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

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### 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.

**Keywords :** Bimodal respiration, Chemoreception, Hypercapnia, Hypercarbia, Hypoxaemia, Hypoxia

## INTRODUCTION

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

10 Air is much richer in oxygen and fishes were the first vertebrates to evolve adaptations  
11 to breathe air, the fossil record dates to the late Silurian, ~420 million years ago. This predates  
12 the conquest of land by the ancestors of tetrapods, which evolved from lobe-finned fishes  
13 (Sarcopterygii) that resembled the extant Dipnoi (Panchen 1980; Little 1983; Little 1990;  
14 Gordon and Olson 1994; Long 1995; Schultze and Trueb 1991; Amemiya et al. 2013). Aquatic  
15 hypoxia or periodic emersion (caused by tidal oscillations or by unfavorable environmental  
16 conditions), are considered the two main circumstances that exerted evolutionary pressure for  
17 selection of aerial respiration in fishes (Inger 1957; Johansen 1970; Graham et al. 1978; Randall  
18 et al., 1981; Horn and Gibson 1988; Sayer and Davenport 1991; Graham 1997). However, it is  
19 important to emphasize that these were probably not the only selective pressures involved in  
20 the evolution of air-breathing, because it is a very diverse adaptation found in over 40 families,  
21 such that it seems to have evolved independently on numerous occasions (Randall et al., 1981;  
22 Graham 1997; Hsia et al. 2013). All air-breathing fishes are ‘bimodal breathers’, they possess  
23 gills that play a role in gas exchange and they vary in the extent to which they rely on air-  
24 breathing to meet their routine O<sub>2</sub> demands, from entirely ‘obligate’ to entirely ‘facultative’  
25 (Johansen 1970; Graham 1997; Lefevre et al., 2014).

26 Aquatic surface respiration (ASR) is a common adaptation of unimodal water-breathing  
27 fishes, that apparently helps to maintain O<sub>2</sub> uptake and aerobic metabolism during aquatic  
28 hypoxia. It consists of rising to the surface to ventilate the gills with the uppermost layer of  
29 water in contact with air, where there is constant diffusion of gases from the atmosphere  
30 (Kramer and Mehegan 1981; Kramer and McClure 1982). This adaptation is a reflex triggered  
31 by low O<sub>2</sub> availability and is believed to have led towards the evolution of true air-breathing in  
32 fishes (Shingles et al., 2005; Florindo et al., 2006; Chapman and McKenzie 2009; Richards  
33 2011). It is postulated that the ASR reflex may have favored the selection of air-breathing based  
34 on the following hypotheses: (1) ASR allowed individuals to survive in waters under severe

35 hypoxia; (2) some individuals inadvertently came into contact with the air during ASR (e.g. by  
36 inhaling it), which provided conditions for O<sub>2</sub> uptake from the air across vascularized epithelia,  
37 making it possible to select them as air-breathing organs (ABO) (Burggren 1982; Gee and Gee  
38 1995); and (3) ASR exposes the animals to predation, so individuals with the capacity to gulp  
39 and hold air could protect themselves from predators by temporarily returning to the depths,  
40 hence further favoring the evolution of adaptations for true aerial respiration (Kramer et al.  
41 1983; Smith and Kramer 1986; Gee and Gee 1995; Shingles et al. 2005; Chapman and  
42 McKenzie 2009).

43 Despite being a phylogenetically ancient specialization, aerial respiration retains great  
44 importance in the natural history of many extant fish species, especially in tropical freshwaters  
45 that can become hypoxic due to reduced O<sub>2</sub> capacitance at high temperatures (Rahn 1966;  
46 Kramer et al. 1978; Graham 1997; Diaz and Breitburg 2009; Pörtner and Lannig 2009), a  
47 condition that may be intensified by climate global change (Lehtonen 1996; Diaz 2001; Diaz  
48 and Breitburg 2009). In addition to its importance in O<sub>2</sub>-poor environments, air-breathing  
49 behavior in fishes can also supply O<sub>2</sub> to support aerobic activities such as exercise or digestion,  
50 although this has received less research attention than responses to hypoxia (Johansen 1970;  
51 Gee and Graham 1978; Stevens and Holeyton 1978; Dejours 1994; Brauner et al. 1995; Graham  
52 1997; Seymour et al. 2004; Seymour et al. 2007; McKenzie et al., 2012; Lefevre et al., 2014;  
53 Blasco et al. 2017).

54 Fishes possess specialized chemosensitive cells, located in the central and/or peripheral  
55 nervous system, capable of monitoring the partial pressure of O<sub>2</sub> ( $P_{O_2}$ ) or CO<sub>2</sub> ( $P_{CO_2}$ ), as well  
56 as the hydrogenionic potential (pH), in the blood and/or the environment (internally and/or  
57 externally oriented chemoreceptors) (see Hara 1992 and Milsom 2012 for reviews). These  
58 chemoreceptors modulate a wide range of behavioral and physiological adjustments that favor  
59 the survival of fishes during situations of hypoxia/hypoxaemia (i.e. reduced levels of O<sub>2</sub> in the  
60 environment or in the body, respectively) and hypercarbia/hypercapnia (i.e. increased levels of  
61 CO<sub>2</sub> in the environment or in the body, respectively), and air-breathing behavior is a prime  
62 example (Smatresk et al. 1986; McKenzie et al. 1991a; Milsom et al. 2002; Florindo et al. 2004;  
63 Florindo et al. 2006; Boijink et al. 2010; Lopes et al. 2010; Milsom 2012; Zeraik et al. 2013;  
64 Belão et al. 2015). There are differences in the location, distribution and orientation of these  
65 chemoreceptors among species, and their functions may vary depending on the specificity of  
66 these cells – such characteristics of fish chemoreceptors and their respective physiological  
67 influences have been previously reviewed by Gilmour (2001), Perry and Gilmour (2002),

68 Gilmour and Perry (2006), Milsom (2012), Perry and Abdallah (2012), Porteus et al. (2012)  
69 and Zachar and Jonz (2012).

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

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### STIMULATORS OF REFLEX AIR-BREATHING RESPONSES

81 Several factors stimulate air-breathing behaviors in fishes, which can be classified as either  
82 "systemic" or "environmental" (Fig. 1). Systemic factors are states of the organism that increase  
83 O<sub>2</sub> demand for aerobic metabolism, in particular warming, exercise and digestion, which then  
84 stimulate overall ventilatory activity. Environmental factors, on the other hand, are external  
85 conditions that increase the animals' O<sub>2</sub> demand; challenge respiratory gas exchange, and/or  
86 damage the fragile epithelium of the gill lamellae. This includes warming, hypoxia,  
87 hypercarbia, pH and pollutants. In species that are obligate air-breathers such factors will alter  
88 the intensity of aerial respiration whereas, in facultative air-breathers, such factors can trigger  
89 the air-breathing behavior as well as modulate its intensity.

