



Review

Role of the Neuroendocrine System of Marine Bivalves in Their Response to Hypoxia

Elena Kotsyuba and Vyacheslav Dyachuk *

A.V. Zhirmunsky National Scientific Center of Marine Biology, Far Eastern Branch, Russian Academy of Sciences, 690041 Vladivostok, Russia

* Correspondence: slavad83@gmail.com

Abstract: Mollusks comprise one of the largest phylum of marine invertebrates. With their great diversity of species, various degrees of mobility, and specific behavioral strategies, they have occupied marine, freshwater, and terrestrial habitats and play key roles in many ecosystems. This success is explained by their exceptional ability to tolerate a wide range of environmental stresses, such as hypoxia. Most marine bivalve mollusks are exposed to frequent short-term variations in oxygen levels in their marine or estuarine habitats. This stress factor has caused them to develop a wide variety of adaptive strategies during their evolution, enabling to mobilize rapidly a set of behavioral, physiological, biochemical, and molecular defenses that re-establishing oxygen homeostasis. The neuroendocrine system and its related signaling systems play crucial roles in the regulation of various physiological and behavioral processes in mollusks and, hence, can affect hypoxia tolerance. Little effort has been made to identify the neurotransmitters and genes involved in oxygen homeostasis regulation, and the molecular basis of the differences in the regulatory mechanisms of hypoxia resistance in hypoxia-tolerant and hypoxia-sensitive bivalve species. Here, we summarize current knowledge about the involvement of the neuroendocrine system in the hypoxia stress response, and the possible contributions of various signaling molecules to this process. We thus provide a basis for understanding the molecular mechanisms underlying hypoxic stress in bivalves, also making comparisons with data from related studies on other species.



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1. Introduction

Mollusks comprise the largest phylum of marine invertebrates. With their great diversity of species, various degrees of mobility, and specific behavioral strategies, they have occupied marine, freshwater, and terrestrial habitats, playing key roles in many ecosystems. Bivalves are common inhabitants of coastal marine waters. A number of marine bivalves (e.g., oysters, clams, and mussels) with wide geographic distribution are target aquaculture species, and are of high commercial value and scientific importance [1]. Bivalve aquaculture facilities are traditionally installed in coastal waters, where cultured animals can be exposed to permanent or periodic hypoxia, especially in the case of eutrophication expanding across coastal habitats, which leads to a decrease in their growth rates, impaired reproduction and development, diseases, and sometimes mass mortality [2–6]. Oxygen deficiency exerts the most adverse effect on juvenile mollusks by reducing, in particular, their growth, settlement, and survival rates [7]. In this regard, the knowledge of the molecular mechanisms associated with physiological and biochemical responses to hypoxia and resistance is essential to developing technologies for rearing certain mollusk species.

During their evolution, most marine bivalves have been exposed to frequent short-term fluctuations in oxygen levels in their marine or estuarine habitats. This stress factor

has caused them to develop certain adaptive strategies [8,9] to rapidly mobilize behavioral, physiological, biochemical, and molecular mechanisms that re-establish oxygen homeostasis [10–15].

Within the phylum Mollusca, due to the need for adaptive resistance to low dissolved oxygen levels, the behavioral and survival strategies against hypoxia have diverged widely across hypoxia-tolerant, slow-moving or sessile mollusk species that cannot use avoidance, and have to rely on physiological adjustments for coping with adverse conditions, in contrast to hypoxia-sensitive mollusks with enhanced mobility, which can avoid the hypoxic zone [2,16–18].

Hypoxia-tolerant intertidal species (e.g., mussels and oysters), the so-called oxygen conformers, reduce metabolic demand for O₂ consumption as a response to environmental O₂ levels [19–21], and also minimize energy demand [16,22–24]. These adaptations involve metabolic rate depression, the use of alternative glycolytic pathways that produce more ATP, the maintenance of high glycogen levels, and increases in the proton buffering capacities of tissues [12,24,25]. One of the behavioral responses exhibited by hypoxia-tolerant bivalves in the case of hypoxia is the closure of their shells and the regulation of the internal environment [26] (Figure 1).

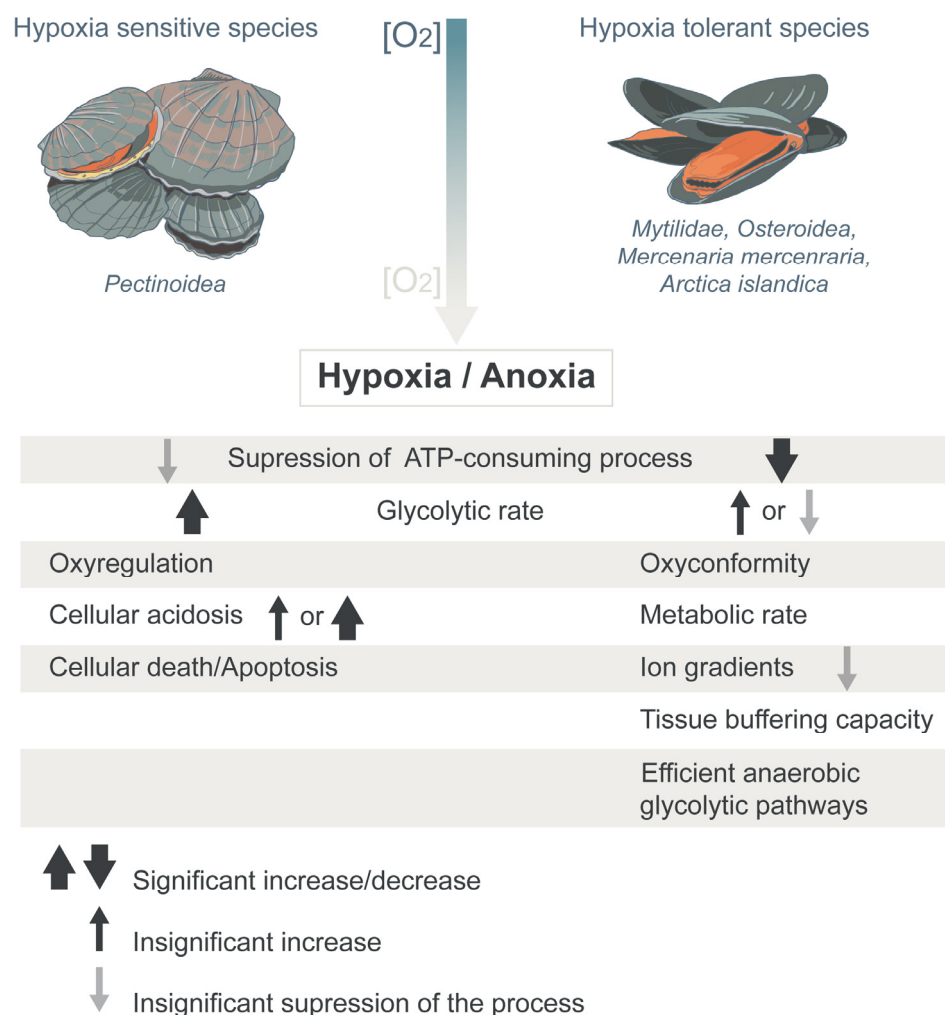


Figure 1. Division of marine bivalves on the basis of their metabolic response to hypoxia and the differences in the molecular mechanisms of their tolerance to low-oxygen conditions.

Hypoxia-sensitive subtidal species (e.g., scallops), the so-called oxygen regulators [26], maintain O₂ consumption independently of environmental O₂ levels, up to the point where O₂ consumption is limited to a level sufficient to maintain the aerobic process [23,27,28].

Therefore, they, like other mobile benthic animals, primarily exhibit developed behavioral and physiological mechanisms, such as the avoidance reaction, which allows for escaping the adverse effects of the hypoxic zone (Figure 1).

Though hypoxia-sensitive and hypoxia-tolerant animals show different homeostatic strategies to cope with oxygen deprivation [29], the major reaction of mollusks in response to environmental stressors, including hypoxia, is the neuroendocrine stress reaction [26]. This adaptive response, caused by stress-induced processes in the mollusk's nervous system, induces behavioral and physiological changes in order to maintain homeostasis. The regulation of the stress response in mollusks involves the general mechanisms and signaling molecules preserved throughout evolution, having a molecular base similar to those in vertebrates [30–32]. As has recently been found, hemocytes in marine bivalves are an important component of the neuroendocrine-immune regulation that is undertaken in response to environmental stress [30]. Enzymes for catecholamine synthesis [33–35] and acetylcholine (ACh) degradation (acetylcholinesterase (AChE)) [36] are detected in molluscan hemocytes. The inhibitory effects of catecholamines on hemocytes' functional responses have also been reported. Furthermore, hemocytes mediate the regulation of different effectors via specific receptors of neurotransmitters/hormones/neuropeptides/cytokines on the cell surface [30,37,38].

The neuroendocrine system in marine mollusks is sensitive to fluctuations in O_2 concentrations. The synthesis of several neurotransmitters/modulators is regulated by O_2 -requiring rate-limiting enzymes. The hypoxia resulting from perturbations in the O_2 homeostasis can affect neurotransmitter synthesis, thus causing altered neuronal functions and, consequently, affecting the physiological systems in mollusks and their stress response.

Although the role of neurotransmitters in the regulation of functions in mollusks has long been a subject of research, their role in the hypoxia stress responses of marine mollusks is reported only in a few studies. In some marine invertebrates, variations in the level of biogenic amines (serotonin and dopamine) are considered as part of the hypoxia response, and act to arrest processes such as growth, reproduction, and immunity [39–42]. The changes of neurotransmitters lead to the redirection of bioenergetic resources to specific physiological functions (e.g., increased oxygen uptake, mobilization of energy substrates) that are immediately required for adaptation and survival under stress [43,44]. Several studies have reported the role of nitric oxide in invertebrates' responses to stressful environmental conditions [45,46]. Other studies focus on gene expression during hypoxia responses and the role of a transcription factor referred to as the hypoxia-inducible factor-1 (HIF-1), which triggers and coordinates the up-regulation of multiple genes in response to low oxygen signals [47–50].

Even with recent advances, our understanding of the neuroendocrine system and its involvement in hypoxia stress responses of marine bivalves still remains very limited. Therefore, the study of the role of signaling systems in mollusks with different resistances to hypoxia is a key to the knowledge of the strategies for their survival. Understanding and determining this spectrum of neuroendocrine reactions to hypoxia will be useful for predicting the physiological condition of mollusks in aquaculture and their acclimation, which is important for the management of shellfish farms in coastal areas.

In this review, we have attempted to summarize data on some regulatory mechanisms of mollusks' hypoxia resistance using available publications that consider the effect of hypoxia on the behavior and metabolic processes in mollusks, making also conceptual comparisons with data from related studies on other species. Here, we overview the current state of knowledge about the neuroendocrine regulation of oxygen homeostasis and the molecular mechanisms of hypoxia resistance on the basis of published data and the results of our research. The present review provides the current body of evidence elucidating the involvement of the neuroendocrine system in the hypoxic stress response, and the possible contributions of various signaling molecules in this process.

2. Biogenic Amines

Biogenic amines belong to the evolutionarily ancient signaling systems that are involved in the regulation of various physiological and behavioral processes, and in the processes of adaptation to various environmental factors in vertebrates and invertebrates exposed to stressful conditions [51]. These act not only as neurotransmitters and neuromodulators in nervous tissue, but also, depending on the situation, can be released into body fluids and act as neurohormones [51–53]. The major biogenic amines identified in mollusks are norepinephrine (NE), serotonin (5-HT), dopamine (DA), and epinephrine (E) [30,54]. In the neuroendocrine system of marine bivalves, the catecholamines and serotonin regulations play major roles in stress responses [55,56]. Being involved in the physiological response regulation in mollusks to maintain homeostasis through functional responses of the heart, hemolymph redistribution, and metabolic depression, these neuroendocrine messengers are immediately required for hypoxia tolerance.

2.1. Catecholamines

DA, NE, and E are present in various tissues of mollusks (in particular, bivalves), including the ganglion, hepatopancreas, and hemocytes [30,57–60]. The source of catecholamines in bivalves is predominantly the neurosecretory neurons of the central nervous system (CNS) [30,61]; their secretion in hemocytes has also been reported [30,35]. Although DA, NE, and E have been identified in the mollusk CNS [30,54], DA is the only catecholamine recorded in bivalve ganglia, according to immunohistochemical methods.

In the CNS, DA-ergic neurons have been found in *Mytilus edulis* [62], *Placopecten magellanicus* [59,63], and *Patinopecten yessoensis* [64,65]. A number of experimental studies have shown variations in the CA level in the CNS and hemolymph of mollusks exposed to various stress factors [61,66–68].

An increase in the CA concentration in the hemolymph is the primary adaptive neuroendocrine response exhibited by mollusks to any stress, which provides the metabolic and behavioral adaptation of these animals to adverse conditions [31,61,69]. In many invertebrates, including marine bivalves, hypoxia stimulates the secretion of the CA hormones [55,70] (Figure 2). In marine mollusks, NE and DA are released into the hemolymph within the first minutes after stress exposure [70]. The blood levels of both hormones in stressed octopus (*Eledone cirrhosa*) increased about 2–2.5-fold after 5 min of air exposure [70]. Concomitantly, a significant decrease in the number of circulating hemocytes was observed, whereas the hemocyte phagocytic activity and the superoxide anion production increased transiently between 5 and 60 min after the onset of the stress exposure. Scallops (*Chlamys farreri*) exposed to air for 12 h showed a significant increase in the hemolymph concentrations of E and NE [55]. During this period, the DA level significantly increased regardless of temperature (both at 5 and 17 °C) [55]. After entering the circulation, CAs contribute to reductions in the detrimental effects that are often associated with oxygen deficiency.

In vertebrates and invertebrates, the beneficial effects of CAs are achieved, in part, by the modulation of the cardiovascular and respiratory systems [39–41,71]. The rise in CA levels initiates a series of compensatory physiological processes enhancing branchial O₂ transfer and blood O₂ transport.

In many bivalves, including *M. edulis* and *Crassostrea virginica*, the beating rates of lateral cilia are controlled by the branchial nerve via the reciprocal DA-ergic and serotonergic innervation originating from the cerebral and visceral ganglia [72,73]. DA is cilio-inhibitory and, with a few exceptions, it mostly decreases the ciliary beat frequency [72,74–76]. The activity of cilia can change in response to hypoxia, and is generally controlled by the nervous system [76]. The increase in DA level in the gills of *Cr. virginica* exposed to hypoxia had an inhibitory effect on gill ciliary beating [72]. Experimental evidence has shown that DA, applied directly to the ganglia or stimulating the branchial nerve (20 Hz, 2 ms duration, 10 V current), causes a terminal release of DA in the gill, decreasing the beating rates of lateral cell cilia [74,77,78]. In *Cr. virginica*, the direct application of dopamine to an isolated gill reduced the lateral ciliary activity in a dose-dependent manner (10^{−7} to 10^{−3} M), with

10^{-5} M being the ED₅₀ dose [72]. However, as an exception, DA-ergic neurons induced an increase in the ciliary beat frequency during the hypoxia response in embryos of the snail *Lymnaea* [79]. In sea urchin embryos, DA increased the swimming speed, apparently through a cilioexcitatory effect [80,81]. In experimental long-time air exposure, the DA concentration was observed to decrease.

