH and CO<sub>2</sub> on affinity of hemoglobin for O<sub>2</sub>, the changes in respiratory patterns in *H. littorale* were probably not mediated by internal O<sub>2</sub> chemoreceptors but by internal or external CO<sub>2</sub>/H<sup>+</sup> chemoreceptors, because this species exhibited practically no Root effect (Willmer, 1934; Brauner et al., 1995).

Finally, another environmental factor that can stimulate air-breathing in fishes is aquatic pollution. Contaminants in aquatic environments can be of anthropic origin or even natural, such as the hydrogen sulfide (H<sub>2</sub>S) that is mainly produced by bacterial sulfate reduction in sediments and anaerobic decomposition of organic matter (Jorgensen, 1984). These compounds can stimulate aerial respiration in fishes for a variety of reasons. Hydrogen sulfide, for example, can reduce the affinity of hemoglobin for O<sub>2</sub> and impair the electron transport chain reaction by binding to cytochrome-c oxidase (Bagarinao and Vetter, 1989, 1992; Völkel and Berenbrink, 2000; Affonso et al., 2002, 2004), which may lead to both hypoxaemia and an impaired ability to produce ATP, that in turn triggers an increase in air-breathing frequency (Brauner et al., 1995; Affonso and Rantin, 2005). An alternative explanation would be that these animals use air-breathing as a strategy to partially and temporarily uncouple themselves from contaminated water (Brauner et al., 1995). Other pollutants, on the other hand, may irritate the gill epithelium of the animals, inducing changes in gill morphology (such as an increase in the number of interlamellar cells, cell hyperplasia and a greater production of mucus) that inhibits both xenobiotics absorption and branchial gas exchange (Hayton and Barron, 1990; Laurén, 1991; Laurent and Perry, 1991; Alazemi et al., 1996; Biagini et al., 2009) – a situation that may increase the

requirement for air breathing. The influence of all environmental and systemic factors on air-breathing behavior in facultative and obligate air-breathing fishes are summarized in Table 1.

### 3. Peripheral receptors mediating air-breathing responses

According to Milsom (2012), the location of peripheral chemoreceptors (gills, orobranchial cavity or elsewhere) and their orientation (external water or internal blood) are highly variable among fishes, whether unimodal or bimodal breathers. Their response modality (O<sub>2</sub> or CO<sub>2</sub>) and the reflex cardiorespiratory responses they engender (changes in gill ventilation rate or amplitude, heart rate, systemic vascular resistance, ASR or air-breathing) are also highly variable among species. Considering unimodal and bimodal breathers, there is a trend whereby the receptors involved in triggering changes in heart rate and gill ventilation rate in response to hypoxia and hypercarbia are preferentially located in the gills, whereas those that produce increases in gill ventilation amplitude are more extensive, often also being found in extrabranchial locations. Also, the distribution of CO<sub>2</sub>-sensitive chemoreceptors in the gills tends to be more restricted than O<sub>2</sub>-sensitive chemoreceptors, and the location of the CO<sub>2</sub> receptors may differ from the O<sub>2</sub> receptors.

Milsom (2012) proposed that most unimodal water breathers primarily increase respiratory amplitude during hypoxia. Bimodal breathing species may, however, reduce gill ventilation in aquatic hypoxia while they increase reliance on air-breathing (see Hughes and Shelton, 1962; Shelton et al., 1986; Perry et al., 2009 for reviews).

#### 3.1. O<sub>2</sub> chemoreceptors

During the dry season in tropical regions, fishes can be confined for weeks or even months to hypoxic and hypercarbic water. Aerial respiration is a common adaptation in fish species in these ecosystems (Dehadrai and Tripathi, 1976; Kramer et al. 1978; Glass et al., 1986; Graham, 1997). The ecological success of these fishes will depend on, amongst other things, their ability to sense O<sub>2</sub> in the environment and rapidly engage the metabolic, cardiovascular and ventilatory adjustments that match O<sub>2</sub> supply to their demand (Fritsche and Nilsson, 1993). This, in turn depends on the central interaction of a variety of sensory inputs, including inputs from chemoreceptors that monitor external (water) and internal (blood) gas tensions and acid-base balance (Milsom, 1997; Perry and Gilmour, 2002).

The primary sites of peripheral O<sub>2</sub> sensing in fish appear to be the gills (including the pseudobranch in those species that possesses one) and orobranchial cavity (Laurent and Rouzeau, 1972; Randall and Jones, 1973; Butler et al., 1977; Daxboeck and Holeton, 1978; Smith and Davie, 1984; Smatresk et al., 1986; Burselson and Smatresk, 1990; McKenzie et al., 1991a; Burselson and Milsom, 1993; Sundin et al., 1999, 2000; Milsom et al., 2002). Chemoreceptors in the orobranchial cavity are innervated by branches of the Vth (trigeminal) and/or VIIth (facial) cranial nerves, those on the pseudobranch by branches of the VIIth and/or IXth (glossopharyngeal) cranial nerves, and those on the gill arches by branches of the IXth and/or Xth (vagus) cranial nerves (Butler et al., 1977; Burselson et al., 1992; Milsom et al., 2002; Reid et al., 2005). Some of these chemoreceptors respond only, or preferentially, to changes in external (water) O<sub>2</sub>, others respond only, or preferentially, to changes in internal (blood) O<sub>2</sub>, and some respond to both (Milsom and Brill, 1986; Burselson and Milsom, 1993).

Highly sensitive mechanisms to monitor O<sub>2</sub> and acid-base balance are important for the survival of all vertebrate species. In fishes, histological and neurophysiological evidence indicates that this requirement is primarily filled by endoderm-derived neuroepithelial cells (NECs) in the gills (Porteus et al., 2012; Zachar and Jonz, 2012; Hockman et al., 2017), however, other types of cells (which have not yet been characterized, but are neural crest-derived) may also be involved in this function (Hockman et al., 2017). So, as the predominant

putative  $O_2/CO_2/H^+$  chemoreceptors in fishes, NECs are mainly located on the gill filaments and secondary lamellae of all branchial arches and are innervated by afferent fibers of the central nervous system (Bailly et al., 2009; Porteus et al., 2012). Also, these cells may contain several neurotransmitters in their vesicles such as serotonin, acetylcholine, catecholamines, nitric oxide, hydrogen sulfide, leu-5-enkephalin, met-5-enkephalin and neuropeptide Y (Zaccone et al., 1992; Burlison et al., 2002; Zaccone et al., 2003; Jonz and Nurse, 2003; Jonz et al., 2004; Coolidge et al., 2008; Porteus et al., 2015; Zaccone et al., 2017) – although serotonin-containing NECs located along the gill filaments are the most abundant and are the only type that has been found in all fishes studied to date (Bailly et al., 2009; Porteus et al., 2012).

NECs are involved in local and central control of branchial functions through the paracrine production of serotonin and their synaptic relationships with the sympathetic and intrinsic branchial nervous systems (Bailly et al., 2009; Zaccone et al., 2017). In cell culture, some NECs respond immediately, and in a dose-dependent manner, to changes in local  $P_{O_2}$ . Thus, the hypoxic stimulation of the gill NECs seems to initiate the adaptive cardiorespiratory reflexes, which allows for  $O_2$  uptake and delivery to meet metabolic demands (Zachar and Jonz, 2012). Different responses can be triggered by distinct types of NECs, and it is not yet clear whether interspecific differences in the location of the NECs or in the responses triggered by each type of NECs might be attributable to differences in lifestyle (active versus sluggish fish), habitat (hypoxia tolerant versus intolerant fish) or phylogeny (Milsom et al., 1999; Perry and Gilmour, 2002; Reid et al., 2005; Coolidge et al., 2008).

There is considerable amount of data concerning the  $O_2$  chemoreceptors that drive gill versus air-breathing reflexes in bimodal breathing fishes, or the cardiovascular adjustments that accompany these. The most commonly observed adjustments to hypoxia/hypoxaemia is a decrease in gill ventilation once air-breathing is initiated (Johansen et al., 1970; Singh, 1976; Randall et al., 1981; Smatresk and Cameron, 1982; Smatresk, 1986; Shelton et al., 1986; McKenzie et al., 1991a; Graham, 1997). Also, a hypoxic bradycardia, which is a hallmark in most fishes, gives way to a tachycardia following each air breath, often accompanied by increases in cardiac output and perfusion of the air-breathing organ (Johansen, 1966; Johansen et al., 1968; Singh and Hughes, 1973; Jordan, 1976; Axelsson et al., 1989; Skaals et al., 2006; McKenzie et al., 2007; Nelson et al., 2007; Lopes et al., 2010; Belão et al., 2011; Iversen et al., 2011; Teixeira et al., 2015).

Sodium cyanide (NaCN) injections, which mimic hypoxia/hypoxaemia, have been used to elucidate the relative roles of externally versus internally  $O_2$ -sensing chemoreceptors in such responses. In *L. osseus*, external NaCN stimulates air-breathing but not gill ventilation rate and gill ventilation amplitude (Smatresk, 1986; Smatresk et al., 1986). In *A. calva*, external NaCN stimulates air-breathing, gill ventilation rate and gill ventilation amplitude – although the stimulation of air-breathing occurs only when internal  $O_2$  chemoreceptors are costimulated (McKenzie et al., 1991a). Similarly, in *L. osseus*, when blood  $P_{O_2}$  levels are low, stimulation of external  $O_2$  chemoreceptors increases air-breathing events even further (Smatresk et al., 1986; Smatresk, 1988). Internal injections of NaCN stimulate air-breathing, gill ventilation rate and gill ventilation amplitude in *L. osseus* (Smatresk, 1986; Smatresk et al., 1986), but display no effect on air-breathing in *A. calva* (McKenzie et al., 1991a). In no instance did stimulation of either group of  $O_2$  receptors in this manner produced a decrease in gill ventilation in these animals. In *L. osseus*, however, when internal  $P_{O_2}$  levels were low, simultaneous stimulation of external  $O_2$  chemoreceptors eliminated the increase in gill ventilation (Smatresk et al., 1986; Smatresk, 1988). Complete branchial denervation (gills and pseudobranch) eliminates the cardiorespiratory responses to hypoxia/hypoxaemia in *L. osseus* and *A. calva* (Smatresk, 1988, 1989; McKenzie et al., 1991a).