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#### *Systemic factors*

92 The O<sub>2</sub> demands of fishes increase considerably during physical exercise, and this leads to an  
93 increase in air-breathing frequency in all species studied to date (Smatresk 1988; Lefevre et al.  
94 2014). Although this response would be expected in obligate air-breathers, it also occurs in all  
95 facultative species that have been studied, namely *Amia calva*, *Clarias gariepinus*, *Gymnotus*  
96 *carapo*, *Hoplosternum littorale*, *Lepisosteus oculatus*, *Megalops cyprinoides*, *Neoceratodus*  
97 *forsteri*, and *Pangasianodon hypophthalmus* (Grigg 1965; Gee and Graham 1978; Farmer and  
98 Jackson 1998; Seymour et al. 2004; Seymour et al. 2007; McKenzie et al. 2012; Lefevre et al.  
99 2013; Blasco et al. 2017). Food consumption also causes a transient increase in metabolic rate  
100 and O<sub>2</sub> demand, which can be extremely pronounced in some ectotherms (Secor 2009; McCue  
101 2006). There is evidence that obligate air-breathing fishes increase aerial respiration when

102 feeding in normoxic water, but this phenomenon is also expected to occur in facultative air-  
103 breathing fishes (Pandian and Vivekanandan 1976; Lefevre et al. 2012).

104 An increase in temperature is a combined systemic/environmental factor that stimulates  
105 air-breathing behavior in fishes because it increases the demand for O<sub>2</sub> in the tissues and  
106 requires increased O<sub>2</sub> delivery (Johansen et al. 1970; Rahn et al. 1971; Horn and Riggs 1973;  
107 Gee 1980; Graham and Baird 1982; Glass et al. 1986; Johnston and Dunn 1987; McMahon and  
108 Burggren 1987; Smatresk 1988; Clarke and Johnston 1999; Geiger et al. 2000; Silva et al.  
109 2017). Indeed, warming also lowers O<sub>2</sub> solubility in water, which reduces aquatic P<sub>O<sub>2</sub></sub> and  
110 additionally contributes to stimulate air-breathing behavior (Rahn 1966; Johansen et al. 1970;  
111 Graham and Baird 1982; McMahon and Burggren 1987). Nevertheless, Gee (1980), Glass et  
112 al. (1986) and Geiger et al. (2000) performed experiments in which water temperature was  
113 manipulated without affecting its P<sub>O<sub>2</sub></sub> levels (normoxia preserved by bubbling pure O<sub>2</sub> in the  
114 water when necessary), and observed an increase in air-breathing frequency associated with  
115 temperature elevation in *Channa argus*, *Megalops atlanticus* and *Umbra limi* – demonstrating  
116 that the stimulatory influence of temperature on this behavior is not a mere consequence of  
117 aquatic hypoxia.

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

127 The response may in fact be an inescapable chemoreflex, driven by internal  
128 chemoreceptors that monitor blood O<sub>2</sub> levels (Lefevre et al., 2014; McKenzie et al. 2016). It  
129 has been suggested that the spontaneous aperiodic episodes of air-breathing that are observed  
130 in many facultative air-breathing fishes in normoxia, when external O<sub>2</sub> chemoreceptors should  
131 be quiescent, are driven by the internal chemoreceptors: as blood O<sub>2</sub> levels fall after an air-  
132 breath, this eventually stimulates another breath (Shelton et al., 1986; Smatresk 1988). There is  
133 some indirect evidence for this ‘internal’ respiratory drive because, in the spiny catfish *C.*  
134 *garipepinus*, individuals with higher intrinsic metabolic rates and O<sub>2</sub> demands spontaneously  
135 breathed more air in normoxia (McKenzie et al. 2016). When fishes exercise at increasing

136 intensity, this progressively depletes venous blood of O<sub>2</sub> (Stevens and Randall 1967; Farrell  
 137 and Clutterham 2003). In bimodal breathing fishes, this venous hypoxaemia may cause  
 138 inescapable chemoreflexive stimulation of air-breathing, that increases with intensity as they  
 139 exercise harder (McKenzie et al. 2012; Lefevre et al. 2014). This is an area that deserves further  
 140 investigation.

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### *Environmental factors*

143 Fishes with facultative aerial respiration (both Actinopterygii and Sarcopterygii) typically shift  
 144 from gill ventilation to air-breathing as O<sub>2</sub> levels in water fall. This transition has been described  
 145 in numerous species, namely *A. calva*, *Anabas testudineus*, *Ancistrus chagresi*, *C. gariepinus*,  
 146 *Erpetoichthys calabaricus*, *Heteropneustes fossilis*, *Hoplerythrinus unitaeniatus*, *H. littorale*,  
 147 *Hypostomus plecostomus*, *Hypostomus regani*, *L. oculatus*, *Lepisosteus osseus*, *M. atlanticus*,  
 148 *M. cyprinoides*, *N. forsteri*, *P. hypophthalmus*, *Rhinelepis strigosa* and *Synbranchus*  
 149 *marmoratus*. The response is based on a chemoreflex, capable of providing sufficient O<sub>2</sub> to  
 150 maintain aerobic metabolism during aquatic hypoxia, and the transition from water to air-  
 151 breathing can be elicited either by external or internal [if environmental hypoxia induces  
 152 hypoxaemia] O<sub>2</sub> chemoreceptors (Hughes and Singh 1970; Johansen et al. 1970; Hughes and  
 153 Singh 1971; Gee and Graham 1978; Graham and Baird 1982; Smatresk and Cameron 1982;  
 154 Graham and Baird 1984; Pettit and Beitinger 1985; Smatresk 1986; Fritsche et al. 1993;  
 155 Takasusuki, 1994; Brauner et al. 1995; Mattias et al., 1998; Geiger et al. 2000; Kind et al. 2002;  
 156 Seymour et al. 2004; Affonso and Rantin 2005; McKenzie et al., 2007; Lopes et al. 2010; Belão  
 157 et al. 2011; Lefevre et al. 2011; Belão et al. 2015; Thomsen et al. 2017). It is interesting that,  
 158 regarding obligate air-breathing fishes, this response varies among actinopterygians (e.g.  
 159 *Electrophorus electricus* exhibits no change in air-breathing frequency during aquatic hypoxia  
 160 while *Trichogaster trichopterus* exhibits an increase) (Burggren 1979; Johansen et al. 1968)  
 161 but not among sarcopterygians (aquatic hypoxia does not change air-breathing frequency in  
 162 *Lepidosiren paradoxa*, *Protopterus aethiopicus* and *Protopterus dolloi*) (Johansen and Lenfant  
 163 1968; Sanchez et al. 2001a; Perry et al. 2005a). It is conceivable that obligate sarcopterygians  
 164 do not possess externally oriented O<sub>2</sub> chemoreceptors in the gills (Lahiri et al. 1970; Perry et  
 165 al. 2005a; Silva et al. 2017). However, the actinopterygian and sarcopterygian species just cited,  
 166 as well as the obligate air-breathing teleosts *C. argus* and *Monopterus cuchia*, show an increase  
 167 in air-breathing frequency when exposed to aerial hypoxia, which may have been triggered by  
 168 hypoxaemia through internally oriented chemoreceptors or by external chemoreceptors that  
 169 monitor the P<sub>O<sub>2</sub></sub> of air in the ABO (Johansen et al. 1968; Johansen and Lenfant 1968; Lomholt

