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Review article

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

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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

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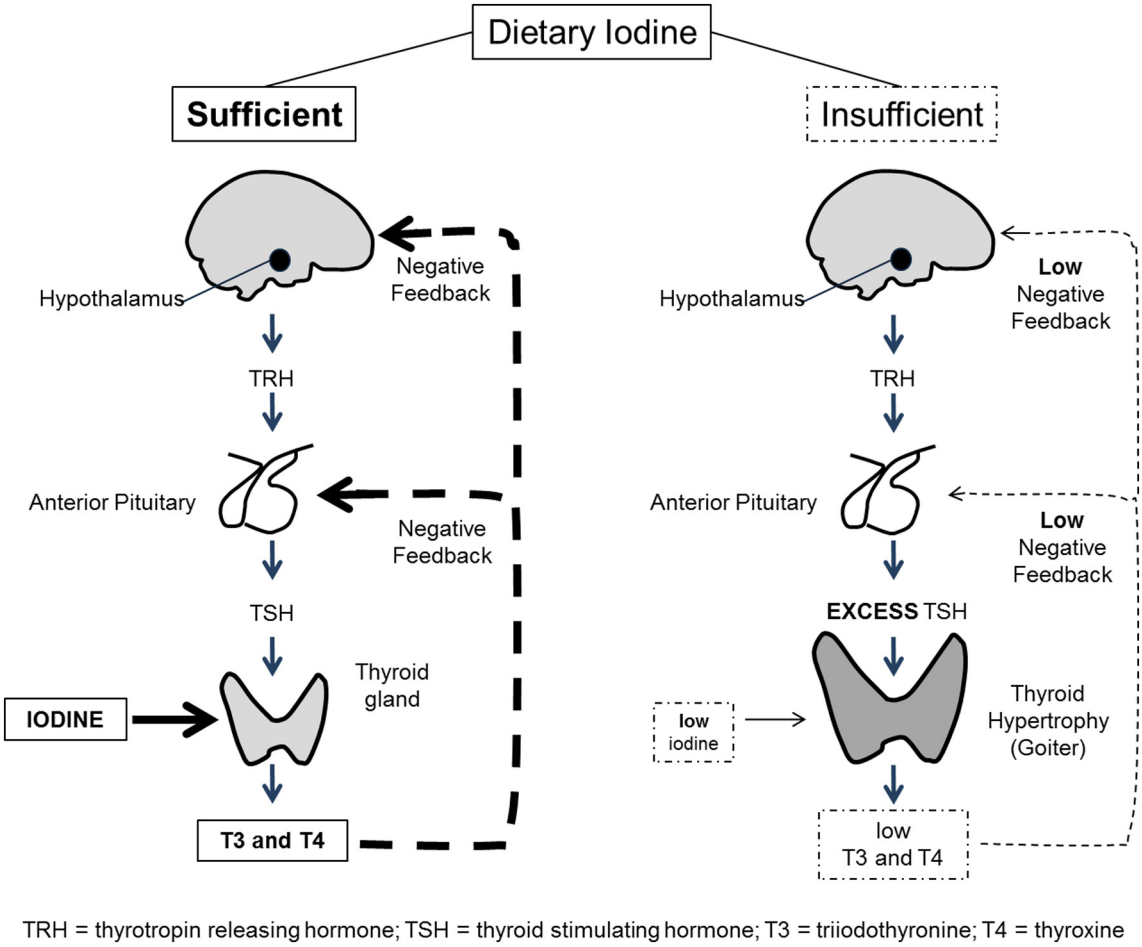

Fig. 1. The thyroid gland is stimulated by the hypothalamic-pituitary-thyroid (HPT) axis to trap iodine and to produce and release thyroxine (T4) and triiodothyronine (T3). When the amount of dietary iodine is sufficient (left side) the adequate concentrations of T3 and T4 levels in the circulation have 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

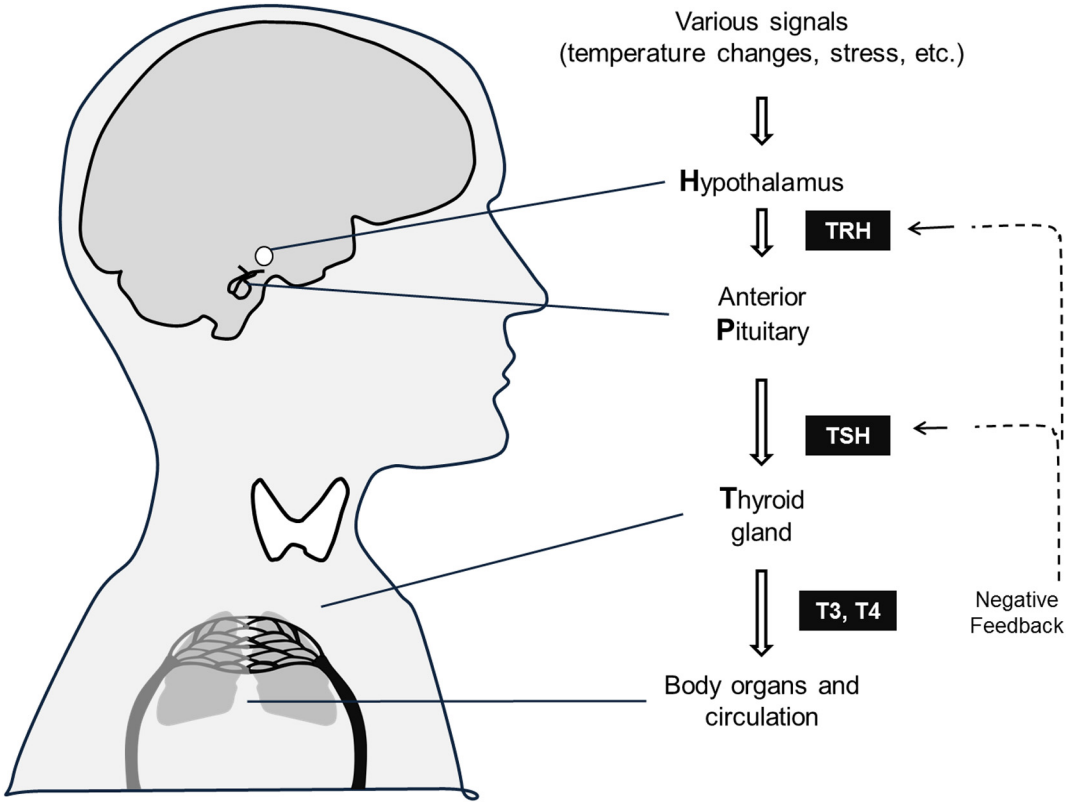

Fig. 2. Functioning of the hypothalamic–pituitary–thyroid (HPT) axis. Thyrotropin-releasing (TRH) from the hypothalamus stimulates the secretion of thyroid-stimulating hormone (TSH) by the pituitary, which leads to the synthesis of thyroid hormones (T3 and T4) and their secretion into the bloodstream by the thyroid gland. Rising T3 and T4 concentrations exert negative feedback on the production of TRH and TSH.

(Köhrle, 1999; Power et al., 2001; Refetoff and Nicoloff, 1995; Tomasi, 1991; Visser, 1994). Only 20% of circulating T3 is directly secreted by the thyroid gland, while 80% is produced by peripheral mono-deiodination from T4. Thus, T4 concentration in blood is 10 to 100 times higher than T3 concentration (Burke and Eastman, 1974; Refetoff and Nicoloff, 1995).

2.3. Hypothalamic-pituitary-thyroid axis and thyroid hormone secretion

The synthesis of THs is controlled by the hypothalamic-pituitary-thyroid (HPT) axis (Fig. 2). Thyrotropin-releasing hormone (TRH) is produced and released by the hypothalamus, stimulating the anterior pituitary gland to secrete thyroid-stimulating hormone (TSH, or thyrotropin) into the bloodstream (e.g., Bassett and Williams, 2016; Vassart and Dumont, 1992). In the thyroid gland, TSH stimulates the production of T3 and T4 from thyroid follicles (e.g., Power et al., 2001). The release of TRH and TSH is regulated by T3 and T4 concentrations via negative feedback mechanisms (Bassett and Williams, 2016; Dumont and Vassart, 1995; Fisher, 1996; Vassart and Dumont, 1992) (Fig. 2).

2.4. Thyroid hormone binding proteins

As hydrophobic molecules, THs are transported to target tissues bound to carrier proteins present in blood (Bartalena and Robbins, 1992; Burke and Eastman, 1974; Fisher, 1996; Köhrle, 1999; Refetoff and Nicoloff, 1995). Only unbound, “free” THs are able to bind to TH receptors and exert their actions in target tissues. In human blood, only 0.03% of total T4 (TT4) and 0.3% of total T3 (TT3) are unbound (Köhrle, 1999; Refetoff and Nicoloff, 1995). In most mammals, the majority of circulating THs are reversibly bound to three different serum proteins: thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin (Farer et al., 1962; Refetoff et al., 1970). The amino acid sequences of these proteins are comparable among mammals; homology ranges from 67 to 92% (Choksi et al., 2003; Power et al., 2000), but not all mammals produce all three carrier proteins. The three TH binding proteins exist in humans; however, the binding affinity of each carrier protein differs by TH. For example, TBG has the highest affinity for T4, whereas TTR possesses only medium affinity for T4. In contrast, albumin binds T4 with high capacity but low affinity (Bassett and Williams, 2016; Köhrle, 1999; Schussler, 2000). TBG has been documented in some primate species, while TTR is almost ubiquitous in animals as far as investigated yet (Köhrle, 1999). Variations in the production and abundance of certain binding proteins underlie species-specific differences in the primary transport mechanisms. For example, while albumin is the primary binding protein in rats, TBG is the primary binding protein in humans (Choksi et al., 2003).

As circulating THs are free and bound in different amounts, it is critical to distinguish between total (T) and free (f) concentrations when reporting circulating TH concentrations. In this review, we provide free and total concentrations whenever this information was reported. In cases where authors did not distinguish between free and total concentrations, we report their findings simply as “TH concentration”.