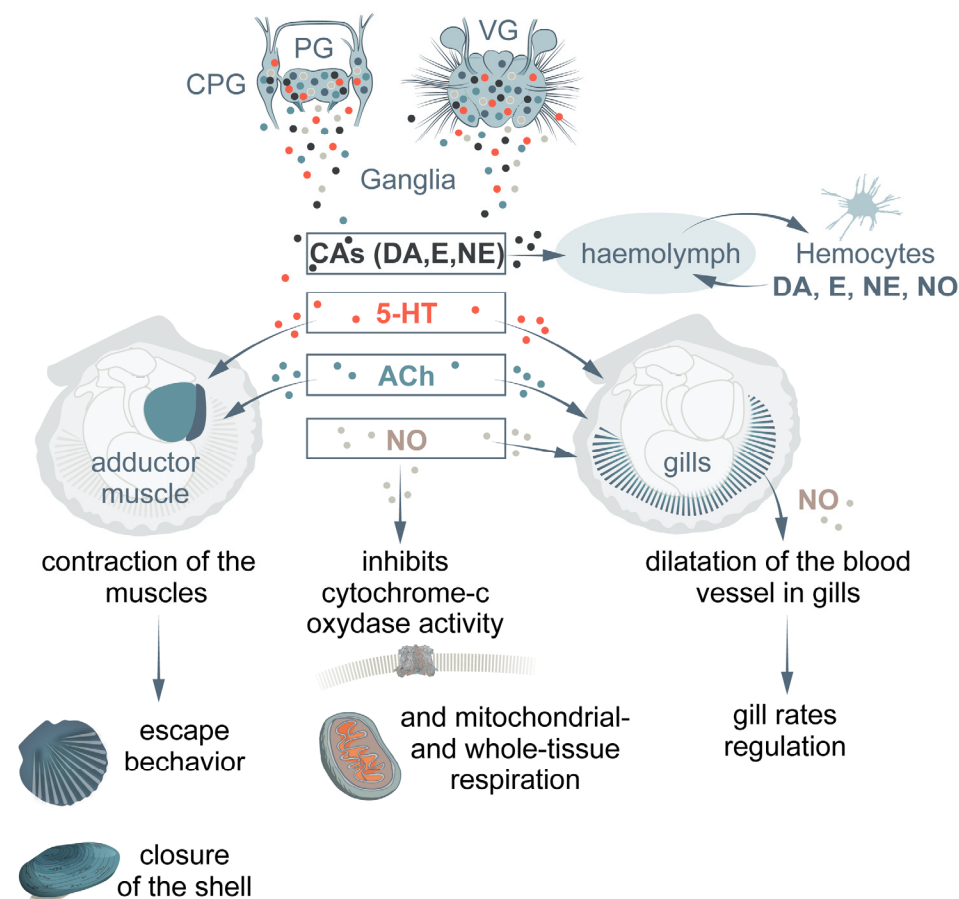


Figure 2. Diagram summarizing available data on the hypoxia stress control and the role of neuroendocrine regulation in the hypoxic response in bivalves. The involvement of CAs, 5-HT, ACh, and NO under hypoxic conditions is shown.

In scallop (*Ch. farreri*), a significant decrease in the DA concentration in hemolymph was observed after 24 h of air exposure, which may be due to the moribund condition caused by the long-time air exposure that resulted in the disruption of DA responses [55]. A significant decrease in DA concentration was also observed in muscles of mussels (*Perna perna*) exposed to air for 24 h [82]. This effect is probably related to the contraction of adductor muscles for avoiding desiccation, as DA has been reported to cause acontractile effect in the adductor muscle of the freshwater mussel *Anodonta cygnea* [83].

Decreased tyrosine hydroxylase activity and dopamine deficiency are the major pathogenetic links in stress development in vertebrates and invertebrates [84]. Experiments using the neurotoxin 6-hydroxydopamine and the organic pesticide rotenone have shown the degeneration of a significant number of DA-synthesizing neurons and the dopamine deficiency in the CNS in insects [85] and mollusks [86], which caused the disturbance of their behavioral and locomotor reactions.

2.2. Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter implicated in a wide range of physiological and behavioral processes in both invertebrates and vertebrates [87–90]. 5-HT is a major neuromodulator of motor behaviors in many species of invertebrate phyla,

including mollusks [91–94]. It has been shown to modulate cognitive functions and play a fundamental role in the modulation of stress-induced excitability (arousal), in defensive behavior, in the modulation of aggressive behaviors, and in anxiety control [94,95].

5-HT and its receptors have been identified in the CNS in vertebrates and all groups of invertebrates, including mollusks [62,94,96–101]. In the bivalve CNS, the organization of the 5-HT systems and 5-HT content differs between species and sexes, and is subject to seasonal variations [96,101–103]. Hypoxia exposure causes the 5-HT-immunoreactivity level to decrease in the ganglia and increase in the gills and other non-nervous tissues [72,104] (Figure 3). These data agree with the long-established fact that 5-HT has a cilio-excitatory and metabolic stimulatory effect on the gills of several bivalve mollusks [62,72,74,75,105,106] (Figure 2). 5-HT-immunoreactivity has been detected in ciliary nerves in most groups of ciliated animals [107], and similarities in the regulation of ciliary locomotion across different groups of animals have been shown [76]. In the gills of *Cr. virginica*, 5-HT activated movements of lateral cilia at a frequency proportional to the neuromodulator concentration, whereas DA had an inhibitory effect [72]. However, when the organism flushed the mantle cavity without feeding, the beating of laterofrontal cilia was arrested by high concentrations of 5-HT released from the serotonergic fibers [72].

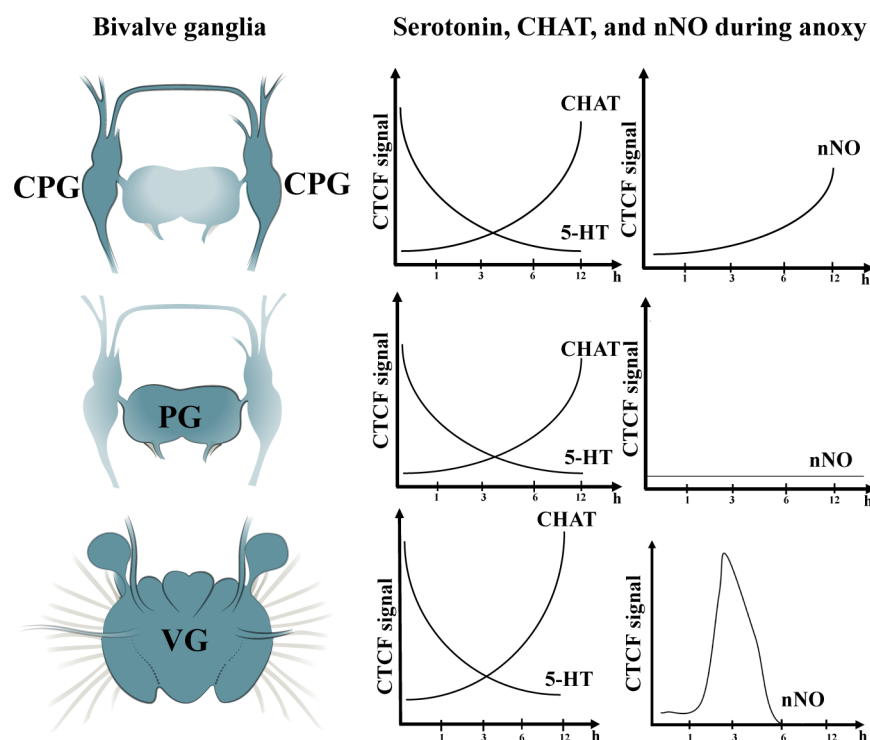


Figure 3. Temporary changes in distribution of neurotransmitters in scallop ganglia during air exposure-induced hypoxia. (Left) Quantitative representation of neurotransmitters. (Right) Variations in 5-HT, CHAT, and uNOS in cerebropleural ganglia (CPG), pedal ganglia (PG), and visceral ganglia (VG) during hypoxia exposure (at 0 (normoxia), 1, 3, 6, and 12 h).

Experimental studies have repeatedly confirmed the involvement of 5-HT in behavioral hypoxia adaptations that help mitigate the effects of hypoxia in encapsulated embryos of pond snails [79,108–110]. Encapsulated organisms are vulnerable to the adverse effects of hypoxia because of their inability to relocate through locomotion. In encapsulated embryos of *Helisoma trivolvis* and *Lymnaea stagnalis*, specific sensorimotor neurons release serotonin onto postsynaptic ciliary cells in response to hypoxia, resulting in faster ciliary beating and embryonic rotation [79,108,109]. This induces more efficient oxygen diffusion due to increased stirring, and this maintains an adequate O₂ supply during hypoxia [79]. The rotational behavior is a ventilation response that facilitates O₂ diffusion to the embryo by

reducing unstirred boundary layers [111]. This serotonin-mediated response acts through G-protein-coupled receptors. One of the receptors signals through the Gq pathway, leading to increases in intracellular Ca^{2+} [112]. The hypoxia response is also accompanied by increased cAMP levels in ciliated cells, mediated by another, Gs-coupled, serotonin receptor [113]. Similar cilio-excitatory effects were investigated in experiments on crustaceans, where 5-HT increased the rate of scaphognathite movement [114], which increased water circulation [114] and promoted a more rapid oxygen exchange in tissues as a response to higher oxygen demand.

Bivalves can obtain more oxygen by increasing the heart rate and dilating blood vessels in the case of hypoxia [115]. 5-HT is an excitatory agent that regulates the cardiac performance in various animals, including marine bivalves [116–118]. An increase in its level in response to declining oxygen leads to an increase in the heart rate and the amplitude of the heartbeat in mollusks [116]. The underlying mechanism for 5-HT's effects involves the increase in cAMP [119]. In hypoxia-tolerant slow-moving or sessile mollusk species, a decrease in ambient $p\text{O}_2$ is usually accompanied by a reduction in the heart rate and the amplitude of the heartbeat [116,120]. The heart rate in these mollusks decreases in response to a decrease in ambient $p\text{O}_2$, presumably as an energy-saving response [120]. At intermediate levels of hypoxia, animals that regulate oxygen consumption may increase their heart rate. As has been shown by the Doppler ultrasonography method, the heart and respiratory rates in scallop (*Argopecten irradians*) increase when dissolved oxygen falls below 5 mg/L, which indicates that scallops rapidly adjust the circulatory rhythm to adapt to the stress [120]. Phasic changes in the heart rate in some species also appear to correlate with phasic movements of other organs. In scallops, moderate hypoxia (3 mg/L dissolved oxygen, DO) causes an increase in the blood flow, especially in the gill, to acquire more oxygen from the water and transport to other tissues; in *Perna viridis*, it causes an increase in the blood output to maintain the hemolymph circulation [121]. Neurotransmitters and mechanisms involved in the regulation of these changes have not been studied, however. The study of scallops by the Doppler ultrasonography method has shown that blood vessels dilate, and blood is redistributed to the gill for oxygen acquirement and to the adductor muscle for avoiding tissue damage [120]. In cases of severe hypoxia exposure in scallops, although the heart rate (HR) and blood velocity (PS) of all tissues largely increase, the blood flow volume (FV) in the tissue inevitably becomes reduced due to the constriction of the blood vessel, which means that the circulatory regulation has failed and functional damage is inevitable [120].

5-HT regulates the contraction and relaxation of the adductor and the anterior byssus retractor muscle (ABRM), and is involved in the regulation of complex changes in the protective behavioral reactions of mollusks during hypoxia. In bivalves such as the blue mussel *M. edulis*, smooth muscles such as the ABRM can be locked in the contracted state (i.e., “catch”), a crucial function that keeps the shell valves firmly closed during periods of air exposure [122,123]. This occurs following the initial activation of the muscle. This state is characterized by prolonged force maintenance in the face of low Ca^{2+} , high instantaneous stiffness, a very slow cross-bridge cycling rate, and low ATP usage [124–126]. Tension is maintained until the serotonergic fibers release 5-HT, which stimulates the AC/cAMP/PKA system. Protein kinase A (PKA) is then responsible for the rapid muscle relaxation through the phosphorylation of twitchin, a myosin-binding protein [119,125]. The ABRM fibers in the catch state can be relaxed by serotonergic nerve stimulation or by the external application of 5-HT [123,125,127–129]. 5-HT induces an increase in the intracellular cyclic AMP (cAMP) concentration [130], which activates cAMP-dependent PKA to result in the phosphorylation of twitchin, a high-molecular-weight protein terminating the catch state [131].

Unlike slow-moving or sessile mytilids exposed to hypoxic conditions, scallops show an obvious escaping behavior, with the shells clapping frequently, which induces a high demand for energy and oxygen [120]. However, the poor regulation ability of tissues under

severe hypoxia means that the scallop may have lost this ability to escape the hypoxic “dead zone” to survive.

In bivalves exposed to chronic hypoxia, the 5-HT level in the CNS has been found to decrease [104] (Figure 3), while the level of 5-HT in the hemolymph and mantle may increase significantly against air exposure stress [56]. In Pacific oysters (*Crassostrea gigas*) after exposure to air for 24 h, the high concentration of 5-HT in the hemolymph may decrease the apoptosis rate of hemocytes. The stimulation by 5-HT can enhance the resistance of oysters to oxidative stress under air exposure by increasing the activity of superoxide dismutase (SOD), and reduce the accumulation of H₂O₂ in the hemolymph [56]. These protective effects of 5-HT were tested by estimating the survival rate of oysters after the stimulation of 5-HT in air, which showed an increase in the survival rate of oysters upon exposure to air stress [56].

3. Acetylcholine

Acetylcholine (ACh) is one of the conserved neurotransmitters in the nervous system, and at the neuromuscular junction in vertebrates and invertebrates including mollusks [132,133]. ACh is synthesized in the cytosol from acetyl-coenzyme A and choline (produced via lipid metabolism) by the catalytic action of choline acetyl transferase (CHAT) [134]. Many indices of ACh neurotransmission recorded in invertebrates, such as ACh content, CHAT activity, acetylcholinesterase activity, transporter mechanisms, and receptor-mediated responses, have also been detected in invertebrates [135,136].

Biochemical and histochemical studies on mollusks have demonstrated the presence of the enzyme synthesizing acetylcholine (CHAT) and the enzyme hydrolyzing it (acetylcholinesterase, AChE) in a multitude of taxonomic groups [36,104,132,135–137]. Furthermore, substantial homologies have been found between the ACh receptors cloned to date from invertebrate and vertebrate animals [138,139]. One AChE has also been identified in *Ch. farreri* [36], as have nicotinic ACh receptors (nAChR) in *Ch. farreri* [32], *Cr. gigas*, *Pinctada fucata martensii*, *Lottia gigantea*, *Aplysia californica*, *Octopus bimaculoides*, and *Helobdella robusta* [140], and a homolog of the muscarinic ACh receptor in *Cr. gigas* [32].

Cephalopods and gastropods with enhanced mobility have fewer nAChR genes than stationary bivalves [140]. The massive expansion and diversity of nAChR in stationary bivalve mollusks with simple nervous systems may be an adaptation to stationary life under a variable environment. In representatives of different mollusk groups such as cephalopods (*Octopus vulgaris*) [141]), including an octopus arm [142], pteropods (*Clione limacina*) [143,144], and bivalves (the scallop *Azumapecten farreri*) [104], CHAT-lir neurons were identified in the CNS, where most of them are localized in the motor centers and are involved in locomotor reactions [143,144], as well as in the escape behavior [141] (Figure 2).

