Thyroid hormones in female and male reproduction with special reference to dogs and cats

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Abstract

Thyroid hormones have an important function in numerous physiological processes in humans and animals, including the regulation of metabolism, growth and development of individual and reproductive function. The thyroid hormones, triiodothyronine (T3) and thyroxine (T4), have a direct effect on the reproductive organs and an indirect effect in interaction with other hormones. Thyroid hormones influence the reproductive system by regulating metabolism and tissue development of the ovaries, uterus and placenta. Changes in the serum concentrations of T3 and T4 lead to disturbances in overall body function. Thyroid dysfunction, including hypothyroidism and hyperthyroidism, can lead to significant reproductive problems. The aim of this review was to describe the functions of thyroid hormones and the effects of hypothyroidism and hyperthyroidism on the animal reproductive system. Hypothyroidism is often caused by autoimmune diseases such as lymphocytic thyroiditis, and is associated with later puberty, reduced fertility and abnormalities in reproductive organ development. Hypothyroidism can lead to a prolonged interval, absent cycles, silent oestrus cycles, prolonged oestrus bleeding, and a lack of libido, with the occurrence of infertility, miscarriages, stillbirths and mummified foetuses. In males, hypothyroidism leads to a decrease in libido, semen quality, ejaculate volume, testicular atrophy, hypospermia and azoospermia. Hyperthyroidism, on the other hand, is usually the result of thyroid cancer, which produces excessive amounts of thyroid hormones. Increased concentrations of thyroid hormones lead to disturbances in the physiological balance of reproductive hormones, irregular oestrus cycles, anovulation and reduced fertility, as well as a decrease in the weight of the ovaries and the number of healthy follicles, with a simultaneous increase in the number of atretting follicles. The effects of hyperthyroidism on male fertility include disorders of spermatogenesis, changes in sex hormone levels and changes in sperm quality, such as hypospermia, oligozoospermia, asthenozoospermia and teratozoospermia. It is important to diagnose and treat thyroid disorders in time in order to prevent negative effects on fertility and reproduction in animals.

Key words: *thyroid hormones; reproductive system; hypothyroidism; hyperthyroidism*

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Introduction

Thyroid hormones, particularly triiodothyronine (T3) and thyroxine (T4), play an important role in the regulation of various physiological processes in animals, including metabolism, growth and development. Changes in the serum concentrations of T3 and T4 lead to disturbances in overall body function. Among their numerous functions, thyroid hormones have a significant influence on the reproductive system, i.e., they have a direct effect on reproductive organs and an indirect effect in interaction with other hormones. Thyroid hormones influence the reproductive system by regulating metabolism and tissue development of the ovaries, uterus and placenta. The effects of thyroid hormones on reproduction and the development of the reproductive system can vary, so thyroid dysfunction, including hypothyroidism and hyperthyroidism, can lead to significant reproductive problems. Hypothyroidism is often associated with later sexual maturation, reduced fertility and disorders of ovarian and uterine development (Choksi et al., 2003). Hyperthyroidism is associated with irregular oestrus cycles and reduced fertility in females, and decreased libido and reduced sperm quality in males (Sontes et al., 2014). Thyroid disorders can therefore have a negative impact on both male and female fertility, pregnancy and offspring, i.e., they can significantly affect the reproductive health of animals, but with timely diagnosis and appropriate treatment, negative effects can be prevented. Thyroid disease can also be hereditary, making it an undesirable trait for an individual's reproduction (La Vignera and Vita, 2018; Silva et al., 2018). The aim of this review was to describe the functions of thyroid hormones and to highlight the effects of hypothyroidism and hyperthyroidism on the reproductive system of animals.

Anatomy of the thyroid gland

The thyroid gland is an endocrine organ that occurs in all species of vertebrates. It has a similar basic structure and function in vertebrates, but there are considerable anatomical differences, particularly in the number of lobes and the connection of the isthmus, which vary between species (König and Liebich, 2009). The thyroid gland is located in the neck area, ventrally on both sides of the trachea and its most cranial part sometimes covers the larynx. The thyroid gland is relatively small and accounts for only about 0.20% of the total body mass in all animal species. The functional units of the thyroid gland are follicles, round structures consisting of an inner colloid core (thyroglobulin-hormone complex) surrounded by a single layer of follicular epithelial cells. The follicular cells can range from inactive squamous epithelial cells to very active, large prismatic cells, depending on the functional state of the thyroid gland (Singh and Beigh, 2013).

Physiology of the thyroid gland

Thyroides hormones, T4 and T3, have an important function in the regulation of various physiological processes in animals and influence metabolism, growth, development and homeostasis. These hormones significantly increase basal metabolic activity by stimulating mitochondrial activity, resulting in higher oxygen consumption and heat production. They promote glucose uptake and utilisation by stimulating glycogenolysis and gluconeogenesis in the liver, and also stimulate lipolysis and fatty acid oxidation.