2.5. Peripheral conversion of thyroid hormones

THs are metabolized by different pathways or mechanisms: glucuronidation, sulfation, and deiodination. The metabolism and the activation or deactivation of THs is based on three deiodinase (D) types, with distinct functions, tissue distributions, and regulations (Fig. 3), which are important for TH homeostasis (Bianco and Kim, 2006; Visser et al., 2017). They regulate the activity of THs by removing iodine molecules and they differ in respect to their outer and/or inner ring deiodinase (ORD/IRD) activities (Fig. 3). Therefore, Ds are capable of

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	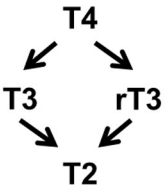	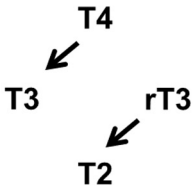	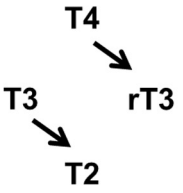
activity	5 and 5' deiodinase	5' deiodinase	5 deiodinase
tissue distribution	liver, kidney, thyroid gland, CNS*, skeletal muscles, placenta	brain, CNS*, BAT**, pituitary, placenta	almost all tissues, except kidney, thyroid gland, liver, pituitary
induction	T3	e.g., cold exposure, overfeeding, catecholamines	e.g., tissue injury T3
repression	fasting, illness	T3	growth hormone, glucocorticoids

* CNS = Central nervous system
** BAT = brown adipose tissues

Modified from :
Bianco & Kim (2006), Choski et al. (2003), Visser (1996)

Fig. 3. Characteristics and properties of the three deiodinase types.

converting T4 either to T3 or rT3, depending on the D type and tissue. For example, in peripheral tissues, type I and type II Ds, convert T4 by ORD to T3 or by IRD to rT3. Ds also catalyze the IRD of T3 and the ORD of rT3 to inactive products, especially to 3,3′-diiodothyronine (3,3′-T2) (Bernal and Nunez, 1995; Dumont and Vassart, 1995). Some tissues express none, while other tissues express all three D types. For example, the pituitary gland expresses all three, whereas D type III deiodinates T4 into rT3 in most non-hepatic tissues (Bianco and Kim, 2006; Fisher, 1996). Additional information on the properties of different deiodinase types is available in Fig. 3 and in Choksi et al. (2003) as well as in Bianco and Kim (2006).

2.6. Degradation of thyroid hormones in liver and kidney

The D type I is largely expressed in the liver and kidney, where the enzyme clears rT3 from the circulation and contributes to T3 concentration in the circulation. Furthermore, it catalyses the degradation of especially sulphated T3 and T4 by IRD activity (Visser et al., 2017). In the liver and kidney, iodothyronines are further metabolized by conjugation of the phenolic hydroxyl group with sulphate or glucuronic acid to increase their water-solubility and, thus, to facilitate their clearance. Iodothyronine glucuronides are rapidly excreted in the bile (Burke and Eastman, 1974; Visser et al., 2017).

2.6.1. Thyroid hormones in urine

TH metabolites in urine are present in conjugated or unconjugated form (Burke and Eastman, 1974; Flock et al., 1960; Shakespear and Burke, 1976). The proportion of conjugated TT3 in urine ranges from less than 23% to 50% (Gaitane et al., 1975; Orden et al., 1988; Shakespear and Burke, 1976). The proportion of conjugated urinary TT4 varies between 27% and 61% (Burke et al., 1972; Orden et al., 1987). This needs to be considered when selecting an extraction method (see Section 5).

In humans, the ratio of T4 to T3 in serum is 70:1, but it is approximately 2:1 in urine (Burke and Eastman, 1974). The most abundant free TH in urine is T4; urinary concentrations of T3 and T2 are less than half that of T4. When measuring total concentration (i.e., both free and conjugated concentrations), T4 is again the most abundant TH. However, TT2 concentrations are nearly as high as TT4, while TT3 remains at approximately half the concentration of TT4 (Faber et al., 1981).

Numerous studies report a positive correlation between urinary and serum free T3 (fT3) levels (e.g., Burke and Eastman, 1974; Gaitane et al., 1975; Orden et al., 1988; Yoshida et al., 1980). For example, after administration of exogenous T3, increased concentrations of this hormone were found in both serum and urine (Gaitane et al., 1975). However, urinary T3 probably represents the sum of conjugated and unconjugated T3 as well as T3 derived by partial deiodination of T4 (Burke and Eastman, 1974; Gaitane et al., 1975), when measured with an assay system (see Section 5).

Urinary T4 and serum free T4 (fT4) levels are also positively correlated (Burke and Eastman, 1974). One study comparing unextracted urinary fT4 with serum TT4 and fT4 reports correlation coefficients of $r = 0.85$ and $r = 0.93$, respectively (Orden et al., 1987), indicating that urinary T4 levels reflect unbound serum T4 concentrations. Consequently, the measurement of TH levels in urine can be used as a useful

indicator of thyroid function (Burke and Shakespear, 1976; Orden et al., 1988).

2.6.2. Thyroid hormones in feces

As in urine, THs derived from fecal samples provide an integrated measure over time, depending on gut passage time of the respective species (Behringer and Deschner, 2017; Palme et al., 1996; Schwarzenberger et al., 1996). Thus, fecal TH measurements are less sensitive to minor fluctuations (e.g., diurnal changes in TH levels) than blood measurements and are more suitable for investigating of broader patterns.

In humans, approximately 20% of T4 produced per day is excreted in feces (Visser et al., 2017). However, to our knowledge, detailed comparisons of fecal and blood TH levels have not been conducted. Separate studies that investigated TH changes regarding reproductive status, developmental stages, and during fasting with either blood or fecal samples reported comparable TH patterns in both matrixes (e.g., Ayres et al., 2012; Dias et al., 2017; Joly et al., 2015; Schaebs et al., 2016). Still, a direct comparison is lacking.

2.7. Cross-talks between HPT, HPA, and HPG axes

The HPT axis regulates TH concentration; however, it further cross-talks with the hypothalamic–pituitary–gonadal (HPG) and the hypothalamic–pituitary–adrenocortical (HPA) axes. These interactions have been mainly investigated in fish and birds, but also, to a lesser degree, in mammals (Castañeda Cortés et al., 2014; De Groef et al., 2006; Liu et al., 2016; Sower et al., 2009).

The HPA axis is stimulated by corticotropin-releasing hormone (CRH), resulting eventually in the secretion of glucocorticoids from the adrenal cortex; however, CRH also induces TSH secretion in fish, amphibians, reptiles, and bird species (Castañeda Cortés et al., 2014; De Groef et al., 2003). This cross-talk is adaptive in stressful environments. For example, in frogs during warm phases with declining water availability, high CRH levels lead to increases in both glucocorticoid hormones and THs, ultimately increasing the pace of metamorphosis (Bonett et al., 2010; Manzon, 2004). While CRH stimulates TSH in these non-mammal vertebrates, the capacity for TRH to stimulate TSH is not clear. For example, in birds, injection of TRH increases T3 but not T4 concentration (De Groef et al., 2006). Perhaps, in this case, TRH stimulates the secretion of growth hormone (GH), which then inhibits the degradation of T3 (De Groef et al., 2006). Regardless, in non-mammal vertebrates, CRH leads to a much greater output in TSH secretion (De Groef et al., 2006).

In contrast to non-mammal vertebrates, the activation of the HPA axis in mammals results in decreased TH levels. In humans, high levels of adrenal glucocorticoids, released by the adrenal glands in response to stressful situations, are associated with decreased serum T3 levels (Burr et al., 1976). During an acute stressful situation, the activation of the HPA axis results in a decrease of TSH excretion from the anterior pituitary gland, which leads to reduced TH secretion by the thyroid gland. Charmandari et al. (2005) conclude that increased CRH secretion, as a consequence of HPA axis activation, induces somatostatin secretion in the digestive system, which suppresses the release of TRH from the hypothalamus and TSH from the pituitary (Fig. 4). This downregulation ultimately leads to a decrease in TH secretion by the thyroid gland (Danforth and Burger, 1989). Furthermore, glucocorticoids inhibit the activity of deiodinases, thus causing a decrease in peripheral conversion of T4 to T3 (Charmandari et al., 2005). The effects of HPA axis activation on THs seem transient. After three days of exogenous glucocorticoid administration, the effect of reduced serum TH and TSH values abates (Nicoloff et al., 1970). This perhaps results from adaption of the HPT axis to long-lasting challenges (Baumgartner et al., 1988).

Prior experience with a particular challenge may also mitigate adverse effects on TH levels. For example, in a study of sport horses, all transported individuals exhibited increased cortisol levels, but only inexperienced individuals exhibited corresponding reductions in TH levels. The authors conclude that experienced horses probably adjust their metabolism in anticipation of transport and competition (Fazio et al., 2008). However, another possibility is that lower TH levels are not directly related to the psychological challenge of transport but to energetic deficits—i.e., inexperienced horses refused feeding during transport. The combination of THs and glucocorticoids was used in killer whales (*Orcinus orca*) to distinguish between the physiological effects of energy intake and human traffic, suggesting that energy intake had a greater impact than human traffic. On one hand, glucocorticoids levels were negatively correlated with short-term increases in prey availability; on the other hand, T3 levels corresponded with long-term prey availability (Ayres et al., 2012).

Cross-talk between the HPA and HPT axes is also evident in the circadian rhythm of hormone secretion. For instance, glucocorticoids exhibit a pronounced circadian rhythm, with peak levels in the morning and a day-long decline (Knutsson et al., 1997; Selmaoui and Touitou, 2003). The morning increase in cortisol levels is accompanied by a decrease in TSH levels and iodine release (Nicoloff et al., 1970).

The HPG axis is stimulated by gonadotropin-releasing hormone (GnRH), which may directly stimulate thyroid activity. For instance, increased GnRH levels correspond with TSH secretion in frogs and T4 levels in fish (Flood et al., 2013). However, GnRH may also indirectly interact with the thyroid through the biosynthesis of sex steroid hormones. GnRH regulates the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Changes in FSH and LH influence androgen secretion or the other way around, for example in humans, artificial androgen steroid administration significantly decreased TSH, T4, T3, fT4, and TBG (Alen et al., 1987). An increase in circulating TH levels leads to subsequent changes in FSH and LH secretion and thereby impacting the synthesis, secretion, circulation levels, metabolism, and physiological action of androgens. THs also regulate and influence androgen biosynthesis through the regulation of steroidogenic enzymes (Castañeda Cortés et al., 2014; Flood et al., 2013). In return, androgen signaling also influences TH metabolism through, among other mechanisms, the spatiotemporal distribution and expression of deiodinases (Flood et al., 2013). Moreover, androgen and estrogen binding receptors have been identified in the thyroid glands of various mammalian species (Pelletier, 2000), indicating that steroids may directly influence TH secretion. The cross-talk between androgens, FSH, LH, and THs suggests the existence of a vertebrate-wide interaction between the HPT and HPG axes (Castañeda Cortés et al., 2014). Studies on the effects of energy supply and reproduction may also benefit from simultaneous measures of steroid hormone and TH levels. For example, greater energy availability is correlated with earlier onset of menarche. In contrast, limitation of food sources is likely to delay maturation, because female reproductive life should not start until her energy reserves are sufficient to support pregnancy and lactation, and variation in food availability is a common cause for significant differences in the onset of maturation between wild and captive populations (Bercovitch and Strum, 1993; Bronson, 2000; Stearns, 1992). Furthermore, in mammals, the probability of conception is also influenced by energy balance: caloric deficit is a potential source of infertility, as, for example, demonstrated in cows (Butler, 2003; Villa-Godoy et al., 1988), and in humans, for whom energetic stress decreases HPG functioning leading to ovulatory failure and decreased progesterone levels (Loucks, 2003; Vitzthum et al., 2004). Therefore, combining measurements of steroid hormone as well as TH levels offers a promising approach in the context of energy metabolism in reproduction.

