Rocz. Nauk. Zoot., T. 46, z. 1 (2019) 3–9

THE ROLE OF THYROID HORMONES IN SHEEP LACTATION*

Edyta Molik, Zuzanna Flis, Monika Staroń, Klaudia Hell

Department of Animal Biotechnology, Agricultural University of Krakow,
Al. Mickiewicza 24/28, 30-059 Kraków, e-mail: rzmolik@cyf-kr.edu.pl

Lactation, during which the young receive the necessary nutrients from milk, is extremely important in the rearing of healthy offspring. The lactation process requires proper functioning of the endocrine system, and the impact of many factors is crucial to its initiation and maintenance. The group of these compounds includes prolactin (PRL), vasoactive intestinal peptide (VIP), growth hormone (GH), thyrotropin-releasing hormone (TRH), or thyrotropin hormone (TSH). Thyroid hormones: triiodothyronine (T3) and thyroxine (T4), affect the development of the mammary gland. The control of the secretion of these hormones works on the principle of negative feedback through the hypothalamic-pituitary-thyroid (HPT) axis. Sheep reproduce during autumn when the daylight is shortened. The transmission of light stimuli takes place through the eyes of the sheep. In response to shorter days, the pineal gland increases melatonin secretion. Under the influence of these transformations, the breeding period begins.

Key words: thyroid hormones, lactation, sheep

*Source of financing: DS/KBZ/2018.

List of abbreviations:

D1 – D1 dopamine receptors, D2 – D2 dopamine receptors, EGF – epidermal growth factor, FGF-2 – fibroblast growth factor-2, GH – growth hormone, HPT – hypothalamic-pituitary-thyroid axis, HyperT – hyperthyroidism, HypoT – hypothyroidism, IGF – insulin-like growth factor, PIH – dopamine, PRF – prolactin-releasing factors, PRL – prolactin, PT – pars tuberalis, STAT5a – signal transducer and activator of transcription 5a, T3 – triiodothyronine, T4 – thyroxine, TG – thyroglobulin, TH – thyroid hormones, TRH – thyrotropin releasing hormone, TSH – thyroid-stimulating hormone, VIP – vasoactive intestinal peptide.

Lactation is a crucial process by which milk is secreted by the mammary gland of female mammals (Lakhani et al., 2017). Central to the maintenance of lactation is the suckling reflex, which is a strong physiological stimulus that stimulates oxitocin and prolactin secretion (Ben-Jonathan and LaPensee, 2009). Prolactin (PRL), also known as luterotropic hormone, lutetropin, and mammotrophin, is a hormone produced by lactotropic cells in the anterior pituitary gland, which form around 20–40% of the pituitary (Ben-Jonathan and LaPensee, 2009). In sheep, prolactin secretion is mainly regulated by dopaminergic pathways. Prolactin is a feedback regulator of dopaminergic systems (Ben-Jonathan, 1985; Ben-Jonathan and LaPensee, 2009). In the pituitary gland, dopamine acts on specific D2 receptors and reduces prolactin synthesis and secretion. When dopamine binds to D1 receptor, stimulation of prolactin secretion is observed (Mezey and Palkovitz, 1982; Ben-Jonathan, 1985). An important function in prolactin release process is also played by estrogens, oxytocin, thyrotropin releasing hormone, and growth factors (including EGF – epidermal growth factor and FGF-2 – fibroblast growth factor-2) (Bredow et al., 1994; Porter et al., 1994; Forsyth et al., 1999). Thyrotropin releasing hormone (TRH) stimulates prolactin secretion. It is a tripeptide with a molecular weight of 359.5 Da. Secreted by the hypothalamus, it triggers the pituitary gland to secrete thyrotropin (TSH – thyroid-stimulating hormone), which influences thyroid hormones (TH) secretion (Ben-Jonathan and LaPensee, 2009). As an endocrine gland, thyroid produces triiodothyronine (T3), thyroxine (T4) and calcitonin. Before the first two hormones are released into the blood, the thyroid stores them as iodized thyroglobulin (TG) in the follicular colloid (Braun and Schweizer, 2018; Carvalho and Dupuy, 2017). The hypothalamic-pituitary-thyroid (HPT) axis has a negative feedback action. The level of TRH, and thus also of TSH, decreases when thyroid hormones are produced in excess (hyperthyroidism), and increases when these hormones are deficient (hypothyroidism) (Carvalho and Dupuy, 2017).

