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ROLE OF THYROID HORMONES IN FISHES

Dolomatov S.I.¹, Kubyshkin A.V.¹, Kutia S.A.¹, Zukow W.².

¹State Institution “Crimea State Medical University named after S.I. Georgievsky”, Simferopol, Ukraine

²Kazimierz Wielki University, Bydgoszcz, Poland

Abstract

Literature review is devoted to analysis of role of thyroid hormones in fishes. Structural features of secretory epithelium and neuro-endocrine control of thyroid status in fishes are described. Function of thyroid hormones in development of biorhythms as well as in molecular mechanisms of maintenance of cellular and tissue chronobiological activities in fishes are characterized. Issue about role of thyroid hormones in fish adaptation in response to changes of intensity of abiotic environmental factors – water salinity and temperature are considered.

Key words: fish, thyroid hormones, thyroid status control, ontogenesis.

Thyroid gland produces mainly prohormone thyroxine (T₄). In tissues type I and type II monodeiodinases catalyze it's conversion into physiologically active form – triiodothyronine (Bianco A.C. et al., 2002; Gereben B. et al., 2008). Main trends of investigation in thyroidology relate to study of controlling mechanisms of hormonogenesis and tissue metabolism of thyroid hormones (TH). These mechanisms are based on delicately organized interactions of TH receptor's group (Yen P.M., 2001), deiodinases (Gereben B. et al., 2008), transport complex of carrier proteins, providing TH entry into cell through plasmalemma (Hennemann G. et al., 2001; Ritchie J.W. et al., 2003; Heuer H., Visser Th.J., 2009) and mechanisms, maintaining systemic levels of T₃. They are realized due to conversion of T₄ into T₃ with subsequent T₃ release into extracellular fluid (Neves F.A. et al., 2002; Heuer H., Visser Th.J., 2009).

It must be admitted that current viewpoint on physiological mechanisms of integration of thyronogenesis and TH metabolism at tissue and cellular level is reasonably efficient. It is confirmed by significant progress in ascertainment of role of deiodinases in regulation of systemic and intraorganic TH metabolism, in maintenance of thyroid status constants, as well as some important TH effects, including coordination of embryogenesis in vertebrates (Köhrle J., 1999; Bianco A.C. et al., 2002; Peeters R.P. et al., 2006; Stoykov I. et al., 2006; Barrett P. et al., 2007; Gereben B. et al., 2008; St. Germain D.L. et al., 2009; Chiamolera M.I., Wondisford F.E., 2009; Salvatore D., 2011).

It is necessary to mention that total lack or minor evidence of own regulatory effects of T_4 is far from incontestability (Incerpi S. et al., 2002; 2005; Lin H.-Y. et al., 2009).

It's essential to note that researches are strenuously interested by evolutionary aspects of formation of thyroid status controlling mechanisms in vertebrates. At the same time, facts about some interspecies differences of TH metabolism in mammals were progressively accumulated (Kuiper G.G. et al., 2003). However, most numerous phylogenetically ancient representatives of vertebrates are fishes. Their distinctive feature is fairly wide range of systemic parameters of humoral regulation of physiological functions. Therefore, discussed in literature issues about role of various thyroid status regulatory mechanisms in fishes, including role of deiodinases (Darras V.M. et al., 1998; Bianco A.C. et al., 2002; Shepherdley C.A. et al., 2004), neuro-endocrine mechanisms of thyroid gland activity control (Geven E. et al., 2007; Carr J.A., Patiño R., 2011), iodothyronines transport system state (Santos C.R. et al., 2002; Richardson S. et al., 2005) are of interest not only to fundamental science, but also to ichthyology, as well as development of aquaculture methods.

Earlier studies have shown that inorganic iodine compounds, required for TH biosynthesis, get into fish by food intake and active absorption of iodide-anions in gill's epithelium (Eales J.G., Brown S.B., 1993). Also, authors of cited publication, state that teleost fishes as well as homoiotherms, have basic components of thyroid status control, including hypothalamo-pituitary axis; specific plasma proteins, responsible for TH delivery to tissues; presence of specific enzymes – deiodinases and TH receptors. Besides they suggest that peculiarities of thyroid status regulation in fishes unlike homoiotherms are due to less effective activity of ion-transporting system, responsible for accumulation of biologically important iodide-anions, and weaker neuro-endocrine control of TH tissue metabolism.