3. The role of thyroid hormones in mammalian ecology

In the following section, we review the role of THs in regulating metabolic activity in response to changing environmental or physiological circumstances such as food deprivation or pregnancy. We focus on mammalian studies but have supplemented our review with findings

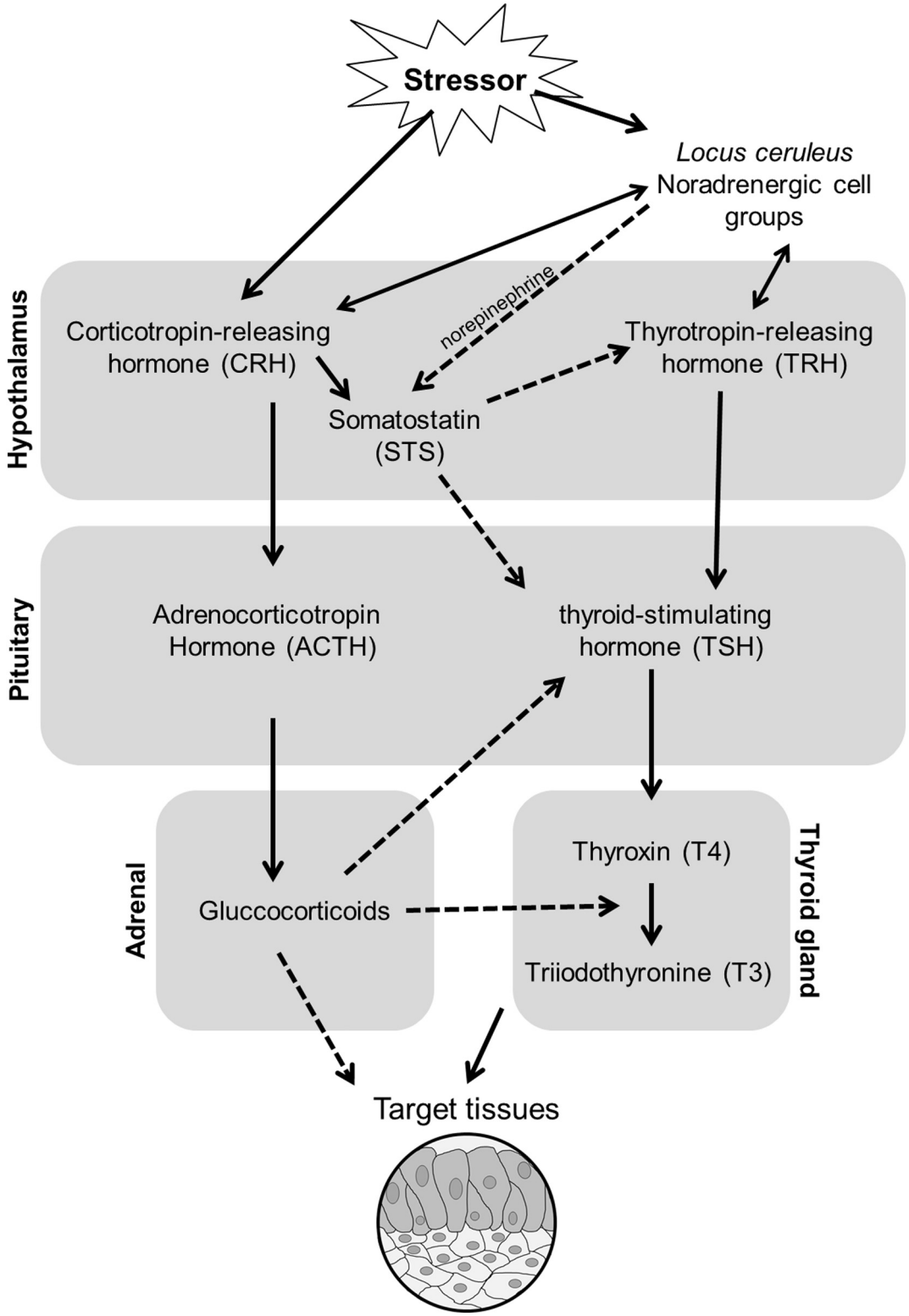

Fig. 4. Cross-talk between the hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–thyroid (HPT) axes during the acute stress response. After Chrousos and Gold (1992).

from other vertebrates.

3.1. Thyroid hormones and metabolic changes

Changes in TH levels can reflect variation in energy availability, as well as variation in metabolic demands, and, under certain circumstances, iodine depletion. The HPT axis and THs are modulators of homeostatic energy metabolism and lipid metabolism. THs regulate basal metabolic rate (BMR) as shown in humans with pathologically high (hyperthyroidism) or low (hypothyroidism) TH levels (López et al., 2010, 2013). THs act directly on metabolically active tissues like brown adipose and hepatic tissue as well as cardiac and skeletal muscle (López

et al., 2013). In addition, THs exert peripheral effects on thermogenesis as well as food intake. For example, in humans and rodents, abnormally elevated appetite (hyperphagia) is associated with high TH levels (López et al., 2013). Furthermore, THs affect hepatic glucose metabolism. The liver is crucial for the maintenance of glucose homeostasis; it both stores and produces glucose during fasting (Petersen et al., 2017). In this context, THs promote intestinal glucose absorption and uptake of glucose by adipose and muscle tissue, influence hepatic glycogen synthesis and glycogenolysis, and modulate the responsiveness of liver and muscle tissues to other hormones e.g., insulin (López et al., 2013).

3.1.1. Thyroid hormones and energetic changes in humans

Responding to energetic changes is considered one of the primary regulatory functions of the thyroid gland (Flier et al., 2000). During periods of severe energy deprivation, vital body functions are maintained via hormone-mediated metabolic changes — for instance, the preservation of muscle mass at the expense of adipose tissue (Weissman and Hashem, 2014). More than the other THs, T3 appears to determine metabolic state (Danforth and Burger, 1989; Yoshida et al., 1980). T3 levels decrease when food availability is inadequate and increase when food is abundant. This mechanism decreases metabolic rate and allows for energy conservation when food is scarce, and increases metabolic rate and energy expenditure in times of plenty (e.g., Eales, 1988; Flier et al., 2000; van der Heyden et al., 1986). Several studies have demonstrated the correlative relationship between T3 levels and energy expenditure (Delgiudice et al., 1987; Harlow and Seal, 1981; Palmblad et al., 1977; Rosenbaum et al., 2000). As has been illustrated by a range of human fasting studies, decreased T3 levels in response to food restriction are related to a decrease in energy expenditure (Fontana et al., 2006; Merimee and Fineberg, 1976; Spaulding et al., 1976). The response of THs to changes in energy availability is fast—i.e., TH levels rapidly decrease in response to nutritional deficits (e.g., Eales, 1988; Flier et al., 2000; van der Heyden et al., 1986). This decline is even steeper during starvation (Danforth and Burger, 1989; Spaulding et al., 1976). However, this immediate reaction to energy restriction seems to level out if energy restriction lasts for more than three days. During prolonged food restriction, T3 levels eventually increase again but remain lower than during periods of adequate energy intake (Danforth and Burger, 1989).

Contradictory results have been reported in the T4 and rT3 responses to fasting. While one study found no changes in serum rT3 levels (Palmblad et al., 1977), other studies report increased rT3 levels during fasting (Rosenbaum et al., 2000; Spaulding et al., 1976). Furthermore, several studies report little or no changes in T4 levels during fasting (Danforth and Burger, 1989; Merimee and Fineberg, 1976), perhaps explained by the longer half-life of T4 (Weissman and Hashem, 2014). These differences in rT3 and T4 during fasting maybe result from different study designs — for example, differences in the length of the fasting period, given that short fasting periods may not affect the T4 reservoir.

Additionally, fasting affects the different deiodinases converting T4 into T3 or rT3 and rT3 into T2 (Bianco and Kim, 2006). Under normal energetic conditions, the body converts about 40% of T4 into T3 and 60% into rT3, the latter of which is rapidly converted into T2 (Fisher, 1996). During fasting, more T4 is converted into rT3. At the same time, metabolic rate slows, as does the rT3 to T2 conversion rate. Therefore, during fasting, the conversion of T4 into T3 decreases, but the conversion of T4 into rT3 increases, resulting in roughly equivalent T4 concentrations (Bianco and Kim, 2006). Consequently, during periods of fasting the amount of rT3 and T3 will change.

3.1.2. Thyroid hormones and energetic changes in nonhuman mammals

The link between energetic changes and TH levels has been investigated in a number of nonhuman model species. As in humans, serum T4 and T3 levels decrease in periods of energy deprivation in most mammals (Table 1).

T3 and T4 levels are higher when food quality (i.e., caloric density) is better; incidentally, these TH changes are accompanied by increases in body weight (Table 1). However, in aquatic mammals, TH patterns are less explicit; some studies report no TH changes in response to food fluctuations (Table 1). One explanation might be that cetaceans have a larger thyroid gland in proportion to body weight, resulting in higher concentrations of circulating THs than those of most terrestrial mammals. These characteristics might enable cetaceans to maintain a large reserve of THs for periods of increased TH demand (Flower et al., 2015). Another possible explanation is that cetaceans have exceptional fat reserves (Lockyer, 2007) and consequently do not need to downregulate metabolic rate during times of food scarcity.

Together, these data demonstrate that TH levels reliably trace energy availability in terrestrial mammals, decreasing during periods of energy restriction and increasing when energy is abundant. Thus, THs are promising biomarkers of metabolic state to complement studies of energy availability in wild mammals.

3.2. Adaptive thermogenesis

THs are critically involved in thermogenesis and regulation of body temperature in euthermic animals (Dauncey, 1990; Laurberg et al., 2005; Silva, 1995), interacting with the sympathetic nervous system and brown adipose tissue to produce heat (reviewed in Silva (1995, 2006)).

Usually, TH levels are negatively related to ambient temperature. Animals living in desert environments, subject to extreme heat and the threat of overheating, commonly exhibit lower TH levels than animals in temperate environments, as demonstrated in studies of rodents and cattle (Magdub et al., 1982; Silanikove, 2000; Yousef and Johnson, 1975). Consequently, desert animals have lower metabolic rates (Yousef and Johnson, 1975). These population-specific patterns are paralleled by decreases in metabolic rate and food intake during heat stress in individual cattle (Beede and Collier, 1986; Silanikove, 2000).