In a study performed by Belão et al. (2015) in *C. gariepinus*, both external and internal NaCN injections revealed that  $O_2$  chemoreceptors

mediating hypoxic gill ventilatory responses (gill ventilation rate and amplitude) are internally oriented, while  $O_2$  chemoreceptors mediating cardiovascular responses (heart rate) are both externally and internally oriented. Moreover, external and internal NaCN injections in fish that underwent a bilateral excision of the first gill arch, indicated that the gill ventilation rate responses were receptor-mediated predominantly in the first pair of gill arches, but the gill ventilation amplitude and heart rate responses were mediated by receptors located in all the gill arches (Belão et al., 2015). Still in *C. gariepinus*, air-breathing responses were predominantly mediated by external and internal  $O_2$  receptors in the first pair of branchial arches (Belão et al., 2015). In the facultative air-breathing fish *H. unitaeniatus*, the  $O_2$  receptors involved in eliciting cardiorespiratory responses to hypoxia are present in all gill arches (Lopes et al., 2010). In this species, there is evidence that externally and internally oriented  $O_2$  chemoreceptors mediate gill ventilation and cardiovascular responses, while internally oriented  $O_2$  chemoreceptors triggers air-breathing responses – however, as in *A. calva*, the stimulation of externally oriented  $O_2$  chemoreceptors induces air-breathing only when internally oriented  $O_2$  chemoreceptors are stimulated together (Lopes et al., 2010). Smatresk et al. (1986) hypothesized that the internally oriented  $O_2$  chemoreceptors set the level of hypoxic drive and are the main stimulators of air-breathing, but that input from externally oriented  $O_2$  chemoreceptors may modulate the threshold for this behavioral response, and most actinopterygians studied to date seem to corroborate this hypothesis.

Regarding sarcopterygians, there is one report that external nicotine injections stimulate air-breathing in the African lungfish (*P. aethiopicus*) (Johansen and Lenfant, 1968), but such kind of external stimuli has more often failed to trigger this behavior in dipnoans (Johansen and Lenfant, 1968; Sanchez et al., 2001a; Perry et al., 2005a). On the other hand, internal NaCN injections triggered air-breathing responses in *P. aethiopicus* (Lahiri et al., 1970), as well as exposure to aerial hypoxia did in *L. paradoxa*, *P. aethiopicus* and *P. dolloi* (Johansen and Lenfant, 1968; Sanchez et al., 2001a; Perry et al., 2005a; Silva et al., 2011, 2017). As pulmonary NECs were already found in lungfish (Zaccone et al., 1989, 1997; Kemp et al., 2003), it is possible that the exposure to aerial hypoxia stimulated air-breathing in these animals via external  $O_2$  chemoreceptors in the lungs rather than internal  $O_2$  chemoreceptors – however, at least in the case of *P. aethiopicus*, such air-breathing response is eliminated by complete gill denervation (Lahiri et al., 1970). The location, orientation and innervation of peripheral  $O_2$ -sensitive chemoreceptors involved in the control of gill ventilation rate, gill ventilation amplitude and air-breathing in fishes with bimodal respiration are summarized in Tables 2–4, respectively.

### 3.2. $CO_2/H^+$ chemoreceptors

Acute exposure of fish to aquatic hypercarbia typically elicits significant increases in gill ventilatory amplitude and/or gill ventilation rate, resulting in an increase in total gill ventilation (Janssen and Randall, 1975; Thomas and Le Ruz, 1982; Smith and Jones, 1982; Reid et al., 2000; Burlison and Smatresk, 2000; Perry and McKendry, 2001; McKendry and Perry, 2001; McKendry et al., 2001; Gilmour, 2001; Milsom et al., 2002; Perry and Reid, 2002). This is usually accompanied by a decrease in heart rate (Kent and Peirce, 1978; Perry et al., 1999; Sundin et al., 2000; Reid et al., 2000; Crocker et al., 2000; McKendry and Perry, 2001; McKendry et al., 2001; Perry and Reid, 2002) and increase in systemic vascular resistance (Perry et al., 1999; McKendry and Perry, 2001). There is strong evidence that these responses arise from the stimulation of specific  $CO_2/H^+$  chemosensitive NECs and are not dependent on changes in water or blood  $O_2$  concentration (Butler and Taylor, 1971; Reid et al., 2000; Sundin et al., 2000; Heisler et al., 1988; Graham et al., 1990; Kinkead and Perry, 1991; Milsom, 1995a,b; Perry and Gilmour, 1996; Gilmour, 2001; Burlison and Smatresk, 2000; Milsom, 2012).

At present, the cardiorespiratory responses to  $CO_2/H^+$  in fish are

**Table 2**Location, orientation and innervation of peripheral O<sub>2</sub>- and CO<sub>2</sub>/pH-sensitive chemoreceptors involved in gill ventilation rate responses.

Species	Receptor Location	Orientation	Innervation	References
<b>O<sub>2</sub> Chemoreceptors</b>				
<i>Amia calva</i> (A)	Pseudobranch + All gill arches	E + I	VII, IX, X	McKenzie et al. (1991a)
<i>Clarias gariepinus</i> (A)	First gill arch	I	IX, X	Belão et al. (2015)
<i>Hoplerythrinus unitaeniatus</i> (A)	All gill arches	E + I	IX, X	Lopes et al. (2010)
<i>Lepisosteus osseus</i> (A)	All gill arches	I	IX, X	Smatresk (1986); Smatresk et al. (1986); Smatresk (1988, 1989)
<i>Pangasianodon hypophthalmus</i> (A)	First gill arch + ?	E + I	IX, X, ?	Thomsen et al. (2017); V.A. Armelin, M.T. Teixeira, M.T. Thomsen, L.H. Florindo, M. Bayley, and T. Wang, unpublished data.
<b>CO<sub>2</sub>/H<sup>+</sup> Chemoreceptors</b>				
<i>Hoplerythrinus unitaeniatus</i> (A)	First gill arch	E	IX, X	Bojink et al. (2010)

Note: (A) Actinopterygii; (S) Sarcopterygii; (E) External – water – orientation; (I) Internal – blood – orientation; (?) Unknown; (VII) Facial nerve; (IX) Glossopharyngeal nerve; (X) Vagus nerve.

believed to arise primarily from receptors distributed throughout the gill arches innervated by the IX<sup>th</sup> and X<sup>th</sup> cranial nerves. It is clear that these receptors in the gills monitor the CO<sub>2</sub> in the water, but it is not clear whether they also respond to changes in the CO<sub>2</sub> of arterial blood. There is evidence to suggest both that they do (Janssen and Randall, 1975; Wood and Perry, 1985; Perry and Wood, 1989; Aota et al., 1990; Wood and Munger, 1994; Gilmour and Perry, 1996) and do not (McKenzie et al., 1991b; Perry et al., 1999; Sundin et al., 2000; Reid et al., 2000; McKendry et al., 2001; Perry and McKendry, 2001; McKendry and Perry, 2001; Perry and Reid, 2002; Gilmour et al., 2005). Data suggest that the receptors responding to external stimuli respond specifically to changes in CO<sub>2</sub> in the water (not pH) (Neville, 1979; Thomas and Le Ruz, 1982; Sundin et al., 2000; Reid et al., 2000), while to the extent that there is evidence for ventilatory responses arising from receptors responding to internal stimuli, there is a better correlation between the changes in ventilation and changes in arterial pH rather than arterial CO<sub>2</sub> (Heisler et al., 1988; Graham et al., 1990; Wood et al., 1990; McKenzie et al., 1991b; Wood and Munger, 1994).

McKenzie et al. (1991a,b) observed that dorsal aortic infusions of HCl elicit air-breathing reflexes in *A. calva*, however, it is possible that internal H<sup>+</sup>-sensitive receptors are not involved in the control of this response because air-breathing was only triggered when blood O<sub>2</sub> content decreased below normoxic levels along with blood pH in these animals. The data of Bojink et al. (2010) indicate that the chemoreceptors eliciting gill ventilatory responses to hypercarbia in *H. unitaeniatus* are exclusively branchial (located primarily on the first gill arch), externally oriented, and respond specifically to changes in CO<sub>2</sub> and not H<sup>+</sup>. In this species, high levels of aquatic P<sub>CO2</sub> depressed gill ventilation and stimulated air-breathing. The chemoreceptors involved in stimulating air-breathing in response to hypercarbia also appeared to be branchial, distributed across all gill arches and responded specifically to changes in aquatic P<sub>CO2</sub>. This would suggest that chemoreceptor groups with different orientations – external water versus internal blood – are involved in eliciting air-breathing responses to hypercarbia and hypoxia (respectively) in *H. unitaeniatus*. With respect to

sarcopterygians, Amin-Naves et al. (2007a) demonstrated that *L. paradoxo* presents peripheral CO<sub>2</sub>/H<sup>+</sup> chemoreceptors capable of modulating pulmonary ventilation, but did not report data on the location, orientation and innervation of these receptors.

As previously commented, aquatic hypercarbia induces an increase in gill ventilation in most air-breathing fishes (Johansen and Lenfant, 1968; Perry et al., 2008; Bojink et al., 2010). Yet, in some species (such as *H. unitaeniatus*), if the increases in aquatic P<sub>CO2</sub> are large enough, they can inhibit gill ventilation and stimulate air-breathing (Johansen et al., 1967; Graham and Baird, 1982; Graham, 1997; Sanchez and Glass, 2001; Sanchez et al., 2005; Bojink et al., 2010). In other species, however, increases in aquatic P<sub>CO2</sub> are without effect on gill ventilation (Johansen, 1966; Todd, 1972; McMahon and Burggren, 1987) or air-breathing (Johansen et al., 1968; Lomholt and Johansen, 1974). Just as with aquatic P<sub>CO2</sub>, bimodal breathing fishes exhibit a wide range of air-breathing responses to increasing levels of P<sub>CO2</sub> in inspired air, such as an increase (Smith, 1930; Johansen et al., 1968; Delaney et al., 1974, 1976; Delaney et al., 1977; Babiker, 1979; Burggren, 1979; Smatresk, 1988; Sanchez et al., 2005), a decrease (Jesse et al., 1967), or no change (Smatresk and Cameron, 1982; Sanchez and Glass, 2001; Perry et al., 2008).

The equivocal nature of the data raises questions about the existence and role of peripheral internally oriented CO<sub>2</sub>/H<sup>+</sup> sensitive chemoreceptors in driving gill ventilation or air-breathing in facultative and obligate air-breathing fishes. Clearly much remains to be investigated to resolve this issue. To date, this has not been deeply investigated in any air-breathing species and it will be intriguing to study the extent to which similar trends appear in air-breathing primitive actinopterygians and sarcopterygians. To provide an overview, the location, orientation and innervation of peripheral CO<sub>2</sub>/H<sup>+</sup> sensitive chemoreceptors involved in the control of gill ventilation rate, gill ventilation amplitude and air-breathing in fishes with bimodal respiration are summarized in Tables 2–4, respectively.

**Table 3**Location, orientation and innervation of peripheral O<sub>2</sub>- and CO<sub>2</sub>/pH-sensitive chemoreceptors involved in gill ventilation amplitude responses.