The biological effect of thyroid hormones is achieved by T3 (Heseltine, 2024a). Thyroid hormones are necessary for normal growth and development, especially in foetal development, where they influence the central nervous system and the bone system, and in postnatal growth, by promoting bone maturation and acting synergistically with growth hormone (Choksi et al., 2003). They also have an important function in thermoregulation by increasing heat production, which is essential for maintaining body temperature in cold weather. Cardiovascular effects include increased heart rate, stroke volume and cardiac output, and decreased peripheral vascular resistance, which allows for increased blood flow to tissues (Heseltine, 2024a). In the nervous system, thyroid hormones are important for brain development and maturation, they influence neurogenesis and myelination, and in adults they affect mood, cognitive abilities and attention (Choksi et al., 2003). In addition, they influence the development and activity of various immune cells in innate and acquired immunity (Joseph-Bravo et al., 2017). An imbalance in thyroid hormone levels can lead to significant health problems such as hypothyroidism, which is characterised by a reduced metabolic rate and lethargy, while in hyperthyroidism the metabolism is accelerated and cardiovascular complications are also possible (Heseltine, 2024b).

Synthesis and secretion of hormones and the thyroid regulatory system

In humans and animals, the thyroid gland produces the thyroid hormones (TH) T3 and T4 (Figure 1). The mechanisms regulating the production and release of T3 and T4 are similar in humans and animals (Choksi et al., 2003), and the control of serum concentrations of these hormones is regulated by a negative feedback loop involving the hypothalamus, pituitary and thyroid gland. Iodine is an essential component of thyroid hormone, making up 58% of T3 and 65% of T4. For the biosynthesis of these hormones in the thyroid gland, iodide must enter into the thyroid follicle, and this depends on the activity of two transmembrane glycoproteins present in the thyroid gland, sodium iodide symporter (NIS) and pendrin (Silva et al., 2018). After entering the thyroid follicle, iodide is oxidised by thyroperoxidase and incorporated into thyroglobulin, resulting in monoiodothyronine and diiodothyronine, followed by the production of T3 and T4 (Rousset et al., 2000). This oxygenation is necessary because without it, iodine could not be incorporated into tyrosine molecules (Sjaastad et al., 2017). The expression of NIS and pendrin, as well as thyroperoxidase (TPO) and tireoglobulin, depends on the expression of the transcription factor Pax8, which is important for the development and proper functioning of the thyroid gland (Di Palma et al., 2003). Thyroglobulin is the most abundant protein in the thyroid gland. Its concentration in the follicular lumen can reach 200 to 300 g/L. Its main function is to provide a polypeptide bond for the synthesis and storage of thyroid hormones (Dunn and Dunn, 2000). T3 and T4 are released from thyroglobulin in the epithelial cells of the thyroid gland by the action of lysosomal enzymes. They then diffuse from the epithelial cell into the tissue fluid, where 70 to 80% are selectively bound to thyroxine-binding globulin, while the rest of the TH binds non-specifically to albumin (Sjaastad et al., 2017). Circulating TH, especially T4, can be metabolised via different pathways leading to: formation of the active hormone triiodothyronine (T3), deactivation of T4 and T3, or excretion of

T4 and the subsequently formed metabolites, i.e., glucuronidation, sulfation and deiodination, with deiodination being the most important. These metabolic pathways have a key function in determining TH bioavailability (Van Der Spek et al., 2017). Circulating T3 levels are mainly derived from the peripheral conversion of T4 (80%) to T3, while only 20% is secreted by the thyroid gland itself. This extrathyroidal production of T3 is carried out by the 5'-deiodinase enzymes D1 and D2 (Visser and Peeters, 2012).

The regulation of the thyroid gland involves complex interactions between the hypothalamus, pituitary gland and thyroid gland that enable precise control of thyroid hormone production (Figure 1) (Engelking, 2012). The thyroid regulatory system ensures the balance of thyroid hormones (T3 and T4) in the body. The hypothalamus releases thyrotropin-releasing hormone (TRH) in response to low levels of T3 and T4 in the blood. The hypophysiotropic TRH is produced in neurons whose cell bodies are located in the paraventricular nucleus of the hypothalamus (Visser, 2018). TRH stimulates the adenohypophysis to release thyroid-stimulating hormone (TSH). TSH, TRH and TH form the hypothalamic-pituitary-thyroid axis (Scanlon and Toft, 2000). TSH is released in a pulsatile pattern and binds to TSH receptors on the membrane of the thyroid follicle cells. Activation of the G-protein-coupled TSH receptors stimulates adenylyl cyclase, which catalyses the conversion of ATP into cyclic adenosine monophosphate. Thyroid hormones regulate the number and size of follicular cells, therefore long-term stimulation of the thyroid gland with TSH leads to hyperplasia and hypertrophy of the glandular tissue, which is noticeable (Figure 2). An increase in the concentration of thyroid hormones in plasma inhibits TSH secretion by the pituitary gland (Sjaastad et al., 2017). The release of TSH decreases when the T3 con-

