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Review article

Applications for non-invasive thyroid hormone measurements in mammalian ecology, growth, and maintenance

V. Behringer[a,*], C. Deimel[b], G. Hohmann[a], J. Negrey[c], F.S. Schaebs[a], T. Deschner[a]

[a] Department of Primatology, Max Planck Institute for Evolutionary Anthropology, Deutscher Platz 6, 04103 Leipzig, Germany
[b] Department of Anthropology, Indiana University Bloomington, 701 E Kirkwood Ave, Bloomington, IN 47405, USA
[c] Department of Anthropology, Boston University, 232 Bay State Road, Boston, MA 02215, USA

ABSTRACT

Thyroid hormones (THs) play a pivotal role in the regulation of metabolic activity throughout all life stages. Cross-talk with other hormone systems permits THs to coordinate metabolic changes as well as modifications in growth and maintenance in response to changing environmental conditions. The scope of this review is to explain the relevant basics of TH endocrinology, highlight pertinent topics that have been investigated so far, and offer guidance on measuring THs in non-invasively collected matrices.

The first part of the review provides an overview of TH biochemistry, which is necessary to understand and interpret the findings of existing studies and to apply non-invasive TH monitoring. The second part focuses on the role of THs in mammalian ecology, and the third part highlights the role of THs in growth and maintenance. The fourth part deals with the advantages and difficulties of measuring THs in non-invasively collected samples. This review concludes with a summary that considers future directions in the study of THs.

1. Introduction

Thyroid hormones (THs) are produced, stored, and secreted by the thyroid gland and regulate numerous metabolic and ontogenetic processes in mammals (Bassett and Williams, 2016; Kaack et al., 1979; Silva, 2006). Through extensive interactions with other hormone systems, THs coordinate growth and metabolic changes in all life stages (Venturi and Begin, 2010). Thus, THs are attractive biomarkers for the study of mammalian ecology, energy allocation, and growth.

Despite many potential applications, THs have remained relatively unexplored in mammals, as most studies have focused on pathologies of the thyroid gland and/or measured TH concentrations from blood samples. These circumstances have likely limited interest from evolutionary biologists in exploring these biomarkers in natural contexts. Recently, appropriate methods to measure TH levels in urine and feces have been validated for several species. These methods enable long-term, high-density, non-invasive monitoring of TH levels in wild-living mammals and permit the investigation of THs as valuable biomarkers of mammalian energy allocation and growth.

This five-part review focuses mainly on THs in healthy mammals, with special attention to two main topics: energy and growth (Sections 3 and 4). In part one, we provide an introduction to TH biochemistry, including the relationship between THs and iodine, TH production and transportation, and the cross-talk between THs and other hormone systems. Part two addresses metabolic regulation, including adaptive thermogenesis, hibernation, and reproduction, with a special emphasis on pregnancy. Part three concerns growth and maintenance, including postnatal development, molting, and aging. In part four, we review the advantages and drawbacks of non-invasive sample collection, proper methods for collection, storage, and measurement of THs in feces and urine, and assay validation. Finally, we outline future prospects for the use of non-invasively measured THs. In all sections, we initially present information on humans—as most topics have been thoroughly investigated in our species—and then summarize what is known in other mammals, where, in many cases, only limited information is available.

2. Thyroid hormone biochemistry

2.1. Iodine

THs contain iodine (Refetoff and Nicoloff, 1995). Therefore, iodine deficiency results in insufficient production of THs (Fig. 1) (Andersson et al., 2012; Ristić-Medić et al., 2014). Usually, adequate iodine levels to achieve euthyroidism (normal thyroid function) can be attained through dietary intake and low iodine levels are readily corrected by increasing iodine uptake. Although the thyroid gland recycles iodine to compensate for inadequate intake, prolonged inadequate iodine intake can lead to goiter, cretinism, and hypothyroidism (pathologically low TH levels) as well as to developmental impairments in utero and after birth (Delange, 2001; Zimmermann, 2009). In humans, the

* Corresponding author.
E-mail address: verena_behringer@eva.mpg.de (V. Behringer).