In the scallop *Az. farreri* exposed to hypoxia, an increase in CHAT in the motor neurons of the visceral ganglion [104], involved in adductor muscle contraction, correlates with changes in the adaptive behavior that manifests as attempts to escape hypoxic water [145]. In stationary bivalve mollusks, ACh is also involved in the adaptive behavioral response to anoxia or low oxygen concentrations in seawater. It has been shown that the phosphorylation of PFK-1 alters the enzyme's kinetic properties to convert it into a less active form in the anterior byssus retractor muscle (ABRM) of *M. edulis*, and to allow it to be mediated via cGMP [122]. An increase in cGMP occurs in the ABRM in response to ACh, which stimulates the contraction of this catch muscle [146]. The ABRM fibers can be made to contract actively by cholinergic nerve stimulation or by the external application of ACh [147]. The catch state is established only after the removal of ACh, producing the maximum tension. This indicates that the development of ACh-induced tension to the maximum tension is the necessary prerequisite for the establishment of the catch state [148]. In bivalve mollusks, catch muscles such as the ABRM show an increased demand for energy during the first hours of recovery after valve closure, which is met by the activation of glycolysis [12,149].

Mollusks' typical responses to hypoxia area variation in CHAT activity in all the ganglia and peripheral (branchial) nerves [104] (Figure 3). Cholinergic innervation has

been characterized in ciliary bands of echinoderms, annelids, and mollusks [76,150]. In *M. edulis*, ACh is a modulator of the frontal cilia, with this effect being concentration-dependent [151,152]. In different groups of invertebrates, ACh decreases the ciliary beat frequency and increases closures [76]. The receptors to ACh involved in the ciliary movement in the gill plates have been found in scallop gills [36]. Due to the fact that bivalve mollusks' gills have the highest exposure to the surrounding environment, the exceptionally high expression of nAChR genes in the gill may be an adaptation providing rapid response to dynamic environmental conditions [140].

Very little is known about the effect of chronic hypoxia on cholinergic transmission in the nervous system of invertebrates. Scallops (*Az. farreri*) exposed to long-term (12 h) anoxia showed a significant increase in CHAT-lir in motor neurons of the visceral ganglion, as well as the involvement of neurons of the cerebral and pedal ganglia in the anoxia response (this did not show histochemical activity in the control) [104] (Figure 3). The mechanisms and functional consequences of the hypoxia-induced increase in the ACh synthesis enzyme in bivalves' ganglia have not been elucidated. In recent studies, a significant increase in the production of CHAT has been recorded from the gills of the bivalve mollusks *Tapes decussatus* and *T. laeta* living in habitats with higher temperature and salinity and lower dissolved oxygen levels. The authors [153] assume this to be an adaptive compensatory response for preventing the disruption of gill function. Previously, experiments on vertebrates showed that a 10 min complete ischemia (bilateral occlusion of the carotid artery in mice) caused choline (Ch) accumulation [154]. The major source of Ch accumulation during ischemia arises from the hydrolysis of Ch-containing phospholipids and phospholipid Ch-derived intermediates, with the contribution of ACh hydrolysis being small [155]. In the cholinergic neurons, the phospholipids containing Ch represent a large source of Ch that can potentially be used for ACh synthesis [156]. Neurons in mollusks contain large amounts of phospholipids [157]. Phospholipids such as phosphatidylethanolamine and phosphatidylcholine, exhibiting neurotrophic and neuroprotective effects, have been identified in mussels *M. edulis* [158]. Earlier, it was shown that Ch confers brain protection against ischemic stroke in mammals [159]. These data suggest that an increase in CHAT immunoreactivity in the scallop ganglia after long-term anoxia may be caused by an increase in the Ch levels, and is a conserved mechanism for protecting cells from hypoxia.

4. Nitric Oxide

Nitric oxide (NO) is an evolutionarily ancient, diffusible, gaseous low-molecular-weight signaling molecule occurring in all major groups of organisms, and a common regulator of metabolism [160–163]. It is involved in many physiological functions, including cellular signaling in the nervous system, the regulation of vascular tone, responses to hypoxia, and nonspecific immune responses in both vertebrates and invertebrates [46,161,162,164–166]. NO is synthesized in cells from L-arginine and O₂ by nitric oxide synthase (NOS), and acts as a nonspecific neurotransmitter and neuromodulator in the central and peripheral nervous systems. NO synthesis requires molecular oxygen and, therefore, its cellular production can be altered by hypoxia [133]. In mammals, NOS exists in three distinct isoforms: neuronal (nNOS, type I), endothelial (eNOS, type III), and inducible (iNOS, type II) [167].

NOS in mollusks shows a strong similarity with vertebrate nNOS in structure, with nNOS and iNOS in biochemical characteristics, and with iNOS in immunological features [168,169]. All the NOS forms require reduced nicotinamide adenine dinucleotide phosphate (NADPH) as an essential cofactor (an electron donor). Both NOS and NADPH-d are capable of transferring electrons from NADPH to tetrazolium salts and converting them into water-insoluble dark blue formazan crystals. The activity of NADPH-diaphorase (NADPH-d), a NADPH-dependent oxido-reductase, was shown to colocalize with nNOS immunostaining [170,171]. Positive NADPH-d staining has been successfully used as a marker for NOS in the CNS of both vertebrates [170,172] and invertebrates, including mollusks [173–177]. Furthermore, NOS-immunoreactivity has been recorded from different

invertebrate phyla by the use of antibodies specific for the mammalian enzyme [162,176,178] (NADPH-d/NOS activity has been detected in the CNS, in peripheral tissues, and in hemocytes of marine invertebrates including mollusks [45,46,162,174,179–184] (Figure 2). In the hypoxia-tolerant mollusks *C. grayanus* and *Modioluskurilensis*, the NADPH-d/NOS activity in the CNS in control and hypoxia was significantly higher than in the hypoxia-sensitive species [104,177,181]. The increase in the NO level in invertebrate nerve cells under the effects of various environmental factors has been discussed in recent years [45,46,177,185]. The synthesis of NO is followed by its rapid diffusion within neurons and in adjacent cells [186]. Since the generation of NO occurs together with its release, a balanced NOS activity is a crucial step in the control of NO-mediated signaling [187]. Moreover, excessive NO release may lead to apoptosis, and exerts direct cytotoxic effects [186–188]. One of the ways to measure the detrimental effects of hypoxia in mollusks is to assess the severity of changes in the structure of nerve cells via an ultrastructural examination. Higher morphological stability was found in NO-positive CNS neurons in hypoxia-tolerant mollusk species [189]. The hypoxia-tolerant bivalve species (oysters or clams) have a greater mitochondrial tolerance to hypoxia stress compared to hypoxia-sensitive species [24]. Mytilids belong to the group of marine invertebrates outstandingly tolerant to hypoxia and anoxia, endowed with specialized “anaerobic mitochondria” that can alternate between the use of oxygen (O₂) and endogenous fumarate as the electron acceptor for anaerobic ATP production [46,190].

The survival strategy of these mollusks under hypoxia conditions is to reduce the total ATP uptake by switching to anaerobic metabolic pathways, or through metabolic depression [12,191–193]. NO plays a key role in reducing the metabolic rate in both vertebrates and invertebrates exposed to hypoxia [12,191–193]. To date, NO has been recognized as a potent mitochondrial regulator in vertebrate and invertebrate cells, where it reduces the oxygen affinity of cytochrome-*c*-oxidase (CytOx), the terminal electron acceptor of the mitochondrial electron transport chain [46,194,195]. NO binding to the enzyme is reversible and competitive with oxygen, and therefore depends on the cellular oxygen concentration [194,196]. Under nanomolar concentrations of oxygen in cells and reduced internal oxygen partial pressure (*p*O₂) conditions, NO completely inhibits CytOx activity and, hence, mitochondrial and tissue respiration. It is also involved in switching neurons from aerobic respiration to glycolysis under conditions of reduced intracellular oxygen concentrations, a process that minimizes the production of reactive oxygen species [184,195].

NO also plays an important role in improving the perfusion of hypoxic invertebrate tissues [46,184]. In mollusks, hypoxia increases the NO production in certain ganglia [104] (Figure 3) and in gill tissues [184]. The gills are the main organs of respiration in bivalves, where big hemolymphatic vessels run through the gill branches and filaments and connect the heart with the major tissues and organs. The local NO-dependent regulatory mechanisms that provide adequate blood flow in hemolymph vessels depending on the animal's mode of life and habitat conditions have been identified relatively recently in the gills of hypoxia-tolerant mollusks [46]. In mussels (*M. edulis*) inhabiting the intertidal zone under hypoxic conditions, NO is also generated in the muscle cells surrounding the hemolymph vessels of gill filaments. There, it functions as a hypoxic messenger and local vasodilator causing the blood vessels to dilate, which facilitates hemolymph flow and gas exchange at low *p*O₂, and functionally stabilizes the rates of whole animal respiration [46]. In *M. edulis*, *p*O₂-dependent NO generation is a key mechanism in withstanding rapid environmental O₂ fluctuations during low tide [46], when fast metabolic adjustments upon shell closure are required [184]. Unlike mussels, the infaunal clam *Arctica islandica* is a hypoxia-adapted species that actively regulates hemolymph and shell water *p*O₂ at low levels (<5 kPa) through intermittent ventilation [197,198]. Obviously, there is no need for *Ar. islandica* to perform rapid adjustments of tissue oxygenation by NO-induced dilation of blood vessels. The NO formation itself remains constant under normoxia and hypoxia in the *Ar. islandica* gills. However, the active adjustment of mean internal *p*O₂ to <5 kPa in these animals in vivo [197,198] appears to promote a stable NO concentration in body fluids and tissues,

and the lowering of mitochondrial respiration by NO-induced CytOx inhibition during self-induced burrowing and shell closure [184]. Thus, when the internal pO_2 of tissues and hemolymph in *Ar. islandica* drops to values of ≤ 10 kPa during frequent burrowing periods or >24 h of shell-closure, accumulating NO may indeed diffuse from hemocytes into tissues and cells, reduce the oxygen binding at complex IV of the mitochondrial respiratory chain, and reduce metabolic rate [184]. Controlled metabolic shut down and a tiered reduction in electron transport system (ETS) activities, including CytOx, may prevent significant reactive oxygen species' (ROS) formation during hypoxic and anoxic transgression [46]. An ancient mechanism for controlling the respiratory electron transport under conditions of variable environmental oxygenation, typical of hypoxia-tolerant organisms inhabiting coastal marine environments (e.g., intertidal and subtidal habitats), has been developed [12,22]. In the hypoxia-sensitive, mobile scallop *Az. farreri*, the uNOS-lir level in the CNS increases only slightly with hypoxia. This contrasts with the NO-ergic activity in the ganglia [177], muscle cells, and hemolymph vessels of gill filaments in mytilids under both control and hypoxic conditions [46]. The significant differences in NO expression between the bivalve species may be related to their different modes of life and strategies of ecological adaptation [184].

In contrast to slow-moving mollusk species, scallops are less adapted to hypoxia owing to the high-energy cost of movement [120,199]. In the case of moderate hypoxia, scallops increase their respiratory and heart rates to maintain aerobic metabolism, which leads to an acceleration of hemolymph circulation [27,120]. However, in severe hypoxia, although the heart rate (HR) is largely increased, the blood flow volume (FV) in tissues drops, which causes the constriction of blood vessels. This means that the circulatory regulation in these mollusks has failed, and functional damage becomes inevitable. It is likely that the scallops' lower tolerance to hypoxia, as compared to that in hypoxia-tolerant mollusks, may be associated with a relatively low level of NO, and with the specific features of the organization and functioning of NO-dependent regulatory mechanisms that can affect the dynamics of blood flow.

5. Hypoxia Inducible Factor-1 α

The hypoxia inducible factor-1 (HIF-1) belongs to a family of highly conserved transcription factors that act as main regulators of oxygen homeostasis and the adaptive response to hypoxia [200–203]. HIF-1 regulates the expression of many genes involved in oxygen metabolism in response to hypoxic conditions [200,202,204–206]. HIF-1 consists of two subunits, α and β [200–202,207,208]. HIF-1 β is constitutively expressed, without any effect of the oxygen level on its expression.

The protein level of HIF-1 α is highly regulated by oxygen tension [209]. The activity of HIF-1 is primarily determined by the expression of the subunit HIF-1 α , but not that of HIF-1 β . Under normoxia, HIF-1 α is selectively degraded, while HIF-1 β persists. During hypoxia, HIF-1 α is stabilized, translocates to the nucleus, binds to HIF-1 β , and initiates transcription [210–212], which triggers the expression of hypoxia-related genes [213] (Figure 4).

The HIF-1-mediated system of oxygen-dependent signaling has also been identified in marine invertebrates [23,47–58,214–216], including several bivalve species such as *Crassostrea virginica* [215], *Cr. gigas* [216], *M. galloprovincialis* [50], the gastropods *Nassarius siquijorensis* and *N. conoidalis* [217], the small abalone *Haliotis diversicolor* [218], and the clam *Cyclina sinensis* [219]. The molecular characterization of HIF-1 α partial coding sequences from various invertebrates (nematodes, oysters, and shrimp) and humans has shown a significant similarity of the sequences and the conserved key functional domains with the previously described isoforms from vertebrates and invertebrates. This also suggests the conserved critical role of these genes in the evolution of the oxygen-sensing pathway and homeostasis throughout the animal kingdom [50,220].

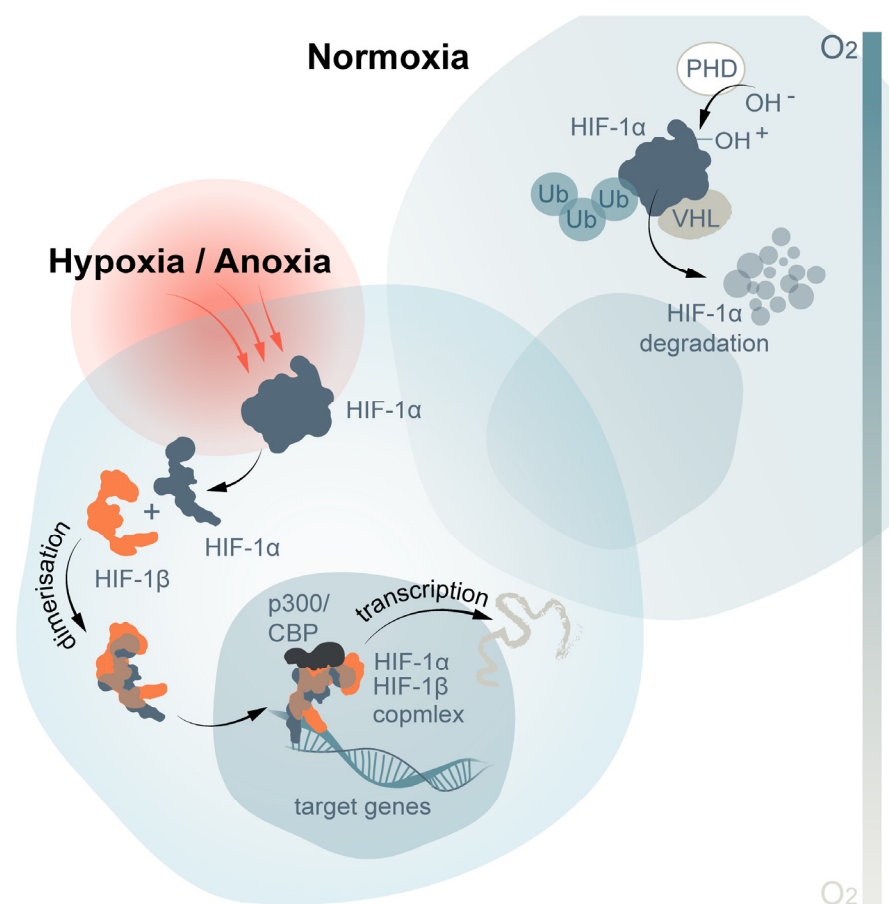


Figure 4. Involvement of HIF-1 in changes of gene expression under hypoxic conditions in bivalves.