It was shown that TH, accumulated in mature fish eggs, play an extremely important role in embryogenesis (Power D.M. et al., 2001). It was established that thyroid status is one of the critical factors in salmon smoltification (Ebbesson L.O. et al., 2008), as well as in fish development and reproduction (Blanton M.L., Specker J.L. et al., 2007). Physiological constants of thyroid status can be recognized as one of the most important selection criterions in commercial fishing (Tymchuk W.E. et al., 2009).

Findings of studies on thyroid physiology in fishes confirmed the great theoretical and practical values of given aspect (Brown D.D., 1997; Blanton M.L., Specker J.L., 2007; Geven E.J. et al., 2009; Carr J.A., Patiño R., 2011; Chang J. et al., 2012). They were carried out within wider aspect of investigations on humoral control of fish physiology (McCormick S.D., 2001; McGonnell I.M., Fowkes R.C., 2006; Geven E. et al., 2007; 2009).

Side by side with mentioned arguments, the use of bony fish as an object in biomedical researches is also important (McGonnell I.M., Fowkes R.C., 2006; Blanton M.L., Specker J.L., 2007; Liu C. et al., 2011; Chang J. et al., 2012). In addition, thyroid status of fishes inhabiting the natural reservoirs can be recognized as perspective marker of intensity of man's impact on water ecosystem (Brar N.K. et al., 2010; Thienpont B. et al., 2011; Park B. et al., 2011).

Thus, we conclude that physiological mechanisms of formation and maintenance of fish's thyroid status is an actual research aspect. Meanwhile, in literature widely presented facts about role of TH in control of fish embryogenesis and metamorphosis. Also, many data about role of TH in fish reparation and adaptation were collected. From our point of view, it deserves special consideration mechanisms of toxic effects of xenobiotics on fish thyroid status.

1. NEURO-ENDOCRINE CONTROL OF FISH THYROID STATUS

We should remember that in higher animals thyrotropin-releasing hormone is a tripeptide produced by hypothalamic neurons. It travels along portal vessels to adenohypophysis and stimulates thyrotrophs to secrete thyroid-stimulating hormone (TSH) (Balabolkin M.I., 1987). TSH controls expression of thyroglobulin mRNA, thyreoperoxidase, TSH receptors and sodium-dependent iodide ions uptake in thyrocytes, i.e. basic determinants of iodothyronine biosynthesis intensity (Kambe F., Seo H., 1997). In vitro experiments have shown TSH ability to increase expression of plasmalemma Na^+/K^+ -ATPase and to stimulate Na^+/K^+ -pump activity (Pressley T.A. et al., 1995). Besides, TSH directly affects rate of T_4 5'-monodeiodination in thyroid tissue (Tourakulov Y.H. et al., 1986). In mammals hypothalamic-pituitary-thyroid axis hormones do not only directly stimulate thyroid gland, but also modulate synthesis and secretion of neuropeptides, specifically vasopressin (antidiuretic hormone) and oxytocin (Ciosek J., 2002). On the other hand, increase of TH plasma level inhibits synthesis and secretion of thyrotropin-releasing hormone and TSH by suppression transcription and posttranslational processing of prohormones as well as modulation of TH receptors expression in thyrotrophs (Chiamolera M.I., Wondisford F.E., 2009). Strong correlation between T_4 and TSH plasma concentrations allows to use them as an indicator of functional activity of thyroid gland (Gitel E.P., Melnitchenko G.A., 1999, Gontcharov N.P., 1995) emphasized that testing of levels of TSH and free T_4 is the most objective criterion for thyroid axis activity.

Though basic mechanisms of neuro-endocrine control of endocrine glands activity in fishes and animals are principally identical, some authors noted specific features of embryogenesis and anatomy of hypothalamus, hypophysis and thyroid gland in bony fishes (McGonnell I.M., Fowkes R.C., 2006; Geven E.J. et al., 2007). They mentioned that one of the most important fish peculiarities is absence of thyroid gland as compact organ. Most of bony fishes have aggregations of follicles in subpharyngeal area and close to ventral aorta. In some fishes, follicles are found around heart, spleen, kidneys and other organs.

