

Thyroid hormones in small ruminants: effects of endogenous, environmental and nutritional factors

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Appropriate thyroid gland function and thyroid hormone activity are considered crucial to sustain the productive performance in domestic animals (growth, milk or hair fibre production). Changes of blood thyroid hormone concentrations are an indirect measure of the changes in thyroid gland activity and circulating thyroid hormones can be considered as indicators of the metabolic and nutritional status of the animals. Thyroid hormones play a pivotal role in the mechanisms permitting the animals to live and breed in the surrounding environment. Variations in hormone bioactivity allow the animals to adapt their metabolic balance to different environmental conditions, changes in nutrient requirements and availability, and to homeorhetic changes during different physiological stages. This is particularly important in the free-ranging and grazing animals, such as traditionally reared small ruminants, whose main physiological functions (feed intake, reproduction, hair growth) are markedly seasonal. Many investigations dealt with the involvement of thyroid hormones in the expression of endogenous seasonal rhythms, such as reproduction and hair growth cycles in fibre-producing (wool, mohair, cashmere) sheep and goats. Important knowledge about the pattern of thyroid hormone metabolism and their role in ontogenetic development has been obtained from studies in the ovine foetus and in the newborn. Many endogenous (breed, age, gender, physiological state) and environmental factors (climate, season, with a primary role of nutrition) are able to affect thyroid activity and hormone concentrations in blood, acting at the level of hypothalamus, pituitary and/or thyroid gland, as well as on peripheral monodeiodination. Knowledge on such topics mirror physiological changes and possibly allows the monitoring and manipulation of thyroid physiology, in order to improve animal health, welfare and production.

Keywords: goats, nutrition, seasons, sheep, thyroid hormones

Introduction

Appropriate thyroid gland function and activity of thyroid hormones (TH) are considered crucial to sustain the productive performance in domestic animals (growth, milk, hair fibre production) and circulating TH can be considered as indicators of the metabolic and nutritional status of the animals (Riis and Madsen, 1985; Todini *et al.*, 2007). Changes of blood TH concentrations are an indirect measure of the changes in thyroid gland activity. Many papers report marked seasonal variation in thyroid activity and in blood TH concentration. These hormone variations are particularly important in the free-ranging and grazing animals, whose main physiological functions (feed intake, reproduction, hair growth) are markedly seasonal. This is the case of small ruminants traditionally reared. Such variations in hormone concentration, in fact, allow the animals

to adapt their metabolic balance to different environmental conditions, variations in nutrient requirements and availability, and to homeoretic changes during different physiological stages.

The present paper aims to review and summarise literature data about actions specifically described in domestic small ruminants and the effects that several factors may exert on thyroid activity and circulating TH. Endogenous factors (breed, age, gender, physiological state), environmental factors (climate, season) and nutrition are considered. Many other particular conditions are well known to alter thyroid functions in small ruminants, but they are not discussed in the present paper as they are not physiological: illness, iodine excess or deficiency, ingestion of goitrogenic substances, phytoestrogens and other endocrine-disrupting compounds, exogenous hormones or drugs intake. The values of blood hormone concentrations are characterised by an extreme variability, which is of course very meaningful in each particular study. On the other hand, values

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reported in different papers are not comparable due to the very large differences of the experimental animals and conditions, as well as assay methods. For this reason, the author's choice was not to report the absolute numerics of hormone values in the text.

Overview of thyroid hormone physiology

TH, tetra-iodothyronine or thyroxine (T₄) and 3-5-3'-tri-iodothyronine (T₃), are iodinated derivatives from the amino acid tyrosine. T₄ can be deiodinated to the biologically active hormone T₃ by a 5'-deiodinase enzyme (outer-ring deiodination), and to the inactive reverse T₃ (rT₃) by the enzyme 5-deiodinase (inner-ring deiodination) (Utiger, 1995). Thyroid gland of adult sheep contains about 90.4%, 8.8% and 0.7% of T₄, T₃ and rT₃, respectively, and T₄ is the main secretory product (about 77%) (Chopra *et al.*, 1975). In adult sheep more than 99.9% of T₄ and 99.5% of T₃ circulate in blood bound to plasma proteins (Chopra *et al.*, 1975). Only the free hormone is responsible for the biological activity and protein-bound hormones function as a promptly utilisable storage, delaying the effects of decreased thyroid secretion, as well as buffer against sudden increases in thyroid's secretory activity (Bartalena, 1990; Utiger, 1995).