As in mammals, the HIF-1 α of marine invertebrates is detected in multiple tissues, but its relative expression varies between different tissues [23,49,215,221]. The expression of the HIF-1 α gene at both molecular transcription and protein levels indicates that various tissues within the same species may exhibit different hypoxic tolerances or oxygen demands, whereas the hypoxia intensity, as well as its duration, may affect HIF-1 in different ways [203,215,219].

The differences in HIF-1 α transcript level after hypoxia exposure between various tissues in invertebrates may evincethe demand for a greater physiological response in certain tissues during adaptation to hypoxic conditions. In mobile crustaceans, the hypoxia exposure results in physiological or behavioral changes, such as an increased ventilation frequency and cardiac output [11,49,219,222]. Therefore, the marked upregulation of HIF-1 α transcript levels in the heart of mantis shrimp (*Oratosquilla oratoria*) may reflect an HIF-induced enhancement of cardiovascular system functions, such as angiogenesis and vasodilation, to achieve efficient oxygen transport for providing survival under chronic hypoxia [49,223,224]. These results suggest that the upregulation of HIF-1 α transcript levels in the two hypoxia-sensitive organs, the heart and the cerebral ganglion, is an important component of adaptation to chronic hypoxia in mantis shrimp and other marine invertebrates [49].

In many bivalves under normoxia, HIF-1 α transcript levels were higher in the gills than in other tissues [215,219], most likely because the gill is a vital organ involved in oxygen detection and gas exchange [219,225]. Furthermore, the gills perform the important function of regulation in the progress of osmotic pressure adjustment, acid balance, and detoxification [226,227].

Under hypoxia, HIF-1 α transcript levels areincreased in all tissues [29,228] and are particularly high in the gills of *Cr. virginica* [215], *H. diversicolor* [218], *Cy. sinensis* [219], *M.*

galloprovincialis [50], *N. siquijorensis*, *N. conoidalis* [217] and *Ruditapes philippinarum* [14]. The transcript levels of HIF-1 α mRNA in different tissues of mollusks significantly differed in time during hypoxia [219]. Thus, in the small abalone *H. diversicolor* exposed to hypoxia (2.0 mg/L DO at 25 °C) stress, the HIF-1 α expression was upregulated in gills at 4, 24, and 96 h, and in hemocytes at 24 and 96 h [218]. In *Cy. sinensis*, the transcript level declined continuously after 12 h hypoxia [219].

The nervous system is an important component of the organism that requires oxygen. In mammals, HIF-1 α plays a crucial role in protecting neurons from hypoxic/ischemic stroke. In the invertebrate nervous system, the function of HIF-1 α is poorly understood [49]. In hypoxia-sensitive scallops (*Mizuhopecten yessoensis*) exposed to hypoxia, HIF-1 α expression appears primarily in the nuclei of neurons of the cerebral ganglia [229]. The high sensitivity of these bivalve ganglia to hypoxia has been confirmed experimentally [230], with their involvement in respiratory metabolism also shown [231,232]. After 4 h of anoxia, the number of HIF-1 α immunopositive neurons in the visceral ganglion sharply increases. The ganglion is an integrative center in mollusks that is involved in the respiration regulation, controls motor behavior, and plays a major role in metabolic processes and in the escape behavior under extreme conditions [233]. The expression of the HIF-1 α factor in the cerebral and visceral ganglia controlling the critical functions in scallops is probably associated with the involvement of this factor in the adaptation of neurons to hypoxia.

An increase in the HIF-1 α content in the mammalian brain correlates with neuroprotective reactions, and prevents or reduces damage in moderate hypoxia/ischemia [234–236]. In the case of chronic and severe hypoxia, the expression of HIF-1 α in the rat brain is reduced due to an increase in the rate of its degradation, which correlates with a decrease in the function of the mitochondria and apoptosis of neurons [237]. An increase in the HIF-1 α expression in neurons' nuclei causes the activation of the genetic apparatus and primarily genes, which triggers a cascade of neuroprotective mechanisms that protect neurons, macro- and microglia, and the endothelium of brain vessels from damage caused by oxygen starvation [234–236]. In the mammalian brain, these mechanisms induce rapid and adequate responses to hypoxia through stimulation of the respiratory and vasomotor centers, and lead to the induction of genes necessary to provide the energy metabolism of cells [238,239].

The role of HIF-1 α in the CNS of marine invertebrates in the formation of hypoxia tolerance has not been extensively studied. Currently, there are data on the HIF-1 α expression in the brain of mantis shrimp (*O. oratoria*) during adaptation to chronic hypoxia caused by the anthropogenic pollution of the habitat [49]. Furthermore, HIF-1 α -immunoreactive neurons that are involved in behavioral and metabolic reactions to hypoxia have been identified in the CNS of nematodes, *Caenorhabditis elegans* [240]. In scallops, anoxia has a pronounced effect on the activity of HIF-1, significantly increasing the expression of its regulatory oxygen-sensitive subunit HIF-1 α in the ganglia neurons that control critical functions of the organism, which can provide the development of compensatory processes in hypoxia. This is confirmed by the results of a study on the metabolism and activity of oxidant enzymes in scallops [27,241].

6. Conclusions

The issue of adaptation to oxygen deficiency and its role in diseases has been studied for many decades using models of animals with different resistances to hypoxia. Despite the recent advance in invertebrate neuroendocrinology, very little is known about the neurohormonal regulation of this process in marine bivalves. Marine mollusks' tolerance to hypoxia is provided by the integration of various signaling systems whose activation causes changes in the expression of neurotransmitters such as DA, 5-HT, CHAT, and NO. Their activity varies significantly between species living in different conditions and having different survival strategies, which indicates the different roles that they play in mollusks with different tolerances to hypoxia. Of particular interest are the dynamics of activity of 5-HT, uNOS, and the HIF-1 α transcription factor in the ganglia, branchial nerves, and gills,

which probably reflect their key roles in the regulation of gas exchange and cardiorespiration in marine mollusks exposed to hypoxia. Data on the topography and dynamics of CHAT activity in hypoxia-sensitive scallops indicate a possible neuroprotective role of choline, which may be one of the mechanisms responsible for protecting nerve cells from hypoxia in mollusks. However, further studies are required to obtain physiological evidence of the involvement of DA, 5-HT, CHAT, NO, and HIF-1 α in providing hypoxia tolerance.

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References

1. Wijsman, J.W.M.; Troost, K.; Fang, J.; Roncarati, A. Global production of marine bivalves. Trends and challenges. In *Goods and Services of Marine Bivalves*; Smaal, A., Ferreira, J., Grant, J., Petersen, J., Strand, Ø., Eds.; Springer: Cham, Switzerland, 2019; pp. 7–26.
2. De Zwaan, A.; Cortesi, P.; Thillart, G.V.D.; Roos, J.; Storey, K. Differential sensitivities to hypoxia by two anoxia-tolerant marine molluscs: A biochemical analysis. *Mar. Biol.* **1991**, *111*, 343–351. [\[CrossRef\]](#)
3. Sobral, P.; Widdows, J. Influence of hypoxia and anoxia on the physiological responses of the clam *Ruditapes decussatus* from southern Portugal. *Mar. Biol.* **1997**, *127*, 455–461. [\[CrossRef\]](#)
4. Toba, M. The decline of Manila clam stock in Tokyo Bay. *Bull. Fish. Res. Agency* **2005**, *1*, 13–18.
5. Vaquer-Sunyer, R.; Duarte, C.M. Thresholds of hypoxia for marine biodiversity. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 15452–15457. [\[CrossRef\]](#)
6. Sussarellu, R.; Dudoignon, T.; Fabioux, C.; Soudant, P.; Moraga, D.; Kraffe, E. Rapid mitochondrial adjustments in response to short-term hypoxia and re-oxygenation in the Pacific oyster *Crassostrea gigas*. *J. Exp. Biol.* **2013**, *216*, 1561–1569. [\[CrossRef\]](#)
7. Hyvärinen, H.S.; Sjöberg, T.; Marjomäki, T.J.; Taskinen, J. Effect of low dissolved oxygen on the viability of juvenile *Margaritifera margaritifera*: Hypoxia tolerance ex situ. *Aquat. Conserv. Mar. Freshw. Ecosyst.* **2022**, *32*, 1393–1400. [\[CrossRef\]](#)
8. Babarro, J.M.; De Zwaan, A. Anaerobic survival potential of four bivalves from different habitats. A comparative survey. *Comp. Biochem. Physiol. Part A Mol. Integr. Physiol.* **2008**, *151*, 108–113. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Spicer, I.J. What can an ecophysiological approach tell us about the physiological responses of marine invertebrates to hypoxia? *J. Exp. Biol.* **2014**, *217*, 46–56. [\[CrossRef\]](#)
10. Chrousos, G.P. Stressors, stress, and neuroendocrine integration of the adaptive response. *Ann. N.Y. Acad. Sci.* **1997**, *851*, 311–335. [\[CrossRef\]](#)
11. Wu, R.S. Hypoxia: From molecular responses to ecosystem responses. *Mar. Pollut. Bull.* **2002**, *45*, 35–45. [\[CrossRef\]](#)
12. Larade, K.; Storey, K.B. Chapter 3. A profile of the metabolic responses to anoxia in marine invertebrates. In *Cell and Molecular Response to Stress*; Elsevier: Amsterdam, The Netherlands, 2002; Volume 3, pp. 27–46.
13. Kozuki, Y.; Yamanaka, R.; Matsushige, M.; Saitoh, A.; Otani, S.; Ishida, T. The after-effects of hypoxia exposure on the clam *Ruditapes philippinarum* in Omaehama beach, Japan. *Estuar. Coast. Shelf Sci.* **2013**, *116*, 50–56. [\[CrossRef\]](#)
14. Nie, H.; Wang, H.; Jiang, K.; Yan, X. Transcriptome analysis reveals differential immune related genes expression in *Ruditapes philippinarum* under hypoxia stress: Potential HIF and NF- κ B crosstalk in immune responses in clam. *BMC Genom.* **2020**, *21*, 318. [\[CrossRef\]](#)
15. Sun, H.; Huang, W.; Luo, Z.; Zheng, C.; Wang, G.; Luo, P.; Wang, S.; Liu, J.; Li, H.; Shu, H. Unraveling the characterization of minichromosome maintenance complex component 2 (MCM2) gene and its SNPs associated with cold-tolerance trait in Pacific white shrimp (*Litopenaeus vannamei*). *Aquac. Rep.* **2021**, *19*, 100610. [\[CrossRef\]](#)
16. Grieshaber, M.K.; Hardewig, I.; Kreutzer, U.; Pörtner, H.O. Physiological and metabolic responses to hypoxia in invertebrates. *Rev. Physiol. Biochem. Pharmacol.* **1994**, *125*, 43–147. [\[PubMed\]](#)
17. Diaz, R.J.; Rosenberg, R. Marine benthic hypoxia: A review of its ecological effects and the behavioural responses of benthic macrofauna. *Oceanogr. Mar. Biol. Ann. Rev.* **1995**, *33*, 245–303.
18. Wannamaker, C.M.; Rice, J.A. Effects of hypoxia on movements and behavior of selected estuarine organisms from the southeastern United States. *J. Exp. Mar. Biol. Ecol.* **2000**, *249*, 145–163. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Loudon, C. Development of *Tenebrio molitor* in low oxygen levels. *J. Insect Physiol.* **1988**, *34*, 97–103. [\[CrossRef\]](#)

