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EFFECT OF GABA MIMETIC PHENIBUT ON OXIDOREDUCTASE ACTIVITY IN THE BRAIN COMPARTMENTS OF ADULT AND JUVENILE SCORPIONFISH *SCORPAENA PORCUS* LINNAEUS, 1758

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An increase in GABA levels serves to the survival of neurons during hypoxia/anoxia. During ontogenesis, GABA is capable of transforming its mediator function from excitatory to inhibitory. The oxidoreductase activity (MDH, 1.1.1.37; LDH, 1.1.1.27; and catalase, 1.11.1.6) was studied in the brain compartments – the medulla oblongata (MB) and the forebrain, diencephalon, and midbrain (AB) – in juvenile and adult black scorpionfish *Scorpaena porcus* against the backdrop of injection of GABA mimetic phenibut (400 mg·kg^{-1}, i. p.). AB structures of juvenile scorpionfish were characterized by an intensity of aerobic metabolism comparable to that of adults. At the same time, an elevated LDH activity in juvenile MB and AB was observed which may serve to increased survivorship at low environmental PO_2. Catalase activity in both age groups was somewhat higher in MB which may be related both to the intensity of oxidative phosphorylation and MB tolerance to injuries during hypoxia. Moreover, catalase activity in the brain of juveniles (especially in AB) was slightly lower than that of adults. Phenibut simultaneously increased MDH and LDH activity in the brain compartments of adult scorpionfish which may be associated with the activation of the malate-aspartate shuttle, with an opposite trend towards the restriction of anaerobic glycolysis in the juvenile brain being mostly pronounced in AB ($p < 0.05$). Simultaneously, phenibut contributed to a rise in catalase activity in all brain compartments, regardless of the age of scorpionfish ($p < 0.05$). Catalase activity was the highest in MB of adult individuals ($p < 0.05$). Apparently, catalase-controlled H_2O_2 level translates the changes in cellular metabolism into a meaningful physiological response by influencing H_2O_2-sensitive ion channels that determine neuronal excitability and modulates GABAergic transmission. Such a mechanism may be involved in the brain maturation, maintain brain resistance to hypoxia, and ensure adaptive processes in juvenile and adult scorpionfish.

Keywords: teleost fish, brain, phenibut, GABA receptors, oxidoreductases

Freshwater and marine aquatic ecosystems are subjected to episodes of hypoxia (dissolved oxygen deficiency) of varying severity, periodicity, and duration. Animals appeal to various ways of adaptation to hypoxia, including physiological and molecular mechanisms, metabolic depression, or intensification of anaerobic glycolysis [Hochachka, Somero, 2002]. In any case, fish survival under hypoxia requires a well-coordinated response to either obtain more O_2 from the hypoxic aquatic environment or limit the metabolic consequences of O_2 deficiency.

The brain is the most actively functioning organ of vertebrates requiring O_2 to produce energy. A significant part of energy consumed by the brain (50–60%) is spent on maintaining ionic gradients and restoring them after depolarization of cell membranes. Under hypoxia, the primary and universal

cause of fish death is a violation of ATP homeostasis in the brain, regardless of the general hypoxic tolerance of a particular species [Nilsson, Ostlund-Nilsson, 2008].

Hypoxia- and anoxia-tolerant vertebrates can serve as model organisms in the studies of mechanisms of neuronal cell survival under conditions of O_2 starvation [Little et al., 2021]. A common feature for all groups of hypoxia/anoxia-tolerant animals, as O_2 decreases, is the release of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) [Hylland, Nilsson, 1999; Nilsson et al., 1991] against the backdrop of a relative decrease in the level of excitatory mediator glutamate [Nilsson et al., 1991]. At the same time, GABA is the only inhibitory amino acid in anoxia-sensitive species the level of which increases during hypoxia, while concentrations of glutamate and glutamine, as its precursor, remain unchanged or even rise [Nilsson et al., 1991]. It is assumed that one of the main ways of neuronal survival during hypoxia/anoxia is an increase in GABA level, in particular, providing the suppression of electrical activity and limiting energy consumption [Nilsson et al., 1991]. A feature of GABA is the transformation of its mediator function from excitatory to inhibitory during ontogenesis [Ben-Ari, 2014].

The adaptive capabilities of inhabitants of an aquatic environment with constantly varying levels of O_2 and periodic episodes of hypoxia/anoxia largely depend on the effectiveness of the interaction of aerobic and anaerobic pathways of energy metabolism. Oxidoreductases, malate dehydrogenase (MDH, L-malate: NAD-oxidoreductase, 1.1.1.37) and lactate dehydrogenase (LDH, L-lactate: NAD-oxidoreductase, 1.1.1.27), are directly involved in energy production, regulate the redox potential of cells, and serve as markers of the oxidative and glycolytic capacity of energy metabolism. About 90% of MDH activity is localized in the cytoplasm, and only 10%, in mitochondria. The involvement of cytosolic MDH in the transport of NADH equivalents across the mitochondrial membrane allows it to control the format of the tricarbonic acids (TCA) cycle pool size. LDH takes part in the anaerobic fermentation of the end product of glycolysis, *i. e.*, in the reversible pyruvate-to-lactate conversion in cytosol in the absence of O_2, being the terminal enzyme of anaerobic glycolysis. Any change in O_2 intake causes shifts between aerobic and anaerobic pathways of energy metabolic processes oxidoreductases are involved in. The reactions of glycolysis provided by oxidoreductases are an integral part of the mechanism of adaptation to hypoxia.

Disturbances in normal O_2 metabolism in cells lead to enhanced generation of reactive oxygen species (hereinafter ROS) the excess of which forms conditions for oxidative stress. For a whole host of reasons, the brain is very vulnerable to oxidative stress: its tissues are adapted to intensive O_2 consumption, contain more oxidizable substrates, and have a less active antioxidant defense system. Catalase (H_2O_2-oxidoreductase, 1.11.1.6) is one of the key enzymes of the antioxidant system. Catalase provides transformation of peroxide (H_2O_2), a product of side reactions in the mitochondrial respiratory chain, into water and O_2. A peculiarity of brain tissues is a very low catalase activity in comparison with that of other organs [Galkina, 2013]. The different activity of antioxidant enzymes and the intensity of spreading of thiobarbituric acid (TBA) reaction products in the brain compartments [Mizuno, Ohta, 1986] may be indicative of different degrees of their vulnerability to ROS.