Earlier findings have shown species differences in TH plasma dynamics in response to injections of exogenic thyrotropin-releasing hormone (Eales J.G., Himick B.A., 1988). Hamano K. et al. (1990) revealed immunohistochemically high concentrations of thyrotropin-releasing hormone in hypothalamus and olfactory bulb of carp. Further immunohistochemical studies found out presence of

high concentrations of thyrotropin-releasing hormone in other part of juvenile chinook salmon brain (Matz S.P., Takahashi T.T., 1994). Authors suggested that in fish brain, as well as in higher vertebrates, thyrotropin-releasing hormone acts not only as humoral control factor, but also neuromediator. Another study detected strong correlation between thyrotropin-releasing hormone concentration in hypothalamus and T₄ in carp plasma. Their levels depend on water temperature (van den Burg E.H. et al., 2003). In publications, devoted to study of fish hypothalamic-pituitary-thyroid axis, it is noted that this physiological mechanism of endocrine status control contains basic molecular components which correspond closely to those of higher animals (Blanton M.L., Specker J.L., 2007). During early stages of fish embryogenesis, when own secretory follicles and hypothalamic-pituitary axis are not formed yet, maternal TH (mostly T₄) are used (Tagawa M., Hirano T., 1989). It is established that in embryogenesis, tissue iodothyronin kinetics control is realized due to modulation of TH receptors' expression (Power D.M. et al., 2001; Liu Y.W., Chan W.K., 2002; Raine J.C. et al., 2004) and enzymatic activity of various deiodinases isoforms (Walpita C.N. et al., 2007; 2009).

The primary structure of TSH beta-subunit in vertebrates is characterized by a high homology (Han Y.S. et al., 2004). At the same time, authors reported that its intensive transcription correlates with the increased T₄ plasma concentration during maturation of Japanese eel. It is informed that the selective inhibition of thyroid hormonogenesis in *Pimephales promelas* is accompanied with the reduction of T₄ in blood on the background of stimulation of TSH beta-subunit transcription (Lema S.C. et al., 2009). Authors emphasized tissue-specific and gender features of changes in TH receptors mRNA transcription depending on alterations of fish thyroid status.

At once, it was shown that in most of the bony fish species, unlike mammals, corticotropin-releasing hormone stimulates TSH synthesis and secretion (Matz S.P., Hofeldt G.T., 1999; De Groef B. et al., 2006; McGonnell I.M., Fowkes R.C., 2006). At the same time it was revealed that this neuropeptide stimulation of ACTH and TSH synthesis and secretion is realized via different receptors – type I and type II respectively (De Groef B. et al., 2006). On the other hand earlier studies showed that exogenic corticosteroids affect T₄ plasma concentrations, thyroid index value and thyroid tissue sensitivity to TSH (Leatherland J.F., 1987). Further findings allowed to establish that thyrotropin-releasing hormone does not control TSH secretion in carp, while ACTH and α -melanocyte-stimulating hormone have direct effects (Geven E.J. et al., 2009). In the author's opinion, this proves strong integration between interrenal and thyroid axis of humoral control of metabolism. They pay attention on significant differences between *in vivo* and *in vitro* studies devoted to the sensitivity of hypothalamo-pituitary-thyroid and hypothalamo-pituitary-interrenal axes to various humoral factors. The biological role of hypothalamo-hypophyseal-interrenal axes in TH secretion control in fishes is an issue. However, lack of stimulating effect of thyrotropin-releasing hormone on TSH secretion, except for some bony fishes, was recorded in some amphibians and terrestrial vertebrates (Geven E.J. et al., 2006; 2009).

In literature, the reasoned opinion is expressed that TH and corticosteroid synergism is important for adaptation, organogenesis and metamorphoses in anadromous fishes (Geven E.J. et al., 2009). Really, these findings have confirmed conception about TH importance in the formation of adaptive response in fishes (Sreejith P. et al., 2007; Peter M.C. et al., 2011; Peter V.S., Peter M.C.,

2011), their role in critical stages of fish growth and development (Itoh K. et al., 2010; Ojima D., Iwata M., 2010). It is emphasized too that cortisol and TH, along with growth hormone, modulate synthesis insulin-like growth factor-I in fish hepatocytes (Leung L.Y. et al., 2008). Therewith authors noted that corticotrophin-releasing hormone, but not thyrotropin-releasing hormone, besides T₄ synthesis stimulation, triggers downstream migration in anadromous salmonids (Ojima D., Iwata M., 2010).

