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ROLE OF THYROID HORMONES IN BIRDS IN THE LIGHT OF RECENT KNOWLEDGE

Kinga Kowalik*, Andrzej Sechman

University of Agriculture in Krakow, Faculty of Animal Science, Department of Animal Physiology and Endocrinology, Al. Mickiewicza 24/28, 30-059 Krakow;

*e-mail: kinga.kowalik@urk.edu.pl

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Abstract

Thyroid hormones (THs), thyroxine (T_4) and triiodothyronine (T_3), are the basic regulators of the metabolic rate and participate in the thermoregulation process. They are essential for normal growth and the functioning of almost all body tissues. They participate in the regulation of the photoperiod, influence the functions of the gonadal axis and are involved in moulting. The metabolic effect of THs in target cells depends on the presence of nuclear and/or membrane receptors for these hormones and their supply. As the avian thyroid gland synthesizes and secretes small amounts of T_3, the concentration of this hormone in the blood depends primarily on the level of expression and activity of deiodinases, which are involved in the synthesis and metabolism of this iodothyronine in peripheral tissues. The article presents current data on the structure and function of the avian thyroid gland, the synthesis of iodothyronines, transport of

THs in the blood and into target cells, the molecular mechanism of their action, and their physiological role in birds.

Key words: thyroid hormones, synthesis, deiodinases, receptors, physiological role, birds

Introduction

Thyroid hormones (THs), 3,3',5,5'-tetraiodothyronine (thyroxine; T_4) and 3,3',5-triiodothyronine (T_3) play an essential role in the organism, influencing the processes related to the maintenance of the basic metabolism and homeostasis of the organism. They are crucial for appropriate growth and development and play an important role in the proper functioning of the cells of the nervous, muscular, circulatory and reproductive systems. In birds, the thyroid gland mainly synthesizes T_4, while T_3 comes from extra-thyroid conversion (deiodination) of T_4. The action of T_3, the main metabolic hormone, in target tissues depends, among others, on: (1) synthesis and secretion of THs from thyrocytes, (2) transport of T_4 and T_3 in the cardiovascular system, (3) TH uptake by target cells, (4) deiodination rates of T_4 to T_3 and T_3 to 3,3'- diiodothyronine (3,3'-T_2) in peripheral tissue cells, (5) iodothyronine binding to nuclear and/or membrane receptors. Their presence in target cells and the level of mRNA expression of these receptors determine the occurrence of physiological effects. The aim of this study is to present the current knowledge on the structure and function of the avian thyroid gland, the way of the iodothyronine synthesis in the thyroid gland and in deiodination process in peripheral tissues, the molecular mechanism of TH action in target cells, as well as their physiological role.

Anatomy and histology of the thyroid gland

The avian thyroid is an oval, well-vascularized endocrine gland. In contrast to mammals, there are two separate lobes (left and right) located near the posterior larynx, on both sides of the trachea at the junction of the carotid arteries with the subclavian arteries (McNabb and Darras 2015) (Fig. 1). The histological structure of this gland in birds does not show significant differences in comparison with other vertebrates. The structural and functional units are the thyroid follicles (clusters), which constitute about 80% of the gland's mass. The follicles are

formed by a single layer of thyroid epithelial cells, so-called thyrocytes, which have a three-dimensional oval structure. These cells become cylindrical under the influence of thyroid stimulating hormone (TSH) stimulation while at rest, they are flattened. The interior of the follicles contains a protein colloid surrounded by a single layer of epithelial cells. The main component of the colloid is thyroglobulin (TG) which belongs to the class of glycoproteins. This protein has two main functions: 1) it is a substrate for synthesis of THs due to the presence of tyrosyl residues, 2) it provides intra-thyroid, huge store of T_4 and T_3. This way of accumulating hormones is characteristic of this organ and is considered as an adaptation to periodic iodine deficiency in body. Iodine is the essential nutritional trace element necessary for the proper synthesis of iodothyronines. The outer part of the thyroid follicle is limited by the basal membrane of thyrocyte and is in contact with the large network of blood capillaries, allowing intensive transport of components between the blood and the follicle. In these cells, blood connections create a strong intercellular barrier, which controls diffusion of transmembrane proteins and prevents the release of the contents of the thyroid follicle into the bloodstream. Between follicles are also localized C cells which are involved in synthesis and secretion of calcitonin, a hormone that affects the calcium-phosphate metabolism (Ritchie and Pilny 2008, McNabb and Darras 2015).

