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# The acute humoral adrenergic stress response in fish: facts and fiction

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**Abstract**

The goal of this review is to discuss and clarify some of the issues currently being debated regarding the acute humoral adrenergic stress response in fish. The afferent limb of the response, consisting of catecholamine secretion into the circulation, occurs under conditions of extreme physiological impairment. During mild or moderate stress, however, circulating catecholamine levels generally do not change and thus are unlikely to play a role in the mediation of physiological/metabolic responses at such times. The mechanisms leading to catecholamine secretion during severe stress involve the classical sympathetic pre-ganglionic neuronal cholinergic pathway in addition to a multitude of non-cholinergic pathways of neuronal and humoral origin. With respect to the efferent limb of the acute stress response, there is considerable controversy surrounding the importance of circulating catecholamines on influencing physiological function. For example, the control of ventilation in fishes may be less dependent on circulating catecholamines than previously thought. On the other hand, the levels of catecholamines achieved in the circulation of trout during severe stress are indeed sufficient to markedly influence red blood cell and cardiovascular function. 

*Keywords:* Stress; Catecholamines; Adrenaline; Noradrenaline; Chromaffin tissue; Fish; Breathing; Cardiovascular; Red blood cell

## 1. Introduction

The secretion into the circulation of the catecholamine hormones, adrenaline and noradrenaline, occurs when fish experience acute severe stress. It is widely believed that

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under such conditions, an elevation of circulating catecholamine levels helps to minimise the detrimental effects of stress on physiological function (reviewed by Randall and Perry, 1992; Thomas and Perry, 1992; Epple, 1993; Wendelaar Bonga, 1997; Reid et al., 1998). The secretion of catecholamines into the blood and their interaction with physiological systems is termed the acute humoral adrenergic stress response. For convenience, this reflex response may be divided into two discrete components, an afferent limb comprising the secretory process itself, and an efferent limb that encompasses the physiological reactions elicited by the secreted catecholamines.

Although the acute humoral adrenergic stress response in fish has been the topic of extensive investigation (reviewed by Epple et al., 1989; Perry and Wood, 1989; Randall and Perry, 1992; Thomas and Perry, 1992; Gamperl et al., 1994; Reid et al., 1998), there are numerous misconceptions that exist concerning the nature, and physiological significance, of this response. In this brief review, an attempt is made to clarify some of these issues and distinguish fact from fiction with respect to both the afferent and efferent limbs of the acute adrenergic stress response. Although several other aspects of the adrenergic stress response remain contentious (e.g., the metabolic, osmoregulatory, and catecholaminotropic roles of circulating catecholamines; see above reviews), these topics fall beyond the scope of this focused review. Furthermore, while the origin and possible roles of circulating dopamine in fish are the subject of current investigation (Kraschinski et al., 1996), only the roles of the two primary circulating catecholamines (adrenaline and noradrenaline) are discussed.

## 2. The afferent limb

### *2.1. Is catecholamine release a general response to stress in fish?*

Over the last 30 years, a number of different conditions have been identified as being associated with elevated plasma catecholamine levels in fish. For example, stressors including air exposure, environmental hypoxia or hypercapnia, metabolic acidosis, exercise, handling, physical disturbance, anemia, anesthesia, and hypotension, have all been shown to evoke an increase in circulating catecholamines (Randall and Perry, 1992; Thomas and Perry, 1992; Gamperl et al., 1994; Reid et al., 1998). The wide variety of catecholamine-eliciting stressors has led to the perception that catecholamine secretion, like cortisol, is a general feature of the primary stress response in fish. However, a closer examination of the specific conditions under which catecholamines are released does not support this contention.

In general, fish do not release catecholamines in response to mild or moderate environmental hypoxia (Boutilier et al., 1988; Ristori and Laurent, 1989; Kinkead and Perry, 1990; Perry and Reid, 1992). Severe hypoxic conditions, air exposure, or prolonged moderate hypoxia are required to elicit a significant increase in plasma catecholamines (see Randall and Perry, 1992; Thomas and Perry, 1992 for references). Although blood acidosis resulting from either environmental hypercapnia (Perry et al., 1987, 1989) or acid infusion (Boutilier et al., 1986; Aota et al., 1990) has been correlated with catecholamine release, hypoxemia, rather than blood acidosis, appears to