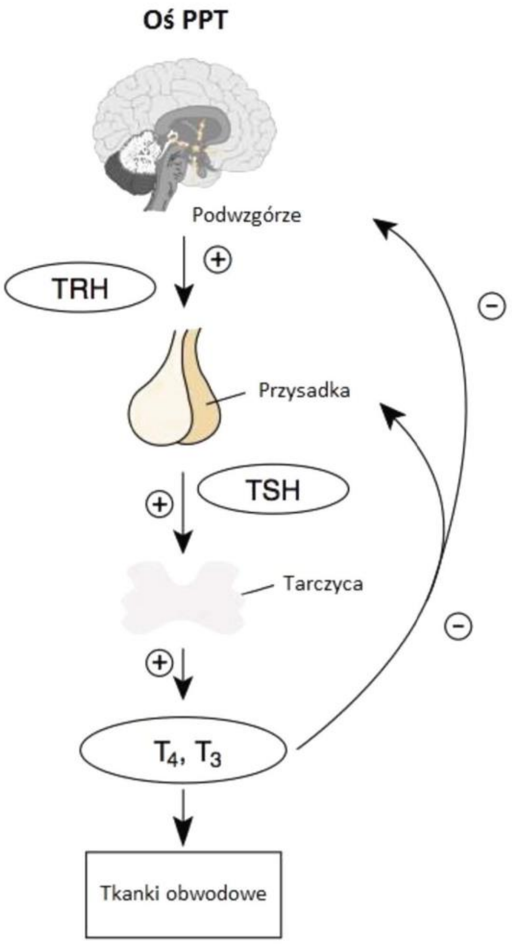

Figure 1. Schematic representation of the hypothalamic-pituitary-thyroid (HPT) axis. The hypothalamus releases thyrotropin-releasing hormone (TRH), which triggers the pituitary to release thyroid-stimulating hormone (TSH). TSH stimulates the thyroid to produce thyroid hormones T3 (triiodothyronine) and T4 (thyroxine), which affect peripheral tissues. Plus stands for stimulatory action, minus for inhibitory action. Source: Hiller-Sturmhöfel and Bartke, 1998

The role of thyroid hormones in reproduction and lactation

Temperate zone animals live in a changing climate, i.e. temperature, precipitation and photoperiod. These animals have adapted to different climate factors by modifying their physiology and behaviour. Alterations were seen in aspects of life such as growth, hibernation, moulting, migration, and reproduction. Among the many cues indicating the change of seasons, animals typically use the photoperiod (day length). This mechanism is closely linked to the biological clock. Using the photoperiod seems reasonable because other signals, such as temperature and precipitation, are highly unstable indicators. This means that the above adaptive processes may go awry in abnormal weather conditions (e.g. warm winter, cold summer, absence of precipitation in the autumn). It appears that the only stable element is day length, which occurs cyclically during the year (Ikegami and Yoshimura, 2017).

In mammals, photoreception is restricted to the eyes. The retina absorbs light impulses and then acts via the retinohypothalamic tract to transmit information to the pineal gland, where melatonin is synthesized. Melatonin production increases during the dark phase and decreases during the light phase. Thus, the pineal is an endocrine gland which informs the body about external environmental changes concerning the change of day length. Sheep are seasonal animals and show breeding activity during the decreasing photoperiod (in autumn), when the reproductive system is activated by increased melatonin secretion (Misztal et al., 1996; Wilsterman et al., 2018).