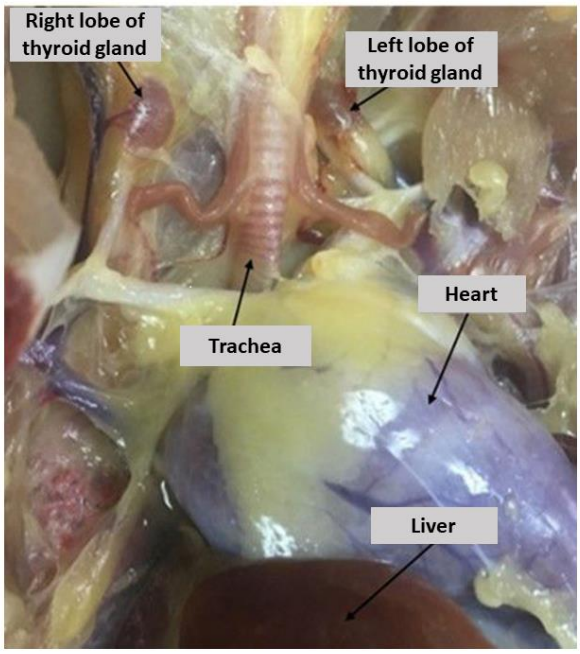

Figure 1. Localization of the thyroid gland in relation to the trachea, heart and liver in the domestic hen (Gallus domesticus) (photo K. Kowalik)

The hypothalamo-pituitary-thyroid axis

The synthesis and secretion of THs is primarily controlled by hormones of the hypothalamo-pituitary-thyroid axis (HPT). Compared to mammals, in birds, the function of this axis and the mechanism related to the regulation of T_4 and T_3 levels in the blood show many similarities (McNabb 2007). The HPT axis is a system of endocrine glands. The functioning mechanism of which is based on negative feedback. When in the organism deficiency of THs appears, thyrotropin releasing hormone (TRH) is secreted from the hypothalamus. After reaching the pituitary gland via hypothalamo-pituitary circulation, it stimulates synthesis and release of TSH into blood circulation. TRH regulates function of pituitary gland cells during embryogenesis (Kühn et al. 1991) and growth (Abdel-Fattah et al. 1990). In mature birds, the thyrotropic effect of TRH is significantly reduced in favour of the somatotropic properties related to the stimulation of growth hormone (GH) secretion from the pituitary gland (Kühn et al. 1991). TSH stimulates avian thyroid gland to increase in size and to stimulate them to synthesis and release of T_4 and in small extend T_3. These hormones enter the blood, where they are present in free form and bound to a protein fraction (Zooler et al. 2007). Once physiological blood levels are reached, T_4 and T_3 act on the hypothalamus and pituitary gland to reverse TRH and TSH secretion (Figure 2). It has been shown that corticotropin-releasing hormone (CRH,

corticoliberin) is also an important thyrotropic factor in birds which, acting through the second type of CRH receptors (CRHR2), stimulates the synthesis and secretion of TSH from thyrotropes of the anterior pituitary gland (De Groef et al. 2006, Watanabe et al. 2018). In addition to TRH and CRH, the regulation of the functions of the HPT axis of birds also involves the hypothalamic somatostatin (SRIF; Somatotropin Release Inhibiting Factor), which inhibits the synthesis and secretion of TSH from the pituitary gland (Geris et al. 2000).

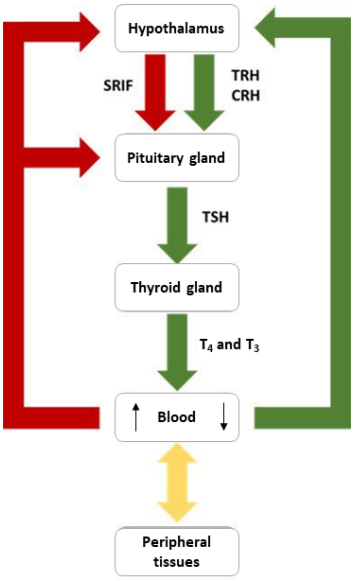

Figure 2. The hypothalamo-pituitary-thyroid axis (description in the text, author's diagram). TRH - thyreoliberin; CRH - corticotropin; SRIF - somatostatin; TSH - thyroid stimulating hormone; T4 - 3,3',5,5'-tetraiodothyronine; T3 - 3,3',5-triiodothyronine