170 and Johansen 1974; Burggren 1979; Glass et al. 1986; Sanchez et al. 2001a; Zacccone et al.  
171 2003; Zacccone et al. 2006; Perry et al. 2005a; Silva et al. 2011; Silva et al. 2017). Nonetheless,  
172 the facultative sarcopterygian *N. forsteri* did not exhibit this response after the injection of  
173 nitrogen into the lung (Johansen et al. 1967).

174 Aquatic hypercarbia can increase the frequency of aerial respiration in several species  
175 of fish with obligatory or facultative air-breathing, such as *A. chagresi*, *E. calabaricus*, *H.*  
176 *unitaeniatus*, *H. plecostomus*, *L. paradoxa*, *N. forsteri*, *P. aethiopicus*, *P. dolloi*, *S. marmoratus*  
177 and *T. trichopterus* (Johansen 1966; Johansen et al. 1967; Johansen and Lenfant 1968; Burggren  
178 1979; Graham and Baird 1982; Pettit and Beitinger 1985; Smatresk 1988; Sanchez and Glass  
179 2001; Sanchez et al. 2005; Perry et al. 2008; Boijink et al. 2010), although there are species  
180 where water CO<sub>2</sub> does not influence air-breathing behavior (e.g. *E. electricus*, *M. cuchia* and  
181 *P. hypophthalmus*) (Johansen et al. 1968; Lomholt and Johansen 1974; Thomsen et al. 2017).  
182 As CO<sub>2</sub> is much more soluble in water than O<sub>2</sub> (Rahn 1966) bimodal breathing fishes, including  
183 obligate air-breathing species with reduced gills, eliminate large amounts of metabolic CO<sub>2</sub>  
184 through water breathing (Lenfant et al. 1966; Johansen and Lenfant 1967; Babiker 1979; Perry  
185 et al. 2005b; Perry and Gilmour 2006). However, hypercarbia decreases or even reverses the  
186 CO<sub>2</sub> concentration gradient between water and blood, leading to an increase in plasma  $P_{CO_2}$ .  
187 The accumulation of CO<sub>2</sub> can then produce a respiratory acidosis that hinders blood O<sub>2</sub>  
188 transport through Bohr and Root effects, potentially challenging O<sub>2</sub> supply (Perry and Kinkead  
189 1989; Randall et al. 2014). In bimodal breathers, the accumulation of CO<sub>2</sub> may be alleviated by  
190 direct elimination of this gas to the atmosphere (Lefevre et al., 2016). This could explain why  
191 air-breathing reflexes can be triggered by internal and/or external chemoreceptors sensitive to  
192 CO<sub>2</sub>/H<sup>+</sup> (Boijink et al. 2010; Milsom 2012). Nonetheless, in *A. calva*, infusions of NH<sub>4</sub>HCO<sub>3</sub>  
193 into the dorsal aorta caused large increases in plasma  $P_{CO_2}$  and stimulated gill ventilation, but  
194 had no effect on air-breathing, indicating that aerial respiration is not stimulated by internal  
195 CO<sub>2</sub> in this species (McKenzie et al., 1991b).

196 Several studies demonstrated that aerial hypercarbia can also increase air-breathing  
197 frequency in some air-breathing fishes, such as *C. gariepinus*, *E. electricus*, *L. paradoxa*, *P.*  
198 *aethiopicus*, *Protopterus annectens* and *T. trichopterus* (Smith 1930; Johansen et al. 1968;  
199 Delaney et al. 1974; Delaney et al. 1976; Delaney et al. 1977; Babiker 1979; Burggren 1979;  
200 Smatresk 1988; Sanchez et al. 2005), while other studies showed that it can lead to a decrease  
201 (*P. aethiopicus* and *P. dolloi*) (Jesse et al. 1967), or even no changes (in *L. oculatus*, *L. paradoxa*  
202 and *P. dolloi*) (Smatresk and Cameron 1982; Sanchez and Glass 2001; Perry et al. 2008).  
203 Although many of these air-breathing responses may reveal direct chemosensitivity to CO<sub>2</sub>,

204 some of them may be an indirect effect of reductions in blood O<sub>2</sub> levels consequent to a  
205 respiratory acidosis. Also, the divergent responses may be explained by interspecific  
206 differences in the existence, orientation and function of O<sub>2</sub> and CO<sub>2</sub>/H<sup>+</sup> chemoreceptors, or by  
207 differences in CO<sub>2</sub> diffusivity at the gills and ABO of these species. The divergent results may  
208 also reflect differences in the CO<sub>2</sub> concentrations to which the animals were submitted, or even  
209 interspecific variation in the thresholds for CO<sub>2</sub> concentrations in water or air that stimulate air-  
210 breathing.

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

230         Finally, another environmental factor that can stimulate air-breathing in fishes is aquatic  
231 pollution. Contaminants in aquatic environments can be of anthropic origin or even natural,  
232 such as the hydrogen sulfide (H<sub>2</sub>S) that is mainly produced by bacterial sulfate reduction in  
233 sediments and anaerobic decomposition of organic matter (Jorgensen 1984). These compounds  
234 can stimulate aerial respiration in fishes for a variety of reasons. Hydrogen sulfide, for example,  
235 can reduce the affinity of hemoglobin for O<sub>2</sub> and impair the electron transport chain reaction  
236 by binding to cytochrome-c oxidase (Bagarinao and Vetter 1989; Bagarinao and Vetter 1992;  
237 Völkel and Berenbrink 2000; Affonso et al. 2002; Affonso et al. 2004), which may lead to both



238 hypoxaemia and an impaired ability to produce ATP, that in turn triggers an increase in air-  
239 breathing frequency (Brauner et al. 1995; Affonso and Rantin 2005). An alternative explanation  
240 would be that these animals use air-breathing as a strategy to partially and temporarily uncouple  
241 themselves from contaminated water (Brauner et al. 1995). Other pollutants, on the other hand,  
242 may irritate the gill epithelium of the animals, inducing changes in gill morphology (such as an  
243 increase in the number of interlamellar cells, cell hyperplasia and a greater production of  
244 mucus) that inhibits both xenobiotics absorption and branchial gas exchange (Hayton and  
245 Barron 1990; Laurén 1991; Laurent and Perry 1991; Alazemi et al. 1996; Biagini et al. 2009) –  
246 a situation that may increase the requirement for air breathing. The influence of all  
247 environmental and systemic factors on air-breathing behavior in facultative and obligate air-  
248 breathing fishes are summarized in Table 1.

