Clinical endocrinology of thyroid gland function in ruminants

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ABSTRACT: After briefly introducing the basic steps in production and metabolism of thyroid hormones, the author gives an overview of nutritional, metabolic and disease-related factors and endocrine interactions influencing thyroid gland function in ruminants, particularly in the postpartum dairy cow. Involvement of thyroid hormonal regulation of seasonal patterns of reproduction as well as ovarian endocrine function are discussed.

Keywords: thyroxin; triiodothyronine; ovary; metabolism; ruminants

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1. Introduction

In the past the thyroid hormones were thought to influence mainly the thermoregulation and homeostasis of energy and protein metabolism, and direct clinical relevance was attributed to thyroid malfunctions almost exclusively in the companion animal (dog, cat) and horse medicine. Recently, however, several studies have confirmed their involvement in the metabolic response of animals to certain nutritional, environmental and/or disease-related challenges, as well as in regulation of certain ovarian functions also in ruminants, particularly in postpartum dairy cows. In addition, as markers thyroid hormones could be used for selection of high genetic merit breeds/lines in the future. Therefore the overview of the recent data available in the literature is considered to have importance for both the animal science and veterinary diagnostic endocrinology.
2. Basic physiology. Nutritional factors influencing thyroid function

Thyroxine (T₄) has been known as the predominant product of the thyroid gland for many years. Its production and liberation is governed by the hypothalamus/anterior pituitary axis. First, thyrotropin-releasing hormone (TRH), a neuropeptide produced in the paraventricular nucleus (PVN) of the hypothalamus, controls the release of thyroid-stimulating hormone (TSH) from the anterior pituitary. TSH acts on receptors on the thyroid to promote synthesis and release of the thyroid hormones, mainly of T₄, but also in a small quantity of 3,3’,5-triiodothyronine (T₃). In the brain and the peripheral tissues (liver, mammary epithelium and others) the almost inactive T₄ may undergo extrathyroidal enzymatic activation (e.g. outer-ring deiodination) by 5’-deiodinase (5’D) producing the much more potent T₃, or inactivation (e.g. inner-ring deiodination) by 5-deiodinase (5D) producing fully inactive forms of 3,3’,5’-triiodothyronine (syn.: reverse-triiodothyronine; rT₃). All three thyroid hormones are present in the circulation, however inherent physiological effects are attributed almost only to T₃ (Leonard and Visser, 1986; Dickson, 1990; Flier et al., 2000). In primary hypothyroidism (know as a common thyroid malfunction in dog, horse and human, but not in ruminants) when T₃ and T₄ levels fall because of a defect within the thyroid, a two-part compensatory system kicks in. In the PVN of the hypothalamus, TRH gene expression increases because of the lack of negative feedback by thyroid hormones. In the pituitary TSH production increases due to both increased TRH production and decreased negative feedback by thyroid hormones on the genes encoding TSH subunits. The increased TSH serves to drive the failing thyroid and is the most sensitive test for the diagnosis of this form of thyroid failure in these species (reviewed by Flier et al., 2000).

Thyroid hormones have circadian and ultradian rhythmicity also in the plasma of lactating dairy cows (Bitman et al., 1994), and concentrations of T₄ and T₃ in cattle are influenced by a variety of environmental factors, such as the ambient temperature (Pratt and Wettemann, 1986; McGuire et al., 1991) and dietary components and intake (Awadeh et al., 1998; Richards et al., 1995; Tiirats, 1997). The positive correlation between circulating thyroid hormone concentrations and energy balance is well known in many species including cattle (Kunz and Blum, 1985; Janan et al., 1995; Leyva-Ocariz et al., 1997; Nikolić et al., 1997; Capuco et al., 2001; Cassar-Malek et al., 2001). Cows in postpartum negative energy balance (NEB) respond to decrease the concentrations of T₃ and T₄ and increase the concentration of rT₃ (Pethes et al., 1985; Ronge et al., 1988; McGuire et al., 1991; Yambayamba et al., 1996). In dairy cows low T₃ and T₄ have been observed in the first trimester of lactation (Pethes et al., 1985), even after BOH-butyrate (BHB) and non-esterified fatty acids (NEFA) had returned to normal levels (Eppinga et al., 1999). In lactating dairy cows plasma T₃ and T₄ concentrations are negatively correlated with daily milk yield (Tiirats, 1997) and are reduced by growth hormone (GH) treatment (Johnson et al., 1991) and high environmental temperatures (McGuire et al., 1991). Alterations in plasma T₄ levels associated with the energy balance and metabolism reflect both the changes in TSH-regulated thyroid secretion rate (central regulation; Riis and Madsen, 1985), and the balance of extrathyroidal enzymatic T₄ activation and inactivation (peripheral autoregulation; Pethes et al., 1985; Capuco et al., 2001; Cassar-Malek et al., 2001). Peripheral T₃ concentrations are influenced mainly by extrathyroidal 5’D activity. Because T₃ is a potent regulator of energy and protein metabolism, the extrathyroidal activity of 5’D (and perhaps also of 5D) is an important control point for regulating the metabolic status (Kaplan, 1986). In the cow, the highly efficient type II 5’D predominates in the mammary gland enabling T₃ production in support of lactation to proceed at the expense of other tissues, such as the liver, where the type I 5’D prevails (Ślebodziński et al., 1999).