Synthesis of iodothyronines

The activity of the thyroid gland is mainly related to the synthesis, storage and release of iodothyronine (T_4 and T_3) into the blood. These processes are similar in mammals and birds; however, in birds, the advantage in T_4 synthesis among iodothyronines is more noticeable than in other vertebrates. Recent studies have confirmed that both in the basal states and in the period of stimulation by endogenous and exogenous factors, the avian thyroid synthesizes and secretes into the bloodstream almost exclusively T_4 (which is over 99% of all THs synthesized in this gland) and small amounts of T_3 (McNabb and Darras 2015). The mechanisms of the synthesis and release of hormones by this gland in birds and mammals have many similarities and are equivalent. TH biosynthesis is conditioned by the presence of at least four molecules that affect the apical cell membrane of thyrocytes. These are: iodide, TG, hydrogen peroxide (H_2O_2) and thyroid peroxidase (TPO). The iodide absorbed in the gastrointestinal tract is transported with the blood to thyrocytes. Although some other tissues are also able to uptake iodide from the circulatory system, the thyroid gland is the only one that concentrates iodine intensively and stores it over a long period of time. This is due to the histological structure of thyroid follicles and the ability of thyrocytes to incorporate iodine into TG tyrosyl residues. The avian thyroid gland shows an unusually high concentration of iodide and prolonged retention of this element (McNabb and Darras 2015).

TH synthesis occurs at the border of the follicular cell wall and the colloid, and the T_4 and T_3 containing TG molecules are stored in the follicle lumen. The process consists of several steps; at first, iodide (I^-) anions are transported from the blood to thyroid cells across the basal membrane by a sodium iodide symporter (NIS). The ion gradient caused by the movement of the I^- ion with two Na^+ ions inside the cell is compensated by the activity of Na^+/K^+-ATPase, which is responsible for the transport of Na^+ ions to the outside of the thyrocyte. In this system, NIS acts as an active I^- ion transporter, which allows to maintain a much higher concentration of free iodides in thyrocytes compared to the concentration in blood plasma. Another I^- transporter is pendrin which is responsible for the transfer of the I^- anion further, i.e. from the follicular cells to the colloid lumen. Then, TPO with the participation of H_2O_2 oxidizes I^- ions and enables their binding with TG tyrosine residues and leads to formation of monoiodothyrosine (MIT) and diiodothyrosine (DIT) within the TG. These are conjugated by TPO to yield the iodothyronines, T_4 (DIT is coupled with DIT) and T_3 (MIT is coupled with DIT). Except for T_4 and T_3, TG also contains small amounts of 3,3',5'-triiodothyronine (reverse

triiodothyronine; rT3) and 3,3'-T_2 (Ritchie and Pilny 2008, McNabb and Darras 2015, Carvalho and Dupuy 2017).

The secretion of thyroid hormones depends on the resorption of iodinated TG, its proteolysis and the subsequent release of T_4 and T_3 into the blood, which partly occurs via transporters in the lateral plasma membrane of thyrocytes. Lysosomal enzymes such as proteases, endopeptidases, glycosidic hydrolases, phosphatases and others participate in the TG proteolysis. At the border of the follicular cell and colloid, TG is absorbed into the colloidal vesicles by macropinocytosis or micropinocytosis, and then it is absorbed into the thyroid cells. Then, the enzymes in the lysosomes hydrolyse the TG molecule, releasing MIT, DIT, T_4 and T_3. The THs are released into the bloodstream. The enzyme, iodothyrosine dehydrogenase removes iodine from MIT and DIT releasing the tyrosine and iodide (McNabb and Darras 2015).

The deiodination process

In birds, the main source of T_3 in blood circulation is extra-thyroidal monodeiodination (conversion) of T_4. This process, catalyzed by enzymes belonging to the iodothyronine deiodinase family, consists of a single iodine atom removal from the particular iodothyronine molecule. T_4 deiodination can proceed in two directions: (i) removal of iodine atom located in the 5' position of the phenolic outer ring leads to formation of metabolically active T_3, while deiodination in the 5 position of the tyrosyl or inner ring transforms T_4 into rT_3, the metabolically inactive iodothyronine in mammals and hypometabolic in birds (Abdel-Fattah et al. 1990; Bobek 2006). So far, three types of deiodinase have been classified: type I deiodinase (D1), type II deiodinase (D2) and type III deiodinase (D3). Each of them has its own characteristics. Type I deiodinase is a bifunctional enzyme as it catalyzes the deiodination of both the outer (ORD; 5'-monodeiodination) and inner (IRD; 5-monodeiodination) ring of iodothyronine. Type II deiodinase has IRD activity, while type III deiodinase is responsible for the ORD process. D1 and D2 deiodinases play an important role in the synthesis of T_3 from T_4, and D3 deiodinase is involved in degradation of both iodothyronines (Figure 3). All deiodinases are selenoproteins with redox properties (Van Der Spek et al. 2017). Studies on the chemical structure of avian deiodinases have shown that their chemical structure is very similar to mammals (Köhrle 2000). There are three main domains in each enzyme molecule: NH_2-

terminal domain, catalytic core and COOH-terminal domain. The catalytic core is the structure that shows the highest homology in deiodinase molecules and contains the selenocysteine amino acid residue. Unlike the catalytic core, the -NH_2 and -COOH terminal domains vary in chain length (Köhrle 2000).