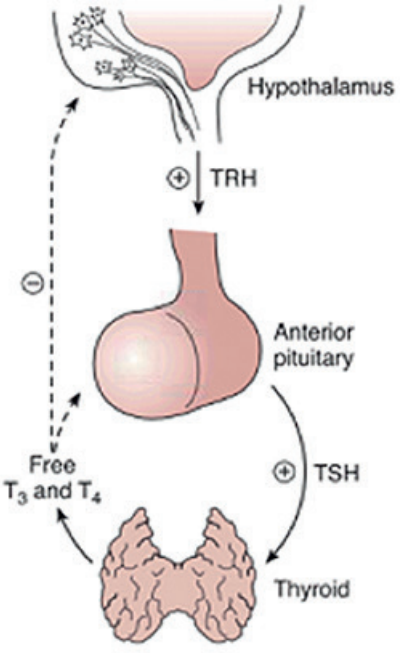

Figure 1. Regulation of hormone secretion (Engelking, 2012)

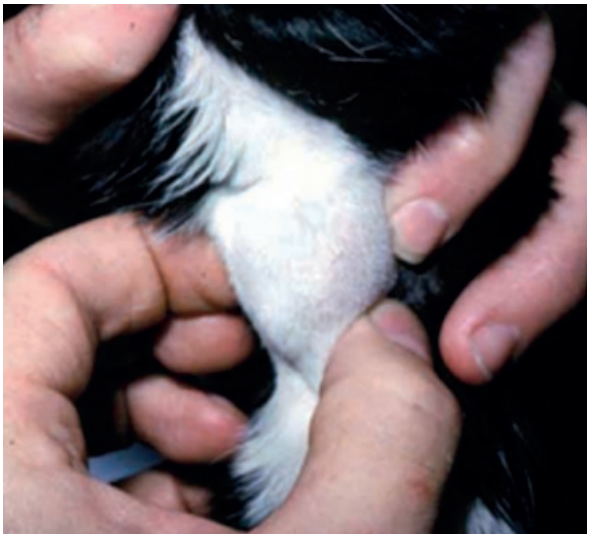

Figure 2. Palpation of a thyroid nodule in cats with suspected hyperthyroidism (Peterson, 2012)

centration in the circulation increases, and there is also regulation by the gland itself, which is important in the case of increased or decreased iodine intake in the body. When there is an acute increase in iodine concentration, there is an acute adaptation in which the expression of genes coding for NIS and TPO is reduced. In iodine deficiency, thyroid function increases before iodine reserves are depleted, and the thyroid adapts to low doses by synthesising T3 instead of T4 (Rijnberk and Kooistra, 2010). T3 and T4 concentrations drop sharply when animals are starved or exposed to restrictive feeding under experimental conditions (Sjaastad et al., 2017).

Diseases of the thyroid gland affecting reproduction

There is a significant correlation between the effects of thyroid hormones and reproductive function in humans and animals. Hereditary thyroid disorders, such as autoimmune thyroiditis, and reproductive problems caused by an imbalance of thyroid hormones are two important factors in animal reproduction (La Vignera and Vita, 2018; Silva et al., 2018).

Hypothyroidism

The most common examples of hypothyroidism are autoimmune diseases such as lymphocytic thyroiditis and idiopathic thyroid atrophy. Other causes of hypothyroidism are reduced synthesis and secretion of hormones due to disorders in the thyroid gland, reduced synthesis of thyroid hormones due to a deficit of TRH and TSH and insufficient iodine intake from the diet (Sjaastad et al., 2017, Petca et al., 2023; Shi et al., 2023).

Hereditary disorder of the thyroid gland

Autoimmune lymphocytic thyroiditis is a common hereditary disorder that causes hypothyroidism in dogs and other animals, in which the immune system damages the thyroid gland. To diagnose the disorder, it is necessary to determine the presence of autoantibodies in the patient's blood. In the initial phase of the disorder, the dog starts to produce autoantibodies against its thyroid gland, usually at the age of one to three years

(Ziener et al., 2015). The thyroid hormone level and thus also the TSH value remain within the physiological range as long as most of the gland is not damaged. If the gland is more than 75% damaged and the thyroid hormone level drops significantly, the antigenic stimulus for the production of autoantibodies is removed (Bell, 2007). The animal remains in a permanent state of hypothyroidism, i.e., with a low T4 level, a high TSH level, and without the presence of autoantibodies in the blood. The diagnosis of autoimmune thyroiditis can be made during immunological damage to the thyroid gland, because in the final stage of the disease the autoantibody level is normal. In most affected dogs, a hereditary thyroid disorder can be diagnosed by determining the thyroid profile and the presence of autoantibodies in the blood at the age of 2 to 4 years. In a study presented by Bell (2007), 9.84% of dogs tested for blood levels of thyroid hormones were positive for thyroglobulin autoantibodies. The breeds with the highest percentage were English Setters (33.5%), Polish Lowland Dogs (30.7%), Havanese (25.6%), Old English Shepherds (22.8%) and Boxers (19.7%). In mixed breeds, 11.5% of 49,126 dogs tested positive for thyroid autoantibodies (Bell, 2007, Ziener at al., 2015). These data suggest a significant prevalence of autoimmune thyroid disease in certain breeds, which may be important for further research into the genetic and environmental factors contributing to these disorders. Hereditary hypothyroidism is characterised by dwarfism, central and peripheral nervous system disorders and mental disturbances (Greco et al., 1991). In puppies with hereditary hypothyroidism, the growth disturbance is already visible after 3 weeks. By the 8th week, the disorders are so obvious that such puppies are not selected for breeding. For the reproduction of dogs, it is important to determine the cause of hereditary hypothyroidism, so that such individuals can be excluded from further reproduction. Hereditary congenital hypothyroidism has been reported in Schnauzers and Japanese cats (Greco et al., 1991).

