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Review

New insights into thyroid hormone function and modulation of reproduction in goldfish

H.R. Habibi [a,b,*], E.R. Nelson [c], E.R.O. Allan [b]

[a] Institute of Environmental Toxicology and University of Calgary, 2500 University Dr. N.W. Calgary, Alberta, Canada
[b] Department of Biological Sciences, University of Calgary, 2500 University Dr. N.W. Calgary, Alberta, Canada
[c] Pharmacology and Cancer Biology, Duke University Medical Center, NC, United States

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ABSTRACT

A number of studies have provided evidence for a link between thyroid hormones and physiological or pathophysiological conditions associated with reproduction. Most of the information available is based on clinical observations in human or research in mammals. There are also a number of studies in non-mammalian species, primarily investigating thyroid and reproductive endocrinology in isolation. The findings demonstrate that hyperthyroidism or hypothyroidism are associated with altered fertility due to changes in the levels and activities of hormones of the brain–pituitary–gonadal axis. There appears to be a consistent pattern based on a number of studies in mammalian and non-mammalian species, linking thyroid with reproduction. Results obtained in goldfish suggest that increased levels of thyroid hormones may reduce overall reproductive function. Since thyroid hormones influence metabolism and are known to stimulate growth in most species, it is likely that increased thyroid hormone levels may divert energy from reproduction and promote somatotropic functions. This is particularly important in oviparous species such as fish since energy investment in females during reproductive season is very significant, and increasing thyroid hormone levels after ovulation may be a contributing factor in promoting growth response. Thyroid hormones will likely work in concert with other hormones to influence reproduction in fish and other vertebrates.

1. Introduction

The relationship between thyroid function and reproduction has been investigated for many years in different species. It has become clear that the nature of interaction between thyroid hormones (THs) and reproduction is highly species-specific. Information concerning mammalian and human thyroid function and reproductive health have been reviewed previously [21,34,36] and will not be covered here. For the most part, there is a great deal of information available on reproduction and thyroid function, but very few studies investigated the interaction between the two in non mammalian vertebrates (for reviews see: [14,17]). While there are significant variations in the nature of interaction between THs and reproduction in different species, it would appear that THs might impair overall reproductive function in both mammalian and non-mammalian vertebrates by different mechanisms. However, in mammalian species THs have also been shown to positively impact reproductive function through their involvement in the regulation of Leydig and Sertoli cells and reproductive cycle [36].

A number of investigators have used fish as experimental model to investigate TH endocrinology and reproduction because of the diversity of reproduction and plastic nature of gonadal development in fishes. Among teleosts, there are both hermaphroditic and gonochoristic species that are either semelparous, which reproduce once a year or once in a lifetime as well as iteroparous that reproduce several times per year. As a result, there are significant diversity and variations in reproductive biology and related metabolic events among different fish species. These variations are reflected in a limited number of reports that have examined the relationship between THs and reproduction in fish. Despite their clear role in regulating basal metabolism in homeotherms, the influence of THs on teleost metabolic processes is less clear. However, it remains very likely that THs play a significant role in metabolic regulation associated with reproductive function. Therefore it is important to have good understanding of the TH endocrinology in order to elucidate the interaction between TH function and reproduction in fish. Earlier reviews by Cyr and Eales [14,17] have provided a good coverage of the literature up to those dates. However, significantly more information is available on TH receptors and TR regulation, which will be covered here in addition to recent studies on interaction between THs and reproduction in goldfish.

* Corresponding author at: Department of Biological Sciences, University of Calgary, 2500 University Dr. N.W. Calgary, Alberta, Canada. Fax: +1 403 289 9311.
E-mail address: habibi@ucalgary.ca (H.R. Habibi).

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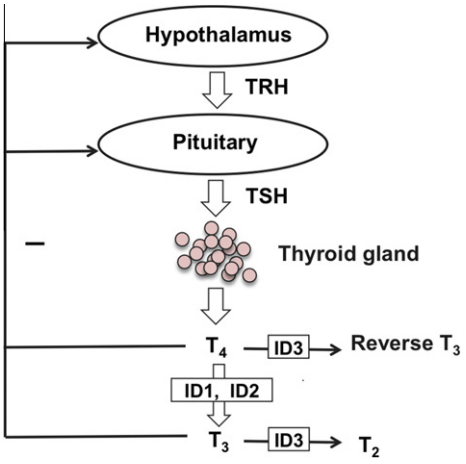

Fig. 1. Brain–pituitary–thyroid axis. Deiodinase types 1, 2, 3 and 4 (ID1, ID2, ID3 and ID4). TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

2. Brain–pituitary–thyroid axis

The hypothalamic tripeptide, thyrotropin-releasing hormone (TRH) is a key regulator of thyroid-stimulating hormone (TSH), which is a glycoprotein consisting of an alpha and a unique ß subunit synthesized in the thyrotope cells in the anterior pituitary (Fig. 1). TRH stimulates the synthesis and glycosylation of TSH-β [17,89]. The pituitary TSH, in turn, stimulates the processes required for T_4/T_3 production by promoting iodide uptake and iodination/synthesis/oxidation of thyroglobulin. It has been suggested that TSH may feedback on the pituitary [89] but this relationship needs to be characterized further by in vitro studies.