be the proximate stimulus causing catecholamine release under such conditions (Perry et al., 1989; Aota et al., 1990). Hypoxemia is also likely to be the specific cause of catecholamine release observed with anemia (Iwama et al., 1987; Perry et al., 1989) and anesthesia (Iwama et al., 1989; Bernier and Randall, 1998). Whereas sustained aerobic exercise is not associated with changes in circulating catecholamine concentrations (Ristori and Laurent, 1985; Butler et al., 1986; Hughes et al., 1988), anaerobic burst swimming in a respirometer elicits an increase in plasma catecholamines (Primmett et al., 1986). Exhaustive exercise, a euphemism for violent chasing until exhaustion or prolonged grabbing of the tail, also results in hypoxemia and a significant increase in plasma catecholamines (Ristori and Laurent, 1985; Butler et al., 1986; Milligan and Wood, 1987; Tang and Boutilier, 1988; Perry et al., 1996). While a 20–25% reduction in the blood pressure of rainbow trout does not influence circulating catecholamines, acute hypotensive conditions that result in a 50% drop in blood pressure elicit a marked increase in plasma catecholamines (N.J. Bernier and S.F. Perry, unpublished observations). Overall, the evidence suggests that significant catecholamine release occurs only under conditions of severe stress. During milder perturbations, which are sometimes considered as stressful to fish (see Barton and Iwama, 1991 for review), plasma catecholamine levels remain essentially unchanged. Also, aside for the condition of severe acute hypotensive stress (see above), plasma catecholamine levels generally only increase significantly in teleosts under conditions that sharply lower blood oxygen content. Thus, physiological responses that are often attributed to circulating catecholamines during mild or moderate stress are almost certainly elicited by other means (see below). The role of circulating catecholamines during mild or moderate stress has been overstated and needs re-examining.

There is mounting evidence that during hypoxia, catecholamine release occurs abruptly at a critical value of $PaO_2$ corresponding to a reduction of hemoglobin (Hb)–$O_2$ saturation of approximately 50%, i.e., the $P_{50}$ value (Perry and Reid, 1992, 1994). By using temperature changes of the water or hypercapnia to experimentally manipulate the $P_{50}$ value of rainbow trout, the hypothesis that during hypoxemic stress, catecholamine release occurs at an $O_2$ content/saturation of approximately 50% was tested. Relative to 5°C-acclimated trout, fish acclimated to 15°C displayed a reduced Hb–$O_2$ affinity (increased $P_{50}$) but also exhibited an increased $PaO_2$ catecholamine release threshold during hypoxia (Perry and Reid, 1994). Similarly, relative to normocapnic fish, acclimating fish to environmental hypercapnia reduced Hb–$O_2$ affinity but also increased the $PaO_2$ catecholamine release threshold during hypoxic stress (Julio et al., 1999). In both experiments, independent of changes in Hb–$O_2$ affinity, the catecholamine release thresholds were approximately equal to 50–55% Hb–$O_2$ saturation. Comparison between fish species also supports the idea of a catecholamine release threshold corresponding to the in vivo $P_{50}$ value. Although hypoxia-elicited catecholamine release is initiated at markedly different $PaO_2$ values in rainbow trout and American eels, it is initiated abruptly at equivalent values of blood $O_2$ content corresponding to their respective $P_{50}$ values (Perry and Reid, 1992). Together, these results provide compelling evidence that a depression of blood oxygen content, rather than a reduction in oxygen partial pressure, is the proximate stimulus for catecholamine release during a variety of severe hypoxemic stressors.

### *2.2. Is catecholamine release controlled largely by cholinergic nerve fibers?*

In teleosts, catecholamines that enter the circulation are synthesized, stored, and released from chromaffin cells that are primarily embedded in the walls of the posterior cardinal vein in the region of the head kidney (Nilsson, 1984; Reid et al., 1995). Early studies investigating the adrenergic system of teleost fish showed that, as in mammals, the chromaffin tissue is innervated by pre-ganglionic sympathetic nerve fibers (Nilsson, 1976; Nilsson, 1984). Electrical stimulation of the cholinergic fibers innervating the chromaffin tissue elicits catecholamine release (Nilsson et al., 1976). Moreover, in situ or in vitro, acetylcholine or different cholinergic agonists (Perry et al., 1991; Fritsche et al., 1993; Reid and Perry, 1994, 1995; Al-Kharrat et al., 1997) elicit the release of catecholamines and this secretion can be blocked by pre-treatment with cholinoceptor antagonists (Fritsche et al., 1993; Reid and Perry, 1995). While these results clearly identify the cholinergic nerves as an important pathway, there is increasing evidence that a large number of non-cholinergic pathways also play an important role in the control of catecholamine release in fish (Reid et al., 1998).

