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## The teleost head kidney: Integrating thyroid and immune signalling

Edwin J.W. Geven<sup>1</sup>, Peter H.M. Klaren<sup>\* 2</sup>

Department of Organismal Animal Physiology, Institute for Water and Wetland Research, Radboud University, Nijmegen, the Netherlands

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## ABSTRACT

The head kidney, analogous to the mammalian adrenal gland, is an organ unique for teleost fish. It comprises cytokine-producing lymphoid cells from the immune system and endocrine cells secreting cortisol, catecholamines, and thyroid hormones. The intimate organization of the immune system and endocrine system in one single organ makes bidirectional signalling between these possible. In this review we explore putative interactions between the thyroid and immune system in the head kidney. We give a short overview of the thyroid system, and consider the evidence for the presence of thyroid follicles in the head kidney as a normal, healthy trait in fishes. From mammalian studies we gather data on the effects of three important pro-inflammatory cytokines (TNF $\alpha$ , IL-1 $\beta$ , IL-6) on the thyroid system. A general picture that emerges is that pro-inflammatory cytokines inhibit the activity of the thyroid system at different targets. Extrapolating from these studies, we suggest that the interaction of the thyroid system by paracrine actions of cytokines in the head kidney is involved in fine-tuning the availability and redistribution of energy substrates during acclimation processes such as an immune response or stress response.

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## 1. Introduction

The thyroid system is an evolutionary well-conserved endocrine system and is present in all vertebrate species investigated thus far. Thyroid hormones, or iodothyronines, are the main effector compounds. Thyroid hormones have pervasive actions on important physiological processes, including basal metabolic rate, growth and development. Proper functioning of the immune system is highly dependent on the adequate regulation of metabolism. It is difficult to conceive, therefore, that major regulatory systems such as the endocrine and immune system, and, for that matter, the nervous system as well, operate in isolation and unaware of each other's actions.

As we will argue below, the fish' immune and thyroid system are, anatomically at least, intimately connected. We here wish to explore putative interactions between the thyroid and immune system in the context of this unique aspect of teleost thyroid anatomy. From this we will attempt to derive new insight in the

thyroid-immune interactions in fish.

## 2. The head kidney is a major lymphoid and endocrine organ

The head kidney, an organ analogous to the mammalian adrenal gland, is an important endocrine and haematopoietic-lymphoid organ in teleostean or "true bony" fish (reviewed by Gallo and Civinini (2003), Uribe et al. (2011)). The head kidney lacks the clear structure of its mammalian counterpart as a zonal cortex and medulla cannot be discerned. Instead, cortisol-producing interrenal cells and catecholamine-producing chromaffin cells are embedded in and surrounded by haematopoietic antibody- and cytokine-producing tissue.

Thyroid hormones are synthesized in thyroid follicles, the functional unit of the thyroid gland in vertebrates. Follicles consist of a monolayer of thyrocytes, enclosing an extracellular lumen filled with a colloid matrix. In many vertebrate classes the thyroid gland is an encapsulated and bilobed gland, located in the anterior neck region, ventral to the larynx and pharynx. Fishes have a different thyroid anatomy, however, as they lack a compact thyroid gland. Instead, individual thyroid follicles appear in different anatomical locations in the fish' body, of which the head kidney is a preferential organ (see Section 4).

In the context of thyroid – immune system interactions, the presence of thyroid follicles in the fish' head kidney is interesting.

\* Corresponding author.

E-mail address: [p.klaren@science.ru.nl](mailto:p.klaren@science.ru.nl) (P.H.M. Klaren).<sup>1</sup> Current affiliation: Experimental Rheumatology, Radboud University Medical Center, Nijmegen, the Netherlands.<sup>2</sup> Current affiliation: Department of Animal Ecology and Physiology, Institute for Water and Wetland Research, Radboud University, Nijmegen, the Netherlands.

This anatomical location would, in principle, greatly facilitate a (paracrine) interaction between the immune system and the thyroid system. Indeed, a similar notion for other endocrines has already been suggested by others (Engelsma et al., 2002; Verburg-van Kemenade et al., 2009; Weyts et al., 1999).

The human thyroid gland is particularly susceptible to autoimmune disease. Graves' disease and Hashimoto's thyroiditis are two well-characterized pathologies (Saranac et al., 2011; Tomer, 2014) affecting more than 400/100,000 females per year worldwide, an incidence rate 4 to 10 times larger than that for males (McGrogan et al., 2008). Rather speculatively, the teleost head kidney can perhaps be considered a natural model for a lymphocyte-infiltrated thyroid gland in patients with Hashimoto's disease. New insights into human thyroid autoimmune disease can possibly be derived from a consideration of the putative interactions between thyroid and immune system in fishes.

### 3. A short introduction to comparative thyroidology

Thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or T4) is the main secretion product of the thyroid gland and can be considered to be a prohormone with little biological activity of its own. The enzymatic removal of an iodine atom from thyroxine's molecular structure yields the biologically active 3,5,3'-triiodo-L-thyronine (T3). Most biological actions of thyroid hormone can be ascribed to the latter. Thyroid hormones have pervasive actions as they affect basal metabolic rate, growth, and major developmental processes, most notably metamorphosis in fishes and amphibians (Eales, 2006; Power et al., 2001).