Species	Receptor Location	Orientation	Innervation	References
<b>O<sub>2</sub> Chemoreceptors</b>				
<i>Amia calva</i> (A)	Pseudobranch + All gill arches	E + I	VII, IX, X	McKenzie et al. (1991a)
<i>Clarias gariepinus</i> (A)	All gill arches	I	IX, X	Belão et al. (2015)
<i>Hoplerythrinus unitaeniatus</i> (A)	All gill arches + Extrabranchial	E + I	IX, X, ?	Lopes et al. (2010)
<i>Lepisosteus osseus</i> (A)	All gill arches	I	IX, X	Smatresk (1986); Smatresk et al. (1986); Smatresk (1988, 1989)
<i>Pangasianodon hypophthalmus</i> (A)	First gill arch + ?	E + I	IX, X, ?	Thomsen et al. (2017); V.A. Armelin, M.T. Teixeira, M.T. Thomsen, L.H. Florindo, M. Bayley, and T. Wang, unpublished data
<b>CO<sub>2</sub>/H<sup>+</sup> Chemoreceptors</b>				
<i>Hoplerythrinus unitaeniatus</i> (A)	First gill arch	E	IX, X	Bojink et al. (2010)

Note: (A) Actinopterygii; (S) Sarcopterygii; (E) External – water – orientation; (I) Internal – blood – orientation; (?) Unknown; (VII) Facial nerve; (IX) Glossopharyngeal nerve; (X) Vagus nerve.



**Table 4**  
Location, orientation and innervation of peripheral O<sub>2</sub>- and CO<sub>2</sub>/pH-sensitive chemoreceptors involved in air-breathing responses.

Species	Receptor Location	Orientation	Innervation	References
<b>O<sub>2</sub> Chemoreceptors</b>				
<i>Amia calva</i> (A)	Pseudobranch + All gill arches	(E <sup>a</sup> )	VII, IX, X	McKenzie et al. (1991a)
<i>Clarias gariepinus</i> (A)	First gill arch	E + I	IX, X	Belão et al. (2015)
<i>Hoplerthrinus unitaeniatus</i> (A)	All gill arches	(E <sup>a</sup> ) + I	IX, X	Lopes et al. (2010)
<i>Lepisosteus osseus</i> (A)	All gill arches	E <sup>a</sup> + I	IX, X	Smatresk (1986); Smatresk et al. (1986); Smatresk (1988, 1989)
<i>Pangasiodon hypophthalmus</i> (A)	First gill arch + ?	E + I	IX, X, ?	Thomsen et al. (2017); V.A. Armelin, M.T. Teixeira, M.T. Thomsen, L.H. Florindo, M. Bayley, and T. Wang, unpublished data.
<i>Protopterus aethiopicus</i> (S)	All gill arches	(E <sup>a</sup> ) + I	IX, X	Lahiri et al. (1970)
<b>CO<sub>2</sub>/H<sup>+</sup> Chemoreceptors</b>				
<i>Hoplerthrinus unitaeniatus</i> (A)	All gill arches	E	IX, X	Bojink et al. (2010)
<i>Lepidosiren paradoxa</i> (S)	?	?	?	Amin-Naves et al. (2007a)

Note: (A) Actinopterygii; (S) Sarcopterygii; (E) External – water – orientation; (I) Internal – blood – orientation; (?) Unknown; (VII) Facial nerve; (IX) Glossopharyngeal nerve; (X) Vagus nerve.

<sup>a</sup> In *A. calva* and *H. unitaeniatus*, external NaCN stimulated air-breathing only if blood P<sub>O<sub>2</sub></sub> levels were low or if NaCN was injected internally as well. In *L. osseus*, external NaCN stimulated air-breathing, but such stimulation was stronger when the animals' blood P<sub>O<sub>2</sub></sub> levels were low. In *P. aethiopicus* the effects of external stimuli are equivocal.

#### 4. Central receptors mediating air-breathing responses

The presence of central CO<sub>2</sub>/H<sup>+</sup> chemoreceptors in fishes, especially in the air-breathing fishes, has been investigated because of the important role of these receptors in the control of ventilation in terrestrial vertebrates. In the descendants of the Sarcopterygii, the tetrapods, pulmonary ventilation is produced by a central pattern generator, whose activity is modulated by central and peripheral CO<sub>2</sub>/H<sup>+</sup> chemoreceptors (Branco et al., 1992, 1993; Milsom, 1995a,b; Noronha-de-Souza et al., 2006). Conversely, in Actinopterygii, there is little evidence for central chemoreceptors sensitive to CO<sub>2</sub>/H<sup>+</sup> influencing aerial respiration. Indeed, there is no evidence for the presence of such receptors in *A. calva* and *Dallia pectoralis* (Hedrick et al., 1991; Hoffman et al., 2009).

Another study, on an isolated brainstem preparation, showed that *L. osseus*, a primitive bony fish with bimodal respiration, possesses central sensitivity to CO<sub>2</sub>/H<sup>+</sup> that control air-breathing frequency but not gill ventilation rate (Wilson et al., 2000). It was observed that the isolated brainstem autonomously produces motor patterns that resemble that of gill ventilation and air-breathing, and that manipulations of the P<sub>CO<sub>2</sub></sub>/H<sup>+</sup> levels in the brainstem produced directly proportional changes in the frequency of air-breathing motor pattern (Wilson et al., 2000). This was the first evidence of a central air-breathing pattern generator and central respiratory chemosensitivity to CO<sub>2</sub>/H<sup>+</sup> in an actinopterygian fish with aerial respiration. Wilson et al. (2000) speculated that the origin of the central rhythm generator for aerial respiration occurred before the divergence of the actinopterygian and sarcopterygian lineages.

Other evidence of the existence of central chemoreceptors in fishes was reported by Sanchez et al. (2001b) and Amin-Naves et al. (2007b) in the obligate sarcopterygian *L. paradoxa*. These studies demonstrated that lung ventilation increased substantially when cerebrospinal fluid (CSF) P<sub>CO<sub>2</sub></sub> was raised from 21 to 42 mmHg, while pH of CSF was held constant at a normal control value of 7.45. Likewise, a decrease in the pH of the CSF from 7.45 to 7.20 caused a large increase in ventilation at a constant P<sub>CO<sub>2</sub></sub> (normocarbic value = 21 mmHg). When associated, however, low pH and high P<sub>CO<sub>2</sub></sub> in CSF (pH = 7.10 and P<sub>CO<sub>2</sub></sub> = 42 mmHg) reduced ventilation. Consequently, the combined effect of a decrease in pH and increase in P<sub>CO<sub>2</sub></sub> of CSF is not additive to ventilation (Amin-Naves et al., 2007b). These results are similar to those of previous studies in toads, wherein the perfusion of the fourth cerebral ventricle with acidic, hypercapnic and acidic-hypercapnic CSF elicited hyperventilation (Smatresk and Smits, 1991; Branco et al., 1992, 1993) – in these animals, the combined effect of low pH and high P<sub>CO<sub>2</sub></sub> in CSF was not additive to ventilation as well (Smatresk and Smits, 1991).

Finally, although there is evidence for central chemosensitivity to CO<sub>2</sub>/H<sup>+</sup> in one air-breathing holostean (Wilson et al., 2000), it is generally considered that peripheral gill receptors are the predominant sites for detecting CO<sub>2</sub>/H<sup>+</sup> in actinopterygian fishes. In sarcopterygians, on the other hand, central CO<sub>2</sub>/H<sup>+</sup> chemoreceptors appear to have a more prominent role as in tetrapods (Burlison and Smatresk, 2000; Reid et al., 2000; Sundin et al., 2000; Gilmour, 2001; McKendry et al., 2001; Perry and Reid, 2002; Amin-Naves et al., 2007a).

#### 5. Conclusions and research perspectives

This review indicates that there is overall understanding of how peripheral and central chemoreceptors can drive cardiorespiratory reflexes in fishes with bimodal respiration. That is, peripheral receptors, innervated by cranial nerves, drive increased air-breathing in response to environmental hypoxia and hypercarbia. These receptors are, in general, sensitive to sensitive to O<sub>2</sub> and/or CO<sub>2</sub>/H<sup>+</sup> levels in the blood and/or the environment. Increased O<sub>2</sub> demand also stimulates air-breathing, which may be a reflex driven by reduced O<sub>2</sub> levels in the blood, as the evidence for peripheral sensitivity to increased plasma P<sub>CO<sub>2</sub></sub> remains equivocal. Air-breathing fishes also possess peripheral receptors that stimulate cardiac and gill ventilatory responses to hypoxia and hypercarbia, such as those found in unimodal water-breathing species but, in bimodal breathers, these receptors can sometimes cause responses that are different from the general unimodal pattern. Beyond these generalities, however, the existing data indicate that bimodal breathers show a great deal of interspecific variation in their reflex responses to dissolved gases, which is consistent with the fact that air-breathing has evolved independently on multiple occasions. There is the need to increase research in this area to see whether common patterns emerge across taxonomic groups. For example, to understand how information from the multiple different internally and externally oriented receptors is integrated to modify the relative intensity of aerial versus aquatic respiration. There is also a need for further research into central sensitivity to CO<sub>2</sub> and H<sup>+</sup> in sarcopterygian and actinopterygian fishes. Although it appears to exist in bony fishes, more work is required to understand what role it plays in reflex cardioventilatory responses in conscious animals.

Finally, there is also now evidence that bimodal breathing fishes may breathe air for reasons that, at first sight, seem uncoupled from stimulation of peripheral or central receptors. McKenzie et al. (2016) found that, in normoxia, the intensity of spontaneous air-breathing was linked to individual boldness in a facultative air-breather, *C. gariepinus*, in a manner that was independent of their O<sub>2</sub> demand. Killen et al. (2018) found that aggression among individuals was a stronger driver of air-breathing than was oxygen demand in groups of *C. gariepinus*. It is



not clear whether these drivers of air-breathing do in fact involve stimulation of peripheral receptors that monitor blood O<sub>2</sub> in the inter-breath interval (Shelton et al., 1986), with bold and/or aggressive individuals perhaps having a lower threshold for stimulation of a surfacing response. It is also possible, however, that once the reflex circuits for air-breathing have evolved, higher order central inputs may subsequently evolve that can influence the intensity of the behavior.