In cyclostomes (hagfishes and lampreys), unlike in teleosts, the chromaffin tissue is not innervated and thus catecholamine release in these 'primitive' fish presumably is mediated exclusively through non-cholinergic means (Epple et al., 1995; Bernier and Perry, 1998). Although the specific mechanisms of catecholamine secretion during stress in vivo have yet to be characterised in hagfish (Perry et al., 1993), there is evidence that adenosine, serotonin, and ACTH may be involved (Perry et al., 1993; Bernier and Perry, 1996; Bernier et al., 1996). Similarly, there is evidence that serotonin (Fritsche et al., 1993), ACTH (Reid et al., 1996), and angiotensin II (Bernier and Perry, 1997) can elicit catecholamine release in teleosts. In acutely hypotensive rainbow trout, angiotensin II, produced by the renin–angiotensin system, acts as a potent secretagogue of catecholamine secretion (Bernier et al., 1999). In addition to the secretagogues listed above, the chromaffin cells of teleosts contain a variety of bioactive peptides (e.g., natriuretic peptides, opioid peptides, neuropeptide Y) that also may be involved in the control of catecholamine release (Hathaway and Epple, 1990; Kloas et al., 1994; Epple et al., 1996; Reid et al., 1998). Finally, there is immunohistochemical evidence for the presence of non-cholinergic neurotransmitters and/or neuromodulators in the nerve fibres innervating the chromaffin tissue of fish (Reid et al., 1995). Altogether, in teleosts, although the cholinergic control of catecholamine release is well established and several potential non-cholinergic secretagogues have been identified, the relative contribution of these various pathways to the overall control of catecholamine release in vivo have yet to be characterised.

## 3. The efferent limb

Numerous physiological regulatory responses have been attributed to elevated plasma catecholamine levels. These include cardiovascular and ventilatory adjustments, metabolic changes, and modulation of red blood cell (RBC) function. There is considerable debate, however, surrounding the importance of circulating catecholamines on

influencing physiological function during stress. The following brief discussion focuses on two particularly contentious issues.

### 3.1. Do circulating catecholamines stimulate breathing during stress?

Peyreaud-Waitzenegger et al. (Peyreaud-Waitzenegger, 1979; Peyreaud-Waitzenegger et al., 1980) first demonstrated that intravascular injections of catecholamines could influence ventilation in eels (*Anguilla anguilla*) in a seasonally dependent manner. On the basis of these early studies and anecdotal evidence that circulating catecholamines are elevated during periods of hyperventilation, an important (teleosts) or essential (elasmobranchs) role for circulating catecholamines in stimulating breathing during stress has been accepted largely as fact. Unfortunately, this view still pervades much of the secondary literature despite the absence of any direct evidence implicating circulating catecholamines as ventilatory stimulants. Arguments both for (Randall and Taylor, 1991) and against (Perry et al., 1992) a role for circulating catecholamines in the stimulation of breathing have been presented in recent reviews. It is clear that catecholamines, when injected into fish, are able to influence ventilation. However, the effects are inconsistent and range from hypoventilatory to hyperventilatory responses (Playle et al., 1990; Kinkead and Perry, 1990, 1991; Kinkead et al., 1991; Aota and Randall, 1993; Burleson and Milsom, 1995). Several facts, however, argue against a role for *naturally released* catecholamines in the stimulation of breathing. First, fish experience hyperventilation during periods of mild or moderate stress, at which times catecholamines are not elevated (see above). Clearly, an increase in the levels of circulating catecholamines is not a prerequisite for hyperventilation. In the elasmobranchs, for which an essential role for catecholamines in the stimulation of breathing has been advocated (Randall and Taylor, 1991), it is also clear that breathing is controlled exclusively by chemoreceptors during environmental hypoxia or hypercapnia; circulating catecholamines play no role whatsoever (Perry and Gilmour, 1996). Second, the injection of catecholamines into moderately stressed fish, to simulate the sudden release of catecholamines that occurs during severe stress, does not further increase the already existing hyperventilation. Indeed, under conditions of moderate hypercapnia, injections of catecholamines significantly reduce ventilation amplitude in rainbow trout and ventilation frequency in dogfish (Kinkead and Perry, 1991; Perry and Gilmour, 1996). Thus, if anything, a sudden elevation of circulating catecholamines during a naturally occurring stress is more likely to cause hypoventilation than hyperventilation. Because ventilation is correlated with blood $O_2$ content in teleosts (Randall, 1982; Smith and Jones, 1982), the theoretical basis for a hypoventilatory effect of circulating catecholamines during stress in trout may reflect the impact of catecholamines on elevating blood oxygen content (Nikinmaa, 1992). Third, the natural sudden release of endogenous catecholamines during progressive stress (e.g., graded hypoxia or graded hypercapnia) in trout is not associated with any increase in ventilation (Perry and Gilmour, 1996). On the other hand, several obvious episodes of hypoventilation were observed following natural catecholamine release (Perry et al., 1992; Fig. 1) that may also originate from an adrenergic increase in blood $O_2$ content. Finally, the idea that circulating catecholamines might stimulate breathing relies on their passage across the blood brain barrier and entry into the central