Small amounts of the active hormone T₃ come from the thyroid, but in adult sheep at least 50% of serum T₃ and 97% of serum rT₃ derive from monodeiodination of T₄ in peripheral tissues (Fisher *et al.*, 1972; Chopra *et al.*, 1975). Deiodination can occur in most if not all tissues, but the liver and the kidney show the highest deiodinating activity. Iodothyronine deiodinase enzymes are selenoproteins and show structural differences and different tissue distribution between various species (Santini *et al.*, 1992; Nicol *et al.*, 1994; Chadio *et al.*, 2006). Type I is predominantly expressed in the liver and kidney; it is inhibited by propylthiouracil (PTU) and stimulated by T₃. The type II enzyme is predominant in the brain, pituitary, skin, skeletal muscle, brown adipose tissue; it is not sensitive to PTU, but it is inhibited by rT₃ and T₄ (Kohrle, 1999). Type III monodeiodinase is a 5-deiodinase, which catalyses the transformation of T₃ to 3-3'-diiodothyronine (T₂) and of T₄ to rT₃. The latter does not bind to the nuclear receptor and is considered biologically inactive, but it is a powerful inhibitor of type II deiodinase (Kaiser *et al.*, 1986) and decreases oxygen consumption and ATP/ADP ratio (Okamoto and Leibfritz, 1997). Type III is widely distributed throughout the body, playing an important role in regulating TH homeostasis and bioavailability (Bianco *et al.*, 2002; Bianco and Kim, 2006). It is particularly expressed in the placenta, in the pregnant uterus and in foetal tissues, limiting TH bioactivity and playing a critical role in the development and maturation of the thyroid axis of the foetus and newborn animal (Galton, 2005; Hernandez *et al.*, 2006). The functions and regulation of the different deiodinase activities are also a mean for allowing the organism to adapt to

changing states such as iodine deficiency or chronic illness (Wartofsky and Burman, 1982; Chopra *et al.*, 1985). Earlier, diiodothyronines also were considered inactive metabolites, but recently their thermogenic actions have been highlighted (Moreno *et al.*, 2002).

TH are mostly inactivated by glucuronidation in the liver and secretion into bile, or by sulphation and deiodination in the liver or kidney (Chopra *et al.*, 1978). Oxidative deamination and decarboxylation occurring in the kidney, liver and muscle, form acid metabolites, which maintain a certain biological activity, but do not contribute to the hormone action in euthyroid subjects because they are produced in very small amounts (Greenspan, 2001). Decarboxylated derivatives of iodothyronines, such as mono-iodothyronamine and thyronamine, actually represent a very interesting field of investigation, because they may have some biological actions, even different from those of TH (Wu *et al.*, 2005).

Thyroid cell growth and all the steps in the synthesis and secretion of TH are stimulated by the pituitary glycoprotein thyrotropin (TSH). TSH synthesis and release are in turn stimulated by the hypothalamic tripeptide TSH-releasing hormone (TRH). The hypothalamus controls the pituitary thyrotrophs also by inhibiting factors (somatostatin, dopamine). Increased plasma levels of TH exert a negative feedback control on both the pituitary and the hypothalamus (Utiger, 1995). Many factors are able to affect thyroid activity and hormone concentrations in blood, acting at the level of hypothalamus, pituitary and/or thyroid gland, as well as on peripheral monodeiodination (Figure 1). In addition, growth factors, prostaglandins, cytokines, by means of paracrine and/or autocrine actions, may modify thyroid cell growth and activity (Greenspan, 2001).

TH acts on many different target tissues, stimulating oxygen utilisation and heat production in every cell of the body. The overall effects are to increase the basal metabolic rate, to make more glucose available to cells, to stimulate protein synthesis, to increase lipid metabolism and to stimulate cardiac and neural functions (Capen and Martin, 1989). Peculiar actions consist in cell and tissue differentiation. TH are the primary endocrine stimulators of non-shivering ('facultative' or 'adaptive') thermogenesis, thus regulating body temperature (Silva, 2005). One main mechanism of this function should be the stimulation of expression and activity of uncoupling proteins (UCPs), which uncouple re-oxidation of reduced coenzymes to ADP phosphorylation, hence producing heat (Collin *et al.*, 2005). UCPs have been found in various tissues, also in ovine species (Darby *et al.*, 1996; Mostyn *et al.*, 2003). Most of the physiological actions of TH are mediated by the binding to nuclear receptors. Recently, several membrane transporters for cellular entry have been identified and they are now considered among the factors on which TH biological activity could depend (Hennemann *et al.*, 2001; Friesema *et al.*, 2005). As it is the case of steroid hormones some actions of TH are rapid and non-genomic (Davis *et al.*, 2002; Hiroi *et al.*, 2006) due to actions on mitochondria and cell

