Melatonin on hypothyroidism and gonadal development in rats: a review

Yuri Mateus Lima de Albuquerque1, Welma Emídio da Silva1, Francisco de Assis Leite Souza1, Valéria Wanderley Teixeira1, Álvaro Aguiar Coelho Teixeira1

1 Departamento de Morfologia e Fisiologia Animal, Universidade Federal Rural de Pernambuco- PE, Brazil

ABSTRACT

We evaluated the evidence in research on the effects of melatonin on hypothyroidism and gonadal development. According to the World Health Organization, thyroid disorders due to iodine deficiency affect about 740 million people worldwide. Hypothyroidism is a thyroid dysfunction characterized by hypometabolism of the gland, with reduced or physiologically normal T3 and T4 serum levels, and high TSH level. This disorder occurs mainly in adult women in the reproductive phase, with a prevalence of 2% among the world's female population, with profound repercussions on gestation and fetal formation. During the gestational period, the thyroid is initially stimulated by high concentrations of human chorionic gonadotrophin; thus, maintaining maternal euthyroidism during pregnancy and lactation is fundamental for fetal growth and development. Besides, the hormones produced by this gland are involved in the formation of various organs, such as the skin, brain and gonads. Hypothyroidism is associated with several menstrual abnormalities, anovulation and hyperprolactinemia, resulting in a high rate of abortions, premature births, placental rupture, and weight-related neonatal deficits. In addition, there are studies showing that hypothyroidism can affect ovarian morphology (number of ovarian follicles) and testicular morphology (changes in the testicular-lumen epithelium). Melatonin is a hormone known to modulate the estrous cycle and pregnancy, and studies show that the exogenous application of melatonin increased T4 levels in the estrous cycle and pregnancy, and studies show that the administration of exogenous melatonin reverses signs of hypothyroidism in hypothyroid rats with the administration of exogenous melatonin (Bondarenko et al., 2011).

This review summarizes the connection between melatonin with hypothyroidism and gonadal embryogenesis.

LITERATURE REVIEW

Thyroid

The thyroid gland weighs 20 grams on average in the human species, and 40 milligrams in rats. It comprises two lobes and an isthmus that unites them. In addition, the pyramidal lobe, which may originate from one of the lobes or from the isthmus itself, is present in 12-65% (Soukup et al., 2001; Ayadi et al., 2017; Kaklamanos et al., 2017). While each lobe is 4-5 cm high, 2-3 cm wide and 2-4 cm thick, the lobes are usually located between the first and fourth tracheal rings. Left and right lobes partially surround the front trachea. Laterally, there is the carotid sheath and the sternocleidomastoid muscle (Menzilcioglu et al., 2016).

The thyroid gland in humans develops from the neural crest and the primitive pharynx, assuming its position still attached to the thyroglossal duct. The thyroid is one of the first endocrine glands to become active in humans, being composed of thyroid follicles, formed by cubic epithelial cells, the thyrocytes (Menzilcioglu et al., 2016). Thyrocytes have polarity: the basal zone is related to the interstitial connective tissue, where the vessels and nerves pass, while the apical pole points to the light of the follicle. The apical zone has pseudopods that play a fundamental role in capturing the elements of the colloid, hormonal synthesis and its release (Chastain & Ganjan, 1986).

The thyroid by through the TSH stimulation (thyroid stimulating hormone) synthesizes thyroxine (T4) and triiodothyronine (T3) hormone, regulating the body's metabolism, of fundamental importance in embryogenesis (Menzilcioglu et al., 2016). However, unlike humans, in which thyroid hormones are secreted even in the first trimester of gestation (Smallridge & Lendenson, 2001), in rats the development of the thyroid is slower, becoming active and producing the thyroid hormones around the 17th day of gestation (Choksi et al., 2003), making the rodents’ fetuses’ embryogenesis dependent on maternal thyroid hormones.

After birth, the thyroid and the hypothalamic-pituitary-thyroid axis in rats are immature compared to humans. During the first 21 postnatal days, this gland grows due to increased colloid deposition and follicular cell proliferation, which remains constant from birth until the 21st day of life, reducing after that period (Parker & Picut, 2016). Histologically, throughout the postnatal period in rats, the thyroid follicles tend to be wider at the periphery of the gland, representing a progression in follicle maturation from the center to the periphery. Rats’ thyroids fully develop on the 21st postnatal day, but becomes

INTRODUCTION

The World Health Organization (WHO) stated that approximately 740 million people worldwide suffer from thyroid disorders due to iodine deficiency (Abalovich et al., 2002). Hypothyroidism is a pathological condition of thyroid hormone deficiency that can lead to serious adverse health effects. Hypothyroidism is divided into two different biochemical types: overt, where the thyroid-stimulating hormone (TSH) concentrations are above the reference range and free thyroxine concentrations below regular range or subclinical, where although the TSH concentrations are above the reference range, free thyroxine concentrations are within the normal range (Chaker et al., 2017). This disorder is present in 2% of the world’s female population (Hapon et al., 2010), interfering directly in gestation and fetal formation (Maciel & Magalhães, 2008).