249

### 250 **PERIPHERAL RECEPTORS MEDIATING AIR-BREATHING RESPONSES**

251 According to Milsom (2012), the location of peripheral chemoreceptors (gills, orobranchial  
252 cavity or elsewhere) and their orientation (external water or internal blood) are highly variable  
253 among fishes, whether unimodal or bimodal breathers. Their response modality ( $O_2$  or  $CO_2$ )  
254 and the reflex cardiorespiratory responses they engender (changes in gill ventilation rate or  
255 amplitude, heart rate, systemic vascular resistance, ASR or air-breathing) are also highly  
256 variable among species. Considering unimodal and bimodal breathers, there is a trend whereby  
257 the receptors involved in triggering changes in heart rate and gill ventilation rate in response to  
258 hypoxia and hypercarbia are preferentially located in the gills, whereas those that produce  
259 increases in gill ventilation amplitude are more extensive, often also being found in  
260 extrabranchial locations. Also, the distribution of  $CO_2$ -sensitive chemoreceptors in the gills  
261 tends to be more restricted than  $O_2$ -sensitive chemoreceptors, and the location of the  $CO_2$   
262 receptors may differ from the  $O_2$  receptors.

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

267

### 268 ***$O_2$ chemoreceptors***

269 During the dry season in tropical regions, fishes can be confined for weeks or even months to  
270 hypoxic and hypercarbic water. Aerial respiration is a common adaptation in fish species in  
271 these ecosystems (Dehadrai and Tripathi 1976; Kramer et al. 1978; Glass et al. 1986; Graham

272 1997). The ecological success of these fishes will depend on, amongst other things, their ability  
273 to sense O<sub>2</sub> in the environment and rapidly engage the metabolic, cardiovascular and ventilatory  
274 adjustments that match O<sub>2</sub> supply to their demand (Fritsche and Nilsson 1993). This, in turn  
275 depends on the central interaction of a variety of sensory inputs, including inputs from  
276 chemoreceptors that monitor external (water) and internal (blood) gas tensions and acid-base  
277 balance (Milsom 1997; Perry and Gilmour 2002).

278 The primary sites of peripheral O<sub>2</sub> sensing in fish appear to be the gills (including the  
279 pseudobranch in those species that possesses one) and orobranchial cavity (Laurent and  
280 Rouzeau 1972; Randall and Jones 1973; Butler et al. 1977; Daxboeck and Høleton 1978; Smith  
281 and Davie 1984; Smatresk et al. 1986; Burlleson and Smatresk 1990; McKenzie et al. 1991a;  
282 Burlleson and Milsom 1993; Sundin et al. 1999; Sundin et al. 2000; Milsom et al. 2002).  
283 Chemoreceptors in the orobranchial cavity are innervated by branches of the V<sup>th</sup> (trigeminal)  
284 and/or VII<sup>th</sup> (facial) cranial nerves, those on the pseudobranch by branches of the VII<sup>th</sup> and/or  
285 IX<sup>th</sup> (glossopharyngeal) cranial nerves, and those on the gill arches by branches of the IX<sup>th</sup>  
286 and/or X<sup>th</sup> (vagus) cranial nerves (Butler et al. 1977; Burlleson et al. 1992; Milsom et al. 2002;  
287 Reid et al. 2005). Some of these chemoreceptors respond only, or preferentially, to changes in  
288 external (water) O<sub>2</sub>, others respond only, or preferentially, to changes in internal (blood) O<sub>2</sub>,  
289 and some respond to both (Milsom and Brill 1986; Burlleson and Milsom 1993).

290 Highly sensitive mechanisms to monitor O<sub>2</sub> and acid-base balance are important for the  
291 survival of all vertebrate species. In fishes, histological and neurophysiological evidence  
292 indicates that this requirement is primarily filled by endoderm-derived neuroepithelial cells  
293 (NECs) in the gills (Porteus et al. 2012; Zachar and Jonz 2012; Hockman et al. 2017), however,  
294 other types of cells (which have not yet been characterized, but are neural crest-derived) may  
295 also be involved in this function (Hockman et al. 2017). So, as the predominant putative  
296 O<sub>2</sub>/CO<sub>2</sub>/H<sup>+</sup> chemoreceptors in fishes, NECs are mainly located on the gill filaments and  
297 secondary lamellae of all branchial arches and are innervated by afferent fibers of the central  
298 nervous system (Bailly et al. 2009; Porteus et al. 2012). Also, these cells may contain several  
299 neurotransmitters in their vesicles such as serotonin, acetylcholine, catecholamines, nitric  
300 oxide, hydrogen sulfide, leu-5-enkephalin, met-5-enkephalin and neuropeptide Y (Zaccone et  
301 al. 1992; Burlleson et al. 2002; Zaccone et al. 2003; Jonz and Nurse 2003; Jonz et al. 2004;  
302 Coolidge et al. 2008; Porteus et al. 2015; Zaccone et al. 2017) – although serotonin-containing  
303 NECs located along the gill filaments are the most abundant and are the only type that has been  
304 found in all fishes studied to date (Bailly et al. 2009; Porteus et al. 2012).

305           NECs are involved in local and central control of branchial functions through the  
306 paracrine production of serotonin and their synaptic relationships with the sympathetic and  
307 intrinsic branchial nervous systems (Bailly, 2009; Zacccone et al., 2017). In cell culture, some  
308 NECs respond immediately, and in a dose-dependent manner, to changes in local  $P_{O_2}$ . Thus,  
309 the hypoxic stimulation of the gill NECs seems to initiate the adaptive cardiorespiratory  
310 reflexes, which allows for  $O_2$  uptake and delivery to meet metabolic demands (Zachar and Jonz  
311 2012). Different responses can be triggered by distinct types of NECs, and it is not yet clear  
312 whether interspecific differences in the location of the NECs or in the responses triggered by  
313 each type of NECs might be attributable to differences in lifestyle (active versus sluggish fish),  
314 habitat (hypoxia tolerant versus intolerant fish) or phylogeny (Milsom et al. 1999; Perry and  
315 Gilmour 2002; Reid et al. 2005; Coolidge et al. 2008).