2. ROLE OF THYROID HORMONES IN REGULATION OF CHRONOBIOLOGICAL STRUCTURE OF PHYSIOLOGICAL FUNCTIONS IN FISHES

Investigation of chronobiological parameters of physiological functions in fishes is very important because of its practical significance (Karlsen Ø. et al., 2006; Leder E.H. et al., 2006; Zhang D. et al., 2009; Almeida F. et al., 2009; Volkoff H. et al., 2010). In modern literature, as one of the main environmental time-setting factors is considered the photoperiod. It is a universal stimulus which coordinates dynamics of environmental conditions and intensity of biochemical, physiological and behavioral reactions in vertebrates (Vanecek J., 1998; Gastel J.A. et al., 1998; Klein D.C., 2007). Certain publications indicate that interseasonal adaptation of fishes depends not only on light intensity dynamics but also spectral composition of optical signal. Its perception efficiency throughout life cycle of, for example, salmonids is controlled by TH (Temple Sh.E. et al., 2008; Cheng Ch. L. et al., 2009).

It will be recalled that the pineal gland in vertebrates is one of the central regulators of the circadian rhythm realizing own action via secretion of a specific hormone – melatonin. Highest rate of melatonin synthesis and secretion is registered at night time. Because the ratio of dark period to light period changes throughout year, melatonin directly participates in the formation of seasonal rhythms as well.

It is generally known that in mammals' pineal gland secretory activity is modified by external signal incoming from photoreceptors or the highest time-giver supraoptic nucleus of hypothalamus (SNH) which also receives information from the retina. Unlike other tissues, the circadian rhythm produced by SNH is characterized by high damping resistance even beyond an external stimulus. Whereas in lower vertebrates, including fishes, namely pineal gland, apart from endocrine function, plays a role of endogenous circadian oscillator which controls rhythmic production of melatonin. In addition, unlike mammals, fish pineal gland is a photoreceptor organ. Due to this specificity, circadian rhythms of melatonin synthesis and secretion, even in isolated organ, are very stable.

Apart from that in lower animals, including fishes, time-givers' hierarchy is not so strict as in higher ones. It is because of the ability of peripheral tissues not only to autonomous maintenance of stable circadian rhythm, but also its sensitivity to light stimulus in the absence of signals, incoming from retina and pineal gland. Due to these mechanisms in various fish cell cultures, the light stimulus synchronizes and stabilizes clearly marked circadian rhythm of gene expression.

It is known that in fishes, photoreceptors of the pineal gland are directly involved in the development of particular reactions to light stimuli. They are circadian rhythm corrections, triggering of mechanisms of circadian rhythms of pineal gland secretion activity at early stages of ontogenesis,

and the acute inhibition of melatonin secretion by light stimuli. It was revealed that the expression of isoforms of the photosensitive pigment; opsin is recorded in fish pineal gland at early stages of embryogenesis (Gothilf Y. et al., 1999).

Numerous chronobiological studies clearly prove significant role of photoperiod in fish life cycle and reveal mechanisms of changes of physiological functions in most important marketable fishes in photoperiod parameters' modulation. In the literature widely presented findings about regulatory effects of melatonin on most obvious target tissues in fishes, including gill epithelium (Kleszczyska A. et al., 2006), gonads (Renuka K., Joshi B.N., 2010), as well as in relation to mechanisms of nitrogen metabolism control (Rodela T.M., Wright P.A., 2006), behavioral reactions (Loipez-Olmeda J.F., 2006), growth hormone secretion (Falcón J. et al., 2003), smoltification (Iigo M. et al., 2005), immune protection (Roy B. et al., 2008). Data about extrapineal sources of melatonin in fishes (Velarde E., 2010), as well as some other effects beyond its time-setting function are also interesting.