20. Hochachka, P.; Rupert, J.; Monge, C. Adaptation and conservation of physiological systems in the evolution of human hypoxia tolerance. *Comp. Biochem. Physiol. A* **1999**, *124*, 1–17. [[CrossRef](#)]
21. Boutilier, R.G. Mechanisms of cell survival in hypoxia and hypothermia. *J. Exp. Biol.* **2001**, *204*, 3171–3181. [[CrossRef](#)]
22. Hochachka, P.W.; Buck, L.T.; Doll, C.J.; Land, S.C. Unifying theory of hypoxia tolerance: Molecular/metabolic defense and rescue mechanisms for surviving oxygen lack. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 9493–9498. [[CrossRef](#)] [[PubMed](#)]
23. Sonanez-Organis, J.G.; Peregrino-Uriarte, A.B.; Gómez-Jiménez, S.; López-Zavala, A.; Forman, H.J.; Yepiz-Plascencia, G. Molecular characterization of hypoxia inducible factor-1 (HIF-1) from the white shrimp *Litopenaeus vannamei* and tissue-specific expression under hypoxia. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2009**, *150*, 395–405. [[CrossRef](#)]
24. Ivanina, A.V.; Nesmelova, I.; Larry, L.; Sokolov, E.P.; Sokolova, I.M. Intermittent hypoxia leads to functional reorganization of mitochondria and affects cellular bioenergetics in marine mollusks. *J. Exp. Biol.* **2016**, *219*, 1659–1674. [[CrossRef](#)]
25. Willmer, P.; Stone, G.; Johnston, J. *Environmental Physiology of Animals*; Blackwell Science: Malden, MA, USA, 2000.
26. McMahon, B.R. Physiological Responses to Oxygen Depletion in Intertidal Animals. *Am. Zool.* **1988**, *28*, 39–53. [[CrossRef](#)]
27. Artigaud, S.; Thorne, M.A.; Richard, J.; Lavaud, R.; Jean, F.; Flye-Sainte-Marie, J.; Peck, L.S.; Pichereau, V.; Clark, M.S. Deep sequencing of the mantle transcriptome of the great scallop *Pecten maximus*. *Mar. Genom.* **2014**, *15*, 3–4. [[CrossRef](#)]
28. Hochachka, P.W. Metabolic suppression and oxygen availability. *Can. J. Zool.* **1988**, *66*, 152–158. [[CrossRef](#)]
29. Gorr, T.A.; Gassmann, M.; Wappner, P. Sensing and responding to hypoxia via HIF in model invertebrates. *J. Insect Physiol.* **2006**, *52*, 349–364. [[CrossRef](#)]
30. Liu, Z.; Li, M.; Yi, Q.; Wang, L.; Song, L. The Neuroendocrine-Immune Regulation in Response to Environmental Stress in Marine Bivalves. *Front. Physiol.* **2018**, *9*, 1456. [[CrossRef](#)]
31. Ottaviani, E.; Franceschi, C. The neuroendocrinology of stress from invertebrates to man. *Prog. Neurobiol.* **1996**, *48*, 421–440. [[CrossRef](#)] [[PubMed](#)]
32. Liu, Z.; Zhou, Z.; Wang, L.; Dong, W.; Qiu, L.; Song, L. The cholinergic immune regulation mediated by a novel muscarinic acetylcholine receptor through TNF pathway in oyster *Crassostrea gigas*. *Dev. Comp. Immunol.* **2016**, *65*, 139–148. [[CrossRef](#)] [[PubMed](#)]
33. Zhou, Z.; Wang, L.; Gao, Y.; Wang, M.; Zhang, H.; Wang, L.; Qiu, L.; Song, L. A monoamine oxidase from scallop *Chlamys farreri* serving as an immunomodulator in response against bacterial challenge. *Dev. Comp. Immunol.* **2011**, *35*, 799–807. [[CrossRef](#)] [[PubMed](#)]
34. Zhou, Z.; Wang, L.; Shi, X.; Zhang, H.; Gao, Y.; Wang, M.; Kong, P.; Qiu, L.; Song, L. The modulation of catecholamines to the immune response against bacteria *Vibrio anguillarum* challenge in scallop *Chlamys farreri*. *Fish Shellfish Immunol.* **2011**, *31*, 1065–1071. [[CrossRef](#)]
35. Zhou, Z.; Wang, L.; Shi, X.; Yue, F.; Wang, M.; Zhang, H.; Song, L. The expression of dopa decarboxylase and dopamine beta hydroxylase and their responding to bacterial challenge during the ontogenesis of scallop *Chlamys farreri*. *Fish Shellfish Immunol.* **2012**, *33*, 67–74. [[CrossRef](#)]
36. Shi, X.; Zhou, Z.; Wang, L.; Yue, F.; Wang, M.; Yang, C.; Song, L. The Immunomodulation of Acetylcholinesterase in Zhikong Scallop *Chlamys farreri*. *PLoS ONE* **2012**, *7*, e30828. [[CrossRef](#)] [[PubMed](#)]
37. Guo, Y.; Wang, L.; Zhou, Z.; Wang, M.; Liu, R.; Wang, L.; Jiang, Q.; Song, L. An opioid growth factor receptor (OGFR) for [Met5]-enkephalin in *Chlamys farreri*. *Fish Shellfish Immunol.* **2013**, *34*, 1228–1235. [[CrossRef](#)] [[PubMed](#)]
38. Shi, X.; Zhou, Z.; Wang, L.; Wang, M.; Shi, S.; Wang, Z.; Song, L. The immunomodulation of nicotinic acetylcholine receptor subunits in Zhikong scallop *Chlamys farreri*. *Fish Shellfish Immunol.* **2015**, *47*, 611–622. [[CrossRef](#)]
39. Rajashekhar, K.P.; Wilkens, J.L. Dopamine and nicotine, but not serotonin, modulate the crustacean ventilatory pattern generator. *J. Neurobiol.* **1992**, *23*, 680–691. [[CrossRef](#)] [[PubMed](#)]
40. Guirguis, M.S.; Wilkens, J.L. The role of the cardioregulatory nerves in mediating heart-rate responses to locomotion, reduced stroke volume, and neurohormones in *Homarus americanus*. *Biol. Bull.* **1995**, *188*, 179–185. [[CrossRef](#)] [[PubMed](#)]
41. Wilkens, J.; Kuramoto, T.; McMahon, B. The effects of six pericardial hormones and hypoxia on the semi-isolated heart and sternal arterial valve of the lobster *Homarus americanus*. *Comp. Biochem. Physiol. C* **1996**, *114*, 57–65. [[CrossRef](#)]
42. Kuo, C.M.; Yang, Y.H. Hyperglycemic responses to cold shock in the freshwater giant prawn, *Macrobrachium rosenbergii*. *J. Comp. Physiol. B* **1999**, *169*, 49–54. [[CrossRef](#)]
43. Chrousos, G.P.; Gold, P.W. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *J. Am. Med. Assoc.* **1992**, *267*, 1244–1252. [[CrossRef](#)]
44. Bonga, S.E.W. The stress response in fish. *Physiol. Rev.* **1997**, *77*, 591–625. [[CrossRef](#)] [[PubMed](#)]
45. Giovine, M.; Pozzolini, M.; Favre, A.; Bavestrello, G.; Cerrano, C.; Ottaviani, F.; Chiarantini, L.; Cerasi, A.; Cangiotti, M.; Zocchi, E.; et al. Heat Stress-Activated, Calcium-Dependent Nitric Oxide Synthase in Sponges. *Nitric Oxide Biol. Chem.* **2001**, *5*, 427–431. [[CrossRef](#)] [[PubMed](#)]
46. González, P.M.; Rocchetta, I.; Abele, D.; Rivera-Ingraham, G.A. Hypoxically Induced Nitric Oxide: Potential Role as a Vasodilator in *Mytilus edulis* Gills. *Front. Physiol.* **2019**, *9*, 1709. [[CrossRef](#)] [[PubMed](#)]
47. Jiang, H.; Guo, R.; Powell-Coffman, J.A. The *Caenorhabditis elegans* hif-1 gene encodes a bHLH-PAS protein that is required for adaptation to hypoxia. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 7916–7921. [[CrossRef](#)] [[PubMed](#)]

48. Hardy, K.M.; Follett, C.R.; Burnett, L.E.; Lema, S.C. Gene transcripts encoding hypoxia-inducible factor (HIF) exhibit tissue and muscle fiber type-dependent responses to hypoxia and hypercapnic hypoxia in the Atlantic blue crab, *Callinectes sapidus*. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **2012**, *163*, 137–146. [\[CrossRef\]](#)
49. Kodama, K.; Rahman, M.S.; Horiguchi, T.; Thomas, P. Assessment of hypoxia-inducible factor-1 α mRNA expression in mantis shrimp as a biomarker of environmental hypoxia exposure. *Biol. Lett.* **2012**, *8*, 278–281. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Giannetto, A.; Maisano, M.; Cappello, T.; Oliva, S.; Parrino, V.; Natalotto, A.; De Marco, G.; Barberi, C.; Romeo, O.; Mauceri, A.; et al. Hypoxia-Inducible Factor α and Hif-prolyl Hydroxylase Characterization and Gene Expression in Short-Time Air-Exposed *Mytilus galloprovincialis*. *Mar. Biotechnol.* **2015**, *17*, 768–781. [\[CrossRef\]](#)
51. Sinakevitch, I.T.; Wolff, G.H.; Pflüger, H.-J.; Smith, B.H. Editorial: Biogenic Amines and Neuromodulation of Animal Behavior. *Front. Syst. Neurosci.* **2018**, *12*, 31. [\[CrossRef\]](#)
52. Budelmann, B.-U.; Bonn, U. Histochemical evidence for catecholamines as neurotransmitters in the statocyst of *Octopus vulgaris*. *Cell Tissue Res.* **1982**, *227*, 475–483. [\[CrossRef\]](#)
53. Williamson, R. Electrophysiological evidence for cholinergic and catecholaminergic efferent transmitters in the statocyst of octopus. *Comp. Biochem. Physiol. Part C Comp. Pharmacol.* **1989**, *93*, 23–27. [\[CrossRef\]](#)
54. Kvetnansky, R.; Sabban, E.L.; Palkovits, M. Catecholaminergic Systems in Stress: Structural and Molecular Genetic Approaches. *Physiol. Rev.* **2009**, *89*, 535–606. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Chen, M.; Yang, H.; Xu, B.; Wang, F.; Liu, B. Catecholaminergic responses to environmental stress in the hemolymph of zhikong scallop *Chlamys farreri*. *J. Exp. Zool. A Ecol. Genet. Physiol.* **2008**, *309*, 289–296. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Dong, W.; Liu, Z.; Qiu, L.; Wang, W.; Song, X.; Wang, X.; Li, Y.; Xin, L.; Wang, L.; Song, L. The modulation role of serotonin in Pacific oyster *Crassostrea gigas* in response to air exposure. *Fish Shellfish Immunol.* **2017**, *62*, 341–348. [\[CrossRef\]](#)
57. O'Connor, E.F.; Watson, W.H.; Wyse, G.A. Identification and localization of catecholamines in the nervous system of *Limulus polyphemus*. *J. Neurobiol.* **1982**, *13*, 49–60. [\[CrossRef\]](#) [\[PubMed\]](#)
58. Franchini, A.; Ottaviani, E.; Caselgrandi, E. Biogenic amines in the snail brain of *Helicella virgata* (Gastropoda, Pulmonata). *Brain Res.* **1985**, *347*, 132–134. [\[CrossRef\]](#)
59. Pani, A.K.; Croll, R. Distribution of catecholamines, indoleamines, and their precursors and metabolites in the scallop, *Placopecten magellanicus* (Bivalvia, Pectinidae). *Cell. Mol. Neurobiol.* **1995**, *15*, 371–386. [\[CrossRef\]](#)
60. Kniazkina, M.; Dyachuk, V. Neurogenesis of the scallop *Azumapecten farreri*: From the first larval sensory neurons to the definitive nervous system of juveniles. *Front. Zool.* **2022**, *19*, 22. [\[CrossRef\]](#)
61. Lacoste, A.; Malham, S.; Cueff, A.; Jalabert, F.; Gelebart, F.; Poulet, S. Evidence for a form of adrenergic response to stress in the mollusc *Crassostrea gigas*. *J. Exp. Biol.* **2001**, *204*, 1247–1255. [\[CrossRef\]](#)
62. Stefano, G.B.; Aiello, E. Histofluorescent localization of serotonin and dopamine in the nervous system and gill of *Mytilus edulis* (Bivalvia). *Biol. Bull.* **1975**, *148*, 141–156. [\[CrossRef\]](#)
63. Smith, S.A.; Nason, J.; Croll, R.P. Distribution of catecholamines in the sea scallop, *Placopecten magellanicus*. *Can. J. Zool.* **1998**, *76*, 1254–1262. [\[CrossRef\]](#)
64. Matsutani, T.; Nomura, T. Localization of monoamines in the central nervous system and gonad of the scallop *Patiniopecten yessoensis*. *Bull. Jpn. Soc. Sci. Fish.* **1984**, *50*, 425–430. [\[CrossRef\]](#)
65. Kotsyuba, E.P. Effects of temperature stress on NO-synthase and tyrosine hydroxylase activities in the central nervous system of bivalve molluscs. *J. Evol. Biochem. Physiol.* **2009**, *45*, 138–146. [\[CrossRef\]](#)
66. Stefano, G.B.; Hiripi, L.; Catapane, E.J. The effects of short and long term temperature stress on serotonin, dopamine and norepinephrine metabolism in molluscan ganglia. *J. Therm. Biol.* **1978**, *3*, 79–83. [\[CrossRef\]](#)
67. Lacoste, A.; Malham, S.K.; Cueff, A.; Poulet, S.A. Stress-Induced Catecholamine Changes in the Hemolymph of the Oyster *Crassostrea gigas*. *Gen. Comp. Endocrinol.* **2001**, *122*, 181–188. [\[CrossRef\]](#) [\[PubMed\]](#)
68. Lansing, M.B.; Gardner, W.S.; Eadie, B.J. Catecholamines as potential sub-lethal stress indicators in Great Lakes macrobenthic invertebrates. *J. Great Lakes Res.* **1993**, *19*, 569–587. [\[CrossRef\]](#)
69. Maule, A.G.; Vanderkooi, S.P. Stress-induced immune-endocrine interaction. In *Stress Physiology in Animals*; Balm, P., Ed.; Sheffield Academic Press Ltd.: Sheffield, UK, 1999; pp. 205–245.
70. Malham, S.K.; Lacoste, A.; Gélébart, F.; Cueff, A.; Poulet, S.A. A first insight into stress-induced neuroendocrine and immune changes in the octopus *Eledone cirrhosa*. *Aquat. Living Resour.* **2002**, *15*, 187–192. [\[CrossRef\]](#)
71. Kinkead, R.; Fritsche, R.; Perry, S.F.; Nilsson, S. The Role of Circulating Catecholamines in the Ventilatory and Hypertensive Responses to Hypoxia in the Atlantic Cod (*Gadus morhua*). *Physiol. Zool.* **1991**, *64*, 1087–1109. [\[CrossRef\]](#)
72. Carroll, M.A.; Catapane, E.J. The nervous system control of lateral ciliary activity of the gill of the bivalve mollusc, *Crassostrea virginica*. *Comp. Biochem. Physiol. Part A Mol. Integr. Physiol.* **2007**, *148*, 445–450. [\[CrossRef\]](#)
73. Bayne, B. *Biology of Oysters (Developments in Aquaculture and Fisheries Science)*, 1st ed.; Academic Press: London, UK, 2017.
74. Catapane, E.J.; Stefano, G.B.; Aiello, E. Pharmacological Study of the Reciprocal Dual Innervation of the Lateral Ciliated Gill Epithelium by the Cns of *Mytilus edulis* (Bivalvia). *J. Exp. Biol.* **1978**, *74*, 101–113. [\[CrossRef\]](#)
75. Aiello, E.L. Nervous control of gill ciliary activity in *Mytilus edulis*. In *Neurobiology of Mytilus edulis*; Stefano, G.B., Ed.; Manchester University Press: Manchester, UK, 1990; Volume 10, pp. 189–208.
76. Marinković, M.; Berger, J.; Jékely, G. Neuronal coordination of motile cilia in locomotion and feeding. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2020**, *375*, 20190165. [\[CrossRef\]](#)