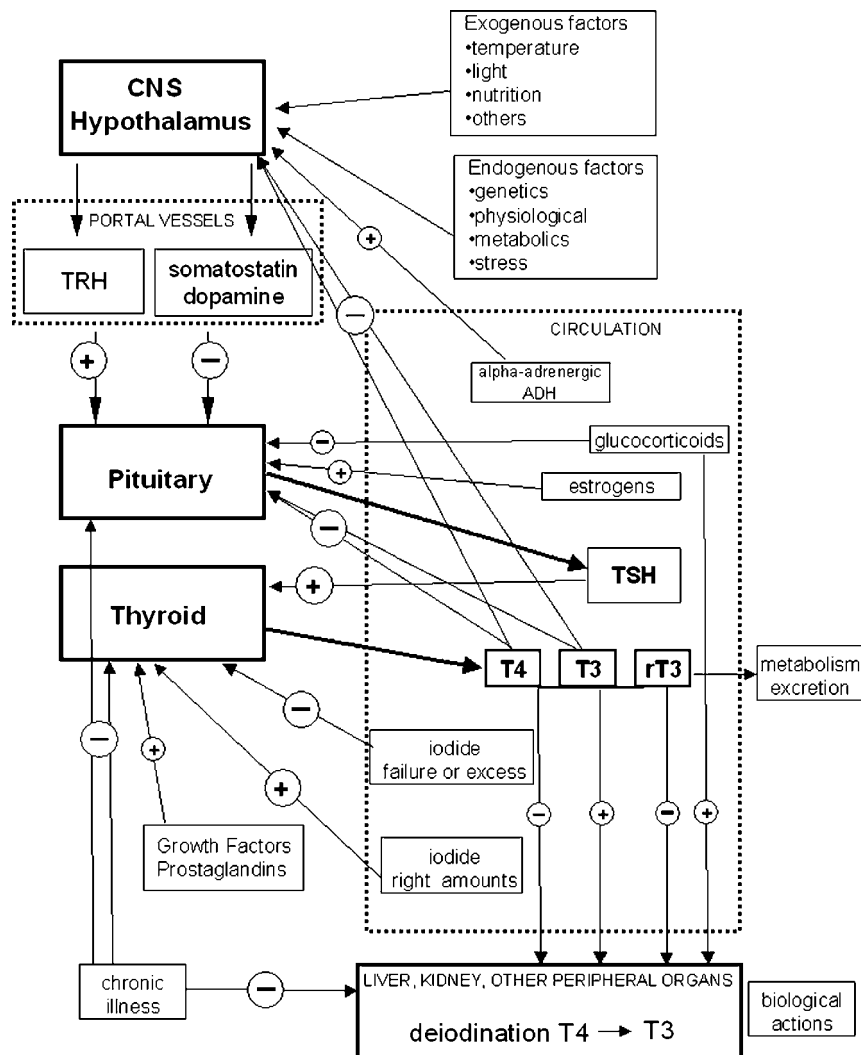


Figure 1 Schematic representation of the regulation of thyroid gland and thyroid hormones activity.

membranes on which binding proteins have been identified (Wrutniak-Cabello *et al.*, 2001; Davis *et al.*, 2005).

Seasonality of reproduction

In ovine species, a notable interest has been excited by the involvement of TH in seasonal reproduction (Karsch *et al.*, 1995). In fact, TH play an important function in the expression of endogenous seasonal rhythms of neuroendocrine reproductive activity in sheep, as in many species of birds (Nicholls *et al.*, 1988b). Thyroidectomised ewes began their sexual season at the same time as intact animals, but continued to cycle when the intact ewes enter seasonal anoestrus (Nicholls *et al.*, 1988a; Maurenbrecher and Barrell, 2003). Similar but less-pronounced effects have been obtained in sheep rendered hypothyroid, in which the end of the reproductive season occurred later than in controls (Follett and Potts, 1990; Hernandez *et al.*, 2003). TH are necessary during a limited period late in the

breeding season to permit transition to seasonal anoestrus (Thrun *et al.*, 1996 and 1997a), acting primarily within the brain to promote inhibition of neuroendocrine reproductive function (Viguié *et al.*, 1999). TH permit the increase of the responsiveness to the oestradiol negative feedback, but are also required for steroid-independent seasonal cycles in luteinising hormone pulse frequency (Anderson *et al.*, 2002). This permissive role of TH seemed limited to changes related to transition to seasonal anoestrus, since thyroidectomy during anoestrus did not affect the onset of the subsequent breeding season (Thrun *et al.*, 1997b). Anyway, TH may be required for the long-term expression and maintenance of the endogenous seasonal reproductive rhythm (Billings *et al.*, 2002).

In male sheep, thyroidectomy abolished seasonal cycles of gonadotropin secretion and testicular size (Parkinson and Follett, 1994; Parkinson *et al.*, 1995).

The anatomical substrate for TH action on seasonal reproduction may be provided by the finding of TH receptor in GnRH and other neurotransmitters-containing neurons

(Jansen *et al.*, 1997). Recently, it has been found that photoperiod regulates the expression of type II deiodinase gene in the mediobasal hypothalamus of the Saanen goat, hence seasonally affecting the bioavailability of TH for the reproductive neuroendocrine axis (Yasuo *et al.*, 2006).

To our knowledge, there is only one report about the requirement of TH in seasonal reproduction in goat species, and these results are in contrast with the above-mentioned numerous investigations carried on in sheep: Cashmere goats thyroidectomised in late breeding season advanced the onset of seasonal anoestrus (Walkden-Brown *et al.*, 1996). Furthermore, T3 at the goat testis level induces the synthesis of a soluble protein in Leydig cells, which in turn stimulates androgen release (Jana and Bhattacharya, 1994; Jana *et al.*, 1996).