Animals confronted with low ambient temperature need to increase their resting metabolic rate and so respond by upregulating TH levels (Knigge, 1957). Indeed, cold stress usually stimulates the secretion of THs (Gale, 1975). This relationship is well supported and has been demonstrated in a variety of species, including rams (*Ovis* spp.), burros (*Equus asinus*), and llamas (*Lama glama*) (Brooks et al., 1962; El-Nouty et al., 1978), wallabies (*Macropus eugenii*) (Kaethner and Good, 1975), ground squirrels (*Citellus tridecemlineatus*) (Bauman and Anderson, 1970), golden hamsters (*Mesocricetus auratus*) (Tashima, 1965; Tomasi and Horwitz, 1987), baboons (*Papio anubis*) (Gale, 1975) and wild Barbary macaques (*Macaca sylvanus*) (Cristóbal-Azkarate et al., 2016). One experiment demonstrated that TH levels in female golden hamsters change during prolonged artificial exposure to high (25.5 °C) and low (4.5 °C) ambient temperature; TH levels increased rapidly in response to cold temperature and were sustained at an elevated level compared to the warm ambient condition (Bauman et al., 1968).

The thermoregulatory correlates of THs are relatively well researched in aquatic mammals—i.e., TH levels are negatively correlated with ambient temperature. For example, in adult harbor seals (*Phoca vitulina*), plasma TT4, TT3, and fT3 levels, but not fT4, were significantly elevated during the cold winter season (Oki and Atkinson, 2004). The pups of several arctic seal species exhibit increased plasma TH concentrations in comparison to adult individuals, presumably for thermoregulatory purposes (Hall et al., 1998; Stokkan et al., 1995), or due to energy investment into growth (see Section 4). However, in newborn pups, THs are markedly elevated, perhaps reflecting high prepartum transfer of T4 from the mother, or the presence of active secretory thyrocytes in the foetus, as shown in pups of the southern elephant seal (*Mirounga leonina*) (Little, 1991) and grey seal (*Halichoerus grypus*) (Stokkan et al., 1995). In contrast, T3 levels are lowest immediately post-partum and increase as a function of age, indicating increased deiodination of T4 to T3 (Woldstad and Jenssen, 1999). In

Table 1
Mammalian studies investigating the relationship between energetically changes and thyroid hormones (triiodothyronine (T3), reverse T3 (rT3), and thyroxine (T4), presented by species and matrix).

Common name	Genus and species	Nutritional status	Matrix	rT3	T3	T4	Publication
Sprague-Dawley rats	NS	Starvation	Feces	–	–	Decrease	(Ingbar and Galton, 1975)
Sprague-Dawley rats	NS	Starvation	Serum	–	Decrease	Decrease	(Harris et al., 1978)
Rats	NS	Starvation	Plasma	–	Decrease	Decrease	(Donati et al., 1963)
Sprague-Dawley rats	NS	Deprivation	Serum	–	Decrease	–	(Blake et al., 1991)
Rabbits	New Zealand White	Fasting	Plasma	–	Decrease	–	(Menchetti et al., 2015)
Rabbits	NS	Fasting	Plasma	–	Decrease	–	(Brecchia et al., 2006)
Woodchuck	*Marmota monax*	Fasting	Plasma	–	Decrease	Decrease	(Young, 1984)
Sheep	NS	Starvation	Serum	Increase	Decrease	Decrease	(Blum et al., 1980)
Goats	NS	Fasting	Feces	–		Decrease	(Abdullah and Falconer, 1977)
White-tailed deer	*Odocoileus virginianus*	Fasting	Serum		Decrease	No change	(Martinez and Hewitt, 1999)
Caribou	*Rangifer tarandus*		Feces	–			(Joly et al., 2015)
Wolves	*Canis lupus*	Fasting	Serum	–	Decrease	–	(Delgiudice et al., 1987)
Badgers	*Taxidea taxus*	Fasting	Serum	–	Decrease	–	(Harlow and Seal, 1981)
Black bears	*Ursus americanus*	Fasting	Plasma	–	Decrease	Decrease	(Tomasi et al., 1998)
Capuchins	*Sapajus xanthosternos*	Fasting	Feces	–	Decrease	–	(Schaebs et al., 2016)
Howler monkeys	*Alouatta palliata*	Fasting	Feces	–	Decrease	–	(Wasser et al., 2010)
Howler monkeys	*Alouatta palliata*	Leaf diet	Feces	–	Decrease	–	(Dias et al., 2017)
Elephant seals	*Mirounga angustirostris*	Natural fasting (mating season)	Serum	–	No change	No change	(Crocker et al., 2012)
Elephant seals	*Mirounga angustirostris*	Natural fasting	Serum		No change	Decrease	(Kelso et al., 2012)
Grey seals pubs	*Halichoerus grypus*	Fasting	Serum	–	Decrease	Decrease	(Bennett et al., 2012)
Harbor seals	*Phoca vitulina*	Fasting	Serum	–	–	Decrease	(Renouf and Noseworthy, 1991)
Monk seal	*Monachus schauinslandi*	Natural fasting	Feces	–	Decrease	–	(Gobush et al., 2014)
Bottlenose dolphins	*Tursiops truncatus*	Fasting	Serum		Decrease	Increase	(Ortiz et al., 2010)
Killer whale	*Orcinus orca*	Natural fasting	Feces	–	Decrease	–	(Ayres et al., 2012)
Sheep	NS	Food surplus	Serum	Decrease	Increase	Increase	(Blum et al., 1980)
Mull deer	*Odocoileus hemionus*	Food surplus	Serum	–	Increase	Increase	(Bishop et al., 2009)
Red deer	*Cervus elaphus atlanticus*	Food surplus	Serum	–	Increase	No change	(Ryg and Langvatn, 1982)
Black bears	*Ursus americanus*	Food surplus	Serum			Increase	(Hellgren et al., 1993)
Howler monkeys	*Alouatta palliata*	Fruit plus	Feces		Increase		(Dias et al., 2017)

NS = not specified.

arctic ruminants, high neonatal TH levels have also been found. For example, newborn muskoxen (*Ovibos moschatus*) and reindeer (*Rangifer tarandus*) have elevated plasma TT3 and TT4 levels (Knott et al., 2005), indicating that the patterns exist in terrestrial as well as in aquatic mammals and might be an adaptation to thermoregulatory challenging environments.

3.3. Hibernation

Among mammals, hibernation is a taxonomically and geographically widespread phenomenon that can be viewed as an extreme example of energetic restriction, given that it is characterized by decreases in body temperature and metabolic rate (Doherty et al., 2014; Williams et al., 2014). Mammalian TH levels decrease during hibernation to reduce metabolic rate and conserve energy, as shown, for example, in brown bears (*Ursus arctos arctos*) (Hissa et al., 1994; Nelson et al., 1973), black bears (*Ursus americanus*) (Azizi et al., 1979; Tomasi et al., 1998) (Fig. 5), golden hamsters (*Mesocricetus auratus*), and ground squirrels (*Citellus tridecemlineatus*) (Bauman and Anderson, 1970; Tashima, 1965).

However, hibernation is composed of alternating dormancy and arousal bouts, and during arousal bouts, free TH levels increase, as has been observed in ground squirrels (*Spermophilus richardsoni*) and woodchucks (*Marmota monax*) (Demeneix and Henderson, 1978; Magnus and Henderson, 1988). Although this increase is accompanied by an increase in TH binding globulins, the increase in serum binding capacity buffers only part of the increase in THs and leads to higher fTHs in comparison to the levels of active animals (Magnus and Henderson, 1988; Wenberg and Holland, 1973).

3.4. Thyroid hormones and reproduction

Normal thyroid function is important for reproductive function in both males and females. Pathological conditions characterized by abnormally high or low TH levels impact fecundity through impaired reproductive function and are well studied in humans and rodent models (reviewed in Krassas et al. (2010)). Hypo- and hyperthyroidism alter reproductive hormone levels and can lead to reduced sperm motility as well as abnormal morphology in males, and to menstrual abnormalities in women leading to infertility (Krassas et al., 2010). Several reviews provide detailed information on pathological thyroid conditions and their impact on reproduction in animal models and humans (Krassas, 2000; Krassas et al., 2010; Poppe and Velkeniers, 2004; Redmond, 2004).

The specific interactions between reproductive functioning and THs remain poorly understood. Yet, investigating the cross-talk between the HPT and HPG axes is a promising approach for quantifying trade-offs in maintenance, growth, and reproduction in both sexually mature and immature individuals (Cyr and Eales, 1996).

3.4.1. Male reproduction

During ontogeny, THs are essential for the proliferation of Sertoli cells in the testes; inadequate TH levels impact fecundity and fertility in adulthood (Cooke et al., 2004; Wagner et al., 2008). Testicular tissue is not highly responsive to THs, and fertility does not seem affected when THs vary within a normal range (Maran et al., 2000; Oppenheimer et al., 1974).

THs affect adult male hormone levels by altering steroid synthesis and metabolism. For example, increased T3 levels lead to a decrease in sex steroid synthesis in many adult vertebrate tissues (e.g., in the gonads), sometimes even causing lower circulating sex steroid hormone levels (see Duarte-Guterman et al. (2014)). The influence of THs on sex steroid synthesis and cross-talk between the HPT and HPG axes are conserved among vertebrates (Duarte-Guterman et al., 2014), but few studies have investigated mammals.

There are relatively few studies exploring the relationship between TH levels and fecundity in healthy males, and the studies that do exist have yielded unclear results. For example, in Khuzestan buffalo

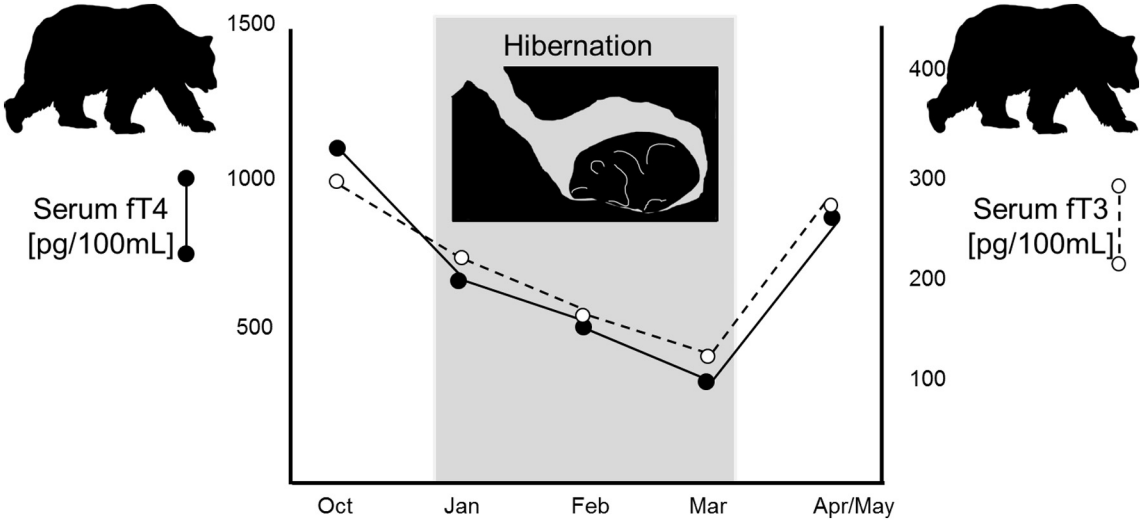

Fig. 5. Changes in free thyroid hormone levels (fT3 and fT4) during hibernation in American black bears (after Azizi et al. (1979)).