Meanwhile, molecular genetic nature of these effects till now is studied poorly. For the most of fishes photoperiod is a major environmental time-setting factor. It forms chronobiological structure of physiological functions and coordinates action of specific genes–molecular clock. In turn, genes-oscillators control circadian and annual rhythms of transcription on tissue level. As a result, many genes are involved in development and maintenance of stable parameters of functional systems chronostructure in fishes (Gothilf Y. et al., 1999; Ziv L., Gothilf Y., 2006; Leder E.H. et al., 2006; Zhang D. et al., 2009; Huang T.S. et al., 2010; Migaud H. et al., 2010). Moreover, in some bony fishes there is no strong correlation between light intensity and expression of genes coding basic enzymes of melatonin biosynthesis (Cahill G.M. et al., 1998). Also, some bony fishes possess low sensitivity of pineal endocrine function to light stimulus (Migaud H. et al., 2006).

Such ideology, recognising chronobiological parameters as integral index of interaction between central and molecular time-setting factors, is supported by many studies devoted to investigation of the role of the photoperiod in chronobiological regulation of fish reproduction (Bayarri M.J. et al., 2004; Leder E.H. et al., 2006; Zhang D. et al., 2009; Renuka K., Joshi B.N., 2010), as well as embryonic and postembryonic development (Gothilf Y. et al., 1999; Ziv L., Gothilf Y., 2006).

However, some researchers mentioned that these effects of melatonin could be realized without growth hormone, but via control of secretory activity of thyroid tissue and TH tissue metabolism is essential for organogenesis (Kalamarz H. et al., 2009). Moreover, TH are most important humoral regulators of gene expression (Aranda A., Pascual A., 2001; Flamant F. et al., 2007). Besides, it is known that TH are one of the major humoral regulators of cell cycle. They determine cell division and differentiation (Kress E. et al. 2008; Kester M. et al., 2009; St. Germain D.L. et al., 2009). It is very important for growing fishes (Power D.M. et al., 2001; Liu Y.W., Chan W.K., 2002; Lam S.H. et al., 2005; Li W. et al., 2011) as well as effective reparation (Mader M.M., Cameron D.A., 2004; Tripathi G., Shasmal J., 2010; Fujimoto K. et al., 2012).

It is known that TH have permissive effect and plasma concentration of total and free fractions of TH narrowly limited. Though it is possible not only to reveal diurnal fluctuations of their plasma concentrations in smolts, but also to identify specific chronobiological parameters of concentrations of

given hormones typical for smoltification (Ebbesson L.O. et al., 2008). Moreover, salmonids possess low sensitivity of pineal secretory activity to light intensity (Cahill G.M. et al., 1998; Migaud H. et al., 2006). However, hypothesis that temperature is a major time-setting environmental factor for salmonids is not experimentally proved too (McCormick S.D. et al., 2002). At the same time, the priority of temperature or photoperiod as a time-setting factor can be determined by geographical distribution of fishes (Condon C.H. et al., 2010).

It is interesting that main parameters of fish thyroid status used in chronobiological studies are plasma concentration of total and free fractions of T_4 and T_3 (Wright M.L., 2002; McCormick S.D. et al., 2002; Ebbesson L.O. et al., 2008; Allen P.J. et al., 2011), production intensity of reverse T_3 (3,3',5'- T_3 , r T_3), deiodinase activity levels in various tissues (Eales J.G. et al., 1993; Morin P.P. et al., 1993), or TH concentration in the whole body of fish (Kalamariz H. et al., 2009).

Mechanism for maintenance of plasma T_4 and T_3 levels and metabolism of TH in tissues are very complicated. Therefore, describing it is necessary to pay attention on neuro-endocrine control of thyroid tissue, temporal dynamics of TH transport proteins, TH receptors expression level in target tissues and parameters of metabolic TH clearance in fishes.

Probably, light signal directly affects hypothalamo-pituitary control of thyroid status in fishes (Ebbesson L.O.E. et al., 2011). Facts about influence of photoperiod on monodeiodinases activity parameters in mammals also exist (Lechan RM, Fekete C., 2005; Barrett P. et al., 2007). It was established interspecies differences of TH kinetics parameters in teleost fishes. Kinetics is determined by: 1) hormonogenesis intensity in thyroid tissue; 2) TH uptake in tissues and their biotransformation (deiodination); 3) TH metabolic clearance rate due to the formation of water-soluble conjugates (Geven E. et al., 2007).