## References

- Affonso, E.G., Rantin, F.T., 2005. Respiratory responses of the air-breathing fish *Hoplosternum littorale* to hypoxia and hydrogen sulfide. *Comp. Biochem. Physiol.* (141C), 275–280.
- Affonso, E.G., Polez, V.L.P., Corrêa, C.F., Mazon, A.F., Araújo, M.R.R., Moraes, G., Rantin, F.T., 2002. Blood parameters and metabolites in the teleost fish *Colossoma macropomum* exposed to sulfide or hypoxia. *Comp. Biochem. Physiol.* (133C), 375–382.
- Affonso, E.G., Polez, V.L.P., Corrêa, C.F., Mazon, A.F., Araújo, M.R.R., Moraes, G., Rantin, F.T., 2004. Physiological responses to sulfide toxicity by the air-breathing catfish, *Hoplosternum littorale* (Siluriformes, Callichthyidae). *Comp. Biochem. Physiol.* (139C), 251–257.
- Alazemi, B.M., Lewis, J.W., Andrews, E.B., 1996. Gill damage in the freshwater fish *Gnathonemus petersii* (Family: mormyridae) exposed to selected pollutants: an ultrastructural study. *Environ. Technol.* 17, 225–238.
- Amemiya, C.T., Alföldi, J., Lee, A.P., Fan, S., Philippe, H., Maccallum, I., Braasch, I., Manousaki, T., Schneider, I., Rohner, N., Organ, C., Chalopin, D., Smith, J.J., Robinson, M., Dorrington, R., Gerold, M., Aken, B., Biscotti, M.A., Barucca, M., Baurain, D., Berlin, A.M., Blatch, G.L., Buonocore, F., Burmester, T., Campbell, M.S., Canapa, A., Cannon, J.P., Christoffels, A., De Moro, G., Edlins, A.L., Fan, L., Fausto, A.M., Feiner, N., Forconi, M., Gaffield, J., Gnerre, S., Gnirke, A., Goldstone, J.V., Haerty, W., Hahn, M.E., Hesse, U., Hoffmann, S., Johnson, J., Karchner, S.I., Kuraku, S., Lara, M., Levin, J.Z., Litman, G.W., Mauceli, E., Miyake, T., Mueller, M.G., Nelson, D.R., Nitsche, A., Olmo, E., Ota, T., Pallavicini, A., Panji, S., Picone, B., Ponting, C.P., Prohaska, S.J., Przybylski, D., Saha, N.R., Ravi, V., Ribeiro, F.J., Sauka-Spengler, T., Scapigliati, G., Searle, S.M.J., Sharpe, T., Simakov, O., Stadler, P.F., Stegeman, J.J., Sumiyama, K., Tabbaa, D., Tafer, H., Turner-Maier, J., van Heusden, P., White, S., Williams, L., Yandell, M., Brinkmann, H., Volff, J.-N., Tabin, C.J., Shubin, N., Schartl, M., Jaffe, D.B., Postlethwait, J.H., Venkatesh, B., Di Palma, F., Lander, E.S., Meyer, A., Lindblad-Toh, K., 2013. The African coelacanth genome provides insights into tetrapod evolution. *Nature* 496, 311–316.
- Amin-Naves, J., Giusti, H., Hoffmann, A., Glass, M.L., 2007a. Components to the acid-base related ventilatory drives in the South American lungfish *Lepidosiren paradoxa*. *Respir. Physiol. Neurobiol.* 155, 35–40.
- Amin-Naves, J., Giusti, H., Hoffmann, A., Glass, M.L., 2007b. Central ventilatory control in the South American lungfish, *Lepidosiren paradoxa*: contributions of pH and CO<sub>2</sub>. *J. Comp. Physiol.* (177B), 529–534.
- Aota, S., Holmgren, K.D., Gallaugh, P., Randall, D.J., 1990. A possible role for catecholamines in the ventilatory responses associated with internal acidosis or external hypoxia in rainbow trout, *Oncorhynchus mykiss*. *J. Exp. Biol.* 151, 57–70.
- Axelsson, M., Abe, A.S., Bicudo, J.E.P.W., Nilsson, S., 1989. On the cardiac control in the South American lungfish, *Lepidosiren paradoxa*. *Comp. Biochem. Physiol.* (93A), 561–565.
- Babiker, M.M., 1979. Respiratory behaviour, oxygen consumption and relative dependence on aerial respiration in the African lungfish (*Protopterus annectens*, Owen) and an air-breathing teleost (*Clarias lazera*, C.). *Hydrobiologia* 65, 177–187.
- Bagarinao, T., Vetter, R.D., 1989. Sulfide tolerance and detoxification in shallow water marine fishes. *Mar. Biol.* 103, 291–302.
- Bagarinao, T., Vetter, R.D., 1992. Sulfide-hemoglobin interactions in the sulfide tolerance salt marsh resident, the California killifish *Fundulus parvipinnis*. *J. Comp. Physiol.* (162B), 614–624.
- Bailly, Y.J.R., 2009. Serotonergic neuroepithelial cells. In: Zaccone, G., Cutz, E., Adriaenssen, D., Nurse, C.A., Mauceri, A. (Eds.), *Structure, Evolution and Function of the Airway Chemoreceptors in the Vertebrates*. Science Publishers, Enfield, pp. 61–97.
- Belão, T.C., Leite, C.A.C., Florindo, L.H., Kalinin, A.L., Rantin, F.T., 2011. Cardiorespiratory responses to hypoxia in the African catfish, *Clarias gariepinus* (Burchell 1822), an air-breathing fish. *J. Comp. Physiol.* (181B), 905–916.
- Belão, T.C., Zeraik, V.M., Florindo, L.H., Kalinin, A.L., Leite, C.A.C., Rantin, F.T., 2015. Control of cardiorespiratory function in response to hypoxia in an air-breathing fish, the African sharp-tooth catfish, *Clarias gariepinus*. *Comp. Biochem. Physiol.* (187A), 130–140.
- Biagini, F.R., David, J.A.O., Fontanetti, C.S., 2009. The use of histological, histochemical and ultramorphological techniques to detect gill alterations in *Oreochromis niloticus* reared in treated polluted waters. *Micron* 40, 839–844.
- Blasco, F.R., McKenzie, D.J., Taylor, E.W., Rantin, F.T., 2017. The role of the autonomic nervous system in control of cardiac and air-breathing responses to sustained aerobic exercise in the African sharp-tooth catfish *Clarias gariepinus*. *Comp. Biochem. Physiol.* (203A), 273–280.
- Bojink, C.L., Florindo, L.H., Leite, C.A.C., Kalinin, A.L., Milsom, W.K., Rantin, F.T., 2010. Hypercarbic cardiorespiratory reflexes in the facultative air-breathing fish jeju (*Hoplerthrinus unitaeniatus*): the role of branchial CO<sub>2</sub> chemoreceptors. *J. Exp. Biol.* 213, 2797–2807.
- Branco, L.G.S., Glass, M.L., Hoffmann, A., 1992. Central chemoreceptor drive to breathing in unanesthetized toads, *Bufo paracnemis*. *Respir. Physiol.* 87, 195–204.
- Branco, L.G.S., Glass, M.L., Wang, T., Hoffmann, A., 1993. Temperature and central chemoreceptor drive to ventilation in toad (*Bufo paracnemis*). *Respir. Physiol.* 93, 337–346.
- Brauner, C.J., Ballantyne, C.L., Randall, D.J., Val, A.L., 1995. Air breathing in the armoured catfish (*Hoplosternum littorale*) as an adaptation to hypoxic, acidic, and hydrogen sulphide rich waters. *Can. J. Zool.* 73, 739–744.
- Burggren, W.W., 1979. Biomodal gas exchange during variation in environmental oxygen and carbon dioxide in the air breathing fish *Trichogaster trichopterus*. *J. Exp. Biol.* 82, 197–213.
- Burggren, W.W., 1982. “Air gulping” improves blood oxygen transport during aquatic hypoxia in the Goldfish *Carassius auratus*. *Physiol. Zool.* 55, 327–334.
- Burleson, M.L., Milsom, W.K., 1993. Sensory receptors in the first gill arch of rainbow trout. *Respir. Physiol.* 93, 97–110.
- Burleson, M.L., Smatresk, N.J., 1990. Evidence for two oxygen-sensitive chemoreceptor loci in channel catfish, *Ictalurus punctatus*. *Physiol. Zool.* 63, 208–221.
- Burleson, M.L., Smatresk, N.J., 2000. Branchial chemoreceptors mediate ventilatory responses to hypercapnic acidosis in channel catfish. *Comp. Biochem. Physiol.* (125A), 403–414.
- Burleson, M.L., Smatresk, N.J., Milsom, W.K., 1992. Afferent inputs associated with cardioventilatory control in fish. In: In: Randall, D.J., Farrell, A.P. (Eds.), *Fish Physiology Vol. XIIB*. Academic Press, New York, pp. 389–426.
- Burleson, M.L., Carlton, A.L., Silva, P.E., 2002. Cardioventilatory effects of acclimatization to aquatic hypoxia in channel catfish. *Respir. Physiol. Neurobiol.* 131, 223–232.
- Butler, P.J., Taylor, E.W., 1971. Response of the dogfish (*Scyliorhinus canicula* L.) to slowly induced and rapidly induced hypoxia. *Comp. Biochem. Physiol.* (39A), 307–323.
- Butler, P.J., Taylor, E.W., Short, S., 1977. The effect of sectioning cranial nerves V, VII, IX and X on the cardiac response of the dogfish *Scyliorhinus canicula* to environmental hypoxia. *J. Exp. Biol.* 69, 233–245.
- Carter, G.S., 1931. Aquatic and aerial respiration in animals. *Biol. Rev.* 6, 1–35.
- Chapman, L.J., McKenzie, D.J., 2009. Behavioral responses and ecological consequences. In: In: Richards, J.G., Farrell, A.P., Brauner, C.J. (Eds.), *Fish Physiology: Hypoxia*, vol. 27. Elsevier, San Diego, pp. 25–77.
- Clarke, A., Johnston, N.M., 1999. Scaling of metabolic rate with body mass and temperature in teleost fish. *J. Anim. Ecol.* 68, 893–905.
- Coolidge, E.H., Ciuhandu, C.S., Milsom, W.K., 2008. A comparative analysis of putative oxygen-sensing cells in the fish gill. *J. Exp. Biol.* 211, 1231–1242.
- Crocker, C.E., Farrell, A.P., Gamperl, A.K., Cech, J.J., 2000. Cardiorespiratory responses of white sturgeon to environmental hypercapnia. *Am. J. Phys.* 279, R617–R628.
- Daxboeck, C., Holeton, G.F., 1978. Oxygen receptors in the rainbow trout, *Salmo gairdneri*. *Can. J. Zool.* 56, 1254–1259.
- Dehadrai, P.V., Tripathi, S.D., 1976. Environment and ecology of freshwater air-breathing teleosts. In: Hughes, G.M. (Ed.), *Respiration of Amphibious Vertebrates*. Academic Press, London, pp. 39–72.
- Dejours, P., 1994. Environmental factors as determinants in bimodal breathing: an introductory overview. *Am. Zool.* 34, 178–183.
- DeLaney, R.G., Lahiri, S., Fishman, A.P., 1974. Aestivation of the African lungfish *Protopterus aethiopicus*: cardiovascular and respiratory functions. *J. Exp. Biol.* 61, 111–128.
- DeLaney, R.G., Shub, C., Fishman, A.P., 1976. Haematologic observations on the aquatic and aestivating African lungfish *Protopterus aethiopicus*. *Copeia* 1976, 423–434.
- DeLaney, R.G., Lahiri, S., Hamilton, R., Fishman, A.P., 1977. Acid-base balance and plasma composition in the aestivating lungfish (*Protopterus*). *Am. J. Phys.* 232, R10–R17.
- Diaz, R.J., 2001. Overview of hypoxia around the world. *J. Environ. Qual.* 30, 275–281.
- Diaz, R.J., Breitburg, D.L., 2009. Hypoxia. In: In: Richards, J.G., Farrell, A.P., Brauner, C.J. (Eds.), *Fish Physiology: Hypoxia*, vol. 27. Elsevier, San Diego, pp. 1–23.
- Driedzic, W.R., Hochachka, P.W., 1978. Metabolism in fish during exercise. In: In: Hoar, W.S., Randall, D.J. (Eds.), *Fish Physiology: Locomotion*, vol. 7. Academic Press, New York, pp. 503–543.
- Eduardo, J., Bicudo, P.W., Johansen, K., 1979. Respiratory gas exchange in the air breathing fish, *Synbranchus marmoratus*. *Environ. Biol. Fishes* 4, 55–64.
- Farmer, C.G., Jackson, D.C., 1998. Air-breathing during activity in the fishes *Amia calva* and *Lepisosteus oculatus*. *J. Exp. Biol.* 201, 943–948.
- Farrell, A.P., Clutterham, S., 2003. On-line venous oxygen tensions in rainbow trout during graded exercise at two acclimation temperatures. *J. Exp. Biol.* 206, 487–496.
- Fernandes, M.N., Rantin, F.T., 1994. Relationships between oxygen availability and metabolic cost of breathing in Nile tilapia (*Oreochromis niloticus*): aquacultural consequences. *Aquaculture* 127, 339–346.
- Fernandes, M.N., Rantin, F.T., Kalinin, A.L., Moron, S.E., 1994. Comparative study of gill dimensions of three erythrinid species in relation to their respiratory function. *Can. J. Zool.* 72, 160–165.
- Florindo, L.H., Reid, S.G., Kalinin, A.L., Milsom, W.K., Rantin, F.T., 2004. Cardiorespiratory reflexes and aquatic surface respiration in the neotropical fish tambaqui (*Colossoma macropomum*): acute responses to hypercarbia. *J. Comp. Physiol.* (174B), 319–328.
- Florindo, L.H., Leite, C.A.C., Kalinin, A.L., Reid, S.G., Milsom, W.K., Rantin, F.T., 2006. The role of branchial and orobranchial O<sub>2</sub> chemoreceptors in the control of aquatic surface respiration in the neotropical fish tambaqui (*Colossoma macropomum*): progressive responses to prolonged hypoxia. *J. Exp. Biol.* 209, 1709–1715.
- Fritsche, R., Nilsson, S., 1993. Cardiovascular and ventilatory control during hypoxia. In: Rankin, J.C., Jensen, F.B. (Eds.), *Fish Ecophysiology*. Chapman & Hill, London, pp. 180–206.
- Fritsche, R., Axelsson, M., Franklin, C.E., Grigg, G.G., Holmgren, S., Nilsson, S., 1993. Respiratory and cardiovascular responses to hypoxia in the Australian lungfish. *Respir. Physiol.* 94, 173–187.