316           There is considerable amount of data concerning the  $O_2$  chemoreceptors that drive gill  
317 versus air-breathing reflexes in bimodal breathing fishes, or the cardiovascular adjustments that  
318 accompany these. The most commonly observed adjustments to hypoxia/hypoxaemia is a  
319 decrease in gill ventilation once air-breathing is initiated (Johansen et al. 1970; Singh 1976;  
320 Randall et al. 1981; Smatresk and Cameron 1982; Smatresk 1986; Shelton et al. 1986;  
321 McKenzie et al. 1991a; Graham 1997). Also, a hypoxic bradycardia, which is a hallmark in  
322 most fishes, gives way to a tachycardia following each air breath, often accompanied by  
323 increases in cardiac output and perfusion of the air-breathing organ (Johansen 1966; Johansen  
324 et al. 1968; Singh and Hughes 1973; Jordan 1976; Axelsson et al. 1989; Skals et al. 2006;  
325 McKenzie et al. 2007; Nelson et al. 2007; Lopes et al. 2010; Belão et al. 2011; Iversen et al.  
326 2011; Teixeira et al. 2015).

327           Sodium cyanide (NaCN) injections, which mimic hypoxia/hypoxaemia, have been used  
328 to elucidate the relative roles of externally versus internally  $O_2$ -sensing chemoreceptors in such  
329 responses. In *L. osseus*, external NaCN stimulates air-breathing but not gill ventilation rate and  
330 gill ventilation amplitude (Smatresk 1986; Smatresk et al. 1986). In *A. calva*, external NaCN  
331 stimulates air-breathing, gill ventilation rate and gill ventilation amplitude – although the  
332 stimulation of air-breathing occurs only when internal  $O_2$  chemoreceptors are costimulated  
333 (McKenzie et al. 1991a). Similarly, in *L. osseus*, when blood  $P_{O_2}$  levels are low, stimulation of  
334 external  $O_2$  chemoreceptors increases air-breathing events even further (Smatresk et al. 1986;  
335 Smatresk 1988). Internal injections of NaCN stimulate air-breathing, gill ventilation rate and  
336 gill ventilation amplitude in *L. osseus* (Smatresk 1986; Smatresk et al. 1986), but display no  
337 effect on air-breathing in *A. calva* (McKenzie et al. 1991a). In no instance did stimulation of  
338 either group of  $O_2$  receptors in this manner produced a decrease in gill ventilation in these

339 animals. In *L. osseus*, however, when internal  $P_{O_2}$  levels were low, simultaneous stimulation of  
340 external  $O_2$  chemoreceptors eliminated the increase in gill ventilation (Smatresk et al. 1986;  
341 Smatresk 1988). Complete branchial denervation (gills and pseudobranch) eliminates the  
342 cardiorespiratory responses to hypoxia/hypoxaemia in *L. osseus* and *A. calva* (Smatresk 1988;  
343 Smatresk 1989; McKenzie et al. 1991a).

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

364 Regarding sarcopterygians, there is one report that external nicotine injections stimulate  
365 air-breathing in the African lungfish (*P. aethiopicus*) (Johansen and Lenfant 1968), but such  
366 kind of external stimuli has more often failed to trigger this behavior in dipnoans (Johansen and  
367 Lenfant 1968; Sanchez et al. 2001a; Perry et al. 2005a). On the other hand, internal NaCN  
368 injections triggered air-breathing responses in *P. aethiopicus* (Lahiri et al. 1970), as well as  
369 exposure to aerial hypoxia did in *L. paradoxa*, *P. aethiopicus* and *P. dolloi* (Johansen and  
370 Lenfant 1968; Sanchez et al. 2001a; Perry et al. 2005a; Silva et al. 2011; Silva et al. 2017). As  
371 pulmonary NECs were already found in lungfish (Zaccone et al. 1989; Zaccone et al. 1997;  
372 Kemp et al. 2003), it is possible that the exposure to aerial hypoxia stimulated air-breathing in

373 these animals via external O<sub>2</sub> chemoreceptors in the lungs rather than internal O<sub>2</sub>  
374 chemoreceptors – however, at least in the case of *P. aethiopicus*, such air-breathing response is  
375 eliminated by complete gill denervation (Lahiri et al. 1970). The location, orientation and  
376 innervation of peripheral O<sub>2</sub>-sensitive chemoreceptors involved in the control of gill ventilation  
377 rate, gill ventilation amplitude and air-breathing in fishes with bimodal respiration are  
378 summarized in Tables 2, 3 and 4, respectively.

379

380

### *CO<sub>2</sub>/H<sup>+</sup> chemoreceptors*

381 Acute exposure of fish to aquatic hypercarbia typically elicits significant increases in gill  
382 ventilatory amplitude and/or gill ventilation rate, resulting in an increase in total gill ventilation  
383 (Janssen and Randall 1975; Thomas and Le Ruz 1982; Smith and Jones 1982; Reid et al. 2000;  
384 Burleson and Smatresk 2000; Perry and McKendry 2001; McKendry and Perry 2001;  
385 McKendry et al. 2001; Gilmour 2001; Milsom et al. 2002; Perry and Reid 2002). This is usually  
386 accompanied by a decrease in heart rate (Kent and Peirce 1978; Perry et al. 1999; Sundin et al.  
387 2000; Reid et al. 2000; Crocker et al. 2000; McKendry and Perry 2001; McKendry et al. 2001;  
388 Perry and Reid 2002) and increase in systemic vascular resistance (Perry et al. 1999; McKendry  
389 and Perry 2001). There is strong evidence that these responses arise from the stimulation of  
390 specific CO<sub>2</sub>/H<sup>+</sup> chemosensitive NECs and are not dependent on changes in water or blood O<sub>2</sub>  
391 concentration (Butler and Taylor 1971; Reid et al. 2000; Sundin et al. 2000; Heisler et al. 1988;  
392 Graham et al. 1990; Kinkead and Perry 1991; Milsom 1995a; Milsom 1995b; Perry and  
393 Gilmour 1996; Gilmour 2001; Burleson and Smatresk 2000; Milsom 2012).

394 At present, the cardiorespiratory responses to CO<sub>2</sub>/H<sup>+</sup> in fish are believed to arise  
395 primarily from receptors distributed throughout the gill arches innervated by the IX<sup>th</sup> and X<sup>th</sup>  
396 cranial nerves. It is clear that these receptors in the gills monitor the CO<sub>2</sub> in the water, but it is  
397 not clear whether they also respond to changes in the CO<sub>2</sub> of arterial blood. There is evidence  
398 to suggest both that they do (Janssen and Randall 1975; Wood and Perry 1985; Perry and Wood  
399 1989; Aota et al. 1990; Wood and Munger 1994; Gilmour and Perry 1996) and do not  
400 (McKenzie et al. 1991b; Perry et al. 1999; Sundin et al. 2000; Reid et al. 2000; McKendry et  
401 al. 2001; Perry and McKendry 2001; McKendry and Perry 2001; Perry and Reid 2002, Gilmour  
402 et al. 2005). Data suggest that the receptors responding to external stimuli respond specifically  
403 to changes in CO<sub>2</sub> in the water (not pH) (Neville 1979; Thomas and Le Ruz 1982; Sundin et al.  
404 2000; Reid et al. 2000), while to the extent that there is evidence for ventilatory responses  
405 arising from receptors responding to internal stimuli, there is a better correlation between the

406 changes in ventilation and changes in arterial pH rather than arterial CO<sub>2</sub> (Heisler et al. 1988;  
407 Graham et al. 1990; Wood et al. 1990; McKenzie et al. 1991b; Wood and Munger 1994).