It is necessary to consider that target tissues most actively uptake free plasma TH fractions, i.e. ones not bound with specific transport proteins. In mammals, principal plasma transport proteins for T_4 and T_3 are thyroxine-binding protein (TBP), albumin and thyroxine-binding prealbumin (transthyretin). They bind and transport at least 99.97% T_4 and 99.7% T_3 (Robbins J., 2000; Kelly G.S., 2000; Cameron S.J. et al., 2005). Plasma concentration of these proteins in humans is 17 mg/l (TBP), 0.27 g/l (transthyretin) and 42 g/l (albumin). However, mostly intravasal TH is transported by TBP – the most important regulator of systemic TH metabolism (Robbins J., 2000; Cameron S.J. et al., 2005; McKinnon B. et al., 2005; Qi X. et al., 2011). The site of TBP molecule responsible for TH binding has a higher affinity to T_4 than T_3 . At the same time, only 20% plasma TBP participates in TH transport (Zhou A. et al., 2006).

It will be recalled that one of the specific humoral regulators of energetic metabolism in mammals is ghrelin (van der Lely A.J. et al., 2004). In addition, ghrelin participates in the formation of free T_4 circadian rhythm (Kluge M. et al., 2010). Authors suggest that ghrelin can modulate TH-transporting ability of TBP.

However, TBP is absent in amphibian and fish blood (Larsson M. et al., 1985). Principal TH-transporting plasma protein in fishes is transthyretin (Yamauchi K. et al., 1999). Authors emphasize that transthyretin, unlike TBP, has more affinity to T_3 but not T_4 . The primary structure of tetramer transthyretin subunit possesses higher homology in vertebrates (Yamauchi K. et al., 1999; Santos C.R.

et al., 2002). Therewith, the most conservative part of transthyretin is hormone-binding site (Morgado I. et al., 2008).

Tissue localization of biosynthesis and physicochemical properties of transthyretin differ in fishes and highest animals (Power D.M. et al., 2000). At early stages of vertebrate ontogenesis, including fishes, the role of TH-transporting plasma proteins in thyroid status control is significant (Richardson S. et al., 2005). Participation of TH in the regulation of transthyretin plasma concentration in teleost fishes is also recorded (Morgado I. et al., 2007). Authors indicated that in experiment hypo- and hyperthyroid fishes, but not euthyroid, have higher transthyretin concentration in blood. Transthyretin is synthesized primarily by the liver. However, in teleost fishes it is produced by intestine, brain, skin, heart, skeletal musculature, kidneys, gonads and gills (Santos C.R. et al., 2002).

The mechanisms responsible for TH acceptance by blood transport proteins and hormone release in target tissues are still in discussion (Zhou A. et al., 2006; Qi X. et al., 2011). However, even humans, having effective and multiple duplicated system of TH-transporting blood proteins, shows high sensitivity to alterations of transthyretin affinity to TH (Cameron S.J. et al., 2005).

Chronobiological aspects of endocrine physiology in fishes attract great researcher's attention. On the other hand, fishes clearly demonstrate phylogenetical features of TH metabolism control.

These results are of value not only for fundamental science, but also in development of modern biotechnology. Therefore, we would like to mention about factors which are able to disturb chronobiology of TH metabolism in fishes.

Firstly, diseases of TH-producing tissue ectopically distributed in fishes. These differ in origin of pathological abnormalities which are well known in modern thyroidology and have specific features in fishes (Fournie J.W. et al., 2005). Secondly, antropogenic environmental toxic factors, which can:

a) directly have a negative affect on TH synthesis in thyroid tissue (Raldúa D. et al., 2009; Thienpont B. et al., 2011; Schmidt F. et al., 2012);

b) disturb neuro-endocrine control of secretory epithelium activity, especially at early ontogenetic stages (Shi X. et al., 2009; Park B. et al., 2011);

c) join in dehalogenation reactions with participation of system of deiodinases (Noyes P.D. et al., 2010; Roberts S. et al., 2011);

d) compete with TH for binding site of TH and transthyretin receptors (Ishihara A. et al., 2003; Crane H.M. et al., 2006; Morgado I. et al., 2007(a));

e) affect monooxygenase activity in hepatocytes (Noyes P.D. et al., 2010) and the increase expression of enzymes, responsible for formation of water-soluble conjugates of lipophilic endogenous substrates (Yu L. et al., 2010). Complexly, these enzymes in fishes control TH metabolic clearance (Parry J.E. et al., 1994; Finnson K.W., Eales J.G., 1997; Geven E.J. et al., 2007).