Hair fibre growth

At the skin level, the availability of bioactive TH may depend not only on the circulating hormone levels but also on the local synthesis of T3. Type II and III, but not type I, deiodinase activity was detected in skin samples from cashmere goats (Villar *et al.*, 1998 and 2000b) and showed marked individual variability between animals and seasonal changes. Type II deiodinase enzyme was higher during winter short-day photoperiod and lower during periods of long daylength, whereas type III showed an opposite pattern. Manipulations of circulating prolactin affected further the seasonal changes in the ratios of type II and type III deiodinase enzymes, and this was associated with differences in follicle activity and cashmere moult (Rhind *et al.*, 2004). In Soay sheep, showing marked seasonal variations in hair growth rate, the quiescent period corresponded to the seasonal physiological decline in plasma TH concentrations (Lincoln *et al.*, 1980). Studies correlating seasonal changes of plasma TH and cashmere growth cycle failed to ascertain the putative regulatory role of TH (Kloren *et al.*, 1993) and contrasting results have been reported (Rhind and McMillen, 1995; Merchant and Riach, 2002; Celi *et al.*, 2003; Rhind and Kyle, 2004). To clarify the role of TH on hair fibre production, many investigations have been carried out on manipulating TH availability for hair growth: on the whole, also the results of such papers were often contradictory (Ryder, 1979; Maddocks *et al.*, 1985; Hynd, 1994; Rhind and McMillen, 1996). It seems that the sensitivity to TH failure or excess may be dependent on breed, season and interactions with other regulatory factors. TH action may be permissive rather than inductive, i.e. they might be present above certain threshold levels. Very important should be the interactions with other factors: firstly prolactin (Villar *et al.*, 2000a; Rhind *et al.*, 2004), as well as the local actions of insulin (Puchala *et al.*, 1998) and growth factors, such as EGF (Hoath *et al.*, 1983). The putative effects of TH on hair fibre diameter are very interesting from a commercial and technological viewpoint. In an earlier study, it was reported that exogenous T4

administration to intact sheep induced increased wool growth, in terms of increased fibre length, without affecting the diameter (Hart, 1957). T4, but not T3, reduced fibre diameter in sheep supplemented with selenium (Donald *et al.*, 1994) but T4 administration failed to avoid the increase in wool diameter following increased feed intake (Lee *et al.*, 2001). Angora goats rendered hyperthyroid by daily subcutaneous injections of T4 showed increased mohair growth, with higher fibre length and lower fibre diameter (Puchala *et al.*, 2001). In Angora kids supplemented with energy and protein (horse bean), the higher plasma TH were associated with increased fibre length, decreased fibre diameter and higher percentage of active secondary follicles than controls (Todini *et al.*, 2005). Anyway, further investigations are needed in order to clarify the role of TH in hair fibre production. This role should be rather different between animals showing a marked seasonality and clear moulting cycles (such as cashmere goats) and animals whose hair growth is more or less continuous throughout the year (Angora goats, Merino sheep).

Foetal life

In foetal sheep, during the last one-third period of gestation, serum T4 concentrations were slightly higher or comparable with those in adult sheep, while foetal serum T3 were much lower and rT3 much higher. The elevated rT3 concentrations in foetal sheep serum decreased progressively after birth and reached comparable levels with those in adults, within few days of life (Chopra *et al.*, 1975). An opposite trend was described for T3 concentrations (Nathanielsz *et al.*, 1973; Klein *et al.*, 1978). These differences in serum hormone concentrations have been related to differences in peripheral deiodinase activity as the relative thyroidal content of T4 and T3 was similar in foetal and adult sheep (Chopra *et al.*, 1975). In fact, type I deiodinase activity in the liver and kidney of foetus up to the fourth month was lower than that in pre-term foetus or in the newborn (Wu *et al.*, 1992). Low foetal T3 levels are maintained also by sulphation and deiodination (Wu *et al.*, 2006). In the foetus, low T3 levels allow anabolic processes to prevail, despite the high rate of foetal T4 secretion, which resulted eight-fold than maternal one during the last one-third period of gestation (Dussault *et al.*, 1971). The *pre-partum* cortisol surge increased hepatic renal and perirenal adipose tissue type I deiodinase, and reduced renal and placental type III deiodinase activities (Forhead *et al.*, 2006). The increased availability of active T3 is important for the latter phases of tissue differentiation. The functional development of brown adipose tissue allows to optimise non-shivering thermogenesis, thus permitting an adequate thermoregulation in the newborn (Schermer *et al.*, 1996). Therefore, UCP1, induced by TH, is of primary importance for the transition from foetal to neonatal life, when cellular energy and thermoregulatory requirements are at maximal rates (Symonds *et al.*, 2003). When the

pre-partum rise of cortisol occurs, TH may also influence the growth and development of foetal liver and skeletal muscle, modulating the local activity of the somatotrophic axis, i.e. the local expression of growth hormone receptor and insulin-like growth factors (Forhead *et al.*, 1998, 2000 and 2002). At the same time TH are essential for foetal gluco-genesis (Fowden *et al.*, 2001), allowing the *pre-partum* rise in glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activity in the foetal liver and kidney Forhead *et al.*, 2003).

Age effects: birth, neonatal period and growth.