In contrast to mammals, hypoxia-tolerant animals provide an opportunity, under experimental conditions, to activate or block selectively single parts of the whole mechanism of survival in order to assess their functions. A 90-fold increase of extracellular [GABA] leading to a coma-like state is observed under anoxia in the brain of a turtle *Chrysemys picta belli* tolerant to O_2 deficiency [Nilsson et al., 1991]. [GABA] increases only 2-fold in the hypoxic brain of crucian carp, while motion activity is maintained [Hylland, Nilsson, 1999]. It is known that the effect of excitatory and inhibitory neurotransmitters appears only upon the release from intracellular stores. The administration of a GABA mimetic (phenibut, γ-amino-β-phenylbutyric acid hydrochloride) makes it possible to recreate features of the GABAergic link activation and evaluate GABA influence on the oxidoreductase functioning similar to that during acute hypoxia/anoxia.

Teleosts are a convenient experimental neurobiological object that allows the data obtained to be extrapolated to higher vertebrates and humans. A zebrafish *Danio rerio*, the most famous Teleostei representative among model organisms, has a high homology with the human genome (about 70%) in view of a certain physiological similarity of the main organ systems and tissues [Lim et al., 2022].

The Black Sea scorpionfish (ruff) *Scorpaena porcus* Linnaeus, 1758 is a hypoxia-tolerant teleost. The scorpionfish is able to survive under severe hypoxia conditions (0.35 mg $O_2 \cdot L^{-1}$ for 4 h) [Soldatov et al., 2021] and can recover after 20–30 min of asphyxia resulting from air exposure [Lushchak et al., 1998]. Establishing features of the GABA function implementation, which allow such vertebrates, as the scorpionfish, to survive with little O_2 or being deprived of it, offers a new look at the problems associated with hypoxia and possible ways of counteracting hypoxic brain damage.

The objective of this study was to investigate the effect of phenibut on oxidoreductase activity in the brain compartments of adult and juvenile scorpionfish.

MATERIAL AND METHODS

Scorpionfish *S. porcus* used for the present study were captured in July 2023 in the Sevastopol Bay using a seine net and were transferred to a laboratory in aerated 60-L plastic tanks within 2–3 h after capture. After transportation, the fish were placed into a flow-through aquarium for one week. The animals were fed on minced fish flesh, and only robust, actively feeding fish specimens were used for further experiments.

The study was carried out using a specially designed stand that made it possible to stabilize the required temperature and oxygen concentration for an unlimited period. The water temperature in the experimental chamber was maintained at the seawater temperature level in the summer season (+21…+22 °C). All fish were kept at oxygen concentration of 5.6–6.7 mg $O_2 \cdot L^{-1}$ in water (normoxia). The oxygen level in water was monitored potentiometrically with an oxygen sensor ELWRO PRL T N5221 (Poland).

Experiments were carried out on adult (n = 16; body length 12–18 cm; weight 70–250 g; gonadal maturity stage IV–V) and juvenile scorpionfish (n = 16; body length 8.5–12.0 cm; weight 35–63 g; gonadal maturity stage I) divided into the control and experimental groups (8 specimens in each group). In the experimental groups, a GABA mimetic, phenibut, was injected intraperitoneally (400 mg·kg^{-1}, i. p.); after that, the animals were returned to the darkened experimental chamber for 60 min. The scorpionfish did not manifest any signs of intoxication or movement disorders after phenibut administration and till the removal of tissue samples.

Fish in the control and experimental groups were killed by transspinal dissection. Brain tissues were sampled on an ice table, (0 ± 4) °C, immediately after fish decapitation and were divided into two parts: medulla oblongata (MB) and forebrain, midbrain, and diencephalon (AB). The weighed brain samples were instantly frozen on dry ice and stored at −80 °C until analysis (Forma 900 Series, Thermo Scientific, USA). The supernatant was obtained by centrifuging the homogenates in an Eppendorf 5424 F centrifuge (refrigerated) at 10,000 rpm for 15 min.

The activities of cytoplasmic oxidoreductases, malate dehydrogenase and lactate dehydrogenase (MDH and LDH, respectively), were evaluated using spectrophotometric measurements of the speed of NADH oxidation in 0.2 M Tris-HCl buffer (pH 7.5) in a 3-mL quartz cuvette with 10-mm pathlength at a wavelength λ = 340 nm and +25 °C. The reaction was initiated by adding 0.025–0.05 mL of extract, and the measurements were taken every 30 s during 2–3 min. Pyruvate was used as a substrate to measure LDH activity, and oxaloacetate was used to measure MDH activity. Each measurement was repeated 2–3 times, and the values of the corresponding measurements were averaged. Specific activity of oxidoreductases was expressed as μmol NADH·min^{-1}·mg^{-1}

of supernatant protein. The ratio of the cytosolic MDH/LDH was defined as MDH activity divided by LDH activity, and this allowed evaluating a potential capacity to conduct aerobic metabolism.

Catalase activity (H_2O_2: H_2O_2-oxidoreductase; 1.11.1.6) was assessed by the change in extinction at λ = 410 nm by a method based on the ability of hydrogen peroxide to form a colored complex with ammonium molybdate. The measurements were repeated two times, and the results were averaged. The tubes were filled with 1 mL of 0.03% hydrogen peroxide solution, 0.25 mL of 0.05 M phosphate buffer, pH 8.0, and 0.05 mL of supernatant. The control sample contained 0.25 mL of 12 mM sodium azide solution. After samples incubation for 10 min at +25 °C, the reaction was stopped by adding 2 mL of 4% ammonium molybdate solution. The specific activity of catalase was expressed in μM $H_2O_2 \cdot min^{-1} \cdot mg^{-1}$ of supernatant protein.

Protein content was estimated using the micro-biuret method. The colorimetric reaction was carried out at +25 °C for 15 min, and the optical density was measured at λ = 330 nm. Crystalline serum albumin was used as a standard for creating a calibration curve.