In lab rodents starvation appears to act, at least in part, by suppressing TRH expression in the PVN. TSH production falls, and simultaneously the pattern of glycosylation on newly synthesized TSH is altered so that the TSH that is produced is of reduced bioactivity. Thus, as a consequence of starvation, T₄ and T₃ levels fall, leading to central hypothyroidism (reviewed by Flier et al., 2000). The postpartum NEB might induce similar changes in TSH production also in dairy cows, although the extrathyroidal deiodination of T₄ and T₃ is undoubtedly involved in this process of metabolic adaptation (Pethes et al., 1985; Capuco et al., 2001; Cassar-Malek et al., 2001).

The mechanism by which the brain orchestrates this feed deprivation related adaptation is now
becoming increasingly clear. The dominant, and perhaps sufficient, signal to the brain that suppresses TRH expression in the PVN is a starvation-induced drop in the level of the hormone leptin (reviewed by Flier et al., 2000). This newly identified 16 kDa cytokine like protein hormone is secreted mainly by the adipose tissue, is believed to act through hypothalamic nerve centers in mediation of neuroendocrine responses to energy supply or deprivation (Zhang et al., 1994). It may signal nutritional status perhaps also for the peripheral organs. This hormone is one of the primary agents communicating information about the level of peripheral energy stores to brain regions concerned with orchestrating feeding behavior, metabolism, and endocrine function so as to maintain energy homeostasis in many species. In mice, rats, humans (Considine and Caro, 1997; Yoshida et al., 1997; Friedman and Halaas, 1998; Foster and Nagatani, 1999) and also in pig (Barb et al., 1999) and ruminants (Bocquier et al., 1998; Chilliard et al., 1998; Delavaud et al., 2002) its circulating concentration may vary directly with changes in body weight and percentage of body fat and leptin contributes to the regulation of body fat content. A substantial body of work now suggests that leptin also signals the switch from the fed to the starved state (Considine and Caro, 1997; Yoshida et al., 1997; Friedman and Halaas, 1998). A fall in leptin acts through the hypothalamus to increase appetite, decrease energy expenditure, and modify neuroendocrine function in a direction that favors survival. The consequences of falling leptin include suppression of reproduction, linear growth, and the thyroid axis, as well as activation of the stress axis (Houseknecht et al., 1998; Houseknecht and Portocarrero, 1998; Barb, 1999; Foster and Nagatani, 1999; Keisler et al., 1999; Flier et al., 2000; Ingvarsen and Boisclair, 2001; Delavaud et al., 2002). Multi-species, and later species-specific assay systems allowing the exact quantification of plasma leptin in various domestic mammals were developed only in the late nineties and at the beginning of this decade (Bocquier et al., 1998; Chilliard et al., 1998; Barb et al., 1999; Amstalden et al., 2000; Delavaud et al., 2000; Ehrhardt et al., 2000; Kadokawa et al., 2000; Block et al., 2001; Chilliard et al., 2001; Delavaud et al., 2002). Since then increasing quantity of information has been available suggesting that leptin may be associated with NEB also in ruminants including postpartum dairy cows. In farm mammals the interrelation between the circulating levels of leptin and thyroid hormones has been poorly documented up to now. In one of our earlier works employing a widely used, but less specific (multi-species) system for leptin assay, in postpartum dairy cows we could hardly demonstrate any correlation in plasma levels of leptin with basal and/or TRH-induced concentrations of T₄ and T₃ (Huszenicza et al., 2001). However, the conclusive value of this study is rather uncertain, due to the less specific character of the assay system used. As reviewed by Houseknecht et al. (1998), Flier et al. (2000) and Ingvarsen and Boisclair (2001), much effort is now directed to understanding the precise neural circuits through which leptin brings about its effects on appetite and neuroendocrine function. With regard to thyroid activity, a crucial question is whether falling leptin levels are sensed directly by leptin receptors found in TRH neurons, or indirectly, through one or more distinct leptin-responsive neurons that communicate with TRH producing neurons. Some studies cited in these reviews suggest that indirect (proopio-melanocortin mediated?) rather than direct pathways might exist, giving further details, however, is not the goal of this paper.