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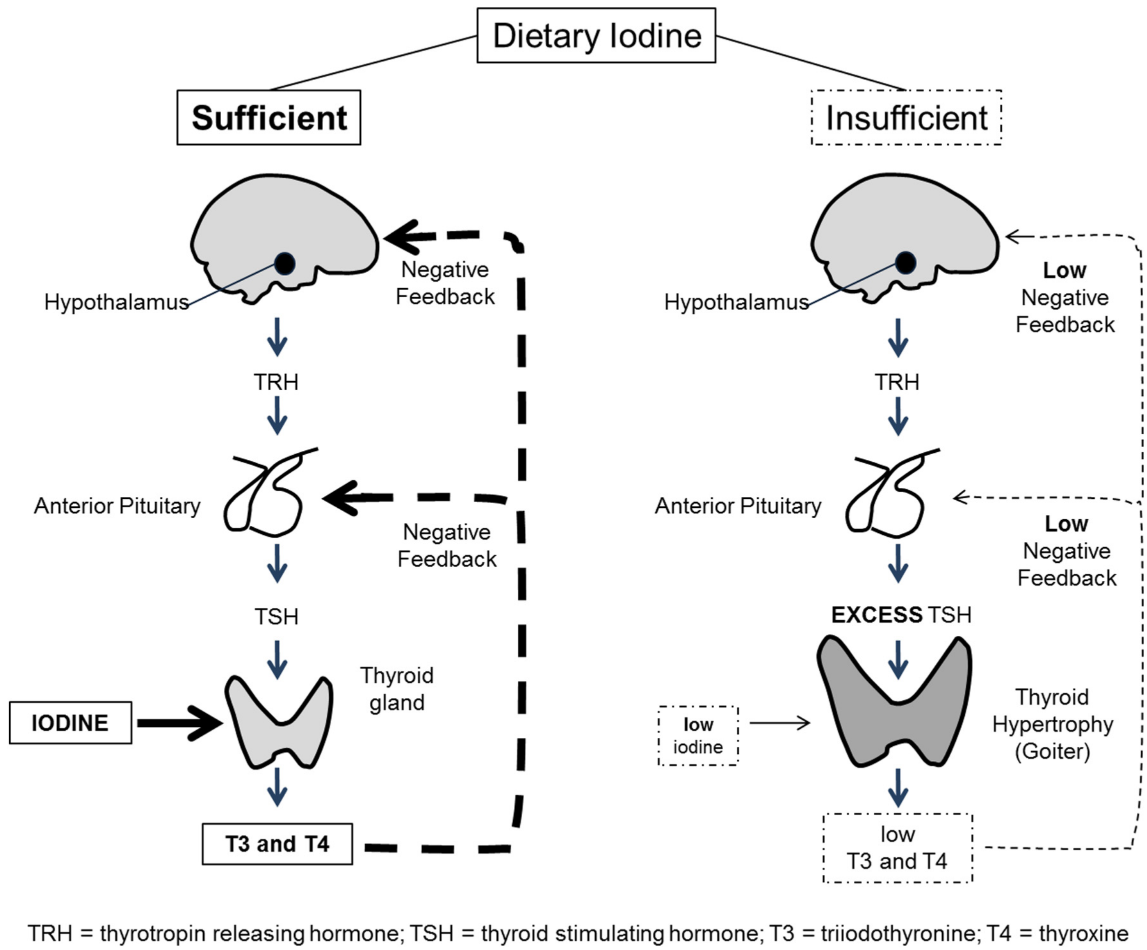

Fig. 1. The thyroid gland is stimulated by the hypothalamic-pituitary-thyroid (HPT) axis to trap iodine and to produce and release thyroxine (T4) and triiodothyronine (T3). When the amount of dietary iodine is sufficient (left side) the adequate concentrations of T3 and T4 levels in the circulation have a negative feedback on the HPT-axis. Changes in T3 and T4 levels are regulated by an increases or/and decreases of in TSH or/and TRH. During an iodine deficiency, the concentrations of T4 and T3 levels in the circulation decrease. The result is an excessive release of TSH, which can result in hypertrophy of the thyroid gland.

requirements for iodine are mainly met by non-plant food resources like sea food and dairy products (Zimmermann, 2009). Additionally, artificially iodized salt is widely used as a simple, cost effective treatment for population-wide iodine deficiencies (Johner et al., 2011).

In animals, most research on iodine deficiencies has focused on livestock (Graham, 1991; Groppel et al., 1989; Schlumberger, 1955), and pets (Dillitzer et al., 2011; Edinboro et al., 2010; Ranz et al., 2002). Iodine deficiency can cause reproductive problems and decrease offspring survival rates, such as elevated abortion rates in cattle (Hidiroglou, 1979; Schlumberger, 1955). Indeed, before the introduction of iodized salt, iodine deficiency resulted in such extreme newborn mortality rates that some US states discontinued the breeding of certain livestock species like sheep, swine and goats in Montana (reviewed in Schlumberger (1955)).

Although few data exist concerning the relationship between iodine availability and TH levels in domesticated animals, even fewer data are available for wild animals. This is surprising, as iodine availability varies greatly between different geographic regions and underlies iodine deficiency rates and related pathologies among human populations (Zimmermann and Boelaert, 2015). However, the existing data suggest that iodine changes in the environment can affect reproductive rates, fitness and thereby population size in wild animals. For example, a population of roe deer (*Capreolus capreolus*) inhabiting an area with low ambient levels of iodine suffer from reduced stag development, which is likely to engender negative fitness consequences (Lehoczki et al., 2011). Similarly, the reproductive rates of elephants in southern Africa increased following the ingestion of water from iodine-rich bore holes (Milewski, 2000). Thus, differences in regional iodine availability may cause considerable variation of iodine as well as TH measurements across populations of the same species.

2.2. Production, metabolism, and regulation of thyroid hormones

Four THs are present in mammalian blood, differentiated by the amount and position of conjugated iodine atoms, and their biological activity in different tissues (Norris, 2007). Thyroxine (T4, 3,3′,5,5′-tetraiodothyronine), containing four iodine atoms, and triiodothyronine (T3, 3′,3,5-triiodothyronine), containing three iodine atoms, are the THs present at the highest concentrations in blood. T3 is commonly considered more biologically active and potent than T4, and therefore has greater biological and clinical importance (Burke and Eastman, 1974; Fisher and Polk, 1989; Tomasi, 1991). Besides T3 and T4, reverse triiodothyronine (rT3, 3,3′,5′-triiodothyronine) and 3,5-diiodo-l-thyronine (T2, two iodine atoms) are present in circulation at a lower concentration, and are considered biologically inactive (Ball et al., 1997; Power et al., 2001; van der Spek et al., 2017). The primary mechanism regulating the availability of biologically active THs in tissues such as the kidney, brain, and skeletal muscles is monodeiodination, an enzymatic, reductive process resulting in the non-random removal of iodine atoms (Engler and Burger, 1984; van der Spek et al., 2017).

In humans, the thyroid gland secretes approximately 100 μg of THs per day (Gnocchi et al., 2016). T4 is the most abundantly produced TH