Deiodinases are tissue-specific enzymes. Type I deiodinase is present mainly in the liver, kidneys and muscles. Type II deiodinase occurs in the brain, mainly in the pituitary gland, where it is responsible for the local synthesis of more than 75% of T_3. In contrast, type III deiodinase occurs in almost all tissues; the highest activity of this enzyme was found in the liver and kidneys in the embryonic period. In adults, the presence of this enzyme has been found in the liver, brain, pituitary gland, heart, skeletal muscles, thyroid gland and skin, among others (Darras et al. 2006).

Deiodination processes play an important role in regulating the concentration of thyroid hormones. As already mentioned, the avian thyroid gland synthesizes almost exclusively T_4, and T_3 is thought as a physiologically active hormone and shows a high affinity for thyroid receptors abundantly located in cells of most tissues. Therefore, the conversion of T_4 to T_3 is the crucial process, being the main source of T_3 in birds (Darras et al. 2006). In the liver, kidneys and muscles, this process is catalyzed by D1 deiodinase, while in the brain by D2 deiodinase. An important role in maintaining peripheral T_3 homeostasis plays also D3 deiodinase which, by participating in the conversion of T_3 to 3,3'-T_2 and T_4 to rT_3, protects the body against unfavourable effects of too high concentrations of metabolic T_3 (Orozco et al. 2012).

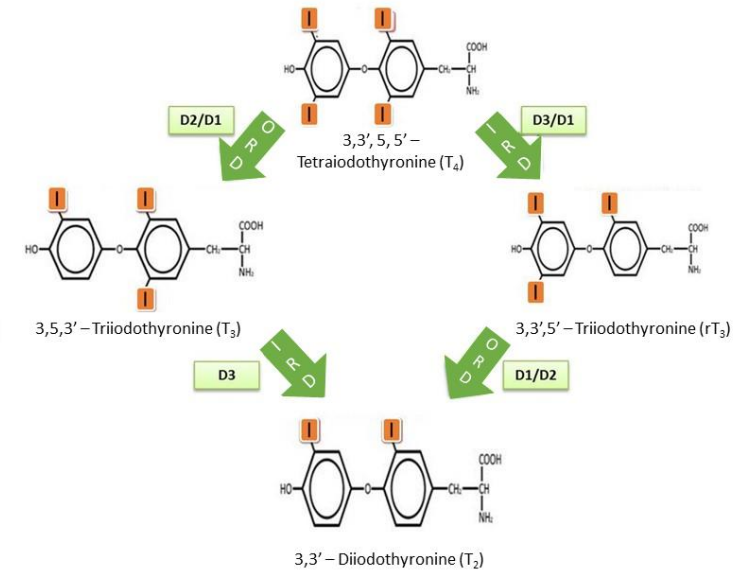

Figure 3. The main pathways of thyroxine deiodination (description in the text, the author's diagram). ORD - 5'-monodeiodination; IRD - 5-monodeiodination, D1 - deiodinase type I; D2 - deiodinase type 2; D3 - deiodinase type 3

Transport of thyroid hormones

THs, synthesized in the thyroid gland and deiodination process which takes place in extrathyroidal tissues, enter the bloodstream where they are bound by transport proteins. In avian blood plasma there are several proteins involved in the transport of iodothyronines: transthyretin (TTR), albumin, vitellogenin (VT), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) and apolipoprotein D (apo D). Most of the iodothyronines are transported by TTR (included in the prealbumin fraction) and albumin. In the blood plasma of sexually mature birds, about 20-30% of T_4 is bound by TTR. However, the participation of VLDL, LDL and VTG in T_4 transport is below 5%. Lipoproteins are more involved in T_3 transport; 13.5% of T_3 is bound by the VLDL/LDL fraction and 5.9% by VTG. The remaining amount of T_4 and T_3 is bound by serum albumin and in this form is transported to target cells. Moreover, apo D is also involved in the transport of iodothyronines, the presence of which has been confirmed in the yolk of avian oocytes, which suggests that it participates in the transport of iodothyronines from the bloodstream into the oocyte (Power et al. 2000).