Gender effects

The *pre-partum* cortisol rise is accompanied by an increase in foetal T3 and a decrease in rT3 concentrations (Sensy *et al.*, 1994). This pattern should be maintained throughout the early postnatal life (Nathanielsz *et al.*, 1973; Klein *et al.*, 1978). Plasma free T3 (fT3) in neonatal lambs increased parallel to total T3 (Cabello and Wrutniak, 1986), whereas the neonatal increase of free T4 (fT4) concentrations was greater and longer lasting than total T4 (Cabello and Wrutniak, 1990). In fact, neonatal plasma T3 and fT4 rises followed that of TSH concentrations, lasting for 24 h after birth, but T4 levels declined before (after 2 h of life), when TSH levels were still elevated (Cabello and Wrutniak, 1990). Therefore, the thyroid gland seems unable to respond, in terms of T4 secretion, to a prolonged stimulation by TSH, probably because a depletion of hormonal stores in the gland occurs during the first minutes of life (Slebozinski, 1972). It is likely that during the first hours of life the thyroid gland can respond to other stimulating factors: small increases of plasma TH followed exogenous prolactin administration in neonatal lamb, but not in growing lambs and ewes (Peeters *et al.*, 1992). Plasma rT3 levels during the first 48 h of life progressively decreased in suckling lambs, but increased in bottle-fed lambs (Cabello and Wrutniak, 1986 and 1990). Plasma T4 concentrations were higher in single lambs than in twins at birth (Assane and Sere, 1990). Plasma TH levels highly correlated with lambs' birth-weight (Dwyer and Morgan, 2006) and were lower in lambs separated from their mothers just after parturition than in those maintained with their mothers (Firat *et al.*, 2005). Neonatal lambs had higher levels of T3 and T4 compared with growing lambs and ewes (Peeters *et al.*, 1992). Growing goat kids displayed higher TH levels than adults (Colavita *et al.*, 1983) and the lowest values were found in elderly animals (Table 1; Lucaroni *et al.*, 1989). Age-related differences were particularly evident during the hot season, especially for T3 blood concentrations (Lucaroni *et al.*, 1989).

In young animals, there is no sex-dependent differences in blood TH concentrations, whereas in adult goats mean plasma TH levels were higher (significantly for T4) in does than in bucks (Table 2; Todini *et al.*, 1992). In young cashmere goats, T3 levels were lower in males than in females after 8 months of age, while T4 was not affected by

Table 1 Serum thyroid hormone concentrations (mean \pm s.d.) in goats (local Umbrian population) at different ages (data grouped from samplings at different seasons), adapted from Lucaroni *et al.* (1989)

Age (years)	n	T3 (ng/ml)	T4 (μ g/dl)
<1	33	2.82 \pm 1.01	8.65 \pm 1.86
1	68	2.75 \pm 1.20	6.93 \pm 2.08
2	47	2.57 \pm 1.49	6.35 \pm 1.63
3	74	1.93 \pm 0.74	7.04 \pm 1.36
4	79	1.78 \pm 0.79	6.98 \pm 1.50
5	111	1.73 \pm 0.73	6.93 \pm 1.71
>6	107	1.57 \pm 0.62	5.67 \pm 1.81

sex (Celi *et al.*, 2003). Sex-related differences are reported in others mammals and are referred to several actions by sexual steroid hormones: differences in total T4 levels can be explained by oestrogen-reduced catabolism of thyroxine-binding globulin (TBG) (Ain *et al.*, 1987), or androgen inhibition of the synthesis of TBG by the liver (Federman *et al.*, 1958). Moreover, androgens inhibit TSH secretion by the pituitary (Christianson *et al.*, 1981).

Breed effects

To our knowledge, there are no published data on goat breed differences. At birth, Blackface lambs had higher T3 and T4 levels than Suffolk lambs and this was correlated with higher body temperature and better thermoregulatory ability (Dwyer and Morgan, 2006). Merino lambs aged 2 to 3 days, submitted to cold stress, showed a stronger increase of TH levels compared with Romney-Marsh lambs (Doubek *et al.*, 2003). Lamb breeds that are usually reared under extensive conditions (hill regions) have an improved thermoregulation than those reared intensively in lowland: this is partly related to birthcoat characteristics, accompanied by higher TH concentrations (important for endogenous heat production and hair growth) in hill than lowland lambs (Dwyer and Lawrence, 2005). Assaf ewes had higher serum T4 concentrations than Rasa Aragonesa and Merino ewes, which was associated with differences in wool growth rate (Abecia *et al.*, 2005). Higher plasma T4 levels in Suffolk ewes than Gulf Coast native ewes in the US were shown to be positively related to larger body size and enhanced growth potential (Williams *et al.*, 2004). Higher levels of T3 and T4 in ram lambs have been associated with higher prolificacy of the Outaouais breed compared with the Suffolk breed (lower prolificacy) (Fallah-Rad and Connor, 1999). The decline in serum T4 levels induced by feed restriction was greater in crossbreed ewes than in native Indian sheep (Naqvi and Rai, 1991).

Changes during oestrus, pregnancy, peri-parturient period and lactation

During induced or spontaneous oestrus in goats, a rise in plasma total T4 (Colavita and Malfatti, 1989) and

Table 2 Plasma thyroid hormone concentrations (mean \pm s.d.) in 16 adult does and 8 adult bucks (dairy Mediterranean breeds), maintained sex-separated and fed a qualitatively constant diet throughout the year (weekly samplings). Monthly mean, minimal and maximal environmental temperatures are also indicated (adapted from Todini et al. (1992)).