3. ROLE OF THYROID HORMONES IF FISH ADAPTATION

Close integration of thyroid and interrenal axes of endocrine system confirms important role of TH in control of adaptive reactions in fishes (Leatherland J.F., 1987; Matz S.P., Hofeldt G.T., 1999; De Groef B. et al., 2006; McGonnell I.M., Fowkes R.C., 2006; Geven E.J. et al., 2009; Peter V.S., Peter M.C., 2011). Realization mechanisms of adaptive changes in controlling humoral systems and

target tissues for TH and corticosteroids in fishes are also the focus of attention (Björnsson BT. et al., 1987; Brown S.B. et al., 1991; Metz J.R. et al., 2006; Geven E.J. et al., 2009; Arjona F.J. et al., 2011).

Results of assessment of interrelation between immune and endocrine systems in fishes in stress conditions have attracted attention (Metz J.R. et al., 2006). Authors have shown that in stress conditions key humoral mediator of congenital immunity and inflammation (interleukin-1 β) can directly participate in regulation of activity of neuroendocrine control which is common for both thyroid and interrenal axes.

Data about activity modulation of the controlling mechanisms of thyroid status in fish's adaptation are also interesting. In fishes, unlike mammals, glucocorticoids have mineralcorticoid properties as well, taking part in regulation of water-salt metabolism (Evans D.H. et al., 2005). It is known that TH play an important function in the making of mechanisms ionic and osmotic homeostasis in anadromous salmons. Features of structure-functional adaptation of efferent organs of ionic and osmotic homeostasis under influence of corticosteroids and TH in other teleost fishes are also of great attention (McCormick S.D., 2001; Walpita C.N. et al., 2007; Arjona F.J. et al., 2011). It was shown that cortisol injections reduced T₃ plasma concentrations along with altered parameters of water-salt, carbohydrate and nitrogen balance in *Clarias gariepinus* (Babitha G.S., Peter M.C., 2010). It was revealed that corticosteroids tissue specifically affect TH local and systemic metabolism, by decreasing hepatic type I and II deiodinases activity, as well as stimulation of activity of type III deiodinase in liver and gills (Walpita C.N. et al., 2007). Authors noted that: 1) corticosteroids do not significantly affect deiodinases activity in kidney and brain; 2) saline injection inhibits type I deiodinase activity in liver, but increases type III deiodinase activity. Comparison of effects of T₃ and selective inhibitor of type I deiodinase establishes important role of TH in fish ionic balance and maintenance of extracellular concentrations of sodium, potassium and calcium (Sreejith P. et al., 2007). It is shown that TH and corticosteroids are major humoral regulators of adaptive alterations of Na⁺/K⁺-ATPase activity in kidney and gill epithelium (Arjona F.J. et al., 2011). Na⁺/K⁺-ATPase activity dynamics in respond to exogenous T₃ is tissue specific. TH control structure-functional remodeling of gill epithelium during fish adaptation to sea water (McCormick S.D., 2001; Peter M.C. et al., 2011). But successful adaptation of gill epithelium is possible only when TH and osmotic stimulus act together. Transfer of fresh-water teleost fishes to sea water increases T₄ plasma concentrations (Sherwani F.A., Parwez I., 2008). At the same time, increased extracellular sodium ions concentration is observed. This is eliminated by administration of exogenous cortisol, which stimulates Na⁺/K⁺-ATPase activity.

Strong evidence exists which indicates that exposure of fish to acidified water increases T₃ and T₄ plasma concentrations as well as inhibits activity of gill but stimulates renal Na⁺/K⁺-ATPase (Peter MC, Rejitha V., 2011).

Tse W. et al. (2007) suggested that regulatory volume increase of gill epithelial cells in respond to hyperosmotic stimulus is due to Na⁺/K⁺/2Cl⁻-cotransporter, Na⁺/H⁺ exchanger-1 and Na⁺/K⁺-ATPase. Authors did not find distinct evidence of T₃ role in mentioned ion transporters adaptation to hyperosmolarity. At the same time they do not deny more complicated mechanisms of TH involvement in osmoadaptation. Further findings showed that, first of all, in vivo and in vitro direct effect of

osmotic stimulus on hepatic type II deiodinase gene expression in teleost fishes is realized because of presence of osmotic response element in the promoter region of the D2 gene (López-Bojórquez L. et al., 2007). Secondly, alterations of D2 activity in hepatocytes coupled with ammonia metabolism changes according to water salinity. Therefore, authors postulated that TH directly affect fish adaptation to osmotic stimulus.