THs, which occurs in blood plasma as free form are transported to target cells. To fulfil their role as regulators of gene transcription, they must cross the plasma membrane. Recent studies indicate that this process is supported by transmembrane proteins that facilitate the transport of iodothyronines into and out of cells (McNabb and Darras 2015, Bourgeois et al. 2016). They belong to three families: (i) monocarboxylate transporters (MCTs), (ii) OATPs (Na-independent organic anion transporting polypeptides) and (iii) L-type amino acid transporters (LATs) (Van Der Deure et al. 2010). In humans and rodents, the transporters showing the highest affinity to thyroid hormones are the OATP1C1 proteins (involved primarily in the transport of T_4 and rT_3 across the cell membrane) and the MCT8 and MCT10 proteins (efficiently transporting both T_4 and T_3) (Visser et al. 2008). Until recently, only one TH transporter has been fully recognized in birds, the OATP1C1 protein (encoded by the *SLCO1C1* gene) which, like in mammals, turns out to be a highly specific T_4 transporter (Nakao et al. 2006). In 2016, Bourgeois et al. [2016] cloned cDNA sequence for chicken MCT8 (*SLC16A1*), MCT10 (*SLC16A10*) and LAT1 (*SLC7A5*) and showed that despite some small differences in ligand specificity and affinity, they have functional characteristics similar to their human orthologs. Moreover, these researchers found that in birds, both OATP1C1 and MCT8 are transporters with high affinity for T_4, T_3 is transported into the cell by MCT8 and MCT10, while LAT1 is responsible for 3,3'-T_2 plasma membrane transport (Bourgeois et al. 2016).

Mechanism of action of thyroid hormones

In birds, as in other vertebrates, thyroid hormones act on cells in target tissues mainly through thyroid hormone receptors (TRs), which belong to the nuclear receptor superfamily (a large group of hormone receptors that share similar domain structures). The physiological effects mediated by these receptors occur in target cells with a time delay of several hours or days. Among all iodothyronines, TRs have the greatest affinity for T_3; they are transcription factors that regulate the expression of genes depend on thyroid function. As nuclear transcription factors, the TRs, which most often form the heterodimer complex with the RXR receptor (RXR-TRs), bind to thyroid hormone response elements (TREs), which are located in the promoter region of genes activated by these hormones. The binding of a ligand to TR receptor results in the exchange of corepressors (CoR) for coactivators (CoA) (Fig. 4). In birds, TRs are encoded by two separate genes (*THRA* and *THRB*), the transcription of which leads to the synthesis of

three different mRNAs, followed by three different TR isoforms (TRα, TRβ0 and TRβ2) (Decuypere et al. 2005, Vella and Hollenberg 2017). TRα and TRβ0 have been identified i.a. in the brain, liver, heart, muscles and ovary (Sechman et al. 2009), while TRβ2 in the hypothalamus and other areas of the brain, as well as in the inner ear and eye retina (Darras et al. 2011).

There is also another, non-genomic (non-canonical) mechanism of iodothyronine action mediated by receptors located in the plasma membrane, cytoplasm and mitochondria. Physiological effects of HT non-genomic actions are observed in few minutes or even seconds following receptor activation (Cheng et al. 2010). An example of this mechanism is an increase in oxygen consumption in cells and tissues, inhibition of D2 deiodinase activity in the pituitary gland, or increased glucose uptake by cells as a result of T_3 influence on its membrane transport. The nongenomic mechanism involves the integrin membrane receptor (ITGRαVβ3), which binds not only T_3, but also other iodothyronines: T_4, rT_3 and 3,5-T_2 (Davis et al. 2008). The αvβ3 integrin contains two TH binding domains. T_3 interacts with the S1 domain of integrin αvβ3, activating the phosphoinositide 3-kinase (PI3K)/AKT protein kinase/protein kinase B (PKB) signal pathway through Src tyrosine kinase, leading to transport of TRα from the cytoplasm to the cell nucleus. THs, mainly T_4, also interact with the S2 domain of the integrin αvβ3, activating the mitogen-activated protein kinase (MAPK)/extracellular-signal regulated kinases (ERK1/2) signaling pathway and causing phosphorylation and nuclear transport of TRβ, estrogen receptor α (ERα) and signal transducer and activator of transcription 3 (STAT3). Activated in the cytoplasm, ERK1/2 and THRβ increase the activity of the sodium-potassium pump (Na^+/K^+-ATPase). By binding to the TRα receptor, T_3 interacts with the p85α subunit of PI3K to activate AKT kinase (Figure 4). THs through the integrin receptor are involved in regulation of membrane ion channels and the sodium-potassium pump (Scapini et al. 2009), G-protein-coupled receptors (Giguere et al. 1996), or tyrosine kinases and MAPK kinases (Davis et al. . 2009). Also, TRβ receptors present in the cytoplasm activate PI3K kinase after binding to iodothyronine. As a result, the concentration of phosphatidylinositol (PIP3) is increased, the effect of which is involved in altering of cell metabolism or reorganizing of the cytoskeleton (Davis et al. 2008). This mechanism has been extensively studied in mammals (Davis et al. 2009). In recent years, both in birds and mammals, researchers have focused on the process of thermogenesis not only through nuclear receptors, but also by mitochondrial receptors involved in the non-genomic mechanism of iodothyronine action (Cheng et al. 2010).