The MDH/catalase and LDH/catalase indices were calculated based on the oxidoreductase activity, in relation to which the ratio of the intensity of functioning of energy metabolism pathways to metabolic tension was assessed.

Data are presented as mean ± *SD*. The normality of data distribution was checked by the Pearson's test. Statistical comparisons were made using the two-sided Student's *t*-test. The differences were considered statistically significant at $p < 0.05$. The two-sided correlation coefficient (r) between MDH, LDH, and catalase activity in the brain compartments was calculated applying the Spearman's rank correlation coefficient. Statistical analysis and graphic representation of the obtained data were carried out using the standard software package of MS Office Excel.

RESULTS

Oxidoreductase activity in the brain compartments of adult and juvenile scorpionfish. In MB and AB of adult scorpionfish, MDH activity was almost identical, while in AB of juvenile individuals, this index was slightly increased (Fig. 1a). In its turn, LDH activity in the brain samples of adult and juvenile fish was lower than that of MDH (Fig. 1b).

Similar rates of catalase activity for the brain compartments in adult individuals contrasted with the lower activity of this enzyme in juvenile fish (Fig. 1d). The lowest catalase activity was registered in juvenile AB ($p < 0.05$).

A trend towards higher values of MDH/LDH index in the mature brain of scorpionfish was observed (Fig. 1d). The lowest ratio of MDH/LDH was recorded in MB of juveniles ($p < 0.05$) (Fig. 1d). At the same time, the values of MDH/catalase and LDH/catalase indices in the brain regions of juveniles exceeded those in adults ($p < 0.05$) (Fig. 2).

MDH and LDH activities in MB of adult scorpionfish positively correlated with body weight ($r = 0.65$ and $r = 0.80$, respectively; $p < 0.05$) and body length ($r = 0.67$ and $r = 0.80$, respectively; $p < 0.05$). Alongside with that, a close relationship was established between MDH and LDH activity in their AB and body weight ($r = 0.62$ and $r = 0.60$, respectively; $p < 0.05$), as well as that of LDH activity and body length ($r = 0.66$; $p < 0.05$).

Oxidoreductase activity in the brain compartments of adult and juvenile scorpionfish under the effect of phenibut. After phenibut administration, MDH activity increased significantly – 2.1-fold and 1.5-fold in MB and AB of adult individuals, respectively ($p < 0.05$) – reaching 4.60 μM $NADH \cdot min^{-1} \cdot mg^{-1}$ of protein in MB and 3.26 μM $NADH \cdot min^{-1} \cdot mg^{-1}$ of protein in AB (Fig. 1a). At the same time, LDH activity rose 1.8-fold in MB and 1.6-fold in AB ($p < 0.05$) acquiring a maximum value in MB: 2.64 μM $NADH \cdot min^{-1} \cdot mg^{-1}$ of protein.

After phenibut administration to juveniles, MDH and LDH activity in their brain compartments decreased insignificantly, with the exception of AB (Fig. 1a), where LDH activity decreased from 1.63 to 1.22 μM NADH·min^{-1}·mg^{-1} of protein ($p < 0.05$). Compared to the adult group, in juvenile fish, MDH activity was lower in MB and AB, and LDH activity was lower in AB ($p < 0.05$). Differences between the brain regions of juveniles were established only in LDH activity under experimental conditions ($p < 0.05$).

It should be noted that after phenibut administration, LDH activity in the fish brain structures remained significantly lower than MDH activity ($p < 0.05$).

At the same time, catalase activity increased in all brain compartments of scorpionfish in both age groups treated with phenibut ($p < 0.05$) (Fig. 1c). The most prominent shifts were observed in MB of mature scorpionfish: the enzyme activity was almost doubled ($p < 0.05$) and amounted to 2.51 μM H_2O_2·min^{-1}·mg^{-1} of protein. Catalase activity increased from 0.54 to 0.83 μM H_2O_2·min^{-1}·mg^{-1} of protein in AB of juveniles (Fig. 1b). At the same time, catalase activity in immature fish remained significantly lower compared to that of adults ($p < 0.05$).