408 McKenzie et al. (1991) observed that dorsal aortic infusions of HCl elicit air-breathing  
409 reflexes in *A. calva*, however, it is possible that internal H<sup>+</sup>-sensitive receptors are not involved  
410 in the control of this response because air-breathing was only triggered when blood O<sub>2</sub> content  
411 decreased below normoxic levels along with blood pH in these animals. The data of Boijink et  
412 al. (2010) indicate that the chemoreceptors eliciting gill ventilatory responses to hypercarbia in  
413 *H. unitaeniatus* are exclusively branchial (located primarily on the first gill arch), externally  
414 oriented, and respond specifically to changes in CO<sub>2</sub> and not H<sup>+</sup>. In this species, high levels of  
415 aquatic P<sub>CO2</sub> depressed gill ventilation and stimulated air-breathing. The chemoreceptors  
416 involved in stimulating air-breathing in response to hypercarbia also appeared to be branchial,  
417 distributed across all gill arches and responded specifically to changes in aquatic P<sub>CO2</sub>. This  
418 would suggest that chemoreceptor groups with different orientations – external water versus  
419 internal blood – are involved in eliciting air-breathing responses to hypercarbia and hypoxia  
420 (respectively) in *H. unitaeniatus*. With respect to sarcopterygians, Amin-Naves et al. (2007a)  
421 demonstrated that *L. paradoxa* presents peripheral CO<sub>2</sub>/H<sup>+</sup> chemoreceptors capable of  
422 modulating pulmonary ventilation, but did not report data on the location, orientation and  
423 innervation of these receptors.

424 As previously commented, aquatic hypercarbia induces an increase in gill ventilation in  
425 most air-breathing fishes (Johansen and Lenfant 1968; Perry et al. 2008; Boijink et al. 2010).  
426 Yet, in some species (such as *H. unitaeniatus*), if the increases in aquatic P<sub>CO2</sub> are large enough,  
427 they can inhibit gill ventilation and stimulate air-breathing (Johansen et al. 1967; Graham and  
428 Baird 1982; Graham 1997; Sanchez and Glass 2001; Sanchez et al. 2005; Boijink et al. 2010).  
429 In other species, however, increases in aquatic P<sub>CO2</sub> are without effect on gill ventilation  
430 (Johansen 1966; Todd 1972; McMahon and Burggren 1987) or air-breathing (Johansen et al.  
431 1968; Lomholt and Johansen 1974). Just as with aquatic P<sub>CO2</sub>, bimodal breathing fishes exhibit  
432 a wide range of air-breathing responses to increasing levels of P<sub>CO2</sub> in inspired air, such as an  
433 increase (Smith 1930; Johansen et al. 1968; Delaney et al. 1974; Delaney et al. 1976; Delaney  
434 et al. 1977; Babiker 1979; Burggren 1979; Smatresk 1988; Sanchez et al. 2005), a decrease  
435 (Jesse et al. 1967), or no change (Smatresk and Cameron 1982; Sanchez and Glass 2001; Perry  
436 et al. 2008).

437 The equivocal nature of the data raises questions about the existence and role of  
438 peripheral internally oriented CO<sub>2</sub>/H<sup>+</sup> sensitive chemoreceptors in driving gill ventilation or air-  
439 breathing in facultative and obligate air-breathing fishes. Clearly much remains to be

440 investigated to resolve this issue. To date, this has not been deeply investigated in any air-  
441 breathing species and it will be intriguing to study the extent to which similar trends appear in  
442 air-breathing primitive actinopterygians and sarcopterygians. To provide an overview, the  
443 location, orientation and innervation of peripheral  $\text{CO}_2/\text{H}^+$  sensitive chemoreceptors involved  
444 in the control of gill ventilation rate, gill ventilation amplitude and air-breathing in fishes with  
445 bimodal respiration are summarized in Tables 2, 3 and 4, respectively.

446

#### 447 **CENTRAL RECEPTORS MEDIATING AIR-BREATHING RESPONSES**

448 The presence of central  $\text{CO}_2/\text{H}^+$  chemoreceptors in fishes, especially in the air-breathing fishes,  
449 has been investigated because of the important role of these receptors in the control of  
450 ventilation in terrestrial vertebrates. In the descendants of the Sarcopterygii, the tetrapods,  
451 pulmonary ventilation is produced by a central pattern generator, whose activity is modulated  
452 by central and peripheral  $\text{CO}_2/\text{H}^+$  chemoreceptors (Branco et al. 1992; Branco et al. 1993;  
453 Milsom 1995a; Milsom 1995b; Noronha-de-Souza et al. 2006). Conversely, in Actinopterygii,  
454 there is little evidence for central chemoreceptors sensitive to  $\text{CO}_2/\text{H}^+$  influencing aerial  
455 respiration. Indeed, there is no evidence for the presence of such receptors in *A. calva* and *Dallia*  
456 *pectoralis* (Hedrick et al. 1991; Hoffman et al. 2009).

457 Another study, on an isolated brainstem preparation, showed that *L. osseus*, a primitive  
458 bony fish with bimodal respiration, possesses central sensitivity to  $\text{CO}_2/\text{H}^+$  that control air-  
459 breathing frequency but not gill ventilation rate (Wilson et al. 2000). It was observed that the  
460 isolated brainstem autonomously produces motor patterns that resemble that of gill ventilation  
461 and air-breathing, and that manipulations of the  $P_{\text{CO}_2}/\text{H}^+$  levels in the brainstem produced  
462 directly proportional changes in the frequency of air-breathing motor pattern (Wilson et al.  
463 2000). This was the first evidence of a central air-breathing pattern generator and central  
464 respiratory chemosensitivity to  $\text{CO}_2/\text{H}^+$  in an actinopterygian fish with aerial respiration.  
465 Wilson et al. (2000) speculated that the origin of the central rhythm generator for aerial  
466 respiration occurred before the divergence of the actinopterygian and sarcopterygian lineages.