The synthesis of THs, thyroxin (T_4) and tri-iodothyronine (T_3) is stimulated by the actions of TSH on the thyroid gland. T_4 contains four iodine residues and T_3 containing three iodine residues. T_4 is the primary hormone synthesized and released by the thyroid gland [17,74]. However, while both THs exhibit activity, T_3 is the main physiological form of hormone that interacts with thyroid hormone receptors (TRs). Deiodinases, selano-cysteine containing enzymes located in peripheral tissues, are responsible for the conversion and metabolism of the THs. Deiodinase types 1 and 2 (ID1 and ID2) convert T_4 to T_3, while ID3 is responsible for metabolizing T_4 or T_3 to inactive forms including reverse-T_3 or di-iodothyronine (T_2), respectively [3,4,60] (Fig. 2). In fact, most circulating T_3 results from peripheral conversion of T_4 by ID1 or ID2 in tissues such as the liver and gonads [11]. In most species tested, THs inhibit further release of TSH through negative feedback mechanisms at the hypothalamic and pituitary levels, inhibiting further release of TRH and/or TSH, respectively. On the other hand, the ID3, reduces production of T_3 by converting T_4 to reverse T_3 which is an inactive metabolite. In addition to deiodinase metabolism THs are also cleared from the blood by sulfation or glucuronidation in the liver. The modified thyroid hormones can be eliminated in the bile [89]. Circulating Thyroid hormones are transported in the blood bound to either thyroxine binding globulin, transthyretin or albumin. In general, there are good similarities between brain–pituitary–thyroid axis in fish and mammals [17]. TRH has been shown to increase mRNA synthesis of TSH-β in the pituitary [9]. The thyroid hormones have been shown to feedback and inhibit TSH secretion. However, in fish, TSH itself may have other controlling mechanisms that are not fully understood [9,62–66,73].

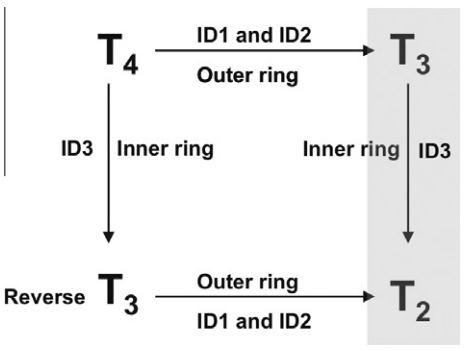

Fig. 2. Deiodination of thyroid hormones by deiodinase 1, 2, and 3 (ID1, ID2, and ID3).

The circulating concentrations of both T_3 and T_4 are at their highest during summer in the post-spawn goldfish [72]. The levels drop off to the lowest levels during the period of ovulation and spawning. In female goldfish, T_3 plasma levels changes from approximately 3 ng/ml in mid-late recrudescent fish to a high of about 10 ng/ml in post-spawning fish. Hormonal profiles in male and female fish are not identical, but similar. Interestingly, in goldfish, there is an inverse relationship between TSHβ transcript level and circulating T_3 level [72]. A more recent study found that T_3 treatment directly inhibits TSH-β subunit expression in the goldfish pituitary, in vitro, but its action may be altered by other factors in vivo [1]. This is consistent with reports that treatment of primary cultured pituitary cells with T_3 or prolonged water-borne exposure to fish inhibits TSHβ expression in goldfish [73,87], and other fish and mammals [17,37,66,89]. There are also reports that glycoprotein α subunit is altered following treatment with T_3, although there appear to be differences between male and female fish and different stages of reproduction [73,87]. The significance of changes in glycoprotein α subunit is unclear as it could also be affected by factors interacting with brain–pituitary–gonadal axis such as gonadal steroids [31].

3. Thyroid hormone receptors structure and function

Actions of thyroid hormones are mediated through binding to specific receptors. Most of our current understanding of TH action is based on studies focusing on the intracellular TRs. As members of the nuclear receptor superfamily, TRs act as ligand-inducible transcription factors. Nuclear receptors share defining sequence similarities and domain structures that evolved from a common ancestral protein [18,38,44]. In addition, there is some evidence demonstrating the presence of a membrane integrin surface receptor for thyroid hormone that mediates some nongenomic actions of T_3 and T_4. The findings suggest that the surface receptors mediate thyroid hormone-induced increases in angiogenesis, tumor cell proliferation, ion transport, and intracellular protein trafficking. The information on surface receptors and their biological significance have recently been reviewed by Davis et al. [15], and will not be discussed here.

The nuclear TRs are comprised of six characteristic domains, including the DNA-binding domain (DBD), and the ligand-binding domain (LBD). TRs interact with specific thyroid response elements in the DNA as heterodimers with a retinoid-X receptor (RXR); however, TRs may also form heterodimers with peroxisome proliferator-activated receptors (PPARs) or other transcription factors, and there are reports of TRs forming homodimers or homotrimers, although the physiological relevance of differential partner dimerization is unclear [2,5,6,39,48]. In the absence of thyroid hormone, TRs actively suppress the transcription of target genes by interaction with co-repressor proteins, some associated with histone deacetylase (HDAC) activity, resulting in deacetylation of histone proteins and condensation of chromatin [12,42]. Following binding