The secretory activity of the thyroid gland is regulated centrally by a hypothalamo-pituitary axis. Typical for the thyroid system is the involvement of peripheral processes and mechanisms that greatly determine the thyroid status of an animal. Different components of the thyroid system are potential targets for thyroid-immune interactions, and a very short overview of general thyroid physiology is warranted.

#### 3.1. Thyroid hormone biosynthesis

Thyroid hormones, or iodothyronines by their chemical group name, are derivatives of the amino acid tyrosine containing one or two iodine substituents. Biosynthesis starts with the uptake of plasma-borne iodide by the thyroid gland via a sodium-iodide symporter (NIS) located in the basolateral membrane of the thyrocyte (Dai et al., 1996). Iodide moves transcellularly to the apical membrane of the thyrocyte, where it is secreted into the follicular lumen by the SLC26A4 pendrin ion transporter in mammals (Bizhanova and Kopp, 2009; Royaux et al., 2000). Although zebrafish (*Danio rerio*) express pendrin in their branchial ionocytes (Bayaa et al., 2009), the apical iodide transporter in teleost thyrocytes in general has not yet been identified. Extracellularly, at the interface of the apical membrane and the colloid, iodide is oxidized by thyroid peroxidase (TPO) to the reactive iodonium ion,  $H_2I^+$ . This reaction requires hydrogen peroxide,  $H_2O_2$ , supplied by thyroid oxidase type 2, also known as dual oxidase type 2 (Moreno et al., 2002; Ohye and Sugawara, 2010).

Thyroid hormone synthesis (reviewed by Miot et al., 2015) takes place on thyroglobulin (TG), a 660 kDa homodimeric protein that is synthesized by the thyrocyte and secreted via exocytosis into the lumen of the thyroid follicle. TG is the main protein component of the follicle's colloid. Selected tyrosines on the TG molecule are iodinated by iodonium. TPO catalyses the chemical coupling of two iodinated tyrosines to yield T4 and, to a lesser extent, T3 (de Vijlder and den Hartog, 1998). Upon stimulation of the thyroid gland by TSH, the colloid is partly resorbed by endocytosis, TG is degraded in

lysosomes, T4 and T3 are cleaved by proteinase action, and the hormones are released into the bloodstream.

Circulating thyroid hormones are bound to carrier proteins: transthyretin (TTR), thyroxine-binding globulin (TBG) and albumin (Richardson et al., 1994, 2005). As a consequence, free thyroid hormone concentrations in fish plasma are generally less than 0.5% of the total concentration (Eales and Shostak, 1985), a value comparable to that of mammals.

#### 3.2. Regulation of the thyroid axis

The mammalian hypothalamus-pituitary-thyroid (HPT) axis is often described as a classical endocrine example of negative feedback regulation. According to this view, hypothalamic thyrotropin stimulating hormone (TRH) stimulates the pituitary pars distalis to secrete thyrotropin or thyroid-stimulating hormone (TSH), which in turn stimulates the thyroid gland to produce and secrete thyroid hormone. In particular T4 negatively feeds back on the release of hypothalamic TRH and pituitary TSH.

In fishes the central regulation of the thyroid gland definitely differs between species. Teleosts lack a median eminence with a capillary portal system that connects the hypothalamus with the pituitary pars distalis. Instead, hypothalamic neurons project directly on or near cells in the pars distalis that secrete trophic factors such as TSH. This might explain that, besides TRH, other hypothalamic factors such as corticotropin releasing hormone (CRH) and dopamine, and likely more, are involved in the regulation of the thyroid axis (reviewed by Bernier et al., 2009).

#### 3.3. Extrathyroidal thyroid hormone metabolism

Specific membrane transporters regulate access of T4 and T3 to their intracellularly located targets, i.e. iodothyronine deiodinases and intracellular receptors. Thyroid hormone membrane transporters are therefore key for undisturbed thyroid hormone action (Heuer and Visser, 2013; van der Deure et al., 2010).

The enzymatic conversion by 5'-deiodination of T4 to T3 can be regarded as an activation pathway of T4. Further deiodination reactions at other C-positions of the iodothyronine molecule can subsequently convert T3 to metabolites with no or little biological activity, and thus serve to terminate a hormone signal. Deiodination reactions are catalysed by a family of deiodinases, each with different substrate affinities, cosubstrate requirements and type of deiodination reaction catalysed (Gereben et al., 2008; Köhrle, 1999). Fish deiodinases largely resemble their mammalian counterparts (Mol et al., 1998; Orozco et al., 2012), but with some subtle differences in biochemistry (Klaren et al., 2005, 2012; Mol et al., 1997; Orozco and Valverde-R, 2005).

#### 3.4. Thyroid hormone receptors

Thyroid hormone receptors (TRs) are members of a superfamily of ligand-dependent zinc-finger transcription factors. TRs are encoded by two genes,  $\alpha$  and  $\beta$ , and alternative splicing produces at least three receptor isoforms for every gene product (Brent, 2012; Ortiga-Carvalho et al., 2014). Virtually every body cell, including cells of the immune system (Luo et al., 1989; Villa-Verde et al., 1992) expresses one or more TRs, explaining the pervasive effects of thyroid hormone. Multiple transcripts of TR $\alpha$  and TR $\beta$  genes have also been detected in fish (reviewed by Heijlen et al., 2013).

All TRs have a DNA-binding domain that bind to a thyroid hormone response element in or near the promoter region of their target genes (Yen, 2001). The genomic action of T3 is via the regulation of gene expression, and explains most biological effects of thyroid hormone. Still, important non-genomic effects of the

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