The influence of hypothyroidism on the female reproductive system

Thyroid hormones regulate the secretion of oestradiol and progesterone, which are necessary for egg maturation and development, prepare the endometrium for embryo implantation, and are important for the development and maintenance of early pregnancy. Hypothyroidism causes changes in the expression of prostaglandin signalling pathways and changes in the concentration of prostaglandins in uterine tissue. It is known that prostaglandins are important for the function of the uterus, such as implantation of the blastocyst. Therefore, hypothyroidism causes changes in the female reproductive system, leading to a weakening of uterine receptivity due to reduced oestradiol and progesterone levels (Kowalczyk-Zieba et al., 2021). In bitches with hypothyroidism, uterine contractions are longer during birth though the strength of the contractions is weaker. The perinatal mortality of puppies is significantly higher in litters of bitches with hypothyroidism (Panciera et al., 2007). In women with hypothyroidism, menstrual irregularities, infertility, miscarriages, stillbirths, premature births and low birth weight are possible. Very little is known about the effects of reduced thyroid hormone levels on the reproductive capacity of bitches. In bitches, hypothyroidism can lead to prolonged intervals, absent cycles, silent oestrus cycles, lack of libido and prolonged oestrus bleeding (Panciera, 2001). In hypothyroid bitches of the Russian Greyhound breed, infertility, a higher frequency of miscarriages,

stillbirths and mummified foetuses have been reported (Johnson, 1994). The results of experimentally induced hypothyroidism in bitches during reproduction over 19 weeks were prolonged parturition, reduced vitality of the pups, increased peripartum mortality and reduced birth weight, while fertility, cycle length and frequency of pregnancy remained unchanged. Prolonged hypothyroidism, lasting about a year, would lead to infertility, though this is treatable with thyroid hormone therapy (Panciera et al., 2012). During pregnancy, numerous hormonal changes and metabolic demands occur, leading to complex changes in maternal thyroid function. Despite these changes in thyroid function, a normal pregnancy is considered a euthyroid state. Pregnancy is a state of dynamic metabolic changes with an accumulation of lipids and nutrients in the first half of pregnancy. In late pregnancy and during breastfeeding, the accumulated reserves are used for the growth of the foetus and subsequently for milk production. Thyroid hormones strongly influence these processes. Pregnancy increases maternal thyroxine requirements, so that maternal thyroxine production increases by 25% to 50% in euthyroid women. Thyroxine concentrations increase by the end of the first trimester due to the increase in serum concentrations of globulin, which binds thyroid hormones. In humans, the placenta produces large amounts of human chorionic gonadotropin, which has similar bioactivity to thyrotropin (Kimura et al., 1990) and provides sufficient progesterone to maintain pregnancy. In dogs, progesterone increases continuously after ovulation and peaks around the 20th to 30th day of gestation. The corpus luteum is the main source of progesterone during pregnancy in dogs, as the placenta does not release progesterone (Thuróczy et al., 2016). Serum T4 concentrations are higher in pregnant and non-pregnant bitches than in bitches with abortions. In the third week of gestation, when progesterone concentrations began to decrease in bitches with an abortion, serum T4 concentrations also decreased and remained below the physiological range until the end of the abortion. In the second half of gestation, the thyroid gland was unable to respond to the increased demand for thyroid hormones, although there were no clinical signs of hypothyroidism. This phenomenon led to abortion in bitches with hypothyroidism (Thuróczy et al., 2016). In several studies, thyroid hormone concentrations were determined during pregnancy in bitches. Reimers et al. (1984) were the first to investigate the effects of T3 and T4 concentrations on the reproductive system. Although a small number of animals were involved, the study showed that the concentrations of total thyroxine (tT4) were elevated in pregnant and non-pregnant bitches in dioestrous. More recent studies found that tT4 concentrations were significantly higher during oestrous and dioestrous than during proestrous and anoestrous (Cardinali et al., 2017; Thuróczy et al., 2017), and TSH was also found to be higher during pregnancy (Cardinali et al., 2017). It was also found that the concentrations of total thyroxine (tT4) and free thyroxine (fT4) were highest during early pregnancy and the levels of tT4 and fT4 were lowest during lactation. The highest TSH concentration was found during lactation, indicating the greatest need for thyroid hormones during lactation (Hinderer et al., 2023). Bitches with hypothyroidism experience galactorrhea, which manifests as increased milk production and occurs in response to pregnancy or pseudopregnancy (Figure 3) (>90 days post-oestrous). Hyperprolactinemia is thought to be the cause of galactorrhea in hypothyroid bitches, as it is released in