	Does		Bucks		Environmental temperature (°C)		
	T3 (ng/ml)	T4 (μ g/dl)	T3 (ng/ml)	T4 (μ g/dl)	Minimum	Maximum	Mean
Jan.	0.96 \pm 0.29	7.90 \pm 3.35	0.88 \pm 0.31	4.83 \pm 0.89	0.4	11.8	6.1
Feb.	0.84 \pm 0.31	7.50 \pm 3.66	0.84 \pm 0.16	5.40 \pm 1.53	2.7	16.8	9.7
Mar.	1.10 \pm 0.43	8.15 \pm 2.22	0.75 \pm 0.17	4.40 \pm 0.86	2.0	17.2	9.6
Apr.	1.35 \pm 0.40	7.55 \pm 3.55	0.83 \pm 0.04	5.72 \pm 1.38	7.3	19.7	13.5
May	0.95 \pm 0.23	6.34 \pm 2.01	0.79 \pm 0.10	5.16 \pm 0.95	9.1	24.7	16.9
Jun.	0.84 \pm 0.20	7.07 \pm 3.27	0.82 \pm 0.22	4.41 \pm 0.72	12.9	28.3	20.60
Jul.	0.59 \pm 0.12	6.10 \pm 2.47	0.69 \pm 0.06	3.88 \pm 0.79	16.5	32.3	24.4
Aug.	0.71 \pm 0.23	6.82 \pm 2.32	0.50 \pm 0.08	4.09 \pm 1.30	15.8	30.3	23.0
Sep.	0.63 \pm 0.14	6.80 \pm 3.17	0.58 \pm 0.06	3.75 \pm 0.81	12.1	26.5	19.3
Oct.	0.78 \pm 0.19	7.05 \pm 2.75	0.82 \pm 0.13	4.31 \pm 1.20	6.6	21.2	16.9
Nov.	0.85 \pm 0.20	7.28 \pm 2.47	0.95 \pm 0.14	5.00 \pm 0.89	4.5	15.3	9.9
Dec.	0.88 \pm 0.33	7.61 \pm 3.15	0.98 \pm 0.27	5.11 \pm 1.27	2.2	13.3	7.7
Year	0.87 \pm 0.32	7.17 \pm 2.89	0.79 \pm 0.19	4.65 \pm 1.17			

fT4 (Blaszczyk *et al.*, 2004) levels has been observed. In ewes, plasma T4 levels were higher during oestrus and lower during the luteal phase, T3 concentrations were higher during the luteal phase, while the concentrations of rT3 were not associated with the oestrous cycle (Peeters *et al.*, 1989).

During pregnancy, thyroid activity and circulating hormone levels are reported to increase in all the investigated mammalian species. Several mechanisms have been claimed to explain these observations: increased binding protein concentrations in plasma, secretion of thyrotropic factors by the placenta, enhanced responsiveness of pituitary TSH secretion to hypothalamic TRH and changes in maternal TH catabolism (De Leo *et al.*, 1998; Glinoe, 2001). Towards the end of pregnancy, the goat foetus(es) should play a competitive role (higher thyroid activity, iodine affinity and uptake than maternal ones), so that a decrease in maternal plasma fT4 concentrations has been observed (McDonald *et al.*, 1988). Plasma T3 and T4 levels in goats at mid-pregnancy rised compared with the low levels observed just before oestrus and mating. Then, during the second half of pregnancy, maternal hormone levels progressively decrease, probably because of the negative energy balance (Todini *et al.*, 2007). This is supported by the lower maternal serum TH levels (more marked and significant for T4) observed in twin-bearing does, that are often characterised by negative energy balance, compared with aborted and single-bearing does (whose energy balance is usually less negative) (Manalu *et al.*, 1997). Very similar findings are reported for ewes. Plasma T4 concentration was highest during early pregnancy and decreased gradually, reaching lowest values during late pregnancy and *post partum* (Assane and Sere, 1990; Okab *et al.*, 1993; Yildiz *et al.*, 2005). Like in goats, maternal T3 and T4 in twin pregnancy

were lower compared with single-bearing sheep (Yildiz *et al.*, 2005), especially at the end of pregnancy (Assane and Sere, 1990).

In goats, maternal plasma T3 levels remained rather steady around parturition, while T4 concentrations markedly decreased and remained low until day 10 *post partum* (Lucaroni and Todini, 1989). Khan and Ludri (2002b) reported that both TH concentrations did not change from day 20 before parturition until the day of kidding, when they reached a minimal level, followed by an increase until day 20 *post partum*. In ewes, plasma TH concentrations were lower *post partum* than during pregnancy (Okab *et al.*, 1993), tended to decrease from 36 h to 21 days *post partum* and thereafter constantly rose until day 51 *post partum* (Bekeova *et al.*, 1991).

Blood TH levels were low at the beginning of lactation, afterwards gradually rose in does (Riis and Madsen, 1985; Emre and Garmo, 1985) and in ewes (Mitin *et al.*, 1986). Administration of TH is known to stimulate lactation in many species (Tucker, 1994 and 2000) but an inverse relationship between blood hormone concentration and milk yield has been observed in goats (Riis and Madsen, 1985), at least during the first phases of lactation. In ewes, during late lactation, the increase of T4 concentration in blood seems related to the decrease of milk production (Bass, 1989).

Within the first 20 days *post partum*, in twin-bearing does, plasma TH levels were significantly lower compared with single-bearing does (Khan and Ludri, 2002a), but throughout lactation very slight or no differences between single and twin-suckling ewes were found (Bass, 1989; Rhind *et al.*, 1991). Taken together, these findings may support the meaning of blood TH levels as indicators of the energy balance, also in lactating animals.

Circadian rhythms

Circadian changes in hormone secretion are probably associated with the rhythms of environmental temperature and light, as well as with feed intake and metabolism, which in turn are related to the alternance activity/rest throughout the day. Moreover, overlapping effects by season and physiological state are expected. Because many factors can influence T4 and T3 levels and because interactions between these factors are likely, the few data available in the literature on such topics are rather discordant.