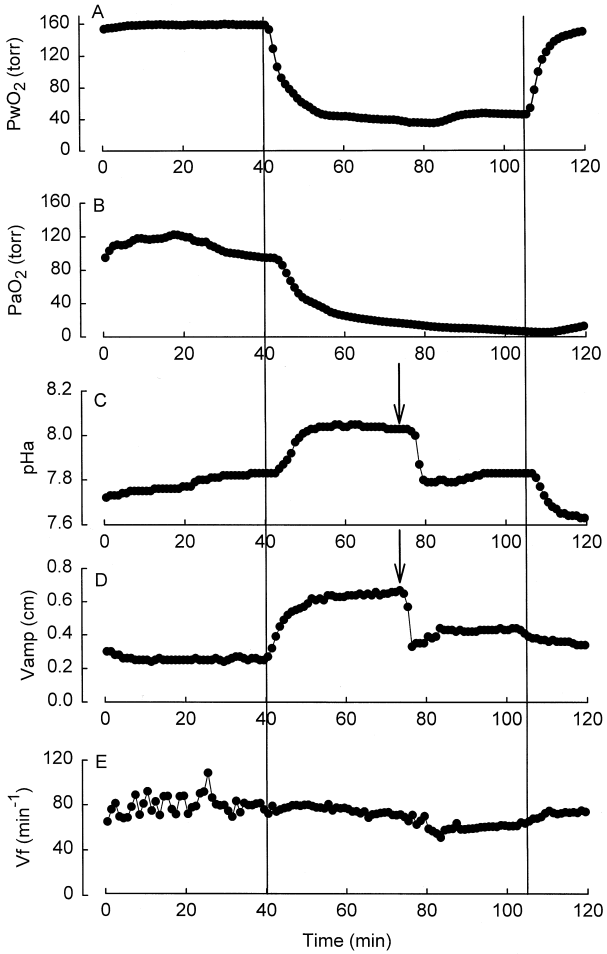


Fig. 1. Continuous recordings of (A) water $P_{O_2}$ ($PwO_2$), (B) arterial blood $P_{O_2}$ ($PaO_2$), (C) arterial blood pH ($pH_a$), (D) ventilation amplitude ($V_{amp}$; as determined from opercular displacement using impedance electrodes), and (E) ventilation frequency ($V_f$) from a single rainbow trout (*Oncorhynchus mykiss*) exposed to progressive hypoxia. The dashed lines indicate the duration of the hypoxic exposure. Arrows in panels C and D indicate the abrupt release of catecholamines (as determined by analyzing plasma samples using an HPLC). Note that the release of catecholamines was associated with a marked metabolic acidosis resulting from activation of RBC $Na^+/H^+$ exchange and a pronounced reduction in $V_{amp}$. (A. Julio and S.F. Perry, previously unpublished observations).

nervous system (CNS) (Randall and Taylor, 1991). In rainbow trout, however, the blood brain barrier is impermeable to adrenaline (Nekvasil and Olson, 1986), which is the predominant circulating catecholamine during stress in most teleosts. Although the blood brain barrier is permeable to noradrenaline in trout, the brain largely excludes this catecholamine (Nekvasil and Olson, 1986) and given the low levels of circulating noradrenaline during various types of stress (Randall and Perry, 1992), its ability to

activate centres within the CNS remains uncertain. That catecholamines released centrally might influence breathing as shown by Randall and Taylor (1991) is not disputed. There is no evidence, however, that circulating catecholamines are transferred to the CNS to affect breathing.

### *3.2. Do plasma catecholamine levels increase sufficiently to influence physiological function?*

Over the years, an on-going debate has focussed on the relative involvement of humoral vs. neural catecholamines in physiological control (Nilsson, 1994). In part, the debate has highlighted the possibility that the relatively low levels of catecholamines achieved in the blood of fish during stress might be inadequate to trigger physiological responses. Unfortunately, it is not possible, to reach a conclusion that would be correct for all fish, in general. This is because of the enormous inter-specific variability in the levels of catecholamines achieved during stress as well the enormous discrepancies in the extent of the adrenergic neuronal innervation of tissues amongst the species. Thus, the following brief discussion will focus specifically on a few selected teleost species.

