Clinical endocrinology of thyroid gland function in ruminants

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ABSTRACT: After briefly introducing the basec 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

Abbreviations: **5'D** = 5'-deiodinase (syn.: outer-ring deiodinase); **5D** = 5-deiodinase (syn.: inner-ring deiodinase); **BHB** = βOH-butyrate; **E_2** = 17β-estradiol; **FSH** = follicle stimulating hormone; **GH** = growth hormone; **GnRH** = gonadotropin releasing hormone; **hCG** = human chorionic gonadotropin; **IGF-I** = insulin-like growth factor-I (syn.: somatomedin C); **IL** = interleukin; **LH** = luteinizing hormone; **mRNA** = messenger ribonucleic acid; **NEB** = negative energy balance; **NEFA** = non-esterified fatty acids; **P_4** = progesterone; **PVN** = paraventricular nucleus of the hypothalamus; **rT_3** = 3,3',5'-triiodothyronine (syn.: reverse-triiodothyronine); **T_3** = 3,3',5-triiodothyronine; **T_4** = thyroxine; **TNFα** = tumor necrosis factor-α; **TRH** = thyrotropin-releasing hormone; **TSH** = thyroid-stimulating hormone (syn.: thyrotropin)

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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.

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2. Basic physiology. Nutritional factors influencing thyroid function

Thyroxine (T_4) 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 T_4, but also in a small quantity of 3,3',5-triiodothyronine (T_3). In the brain and the peripheral tissues (liver, mammary epithelium and others) the almost inactive T_4 may undergo extrathyroidal enzymatic activation (e.g. outer-ring deiodination) by 5'-deiodinase (5'D) producing the much more potent T_3, or inactivation (e.g. inner-ring deiodination) by 5-deiodinase (5D) producing fully inactive forms of 3,3',5'-triiodothyronine (syn.: reverse-triiodothyronine; rT_3). All three thyroid hormones are present in the circulation, however inherent physiological effects are attributed almost only to T_3 (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 T_3 and T_4 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 T_4 and T_3 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; Nikolič *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 T_3 and T_4 and increase the concentration of rT_3 (Pethes *et al.*, 1985; Ronge *et al.*, 1988; McGuire *et al.*, 1991; Yambayamba *et al.*, 1996). In dairy cows low T_3 and T_4 have been observed in the first trimester of lactation (Pethes *et al.*, 1985), even after βOH-butyrate (BHB) and non-esterified fatty acids (NEFA) had returned to normal levels (Eppinga *et al.*, 1999). In lactating dairy cows plasma T_3 and T_4 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 T_4 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 T_4 activation and inactivation (**peripheral autoregulation**; Pethes *et al.*, 1985; Capuco *et al.*, 2001; Cassar-Malek *et al.*, 2001). Peripheral T_3 concentrations are influenced mainly by extrathyroidal 5'D activity. Because T_3 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 T_3 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, T_4 and T_3 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 T_4 and T_3 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; Ingvartsen 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 T_4 and T_3 (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 Ingvartsen 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 T_4 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 T_3 and rT_3

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; Huszenicza *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; Nikolič *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_4 with T_3 and IGF-I levels during the puerperium were found in two experiments involving 60 healthy cows (Nikolič *et al.*, 2001). Interaction of GH/IGF-I system and thyroid hormones exists 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; Haastaren *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; Bertók, 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 interrelation 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 (Lowe *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_3 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, T_3 and T_4 directly alter ovarian granulosa cell steroidogenesis in pigs and humans. Specifically, Hayashi *et al.* (1985) and Maruo *et al.* (1987) observed that T_4 stimulated follicle stimulating hormone (FSH) induced estradiol (E_2) production by porcine granulosa cells. Later Wakim *et al.* (1995a, b) found that T_4 stimulated progesterone (P_4) and E_2 production by human granulosa cells. In an *in vitro* system, T_3 caused about a twofold increase of protein synthesis in rat granulosa cells compared to cells without T_3 (Bandyopadhyay *et al.*, 1996). *In vitro* T_3 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 T_3 mediated stimulation of P_4 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 T_3 and T_4 on steroidogenesis of ovarian cells in cattle: Spicer *et al.* (2001) reported a direct stimulatory effect of T_3 and T_4 on thecal cell steroidogenesis. The stimulatory effect of T_3 and T_4 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 T_3 was observed at low dose while high dose had no effect, however the influence of T_4 was similar at both doses. In contrast, T_3 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) T_4 was a much weaker (i.e. 1.3-fold increase) inducer of thecal cell P_4 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); T_3 had no effect on granulosa and thecal cell P_4 production in this study. Collectively, these data indicated that the stimulatory effect of T_3 and T_4 on bovine androstenedione production was directed toward the enzymes that convert progestins into androgens (i.e., 17.20 lyase or 17α-hydroxylase). Although T_3 and T_4 had little or no effect on aromatase activity per se, the stimulatory effect of T_3 and T_4 on androstenedione production could provide important estrogen precursors to granulosa cells and thus increase E_2 production indirectly *in vivo*. In conclusion, the study of Spicer *et al.* (2001) provided supportive evidence for a role of T_3 and T_4 in regulating steroidogenesis of bovine follicles. The stimulatory effects of T_3/T_4 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 E_2 concentration than euthyroid rats (Mattheij *et al.*, 1995; Osorio *et al.*, 1998; Tohei *et al.*, 1998). The association between NEB and low circulating T_3, and low circulating E_2 were found also in young women distance runners (Zanker and Swaine, 1998). T_3 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 5 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 large, ≥ 8 mm follicles). However, the embryo recovery rate, the fertilization rate, and the percentage of transferable blastocysts obtained were lower in the hypothyroid cows than in the control animals. The hypothyroid cows had greater numbers of luteinized follicles, greater concentrations of P_4 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 P_4 was greater in these hypothyroid 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 T_3 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 T_3 concentrations were depressed by the

induction of hypothyroid in lactating heifers, P_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 allels, as well as to confirm the clinical relevance of low T_3 in pathogenesis of certain ovarian malfunctions.

6. References

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