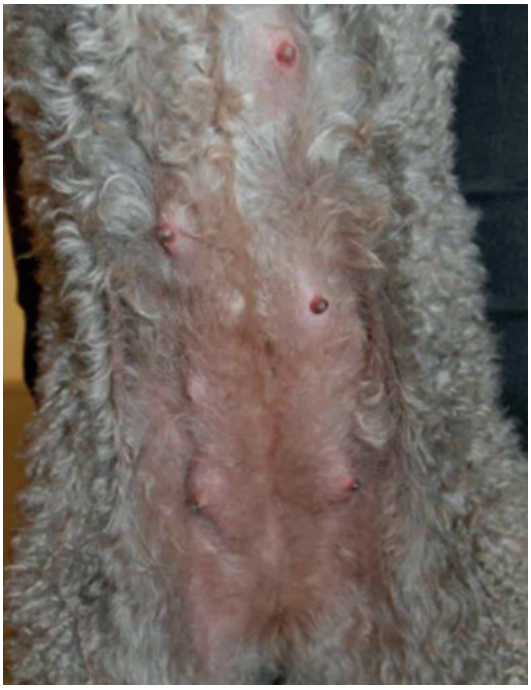

Figure 3. Pseudopregnancy and galactorrhea, taken from https://snl.no/pseudograviditet

response to TRH. In hypothyroidism, the lack of negative feedback from thyroid hormone to TRH leads to increased secretion of TRH by the hypothalamus and subsequent stimulation of the release of prolactin from the pituitary gland (Panciera, 2001).

The influence of hypothyroidism on the male reproductive system

Male reproductive problems due to hypothyroidism include low libido, testicular atrophy, hypospermia and azoospermia. Reduced testicular size, infertility or sterility have been reported in Beagles with thyroiditis and orchitis (Fritz et al., 1976). However, a prospective study of six male Beagles (small sample size) with ^{131}I-induced hypothyroidism showed no reduction in libido or sperm quality over a two-year period (Johnson et al., 1999). For many years, hypothyroidism has been recognised as a cause of reduced fertility or infertility in dogs, especially in large breeds. Reduced fertility, poor semen quality, testicular atrophy and reduced libido have been suspected in hypothyroid dogs, but have not been proven (Panciera, 2001). However, Johnson et al. (2002) reported that hypothyroidism reduces libido, semen quality and ejaculate volume in male dogs. Hypothyroidism is associated with teratozoospermia, or pathological forms of sperm in the ejaculate. Hypothyroidism reduces sperm vitality, slows sperm transfer through the epididymis and reduces the effectiveness of antioxidant defence mechanisms, which impairs sperm quality, maturation and motility and leads to oxidative stress (La Vignera and Vita, 2018; Ahmed et al., 2019).

Hyperthyroidism

Hyperthyroidism is characterised by excessive production of thyroid hormones, which can have a significant impact on animal health. Although hyperthyroidism is most common in cats, it can also occur in other animals, including dogs. Hyperthyroidism in dogs is extremely rare and is usually the result of a thyroid cancer that produces excessive amounts of thyroid hormones (Mooney and Peterson, 2004). Thyroid cancer is rare and occurs in less than 3% of cases. Other causes of increased thyroxine concentrations in dogs include overtreatment with levothyroxine (Feldman et al., 2015), discontinuation of T4 synthesis blockers (Frank et al., 2005) and thyroid trauma (Rau et al., 2007). Iatrogenic hyperthyroidism can occur from the overuse of levothyroxine to treat hypothyroidism in dogs, and nutritional hyperthyroidism can occur in dogs fed raw food containing excessive amounts of thyroid tissue. Falsely elevated thyroxine concentrations are possible with anti-thyroxine antibodies that interfere with specific immunoassays (Choi et al., 2006) or with prolonged storage of serum at high temperatures (Behrend et al., 1998). Hyperthyroidism is a relatively common endocrine disorder in cats and usually affects middle-aged and older cats. Hyperthyroidism has been diagnosed in cats as young as 4 years, though 95% of cats are older than 8 years and 90% are older than 10 years at the time of diagnosis (Feldman and Nelson, 2015). A functional thyroid adenoma or adenomatous hyperplasia affecting one or both lobes of the thyroid gland (Figure 2) is the most common abnormality associated with hyperthyroidism in cats (Peterson, 2012).