- Gee, J.H., 1980. Respiratory patterns and antipredator responses in the central mudminnow, *Umbra limi*, a continuous, facultative, air-breathing fish. *Can. J. Zool.* 58, 819–827.
- Gee, J., Gee, P., 1995. Aquatic surface respiration, buoyancy control and the evolution of air-breathing in gobies (Gobiidae: pisces). *J. Exp. Biol.* 198, 79–89.
- Gee, J.H., Graham, J.B., 1978. Respiratory and hydrostatic functions of the intestine of the catfishes *Hoplosternum thoracatum* and *Brochis splendens* (Callichthyidae). *J. Exp. Biol.* 74, 1–16.
- Geiger, S.P., Torres, J.J., Crabtree, R.E., 2000. Air breathing and gill ventilation frequencies in juvenile tarpon, *Megalops atlanticus*: responses to changes in dissolved oxygen, temperature, hydrogen sulfide, and pH. *Environ. Biol. Fishes* 59, 181–190.
- Gilmour, K.M., 2001. The CO<sub>2</sub>/pH ventilatory drive in fish. *Comp. Biochem. Physiol.* (130A), 219–240.
- Gilmour, K.M., Perry, S.F., 1996. Effects of metabolic acid–base disturbances and elevated catecholamines on the acid–base disequilibrium in the arterial blood of rainbow trout. *J. Exp. Biol.* 274, 281–290.
- Gilmour, K.M., Perry, S.F., 2006. Branchial chemoreceptor regulation of cardiorespiratory function. In: Hara, T., Zielinski, B. (Eds.), *Fish Physiology: Sensory Systems Neuroscience*, vol. 25. Elsevier, San Diego, pp. 97–151.
- Gilmour, K.M., Milsom, W.K., Rantin, F.T., Reid, S.G., Perry, S.F., 2005. Cardiorespiratory responses to hypercarbia in tambaqui (*Colossoma macropomum*): chemoreceptor orientation and specificity. *J. Exp. Biol.* 208, 1095–1107.
- Glass, M.L., Ishimatsu, A., Johansen, K., 1986. Responses of aerial ventilation to hypoxia and hypercapnia in *Channa argus*, an air-breathing fish. *J. Comp. Physiol.* (156B), 425–430.
- Gordon, M.S., Olson, E.C., 1994. *The Invasions of the Land*. Columbia University Press, New York.
- Graham, J.B., 1983. The transition to air breathing in fishes: II. Effects of hypoxia acclimation on the bimodal gas exchange of *Ancistrus chagresi* (Loricariidae). *J. Exp. Biol.* 102, 157–173.
- Graham, J.B., 1997. *Air-breathing Fishes: Evolution, Diversity and Adaptation*. Academic Press, San Diego.
- Graham, J.B., Baird, T.A., 1982. The transition to air breathing in fishes: I. Environmental effects on the facultative air breathing of *Ancistrus chagresi* and *Hypostomus plecostomus* (Loricariidae). *J. Exp. Biol.* 96, 53–67.
- Graham, J.B., Baird, T.A., 1984. The transition to air breathing in fishes: III. Effects of body size and aquatic hypoxia on the aerial gas exchange of the Swamp Eel *Synbranchus marmoratus*. *J. Exp. Biol.* 108, 357–375.
- Graham, J.B., Kramer, D.L., Pineda, E., 1978. Comparative respiration of an air-breathing and a non-air-breathing characid fish and the evolution of aerial respiration in characins. *Physiol. Zool.* 51, 279–288.
- Graham, M.S., Turner, J.D., Wood, C.M., 1990. Control of ventilation in the hypercapnic skate *Raja ocellata*: I. Blood and extracellular fluid. *Respir. Physiol.* 80, 259–277.
- Grigg, G.C., 1965. Studies on the Queensland lungfish, *Neoceratodus forsteri* (Krefft). *Aust. J. Zool.* 13, 243–254.
- Hara, T.J., 1992. *Fish Chemoreception*. Chapman & Hall, New York.
- Hayton, W.L., Barron, M.G., 1990. Rate-limiting barriers to xenobiotic uptake by the gill. *Environ. Toxicol. Chem.* 9, 151–157.
- Hedrick, M.S., Burleson, M.L., Jones, D.R., Milsom, W.K., 1991. An examination of central chemosensitivity in an air-breathing fish (*Amia calva*). *J. Exp. Biol.* 155, 165–174.
- Heisler, N., Toews, D.P., Holeton, G.F., 1988. Regulation of ventilation and acid–base status in the elasmobranch *Scyliorhinus stellaris* during hyperoxia-induced hypercapnia. *Respir. Physiol.* 71, 227–246.
- Hockman, D., Burns, A.J., Schlosser, G., Gates, K.P., Jevans, B., Mongera, A., Fisher, S., Unlu, G., Knapik, E.W., Kaufman, C., Mosimann, C., Zon, L.I., Lancman, J.J., Dong, P.D.S., Lickert, H., Tucker, A.S., Baker, C.V.H., 2017. Evolution of the hypoxia-sensitive cells involved in amniote respiratory reflexes. *eLife* 6, e21231.
- Hoffman, M., Harris, M.B., Taylor, B.E., 2009. Characterization and validation of aerial respiration and central CO<sub>2</sub> chemosensitivity in the Alaska blackfish, *Dallia pectoralis*. *FASEB J.* 23 598.16.
- Horn, M.H., Gibson, R.N., 1988. Intertidal fishes. *Sci. Am.* 256, 64–70.
- Horn, M.H., Riggs, C.D., 1973. Effects of temperature and light on the rate of air breathing of the Bowfin, *Amia calva*. *Copeia* 653–657 1973.
- Hsia, C.C.W., Schmitz, A., Lambert, M., Perry, S.F., Maina, J.N., 2013. Evolution of air breathing: oxygen homeostasis and the transitions from water to land and sky. *Compr. Physiol.* 3, 849–915.
- Hughes, B., Shelton, G., 1962. Respiratory mechanisms and their nervous control in fish. *Adv. Comp. Physiol. Biochem.* 1, 275–364.
- Hughes, G.M., Singh, B.N., 1970. Respiration in an air-breathing fish, the climbing perch *Anabas testudineus* block. *J. Exp. Biol.* 53, 265–280.
- Hughes, G.M., Singh, B.N., 1971. Gas exchange with air and water in an air-breathing catfish, *Saccobranchius* (= *Heteropneustes*) *fossilis*. *J. Exp. Biol.* 55, 667–682.
- Inger, R.F., 1957. Ecological aspects of the origins of the tetrapods. *Evolution* 11, 373–376.
- Iversen, N.K., Huong, D.T.T., Bayley, M., Wang, T., 2011. Autonomic control of the heart in the Asian swamp eel (*Monopterus albus*). *Comp. Biochem. Physiol.* 158, 485–489.
- Janssen, R.G., Randall, D.J., 1975. The effects of changes in pH and P<sub>CO2</sub> in blood and water on breathing in rainbow trout, *Salmo gairdneri*. *Respir. Physiol.* 25, 235–245.
- Jesse, M.J., Shub, C., Fishman, A.P., 1967. Lung and gill ventilation of the African lung fish. *Respir. Physiol.* 3, 267–287.
- Johansen, K., 1966. Air breathing in the teleost *Synbranchus marmoratus*. *Comp. Biochem. Physiol.* 18, 383–395.
- Johansen, K., 1970. Air breathing in fishes. In: Hoar, W.S., Randall, D.J. (Eds.), *Fish Physiology: The Nervous System, Circulation and Respiration*, vol. 4. Academic Press, New York, pp. 361–411.
- Johansen, K., Lenfant, C., 1967. Respiratory function in the South American lungfish, *Lepidosiren paradoxa* (Fitz). *J. Exp. Biol.* 46, 205–218.
- Johansen, K., Lenfant, C., 1968. Respiration in the African lungfish *Protopterus aethiopicus*. II. Control of breathing. *J. Exp. Biol.* 49, 453–468.
- Johansen, K., Lenfant, C., Grigg, G.C., 1967. Respiratory control in the lungfish, *Neoceratodus forsteri* (Krefft). *Comp. Biochem. Physiol.* 20, 835–854.
- Johansen, K., Lenfant, C., Schmidt-Nielsen, K., Petersen, J.A., 1968. Gas exchange and control of breathing in the electric eel, *Electrophorus electricus*. *Zeitschrift für vergleichende Physiologie* 61, 137–163.
- Johansen, K., Hanson, D., Lenfant, C., 1970. Respiration in a primitive air breather, *Amia calva*. *Respir. Physiol.* 9, 162–174.
- Johnston, I.A., Dunn, J., 1987. Temperature acclimation and metabolism in ectotherms with particular reference to teleost fish. *Symp. Soc. Exp. Biol.* 41, 67–93.
- Jonz, M.G., Nurse, C.A., 2003. Neuroepithelial cells and associated innervation of the zebrafish gill: a confocal immunofluorescence study. *J. Comp. Neurol.* 461, 1–17.
- Jonz, M.G., Fearon, I.M., Nurse, C.A., 2004. Neuroepithelial oxygen chemoreceptors of the zebrafish gill. *J. Physiol.* 560, 737–752.
- Jordan, J., 1976. The influence of body weight on gas exchange in the air-breathing fish, *Clarias batrachus*. *Comp. Biochem. Physiol.* (53A), 305–310.
- Jorgensen, B.B., 1984. The microbial sulfur cycle. In: Krumbein, W.E. (Ed.), *Microbial Geochemistry*. Blackwell Science Publishers, Oxford, pp. 91–124.
- Kemp, P.J., Searle, G.J., Hartness, M.E., Lewis, A., Miller, P., Williams, S., Wootton, P., Adriaensens, D., Peers, C., 2003. Acute oxygen sensing in cellular models: relevance to the physiology of pulmonary neuroepithelial and carotid bodies. *Anat. Rec. (270A)*, 41–50.
- Kent, B., Peirce II, E.C., 1978. Cardiovascular responses to changes in blood gases in dogfish shark, *Squalus acanthias*. *Comp. Biochem. Physiol.* 60, 37–44.
- Killen, S.S., Esbaugh, A.J., Martins, N.F., Rantin, F.T., McKenzie, D.J., 2018. Aggression supersedes individual oxygen demand to drive group air-breathing in a social catfish. *J. Anim. Ecol.* 87, 223–234.
- Kind, P.K., Grigg, G.C., Booth, D.T., 2002. Physiological responses to prolonged aquatic hypoxia in the Queensland lungfish *Neoceratodus forsteri*. *Respir. Physiol. Neurobiol.* 132, 179–190.
- Kincaid, R., Perry, S.F., 1991. The effects of catecholamines on ventilation in rainbow trout during external hypoxia or hypercapnia. *Respir. Physiol.* 84, 77–92.
- Kramer, D.L., 1987. Dissolved oxygen and fish behavior. *Env. Biol. Fish.* 18, 81–92.
- Kramer, D.L., McClure, M., 1982. Aquatic surface respiration, a widespread adaptation to hypoxia in tropical freshwater fishes. *Env. Biol. Fish.* 7, 47–55.
- Kramer, D.L., Mehegan, J.P., 1981. Aquatic surface respiration, an adaptive response to hypoxia in the guppy, *Poecilia reticulata* (Pisces, Poeciliidae). *Environ. Biol. Fishes* 6, 299–313.
- Kramer, D.L., Lindsey, C.C., Moodie, G.E.E., Stevens, E.D., 1978. The fishes and the aquatic environment of the central Amazon basin, with particular reference to respiratory patterns. *Can. J. Zool.* 56, 717–729.
- Kramer, D.L., Manley, D., Bourgeois, R., 1983. The effect of respiratory mode and oxygen concentration on the risk of aerial predation in fishes. *Can. J. Zool.* 61, 653–665.
- Lahiri, S., Szidon, J.P., Fishman, A.P., 1970. Potential respiratory and circulatory adjustments to hypoxia in the African lungfish. *Fed. Proc.* 29, 1141–1148.
- Lauren, D.J., 1991. The Fish Gill: a sensitive target for waterborne pollutants. In: Mayes, M.A., Barron, M.G. (Eds.), *Aquatic Toxicology and Risk Assessment*, vol. 14. American Society for Testing and Material, Philadelphia, pp. 223–244.
- Laurent, P., Perry, S.F., 1991. Environmental effects on fish gill morphology. *Physiol. Zool.* 64, 4–25.
- Laurent, P., Rouzeau, J.D., 1972. Afferent neural activity from the pseudobranch of teleosts. Effects of P<sub>O2</sub>, pH, osmotic pressure and Na<sup>+</sup> ions. *Respir. Physiol.* 14, 307–331.
- Lefevre, S., Huong, D.T.T., Wang, T., Phuong, N.T., Bayley, M., 2011. Hypoxia tolerance and partitioning of bimodal respiration in the striped catfish (*Pangasianodon hypophthalmus*). *Comp. Biochem. Physiol.* 158, 207–214.
- Lefevre, S., Huong, D.T.T., Phuong, N.T., Wang, T., Bayley, M., 2012. Effects of hypoxia on the partitioning of oxygen uptake and the rise in metabolism during digestion in the air-breathing fish *Channa striata*. *Aquaculture* 364–365, 137–142.
- Lefevre, S., Wang, T., Huong, D.T.T., Phuong, N.T., Bayley, M., 2013. Partitioning of oxygen uptake and cost of surfacing during swimming in the air-breathing catfish *Pangasianodon hypophthalmus*. *J. Comp. Physiol.* (183B), 215–221.
- Lefevre, S., Domenici, P., McKenzie, D.J., 2014. Swimming in air-breathing fishes. *J. Fish Biol.* 84, 661–681.
- Lefevre, S., Bayley, M., McKenzie, D.J., 2016. Measuring oxygen uptake in fishes with bimodal respiration. *J. Fish Biol.* 88, 206–231.
- Lehtonen, H., 1996. Potential effects of global warming on northern European freshwater fish and fisheries. *Fish. Manag. Ecol.* 3, 59–71.
- Lenfant, C., Johansen, K., Grigg, G.C., 1966. Respiratory properties of blood and pattern of gas exchange in the lungfish. *Respir. Physiol.* 2, 1–21.
- Lin, H., Randall, D.J., 1990. The effect of varying water pH on the acidification of expired water in rainbow trout. *J. Exp. Biol.* 149, 149–160.
- Little, C., 1983. *The Colonisation of Land: Origins and Adaptations of Terrestrial Animals*. Cambridge University Press, Cambridge.
- Little, C., 1990. *The Terrestrial Invasion*. Cambridge University Press, Cambridge.
- Lomholt, J.P., Johansen, K., 1974. Control of breathing in *Amphipnonus cuchia*, an amphibious fish. *Respir. Physiol.* 21, 325–340.
- Lomholt, J.P., Johansen, K., 1979. Hypoxia acclimation in Carp: how it affects O<sub>2</sub> uptake, ventilation, and O<sub>2</sub> extraction from water. *Physiol. Zool.* 52, 38–49.
- Long, J.A., 1995. *The Rise of Fishes: 500 Million Years of Evolution*. Johns Hopkins University Press, Baltimore.
- Lopes, J.M., Bojink, C.L., Florindo, L.H., Leite, C.A.C., Kalinin, A.L., Milsom, W.K., Rantin, F.T., 2010. Hypoxic cardiorespiratory reflexes in the facultative air-breathing fish jeju (*Hoplerthrinus unitaeniatus*): role of branchial O<sub>2</sub> chemoreceptors. *J. Comp.*