77. Martin, K.; Huggins, T.; King, C.; Carroll, M.A.; Catapane, E.J. The neurotoxic effects of manganese on the dopaminergic innervation of the gill of the bivalve mollusc, *Crassostrea virginica*. *Comp. Biochem. Physiol. Part C* **2008**, *148*, 152–159. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Nelson, M.; Huggins, T.; Licorish, R.; Carroll, M.A.; Catapane, E.J. Effects of p-Aminosalicylic acid on the neurotoxicity of manganese on the dopaminergic innervation of the cilia of the lateral cells of the gill of the bivalve mollusc, *Crassostrea virginica*. *Comp. Biochem. Physiol. Part C* **2010**, *151*, 264–270. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Goldberg, J.I.; Rich, D.R.; Muruganathan, S.P.; Liu, M.B.; Pon, J.R.; Tam, R.; Diefenbach, T.J.; Kuang, S. Identification and evolutionary implications of neurotransmitter-interactions underlying the behavioral response to hypoxia in *Lymnaea stagnalis* embryos. *J. Exp. Biol.* **2011**, *214*, 2660–2670. [\[CrossRef\]](#)
80. Soliman, S. Pharmacological control of ciliary activity in the young sea urchin larva. Effects of monoaminergic agents. *Comp. Biochem. Physiol. Part C Comp. Pharmacol.* **1983**, *76*, 181–191. [\[CrossRef\]](#)
81. Katow, H.; Suyemitsu, T.; Ooka, S.; Yaguchi, J.; Jin-Nai, T.; Kuwahara, I.; Katow, T.; Yaguchi, S.; Abe, H. Development of a dopaminergic system in sea urchin embryos and larvae. *J. Exp. Biol.* **2010**, *213*, 2808–2819. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Almeida, E.A.; Bains, A.C.; Medeiros, M.H.; Di Mascio, P. Effects of trace metal and exposure to air on serotonin and dopamine levels in tissues of the mussel *Perna perna*. *Mar. Pollut. Bull.* **2003**, *46*, 1485–1490. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Nemcsók, J.; Hiripi, L.; Patócskai, M.; Salánki, J.; Kufcsák, O. The effects of pesticides on monoaminergic system related to periodic activity of mussels (*Anodonta cygnea* L.). *Gen. Pharmacol.* **1997**, *29*, 79–83. [\[CrossRef\]](#)
84. Sang, T.-K.; Chang, H.-Y.; Lawless, G.M.; Ratnaparkhi, A.; Mee, L.; Ackerson, L.C.; Maidment, N.T.; Krantz, D.E.; Jackson, G.R. A Drosophila Model of Mutant Human Parkin-Induced Toxicity Demonstrates Selective Loss of Dopaminergic Neurons and Dependence on Cellular Dopamine. *J. Neurosci.* **2007**, *27*, 981–992. [\[CrossRef\]](#)
85. Coulom, H.; Birman, S. Chronic exposure to rotenone models sporadic Parkinson's disease in *Drosophila melanogaster*. *J. Neurosci.* **2004**, *24*, 10993–10998. [\[CrossRef\]](#)
86. Vehovszky, A.; Szabo, H.; Hiripi, L.; Elliott, C.J.H.; Hernadi, L. Behavioural and neural deficits induced by rotenone in the pond snail *Lymnaea stagnalis*. A possible model for Parkinson's disease in an invertebrate. *Eur. J. Neurosci.* **2007**, *25*, 2123–2130. [\[CrossRef\]](#)
87. Wu, W.-H.; Cooper, R.L. Serotonin and Synaptic Transmission at Invertebrate Neuromuscular Junctions. *Exp. Neurobiol.* **2012**, *21*, 101–112. [\[CrossRef\]](#)
88. Voigt, J.-P.; Fink, H. Serotonin controlling feeding and satiety. *Behav. Brain Res.* **2015**, *277*, 14–31. [\[CrossRef\]](#) [\[PubMed\]](#)
89. Tierney, A.J. Feeding, hunger, satiety and serotonin in invertebrates. *Proc. R. Soc. B* **2020**, *287*, 20201386. [\[CrossRef\]](#)
90. Bacqué-Cazenave, J.; Bharatiya, R.; Barrière, G.; Delbecq, J.-P.; Bouguiyoud, N.; Di Giovanni, G.; Cattaert, D.; De Deurwaerdère, P. Serotonin in Animal Cognition and Behavior. *Int. J. Mol. Sci.* **2020**, *21*, 1649. [\[CrossRef\]](#) [\[PubMed\]](#)
91. Parsons, D.W.; Pinsker, H.M. Swimming in *Aplysia brasiliana*: Behavioral and cellular effects of serotonin. *J. Neurophysiol.* **1989**, *62*, 1163–1176. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Newcomb, J.M.; Katz, P.S. Different functions for homologous serotonergic interneurons and serotonin in species-specific rhythmic behaviours. *Proc. Biol. Sci.* **2009**, *276*, 99–108.
93. Lewis, S.L.; Lyons, D.E.; Meekins, T.L.; Newcomb, J.M. Serotonin Influences Locomotion in the Nudibranch Mollusc *Melibe leonina*. *Biol. Bull.* **2011**, *220*, 155–160. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Alavi, S.M.H.; Nagasawa, K.; Takahashi, K.G.; Osada, M. Structure-function of serotonin in bivalve molluscs. In *Serotonin—A Chemical Messenger between All Types of Living Cells*; InTech: London, UK, 2017.
95. Il-Han, J.; Janes, T.; Lukowiak, K. The role of serotonin in the enhancement of long-term memory resulting from predator detection in *Lymnaea*. *J. Exp. Biol.* **2010**, *213*, 3603–3614. [\[CrossRef\]](#)
96. Matsutani, T.; Nomura, T. Serotonin-like immunoreactivity in the central nervous system and gonad of the scallop, *Patinopecten yessoensis*. *Cell Tissue Res.* **1986**, *244*, 515–517. [\[CrossRef\]](#)
97. Vitellaro-Zuccarello, L.; De Biasi, S.; Bernardi, P.; Oggioni, A. Distribution of serotonin-, gamma-aminobutyric acid- and substance P-like immunoreactivity in the central and peripheral nervous system of *Mytilus galloprovincialis*. *Tissue Cell* **1991**, *23*, 261–270. [\[CrossRef\]](#) [\[PubMed\]](#)
98. Croll, R.P.; Too, C.K.; Pani, A.K.; Nason, J. Distribution of serotonin in the sea scallop *Placopecten magellanicus*. *Invertebr. Reprod. Dev.* **1995**, *28*, 125–135. [\[CrossRef\]](#)
99. Siniscalchi, A.; Cavallini, S.; Sonetti, D.; Sbrenna, G.; Capuano, S.; Barbin, L.; Turolla, E.; Rossi, R. Serotonergic neurotransmission in the bivalve *Venus verrucosa* (Veneridae): A neurochemical and immunohistochemical study of the visceral ganglion and gonads. *Mar. Biol.* **2004**, *144*, 1205–1212. [\[CrossRef\]](#)
100. Jia, Y.; Yang, B.; Dong, W.; Liu, Z.; Lv, Z.; Jia, Z.; Qiu, L.; Wang, L.; Song, L. A serotonin receptor (Cg5-HTR-1) mediating immune response in oyster *Crassostrea gigas*. *Dev. Comp. Immunol.* **2018**, *82*, 83–93. [\[CrossRef\]](#) [\[PubMed\]](#)
101. Kotsyuba, E.; Kalachev, A.; Kameneva, P.; Dyachuk, V. Distribution of Molecules Related to Neurotransmission in the Nervous System of the Mussel *Crenomytilus grayanus*. *Front. Neuroanat.* **2020**, *14*, 35. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Stefano, G.B.; Catapane, E.J. Seasonal monoamine changes in the central nervous system of *Mytilus edulis* (Bivalvia). *Experientia* **1977**, *33*, 1341–1342. [\[CrossRef\]](#)
103. Klouche, M.S.; De Deurwaerdère, P.; Dellu-Hagedorn, F.; Lakhdar-Ghazal, N.; Benomar, S. Monoamine content during the reproductive cycle of *Perna perna* depends on site of origin on the Atlantic Coast of Morocco. *Sci. Rep.* **2015**, *5*, 13715. [\[CrossRef\]](#)

104. Kotsyuba, E.; Dyachuk, V. Effect of Air Exposure-Induced Hypoxia on Neurotransmitters and Neurotransmission Enzymes in Ganglia of the Scallop *Azumapecten farreri*. *Int. J. Mol. Sci.* **2022**, *23*, 2027. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Stephens, R.E.; Prior, G. Dynein from serotonin-activated cilia and flagella: Extraction characteristics and distinct sites for cAMP-dependent protein phosphorylation. *J. Cell Sci.* **1992**, *103*, 999–1012. [\[CrossRef\]](#)
106. Gainey, L.F.; Greenberg, M.J. Nitric oxide mediates seasonal muscle potentiation in clam gills. *J. Exp. Biol.* **2003**, *206*, 3507–3520. [\[CrossRef\]](#) [\[PubMed\]](#)
107. Hay-Schmidt, A. The evolution of the serotonergic nervous system. *Proc. R. Soc. B* **2000**, *267*, 1071–1079. [\[CrossRef\]](#)
108. Kuang, S.; Doran, S.A.; Wilson, R.J.A.; Goss, G.G.; Goldberg, J.I. Serotonergic sensory-motor neurons mediate a behavioral response to hypoxia in pond snail embryos. *J. Neurobiol.* **2002**, *52*, 73–83. [\[CrossRef\]](#) [\[PubMed\]](#)
109. Koss, R.; Diefenbach, T.J.; Kuang, S.; Doran, S.A.; Goldberg, J.I. Coordinated development of identified serotonergic neurons and their target ciliary cells in *Helisoma trivolvis* embryos. *J. Comp. Neurol.* **2003**, *457*, 313–325. [\[CrossRef\]](#)
110. Byrne, R.A.; Rundle, S.D.; Smirthwaite, J.J.; Spicer, J.I. Embryonic rotational behaviour in the pond snail *Lymnaea stagnalis*: Influences of environmental oxygen and development stage. *Zoology* **2009**, *112*, 471–477. [\[CrossRef\]](#) [\[PubMed\]](#)
111. Goldberg, J.I.; Doran, S.A.; Shartau, R.B.; Pon, J.R.; Ali, D.W.; Tam, R.; Kuang, S. Integrative biology of an embryonic respiratory behaviour in pond snails: The ‘embryo stir-bar hypothesis’. *J. Exp. Biol.* **2008**, *211*, 1729–1736. [\[CrossRef\]](#)
112. Goldberg, J.I.; Koehncke, N.K.; Christopher, K.J.; Neumann, C.; Diefenbach, T.J. Pharmacological characterization of a serotonin receptor involved in an early embryonic behavior of *Helisoma trivolvis*. *J. Neurobiol.* **1994**, *25*, 1545–1557. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Mapara, S.; Parries, S.; Quarrington, C.; Ahn, K.-C.; Gallin, W.J.; Goldberg, J.I. Identification, molecular structure and expression of two cloned serotonin receptors from the pond snail, *Helisoma trivolvis*. *J. Exp. Biol.* **2008**, *211*, 900–910. [\[CrossRef\]](#)
114. Berlind, A. Neurohumoral and reflex control of scaphognathite beating in the crab *Carcinus maenas*. *J. Comp. Physiol. A* **1977**, *116*, 77–90. [\[CrossRef\]](#)
115. Bayne, B. Ventilation, the heart beat and oxygen uptake by *Mytilus edulis* L. in declining oxygen tension. *Comp. Biochem. Physiol. Part A Physiol.* **1971**, *40*, 1065–1085. [\[CrossRef\]](#)
116. Koester, J.; Dieringer, N.; Mandelbaum, D. Cellular Neuronal Control of Molluscan Heart. *Am. Zool.* **1979**, *19*, 103–116. [\[CrossRef\]](#)
117. Kuwasawa, K.; Hill, R. Evidence for cholinergic inhibitory and serotonergic excitatory neuromuscular transmission in the heart of the bivalve *Mercenaria mercenaria*. *J. Exp. Biol.* **1997**, *200*, 2123–2135. [\[CrossRef\]](#)
118. Kodirov, S.A. The neuronal control of cardiac functions in Molluscs. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **2011**, *160*, 102–116. [\[CrossRef\]](#) [\[PubMed\]](#)
119. Fabbri, E.; Capuzzo, A. Cyclic AMP Signaling in Bivalve Molluscs: An Overview. *J. Exp. Zool. A Ecol. Genet. Physiol.* **2010**, *313*, 179–200. [\[CrossRef\]](#) [\[PubMed\]](#)
120. Hao, Y.; Sun, C.; Rong, Y.; Wang, H.; Xu, Q.; Gao, F.; Wang, A. Circulatory and Metabolic Physiology Disorder in Different Organs of the Subtropical Scallop Species *Chlamys nobilis* Under Thermal and Hypoxia Stress, Revealed by Doppler Ultrasonography Technique. *Front. Mar. Sci.* **2022**, *9*, 880112. [\[CrossRef\]](#)
121. Nicholson, S. Ecophysiological aspects of cardiac activity in the subtropical mussel *Perna viridis* (L.) (Bivalvia: Mytilidae). *J. Exp. Mar. Biol. Ecol.* **2002**, *267*, 207–222. [\[CrossRef\]](#)
122. Michaelidis, B.; Storey, K. Phosphofructokinase from the anterior byssus retractor muscle of *Mytilus edulis*: Modification of the enzyme in anoxia and by endogenous protein kinases. *Int. J. Biochem.* **1990**, *22*, 759–765. [\[CrossRef\]](#)
123. Canesi, L.; Miglioli, A.; Balbi, T.; Fabbri, E. Physiological Roles of Serotonin in Bivalves: Possible Interference by Environmental Chemicals Resulting in Neuroendocrine Disruption. *Front. Endocrinol.* **2022**, *13*, 792589. [\[CrossRef\]](#)
124. Odintsova, N.; Dyachuk, V.; Kiselev, K.; Sheludko, N. Expression of thick filament proteins during ontogenesis of the mussel *Mytilus trossulus* (Mollusca: Bivalvia). *Comp. Biochem. Physiol. Part B Biochem. Mol. Biol.* **2006**, *144*, 238–244. [\[CrossRef\]](#)
125. Dyachuk, V.; Wanninger, A.; Voronezhskaya, E.E. Innervation of bivalve larval catch muscles by serotonergic and FMRFamideergic neurons. *Acta Biol. Hung.* **2012**, *63*, 221–229. [\[CrossRef\]](#) [\[PubMed\]](#)
126. Lazarev, S.S.; Shevchenko, U.V.; Dyachuk, V.A.; Vyatchin, I.G. A Preparative Method for the Isolation of Calponin from Molluscan Catch Muscle. *Int. J. Mol. Sci.* **2022**, *23*, 7993. [\[CrossRef\]](#)
127. Twarog, B.M. Responses of a molluscan smooth muscle to acetylcholine and 5-hydroxytryptamine. *J. Cell Physiol.* **1954**, *44*, 141–163. [\[CrossRef\]](#) [\[PubMed\]](#)
128. Hoyle, G.; Lowy, J. The Paradox of *Mytilus* Muscle: A New Interpretation. *J. Exp. Biol.* **1956**, *33*, 295–310. [\[CrossRef\]](#)
129. York, B.; Twarog, B.M. Evidence for the release of serotonin by relaxing nerves in molluscan muscle. *Comp. Biochem. Physiol. Part A Physiol.* **1973**, *44*, 423–430. [\[CrossRef\]](#)
130. Achazi, R.K.; Dolling, B.; Haakshorst, R. 5HT-induced relaxation and cyclic AMP in a molluscan smooth muscle. *Pflug. Arch. Eur. J. Phys.* **1974**, *349*, 19–27. [\[CrossRef\]](#) [\[PubMed\]](#)
131. Siegman, M.J.; Mooers, S.T.J.; Li, C.; Narayan, S.; Trinkle-Mulcahy, L.; Watabe, S.; Hartshorne, D.J.; Butler, T.M. Phosphorylation of a high molecular weight (approximately 600 kDa) protein regulates catch in invertebrate smooth muscle. *J. Muscle Res. Cell Motil.* **1997**, *18*, 655–670. [\[CrossRef\]](#)
132. D’Este, L.; Kimura, S.; Casini, A.; Matsuo, A.; Bellier, J.-P.; Kimura, H.; Renda, T.G. First visualization of cholinergic cells and fibers by immunohistochemistry for choline acetyltransferase of the common type in the optic lobe and peduncle complex of *Octopus vulgaris*. *J. Comp. Neurol.* **2008**, *509*, 566–579. [\[CrossRef\]](#) [\[PubMed\]](#)
133. Kumar, G.K. Hypoxia. 3. Hypoxia and neurotransmitter synthesis. *Am. J. Physiol. Cell. Physiol.* **2011**, *300*, C743–C751. [\[CrossRef\]](#)