In cattle the plasma levels of thyroid hormones may be altered also by other nutrition- and metabolism-related factors, such as selenium and/or iodine deficiency/supplementation (Wichtel et al., 1996; Awadeh et al., 1998), growth hormone releasing factor and somatotropin administration (Kahl et al., 1995), providing fat- or starch-enriched diet (Bunting et al., 1996; Romo et al., 1997; Blum et al., 2000), and feed contaminants, for instance goitrogen chemicals (Gennano-Soffietti et al., 1988; Bernal et al., 1999; Thrift et al., 1999a, b) and certain ergot like alkaloids produced by endophyte fungi (Neotyphodium coenophialum) of tall fescue (Festuca arundinacea; known as a really existing form on feed contamination only in North America) (Hurley et al., 1981; Browning et al., 1998, 2000).

In accordance with the nutritional and metabolic influences in late-pregnant, dry cows relatively high concentrations of thyroid hormones were detected, which were followed by a significant decrease in the periparturient period. Blood levels of T₄ were found to be lower in the earliest days of lactation than in late lactation (Kesler et al., 1981; Pethes et al., 1985; Tiiras, 1997; Huszenicza et al., 2001). Both the plasma concentrations of T₃ and rT₃
were in their nadir in the early postpartum days, possibly owing to increased metabolic clearance of thyroid hormones in peripheral tissues and/or to suppressed secretory capacity of the thyroid gland. Supporting this idea also TRH-induced $T_4$ and $T_3$ responses were less pronounced in the second week of lactation than before calving, or 3 months postpartum (Tveit et al., 1990; Huszenicz et al., 2001).

On the other hand thyroid function was reported to interrelate closely with also the GH/insulin-like growth factor-I (IGF-I) axis (Hoshino et al., 1991; Nikolić et al., 1997; Svanberg et al., 2001). Thus, thyroid hormone status may influence feed intake, which subsequently affects IGF-I levels, and may modify IGF-I concentrations through effects on GH secretion or receptor levels. Administration of GH to lactating cows increased the activity of mammary 5’D twofold (Capuco et al., 1989), thus enhancing the metabolic priority of the udder (Kahl et al., 1995). Significant independent associations of serum $T_3$ with $T_4$ and IGF-I levels during the puerperium were found in two experiments involving 60 healthy cows (Nikolić et al., 2001). Interaction of GH/IGF-I system and thyroid hormones exist also in hair follicle growth of small ruminants (Puchala, 2001).

Duplication of the GH gene was first discovered in primates but further investigation indicated that this event had also occurred in rats, pigs, goats, sheep and cattle (Charrier and Martal, 1988; Wallis et al., 1998). In cattle the two major allelic variants of GH, denoted A (leucine at position 127) and B (valine at position 127), have been identified by Lucy et al. (1993). This polymorphism has been reported to relate to milk production traits although not consistently (Lucy et al., 1993; Sabour and Lin, 1996; Kansaku et al., 2000; Grochowska et al., 2001; Kovács et al., 2002). In the study of Grochowska et al. (2001) the GH and IGF-I concentrations in response to a TRH challenge were significantly different between young dairy cattle with different genotypes: the B allele (Val) was favorable for increased GH response whereas the A allele (Leu) was more favorable for IGF-I response, and the A allele (Leu) was associated with the highest milk production. This observed tendency in milk yield was consistent with the findings of Lucy et al. (1993), but was in contrast to those of Sabour and Lin (1996) and Kansaku et al. (2000). In a field trial carried out in Hungary the average and maximal amounts of monthly checked milk yields of AB cows were higher than that of AA cows (Kovács et al., 2002). Further investigations are required to establish the relationship, if any, between GH variants in thyroid function and reproduction.