- Physiol. (180B), 797–811.
- Mattias, A.T., Rantin, F.T., Fernandes, M.N., 1998. Gill respiratory parameters during progressive hypoxia in the facultative air-breathing fish, *Hypostomus regani* (Loricariidae). *Comp. Biochem. Physiol.* (120A), 311–315.
- McCue, M.D., 2006. Specific dynamic action: a century of investigation. *Comp. Biochem. Physiol.* (144A), 381–394.
- McKendry, J.E., Perry, S.F., 2001. Cardiovascular effects of hypercarbia in rainbow trout (*Oncorhynchus mykiss*): a role for externally oriented chemoreceptors. *J. Exp. Biol.* 204, 115–125.
- McKendry, J.E., Milsom, W.K., Perry, S.F., 2001. Branchial CO<sub>2</sub> receptors and cardiorespiratory adjustments during hypercarbia in Pacific spiny dogfish (*Squalus acanthias*). *J. Exp. Biol.* 204, 1519–1527.
- McKenzie, D.J., Burleson, M.L., Randall, D.J., 1991a. The effects of branchial denervation and pseudobranch ablation on cardioventilatory control in an air-breathing fish. *J. Exp. Biol.* 161, 347–365.
- McKenzie, D.J., Aota, S., Randall, D.J., 1991b. Ventilatory and cardiovascular responses to blood pH, plasma PCO<sub>2</sub>, blood O<sub>2</sub> content and catecholamines in an air-breathing fish, *Amia cava*. *Physiol. Zool.* 64, 432–450.
- McKenzie, D.J., Campbell, H.A., Taylor, E.W., Micheli, M., Rantin, F.T., Abe, A.S., 2007. The autonomic control and functional significance of the changes in heart rate associated with air breathing in the jeju, *Hoplerythrinus unitaeniatus*. *J. Exp. Biol.* 210, 4224–4232.
- McKenzie, D.J., Steffensen, J.F., Taylor, E.W., Abe, A.S., 2012. The contribution of air breathing to aerobic scope and exercise performance in the banded knifefish *Gymnotus carapo* L. *J. Exp. Biol.* 215, 1323–1330.
- McKenzie, D.J., Belão, T.C., Killen, S.S., Rantin, F.T., 2016. To boldly gulp: standard metabolic rate and boldness have context-dependent influences on risk-taking to breathe air in a catfish. *J. Exp. Biol.* 218, 3762–3770.
- McMahon, B.R., Burggren, W.W., 1987. Respiratory physiology of intestinal air breathing in the teleost fish *Misgurnus anguillicaudatus*. *J. Exp. Biol.* 133, 371–393.
- Milsom, W.K., 1995a. Regulation of respiration in lower vertebrates: role of CO<sub>2</sub>/pH chemoreceptors. In: Heisler, N. (Ed.), *Advances in Comparative and Environmental Physiology*, vol. 22. Springer-Verlag, Berlin, pp. 62–104.
- Milsom, W.K., 1995b. The role of CO<sub>2</sub>/pH chemoreceptors in ventilatory control. *Braz. J. Med. Biol. Res.* 28, 1147–1160.
- Milsom, W.K., 1997. Control of breathing in fish: role of chemoreceptors. In: Val, A.L., Almeida-Val, V.M., Randall, D.J. (Eds.), *Physiology and Biochemistry of the Fishes of the Amazon*. INPA, Manaus, pp. 359–377.
- Milsom, W.K., 2012. New insights into gill chemoreception: receptor distribution and roles in water and air breathing fish. *Respir. Physiol. Neurobiol.* 184, 326–339.
- Milsom, W.K., Brill, R.W., 1986. Oxygen sensitive afferent information arising from the first gill arch of yellowfin tuna. *Respir. Physiol.* 66, 193–203.
- Milsom, W.K., Sundin, L., Reid, S., Kalinin, A.L., Rantin, F.T., 1999. Chemoreceptor control of cardiovascular reflexes. In: Val, A.L., Almeida-Val, V.M. (Eds.), *Biology of Tropical Fishes*. INPA, Manaus, pp. 363–374.
- Milsom, W.K., Reid, S.G., Rantin, F.T., Sundin, L., 2002. Extrabranchial chemoreceptors involved in respiratory reflexes in the neotropical fish *Colossoma macropomum* (the tambaqui). *J. Exp. Biol.* 205, 1765–1774.
- Nelson, J.A., Rios, F.S., Sanches, J.R., Fernandes, M.N., Rantin, F.T., 2007. Environmental influences on the respiratory physiology and gut chemistry of a facultative air-breathing, tropical herbivorous fish *Hypostomus regani* (Hering, 1905). In: Fernandes, M.N., Rantin, F.T., Glass, M.L., Kapoor, B.G. (Eds.), *Fish Respiration and Environment*. Sciences Publishers, Enfield, pp. 191–217.
- Neville, C.M., 1979. Ventilatory responses of rainbow trout (*Salmo gairdneri*) to increased H<sup>+</sup> ion concentration in blood and water. *Comp. Biochem. Physiol.* (63A), 373–376.
- Noronha-de-Souza, C.R., Bicego, K.C., Michel, G., Glass, M.L., Branco, L.G.S., Gargaglioni, L.H., 2006. Locus coeruleus is a central chemoreceptive site in toads. *Am. J. Phys.* 291, R997–R1006.
- Oliveira, R.D., Lopes, J.M., Sanches, J.R., Kalinin, A.L., Glass, M.L., Rantin, F.T., 2004. Cardiorespiratory responses of the facultative air-breathing fish jeju, *Hoplerythrinus unitaeniatus* (Teleostei, Erythrinidae), exposed to graded ambient hypoxia. *Comp. Biochem. Physiol.* (139A), 479–485.
- Panchen, A.L., 1980. *The Terrestrial Environment and the Origin of Land Vertebrates*. Academic Press, London.
- Pandian, T.J., Vivekanandan, E., 1976. Effects of feeding and starvation on growth and swimming activity in an obligatory air-breathing fish. *Hydrobiologia* 49, 33–39.
- Perry, S.F., Abdallah, S., 2012. Mechanisms and consequences of carbon dioxide sensing in fish. *Respir. Physiol. Neurobiol.* 184, 309–315.
- Perry, S.F., Gilmour, K.M., 1996. Consequences of catecholamine release on ventilation and blood oxygen transport during hypoxia and hypercapnia in an elasmobranch (*Squalus acanthias*) and a teleost (*Oncorhynchus mykiss*). *J. Exp. Biol.* 199, 2105–2118.
- Perry, S.F., Gilmour, K.M., 2002. Sensing and transfer of respiratory gases at the fish gill. *J. Exp. Zool.* 293, 249–263.
- Perry, S.F., Gilmour, K.M., 2006. Acid-base balance and CO<sub>2</sub> excretion in fish: unanswered questions and emerging models. *Respir. Physiol. Neurobiol.* 154, 199–215.
- Perry, S.F., Kinkead, R., 1989. The role of catecholamines in regulating arterial oxygen content during hypercapnic acidosis in rainbow trout (*Salmo gairdneri*). *Respir. Physiol.* 77, 365–378.
- Perry, S.F., McKendry, J.E., 2001. The relative roles of external and internal CO<sub>2</sub> versus H<sup>+</sup> in eliciting the cardiorespiratory responses of *Salmo salar* and *Squalus acanthias* to hypercarbia. *J. Exp. Biol.* 204, 3963–3971.
- Perry, S.F., Reid, S.G., 2002. Cardiorespiratory adjustments during hypercarbia in rainbow trout *Oncorhynchus mykiss* are initiated by external CO<sub>2</sub> receptors on the first gill arch. *J. Exp. Biol.* 205, 3357–3365.
- Perry, S.F., Wood, C.M., 1989. Control and coordination of gas transfer in fishes. *Can. J. Zool.* 67, 2961–2970.