Blood samplings at 4-h intervals in late spring did not permit to find significant circadian differences in TH concentrations in lactating (milked or suckled) goats, but the maximal levels were observed during the night (Lucaroni *et al.*, 1989). In ewes sampled twice a day, the differences between morning and afternoon were not univocal, depending on the season (Ashutosh *et al.*, 2001). In ewes sampled at 2-h intervals, lowest blood hormone levels were found in the afternoon, concentrations then increased progressively during the night, and reached the highest levels in the morning (Velasquez *et al.*, 1997). In winter, T3 and T4 concentrations reached maximal levels in early morning, probably because of a delayed response to cold stress to which the animals were exposed by night; furthermore, the circadian variations in winter decreased with the increase in wool length (Salem *et al.*, 1991). Combining the results obtained from samplings carried out every 2 months for 1 year, rams showed the highest TH concentrations during the afternoon and the lowest in the early morning (Souza *et al.*, 2002).

Season effects

A major exogenous regulator of thyroid gland activity is the environmental temperature (Dickson, 1993), so an inverse relationship between ambient temperature and blood TH concentrations has been found in sheep (Valtorta *et al.*, 1982; Webster *et al.*, 1991; Starling *et al.*, 2005) and goats (Colavita *et al.*, 1983; Todini *et al.*, 1992).

During heat stress, blood T3 and T4 concentrations, as well as metabolic rate, feed intake, growth and milk production were decreased (Valtorta *et al.*, 1982; Silanikove, 2000). On the other hand, cold stress in ewes (Hocquette *et al.*, 1992) ram lambs (Ekpe and Christopherson, 2000; Doubek *et al.*, 2003) and shearing (Morris *et al.*, 2000; Merchant and Riach, 2002) induced increases in blood TH levels. The seasonal pattern of blood TH levels often showed maximal values during winter (cold months) and minimal during summer (hot months) (Salem *et al.*, 1991; Webster *et al.*, 1991; Okab *et al.*, 1993; Menegatos *et al.*, 2006). However, contrasting results have been reported (Kloren *et al.*, 1993; Rhind *et al.*, 1998; Ashutosh *et al.*, 2001; Yokus *et al.*, 2006). In the Sahel desert, plasma T3 and T4 levels did not change significantly from the beginning of the cool season (December) until the end of the dry

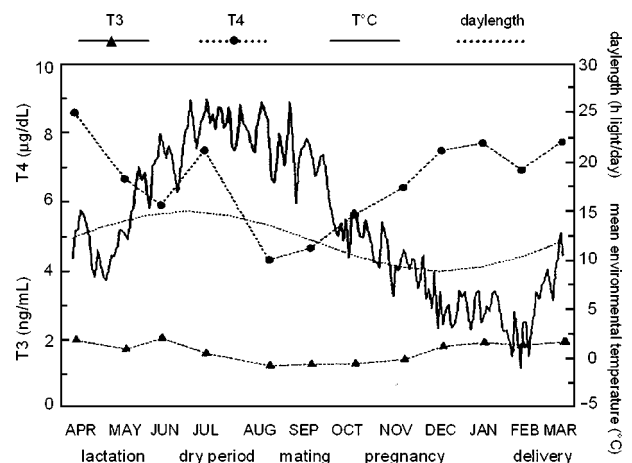


Figure 2 Circannual profiles of mean plasma T3 (3-5-3'-triiodothyronine) and T4 (thyroxine) in 20 female goats (local Umbrian population), mean environmental temperature, daylength and physiological state (modified from Lucaroni *et al.* (1989)).

warm season (May), but a highly significant rise of both hormones was observed at the onset of the humid warm season (June) (Assane and Sere, 1990). It can be supposed that an enhanced thyroid activity during the humid warm season in such environments is functional for the animals facing the increased availability of food (quantity and quality), following the seasons characterised by food shortage.

Blood TH concentrations were high in spring (increasing daylength) and low in autumn (decreasing daylength), which was not fully explained by the changes in environmental temperature (Figure 2; Buys *et al.*, 1990; Todini *et al.*, 1992; Rhind and McMillen, 1995; Clariget *et al.*, 1998; Rhind *et al.*, 2000; Taha *et al.*, 2000; Villar *et al.*, 2000a; Merchant and Riach, 2002; Souza *et al.*, 2002; Blaszczyk *et al.*, 2004; Zamiri and Khodaei, 2005; Menegatos *et al.*, 2006; Todini *et al.*, 2006). It seems that when the temperature ranges are not extreme (mild climate, indoor housing, shelter in the night time), the effect of photoperiod and season-dependent TH profiles (mainly related to the daylength changes) are present.