134. Halder, N.; Lal, G. Cholinergic System and Its Therapeutic Importance in Inflammation and Autoimmunity. *Front. Immunol.* **2021**, *12*, 660342. [\[CrossRef\]](#)
135. Messenger, J.B. Neurotransmitters of cephalopods. *Invertebr. Neurosci.* **1996**, *2*, 94–114. [\[CrossRef\]](#)
136. Bellier, J.P.; Casini, A.; Sakaue, Y.; Kimura, S.; Kimura, H.; Renda, T.G.; D'este, L. Chemical neuroanatomy of the cholinergic neurons in the cephalopod octopus and the gastropod Limax. In *Mollusks: Morphology, Behavior and Ecology*; Nova Science Publishers: New York, NY, USA, 2012.
137. Deiana, S.; Platt, B.; Riedel, G. The cholinergic system and spatial learning. *Behav. Brain Res.* **2011**, *221*, 389–411. [\[CrossRef\]](#)
138. van Nierop, P.; Bertrand, S.; Munno, D.W.; Gouwenberg, Y.; Van Minnen, J.; Spafford, J.D.; Syed, N.I.; Bertrand, D.; Smit, A.B. Identification and functional expression of a family of nicotinic acetylcholine receptor subunits in the central nervous system of the mollusk *Lymnaea stagnalis*. *J. Biol. Chem.* **2006**, *281*, 1680–1691. [\[CrossRef\]](#)
139. Kiss, T.; Krajcs, N.; Pirger, Z.; Hernádi, L. Nicotinic acetylcholine receptors containing the $\alpha 7$ -like subunit mediate contractions of muscles responsible for space positioning of the snail, *Helix pomatia* L. tentacle. *PLoS ONE* **2014**, *9*, e109538. [\[CrossRef\]](#)
140. Jiao, Y.; Cao, Y.; Zheng, Z.; Liu, M.; Guo, X. Massive expansion and diversity of nicotinic acetylcholine receptors in lophotrochozoans. *BMC Genom.* **2019**, *20*, 937. [\[CrossRef\]](#)
141. Casini, A.; Vaccaro, R.; D'Este, L.; Sakaue, Y.; Bellier, J.; Kimura, H.; Renda, T. Immunolocalization of choline acetyltransferase of common type in the central brain mass of *Octopus vulgaris*. *Eur. J. Histochem.* **2012**, *56*, 34. [\[CrossRef\]](#)
142. Sakaue, Y.; Bellier, J.-P.; Kimura, S.; D'Este, L.; Takeuchi, Y.; Kimura, H. Immunohistochemical localization of two types of choline acetyltransferase in neurons and sensory cells of the octopus arm. *Brain Struct. Funct.* **2014**, *219*, 323–341. [\[CrossRef\]](#) [\[PubMed\]](#)
143. Norekian, T.P. Coordination of Startle and Swimming Neural Systems in the Pteropod Mollusk *Clione limacina*: Role of the Cerebral Cholinergic Interneuron. *J. Neurophysiol.* **1997**, *78*, 308–320. [\[CrossRef\]](#) [\[PubMed\]](#)
144. Norekian, T.P.; Satterlie, R.A. Cholinergic Activation of Startle Motoneurons by a Pair of Cerebral Interneurons in the Pteropod Mollusk *Clione limacina*. *J. Neurophysiol.* **1997**, *77*, 281–288. [\[CrossRef\]](#) [\[PubMed\]](#)
145. Li, Q.; Zhang, F.; Wang, M.; Li, M.; Sun, S. Effects of hypoxia on survival, behavior, and metabolism of Zhikong scallop *Chlamys farreri* Jones et Preston 1904. *J. Oceanol. Limnol.* **2019**, *38*, 351–363. [\[CrossRef\]](#)
146. Köhler, G.; Lindl, T. Effects of 5-hydroxytryptamine, dopamine, and acetylcholine on accumulation of cyclic AMP and cyclic GMP in the anterior byssus retractor muscle of *Mytilus edulis* L. (Mollusca). *Pflug. Arch.* **1980**, *383*, 257–262. [\[CrossRef\]](#)
147. Jewell, B.R. The nature of the phasic and the tonic responses of the anterior byssal retractor muscle of *Mytilus*. *J. Physiol.* **1959**, *149*, 154–177. [\[CrossRef\]](#)
148. Sugi, H.; Ohno, T.; Moriya, M. Mechanism and Function of the Catch State in Molluscan Smooth Muscle: A Historical Perspective. *Int. J. Mol. Sci.* **2020**, *21*, 7576. [\[CrossRef\]](#) [\[PubMed\]](#)
149. De Zwaan, A.; Cortesi, P.; van den Thillart, G.; Brooks, S.; Storey, K.B.; Roos, J.; van Lieshout, G.; Cattani, O.; Vitali, G. Energy metabolism of bivalves at reduced oxygen tensions. In *Marine Coastal Eutrophication*; Vollenweider, R.A., Marchetti, R., Viviani, R., Eds.; Elsevier: Amsterdam, The Netherlands, 1992; pp. 1029–1039.
150. Raineri, M. Is a mollusc an evolved bent metatrophophore? A histochemical investigation of neurogenesis in *Mytilus* (Mollusca: Bivalvia). *J. Mar. Biol. Assoc. UK* **1995**, *75*, 571–592. [\[CrossRef\]](#)
151. Bulbring, E.; Burn, J.H.; Shelly, H.J. Acetylcholine and ciliary movement in the gill plates of *Mytilus edulis*. *Proc. Roy. Soc. Lond. Ser. B* **1953**, *141*, 445–466.
152. Aiello, E.; Paparo, A. A role for acetylcholine in the regulation of ciliary activity. *Cotnp. Gen. Pharsnacol.* **1974**, *5*, 285–297. [\[CrossRef\]](#)
153. Maisano, M.; Natalotto, A.; Cappello, T.; Giannetto, A.; Oliva, S.; Parrino, V.; Sanfilippo, M.; Mauceri, A. Influences of Environmental Variables on Neurotransmission, Oxidative System, and Hypoxia Signaling on Two Clam Species from a Mediterranean Coastal Lagoon. *J. Shellfish Res.* **2016**, *35*, 41–49. [\[CrossRef\]](#)
154. Beley, A.; Bertrand, N.; Beley, P. Cerebral ischemia: Changes in brain choline, acetylcholine, and other monoamines as related to energy metabolism. *Neurochem. Res.* **1991**, *16*, 555–561. [\[CrossRef\]](#)
155. Jope, R.S.; Jenden, D.J. Choline and phospholipid metabolism and the synthesis of acetylcholine in rat brain. *J. Neurosci. Res.* **1979**, *4*, 69–82. [\[CrossRef\]](#) [\[PubMed\]](#)
156. Blusztajn, J.K.; Liscovitch, M.; Richardson, U.I. Synthesis of acetylcholine from choline derived from phosphatidylcholine in a human neuronal cell line. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 5474–5477. [\[CrossRef\]](#)
157. Lordan, R.; Tsoupras, A.; Zabetakis, I. Phospholipids of Animal and Marine Origin: Structure, Function, and Anti-Inflammatory Properties. *Molecules* **2017**, *22*, 1964. [\[CrossRef\]](#)
158. Ding, Y.; Wang, R.; Wang, X.; Cong, P.; Liu, Y.; Li, Z.; Xu, J.; Xue, C. Preparation and effects on neuronal nutrition of plasmenylethanoamine and plasmanylocholine from the mussel *Mytilus edulis*. *Biosci. Biotechnol. Biochem.* **2020**, *84*, 380–392. [\[CrossRef\]](#)
159. Jin, X.; Wang, R.-H.; Wang, H.; Long, C.-L.; Wang, H. Brain protection against ischemic stroke using choline as a new molecular bypass treatment. *Acta Pharmacol. Sin.* **2015**, *36*, 1416–1425. [\[CrossRef\]](#)
160. Moncada, S.; Palmer, R.M.; Higgs, E.A. Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacol. Rev.* **1991**, *43*, 109–142.
161. Stefano, G.B.; Ottaviani, E. The biochemical substrate of nitric oxide signaling is present in primitive non-cognitive organisms. *Brain Res.* **2002**, *924*, 82–89. [\[CrossRef\]](#) [\[PubMed\]](#)

162. Palumbo, A. Nitric oxide in marine invertebrates: A comparative perspective. *Comp. Biochem. Physiol. Part A Mol. Integr. Physiol.* **2005**, *142*, 241–248. [\[CrossRef\]](#)
163. Zhou, L.; Zhu, D.-Y. Neuronal nitric oxide synthase: Structure, subcellular localization, regulation, and clinical implications. *Nitric Oxide* **2009**, *20*, 223–230. [\[CrossRef\]](#)
164. Colasanti, M.; Venturini, G. Nitric oxide in invertebrates. *Mol. Neurobiol.* **1998**, *17*, 157–174. [\[CrossRef\]](#) [\[PubMed\]](#)
165. Toda, N.; Ayajiki, K. Phylogenesis of constitutively formed nitric oxide in nonmammals. *Rev. Physiol. Biochem. Pharmacol.* **2006**, *138*, 31–80.
166. Wright, N.J.D. A review of the actions of Nitric Oxide in development and neuronal function in major invertebrate model systems. *AIMS Neurosci.* **2019**, *6*, 146–174. [\[CrossRef\]](#)
167. Alderton, W.K.; Cooper, C.E.; Knowles, R.G. Nitric oxide synthases: Structure, function and inhibition. *Biochem. J.* **2001**, *357*, 593–615. [\[CrossRef\]](#) [\[PubMed\]](#)
168. Jiang, Q.; Zhou, Z.; Wang, L.; Wang, L.; Yue, F.; Wang, J.; Song, L. A Scallop Nitric Oxide Synthase (NOS) with Structure Similar to Neuronal NOS and Its Involvement in the Immune Defense. *PLoS ONE* **2013**, *8*, e69158. [\[CrossRef\]](#)
169. Jiang, Q.; Liu, Z.; Zhou, Z.; Wang, L.; Wang, L.; Yue, F.; Wang, J.; Wang, H.; Song, L. Transcriptional activation and translocation of ancient NOS during immune response. *FASEB J.* **2016**, *30*, 3527–3540. [\[CrossRef\]](#)
170. Bredt, D.S.; Glatt, C.E.; Hwang, P.M.; Fotuhi, M.; Dawson, T.M.; Snyder, S.H. Nitric oxide synthase protein and mRNA are discretely localized in neuronal populations of the mammalian CNS together with NADPH diaphorase. *Neuron* **1991**, *7*, 615–624. [\[CrossRef\]](#)
171. Dawson, T.M.; Bredt, D.S.; Fotuhi, M.; Hwang, P.M.; Snyder, S.H. Nitric oxide synthase and neuronal NADPH diaphorase are identical in brain and peripheral tissues. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 7797–7801. [\[CrossRef\]](#)
172. Hope, B.T.; Michael, G.I.; Knigge, K.M.; Vinsent, S.R. Neuronal NADPH diaphorase is a nitric oxide synthase. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 2811–2814. [\[CrossRef\]](#) [\[PubMed\]](#)
173. Moroz, L.L.; Gillette, R. From Polyplacophora to Cephalopoda: Comparative analysis of nitric oxide signalling systems in Mollusca. *Acta Biol. Hung.* **1995**, *46*, 169–182.
174. Moroz, L.L.; Chen, D.; Gillette, M.U.; Gillette, R. Nitric Oxide Synthase Activity in the Molluscan CNS. *J. Neurochem.* **1996**, *66*, 873–876. [\[CrossRef\]](#) [\[PubMed\]](#)
175. Newcomb, J.M.; Watson, W.H. Modulation of swimming in the gastropod *Melibe leonina* by nitric oxide. *J. Exp. Biol.* **2002**, *205*, 397–403. [\[CrossRef\]](#) [\[PubMed\]](#)
176. Kim, H.-W.; Batista, L.A.; Hoppes, J.L.; Lee, K.J.; Mykles, D.L. A crustacean nitric oxide synthase expressed in nerve ganglia, Y-organ, gill and gonad of the tropical land crab, *Gecarcinus lateralis*. *J. Exp. Biol.* **2004**, *207*, 2845–2857. [\[CrossRef\]](#)
177. Vaschenko, M.; Kotsyuba, E. NADPH-diaphorase activity in the central nervous system of the Gray mussel *Crenomytilus grayanus* (Dunker) under stress conditions: A histochemical study. *Mar. Environ. Res.* **2008**, *66*, 249–258. [\[CrossRef\]](#) [\[PubMed\]](#)
178. Benton, J.L.; Sandeman, D.C.; Beltz, B.S. Nitric oxide in the crustacean brain: Regulation of neurogenesis and morphogenesis in the developing olfactory pathway developmental dynamics. *Develop. Dyn.* **2007**, *236*, 3047–3060. [\[CrossRef\]](#) [\[PubMed\]](#)
179. Conte, A.; Ottaviani, E. Nitric oxide synthase activity in molluscan hemocytes. *FEBS Lett.* **1995**, *365*, 120–124. [\[CrossRef\]](#)
180. Jacklet, J.W. Nitric oxide signaling in invertebrates. *Invertebr. Neurosci.* **1997**, *3*, 1–14. [\[CrossRef\]](#)
181. Dyuizen, I.V.; Annikova, L.V.; Motavkin, P.A. NO-synthase localization in the central nervous system of the bivalve mollusks *Mizuhopecten yessoensis* and *Modiolus kurilensis*. *Russ. J. Mar. Biol.* **1999**, *25*, 277–279.
182. Tafalla, C.; Gómez-León, J.; Novoa, B.; Figueras, A. Nitric oxide production by carpet shell clam (*Ruditapes decussatus*) hemocytes. *Dev. Comp. Immunol.* **2003**, *27*, 197–205. [\[CrossRef\]](#) [\[PubMed\]](#)
183. Gonzalez, P.; Abele, D.; Puntarulo, S. Iron and radical content in *Mya arenaria*: Possible sources of NO generation. *Aquat. Toxicol.* **2008**, *89*, 122–128. [\[CrossRef\]](#) [\[PubMed\]](#)
184. Strahl, J.; Abele, D. Nitric oxide mediates metabolic functions in the bivalve *Arctica islandica* under hypoxia. *PLoS ONE* **2020**, *15*, e0232360. [\[CrossRef\]](#)
185. Smith, K.L.; Galloway, T.S.; Depledge, M.H. Neuro-endocrine biomarkers of population-induced stress in marine invertebrates. *Sci. Total. Environ.* **2000**, *262*, 185–190. [\[CrossRef\]](#) [\[PubMed\]](#)
186. Olgart, C.; Gustafsson, L.E.; Wiklund, N.P. Evidence for nonvesicular nitric oxide release evoked by nerve activation. *Eur. J. Neurosci.* **2000**, *12*, 1303–1309. [\[CrossRef\]](#)
187. Lipton, S.A. Neuronal protection and destruction by NO. *Cell Death Differ.* **1999**, *6*, 943–951. [\[CrossRef\]](#) [\[PubMed\]](#)
188. Schurr, A.; Payne, R.S.; Haine, M.F.; Rigo, B.M. Hypoxia, excitotoxicity and neuroprotection in the hippocampal slice preparation. *J. Neurosci. Meth.* **1995**, *59*, 129–138. [\[CrossRef\]](#)
189. Kotsyuba, E.P. Effect of elevated temperature and of hypoxia on NO activity in the central nervous system of bivalve molluscs. *J. Evol. Biochem. Physiol.* **2008**, *44*, 237–246. [\[CrossRef\]](#)
190. Tielens, A.G.; Rotte, C.; van Hellemond, J.J.; Martin, W. Mitochondria as we don't know them. *Trends Biochem. Sci.* **2002**, *27*, 564–572. [\[CrossRef\]](#) [\[PubMed\]](#)
191. Hochachka, P.W. Defense Strategies against Hypoxia and Hypothermia. *Science* **1986**, *231*, 234–241. [\[CrossRef\]](#)
192. Ballantyne, J.S. Mitochondria: Aerobic and anaerobic design—Lessons from molluscs and fishes. *Comp. Biochem. Physiol. Part B Biochem. Mol. Biol.* **2004**, *139*, 461–467. [\[CrossRef\]](#)