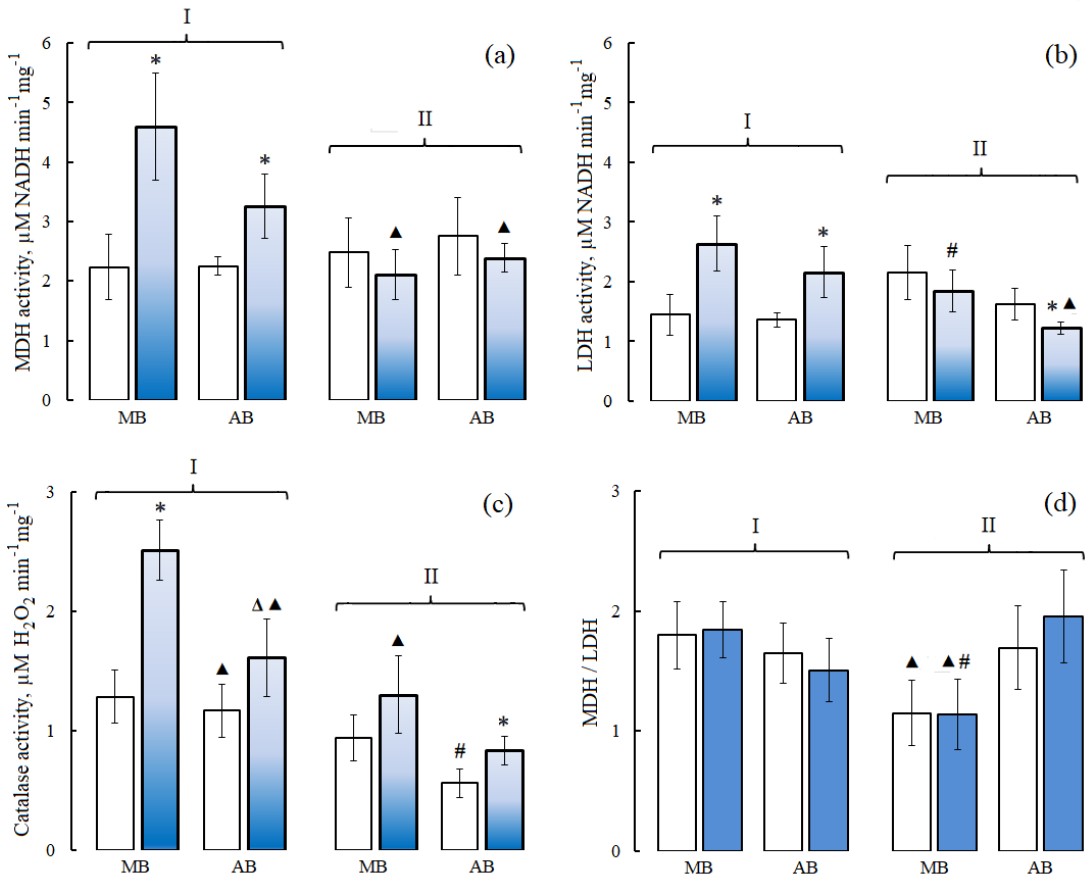

Fig. 1. Effect of phenibut on the activity of MDH (a), LDH (b), and catalase (c) and MDH/LDH index (d) in the brain compartments of *Scorpaena porcus*. White bars, control; dark bars, experiment. I, adults; II, juveniles. MB, medulla oblongata; AB, anterior brain compartments. Significant difference, $p < 0.05$: *, *vs.* control; ▲, *vs.* the same brain compartment of another age group; Δ, between brain compartments of adults; #, between brain compartments of juveniles

Рис. 1. Влияние фенибута на активность МДГ (a), ЛДГ (b) и каталазы (c), индекс МДГ/ЛДГ (d) в отделах мозга *Scorpaena porcus*. Светлые столбики — контроль; тёмные — опыт. I — взрослые особи; II — молодь. MB — продолговатый мозг; AB — передние отделы мозга. Достоверно, $p < 0{,}05$: * — по сравнению с контролем; ▲ — по сравнению с аналогичным отделом мозга другой возрастной группы; Δ — между отделами мозга взрослых особей; # — между отделами мозга молоди

A close relationship was found between MDH and LDH activities in MB ($r = 0.93$; $p < 0.05$) and AB ($r = 0.91$; $p < 0.05$) in juveniles, as well as in adult fish (Table 1).

Table 1. Correlation coefficient (r) between MDH and LDH activities in the brain compartments of adult and juvenile *Scorpaena porcus* after phenibut administration

Таблица 1. Коэффициент корреляции (r) между активностью МДГ и ЛДГ в отделах мозга половозрелых рыб и молоди *Scorpaena porcus* после введения фенибута

Tissues	Adults		Juveniles	
	Control	Phenibut	Control	Phenibut
Medulla oblongata	0.92**	0.63*	0.93**	0.77*
Anterior brain compartments	0.92**	0.80*	0.91**	0.60*

Note: *, $p < 0.05$; **, $p < 0.01$.

Примечание: * — $p < 0{,}05$; ** — $p < 0{,}01$.

MDH/LDH ratio in the brain of adult scorpionfish did not change significantly under the effect of phenibut (Fig. 1d), and a weak trend towards its decrease was observed only in AB. MDH/catalase and LDH/catalase indices also showed some stability (Fig. 2). Alongside with that, a decline of the above-mentioned indices was registered practically in all brain compartments of immature scorpionfish (Fig. 2).

Previously noted high values of the correlation coefficient between MDH and LDH activity in the brain compartments of different age groups of scorpionfish slightly decreased under the effect of phenibut (Table 1). Moreover, phenibut administration canceled the initially established correlation dependence of oxidoreductase activity on the weight and length of adult fish.

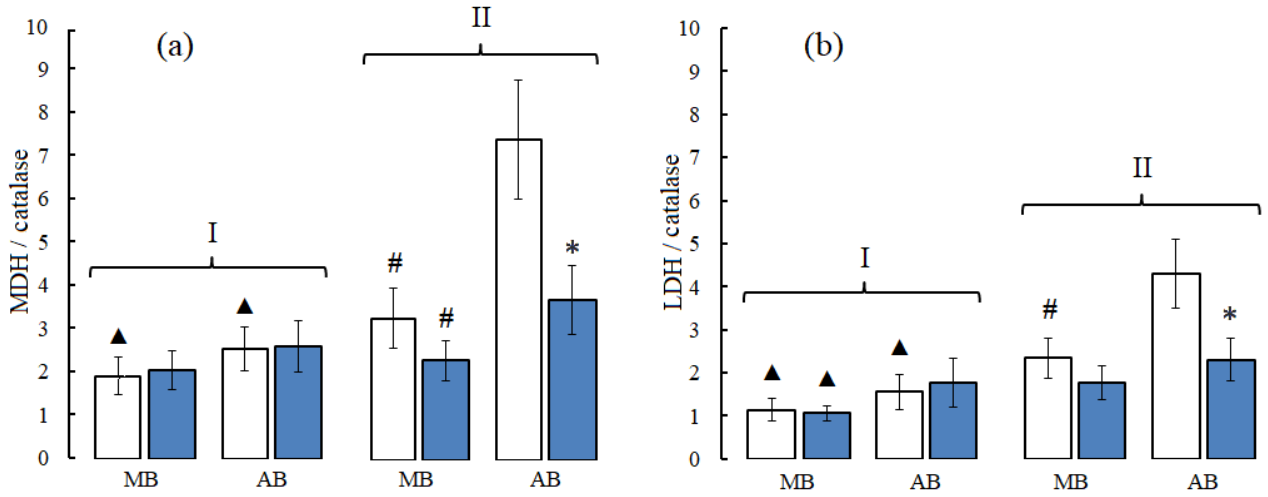

Fig. 2. Effect of phenibut on the ratio of oxidoreductase activity in the brain compartments of *Scorpaena porcus*. White bars, control; dark bars, experiment. A, MDH/catalase; b, LDH/catalase. I, adults; II, juveniles. MB, medulla oblongata; AB, anterior brain compartments. Significant difference, $p < 0.05$: *, *vs.* control; ▲, *vs.* the same brain compartment of another age group; #, between brain compartments of juveniles

Рис. 2. Влияние фенибута на соотношение активности оксидоредуктаз в отделах мозга *Scorpaena porcus*. Светлые столбики — контроль; тёмные — опыт. А — МДГ/каталаза; b — ЛДГ/каталаза. I — взрослые особи; II — молодь. МВ — продолговатый мозг; АВ — передние отделы мозга. Достоверно, $p < 0{,}05$: * — по сравнению с контролем; ▲ — по сравнению с аналогичным отделом мозга другой возрастной группы; # — между отделами мозга молоди

DISCUSSION

Age-related features of MDH and LDH activity in the brain compartments of scorpionfish. The brain regions of adult and juvenile scorpionfish were characterized by comparable values of MDH activity, although this parameter was slightly higher in juveniles.