The influence of hyperthyroidism on the female reproductive system

Hyperthyroidism can significantly affect the female reproductive system and lead to a range of reproductive disorders. The effects are primarily due to increased levels of thyroid hormones, which can disrupt normal physiological processes. Hyperthyroidism leads to increased levels of thyroid hormones, resulting in a disruption of the physiological balance of reproductive hormones such as LH and FSH. An imbalance can lead to irregular oestrous cycles, anovulation and reduced fertility. Hyperthyroid females often suffer from oligomenorrhea (irregular cycles), or amenorrhea (absence of cycles), which is usually due to changes in hormonal signalling (Silva et al., 2018). Anovulation is a condition in which ovulation does not fully occur, leading to infertility. Hyperthyroidism has been shown to reduce the levels of LH and FSH that are crucial for ovulation (Wei et al., 2018). Studies on the effects of hyperthyroidism on the development of the female reproductive system have shown controversial results in mice and rats. Low doses of thyroid hormones administered to young female mice resulted in earlier vaginal opening and earlier onset of the oestrous cycle (Longcope, 2000). In contrast, high doses of T4 administered to newborn female rats delayed vaginal opening and the onset of oestrous (Choksi et al., 2003). An elevated level of thyroid hormones impairs the physiological function of the ovaries. Hyperthyroidism can lead to a decrease in ovarian weight and a reduction in the number of normal follicles, with an increase in the number of atretic follicles (Wei et al., 2018). Thyroid hormones, especially T3, have a function in the maturation of ovarian follicles. Higher T3 levels influence the expression of genes involved in follicle development, possibly leading to changes in the secretion of hormones such as progesterone and oestrogen from the ovaries. Elevated thyroid hormones levels can lead to increased secretion of

progesterone and oestrogen. Hyperthyroidism is associated with increased plasma oestrogen levels. This increase may be the result of increased synthesis and decreased secretion of oestrogen, leading to disruption of the sexual cycle and possible fertility problems (Choksi et al., 2003). Hyperthyroidism can cause significant changes in the uterus. The secretory activity of the fallopian tubes increases and leads to a thickening of the endometrium and myometrium, making the uterine wall thicker. Structural changes in the fallopian tube epithelium can increase the risk of complications during pregnancy and childbirth and affect the health of the mother and foetus (see review by Silva et al., 2018). Hyperthyroidism during pregnancy can lead to several serious complications affecting maternal and foetal health. Pregnant animals with hyperthyroidism have a higher risk of miscarriage and premature birth, especially if the hyperthyroidism is not treated (see review by Petca et al., 2023). Maternal hyperthyroidism is associated with low birth weight of the offspring due to foetal growth retardation. Intrauterine growth retardation may occur, leading to long-term health problems in offspring. Elevated thyroid hormones levels can lead to developmental problems in the foetus, including underdeveloped reproductive organs and other systemic problems. The above changes can have long-term effects on the reproductive health of offspring, potentially leading to infertility (see reviews by Choksi et al., 2003; Silva et al., 2018). In addition, hyperthyroidism can lead to developmental disorders of the foetal brain and other organs, potentially resulting in long-term health problems for offspring. However, it is important to note that the long-term consequences of hyperthyroidism on the development of offspring are not yet fully understood and further research is needed (Andersen and Andersen, 2021).

The influence of hyperthyroidism on the male reproductive system

Unlike hypothyroidism, hyperthyroidism is relatively rare in animals, but it can also have various effects on the male reproductive system and fertility. The main effects of hyperthyroidism on male fertility include changes in sperm quality, spermatogenesis disorders and changes in hormone levels. Hyperthyroidism can cause a significant imbalance of sex hormones in male and is associated with increased levels of sex hormone-binding globulin, which binds to sex hormones, particularly testosterone, reducing the amount of free (bioavailable) testosterone in the body. In men, hyperthyroidism causes gynecomastia, which is a result of an increased oestrogen-androgen ratio, increased androgen-to-oestrogen conversion, increased levels of sex hormone-binding globulin in the serum, and increased levels of testosterone and/or progesterone (see review by Choksi et al., 2003). Hyperthyroidism is associated with a decrease in semen volume, density, motility and pathological sperm forms, and can lead to hypospermia (decreased sperm volume), oligozoospermia (decreased sperm count), asthenozoospermia (decreased sperm motility) or teratozoospermia (pathological forms of sperm). These changes are probably the result of direct effects on sperm and indirect effects on the non-germinal cells in the testicles (see reviews by La Vignera and Vita, 2018; Alahmar et al., 2019). Hyperthyroidism can also cause structural damage to testicular and epididymal tissue, including fluid accumulation and cell destruction. It can also inhibit Sertoli cell proliferation and alter Leydig cell function, further impairing normal spermatogenesis. Impor-

tantly, many of these changes are reversible when thyroid hormone concentrations are brought into the reference range with appropriate treatment (Krajewska-Kulak and Sengupta, 2013; Shi et al., 2023).

Diagnostics

Thyroid dysfunction may be suspected on the basis of the patient's medical history and clinical symptoms. The measurement of thyroid hormones in blood serum is the first diagnostic method used when thyroid disease is suspected (Scott-Moncrieff, 2015). As in most animal species, T4 concentrations provide more reliable information than T3 concentrations (Panciera, 1999). Another indicator of thyroid function is the concentration of TSH in the blood serum. Common clinical signs of hypothyroidism include lethargy, weight gain, cold intolerance and dermatological changes such as hair loss and dry skin (Figure 4) (Engelking, 2012). In terms of reproduction, hypothyroidism can lead to infertility, irregular oestrous cycles and lower litter survival in females, as well as decreased libido and testicular atrophy in males. Thyroid function testing should include an analysis of serum total and free thyroxine, serum TSH levels and serum anti-thyroglobulin autoantibodies (TGAA). In true hypothyroidism, serum total thyroxine and free thyroxine are decreased, TSH is increased and TGAA may be positive if immune-mediated lymphoplasmacytic thyroiditis is present. Definitive diagnosis of hypothyroidism requires histological examination and evaluation of the thyroid gland (Grundy et al., 2002).