In Alpine and Saanen bucks exposed to artificial photoperiodic cycles, alternating 1 or 2 months of long days (LD: 16 h light and 8 h dark) to 1 or 2 months of short days (SD: 16 h dark and 8 h light), plasma T3 levels rapidly followed the photoperiodic changes, increasing during LD and decreasing during SD. The effects of daylength changes on plasma T4 concentrations were seen after a delay of several weeks and the T3:T4 ratio showed very marked variations, increasing during LD and decreasing during SD (Todini *et al.*, 2006). Similar results were obtained by Lincoln *et al.* (1980) in rams submitted to an alternance of 16 weeks of SD and 16 weeks of LD. The mechanisms of the photoperiodic effects on peripheral TH are far from being elucidated. Additional data on actions of the photoperiod in the brain are scanty in small ruminants: TRH from hypothalamic

perfusate samples of ewes only tended to be significantly higher during LD than during SD (Leshin and Jackson, 1987). Long days suppressed the expression of mono-deiodinase gene in the hypothalamus of goats, thus limiting the local bioavailability of TH, which should be related to the role of the thyroid gland in seasonal reproduction (Yasuo *et al.*, 2006).

On the basis of the above-quoted studies, it is not possible to discriminate between the relative role of temperature and photoperiod on the seasonality of thyroid activity, in different environmental conditions. Moreover, when the feed intake is markedly seasonal, it becomes a major factor modifying the seasonal pattern of blood TH profiles.

Nutrition effects

T3 directly stimulates feed intake at the hypothalamic level (Kong *et al.*, 2004), while on the other hand, the quantity and quality of food eaten is a major factor determining plasma concentrations of TH (Dauncey, 1990). Blood TH levels are considered to be good indicators of the nutritional status of an animal (Riis and Madsen, 1985) and were correlated with feed intake in ruminant species, including those that exhibit very marked seasonal cyclicality in feed intake, body weight and reproductive activity, e.g. deers (Ryg and Langvatn, 1982; Chao and Brown, 1984; Rhind *et al.*, 1998).

Circulating TH concentrations seem better correlated with feed intake than adiposity status (McCann *et al.*, 1992; Caldeira *et al.*, 2007a and b).

Energy deprivation decreased concentrations of T3 and fT3 in adult sheep, while subsequent overnutrition increased them. Plasma total T3 concentrations significantly correlated with energy and nitrogen balances. Plasma rT3 levels showed an opposite pattern, increasing during energy deprivation and decreasing during overnutrition (Blum *et al.*, 1980). Concentrate supplementation induced an increase of plasma T4 levels in lactating ewes (Shetaewi and Ross, 1991) and plasma T3 concentrations was higher in rams with high amounts of ingested energy and protein (Zhang *et al.*, 2004). Following feed restriction or food deprivation, plasma TH concentrations were reduced in sheep (Naqvi and Rai, 1991; Wronska-Fortuna *et al.*, 1993; Wester *et al.*, 1995; Ekpe and Christopherson, 2000; Abecia *et al.*, 2001; Rae *et al.*, 2002). Feed-restricted animals also showed an earlier and more marked decline in plasma TH concentrations during the late summer/early autumn, compared with *ad libitum* fed animals (Rhind *et al.*, 1998 and 2000).

Lactating Angora does and their kids supplemented with energy and protein (horse bean) had higher plasma TH concentrations than controls (Todini *et al.*, 2005). Goats with a slightly higher energy intake showed higher plasma TH concentrations during the second half of gestation, and the decrease of plasma TH in mid- and late gestation was attenuated and delayed (Todini *et al.*, 2007). These effects

suggested that energy balance could play a major role in affecting the decrease in plasma TH levels usually observed at the end of gestation in small ruminants (see above). Furthermore, in the higher energy diet-fed goats, the variations of circulating T4 during different physiological states were not significant (Todini *et al.*, 2007). Recently, no significant difference in the rates of type II and type III deiodinase activity in the skin or in blood TH concentrations was found between cashmere goats maintained at a different plane of nutrition (Rhind *et al.*, 2006).

Selenium is present in deiodinase enzymes, and other selenoproteins play a protective role for the thyrocytes against damage by hydrogen peroxide produced for TH biosynthesis (Kohrle *et al.*, 2005). Oral iodine and selenium supplements increased blood concentrations of TH in sheep, and selenium supplementation alone increased plasma T3 concentrations and decreased T4 concentrations (Bik, 2003). Following selenium supplementation, type I deiodinase activity decreased in the liver and increased in the pituitary, while pituitary type II deiodinase was unaffected, indicating that enzyme activity is homeostatically controlled when a sufficient amount of selenium is present, in order to ensure TH homeostasis (Chadio *et al.*, 2006).

Conclusion

Changes of blood TH concentrations are an indirect measure of the changes in thyroid gland and extrathyroidal deiodination activity. Many factors act simultaneously modulating thyroid gland activity and/or peripheral mono-deiodination. Besides endogenous and environmental climatic factors, nutrition plays a primary role on thyroid gland activity and on blood TH concentrations. The physiological range of the endocrine responses to different conditions is very large, thus reference values are very difficult to obtain. Assay results must be carefully evaluated, not only for diagnostic and clinical purposes but also to evaluate the physiological states and responses of the animals. The systemic actions of TH justify their pivotal role in the mechanisms permitting the animals to adapt to the surrounding environment. New insights are gathered from investigations on the regulation of monodeiodinase activity, hence of TH bioavailability, in the central nervous system and at the peripheral level. Little is known about TH receptor expression and activity or about the targets at molecular levels, even in humans and rodents. The field of the non-genomic, rapid TH actions needs further research. Knowledge on such topics will possibly allow the monitoring and manipulation of thyroid physiology, in order to improve animal health, welfare and production (meat, milk, hair fibre).

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