In animals, thyroid hormones influence the body's thermoregulatory processes and modulate metabolic rate. They also play an important function in regulating melatonin secretion, thus modulating the reproduction and lactation processes (Wilsterman et al., 2018). Research shows that TSH and thyroid hormones play a major role in controlling seasonality in animals. Seasonal animals need a stimulus, which after the sexual reproduction period will cause them to return to anestrus. Such a role is also ascribed to the thyroid hormones (Peeters et al., 1989). TSH is secreted in the pars tuberalis (PT) of the anterior pituitary. Circadian rhythms of hormone secretion are controlled by biological clock genes, in particular genes whose activation is determined by the presence of the light or dark phase (including *Cry*, *Bmal1*, *Per* and *Lock* genes). The activation of TSH secretion during the decreasing day length and increasing melatonin secretion initiates the period of sexual activity in sheep. In turn, increased secretion of thyroid hormones during the increasing photoperiod results in the inactivation of gonads (anestrus). Changes in day length and at the same time the seasonal melatonin rhythm modulate the secretion of TSH and thyroid hormones, thus contributing to body function (Ikegami and Yoshimura, 2017). In sheep during the late stage of pregnancy, i.e. over 4 months, T3 and T4 concentrations were similar as in unmated (barren) ewes (Kandiel et al., 2016). During the luteal phase, TSH and T3 concentrations increase. T4 concentration increases during estrus and decreases during the luteal phase. It emerged that thyroid hormones affect the ovulation of the oocyte and also stimulate the fertilizing capacity of oocytes (Błaszczyk et al., 2004).

Thyroid hormones are pivotal to the mammary gland function and development. Maintaining an adequate level of thyroid hormones is central to initiating and maintaining lactation. Abnormal secretion of thyroid hormones, namely hyperthyroidism (HyperT) and hypothyroidism (HypoT), have an effect on mammary gland development and on the secretion and chemical composition of the milk. A deficiency of thyroid hormones adversely affects lipid metabolism in the mammary gland and liver. This results in lower weight gains and increased offspring mortality (Campo Verde Arboccó et al., 2015). Hypothyroidism reduces the concentration of triglycerides in milk, which is due to slower triglyceride synthesis in the liver. Nursing offspring with milk that is low in triglycerides caused a decrease in body weight gains (Hapon et al., 2003, 2007). Experimentally hyperthyroidized (HyperT) female rats showed reduced prolactin levels on days 7 and 14 of lactation. Reductions were also seen in the concentrations of progesterone and insulin-like growth factor (IGF). Corticosterone and growth hormone were observed to increase on day 7 of lactation. In the offspring, T4 concentration increased on days 7 and 14, and T3 concentration as late as on day 14 of lactation. The level of oxytocin in HyperT mothers was much lower than in control female rats. Moreover, HyperT females produced less milk than control mothers (Varas et al., 2002). According to Rosato et al. (1992), exogenous T4 given to rats accelerates lactogenesis and parturition. The study demonstrated that triiodothyronine has an antagonistic effect on prolactin secretion. This takes place through inhibition of signal transducer and activator of transcription 5a (STAT5a), which mediates the prolactin signaling pathway in the mammary gland (Campo Verde Arboccó et al., 2015).

Research showed that thyroidectomized offspring were characterized by considerable dysfunction and slowed growth. Their skeleton and reproductive organs were not completely developed (Vonderhaar and Greco, 1979; Morrissey et al., 2008). In small ruminants, cyclical changes in thyroid activity were found to result from environmental heat stress, energy availability, and seasonal cues. *In vitro* studies showed triiodothyronine and thyroxine secretion to be dependent on day length. During the decreasing photoperiod, T3 and T4 secretion was more intense than during the long photoperiod. These results prove that the regulation of breeding in sheep depends on the interaction of these hormones and the processes they influence (Klocek-Gorka et al., 2010).

In summary, it is concluded that lactation in seasonal sheep requires the presence of many hormones, in particular prolactin. It is a complex process dependent on day length conditions, which is associated with the annual melatonin profile. Research carried out to date with lactating sheep showed a significant effect of day length on milk secretion and chemical composition (Molik et al., 2013). Identification of the mechanisms for the establishment and maintenance of lactation in seasonal sheep, in particular understanding the role of metabolic hormones in this process, may help to better realize the potential of sheep breeds raised for milk production in Poland.

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SUMMARY

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