467 Other evidence of the existence of central chemoreceptors in fishes was reported by  
468 Sanchez et al. (2001b) and Amin-Naves et al. (2007b) in the obligate sarcopterygian *L.*  
469 *paradoxa*. These studies demonstrated that lung ventilation increased substantially when  
470 cerebrospinal fluid (CSF)  $P_{\text{CO}_2}$  was raised from 21 to 42 mmHg, while pH of CSF was held  
471 constant at a normal control value of 7.45. Likewise, a decrease in the pH of the CSF from 7.45  
472 to 7.20 caused a large increase in ventilation at a constant  $P_{\text{CO}_2}$  (normocarbic value = 21  
473 mmHg). When associated, however, low pH and high  $P_{\text{CO}_2}$  in CSF (pH = 7.10 and  $P_{\text{CO}_2}$  = 42

474 mmHg) reduced ventilation. Consequently, the combined effect of a decrease in pH and  
475 increase in  $P_{\text{CO}_2}$  of CSF is not additive to ventilation (Amin-Naves et al. 2007b). These results  
476 are similar to those of previous studies in toads, wherein the perfusion of the fourth cerebral  
477 ventricle with acidic, hypercapnic and acidic-hypercapnic CSF elicited hyperventilation  
478 (Smatresk and Smits 1991; Branco et al. 1992; Branco et al. 1993) – in these animals, the  
479 combined effect of low pH and high  $P_{\text{CO}_2}$  in CSF was not additive to ventilation as well  
480 (Smatresk and Smits 1991).

481 Finally, although there is evidence for central chemosensitivity to  $\text{CO}_2/\text{H}^+$  in one air-  
482 breathing holostean (Wilson et al. 2000), it is generally considered that peripheral gill receptors  
483 are the predominant sites for detecting  $\text{CO}_2/\text{H}^+$  in actinopterygian fishes. In sarcopterygians, on  
484 the other hand, central  $\text{CO}_2/\text{H}^+$  chemoreceptors appear to have a more prominent role as in  
485 tetrapods (Burlison and Smatresk 2000; Reid et al. 2000; Sundin et al. 2000; Gilmour 2001;  
486 McKendry et al. 2001; Perry and Reid 2002; Amin-Naves et al. 2007a).

487

#### 488 **CONCLUSIONS AND RESEARCH PERSPECTIVES**

489 This review indicates that there is overall understanding of how peripheral and central  
490 chemoreceptors can drive cardiorespiratory reflexes in fishes with bimodal respiration. That is,  
491 peripheral receptors, innervated by cranial nerves, drive increased air-breathing in response to  
492 environmental hypoxia and hypercarbia. These receptors are, in general, sensitive to sensitive  
493 to  $\text{O}_2$  and/or  $\text{CO}_2/\text{H}^+$  levels in the blood and/or the environment. Increased  $\text{O}_2$  demand also  
494 stimulates air-breathing, which may be a reflex driven by reduced  $\text{O}_2$  levels in the blood, as the  
495 evidence for peripheral sensitivity to increased plasma  $P_{\text{CO}_2}$  remains equivocal. Air-breathing  
496 fishes also possess peripheral receptors that stimulate cardiac and gill ventilatory responses to  
497 hypoxia and hypercarbia, such as those found in unimodal water-breathing species but, in  
498 bimodal breathers, these receptors can sometimes cause responses that are different from the  
499 general unimodal pattern. Beyond these generalities, however, the existing data indicate that  
500 bimodal breathers show a great deal of interspecific variation in their reflex responses to  
501 dissolved gases, which is consistent with the fact that air-breathing has evolved independently  
502 on multiple occasions. There is the need to increase research in this area to see whether  
503 common patterns emerge across taxonomic groups. For example, to understand how  
504 information from the multiple different internally and externally oriented receptors is integrated  
505 to modify the relative intensity of aerial versus aquatic respiration. There is also a need for  
506 further research into central sensitivity to  $\text{CO}_2$  and  $\text{H}^+$  in sarcopterygian and actinopterygian



507 fishes. Although it appears to exist in bony fishes, more work is required to understand what  
508 role it plays in reflex cardioventilatory responses in conscious animals.

509 Finally, there is also now evidence that bimodal breathing fishes may breathe air for  
510 reasons that, at first sight, seem uncoupled from stimulation of peripheral or central receptors.  
511 McKenzie et al. (2016) found that, in normoxia, the intensity of spontaneous air-breathing was  
512 linked to individual boldness in a facultative air-breather, *C. gariepinus*, in a manner that was  
513 independent of their O<sub>2</sub> demand. Killen et al. (2017) found that aggression among individuals  
514 was a stronger driver of air-breathing than was oxygen demand in groups of *C. gariepinus*. It  
515 is not clear whether these drivers of air-breathing do in fact involve stimulation of peripheral  
516 receptors that monitor blood O<sub>2</sub> in the inter-breath interval (Shelton et al., 1986), with bold  
517 and/or aggressive individuals perhaps having a lower threshold for stimulation of a surfacing  
518 response. It is also possible, however, that once the reflex circuits for air-breathing have  
519 evolved, higher order central inputs may subsequently evolve that can influence the intensity  
520 of the behavior.

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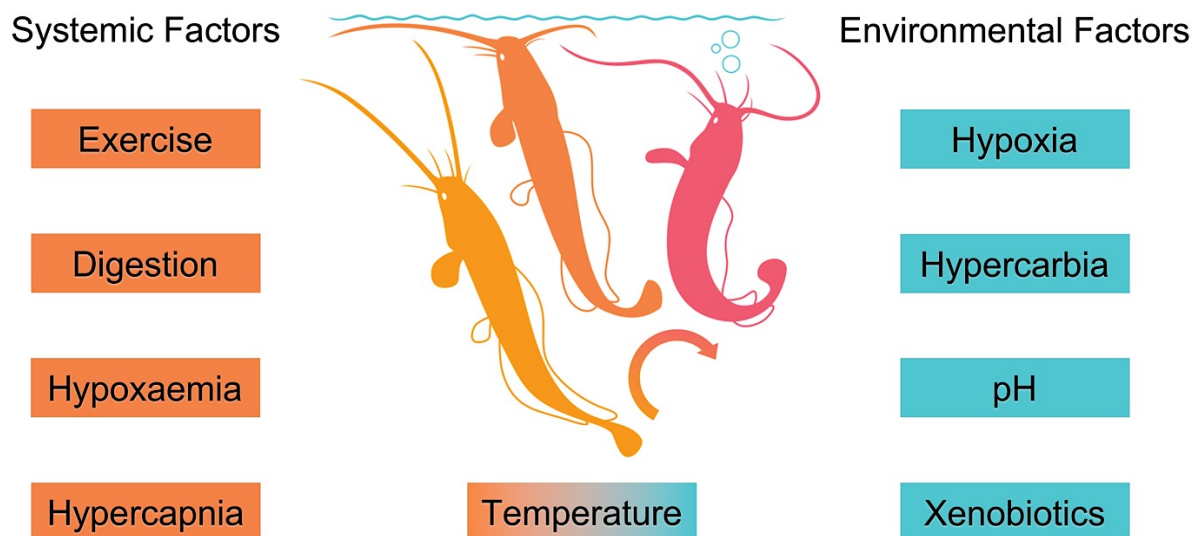
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FIGURE 1