A weak trend to an increase in MDH activity in the brain of juveniles (especially in AB) may serve as an age-related feature of the maturing brain that consumes energy on plastic processes, synaptogenesis, and myelination. In particular, brain development in rats, reaching sexual maturity by two months of age, is completely terminated only on the 90th day after birth, when myelination is completed in the cerebral cortex [Bon, 2021]. Alongside with that, the intensity of energy metabolism in the brain can be indirectly related to the lifestyle and nutrition. Juvenile scorpionfish live mainly on small crustaceans, molluscs, and worms hiding in the thickets of aquatic plants, while adult individuals prefer fish. AB structures can be relatively more active in juveniles compared to adult ambush predators due to differences in foraging behavior. In addition, AB includes the centers of regulation of muscle tone and body balance coordination, as well as smell and vision centers that are necessary for defensive behavior, since juvenile fish are a relatively easy prey for large predators.

LDH activity in the brain of juvenile scorpionfish noticeably exceeded that of adult fish. As shown, the LDH activity level in the fish brain is a significant part of the mechanism of resistance to hypoxia making it possible to endure O_2 starvation and adapt to low PO_2 [Mandic et al., 2013]. Obviously, increased LDH activity in the brain of juvenile scorpionfish (MB and AB) is a part of an adaptive apparatus that enhances the survivorship of young individuals under conditions of varying O_2 in aquatic environments.

There is a close correlation between MDH and LDH activities in the brain compartments of scorpionfish which reflects the features of the regulation of metabolic pathways during energy production. The mixed aerobic and anaerobic functions of MDH occupying an intermediate position between glycolytic enzymes and citrate synthase should be taken into account. Moreover, the activity of above-mentioned oxidoreductases in both brain compartments of adult fish and in MB of immature individuals was positively correlated with body weight. At the same time, an identical positive relationship between oxidoreductase activity and body length was observed in adult fish, and it was completely absent in immature scorpionfish. The changes in energy metabolism during growth have been reported in many fish species and may reflect the way organisms deal with environmental constraints [Almeida-Val et al., 2000]. Such a positive correlation of MDH and LDH with the body size of juvenile *Astronotus ocellatus* allows them to increase their anaerobic potential with growth [Almeida-Val et al., 2000]. It is obvious that survivorship under hypoxia will rise due to a combination of effects of metabolic rate suppression and an increase in anaerobic capacity as the fish grow. At the same time, the constancy of LDH and pyruvate kinase activity in the brain tissues of adult individuals of bathybenthic species (the barred sand bass *Paralabrax nebulifer* and kelp bass *Paralabrax clathratus*) was observed over a wide range of body sizes [Somero, Childress, 1980] which probably reflects the reaching of a certain plateau in the adaptive capability of the mature brain.

Thus, apparently, the degree of MDH and LDH activity in the brain structures in different age groups of scorpionfish is closely intertwined with the lifestyle, including foraging and defensive behavior and the features of biochemical mechanisms of adaptation.

Age-related features of MDH and LDH activity in the brain compartments of scorpionfish under the effect of phenibut. During hypoxia, the amount of released GABA is determined by species differences and the brain's need for metabolic depression which, in turn, depends on the ability for anaerobic ATP production. The extracellular level of neurotransmitters is approximately 1/1000 of intracellular stores in the brain cells. The administration of GABA or its agonists makes it possible to reconstruct the "manners" of metabolic pathways under acute hypoxia *in vivo*. Since hypoxic GABA release

is subjected to significant individual variations [Hylland, Nilsson, 1999], the injection of a GABA mimetic when converted to the body weight of model organisms allows to standardize and detail the influence of GABA on the mechanisms providing the tolerance to O_2 starvation. One of such agents, phenibut, is a nonselective GABA agonist and GABA mimetic affecting both ionotropic GABA(A) and metabotropic GABA(B) receptors.

In the brain compartments of adult scorpionfish, phenibut administration led to a simultaneous increase in MDH and LDH activity, with an opposite trend towards a notable decrease in LDH activity, *i. e.*, limitation of anaerobic glycolysis in the juvenile brain.

The importance of cytoplasmic MDH rises, when there is a need to enhance glycolytic capacity. MDH may support glycolysis in the absence of O_2, since it delivers NAD^+ as a key cofactor required for functioning of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). In its turn, the function of GAPDH as a catalyst is meant to accelerate the reversible oxidative phosphorylation of glyceraldehyde-3-phosphate to 1,3-diphosphoglycerate with NADH formation. During cerebral ischemia, a simultaneous increase in the activity of mitochondrial and cytosolic MDH forms accompanied by an increase in malate is associated with the activation of the malate-aspartate shuttle mechanism for transporting reduced equivalents from cytoplasm into mitochondria [Belenichev et al., 2012].

Simultaneously with an increase in MDH activity, LDH activity under the effect of phenibut also enhanced in the brain of adult scorpionfish. During hypoxia, such a rise in LDH activity fulfils the immediate energy demand for overcoming possible consequences of insufficient O_2 intake. In particular, such an increase in LDH activity during hypoxia is observed in muscles of a catfish *Clarias batrachus* tolerant to O_2 deficiency [Tripathi et al., 2013]. As a dietary supplement, GABA also caused a gain in LDH activity in liver tissues of a hypoxia-tolerant Indian major carp, mrigal *Cirrhinus mrigala*, during O_2 starvation [Varghese et al., 2020]. At the same time, LDH activity in mrigals under the effect of GABA was somewhat lower than that when exposed to hypoxia. The term “pseudohypoxia” is often used to indicate the activation of the pathway to a decrease in O_2 availability under non-hypoxic conditions. Obviously, an increase in LDH activity in the brain compartments of adult scorpionfish subjected to phenibut administration and in the presence of a sufficient amount of O_2 may correspond to the above notion, *i. e.*, it gives evidence of the reaction of this enzyme according to the “pseudohypoxic” type.