Role of TH in adaptation of energy metabolism of homoitherm animals to low temperatures is well known (Silva J.E., 2006; Cheng Sh.-Y. et al., 2010). Involvement of TH in fish adaptation to temperature changes is described (O'Brien K.M., 2011). Van den Burg E.H. et al. (2003) showed that acute cold exposure of carps has no effect on thyroid status. While acclimatization to lower temperature (15C° or 22C°) causes temperature-dependent increase of alpha-melanocyte-stimulating hormone. Highest plasma T₄ concentrations associated with unaffected T₃ level were recorded in case of 22C°. We would like to remind that low temperature negatively affects fish due to presence in tissues easily oxidized polyunsaturated fatty acids. Hence, fresh-water mid-latitude fishes undergo oxidative stress during interseasonal adaptation (Käkelä R. et al., 2008; Grim J. M. et al., 2010). Whereas, in fishes TH are important regulators of enzymatic components of antioxidant system (Sreejith P., Oommen O.V., 2008). However, exceeding of TH physiological levels in blood and tissues contributes to an activation of prooxidant potential. Meanwhile, compensatory mechanism, which limits type II deiodinase stimulation, but creates prerequisites for type III deiodinase activation, is described. This results in decrease T₃ production and stimulation of it's deiodination (Lamirand A. et al., 2008).

In fishes secretion of hypoxia inducible factor (HIF) is stimulated by seasonal decrease of water temperature in normoxia. Sporadic investigations were devoted to study of temperature-dependent HIF secretion mechanisms in fishes (Gracey A.Y. et al, 2001; Rissanen et al, 2006). Temperature-dependent mechanism of stimulation of HIF secretion in fishes can be recognised as an essential element of acclimatization, which provides adaptation of metabolic processes and stimulation of tissue repairment (Semenza G. L., 2000; 2007; Masson N., Ratcliffe P.J., 2003). In addition, hypoxia inducible factor secretion is controlled by TH (Otto T., Fandrey J., 2008).

In anadromous salmonids TH can regulate seasonal modulation of visual analyzer properties taking into an account perception peculiarities of spectral composition of light in sea or fresh-water habitats (Temple Sh.E. et al., 2008).

CONCLUSION

In fishes hypothalamo-pituitary-thyroid axis has an essential structure-functional distinctions. Thyroid tissue does not form compact encapsulated organ (thyroid gland), but is distributed ectopically. There is a close interaction between thyroid and interrenal axes. Moreover, important element of thyroid status thyroxin-binding protein is absent. Its function is performed by thyroxine-binding prealbumin (transthyretin). TH tissue metabolism has some species-specific features (deiodinases expression level, rate of hormonal metabolic clearance etc.).

Investigation of TH role in maintenance of fish chronobiology is very important for science and practice. Role of TH in biorhythm development as well as in molecular mechanisms of maintenance of cellular and tissue chronobiological activity in fishes and animal is interesting for fundamental science. Basically, findings received in this research field touch issues of ontogenesis of commercial fishes and life cycle controlling mechanisms. There are some publications devoted specifically for phenomenon of fishes – role of TH in age-related and seasonal changes of receptivity of visual analyzer in anadromous salmonids to spectral composition of light. Thyroid status control mechanisms involved in alterations of plasma concentrations of TH and their tissue uptake rate and metabolism are in issue too.

It should be also noted that investigation of role of TH in fish adaptation is under meticulous attention of scientists. Strong integration between thyroid and interrenal axes of endocrine control on fishes confirms topicality of this research area. Function of TH in fish adaptation to various levels of water salinity is rather well documented.

Analysis of genetic and nongenomic effects of TH in organs of water-salt metabolism in response to osmotic stimulus is proposed to be recognized as separate research field. Role of TH in adaptation of ionoregulatory, osmoregulatory and acids release functions of gill and kidney in fishes is found. Mechanisms of synergic effects of TH and corticosteroids in tissues are also being studied. Literature data shows topicality of investigation of TH role in fish adaptation to environmental temperature and involvement of TH in control of an antioxidant protection.

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