3. Diseased states

Cytokines such as certain members of the interleukin (IL) family and tumor necrosis factor-α (TNFα) are reported to decrease 5’D activity in peripheral tissues during starvation, as well as in low $T_3$ syndrome (see below) (Pang et al., 1989), and may play a regulatory role in many other physiological states (Bartalena et al., 1998). A number of infectious and inflammatory (mainly endotoxin mediated) diseases are associated with profound liberation of IL-s and TNFα, followed by subsequent, obvious changes in thyroid status in mammals including domestic ruminants (Lohuis et al., 1988; Jánosi et al., 1998). This so-called euthyroid sick syndrome (syn.: low $T_3$ syndrome) is observed during systemic non-thyroidal illness, and consists of a decrease in plasma concentration of $T_3$, an increase in $rT_3$ level and, in severe cases, a decrease in $T_4$ and TSH concentrations. Most of these changes are caused by a lower $T_3$ production rate and a decreased $rT_3$ clearance rate due to the diminished extrathyroidal 5’D activity (Wartofsky and Burman, 1982). During the inflammatory process some of the cytokines (TNFα, IL-1) are important mediators of changes in thyroid status (e.g. inhibition of TSH release from pituitary cells and decreased activity of type-I 5’D in thyroid and liver tissue) (Pang et al., 1989; Haastan et al., 1994; Hashimoto et al., 1995; Jánosi et al., 1998). Endotoxin exposition is a strong stimulus for cytokine release, reducing the production and circulating level of $T_4$ and inhibiting the $T_4$ deiodination to $T_3$ in many species, including lab rodents (Nagy et al., 1983; Berczi, 1993; Bartalena et al., 1998; Bertők, 1998), humans (Berczi, 1993; Bartalena et al., 1998) and also ruminants (Lohuis et al., 1988; Jánosi et al., 1998; Kahl et al., 2000). Almost all steps of thyroid hormone synthesis, secretion and peripheral metabolism may be negatively influenced by this endotoxin-induced cytokine release (Bartalena et al., 1998). In rats the shock-inducing dose of endotoxin inhibited the TSH-challenged $T_4$ response, due to the membrane damaging effect of this substance.
(Nagy et al., 1983). In commercial large-scale dairy herds certain endotoxin-mediated disorders (acute putrid endometritis, endotoxin mastitis) are known to occur frequently in postpartum dairy cows (Huszenicza et al., 1998, 1999). However, up to now only limited data have been published on their interaction with thyroid function (Lohuis et al., 1988; Sandholm, 1995; Sandholm and Pyörälä, 1995).

There are only limited data available in the literature on circulating levels of thyroid hormones in ketotic animals. Using the threshold value of 30.0 nmol/l for T$_4$ and 1.00 nmol/l for T$_3$ Nikolič et al. (1997) could detect both normal and low levels of thyroid hormones in postpartum cows with supposed ketosis, although the number of cows was limited and due to the lack of proper lab methods the diagnosis of ketosis was quite uncertain in the cited study.

4. Involvement of thyroid hormones in reproduction

4.1. Thyroid hormonal regulation of seasonal patterns of reproduction

In birds and in several mammalian species including small ruminants [sheep and red deer (Cervus elaphus)] the role of thyroid hormones in controlling seasonal reproduction has been firmly established (Nicholls et al., 1988; Moenter et al., 1991; Shi and Barrell, 1992; Reinert and Wilson, 1996). In birds depending on the species the thyroid gland may exert both inhibitory and stimulatory effects. In non-pregnant ewes the thyroidectomy during the anoestrus blocked the transition of cyclic ovarian function from the breeding season into anestrus (Nicholls et al., 1988; Moenter et al., 1991), but the onset of the subsequent breeding season was not affected (Thrun et al., 1997). This effect of thyroidectomy can be fully prevented by the administration of exogenous T$_4$ during the breeding season (Webster et al., 1991a; Dahl et al., 1995). Supplementary T$_4$ in thyroid-intact ewes can also shorten the breeding season and advance the beginning of anoestrus (O’Callaghan et al., 1993). Thyroid hormones need to be present only for a short period of time, at the end of the breeding season for the transition (Thrun et al., 1996). Their inhibitory effect on seasonal gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH) secretion is exerted directly at the level of the central nervous system, between the pineal gland and the GnRH neurosecretory system and this effect is independent from the negative feed-back on TSH-secretion (Webster et al., 1991b; Dahl et al., 1994; Viguie et al., 1997).