**Figure 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.



**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 / Blood pH | Contaminants (H <sub>2</sub> S) |
|---------------------------|--|---------------------|-----------------|-----------------------|-----------------------------------|-------------------------|---------------------|------------------------------------|----------------------------------|---------------------------------|
| FACULTATIVE               | <i>Amia calva</i> (A)                  | + <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>Erpetoichthys calabaricus</i> (A)   |                     |                 |                       | + <sup>22</sup>                   |                         | + <sup>22</sup>     |                                    |                                  |                                 |
|                           | <i>Gymnotus carapo</i> (A)             | + <sup>49</sup>     |                 |                       |                                   |                         |                     |                                    |                                  |                                 |
|                           | <i>Heteropneustes fossilis</i> (A)     |                     |                 |                       | + <sup>10</sup>                   |                         |                     |                                    |                                  |                                 |
|                           | <i>Hoplerythrinus unitaeniatus</i> (A) |                     |                 |                       | + <sup>40, 44</sup>               |                         | + <sup>43</sup>     |                                    |                                  |                                 |
|                           | <i>Hoplosternum littorale</i> (A)      | + <sup>15</sup>     |                 |                       | + <sup>15, 29, 37</sup>           |                         |                     |                                    | + <sup>29</sup>                  | + <sup>29, 37</sup>             |
|                           | <i>Hypostomus plecostomus</i> (A)      |                     |                 |                       | + <sup>19</sup>                   |                         | + <sup>19</sup>     |                                    |                                  |                                 |
|                           | <i>Hypostomus regani</i> (A)           |                     |                 |                       | + <sup>31</sup>                   |                         |                     |                                    |                                  |                                 |
|                           | <i>Lepisosteus oculatus</i> (A)        | + <sup>30</sup>     |                 |                       | + <sup>20</sup>                   | + <sup>20</sup>         |                     |                                    | nc <sup>20</sup>                 |                                 |
|                           | <i>Lepisosteus osseus</i> (A)          |                     |                 | + <sup>11</sup>       | + <sup>24</sup>                   |                         |                     |                                    |                                  |                                 |
|                           | <i>Megalops atlanticus</i> (A)         |                     |                 | + <sup>32</sup>       | + <sup>32</sup>                   |                         |                     |                                    |                                  |                                 |
|                           | <i>Megalops cyprinoides</i> (A)        | + <sup>36, 41</sup> |                 |                       | + <sup>36</sup>                   |                         |                     |                                    |                                  |                                 |
|                           | <i>Misgurnus anguillicaudatus</i> (A)  |                     |                 | + <sup>25</sup>       |                                   |                         |                     |                                    |                                  |                                 |
|                           | <i>Neoceratodus forsteri</i> (S)       | + <sup>2</sup>      |                 |                       | + <sup>27, 35</sup>               |                         | nc <sup>5</sup>     | + <sup>5</sup>                     |                                  |                                 |
|                           | <i>Pangasianodon hypophthalmus</i> (A) | + <sup>50</sup>     |                 |                       | + <sup>46, 54</sup>               |                         |                     | nc <sup>54</sup>                   |                                  |                                 |
|                           | <i>Rhinelepis strigosa</i> (A)         |                     |                 |                       | + <sup>28</sup>                   |                         |                     |                                    |                                  |                                 |
|                           | <i>Synbranchus marmoratus</i> (A)      |                     |                 |                       | + <sup>21</sup> / nc <sup>3</sup> |                         |                     | + <sup>3</sup>                     |                                  |                                 |
| <i>Umbra limi</i> (A)     |  |                     | + <sup>18</sup> |                       |                                   |                         |                     |                                    |                                  |                                 |
| <i>Channa argus</i> (A)   |  |                     | + <sup>23</sup> |                       |                                   | + <sup>23</sup>         |                     |                                    |                                  |                                 |
| <i>Channa striata</i> (A) |  | + <sup>14, 48</sup> |                 |                       |                                   |                         |                     |                                    |                                  |                                 |
| OBLIGATORY                | <i>Electrophorus electricus</i> (A)    |                     |                 |                       | nc <sup>7</sup>                   | + <sup>7</sup>          | nc <sup>7</sup>     | + <sup>7</sup>                     |                                  |                                 |
|                           | <i>Lepidosiren paradoxa</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 cuchia</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</sup> / - <sup>4</sup>    |                                  |                                 |
|                           | <i>Protopterus annectens</i> (S)       |                     |                 |                       |                                   |                         |                     | + <sup>16</sup>                    |                                  |                                 |
|                           | <i>Protopterus dolloi</i> (S)          |                     |                 |                       | nc <sup>39</sup>                  | + <sup>39</sup>         | + <sup>42</sup>     | - <sup>4</sup> / nc <sup>42</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> Rahn et al. 1971; <sup>12</sup> Horn and Riggs 1973; <sup>13</sup> Lomholt 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 Beitinger 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> Takasusuki 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> Affonso 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> Bojijink 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> Lefevre 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.

**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   |
|--|--------------------------------|-------------|-------------|--|
| O <sub>2</sub> Chemoreceptors                  |                                |             |             |  |
| <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; Smatresk 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. |
| CO <sub>2</sub> /H <sup>+</sup> Chemoreceptors |                                |             |             |  |
| <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 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  |
|--|----------------------------------|-------------|-------------|---|
| O <sub>2</sub> Chemoreceptors                  |                                  |             |             |   |
| <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; Smatresk 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 |
| CO <sub>2</sub> /H <sup>+</sup> Chemoreceptors |                                  |             |             |   |
| <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   |
|--|--------------------------------|-------------|-------------|--|
| O <sub>2</sub> Chemoreceptors                  |                                |             |             |  |
| <i>Amia calva</i> (A)                          | Pseudobranch + All gill arches | (E*)        | VII, IX, X  | McKenzie et al. 1991a  |
| <i>Clarias gariepinus</i> (A)                  | First gill arch                | E + 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                | E* + I      | IX, X       | Smatresk 1986; Smatresk et al. 1986; Smatresk 1988; Smatresk 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. |
| <i>Protopterus aethiopicus</i> (S)             | All gill arches                | (E*) + I    | IX, X       | Lahiri et al. 1970   |
| CO <sub>2</sub> /H <sup>+</sup> Chemoreceptors |                                |             |             |  |
| <i>Hoplerythrinus unitaeniatus</i> (A)         | All gill arches                | E           | IX, X       | Boijink 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; \* In *A. calva* and *H. unitaeniatus*, external NaCN stimulated air-breathing only if blood  $P_{O_2}$  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  $P_{O_2}$  levels were low. In *P. aethiopicus* the effects of external stimuli are equivocal.