Common clinical signs of hyperthyroidism include weight loss, increased appetite, hyperactivity and poor coat condition (Figure 5). In terms of reproduction, hyperthyroidism can lead to reduced fertility and irregular oestrous cycles (Engelking, 2012). The determination of T4 concentration in the serum is used to diagnose hyperthyroidism. The concentration of thyroxine in healthy cats is between 1 and 4.5 μg/dL (Feldman et al., 2015), and an increased concentration indicates hyperthyroidism. In cases where hyperthyroidism is suspected and the thyroxine concentration is within the reference values, the concentration of free thyroxine in the blood is measured (Ajitkumar and Praseeda, 2020). Moni-

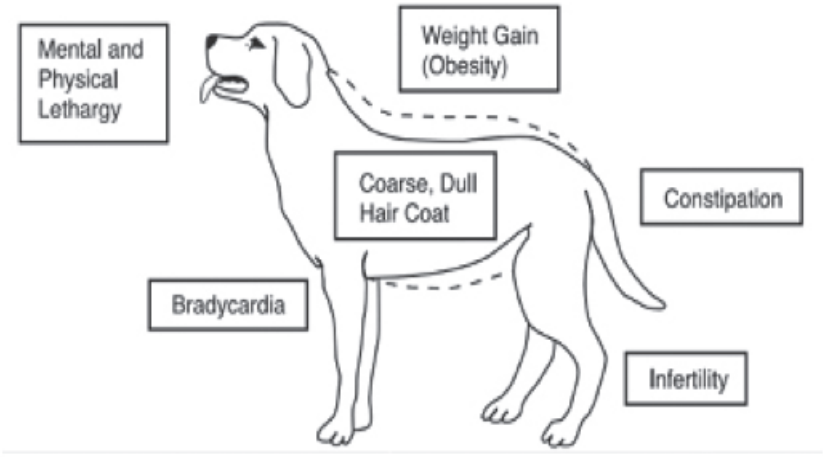

Figure 4. Clinical picture of hypothyroidism (Engelking, 2012)

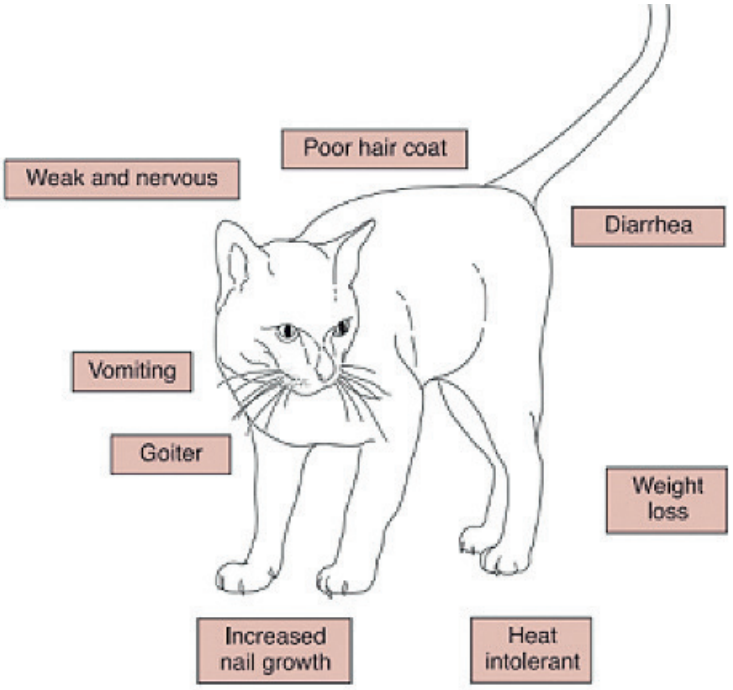

Figure 5. Clinical picture of hyperthyroidism (Engelking, 2012)

toring T4 levels in adult cats is common and therefore some cats have high T4 levels without clinical signs of hyperthyroidism. In this situation, the T4 concentration should be checked again after 2 weeks to rule out a false positive result. If the T4 concentration is again high, treatment is probably warranted due to the morbidity associated with untreated hyperthyroidism (Heseltine, 2024a). In human medicine, various imaging techniques are currently used to diagnose thyroid disorders, each with advantages and disadvantages. Reports on the clinical application of diagnostic imaging in canine thyroid pathology are rare. Most relate to the use of ultrasound and scintigraphy in thyroid cancer. Advances in other imaging modalities make them potentially useful as additional tests in the diagnosis of thyroid disease in veterinary medicine (Taeymans et al., 2007).