#### *3.2.1. The adrenergic response of the teleost RBC*

The trout RBC possesses a membrane-associated $Na^+/H^+$ exchanger (termed βNHE) (Borgese et al., 1992) that is activated by catecholamines via an interaction with β-adrenoceptors. The net result of this activation is an increase in the affinity of haemoglobin for $O_2$ (Nikinmaa, 1992). In rainbow trout, the RBC β-adrenoceptors have a greater affinity for noradrenaline than adrenaline (Tetens et al., 1988). Indeed, a comparison of plasma catecholamine levels during stress with existing RBC catecholamine dose–response curves (Tetens et al., 1988; Salama, 1993; Perry et al., 1996), reveals that adrenaline is likely to play little, if any role, in RBC activation. It is likely that in vivo, noradrenaline, despite its lower levels, is exclusively responsible for the adrenergic activation of RBC $Na^+/H^+$ exchange. Clearly, the levels of noradrenaline achieved in trout during stress are sufficient to influence RBC function.

#### *3.2.2. Cardiovascular function*

The extent of the adrenergic innervation of the various components of the circulatory system varies widely amongst the different groups of fish. Two extensively studied teleosts, the rainbow trout and the Atlantic cod, possess a well-developed adrenergic innervation of the circulatory system while also exhibiting pronounced catecholamine release into the blood during acute severe stress. Fish such as these, therefore, possess the potential for a dual control of cardiovascular function during stress. The involvement of the humoral adrenergic stress response in promoting cardiovascular responses has been the topic of considerable investigation, yet there is little, if any, general agreement as to its relative role (i.e., in comparison to sympathetic nerves). This lack of consensus stems from technical problems associated with distinguishing between neural and humoral adrenergic responses in vivo and the limitations of comparing in vitro and in situ catecholamine dose–response curves with the levels of circulating catecholamines achieved during stress in vivo. Recently, Bernier and Perry (1999) injected a wide range

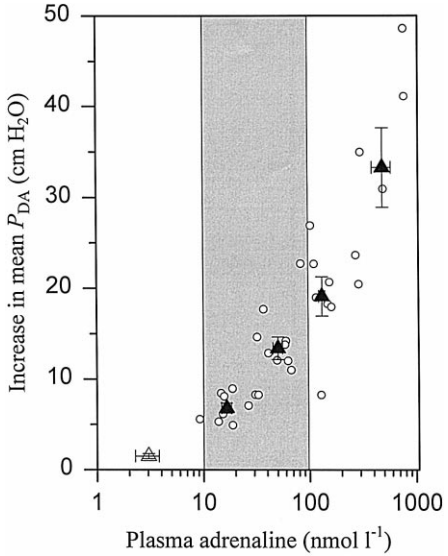


Fig. 2. Increase in mean dorsal aortic pressure ($P_{DA}$) as a function of arterial plasma adrenaline concentration in rainbow trout ($n = 8$). Open circles represent individual adrenaline injections ranging between $1.8 \times 10^{-10}$ and $1.4 \times 10^{-8}$ mol $kg^{-1}$. Open triangles represent mean value ($\pm 1$ S.E.M.) for saline injections. Solid triangles represent mean values ($\pm 1$ S.E.M.) for adrenaline injections. The shaded box highlights the increase in $P_{DA}$ that corresponds to the plasma adrenaline levels (10–100 nmol $l^{-1}$) most commonly observed under conditions that elicit increases in plasma catecholamines (N.J. Bernier and S.F. Perry, previously unpublished observations).

of adrenaline doses into the circulation of rainbow trout while monitoring several cardiovascular variables and withdrawing blood samples for catecholamine analysis by HPLC. This enabled a correlation of cardiovascular function in vivo, with circulating catecholamine levels. This analysis clearly demonstrated for the first time that even relatively low levels of catecholamines, when achieved during stress (e.g., 10–100 nmol $l^{-1}$), are capable of profoundly influencing cardiovascular function in trout (see Fig. 2). Similar experiments have not yet been performed on other species. In Atlantic cod, however, the control of systemic resistance and arterial blood pressure during stress appears to be almost exclusively under the control of adrenergic sympathetic nerve fibres (Nilsson, 1994). Thus, there appear to be profound inter-specific differences amongst the teleosts with respect to the relative roles of circulating vs. neural catecholamines. Future research should continue to focus on establishing the relative contributions of the humoral vs. the neural acute adrenergic stress response.

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