The simultaneous increase in MDH and LDH activity against the backdrop of phenibut reflects an enhanced intensity of glycolytic processes in scorpionfish. The occurring discrepancy in the degree of shifts in the oxidoreductase activity in different brain structures may be a consequence of significant differences in the rate of GABA metabolism and specificity of GABA effect on energy metabolism in the separate brain regions.

Noteworthy, phenibut administration contributed to a decrease in LDH activity (especially in AB) in the absence of a noticeable MDH reaction in juvenile scorpionfish *vs.* mature individuals. It is possible to explain LDH “behavior” in the age-related aspect only using a number of certain assumptions.

Hence, a decrease in LDH activity in juvenile scorpionfish (during catalase activation associated with a probable increase in H_2O_2 production) can be conditioned by oxidation of cysteine residues by ROS in the enzyme molecule determining the formation of its spatial configuration [Ledo et al., 2022].

In addition, variations in the response of oxidoreductases to phenibut in scorpionfish individuals of different age may be indirectly related to the phenomenon of transit of GABA mediator function. It is known that GABA excitatory action is observed in higher vertebrates only at the early stages of development (embryogenesis and early postnatal period) [Ben-Ari, 2014]. In the perinatal period, GABA effect shifts from excitation to inhibition and, accordingly, from depolarization to hyperpolarization of the cell membrane [Ben-Ari, 2014]. Transit of GABA function is mediated through the developmentally regulated expression of cation-Cl-cotransporters NKCC1 (Na^+-K^+-Cl^- cotransporter 1) and KCC2 (K^+-Cl^- cotransporter 2). It is assumed that the ratio between NKCC1 and KCC2 activities

providing incoming and outgoing Cl^- fluxes, respectively, plays a key role in functioning of GABA(A) receptors [Virtanen et al., 2021]. A decrease in NKCC1 activity with an increase in KCC2 activity is the cause for a sharp change in the properties of GABA(A) receptors during mammalian ontogenesis.

After the final formation of interneuronal connections and the establishment of constant network activity, time-averaged Cl^- loading, KCC2 expression level, and hyperpolarizing effect of GABAergic currents reach their peak values [Virtanen et al., 2021]. Alongside with that, ion transport and energy metabolism of neurons tend to their maximum values. In its turn, the neuronal damage leads to KCC2 loss and to a "reversal" of the polarity of GABAergic currents which may be a part of a larger pattern of dedifferentiation that is necessary for the neuronal survival in adverse conditions [Virtanen et al., 2021] and is manifested by a return to immature high $[Cl^-]$ and the excitatory effect of GABA [Ben-Ari, 2014].

The excitatory/inhibitory sequence of GABA function is just one of many aspects of the maturation of brain activity. Since the shift from one to a diametrically opposite functional role of GABA occurs in higher vertebrates at the prenatal and postnatal developmental stages, the oxidoreductase reaction is likely to be observed in the brain of juvenile scorpionfish against the backdrop of a slowed transit of the mediator function (transitional stage of the GABA function) to the classical inhibition of neuronal activity. In case of a possible prolonged transit of the GABA function, the difference and direction of the change in LDH activity in MB and AB of juveniles *vs.* mature scorpionfish correlates directly with the unfolding of KCC expression in the caudal-to-rostral direction in the process of brain maturation [Watanabe, Fukuda, 2015]. At the same time, phenibut makes it possible to maintain the interdependence (observed in the control) between MDH and LDH activity in different brain compartments of juvenile and adult scorpionfish which is indicative of a rather physiological, but not toxic effect of this agent.

Age-related features of catalase activity in the brain compartments of scorpionfish. Energy metabolism is both a source and a target for various oxidants which determines the close coordination of enzymes of metabolic pathways and the antioxidant system. Brain tissue is notable for a particular intensity of oxidative phosphorylation (hereinafter OXPHOS) which makes this tissue more susceptible to oxidative stress. The main source of ROS is the leakage of electrons from the mitochondrial electron transport chain. Approximately 2–5% of the electron flow in the respiratory chain of isolated brain mitochondria produce superoxide anion (O_2^-) and H_2O_2. The high dependence of the brain on ATP production *via* intensive OXPHOS determines the necessity for effective methods of O_2^- and H_2O_2 detoxification. O_2^- is inactivated by superoxide dismutase (SOD). H_2O_2 formed in this process is decomposed by catalase and glutathione peroxidase (hereinafter GPx). While catalase serves as the main H_2O_2 detoxification enzyme, GPx is more efficient in H_2O_2 decomposition [Bagnyukova et al., 2005]. Moreover, GPx has a much higher affinity for H_2O_2 which suggests the importance of GPx at low H_2O_2 concentrations, while the role of catalase increases under severe oxidative stress.

The brain antioxidant system is characterized by a low or moderate activity of catalase and GPx against the backdrop of the predominant SOD activity [Bagnyukova et al., 2005]. The low catalase activity may be associated with the production of H_2O_2 as a transmitter which acquires a specificity in mediating signaling effects [Sies, Jones, 2020] and has the ability to modulate synaptic transmission [Lee et al., 2015]. The level of antioxidant enzyme activity in fish has features that are characteristic and inherent to certain species, and this makes it difficult to compare the antioxidant system parameters [Radi et al., 1985]. Moreover, the discrepancies in the activity of antioxidant enzymes in relation to the brain structures manifest morphological and functional heterogeneity of the brain [Brannan et al., 1981].

Catalase activity in MB was slightly higher than that in AB in both age groups of scorpionfish. The brainstem neurons in the mammalian brain (including MB) have a relatively high degree of catalase immunoreactivity compared to those of the forebrain [Moreno et al., 1995]. However, within the brain

structures themselves, there are regions with different catalase staining intensity [Moreno et al., 1995]. In many cases, densely stained cells appear to be more resistant to ischemia/reperfusion injury, whereas weakly stained cells are more susceptible to ischemic injury.