(*Bubalus bubalis*) bulls, TT4 levels were lower during winter than summer, while TT3 and TSH levels did not differ between the seasons. During the winter, there was a significant positive relationship between spermatozoa concentration and serum T3 levels; during the summer, significant positive correlations were found between spermatozoa count and T3 levels, T4 levels and semen volume, and spermatozoa motility and TSH levels (Mayahi et al., 2014). Another study investigated TH levels in male elephants. After reaching puberty, elephant bulls have periodic episodes characterized by highly aggressive behavior accompanied by a rise in reproductive hormone levels, called musth. In Asian elephant bulls (*Elephas maximus*) exhibiting yearly musth cycles, musth was positively associated with TSH levels, while T3 and T4 levels were negatively correlated with testosterone levels (Brown et al., 2007). Specifically, TH levels rose before testosterone levels were elevated with the onset of musth, and declined until testosterone levels returned to baseline levels. Negative feedback between THs and TSH was probably responsible for the negative relationship between these two hormones during musth. In Asian and African elephant bulls without yearly musth cycles, no significant relationship was found between THs and testosterone levels. The authors conclude that the role of THs in controlling male elephant musth cycles is unclear, but THs might facilitate expression or control of musth cycles in specific individuals (Brown et al., 2007). An alternative explanation would be that the changes in THs levels are related to changes in food consumption, since musth is also characterized by a decrease in food intake and bulls live off on fat reserves (Santiapillai et al., 2011; Schulte and Rasmussen, 1999). Prior to musth, high TH levels might be caused by an elevated level of energy consumption, while an increase in testosterone levels and aggressive behavior increase, elephant's caloric intake declines and TH levels, too. Therefore, musth could also been seen as a period of fasting.

THs are essential for adequate testicular development during ontogeny but do not play a major role in adult male reproductive function. There is some evidence that THs affect steroid production, but the few studies investigating this relationship in mammals have produced unclear results. As more studies explore this relationship, patterns may emerge with regard to seasonal breeding schedules or other ecological variables.

3.4.2. Female reproduction

Excessively high and low TH levels have a profound inhibitory effect on female reproduction (Cooke et al., 2004; Doufas and Mastorakos, 2006; Krassas, 2000; Krassas et al., 2010). In humans, hyper- and hypothyroidism disturb menstrual functioning and decrease fecundity and fertility (Jefferys et al., 2015; Krassas, 2000; Krassas et al., 2010). In addition, adequate TH levels are necessary for ovulation (e.g., Fedail et al., 2014; Krassas et al., 2010; Maruo et al., 1987, 1992; Wakim et al., 1993; Zhang et al., 2013). The molecular mechanisms underlying these associations are poorly understood, but THs seem to exert direct effects on the ovary as well as modulating pituitary gonadotropin production (Cooke et al., 2004).

Despite extensive knowledge about female reproductive functioning and THs in humans, there is little research concerning this topic in nonhuman mammals. In female rodents and rhesus monkeys, ovarian cycles tend to be longer and/or more variable in length in the absence of THs (Maqsood, 1952). In female common seals (*Phoca vitulina*), reduced TH levels due to environmental toxins are associated with reproductive failure (Brouwer et al., 1989; Reijnders, 1986). Similarly, dairy cows that did not exhibit ovarian activity and estrous expression had lower levels of T3 and T4. There was also a positive correlation between T3 and estrogen levels (reviewed in Jorritsma et al., 2003; Suriyasathaporn, 2000). However, in Asian and African elephants, there was no significant difference in TSH, fT3, TT3, fT4, or TT4 between cycling and non-cycling females (Brown et al., 2004).

Mammalian female reproduction is sensitive to food restriction (Somogyi et al., 2011; Torre et al., 2013), and THs are sensitive markers of food restriction (see Section 3). It is therefore intriguing that there may exist a relationship between THs and reproduction mediated by food availability. Unfortunately, there are few studies investigating the relationship between reproduction and THs in relation to food availability. One comprehensive study investigated this relationship in the New Zealand white rabbit (NZW, HY/CR strain). The animals in the experimental condition were food deprived before ovulation was induced with GnRH injections. Before refeeding, plasma levels of T3 were decreased in food restricted groups compared to a control group, and T3 levels increased in food restricted groups after refeeding. The LH peak was diminished in food restricted groups, as were estradiol pulse frequency and amplitude. Although these altered reproductive hormone profiles did not affect ovulation rate, receptivity and fertility rate of food restricted animals declined by ~20% (Brecchia et al., 2006). Another study subjected adult Malpura sheep ewes (*Ovis aries*) to walking stress under controlled food intake and compared them to unstressed control animals. The ewes subjected to walking stress had significantly reduced T3 and T4 levels, but estradiol and progesterone levels did not differ between the groups, indicating no effect on reproductive performance (Sejian et al., 2012b). A related study found that T3, T4, and estradiol levels decreased, while progesterone levels increased, in Malpura ewes subjected to heat stress. Heat stressed animals also had shorter estrous durations than control animals, but there was no

difference in the proportion of estrous females or in estrous cycle length (Sejian et al., 2014). These results contrast with a previous study reporting that heat-stressed, energetically-stressed, and calorically restricted Malpuran ewes were significantly less likely to exhibit estrous, had shorter estrous duration, and lower conception and lambing rates. However, as in the previously mentioned study, estradiol decreased and progesterone increased in animals subjected to these combined stressors. Unfortunately, THs were not assessed in this study (Sejian et al., 2012a). Interestingly, supplementation of ewes subjected to heat stress with minerals and antioxidants ameliorated the effects of heat stress (Sejian et al., 2014). These results suggest that THs might be useful for assessing heat stress, nutritional stress, and energy expenditure in relation to reproductive parameters in females.

THs have a profound effect on female reproduction. TH variation within physiological limits may affect fecundity in healthy individuals, but studies investigating this relationship are rare. The possible role for THs as mediators between environmental factors and the reproductive system—and ultimately, reproductive success—is an interesting and important topic demanding further attention.

3.4.2.1. Pregnancy

3.4.2.1.1. Thyroid hormones during pregnancy in humans. Maternal THs play a fundamental role in embryogenesis and foetal development (Manjunatha et al., 2014; Morreale de Escobar, 2004). In healthy pregnant women, the thyroid gland increases TH output to accommodate increased metabolic demand (Glinoer, 1999, 2001; Manjunatha et al., 2014). In the well documented cases of iodine deficiency, the thyroid gland cannot produce adequate amounts of THs (see Iodine Section 2.1).

The production of TBG and THs during pregnancy is tied to fluctuations in luteinizing hormone (LH) and human chorionic gonadotropin (hCG) levels. During the first trimester of pregnancy, the thyroid gland is stimulated by increases in LH and hCG (Glinoer, 1999, 2001). At the end of the first trimester, increasing estrogen levels cause a two-to-three fold increase in TBG concentration, which in turn stimulates TRH and TSH production (Burrow, 1990; Glinoer, 1997, 1999). Consequently, TT3 and TT4 are elevated in serum during the first half of pregnancy (Dowling et al., 1956; Dumont and Vassart, 1995; Glinoer et al., 1990; Hotelling and Sherwood, 1971; Morreale de Escobar, 2004). More specifically, TT4 levels increase sharply between the sixth and ninth week of gestation and more slowly thereafter, with reaching stable levels from the eighth to the twenty-seventh week of gestation. TT3 levels increase only in the eighteenth week of gestation (Yamamoto et al., 1979).

While the increase in total THs and TBG in serum during pregnancy is well established, changes in free THs and TSH are debated (Glinoer et al., 1990). The results for changes of fT4 and fT3 levels during gestation are inconsistent. Some studies report an early increase in TBG and a moderate decrease in free THs between weeks 10 and 40 (Glinoer, 1999; Glinoer et al., 1990). Contrary to these results, other studies find no change, or an increase, in free TH concentrations during pregnancy (Fereidoun et al., 2013; Harada et al., 1979; Moncayo et al., 2015). One explanation for these inconsistent findings may be the relative availability of iodine. In areas with sufficient iodine in the environment, the decrease in free THs is marginal (10–15%), but in iodine-deficient areas, the decrease is pronounced (Glinoer, 1999). Another explanation for these contradictory findings, as proposed by Glinoer (1997), concerns flawed measurement of fT3 and fT4. A recent study of immunoassay methods reports problems in accuracy and reliability for fT4 measurements from samples taken during pregnancy (Soukhova et al., 2004). Consequently, Soukhova et al. (2004) developed and standardized a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method to measure fT3 and fT4 in human serum samples. Using this new method, T3 levels increased during pregnancy with a peak in the last trimester (Fig. 6) (Soldin et al., 2004a, 2004b). Using LC-MS/MS, increasing TT4 and fT4 were consistent with the results described above for EIA and RIA measurements (Soldin et al., 2004a; Soldin et al., 2004b). When comparing the results of blood samples to 24 h-urine samples, significant differences in T3 levels were found between pregnant and non-pregnant women in serum but not in urine (Gaitane et al., 1975). The serum T3 measurements were 100 times higher than the urine concentrations in this study; therefore, serum values seemingly represent TT3, whereas the 24 h unextracted urinary values represent fT3 (Gaitane et al., 1975). However, because different units were used for serum and urine measurements (i.e., serum: nanogram/deciliter; urine, microgram/24 h), a direct comparison of concentrations is not possible.