- Perry, S.F., Kinkead, R., Gallaugh, P., Randall, D.J., 1989. Evidence that hypoxemia promotes catecholamine release during hypercapnic acidosis in Rainbow Trout (*Salmo gairdneri*). *Respir. Physiol.* 77, 351–364.
- Perry, S.F., Fritsche, R., Hoagland, T., Duff, D.W., Olson, K.R., 1999. The control of blood pressure during external hypercapnia in the rainbow trout (*Oncorhynchus mykiss*). *J. Exp. Biol.* 202, 2177–2190.
- Perry, S.F., Gilmour, K.M., Vulesevic, B., McNeill, B., Chew, S.F., Ip, Y.K., 2005a. Circulating catecholamines and cardiorespiratory responses in hypoxic lungfish (*Protopterus dolloi*): a comparison of aquatic and aerial hypoxia. *Physiol. Biochem. Zool.* 78, 325–334.
- Perry, S.F., Gilmour, K.M., Swenson, E.R., Vulesevic, B., Chew, S.F., Ip, Y.K., 2005b. An investigation of the role of carbonic anhydrase in aquatic and aerial gas transfer in the African lungfish *Protopterus dolloi*. *J. Exp. Biol.* 208, 3805–3815.
- Perry, S.F., Euverman, R., Wang, T., Loong, A.M., Chew, S.F., Ip, Y.K., Gilmour, K.M., 2008. Control of breathing in African lungfish (*Protopterus dolloi*): a comparison of aquatic and cocooned (terrestrialized) animals. *Respir. Physiol. Neurobiol.* 160, 8–17.
- Perry, S.F., Jonz, M.G., Gilmour, K.M., 2009. Oxygen sensing and the hypoxic ventilator response. In: Richards, J.G., Brauner, C.J., Farrell, A.P. (Eds.), *Hypoxia*. Academic Press, Amsterdam, pp. 193–251.
- Pettit, M.J., Beiting, T.L., 1985. Oxygen acquisition in the Reedfish, *Erpetoichthys calabaricus*. *J. Exp. Biol.* 114, 289–306.
- Porteus, C.S., Brink, D.L., Milsom, W.K., 2012. Neurotransmitter profiles in fish gills: putative gill oxygen chemoreceptors. *Respir. Physiol. Neurobiol.* 184, 316–325.
- Porteus, C.S., Pollack, J., Tzaneva, V., Kwong, R.W.M., Kumai, Y., Abdallah, S.J., Zaccaro, G., Lauriano, E.R., Milsom, W.K., Perry, S.F., 2015. A role for nitric oxide in the control of breathing in zebrafish (*Danio rerio*). *J. Exp. Biol.* 218, 3746–3753.
- Pörtner, H.O., Lannig, G., 2009. Oxygen and capacity limited thermal tolerance. In: Richards, J.G., Farrell, A.P., Brauner, C.J. (Eds.), *Fish Physiology: Hypoxia*, vol. 27. Elsevier, San Diego, pp. 143–191.
- Rahn, H., 1966. Aquatic gas exchange: theory. *Respir. Physiol.* 1, 1–12.
- Rahn, H., Rahn, K.B., Howell, B.J., Gans, C., Tenney, S.M., 1971. Air breathing of the garfish (*Lepisosteus osseus*). *Respir. Physiol.* 11, 285–307.
- Randall, D., 1982. The control of respiration and circulation in fish during exercise and hypoxia. *J. Exp. Biol.* 100, 275–288.
- Randall, D.J., Jones, D.R., 1973. The effects of deafferentation of the pseudobranch on the respiratory response to hypoxia and hyperoxia in the trout (*Salmo gairdneri*). *Respir. Physiol.* 17, 291–302.
- Randall, D.J., Burggren, W.W., Farrell, A.P., Haswell, M.S., 1981. *The Evolution of Air Breathing in Vertebrates*. Cambridge University Press, New York.
- Randall, D.J., Rummer, J.L., Wilson, J.M., Wang, S., Brauner, C.J., 2014. A unique mode of tissue oxygenation and the adaptive radiation of teleost fishes. *J. Exp. Biol.* 217, 1205–1214.
- Rantin, F.T., Kalinin, A.L., Glass, M.L., Fernandes, M.N., 1992. Respiratory responses to hypoxia in relation to mode of life of two erythrinid species (*Hoplias malabaricus* and *Hoplias lacerdae*). *J. Fish Biol.* 41, 805–812.
- Reid, S.G., Sundin, L., Kalinin, A.L., Rantin, F.T., Milsom, W.K., 2000. Cardiovascular and respiratory reflexes in the tropical fish, traira (*Hoplias malabaricus*): CO<sub>2</sub>/pH chemoresponses. *Respir. Physiol.* 120, 47–59.
- Reid, S.G., Perry, S.F., Gilmour, K.M., Milsom, W.K., Rantin, F.T., 2005. Reciprocal modulation of O<sub>2</sub> and CO<sub>2</sub> cardiorespiratory chemoreflexes in the tambaqui. *Respir. Physiol. Neurobiol.* 146, 175–194.
- Richards, J.G., 2011. Physiological, behavioral and biochemical adaptations of intertidal fishes to hypoxia. *J. Exp. Biol.* 214, 191–199.
- Richards, J.G., Farrell, A.P., Brauner, C.J. (Eds.), 2009. *Hypoxia*. Fish Physiology, vol. 27. Academic Press/Elsevier.
- Saha, N., Kharbuli, Z.Y., Bhattacharjee, A., Goswami, C., Häussinger, D., 2002. Effect of alkalinity (pH 10) on ureogenesis in the air-breathing walking catfish, *Clarias batrachus*. *Comp. Biochem. Physiol.* (132A), 353–364.
- Sanchez, A.P., Glass, M.L., 2001. Effects of environmental hypercapnia on pulmonary ventilation of the South American lungfish. *J. Fish Biol.* 58, 1181–1189.
- Sanchez, A., Soncini, R., Wang, T., Koldjaer, P., Taylor, E.W., Glass, M.L., 2001a. The differential cardio-respiratory responses to ambient hypoxia and systemic hypoxemia in the South American lungfish, *Lepidosiren paradoxa*. *Comp. Biochem. Physiol.* (130A), 677–687.
- Sanchez, A.P., Hoffmann, A., Rantin, F.T., Glass, M.L., 2001b. Relationship between cerebro-spinal fluid pH and pulmonary ventilation of the South American lungfish, *Lepidosiren paradoxa* (Fitz.). *J. Exp. Zool.* 290, 421–425.
- Sanchez, A.P., Giusti, H., Bassi, M., Glass, M.L., 2005. Acid-base regulation in the South American Lungfish *Lepidosiren paradoxa*: effects of prolonged hypercarbia on blood gases and pulmonary ventilation. *Physiol. Biochem. Zool.* 78, 908–915.
- Sayer, M.D.J., Davenport, J., 1991. Amphibious fish: why do they leave water? *Rev. Fish Biol.* 1, 159–181.
- Schultze, H.P., Trueb, L., 1991. *Origins of the Higher Groups of Tetrapods. Controversy and Consensus*. Comstock Publishing Associates, Ithaca.
- Secor, S.M., 2009. Specific dynamic action: a review of the postprandial metabolic response. *J. Comp. Physiol.* (179B), 1–56.
- Seymour, R.S., Christian, K., Bennett, M.B., Baldwin, J., Wells, R.M.G., Baudinette, R.V., 2004. Partitioning of respiration between the gills and air-breathing organ in response to aquatic hypoxia and exercise in the Pacific tarpon, *Megalops cyprinoides*. *Physiol. Biochem. Zool.* 77, 760–767.
- Seymour, R.S., Farrell, A.P., Christian, K., Clark, T.D., Bennett, M.B., Wells, R.M.G., Baldwin, J., 2007. Continuous measurement of oxygen tensions in the air-breathing organ of Pacific tarpon (*Megalops cyprinoides*) in relation to aquatic hypoxia and exercise. *J. Comp. Physiol.* (177B), 579–587.
- Shelton, G., Jones, D.R., Milsom, W.K., 1986. Control of breathing in ectothermic vertebrates. In: Cherniack, N.S., Widdicombe, J.G. (Eds.), *Handbook of Physiology*.