In mares the role of the thyroid gland in seasonal reproduction has not been studied extensively. In a recent attempt thyroidectomy failed to alter the onset of anoestrus (Porter et al., 1995) which is similar to a previous observation on reproductive activity of thyroid-ectomized mares (Low et al., 1987). In contrast, using another approach, significant difference in plasma T$_4$ levels was found between cyclic and anestrous mares during the anovulatory season (Fitzgerald and Davison, 1998). In one of our studies (Huszenicza et al., 2000) we could detect certain relationships between thyroid function and expression of seasonal reproductive activity also in mares, but these results do not provide indisputable evidence for the involvement of the thyroid gland in the control of seasonality. Our findings were concluded that decreased T$_3$ and T$_4$ levels in anestrous mares are the consequences of similar hypothalamic control of thyroid function and seasonal reproductive activity, rather than the direct involvement of thyroid hormones in regulation of ovarian function in this species.

4.2 Thyroid hormonal regulation of ovarian endocrine function

Continuous infusion of TRH (0.8 mg/day for about 11 days in the summer period via subcutaneous osmotic minipump) suppressed plasma prolactin, doubled the concentration of T$_4$ and T$_3$, and was associated with a wide range of ovarian abnormalities in ewes at the beginning of the breeding season (Robinson et al., 1996). Many factors known to decrease the circulating level of T$_4$ and/or T$_3$ have been associated also with reduced reproductive efficiency. So an association between reduced concentrations of thyroid hormones and decreased reproductive efficiency is plausible. In recent years it has become increasingly clear that an adequate level of circulating T$_4$ is of primary importance for ovarian function in laboratory rodents (Ortega et al., 1990; Osorio et al., 1998; Mattheij et al., 1995).

Under in vitro conditions direct effects of T$_4$ on ovarian cell function were first reported in pigs in
1976 (Channing et al., 1976). Thyroid hormone receptors and/or their messenger ribonucleic acid (mRNA) have been detected in porcine (Maruo et al., 1992) and human (Wakim et al., 1993, 1994; Zhang et al., 1997) granulosa cells from preovulatory antral follicles. Furthermore, T₃ and T₄ directly alter ovarian granulosa cell steroidogenesis in pigs and humans. Specifically, Hayashi et al. (1985) and Maruo et al. (1987) observed that T₄ stimulated follicle stimulating hormone (FSH) induced estradiol (E₂) production by porcine granulosa cells. Later Wakim et al. (1995a, b) found that T₄ stimulated progesterone (P₄) and E₂ production by human granulosa cells. In an in vitro system, T₃ caused about a twofold increase of protein synthesis in rat granulosa cells compared to cells without T₃ (Bandyopadhyay et al., 1996). In vitro, T₃ assisted FSH and LH to enhance steroid biosynthesis in porcine (Chan and Tan, 1986; Maruo et al., 1987; Gregoraszczuk et al., 1998) and human (Goldman et al., 1993; Wakim et al., 1995a, b) granulosa cells. A recent study has reported that T₃ mediated stimulation of P₄ release from human luteal cells is not direct, but is mediated through a putative protein factor (Datta et al., 1998). Up to now there is only one study evaluating the effect of T₃ and T₄ on steroidogenesis of ovarian cells in cattle: Spicer et al. (2001) reported a direct stimulatory effect of T₃ and T₄ on thecal cell steroidogenesis. The stimulatory effect of T₃ and T₄ on androstenedione production (i.e. two- to fourfold increases) was similar to the influence of LH on androstenedione production (i.e. four- to ninefold increases). The stimulatory effect of T₃ was observed at low dose while high dose had no effect, however the influence of T₄ was similar at both doses. In contrast, T₃ inhibited the human chorionic gonadotropin (hCG) induced androgen secretion by porcine thecal cells (Gregoraszczuk and Skalka, 1996). Thus, species differences and/or differences in culture conditions may exist with regard to thyroid hormone regulation of thecal steroidogenesis, as for granulosa cell steroidogenesis. In the study of Spicer et al. (2001) T₄ was a much weaker (i.e. 1.3-fold increase) inducer of thecal cell P₄ production than was LH (i.e. four- to ninefold increases) and its effect was only evident at hyperthyroid levels (i.e., 100 ng/ml, but not 30 ng/ml); T₃ had no effect on granulosa and thecal cell P₄ production in this study. Collectively, these data indicated that the stimulatory effect of T₃ and T₄ on bovine androstenedione production was directed toward the enzymes that convert progestins into androgens (i.e., 17.20 lyase or 17α-hydroxylase). Although T₃ and T₄ had little or no effect on aromatase activity per se, the stimulatory effect of T₃ and T₄ on androstenedione production could provide important estrogen precursors to granulosa cells and thus increase E₂ production indirectly in vivo. In conclusion, the study of Spicer et al. (2001) provided supportive evidence for a role of T₃ and T₄ in regulating steroidogenesis of bovine follicles. The stimulatory effects of T₃/T₄ may be regarded as a part of a complex multihormonal regulation of follicular steroidogenesis in cattle.