3.4.2.1.2. Thyroid hormones during pregnancy in nonhuman mammals. Few studies have used THs to explore pregnancy in nonhuman mammals, and the results of these studies are inconsistent. In some mammals, including goats (Riis and Madsen, 1985) and howler monkeys (*Alouatta palliata*) (Dias et al., 2017), increasing blood and fecal TH levels were found during pregnancy. In contrast, no changes were reported for serum TT3 in pregnant rabbits (Menchetti et al., 2015) or plasma T3, T4, or TSH levels in rhesus macaques (Azukizawa et al., 1976). Moreover, fecal T3 levels were lower in wild lactating and pregnant baboons, which may be an energy saving mechanism (Gesquiere et al., 2018).

4. The role of thyroid hormones in growth and maintenance

4.1. Thyroid hormones in the young and old

In addition to metabolic regulation, THs contribute to mammalian growth and maintenance. In humans, linear growth and skeletal maturation occur during foetal as well as childhood development and continue until epiphyseal fusion occurs. This process results from endochondral ossification in the epiphyseal growth plates of long bones and is regulated by various hormones including THs, growth hormone (GH), insulin-like growth factor 1 (IGF-1) and glucocorticoids (GCs). Changes in TH levels affect the secretion of growth factors, including IGF and erythropoietin, by binding to nuclear receptors (Fisher et al., 1982). Furthermore, GH concentration is positively correlated with T3 concentration (Grunfeld et al., 1988), indicating synergy between THs and GH (Fisher, 1985). THs potentiate the action of IGF-1 on cartilage growth (Dunger et al., 1990; Holder and Wallis, 1977). Therefore, THs are involved in the progression and timing of physiological processes such as skeletal maturation, linear growth, and brain growth. Healthy concentrations of these hormones must be maintained even into adulthood, when THs are necessary to maintain bone mass and regulate bone turnover (Bassett and Williams, 2016; Harvey et al., 2002; Robson et al., 2002).

For information on the effects of THS concentrations on brain development, see Bernal and Nunez (1995), Koibuchi and Chin (2000), Morreale de Escobar (2004), Venturi and Begin (2010), and Zoeller et al. (2002).

4.2. Postnatal development

4.2.1. Thyroid hormones during postnatal development in humans

In most human studies, T3 levels exhibit a characteristic pattern during postnatal development: After birth, T3 levels increase and plateau within one week (Eworo et al., 2015; Ryness, 1972). They remain at this level throughout puberty and begin to decrease only after the adolescent growth spurt (Beckers et al., 1966; Corcoran et al., 1977; Eworo et al., 2015; Michaud et al., 1991; Oliner et al., 1957; Ryness, 1972; Sack et al., 1982) (Fig. 7). However, in other studies, no age-related changes in serum T3 levels were found during postnatal development (AvRuskin et al., 1973; Dunger et al., 1990; Garcia-Bulnes et al., 1977). One explanation for decreasing serum T3 levels is that, with age, TSH secretion becomes less responsive to TRH levels, and consequently, the stimulation of the thyroid gland to produce THs is

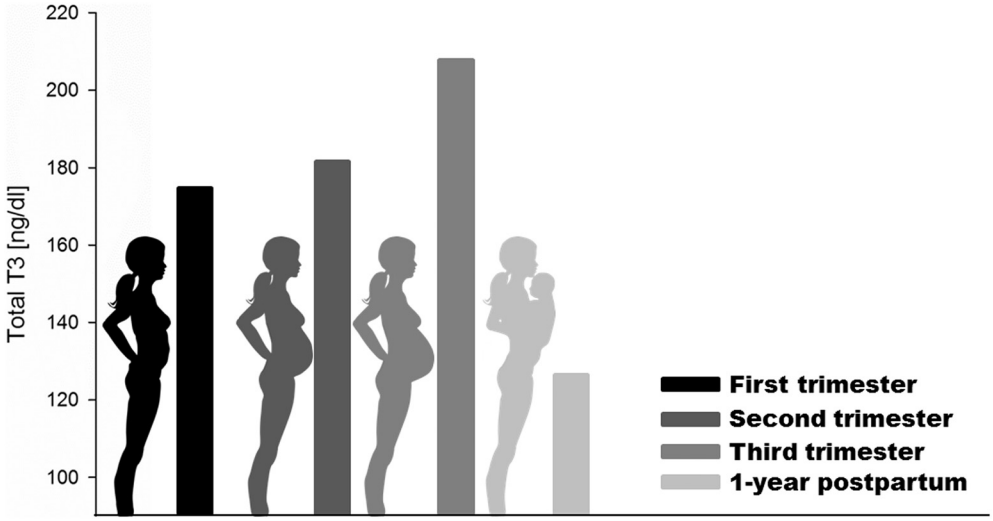

Fig. 6. Serum total T3 increases during gestation and is considerably lower one year postpartum in healthy women. Data are extracted from Soldin et al. (2004a), Table 1.

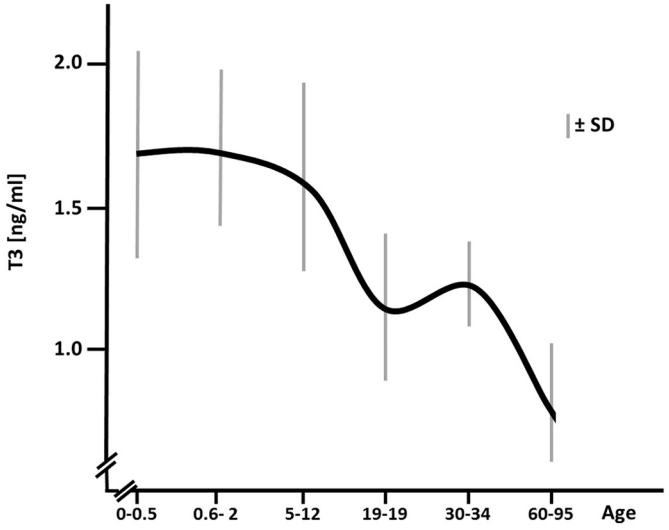

Fig. 7. Changes in triiodothyronine (T3) levels with age in humans. Generally, T3 levels remain relatively stable until they sharply decrease after the adolescent growth spurt. Modified after Ryness (1972).

reduced. Furthermore, serum T3 levels are positively correlated with TBG concentration, and TBG concentration increases during development, resulting in less biological active fT3 (Fisher et al., 1977). The changes in TH levels during and after puberty may also be related to the adolescent growth spurt, which is linked to an increase in energy requirements (Dunger et al., 1990). In studies reporting age-related changes in TH levels, the timing of the decrease is sex dependent: TH concentrations in girls decrease earlier than in boys (Garcia-Bulnes et al., 1977; Parra et al., 1980). This phenomenon might be related to earlier average reproductive maturation and adolescent growth spurt in girls (Garcia-Bulnes et al., 1977; Parra et al., 1980).

4.2.2. Thyroid hormones during postnatal development in nonhuman mammals

THs are central mediators of developmental processes such as growth and reproductive maturation, and patterns of TH secretion during development appear similar across all mammal species that have been investigated (Table 2). Immatures consistently have higher TH levels than adults (Table 2). This relationship is upended in only a single study, in which adult monk seals exhibit significantly higher TH levels than immatures. However, the low TH levels in immatures may be due to metabolic downregulation in response to limited food access (Gobush et al., 2014).

4.3. Molt

Molting is a growth process by which an organism sheds and replaces the epidermis or pelage, including hair, feathers, wool, and fur. This process is influenced by TH levels both directly and indirectly (Ling, 1972). In mammals, THs increase during the molting period. For instance, the annual molt in pinnipeds is regulated by T3, T4, and cortisol. Total and free serum T4 and T3 levels increase with the onset of molting and peak near the end of the process, when hair growth is most rapid (Gobush et al., 2014; Renouf, 1991). Among terrestrial mammals, including minks (*Mustela vison*), T4 levels also increase during molting cycles (Boissin-Agasse et al., 1981) (Fig. 8).

Although THs generally increase during molt, there are notable intra- and interspecific differences—for example, in relation to age, reproductive status, and energy supply (Ashwell-Erickson et al., 1986; Atkinson et al., 2011; Gobush et al., 2014; John et al., 1987; Riviere et al., 1977). Therefore, it is unclear if changes in TH levels primarily reflect molting itself or other processes during this period that require elevated TH levels. For example, a study in captive harbor seals found no clear relationships between TH levels and molting. The authors speculate that the correlations reported by prior studies result from infrequent sampling of young animals, which exhibit larger hormone fluctuations than older individuals. Additionally, increased THs could reflect thermoregulatory requirements or changes in energy intake that are physiologically unrelated to molting (Renouf and Brotea, 1991).

4.4. Aging

THs greatly impact aging rates in mammals (Bowers et al., 2013; Gesing et al., 2012). Buffenstein and Pinto (2009) postulate that the HPT axis modulates aging, primarily through its effect on metabolism (Buffenstein and Pinto, 2009). Research in various animal models has demonstrated that low T4 levels promote longevity. These effects are seemingly caused by lower metabolic rates and, accordingly, reduced oxidative stress (Brown-Borg, 2007).

4.4.1. Thyroid hormones during aging in humans

Thyroid function and TH metabolism, levels, and action change as a consequence of aging (Burroughs and Shenkman, 1982; Mariotti et al.,

Table 2
A selection of studies on thyroid hormone (TH) level changes in relation to age, presented by species.

Common name	Genus and species	High TH levels	Decrease TH levels	Publication
Sprague-Dawley rats	NS	After birth		(Walker et al., 1980)
British alpine goats	NS	After birth		(Abdullah and Falconer, 1977)
Dairy goats	NS		Age-related	(Flamboe and Reineke, 1959)
Murrah buffaloes	NS	After birth	Age-related	(Pandita et al., 2016)
Grey seals	*Halichoerus grypus*	Pups	Age-related	(Hall et al., 1998)
Monk seals	*Monachus schauinslandi*	Adults	–	(Gobush et al., 2014)
Bottlenose dolphins	*Tursiops truncatus*	Youngster	Age-related	(St. Aubin et al., 1996)
Beluga whales	*Delphinapterus leucas*	Youngster	Age-related	(Flower et al., 2015)
Asian elephants	*Elephas maximus*	Youngster	Age-related	(Brown et al., 2007)
African elephants	*Loxodonta africana*	Youngster	Age-related	(Brown et al., 2007)
Chimpanzees	*Pan troglodytes*	Youngster	Age-related	(Behringer et al., 2014)
Bonobos	*Pan paniscus*	Youngster	Age-related	(Behringer et al., 2014)
Galliformes	NS	Embryos, youngsters	Age-related	(Decuypere and Kühn, 1988)

NS = not specified.