- Section 3: The Respiratory System, vol. 2. American Physiological Society, Bethesda, pp. 857–909 Control of Breathing, Part 2.
- Shingles, A., McKenzie, D.J., Claireaux, G., Domenici, P., 2005. Reflex cardioventilatory responses to hypoxia in the flathead gray mullet (*Mugil cephalus*) and their behavioral modulation by perceived threat of predation and water turbidity. *Physiol. Biochem. Zool.* 78, 744–755.
- Silva, G.S.F., Giusti, H., Branco, L.G., Glass, M.L., 2011. Combined ventilatory responses to aerial hypoxia and temperature in the South American lungfish *Lepidosiren paradoxa*. *J. Therm. Biol.* 36, 521–526.
- Silva, G.S.F., Ventura, D.A.D.N., Zena, L.A., Giusti, H., Glass, M.L., Klein, W., 2017. Effects of aerial hypoxia and temperature on pulmonary breathing pattern and gas exchange in the South American lungfish, *Lepidosiren paradoxa*. *Comp. Biochem. Physiol.* (207A), 107–115.
- Singh, B.N., 1976. Balance between aquatic and aerial respiration. In: Hughes, G.M. (Ed.), *Respiration in Amphibious Vertebrates*. Academic Press, London, pp. 125–164.
- Singh, B.N., Hughes, G.M., 1973. Cardiac and respiratory responses in the climbing perch *Anabas testudineus*. *J. Comp. Physiol.* 84, 205–226.
- Skaals, M., Skovgaard, N., Taylor, E.W., Leite, C.A.C., Abe, A.S., Wang, T., 2006. Cardiovascular changes under normoxic and hypoxic conditions in the air-breathing teleost *Symbbranchus marmoratus*: importance of the venous system. *J. Exp. Biol.* 209, 4167–4173.
- Smatresk, N.J., 1986. Ventilatory and cardiac reflex responses to hypoxia and NaCN in *Lepisosteus osseus*, an air-breathing fish. *Physiol. Zool.* 59, 385–397.
- Smatresk, N.J., 1988. Control of the respiratory mode in air-breathing fishes. *Can. J. Zool.* 66, 144–151.
- Smatresk, N.J., 1989. Chemoreflex control of respiration in an air-breathing fish. In: Lahiri, S., Foster, I.I.R.E., Davies, R.O., Pack, A.I. (Eds.), *Chemoreceptors and Chemoreflexes in Breathing – Cellular and Molecular Aspects*. Oxford University Press, London, pp. 29–52.
- Smatresk, N.J., Cameron, J.N., 1982. Respiration and acid-base physiology of the spotted gar, a bimodal breather: III. Response to a transfer from fresh water to 50% sea water, and control of ventilation. *J. Exp. Biol.* 96, 295–306.
- Smatresk, N.J., Smits, A.W., 1991. Effects of central and peripheral chemoreceptor stimulation on ventilation in the marine toad, *Bufo marinus*. *Respir. Physiol.* 83, 223–238.
- Smatresk, N.J., Burleson, M.L., Azizi, S.Q., 1986. Chemoreflexive responses to hypoxia and NaCN in longnose gar: evidence for two chemoreceptive loci. *Am. J. Phys.* 251, 116–125.
- Smith, H.W., 1930. Metabolism of the lung-fish, *Protopterus aethiopicus*. *J. Biol. Chem.* 88, 97–130.
- Smith, F.M., Davie, P.S., 1984. Effects of sectioning cranial nerves IX and X on the cardiac response to hypoxia in the coho salmon, *Oncorhynchus kisutch*. *Can. J. Zool.* 62, 766–768.
- Smith, F.M., Jones, D.R., 1982. The effect of changes in blood oxygen-carrying capacity on ventilation volume in the rainbow trout (*Salmo gairdneri*). *J. Exp. Biol.* 97, 325–334.
- Smith, R.S., Kramer, D.L., 1986. The effect of apparent predation risk on the respiratory behavior of the Florida gar (*Lepisosteus platyrhincus*). *Can. J. Zool.* 64, 2133–2136.
- Stevens, E.D., Holeton, G.F., 1978. The partitioning of oxygen uptake from air and from water by the large obligate air-breathing teleost pirarucu (*Arapaima gigas*). *Can. J. Zool.* 56, 974–976.
- Stevens, E., Randall, D.J., 1967. Changes of gas concentrations in blood and water during moderate swimming activity in rainbow trout. *J. Exp. Biol.* 46, 329–337.
- Sundin, L., Reid, S.G., Kalinin, A.L., Rantin, F.T., Milsom, W.K., 1999. Cardiovascular and respiratory reflexes in the tropical fish, traíra (*Hoplias malabaricus*): O<sub>2</sub> chemoreponses. *Respir. Physiol.* 116, 181–199.
- Sundin, L., Reid, S.G., Rantin, F.T., Milsom, W.K., 2000. Branchial receptors and cardiorespiratory reflexes in the neotropical fish, tambaqui (*Colossoma macropomum*). *J. Exp. Biol.* 203, 1225–1239.
- Takasusuki, J., 1994. Respostas respiratórias de cascudo preto, *Rhinelepis strigosa* (Agassiz, 1829) (Teleostei, Loricariidae), à hipóxia ambiental. Master Thesis. Federal University of São Carlos, SP, Brazil 78 pp.
- Teixeira, M.T., Armelin, V.A., Abe, A.S., Rantin, F.T., Florindo, L.H., 2015. Autonomic control of post-air-breathing tachycardia in *Clarias gariepinus* (Teleostei: clariidae). *J. Comp. Physiol.* (185B), 669–676.
- Thomas, S., Le Ruz, H., 1982. A continuous study of rapid changes in blood acid–base status of trout during variations of water P<sub>CO2</sub>. *J. Comp. Physiol.* 148, 123–130.
- Thomsen, M.T., Wang, T., Milson, W.K., Bayley, M., 2017. Lactate provides a strong pH-independent ventilatory signal in the facultative air-breathing teleost *Pangasianodon hypophthalmus*. *Sci. Rep.* 7, 6378.
- Todd, E.S., 1972. Hemoglobin concentration in a new air-breathing fish. *Comp. Biochem. Physiol.* (42A), 569–573.
- Völkel, S., Berenbrink, M., 2000. Sulphaemoglobin formation in fish: comparison between the haemoglobin of the sulphide-sensitive rainbow trout (*Oncorhynchus mykiss*) and of the sulphide-tolerant common carp (*Cyprinus carpio*). *J. Exp. Biol.* 203, 1047–1058.
- Wilkie, M.P., Wood, C.M., 1991. Nitrogenous waste excretion, acid-base regulation, and ionoregulation in Rainbow Trout (*Oncorhynchus mykiss*) exposed to extremely alkaline water. *Physiol. Zool.* 64, 1069–1086.
- Wilkie, M.P., Wood, C.M., 1996. The adaptations of fish to extremely alkaline environments. *Comp. Biochem. Physiol.* (113B), 665–673.
- Willmer, E.N., 1934. Some observations on respiration of certain tropical freshwater fishes. *J. Exp. Biol.* 11, 283–306.
- Wilson, R.J.A., Harris, M.B., Remmers, J.E., Perry, S.F., 2000. Evolution of air-breathing and central CO<sub>2</sub>/pH respiratory chemosensitivity: new insights from an old fish. *J. Exp. Biol.* 203, 3505–3512.
- Wood, C.M., Munger, R.S., 1994. Carbonic anhydrase injection provides evidence for the role of blood acid–base status in stimulating ventilation after exhaustive exercise in rainbow trout. *J. Exp. Biol.* 194, 225–253.
- Wood, C.M., Perry, S.F., 1985. Respiratory, circulatory and metabolic adjustments to exercise in fish. In: Gilles, R. (Ed.), *Circulation, Respiration and Metabolism*. Springer-Verlag, Berlin, pp. 1–22.
- Wood, C.M., Turner, J.D., Munger, R.S., Graham, M.S., 1990. Control of ventilation in the hypercapnic skate *Raja ocellata*: II. Cerebrospinal fluid and intracellular pH in the brain and other tissues. *Respir. Physiol.* 80, 279–298.
- Zacccone, G., Tagliaferro, G., Goniakowska-Witalinska, L., Fasulo, S., Ainis, L., Mauceri, A., 1989. Serotonin-like immunoreactive cells in the pulmonary epithelium of ancient fish species. *Histochemistry* 92, 61–63.
- Zacccone, G., Lauweryns, J.M., Fasulo, S., Tagliaferro, G., Ainis, L., Licata, A., 1992. Immunocytochemical localization of serotonin and neuropeptides in the neuroendocrine paraneurons of teleost and lungfish gills. *Acta Zool. (Stockholm)* 73, 177–183.
- Zacccone, G., Fasulo, S., Ainis, L., Licata, A., 1997. Paraneurons in the gills and airways of fishes. *Micro Res. Technol.* 37, 4–12.
- Zacccone, G., Ainis, L., Mauceri, A., Lo, Cascio, P., Lo Giudice, F., Fasulo, S., 2003. NANC nerves in the respiratory air sac and branchial vasculature of the Indian catfish, *Heteropneustes fossilis*. *Acta Histochem.* 105, 151–163.
- Zacccone, G., Mauceri, A., Fasulo, S., 2006. Neuropeptides and nitric oxide synthase in the gill and the air-breathing organs of fishes. *J. Exp. Zool.* (305A), 428–439.
- Zacccone, G., Lauriano, E.R., Kuciel, M., Capillo, G., Pergolizzi, S., Alesci, A., Ishimatsu, A., Ip, Y.K., Icardo, J.M., 2017. Identification and distribution of neuronal nitric oxide synthase and neurochemical markers in the neuroepithelial cells of the gill and the skin in the giant mudskipper, *Periophthalmodon schlosseri*. *Zoology* 125, 41–52.
- Zachar, P.C., Jonz, M.G., 2012. Neuroepithelial cells of the gill and their role in oxygen sensing. *Respir. Physiol. Neurobiol.* 184, 301–308.
- Zeraik, V.M., Belão, T.C., Florindo, L.H., Kalinin, A.L., Rantin, F.T., 2013. Branchial O<sub>2</sub> chemoreceptors in Nile tilapia *Oreochromis niloticus*: control of cardiorespiratory function in response to hypoxia. *Comp. Biochem. Physiol.* (166A), 17–25.