The manifestation of catalase activity in the brain compartments of scorpionfish can be regarded in two ways. On the one hand, high activity of antioxidant enzymes (catalase in particular) may be of certain importance for scorpionfish MB that contains cardiorespiratory reflexogenic centers and ensures its viability. On the other hand, AB in a resting ambush predator should be less active functionally at the appropriate OXPHOS intensity and at a lower rate of ROS/H_2O_2 production.

H_2O_2 is considered a dynamic reporter of neuronal activity and a "translational substance" blurring the boundary between energy and information [Lee et al., 2015]. O_2 consumption is believed to be proportional to the activity of brain structures which are characterized by the greatest demand for macroergs in order to support ATP-dependent signaling, *i. e.*, information processes. H_2O_2 produced during OXPHOS rapidly retranslates dynamic shifts in cellular metabolism, especially in the mitochondrial O_2 consumption, into a meaningful physiological signal [Lee et al., 2015]. H_2O_2-sensitive ion channels are the target of such a physiological signal and can affect the excitability of neurons directly producing H_2O_2. H_2O_2 can modulate GABAergic neurotransmission. Cellular transient receptor potential (TRP) ion channels, subclass TRPM2 (transient receptor potential melastatin 2, non-selective cation channel), are uniquely sensitive to the action of H_2O_2, and this leads to the activation of GABAergic neurons. At the same time, such activation of KATP channels (ATP-dependent potassium channels) by H_2O_2 reduces neuronal excitability [Lee et al., 2015]. There are certain differences in the H_2O_2-dependent activation of KATP and TRPM2 channels for different animal species which is indicative of special functions of this regulatory process. Apparently, the resulting effect of H_2O_2 will reflect the balance of activity of the expressed H_2O_2-sensitive target channels (KATP and TRPM2) and thus ensure cellular type-specific modulation patterns.

It should be noted that catalase activity in different brain compartments of juvenile scorpionfish (especially AB) was lower compared to that of adult individuals, and this is consistent with the data on a gain in catalase activity in the mammalian brain in the process of its maturation from the postnatal period to full maturity [Mavelli et al., 1982] and on a further age-dependent increase in the enzyme activity [Vertechy et al., 1993]. On the other hand, under normal conditions, low catalase activity is partially compensated by GPx function [Bagnyukova et al., 2005]. In addition, total glutathione level is quite high in the brain of goldfish highly tolerant to hypoxia (670 nmol *per* g wet weight) which indicates the importance of this antioxidant tripeptide in H_2O_2 neutralization. In its turn, low GPx activity can be compensated by high catalase activity. The activity of the mentioned enzymes is negatively correlated in different mammalian species [Godin, Garnett, 1992]. Thus, GPx is likely to maintain cellular function and adapt to the normal cellular metabolic activity, while catalase will be a part of the stress response mechanism regardless of low metabolic rate or O_2 concentration in the aquatic environment. Moreover, catalase does not require cofactors or energy expenditure for its activity, while GPx oxidizes glutathione to GSSG that must then be processed by NADPH-dependent glutathione reductase. The preference for an enzyme with minimal energy consumption in the environment with limited availability of resources may be an effective survival strategy, especially for immature animals.

Relatively low catalase activity may suggest an increase in H_2O_2 level in the brain regions of juvenile scorpionfish. As mentioned above, H_2O_2 is assigned the function of a volume neurotransmitter [Ledo et al., 2022] and of a second messenger as well [González et al., 2020]. O_2-dependent production of H_2O_2 is a regulator of the erythropoietin (Epo) gene expression [Fandrey et al., 1994], a "multi-purpose" factor of general oxygen homeostasis. In particular, Epo exerts protective functions in different organs, including brain, in case of ischemic injury [Grasso et al., 2004]. Epo gene and Epo receptor (EpoR) expression has been identified in teleost species [Chu et al., 2007].

A decrease in catalase activity is likely to ensure functioning of H_2O_2 as a second messenger in juvenile scorpionfish which provides their adaptive potential and survivorship in hypoxia.

As mentioned above, calculated MDH/catalase and LDH/catalase indices reflect the ratio of energy metabolism intensity to physiological tension (eustress). Adult scorpionfish, as well as juvenile ones, were similarly characterized by slightly higher MDH/catalase and LDH/catalase indices in AB. Moreover, MDH/catalase and LDH/catalase in juvenile individuals were noticeably higher ("their own" age norm), since less intense functioning of "energy-saving" catalase may be associated with an increased "need" for H_2O_2 as a second messenger in the processes of brain maturation and adaptation. Aerobic and anaerobic pathways of energy metabolism in the brain of juvenile scorpionfish that supply ATP for the protein synthesis, the development, and maintenance of synaptic transmission of neural networks acquire special significance. At the same time, a sufficient amount of H_2O_2 ensures the transcription of genetic factors.

Age-related features of catalase activity in the brain compartments of scorpionfish under the effect of phenibut. Increased catalase activity under the effect of phenibut in the scorpionfish brain may serve as an indirect sign of large-scale H_2O_2 production. Any stress response of the organism is accompanied by a short-term burst in ROS production and the development of oxidative stress. A putative increase in H_2O_2 production in the scorpionfish brain under phenibut administration is associated with the ability of GABA derivatives to stimulate OXPHOS [Mokrousov et al., 2019]. In MB of adult scorpionfish, catalase activity reached the highest value among the studied brain samples which may indirectly evidence for the dominant functional activity of this part of the brain of the ambush predator, as mentioned above.

For successful survival in hypoxia, an organism must not only maintain its viability amidst O_2 shortage, but also have an effective mechanism to minimize or prevent oxidative stress during the transition from hypoxia back to aerobic conditions. Some animal species consistently demonstrate high levels of the activity of antioxidant system, while the others increase the antioxidant defense directly on exposure to hypoxia in an anticipatory process coined "preparation for oxidative stress" [Hermes-Lima et al., 1998]. The latter mechanism occurs in stress-tolerant species that are regularly exposed to significant fluctuations in O_2 availability in their habitat [Víg, Nemcsók, 1989]. The enhancement of antioxidant defense during physiological states requiring decreased ROS production is a preparative mechanism that minimizes potential damage due to oxidative stress, including reoxygenation. It is obvious that phenibut has the properties of an agent quickly increasing the antioxidant status of the scorpionfish brain.