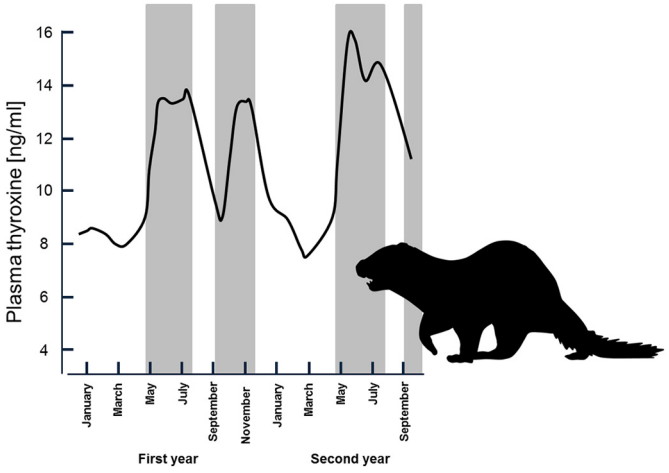

Fig. 8. Changes of plasma thyroxine (T4) in relation to molting periods (grey shades) in the male mink (*Mustela vison*). Schematic diagram after Boissin-Agasse et al. (1981).

1995; Weissel, 2006) as the thyroid gland decreases in weight (Feit, 1988). Dysfunction of the thyroid gland is more common in older individuals and occurs more often in women than in men, perhaps resulting from weight changes in the gland (Feit, 1988; Mariotti et al., 1995; Weissel, 2006).

Despite the well documented morphological deterioration of the thyroid gland, no clear patterns of serum T4 levels have been observed across adulthood. Some studies report a decrease in T4 levels with age, while some report an increase (Burroughs and Shenkman, 1982; Feit, 1988). Several others report stable T4 levels throughout adulthood (Hansen et al., 1975; Harman et al., 1984; Lipson et al., 1979; Nishikawa et al., 1981; Rubenstein et al., 1973).

In contrast to serum T4, there is clear, consistent evidence that serum T3 significantly declines with age (Hansen et al., 1975; Harman et al., 1984; Lipson et al., 1979; Nishikawa et al., 1981; Rubenstein et al., 1973). Although the reasons for this decrease are not well understood, many factors contribute to age related decline in T3 levels, including reduced production of T3 (Hansen et al., 1975), reduced peripheral monodeiodination of T4 to T3 (Nishikawa et al., 1981; Rubenstein et al., 1973), histological atrophy and fibrosis of the thyroid (Rubenstein et al., 1973), and contributions from non-thyroid diseases (Burroughs and Shenkman, 1982). Indeed, some changes in THs in septuagenarians and centenarians are caused by thyroid diseases and/or other acute or chronic illnesses, such as coronary heart disease (Harman et al., 1984; Magri et al., 2002; Mariotti et al., 1995). However, numerous studies of healthy individuals still report significant decreases in serum T3 levels with increasing age, indicating that disease is not solely responsible for this age-related decline (Harman et al., 1984; Lipson et al., 1979; Nishikawa et al., 1981; Olsen et al., 1978; Rubenstein et al., 1973; Sawin, 1979). However, older individuals almost invariably consume less food than younger individuals due to dental issues and reduced appetite (Ahmed and Haboubi, 2010), which may in turn reduce T3 levels. T3 levels and appetite are linked, with high T3 levels increasing appetite and vice versa (Amin et al., 2011). At the same time, low T3 levels in older people may reduce appetite, which may result in reduced energy intake. Thus, malnutrition, sickness, and medication, in addition to aging itself, likely contribute to decreases in serum T3 levels (Olsen et al., 1978). Regardless of cause, the ramifications of age-related decreases in T3 levels are not fully understood, although some authors speculate causal relationships with cognition (Bégin et al., 2008) and longevity (Jansen et al., 2015).

4.4.2. Thyroid hormones during aging in nonhuman mammals

Age-related patterns of THs in nonhuman mammals resemble those found in humans. Aging patterns for serum T4 in nonhuman mammals are clearer than those in humans. While results from humans are ambiguous, serum T4 levels clearly decrease with age in a variety of nonhuman species, including rats (Azizi, 1979; Rao-Rupanagudi et al., 1992), dogs (Gonzalez and Kaleem Quadri, 1988), and rhesus and cynomolgus monkeys (*Macaca mulatta* and *M. fascicularis*, respectively) (Roth et al., 2002; Yoshida et al., 1989). In rats, TH secretion and binding of T4 by tissues decrease with age, while T4 metabolic clearance rates increase (Frolkis and Valueva, 1978; Mariotti et al., 1995). As in humans, lower T4 levels are associated with longevity in various mammalian species, including mice, rats, bats, guinea pigs (*Caviidae*), Damaraland mole-rats (*Cryptomys damarensis*), and naked mole rats (*Heterocephalus glaber*) (Buffenstein and Pinto, 2009). As in humans, most studies of nonhuman mammals report marked T3 decreases with age (Ramsey et al., 2000; Rao-Rupanagudi et al., 1992; Yoshida et al., 1989). In nonhuman primates, the causes for the changes of TH levels might be a reduction in the sensitivity of the thyroid gland to TSH (Yoshida et al., 1989).

5. Measurement of thyroid hormones in non-invasive samples

To date, most studies investigating TH levels have relied on blood samples. While there are methodological advantages for the analysis of circulating THs, obtaining blood samples from wild and/or endangered animals requires highly invasive and stressful procedures that can be detrimental to the animals' health. As the HPT and the HPA axes are linked, the stress of capture and handling can influence measured TH levels. For longitudinal TH studies, the repeated stressor of obtaining blood samples might alter behavior (e.g., food intake) and physiology, thereby obscuring any variation in THs. Furthermore, the body size of some species may simply be too small to obtain blood samples of

sufficient quantity to perform the measurement. Finally, subjecting wild animals to the severe stress of capture (by which to obtain a blood sample) is considered unethical in some species. Additionally, analyses of hormones in blood samples are a snapshot in time, indicating changes in the seconds or minutes before collection. In contrast, urine and fecal samples present cumulative hormone secretion over minutes, hours, or days, depending on body size and digestive physiology. Furthermore, non-invasive sampling enables easy, potentially frequent data collection without disturbance of the animal (Anestis, 2010; Goymann, 2012; Palme, 2012). For all these reasons, non-invasive sample techniques are highly advantageous for the study of THs in wild and captive animals.

However, the analysis of THs in non-invasively collected samples—e.g., urine and feces—introduces other methodological problems. Usually, commercial assays are tested and validated for the assessment of THs in human blood samples. Therefore, urine and/or fecal samples may contain additional analytes that will react on the assay, but were not tested and described by the manufacturer. In addition, hormones are extensively metabolized prior to secretion into the gut or urine, often making hormone extraction necessary in these matrices (see Section 5.1).

To evaluate whether THs can be meaningfully measured in urine and fecal samples, the metabolic pathway of TH excretion has been extensively investigated. In one study, radioactively labeled T3 and T4 were administered to rats; the authors report that THs were partly excreted into the urine, along with deiodinated metabolites, and a large amount of the labeled T3 and T4 was excreted via bile into feces (Shakespear and Burke, 1976). In another rat study, 30% of radioactively labeled T3 and 24% of radioactively labeled T4 were excreted into feces (DiStefano 3rd and Sapin, 1987). Therefore, THs are removed from circulation by the liver and secreted in bile into the gut. THs are absorbed by the gut and eventually conjugated to glucuronide forms (Hays, 1988). In humans, the absorption of T4 from the gut ranges between 60 and 85%; however, the unmodified biliary excretion is small, and conjugated forms cannot be reabsorbed (Bouillon et al., 1993).

The clearance time for THs to be removed from circulation and excreted into urine or feces was estimated in a study on rats. The first radioactively labeled T4 in feces and urine was found after six hours, with concentrations increasing throughout the next five days (Albert et al., 1952). Following intramuscular injections of TSH, fecal T3 levels of Stella sea lions (*Eumetopias jubatus*) peaked in three out of four animals after 48 h (Keech et al., 2010). However, in another study on two dogs, labeled TH peaks were measured in urine after 6 h in one dog and after 20 h in the other; in fecal samples, the TH peaks occurred after 20 h in one dog and after 45 h in the other. Furthermore, the amount of excreted radiolabeled THs varied between the two dogs: One dog excreted two times more radiolabeled TH into urine and 1.5 times more into feces (Wasser et al., 2010). This study indicates that considerable inter-individual variation exists with respect to the lag time and relative amount of THs excreted into urine or feces. As this study only involved two individuals, the causes and consequences of this variability in TH metabolism for non-invasive measurements are unknown. However, as all these studies demonstrate, THs can be reliably quantified in urine and feces.

To ensure reliable measurement of THs, it is crucial to validate a method for each species and matrix (Buchanan and Goldsmith, 2004; Touma and Palme, 2005), as demonstrated for THs by Wasser et al. (2010). A careful validation comprises two major steps: An analytical validation and a physiological or biological validation. Both steps are essential and need to be performed cautiously. An analytical validation must demonstrate that an assay reliably, accurately, and precisely measures a given analyte (e.g., Behringer and Deschner, 2017; Goymann, 2005; Touma and Palme, 2005). For instance, Wasser et al. (2010) present a careful validation for T3 and T4 in urine and fecal samples of numerous species. In another study of immunoreactive T3 (iT3) levels in fecal samples of yellow-breasted capuchin monkeys (*Sapajus xanthosternos*), Schaebs et al. (2016) tested extraction recovery, parallelism, and accuracy of the assay, to demonstrate the reliability of their measurements. These validations demonstrated that recovery of THs in feces differed across a range of mammalian species. For example, commercial T3 assays designed for TH assessment in human blood samples performed accurately and reliably for all species examined. However, T4 levels were not detectable in the feces of herbivorous species and baboons (Gesquiere et al., 2018; Wasser et al., 2010), which emphasizes the importance of publishing findings of undetectable hormone levels and negative results in general.

5.1. Sample collection, storage, assay validation, and extraction

THs and steroid hormones share many biochemical similarities in metabolism as well as their production, transportation, and binding in blood. Thus, collecting, extracting, and assaying THs in urine or fecal samples parallel many considerations for readily analysed steroid hormones (e.g., cortisol and testosterone) rather than those for peptide hormones (e.g., LH, leptin, or insulin). Following this consideration, it can be reasonably predicted that THs and steroid hormones exhibit similar stability–for example, during the extraction process.