However, there are only limited, and sometimes controversial data available in the literature confirming the influence of thyroid hormones on ovarian function under in vivo conditions. Hypothyroid-induced rats had a lower E₂ concentration than euthyroid rats (Mattheij et al., 1995; Osorio et al., 1998; Tohei et al., 1998). The association between NEB and low circulating T₃, and low circulating E₂ were found also in young women distance runners (Zanker and Swaine, 1998). T₃ levels were reported to decrease in growing Carora heifers at 12 months of age, which could be critical for the simultaneous increase in LH secretion at 3 week before puberty (Leyva-Ocariz et al., 1997). Induced hyper- or hypothyroid status did not influence ovarian function in adult Brahman cows (De’Moraes et al., 1998). In multiparous, non-lactating superovulated Brahman cows the 6-n-propyl-2-thiouracil induced hypothyroidism improved the weight gain and body condition score, and increased the ovarian response to FSH (resulting in greater ovarian weights and higher number of luteinized follicles, greater concentrations of P₄ in the follicular fluid at all size categories, and greater number of corpora lutea than their untreated euthyroid counterparts. On day 7 after ovulation the ratio of luteal to serum P₄ was greater in these hypothyroid cows than in the control animals. The hypothyroid cows had greater numbers of luteinized follicles, greater concentrations of P₄ in the follicular fluid at all size categories, and greater number of corpora lutea than their untreated euthyroid counterparts. On day 7 after ovulation the ratio of luteal to serum P₄ was greater in these hypothyroid cows than in euthyroid cows (Bernal et al., 1999). However, these studies used non-pregnant and non-lactating cows that presumably were not in a state of NEB. This may implicate that low T₃ affected reproductive performance of NEB subjects only. A study using non-lactating cows showed that estrus behavior was unaffected by hypothyroidism induced by thyroidectomy (Stewart et al., 1993). When T₃ concentrations were depressed by the
induction of hypothyroid in lactating heifers, $T_4$ concentrations at day 14 of the cycle were significantly lower than those in control animals (Thrift et al., 1999a, b). Thus, it may be hypothesized that low $T_3$ was associated with low reproductive performance in cows during postpartum period. However, future in vivo studies should focus on evaluating the effect of circulating $T_3$ and $T_4$ levels on simultaneous follicular $E_2$, and luteal $P_4$ production, if we want to determine the certain impact of thyroid hormones on reproductive efficiency in postpartum dairy cows.

5. Conclusion

The studies overviewed above gave the doubtless evidence concerning the involvement of thyroid hormones (1) in the adaptation to NEB status, (2) in the course of certain endotoxin mediated diseases, and (3) in the process of resumption of cyclic ovarian function also in ruminants including the postpartum dairy cows. Further trials – including production oriented research activity – are required, however, to verify the really existing interrelations between circulating levels of thyroid hormones and leptin, to demonstrate the tendencies in $T_3$ and/or $T_4$ levels and thyroid function in ketosis, Gram-negative mastitis and acute putrid endometritis, to reveal differences in thyroid secretory capacity of cows with various GH alleles, as well as to confirm the clinical relevance of low $T_3$ in pathogenesis of certain ovarian malfunctions.

6. References


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