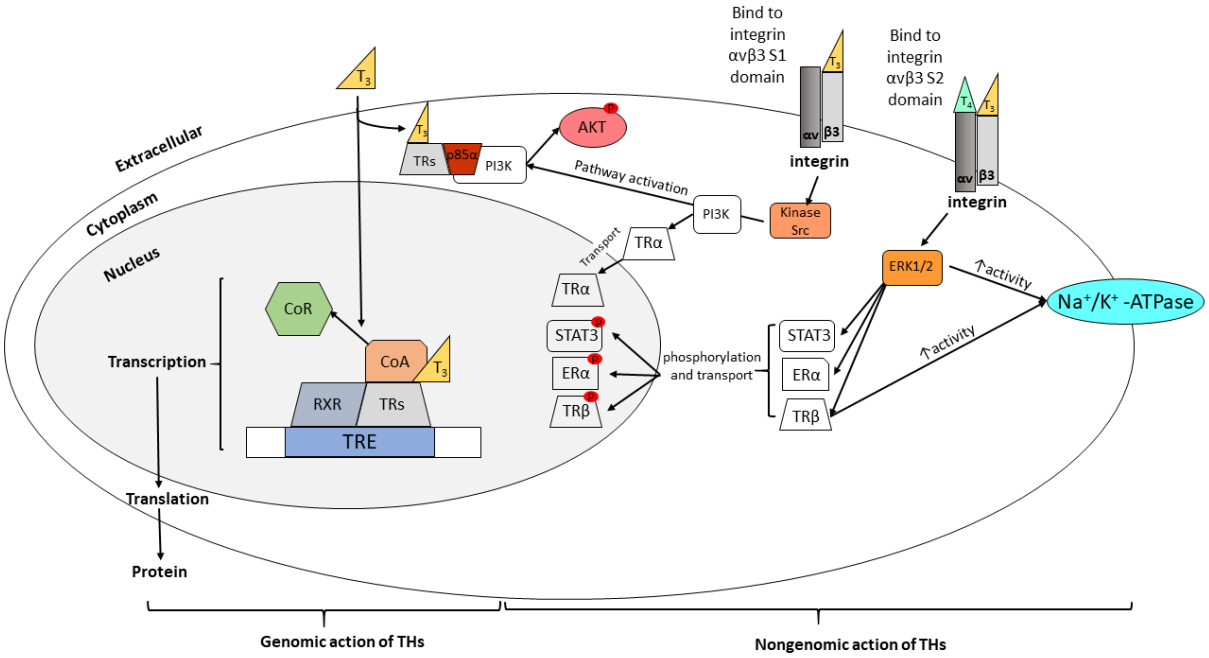

Figure 4. Non-genomic and genomic mechanism of thyroid hormone action (description in the text, author's diagram). THs - thyroid hormones; TR - thyroid hormone receptor; PI3K - phosphatidylinositol 3-kinase; AKT- AKT protein kinase; PKB - protein kinase B; Src- Src tyrosine kinase; ERK 1/2 - extracellular regulated kinase; ERα - estrogen receptor; STAT3 - signal converter and transcription activator 3; Na^+/K^+-ATPase - sodium-potassium pump; p85α - regulatory subunit of phosphoinositide 3-kinase; RXR - 9-cis-retinoic acid receptor; TRE - thyroid hormone responsive element; T_4 - 3,3',5,5'-tetraiodothyronine; T_3 - 3,3',5-triiodothyronine

Factors influencing the concentration of iodothyronines in plasma

The concentration of T_4 in blood plasma of birds is several times higher than T_3. In many avian species, the range of T_4 concentration is between 5–15 ng/mL (6–19 pmol/mL), and for T_3 0.5–4 ng/mL (0.7–1.5 pmol/mL). Compared to mammals, plasma of birds contains nearly 10 times less T_4, while the concentration of T_3 oscillates within a similar range (McNabb and Darras 2015).

The plasma level of TH depends on many endo- (thyroid synthesis, HPT axis, deiodination process) and exogenous factors. Among many external factors that affect the thyroid function, there are e.g. seasonality, period of the day, environmental temperature, pattern of food intake and iodine availability. The breed or age of the animal is also important (McNabb and Darras 2015). However, it seems that food availability and temperature have the greatest influence on blood concentration of iodothyronines. Both short-term and long-term fasting are associated with decrease in concentration of THs in the blood plasma, especially T_3 (Scanes 2009). On the other hand, refeeding after fasting period results in return of TH concentrations to the baseline values (Reyns et al. 2002). Not only the availability of feed, but also its composition and the level of metabolic energy are important. Moreover, during the winter, when the activity of the thyroid gland is reduced, the diameter of the follicles increases and due to accumulation of colloid in the follicles and flattening of the epithelial cells. It is associated with the body's acclimatization to cold and higher energy expenditure (Schmidt and Reavill 2008). Photoperiod changes also affect concentration of THs in blood of birds; during the day, the concentration of T_4 decreases and the level of T_3 increases. At night, this state is reversed. It has been shown that lowering the ambient temperature activates the HPT axis, which results in, increased synthesis of hormones in the thyroid gland, but only a significant increase in T_3 is observed in the blood. This is associated with the decreased half-life of T_4 as well as with an increase in the peripheral conversion of T_4 to T_3, and thus stimulation of mRNA expression and D1 deiodinase activity (Collin et al. 2003).