When collecting samples for the assessment of TH levels, care must be taken to avoid collecting samples contaminated with the urine or feces of the same or another individual, because the amount of THs differ between matrices and could lead to artificially high values (Behringer and Deschner, 2017). Average TH levels are unaffected by one freeze-thaw cycle in fecal samples; however, repeated freeze-thaw cycles should be avoided (Vynne et al., 2012), as the effect of repeated freeze-thaw cycles on urinary THs must still be investigated. Another topic is long-term storage. Storage of fecal samples or extracts leads to TH degradation. Schaebs et al. (2016) report losses of 42.8% and 27.66% in fecal samples and ethanol extracts, respectively, after 17 months. Storage of fecal samples for 8 h at 4 °C or at 25 °C followed by two weeks in a refrigerator did not affect fecal T3 levels when compared to immediately frozen control samples (Gesquiere et al., 2018). These results indicate that storage of samples in less-than-ideal field conditions is possible. Additionally, when measuring TH levels from fecal samples it should be considered that diet could alter the amount of TH in the sample, just as the fibre-rich diet of baboons increases progesterone levels (Wasser et al., 1993). Alternatively, diet may rapidly influence the gut microbiome (David et al., 2014), which could result in changes in the metabolites excreted. Also diet influences the mean transit time (MTT) in the gut, for example, an increase in fibre in the diet, decreased MTT in humans and chimpanzees (*Pan troglodytes*) (Milton and Demment, 1988; Wrick et al., 1983). Shorting of MTT, shortens also the time for the gut microbiome to metabolize hormones. This type of information is particularly relevant when populations differ in terms of dietary parameters such as the content of different fibre fractions or the temporal variation of fibre intake which is often the case with wild versus captive animal populations.

5.1.1. Biological and physiological validation

A physiological validation can be performed, for example, via administration of radiolabeled hormone and subsequent measurement of the target hormone in feces or urine (e.g., Wasser et al. (2010), (Keech et al., 2010)). Given that physiological validation is highly invasive and therefore not feasible in many species, biological validation provides an acceptable and necessary alternative. For such a validation, a known biological pattern is non-invasively tested in a given hormone (Behringer and Deschner, 2017; Higham, 2016). For example, an increase in body mass should be positively associated with higher fecal T3 levels as shown in Hawaiian monk seals (Gobush et al., 2014). Other biological validations were successfully performed in yellow-breasted capuchins and howler monkeys (*Alouatta palliata*) by testing whether reduced caloric intake was associated with a decrease in fecal TT3

levels (Schaebs et al., 2016; Wasser et al., 2010). Similar successful validations have been performed for several other mammalian species, including dogs (Wasser et al., 2010), bonobos (*Pan paniscus*), and chimpanzees (*P. troglodytes*) (Behringer et al., 2014).

5.1.2. Extraction

Extraction refers to the removal of unwanted matrix compounds that might affect hormonal measurement by interfering with the assay system. A variety of extraction procedures have been tested to assess TH levels.

5.1.2.1. Feces extraction. Most studies in which THs were extracted from fecal samples used the protocol described by Wasser et al. (2010), in which samples were dried before extraction.

5.1.2.2. Urine extraction. The measured concentration of THs in unextracted urine is considerably lower than in extracted urine. Hüfner and Hesch (1973) interpret this as potential cross-reactivity of urinary substances with the antibody of the assay, but it could also result from matrix effects in unextracted urine. For these reasons, extraction procedures for THs in urine have been tested.

To separate protein-bound from unbound (free) THs in urine samples, a sephadex column can be used (Rogowski and Siersbaek-Nielsen, 1977). While other studies use ethyl acetate, this method returns erroneously high TH measurements, perhaps caused by hydrolysis of conjugates and deiodination of T4 (Rogowski and Siersbaek-Nielsen, 1977). In this case T4 would be converted into T3 or T2. Therefore, this method would, for example, overestimate T3 levels but underestimate T4. Furthermore, after hydrolysis, serially diluted samples do not exhibit TH levels parallel to the standard curve, indicating the presence of matrix effects (Rogowski and Siersbaek-Nielsen, 1977; Shakespear and Burke, 1976) that preclude the reliable measurement of THs in this case. Another study reports higher T3 and T4 levels in urine after acidic hydrolysis than after enzymatic hydrolysis (Burke et al., 1972). During the extraction, it is not necessary to adapt the sample's pH, because pH does not influence T3 measurements when using a radioimmunoassay (Yoshida et al., 1980).

In conclusion, given that extraction procedures produce artificial TH measurements, unextracted urine should be used to measure TT3, as long as matrix effects can be excluded. Another possibility to reduce matrix effects is for example to dilute the sample, if this is possible, or to evaporate the urine and reconstitute the sample in for example assay buffer of the supplier. However, future studies should focus on better extraction methods for urine samples.

5.1.3. Correction procedures for urine samples

Creatinine concentration is commonly used to correct hormone concentrations for variation in urine dilution across samples and individuals. Burke and Shakespear (1976) report that low levels of creatinine are associated with low levels of T4 and T3, concluding creatinine is a suitable correction factor for TH levels in urine. However, Burke and Shakespear (1976) also note that urinary T4 and T3 are bound to carrier proteins during the filtration process which could influence tubular handling. For example, the renal clearance rate of T3 is higher than the glomerular filtration rate (Orden et al., 1988), resulting in 1.5 times higher T3 than creatinine clearance (Burke and Eastman, 1974; Burke and Shakespear, 1976). Furthermore, if a given study design includes different age-sex classes, correction of TH concentrations with creatinine can systematically bias results, because urinary creatinine concentrations vary by muscle mass, age, sex, and health status (Barr et al., 2005). To avoid these potentially confounding effects, specific gravity (SG) of urine can be used as a cheap and reliable alternative to creatinine corrections (Miller et al., 2004). SG increases with concentration in urine and can be easily measured by refractometry. There are several advantages to this method. First, minimal equipment is necessary to measure SG (i.e., a handheld refractometer and a pipette to transfer urine). Second, because a handheld refractometer is portable, SG can be measured anywhere, even in the field. Finally, SG adjustment can be used even when creatinine concentration is too low (Miller et al., 2004).

6. Conclusion and future perspectives

Thyroid hormones (THs) are crucial for regulating mammalian metabolism and development. Therefore, the measurement of TH levels is a valuable yet insufficiently used biomarker to investigate ecological and evolutionary questions. As the HPT axis is closely connected to other hormonal systems—e.g., the HPA and HPG axes—the simultaneous measurement of hormonal markers for these systems would greatly illuminate adaptive trade-offs. That THs can be readily measured in non-invasive samples such as urine and feces opens up countless opportunities for exploring inter- and intra-individual variation in wild living animals adapted to a range of ecological challenges. Furthermore, measuring THs in combination with other biological markers could elucidate the complicated effects of different environmental factors on host physiology. For instance, measuring both glucocorticoids and THs is valuable for studies of human-wildlife conflict; while glucocorticoids increase in response to both psychological and nutritional challenges, T3 levels are largely unaffected by psychological challenges. Such a study could therefore disentangle the effects of human disturbance—i.e., whether human disturbance directly induces stress or causes food deprivation.

The relationship between THs and adaptive thermogenesis also demands further inquiry. As detailed in this review, mammals respond to high temperatures by decreasing TH levels, thereby reducing BMR. Conversely, in response to cold climates or seasons, mammals increase TH levels to activate metabolic pathways and thereby maintain body temperature. These relationships could be relevant for examining the effects of extreme habitats on mammalian metabolism. Furthermore, intraspecific studies of habitat type and quality on TH levels, in combination with other biomarkers of energetic condition and intake, could illuminate trade-offs between thermal stress and other metabolic requirements—e.g., immune activation in response to infectious disease.

The causal mechanisms driving TH changes during molting also require further investigation. Whether the TH increase is directly related to hair growth or represents a byproduct (resulting, for instance, from increased thermoregulatory demands or energy availability) is not yet clear. In this regard, the complementary measurement of other hormones (e.g., glucocorticoids, insulin, adiponectin) or behavior would illuminate the causes of TH fluctuations during molting. An additional measure of energy could for example provide evidence if the time of the molt is also accompanied by metabolic changes.

To our knowledge, no studies have investigated the impact of TH variation on reproductive development and adult fecundity in wild animals. Considering the increasing burden of endocrine disrupting chemicals in ecosystems around the world, it is intriguing to study their relationship with THs and potential effects on the development of male reproductive function and fertility (e.g., Jugan et al., 2010; Kumar and Holt, 2014). However, care needs to be exercised with respect to temporal effects of THs on male reproductive development—that is, the effects of THs seemingly depend on timing and duration during postnatal development in relation to other ontogenetic processes—e.g. onset of male gonadal development.

While TH fluctuations during gestation have been reported for various mammalian species, the exact patterns are not the same across species. However, the absence of universal, interspecific patterns may result from a scarcity of studies coupled with disparate study designs (e.g., the use of different matrices). Therefore, we suggest that more research monitor TH levels in pregnant, cycling, and lactating females, preferably in combination with measurement of iodine supply. Eventually, TH patterns during pregnancy should be analysed phylogenetically, as different groups of mammals may differ based on

ecology and morphology. For example, mammals with larger brain size might have different patterns of TH production during pregnancy. Furthermore, future research should examine links between variation in maternal TH levels and fitness parameters. For example, do mothers with lower TH levels during pregnancy have more miscarriages or foetal reduction? Does variation in TH levels during pregnancy influence newborn birth size and weight? If so, what are the intergenerational consequences of these effects? Which ecological parameters, such as iodine supply, influence these effects? As we have already indicated, care must be exercised with regard to the THs measured (i.e., T3 or T4) as well as whether free or total amount is measured, as different measures may yield different patterns.

Elevated TH levels are associated with brain and bone growth in most mammals. In humans, the decrease in TH levels starts after the adolescent growth spurt, a developmental stage that may be unique to humans (Bogin, 1999). On average, this growth spurt occurs earlier in girls than in boys, and correspondingly TH levels decline earlier in girls. Therefore, TH levels changes for example in comparison with metric measures of growth could help to identify phases of accelerated growth or principal growth pattern which can be species and/or sex specific. Furthermore, seasonal shrinking and regrowth of bones and brain tissue, which have recently been documented in shrews (*Sorex* spp.) and weasels (*Mustela* spp.) (Lázaro et al., 2017), could be mediated by corresponding changes in TH. These seasonal changes are considered an ecological adaptation that facilitates survival of animals with high metabolic rates during periods of low energy availability. It is intriguing to consider that THs may contribute to this adaptive response.

The causes for declining THs with old age are not well understood, but probably concern the deterioration of the thyroid gland and changes in hormone production. Furthermore, while infectious or chronic diseases also affect TH levels, nonhuman animal studies usually do not control for these factors. Therefore, future studies exploring age-related patterns in TH levels in aged animals must control for disease, infection, and malnutrition. In combination with behavioral observation and other biomarkers of health and energy intake (e.g., C-peptide of insulin and cortisol), changes in TH levels can be used to assess metabolic changes and social strategies in aged animals. Although declining TH levels with age seem to be a side effect of general somatic decline, it is possible that some mechanisms that contribute to lower TH levels (e.g., monodeiodination) are adaptive in long-lived species. Comparative studies between related species with different life-histories would be important to elucidate the role of THs for longevity.

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