Treatment

Only animals that have undergone appropriate testing and in which all other possible causes of infertility have been ruled out should be treated. Hypothyroidism is treated with the administration of levothyroxine. A medical history with appropriate diagnostics, ultrasound examinations of the reproductive system, tests for infectious diseases, a complete blood count and biochemical profiles are mandatory before treatment is started. Intrauterine cytology, culture and/or biopsy should be performed in early proestrous. Levothyroxine usually leads to hyperthyroidism in females,

so therapy should only be prescribed if there is a valid reason. Once daily oral treatment with levothyroxine (0.02 mg/kg) (Dixon et al., 2006) is sufficient for hormone replacement. Breeders often require levothyroxine supplementation long before a clear cause is identified. Treatment options for hyperthyroidism include medications such as methimazole, radioactive iodine therapy, surgery, or a low iodine diet. Methimazole is effective but requires regular monitoring of the patient due to possible side effects that may affect reproductive health. The dose of methimazole for oral administration is 1.25 to 2.5 mg twice a day, and methimazole in gel form is used at a dose of 2.5 mg/24h or 5 mg/12h (Feldman et al., 2015). Therapy with radioactive iodine is considered the gold standard, as it selectively destroys overactive thyroid tissue and thus reduces the risk of reproductive disorders. Regular monitoring of thyroid hormone levels and reproductive function is essential to achieve optimal results and reduce negative effects on fertility (Heseltine, 2024b).

Conclusions

Thyroid hormones play a key role in the normal growth, development and function of the reproductive system. Timely diagnosis of autoimmune thyroiditis is crucial for the treatment of this hereditary disease. Thyroid hormones regulate the oestrous cycle and are necessary for ovulation and fertility in females. In males, they are involved in spermatogenesis and influence the quality of semen. Hypothyroidism, an underactive thyroid gland, can lead to fertility problems, miscarriages, smaller litter size and lactation problems in bitches. Hyperthyroidism, an overactive thyroid, can also have a negative effect on fertility and reproduction by reducing the levels of LH and follicle FSH, which are crucial for ovulation. Hypothyroidism and hyperthyroidism can significantly affect animal reproduction. Understanding the effects on reproduction is essential for managing breeding animals and ensuring their reproductive health. Timely detection, regular monitoring and appropriate treatment can mitigate the negative effects and improve reproductive outcomes.

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Hormoni štitaste žlijezde u reprodukciji ženki i mužjaka s posebnim osvrtom na pse i mačke

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Hormoni štitaste žlijezde imaju važnu funkciju u mnogobrojnim fiziološkim procesima u ljudi i životinja uključujući u regulaciji metabolizam, rasta i razvoj jedinke pa tako u reproduktivnoj funkciji. Hormoni štitaste žlijezde, trijodtironin (T3) i tiroksin (T4), imaju izravan učinak na reproduktivne organe i neizravan u interakciji s drugim hormonima. Hormoni štitaste žlijezde utječu na reproduktivni sustav regulirajući metabolizam i razvoj tkiva jajnika, maternice i posteljice. Promjene u serumskim koncentracijama T3 i T4 dovode do poremećaja u radu cijelog organizma. Disfunkcija štitaste žlijezde, uključujući hipotireozu i hipertireozu, može dovesti do znatnih reproduktivnih problema. Stoga je cilj ovog preglednog rada opisati funkcije hormona štitaste žlijezde te prikazati učinke hipotireoze i hipertireoze na reproduktivni sustav životinja. Hipotireoza, često prouzročena autoimunim bolestima, poput limfocitnog tireoiditisa, povezana je s kasnijim spolnim sazrijevanjem, smanjenom plodnošću i poremećajima u razvoju reproduktivnih organa. Hipotireoza može prouzročiti: produljeni interstrusni interval, izostanak ciklusa, tihe estrusne cikluse, produljeno estrusno krvarenje i nedostatak libida uz pojavu neplodnosti, pobačaja, mrtvorođenosti i mumificiranih fetusa. U mužjaka hipotireoza dovodi do: smanjenja libida, kvalitete sjemena, volumena ejakulata, atrofije testisa, hipospermije i azoospermije. Nasuprot tome, hipertireoza je najčešće posljedica karcinoma štitaste žlijezde koji proizvodi prekomjerne količine hormona štitaste žlijezde. Povećane koncetracije hormona štitaste žlijezde dovode do poremećaja fiziološke ravnoteže reproduktivnih hormona, nepravilnih estrusnih ciklusa, anovulacije i smanjene plodnosti te smanjenja mase jajnika i broja normalnih folikula s povećanjem broja atrezirajućih folikula. Učinci hipertireoze na plodnost mužjaka uključuju: poremećaje u spermatogenezi, promjene u razinama spolnih hormona i promjene u kvaliteti sjemena, poput hipospermije, oligozoospermije, astenozoospermije i teratozoospermije. Važno je naglasiti važnost pravovremene dijagnoze i liječenja poremećaja štitaste žlijezde da bi se spriječili negativni učinci na plodnost i reprodukciju životinja.

Ključne riječi: *hormoni štitaste žlijezde, reproduktivni sustav, hipotireoidizam, hipertireoidizam*