Physiological role of thyroid hormones

The action of THs in the body ensures the appropriate functioning of all tissues and determines the proper development of the body. In addition to the complex systemic effects of maintaining an adequate rate of basal metabolism, constant body temperature and the impact on growth and development processes, THs are necessary for the proper functioning of the reproductive system. Depending on the concentration, THs have a different effect on the metabolism of proteins, carbohydrates and lipids. In low concentrations, they act anabolic, stimulating the synthesis of proteins, glycogen and lipids, while in higher concentrations - catabolically, inhibiting the synthesis and/or stimulating reactions related to decomposition and oxidation of previously mentioned compounds (Decuypere et al. 2005). In addition, during development,

they stimulate the proliferation and differentiation of cells, and also participate in their maturation. Weight gain is associated not only with an increase in cell proliferation, i.e. the division of cells, but also with an increase in their size (cell hyperplasia). Excess THs in the blood due to an hyperthyroidism inhibits growth. This is due to increased metabolism, during which catabolic processes are stimulated. THs play an important role in initiating cell differentiation processes in many tissues. In mammals, their role in development has been carefully studied in the gastrointestinal tract, heart, skeletal muscle, skin, bones and nervous tissue. They regulate the metabolism of creatine in skeletal muscles and contraction processes. In relation to carbohydrate metabolism, they increase intestinal glucose absorption and stimulate glycogen synthesis. It is known that they are crucial for the development of the brain and organs involved in teleceptive sensing (the retina and inner ear; McNabb and Darras 2015). Studies carried out on the chicken cerebellum have shown that THs are necessary for the development of the correct architecture of this brain part and neural connections important for the function of signaling networks. They stimulate the maturation of photoreceptors in the retina (Fischer et al. 2011) and are probably involved in development of the inner ear (Geysens et al. 2012). They are also essential for early learning as they determine beginning of a specific period in which the animal learns its parent's pattern or species-specific behaviour (imprinting). Moreover, they can stimulate the brain to later learning (Yamaguchi et al. 2012). There is an interaction between THs, growth hormone, and insulin-like growth factor (IGF-I), the synthesis of which in the liver is mainly stimulated by GH. In the 1990s, numerous studies were carried out in which authors proved that THs inhibits GH secretion from the pituitary gland, while stimulating hepatic IGF-I synthesis (Decuypere et al. 2005, Scanes 2009).

In warm-blooded animals, THs influence the regulation of basal metabolism and are necessary to maintain a constant body temperature, and are responsible for adaptive changes related to changes in ambient temperature. The development of the thyroid gland and control of the HPT axis seem to be crucial in development of thermoregulation in both precocial and altricial species. In altricial species, the HPT axis begins to function in late period of embryonic development. Even before hatching, in response to a decrease in ambient temperature, the embryonic hypothermia is observed, which is related to the endothermic reaction in which the environment absorbs heat. As chicks, they gain the ability to maintain a constant body temperature. Chicken embryos may show some endothermic reactions in late incubation phase. The situation is different in altricial breeds, in which the HPT axis develops much later, because only a few days after hatching, the ability to exchange temperature with the environment and

to maintain a constant body temperature gradually develops with the passing weeks after hatching (McNabb and Darras 2015).