193. David, E.; Tanguy, A.; Pichavant, K.; Moraga, D. Response of the Pacific oyster *Crassostrea gigas* to hypoxia exposure under experimental conditions. *FEBS J.* **2005**, *272*, 5635–5652. [[CrossRef](#)] [[PubMed](#)]
194. Boveris, A.; Arnaiz, S.L.; Alvarez, S.; Costa, L.E.; Valdez, L. The mitochondrial production of free radicals. In *Free Radicals in Chemistry, Biology and Medicine*; Yoshikawa, T., Toyokuni, S., Yamamoto, Y., Naito, Y., Eds.; Oica International: London, UK, 2000.
195. Turrens, J.F. Mitochondrial formation of reactive oxygen species. *J. Physiol.* **2003**, *552*, 335–344. [[CrossRef](#)]
196. Brown, G.C.; Borutaite, V. Nitric oxide inhibition of mitochondrial respiration and its role in cell death. *Free. Radic. Biol. Med.* **2002**, *33*, 1440–1450. [[CrossRef](#)]
197. Abele, D.; Kruppe, M.; Philipp, E.E.R.; Brey, T. Mantle cavity water oxygen partial pressure (P_{O_2}) in marine molluscs aligns with lifestyle. *Can. J. Fish. Aquat. Sci.* **2010**, *67*, 977–986. [[CrossRef](#)]
198. Strahl, J.; Brey, T.; Philipp, E.E.R.; Thorarinsdóttir, G.; Fischer, N.; Wessels, W.; Abele, D. Physiological responses to self-induced burrowing and metabolic rate depression in the ocean quahog *Arctica islandica*. *J. Exp. Biol.* **2011**, *214*, 4223–4233. [[CrossRef](#)] [[PubMed](#)]
199. Livingstone, D.R. Origins and Evolution of Pathways of Anaerobic Metabolism in the Animal Kingdom. *Integr. Comp. Biol.* **1991**, *31*, 522–534. [[CrossRef](#)]
200. Semenza, G.L. Regulation of Mammalian O_2 Homeostasis by Hypoxia-Inducible Factor 1. *Annu. Rev. Cell Dev. Biol.* **1999**, *15*, 551–578. [[CrossRef](#)]
201. Semenza, G.L. Signal transduction to hypoxia-inducible factor 1. *Biochem. Pharmacol.* **2002**, *64*, 993–998. [[CrossRef](#)] [[PubMed](#)]
202. Semenza, G.L. Regulation of physiological responses to continuous and intermittent hypoxia by hypoxia-inducible factor. *Exp. Physiol.* **2006**, *91*, 803–806. [[CrossRef](#)] [[PubMed](#)]
203. Wang, X.-W.; Xiao, S.-S.; Zhang, R.; Liu, L.; Zhu, H. Physiological changes and transcriptional modulation of HIF- α s in Siberian sturgeon in response to hypoxia. *Aquaculture* **2021**, *545*, 737219. [[CrossRef](#)]
204. Dolt, K.S.; Mishra, M.K.; Karar, J.; Baig, M.A.; Ahmed, Z.; Pasha, M.Q. cDNA cloning, gene organization and variant specific expression of HIF-1 α in high altitude yak (*Bos grunniens*). *Gene* **2007**, *386*, 73–80. [[CrossRef](#)]
205. Loenarz, C.; Coleman, M.L.; Boleining, A.; Schierwater, B.; Holland, P.W.; Ratcliffe, P.J.; Schofield, C.J. The hypoxia inducible transcription factor pathway regulates oxygen sensing in the simplest animal, *Trichoplax adhaerens*. *EMBO Rep.* **2011**, *12*, 63–70. [[CrossRef](#)]
206. Semenza, G.L. Hypoxia-Inducible Factors in Physiology and Medicine. *Cell* **2012**, *148*, 399–408. [[CrossRef](#)]
207. Wang, G.L.; Jiang, B.H.; Rue, E.A.; Semenza, G.L. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O_2 tension. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 5510–5514. [[CrossRef](#)]
208. Heerden, D.; Vosloo, A.; Nikinmaa, M. Effects of short-term copper exposure on gill structure, metallothionein and hypoxia-inducible factor-1 α (HIF-1 α) levels in rainbow trout (*Oncorhynchus mykiss*). *Aquat. Toxicol.* **2004**, *69*, 271–280. [[CrossRef](#)]
209. Kaelin, W.G., Jr.; Ratcliffe, P.J. Oxygen sensing by metazoans: The central role of the HIF hydroxylase pathway. *Mol. Cell* **2008**, *30*, 393–402. [[CrossRef](#)]
210. Kallio, P.J.; Okamoto, K.; O'Brien, S.; Carrero, P.; Makino, Y.; Tanaka, H.; Poellinger, L. Signal transduction in hypoxic cells: Inducible nuclear translocation and recruitment of the CBP/p300 coactivator by the hypoxia-inducible factor-1 α . *EMBO J.* **1998**, *17*, 6573–6586. [[CrossRef](#)] [[PubMed](#)]
211. Maxwell, P.H.; Wiesener, M.S.; Chang, G.-W.; Clifford, S.C.; Vaux, E.C.; Cockman, M.E.; Wykoff, C.C.; Pugh, C.W.; Maher, E.R.; Ratcliffe, P.J. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* **1999**, *399*, 271–275. [[CrossRef](#)]
212. Epstein, A.C.; Gleadle, J.M.; McNeill, L.A.; Hewitson, K.S.; O'Rourke, J.; Mole, D.R.; Mukherji, M.; Metzen, E.; Wilson, M.I.; Dhanda, A.; et al. *C. elegans* EGL-9 and Mammalian Homologs Define a Family of Dioxygenases that Regulate HIF by Prolyl Hydroxylation. *Cell* **2001**, *107*, 43–54. [[CrossRef](#)]
213. Jiang, B.H.; Zheng, J.Z.; Leung, S.W.; Roe, R.; Semenza, G.L. Transactivation and inhibitory domains of hypoxia-inducible factor 1 α : Modulation of transcriptional activity by oxygen tension. *J. Biol. Chem.* **1997**, *272*, 19253–19260. [[CrossRef](#)]
214. Shen, C.; Nettleton, D.; Jiang, M.; Kim, S.K.; Powell-Coffman, J.A. Roles of the HIF-1 hypoxia-inducible factor during hypoxia response in *Caenorhabditis elegans*. *J. Biol. Chem.* **2005**, *280*, 20580–20588. [[CrossRef](#)]
215. Piontkivska, H.; Chung, J.S.; Ivanina, A.V.; Sokolov, E.P.; Tcha, S.; Sokolova, I.M. Molecular characterization and mRNA expression of two key enzymes of hypoxia-sensing pathways in eastern oysters *Crassostrea virginica* (Gmelin): Hypoxia-inducible factor α (HIF- α) and HIF-prolyl hydroxylase (PHD). *Comp. Biochem. Physiol. Part D Genom. Proteom.* **2011**, *6*, 103–114. [[CrossRef](#)]
216. Kawabe, S.; Yokoyama, Y. Role of Hypoxia-Inducible Factor α in Response to Hypoxia and Heat Shock in the Pacific Oyster *Crassostrea gigas*. *Mar. Biotechnol.* **2012**, *14*, 106–119. [[CrossRef](#)] [[PubMed](#)]
217. Liu, C.; Shin, P.; Cheung, S. Isolation and mRNA expression of hypoxia-inducible factor α (HIF- α) in two sublittoral nassariid gastropods: *Nassarius siquijorensis* and *Nassarius conoidalis*. *Mar. Environ. Res.* **2014**, *99*, 44–51. [[CrossRef](#)]
218. Cai, X.; Huang, Y.; Zhang, X.; Wang, S.; Zou, Z.; Wang, G.; Wang, Y.; Zhang, Z. Cloning, characterization, hypoxia and heat shock response of hypoxia inducible factor-1 (HIF-1) from the small abalone *Haliotis diversicolor*. *Gene* **2014**, *534*, 256–264. [[CrossRef](#)] [[PubMed](#)]
219. Ni, Q.; Li, W.; Liang, X.; Liu, J.; Ge, H.; Dong, Z. Unravelling the characterization of hypoxia-inducible factor-1 α (HIF-1 α) and antioxidant enzymes in clam *Cyclina sinensis* in response to hypoxia. *Aquac. Res.* **2022**, *53*, 5937–5945. [[CrossRef](#)]

220. Rytönen, K.T.; Williams, T.; Renshaw, G.M.; Primmer, C.; Nikinmaa, M. Molecular Evolution of the Metazoan PHD–HIF Oxygen-Sensing System. *Mol. Biol. Evol.* **2011**, *28*, 1913–1926. [[CrossRef](#)] [[PubMed](#)]
221. Wei, H.; Jiang, K.; Zhang, F.; Song, W.; Zhao, M.; Meng, Y.; Chen, F.; Zhao, M.; Ma, L. Two transcripts of hypoxia inducible factor-1 (HIF-1) from *Scylla paramamosain* Estampador, 1950 (Brachyura: Portunidae) and their expression profiles under different hypoxic conditions. *J. Crustac. Biol.* **2017**, *37*, 45–52. [[CrossRef](#)]
222. McMahon, B.R. Respiratory and circulatory compensation to hypoxia in crustaceans. *Respir. Physiol.* **2001**, *128*, 349–364. [[CrossRef](#)] [[PubMed](#)]
223. Semenza, G.L. HIF-1 and mechanisms of hypoxia sensing. *Curr. Opin. Cell Biol.* **2001**, *13*, 167–171. [[CrossRef](#)]
224. Nikinmaa, M.; Ress, B.B. Oxygen-dependent gene expression in fishes. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2005**, *288*, R1079–R1090. [[CrossRef](#)]
225. Kim, C.; Park, C.; Kim, E.; Nam, Y. Transcriptional modulation patterns of abalone *Haliotis discus hannai* hypoxia inducible factor-1 α (HIF-1 α) in interdependent crosstalk between hypoxia, infection, and environmental stresses. *Aquac. Rep.* **2021**, *19*, 100566. [[CrossRef](#)]
226. Camacho-Jiménez, L.; Peregrino-Uriarte, A.; Martínez-Quintana, J.; Yepiz-Plascencia, G. The glyceraldehyde-3-phosphate dehydrogenase of the shrimp *Litopenaeus vannamei*: Molecular cloning, characterization and expression during hypoxia. *Mar. Environ. Res.* **2018**, *138*, 65–75. [[CrossRef](#)] [[PubMed](#)]
227. Henry, R.P.; Lucu, C.; Onken, H.; Weihrauch, D. Multiple functions of the crustacean gill: Osmotic/ionic regulation, acid-base balance, ammonia excretion, and bioaccumulation of toxic metals. *Front. Physiol.* **2012**, *3*, 431. [[CrossRef](#)] [[PubMed](#)]
228. Morin, P., Jr.; McMullen, D.C.; Storey, K.B. Hif-1 α involvement in low temperature and anoxia survival by a freeze tolerant Insect. *Mol. Cell. Biochem.* **2005**, *280*, 99–106. [[CrossRef](#)]
229. Kotsyuba, E.P. Hypoxia-inducible factor 1 α in the central nervous system of the scallop *Mizuhopecten yessoensis* Jay, 1857 (Bivalvia: Pectinidae) during anoxia and elevated temperatures. *Russ. J. Mar. Biol.* **2017**, *43*, 293–301. [[CrossRef](#)]
230. Jadhav, M.; Gulave, A.; Bawane, V. Role of cerebral ganglia in regulation of oxygen consumption of freshwater bivalve mollusc, *Lamellidens marginalis* from Godavari River during summer season. *Biosci. Discov.* **2012**, *3*, 337–341.
231. Mane, U.H.; Rao, K.R.; Muley, S.D.; Vedpathak, A.N. Probable role of nerve ganglia in respiration of the estuarine clam, *Katelysia opima*. *Indian J. Comp. Anim. Physiol.* **1990**, *8*, 21–27.
232. Vedpathak, A.N.; Jadhav, M.R.; Misalk, P. Role of cerebral ganglia in regulation of oxygen consumption of freshwater bivalve mollusc, *Indonaiia caeruleus* (Prashad, 1918) from Godavari river during summer. *Bioscan* **2011**, *6*, 609–612.
233. Motavkine, P.A.; Varaksine, A.A. Le reproduction chez les mollusques bivalves role du système nerveux et regulation. In *Rapports Scientifiques et Techniques*; IFREMER: Brest, France, 1989; Volume 10, pp. 1–250.
234. Stroka, D.M.; Burkhardt, T.; Desbaillets, I.; Wenger, R.H.; Neil, D.A.H.; Bauer, C.; Gassmann, M.; Candinas, D. HIF-1 is expressed in normoxic tissue and displays an organ-specific regulation under systemic hypoxia. *FASEB J.* **2001**, *15*, 2445–2453. [[CrossRef](#)] [[PubMed](#)]
235. Siddiq, A.; Ayoub, I.A.; Chavez, J.C.; Aminova, L.; Shah, S.; LaManna, J.C.; Patton, S.M.; Connor, J.R.; Cherny, R.A.; Volitakis, I.; et al. Hypoxia-inducible factor prolyl 4-hydroxylase inhibition: A target for neuroprotection in the central nervous system. *J. Biol. Chem.* **2005**, *280*, 41732–41743. [[CrossRef](#)] [[PubMed](#)]
236. López-Hernández, B.; Posadas, I.; Podlesniy, P.; Abad, M.A.; Trullas, R.; Ceña, V. HIF-1 α is neuroprotective during the early phases of mild hypoxia in rat cortical neurons. *Exp. Neurol.* **2012**, *233*, 543–544. [[CrossRef](#)]
237. Vangeison, G.; Carr, D.; Federoff, H.J.; Rempe, D.A. The good, the bad, and the cell type-specific roles of hypoxia inducible factor-1 α in neurons and astrocytes. *J. Neurosci.* **2008**, *28*, 1988–1993. [[CrossRef](#)] [[PubMed](#)]
238. Zarembek, K.A.; Malech, H.L. HIF-1 α : A master regulator of innate host defenses? *J. Clin. Investig.* **2005**, *115*, 1702–1704. [[CrossRef](#)]
239. Formenti, F.; Constantin-Teodosiu, D.; Emmanuel, Y.; Cheeseman, J.; Dorrington, K.L.; Edwards, L.M.; Humphreys, S.M.; Lappin, T.R.J.; McMullin, M.F.; McNamara, C.J.; et al. Regulation of human metabolism by hypoxia-inducible factor. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 12722–12727. [[CrossRef](#)]
240. Chang, A.J.; Bargmann, C.I. Hypoxia and the HIF-1 transcriptional pathway reorganize a neuronal circuit for oxygen-dependent behavior in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 7321–7326. [[CrossRef](#)]
241. Pörtner, H.O.; Lannig, G. Chapter 4. Oxygen and Capacity Limited Thermal Tolerance. In *Fish Physiology*; Academic Press: Cambridge, MA, USA, 2009; Volume 27, pp. 143–191.

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