The ability of exogenous GABA to enhance H_2O_2 production [Jin et al., 2019] which provides modulation of the currents mediated by GABA(A) receptors constitutes a reversible redox-sensitive signaling mechanism [Hogg et al., 2015]. H_2O_2 can limit GABAergic neurotransmission not only through the effect on presynaptic sites [Sah, Schwartz-Bloom, 1999], but also on postsynaptic sites [Sah et al., 2002]. ROS-induced plasticity of different GABA(A) receptor subtypes suggests oxidation of cysteine residues by ROS in receptor subunits, and this is critical for ion channel activation [González et al., 2020]. In addition, it was shown that the activation of a special type of GABA(A) receptors by ROS, including α3 subunit, may enhance GABAergic synaptic transmission [Accardi et al., 2014]. Obviously, ROS, as a putative homeostatic signaling unit, couple the cellular metabolism with the "strength" of inhibitory neurotransmission [Accardi et al., 2014].

Anyway, the effect of ROS on GABAergic signaling and the resulting effect is likely to depend entirely on the cell type and the region of the central nervous system [González et al., 2020]. The sensitivity of GABA(A) receptors to ROS/H_2O_2 remains an important factor in the development of neuronal injury during ischemia and neurodegenerative processes [Accardi et al., 2014].

The MDH/catalase and LDH/catalase indices, before and after phenibut administration in the different brain compartments of adult scorpionfish, remained comparable which is indicative of the stability of functioning of energy metabolism pathways without signs of oxidative stress. At the same time,

a sharp reduction in similar indices, especially in AB, was observed in juvenile scorpionfish which was determined by a decrease in the activity of energy metabolism-related oxidoreductases and by the increased catalase activity. As MDH/LDG index in MB of adult and juvenile scorpionfish turned out to be quite stable, it is possible to assume greater stability and protection of this part of the brain. However, a simultaneous decrease in MDH/catalase and LDH/catalase in the brain compartments of juveniles indicates pronounced physiological tension. A decline in the mentioned ratios of oxidoreductase/catalase activity occurred mainly due to catalase activation which can be regarded as an indirect sign of a rise in the production of substrate (H_2O_2) for this enzyme. Given that H_2O_2 actually acts as a second messenger [González et al., 2020], the physiological meaning of increased H_2O_2 production is to trigger a regulatory cascade providing increased antioxidant protection through ROS-sensitive transcription factors [Bagnyukova et al., 2005] as a protective mechanism in the maturing brain.

Conclusions. The brain of juvenile scorpionfish is characterized by a trend toward a higher intensity of energy metabolism which may be determined by the completion of growth processes, with a noticeably lower catalase activity. In the mature fish brain, GABA mimetic phenibut causes activation of oxidoreductases according to a "pseudohypoxic" scenario. At the same time, activation of the GABAergic mechanism can suppress LDH activity in the anterior brain compartments of juvenile fish that are more vulnerable to O_2 starvation. A concomitant increase in catalase activity in the brain tissues of both age groups is probably indirect evidence of an increase in H_2O_2 production due to OXPHOS intensification. Deviations in catalase activity are likely to contribute to the implementation of the function of H_2O_2 as a second messenger and a modulator of GABAergic signaling. Such a mechanism involving H_2O_2 may be especially significant for the maturing brain that completes the adjustment of neural networks and also ensures and maintains brain resistance to hypoxia in juvenile and adult scorpionfish.

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ВЛИЯНИЕ МИМЕТИКА ГАМК ФЕНИБУТА НА АКТИВНОСТЬ ОКСИДОРЕДУКТАЗ В КОМПАРТМЕНТАХ МОЗГА ВЗРОСЛЫХ И НЕПОЛОВОЗРЕЛЫХ ОСОБЕЙ СКОРПЕНЫ *SCORPAENA PORCUS* LINNAEUS, 1758

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Повышение уровня ГАМК служит выживанию нейронов при гипоксии/аноксии. В процессе онтогенеза ГАМК способна трансформировать свою медиаторную функцию от возбуждающей к тормозной. Изучали активность оксидоредуктаз (МДГ, 1.1.1.37; ЛДГ, 1.1.1.27; каталазы, 1.11.1.6) в отделах мозга — продолговатом мозге (МВ) и переднем, промежуточном и среднем мозге (АВ) — неполовозрелых и взрослых особей морского ерша *Scorpaena porcus* на фоне введения миметика ГАМК фенибута (400 мг·кг$^{-1}$, i. p.). Структуры АВ неполовозрелых особей скорпены характеризовались интенсивностью аэробного метаболизма, сопоставимой с таковой взрослых особей; в то же время в МВ и АВ молоди была отмечена более высокая активность ЛДГ, служащая, по-видимому, повышению выживаемости при низком PO_2. В обеих возрастных группах показатели активности каталазы были несколько выше в МВ, что может быть связано как с интенсивностью окислительного фосфорилирования, так и с устойчивостью к повреждению МВ при гипоксии. При этом активность каталазы в мозге молоди (особенно АВ) была несколько ниже показателей взрослых особей. Фенибут повышал активность МДГ и ЛДГ в компартментах мозга взрослых особей скорпены, что, вероятно, связано с активацией малат-аспартатного шунта, при противоположном тренде к ограничению анаэробного гликолиза в незрелом мозге, особо выраженном в АВ ($p < 0,05$). Одновременно фенибут способствовал увеличению активности каталазы во всех компартментах мозга вне зависимости от возраста скорпены ($p < 0,05$); наибольшей величины активность каталазы достигала в МВ взрослых особей ($p < 0,05$). Предполагается, что контролируемая каталазой продукция H_2O_2 переводит изменения в клеточном метаболизме в значимый физиологический ответ путём воздействия на H_2O_2-чувствительные ионные каналы, которые определяют возбудимость нейронов, и модулирует ГАМКергическую передачу сигналов. Такой механизм может быть задействован при созревании мозга, поддерживать устойчивость мозга к гипоксии и обеспечивать адаптационные процессы неполовозрелых и взрослых особей скорпены.

Ключевые слова: костистые рыбы, мозг, фенибут, ГАМК-рецепторы, оксидоредуктазы