THs also play an important role in the functioning of the reproductive system and the hypothalamo-pituitary-gonadal axis (Sechman 2013, Tamai and Yoshimura 2017). In female domestic birds, including hens, reproductive capacity and the associated number of eggs laid are of particular importance to many breeders, while in free-living birds it determines the survival of the species. In the ovary of the domestic hen, the presence of THs was found in yolk of oocytes and eggs (Sechman and Bobek 1988), in the ovarian stroma and the wall of all ovarian follicles (Sechman 2003). Iodothyronine accumulated by the ovarian follicles and present in egg yolk may be a valuable source of THs for the developing embryo outside the mother's organism, especially in the early stages of embryogenesis (Sechman and Bobek 1988, Darras 2019). It has also been reported that TR mRNA is expressed in the wall of ovarian follicles of the domestic hen (Sechman et al. 2009). *In vitro* studies on isolated white pre-hierarchical follicles (1-8 mm) and fragments of the theca and granulosa layers of the three largest pre-ovulatory follicles (F3, F2 and F1) have shown that: (i) T_3 is a modulator of steroidogenesis process; this hormone reduces basal and luteinizing hormone (LH) stimulated estradiol secretion from white pre-hierarchical follicles and theca of pre-ovulatory follicles, and stimulates progesterone secretion from the granulosa layer of the pre-ovulatory follicles; (ii) the effects of T_3 in ovarian follicles of the hen are mediated by the genomic mechanism (related to the regulation of mRNA expression and activity of enzymes involved in steroidogenesis process) as well as the non-genomic mechanism related to modulation of cAMP synthesis and activity of adenylate cyclase and/or phosphodiesterase in steroidogenic cells of the theca and granulosa layer; (iii) T_3 affects the mRNA expression of steroidogenic acute regulatory protein (StAR), cholesterol side-chain cleavage enzyme (*CYP11A1*), 3β-hydroxysteroid dehydrogenase (3β-HSD) and aromatase (*CYP19A1*) in ovarian follicles (Sechman et al. 2009, 2011, Sechman 2013). On the other hand, *in vivo* experiments showed that hyperthyroidism caused by the administration of exogenous T_3 inhibits the activity of the hypothalamic-pituitary-ovary axis, influences the process of follicular steroidogenesis by reducing expression *3β-HSD* and *CYP19A1* mRNA in the granulosa and theca layers of the ovarian follicle, respectively, which leads to strong atresia of preovulatory follicles (Sechman 2013).

In birds characterized by seasonal breeding, THs influence the photoperiodic initiation of reproductive cycles. It has been shown that T_4 and T_3 can have both pro- and anti-gonadal

effects. In some avian species, such as the European starling (*Sturnus vulgaris*) or the American tree sparrow (*Spizella arborea*), photostimulation results in increasing of concentration of the gonadotropin releasing hormone I (GnRH-I) (responsible for LH and follicle stimulating hormone synthesis and secretion the pituitary gland) in the hypothalamus and T_4 in the blood. Studies carried out on these birds have shown that T_4 is necessary for the induction of ovarian growth and development during the photostimulation period and determines the occurrence of photorefraction, which ends the breeding period and leads to the beginning of moulting period (Reinert and Wilson 1993). Yoshimura et al. (2003) showed that in Japanese quail (*Coturnix coturnix japonica)*, T_3 synthesized from T_4 with the participation of D2 in the mediobasal hypothalamus is responsible for increasing GnRH-I secretion. Increased mRNA expression of this deiodinase in the hypothalamus depends on TSH derived from pars tuberalis of the pituitary gland (Yoshimura et al. 2003, Tamai and Yoshimura 2017). On the other hand, the anti-gonadal activity of THs has been demonstrated in studies carried out on the Spotted munia (*Lonchura punctulata*). After thyroidectomy, the seasonal gonadal regression was stopped, and the administration of physiological doses of T_4 to birds inhibited development or led to ovarian regression (Pant and Chandola-Saklani 1994). Studies on the relationship between iodothyronines and reproduction in the domestic hen have shown that THs play an important role in the final stage of sexual maturation, i.e. between 15 and 22 weeks of life (Sechman et al. 1998). Experiments carried out on immature chickens that were treated with T_4, led to an inhibition of oogenesis process and regression of the ovary, which confirmed the existence of a negative relationship between the concentration of T_4 and T_3 in blood and ovarian function (Sharp et al. 1984, Sechman et al. 2000). THs regulate also other processes e.g., moulting that require energy and occurs at the same time as reproductive processes, ensuring energy balance (Pietras 1981). The administration of anti-thyroid substances (so-called goitrogens) to Japanese quails caused hypothyroidism and inhibited egg laying. On the other hand, lower doses of goitrogens in chickens did not cause a pause in egg laying (McNabb and Darras 2015).

Summary

The appropriate functioning of the thyroid gland is conditioned by number of mechanisms controlling the synthesis, secretion, degradation and binding of iodothyronines by target cell receptors, which ultimately determine the final concentration of these hormones in blood and

their physiological role in body. THs affect numerous processes and are necessary for the proper functioning of body. They influence development, metabolic changes and thermoregulation. They play an important role in processes related to development, especially of nervous system. Lack of THs reduces number of neurons and their differentiation in the cerebral cortex, hippocampus and cerebellum. In addition, they are required for normal reproduction and play an important role in seasonal events such as initiation of laying or moulting. During the hatching process, an increase in concentration of THs in blood is observed, which is associated with the transition of the embryo to oxygen respiration and an increase in cellular metabolism. The action of THs in birds is pleiotropic, therefore the maintenance of their physiological concentrations in blood plasma is particularly important in maintaining homeostasis as well as the proper functioning of many organs and systems.

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