A hormone that plays a regulatory role in the pregnancy and thyroid physiology is melatonin. This hormone modulates the estrous cycle and pregnancy (Maganhin et al., 2013) and reverses signs of hypothyroidism in hypothyroid rats with the administration of exogenous melatonin (Bondarenko et al., 2011).
endocrinologically complete only on the 28th postnatal day (Parker & Picut, 2016). In addition to follicular cells, the thyroid gland contains the C cells, which produce calcitonin. These cells become visible in a light microscope around the 21st postnatal day, having a low mitotic activity until the 42nd postnatal day. It is reported that from birth to the 120th postnatal day in rats, the number of C cells increases nine fold, and their size increased by up to four times (Parker & Picut, 2016).

Its sexual dimorphism in rats becomes apparent around the 40th postnatal day, in which the male gland has less colloid than in females, and its cells have cytoplasmic vacuoles (Parker & Picut, 2016). This dimorphism is due to the male follicular epithelium synthesizing the androgen hormone through the TSH feedback, where the levels of this hormone are lower in male rats until the 21st postnatal day (Banu et al., 2002).

**Hypothyroidism**

Hypothyroidism is a common thyroid dysfunction, characterized by hypometabolism of the gland, and it can be identified as overt hypothyroidism when T3 and T4 serum levels are reduced, and the TSH level is elevated (Welsh & Soldin, 2016; Feldt-Rasmussen & Klose, 2016); or as subclinical hypothyroidism, when serum levels of T4 and T3 are physiologically normal, and TSH levels are elevated (Shizuma, 2016).

Thyroid disorders represent a major public healthcare problem worldwide, following diabetes as the most common endocrine disorder in adult medical practice, and presenting a myriad of devastating consequences if not treated in advance (Vanderpump, 2011). The epidemiology and clinical features of thyroid disease are determined by the supply of iodine, an essential element in the synthesis of thyroid hormones. In addition, excessive variations in iodine levels may represent adverse health effects (Brotfain et al., 1992). However, the placenta, in addition to expressing receptors for thyroid hormones (Leonard et al., 2001), accumulates and metabolizes T3 and maternal T4 (Calvo et al., 1992). Thus, thyroid dysfunctions are associated with several ovarian and placental morpho-functional changes with impaired reproductive efficiency (Choksi et al., 2003).

Hypothyroidism is common in adult and reproductive women, with a prevalence of 2% in the worldwide female population (Hapon et al., 2010). The incidence of hypothyroidism during pregnancy is between 0.3% and 2.5% (Idris et al., 2005), having profound repercussions on gestation and fetal formation (Maciel & Magalhães, 2008). During gestation, the thyroid is initially stimulated by high concentrations of human chorionic gonadotrophin (hCG); thus, maintaining maternal euthyroidism during gestation and lactation, which is critical for fetal growth and development (Maciel & Magalhães, 2008), since the hormones produced by this gland are involved in the formation of organs such as the skin (Amerion et al., 2013), brain (Morreale de Escobar et al., 2004) and testis (Wagner et al., 2008) of the fetuses. Hypothyroidism is associated with several menstrual abnormalities, anovulation and hyperprolactinemia (Sanyal & Raychaudhury, 2016), resulting in a high rate of miscarriages, premature births, placental rupture, and weight-related neonatal deficiencies (Amerion et al., 2013).

Adaptive changes in the maternal thyroid occur during gestation, in response to the need to provide the fetus with T3 and T4 until the fetal hypothalamic-pituitary-thyroid system is functional. For this, the maternal thyroid increases in volume, as well as its uptake of iodide (Versloot et al., 1997). In addition, estrogen levels stimulate the expression of TBG (thyroxine binding globulin) in the liver and almost double their serum concentration. The serum increase of TBG occurs concomitantly with the increase of total serum concentrations of T3 and T4 (Karabinas & Tolis, 1998).

The main function of T3 is to regulate cell carbohydrates and proteins metabolism. Thus, changes in T3 plasma levels can affect all organs and organ systems, with important effects on the cardiovascular, nervous, immune and genital systems (Choksi et al., 2003). T3 levels in laboratory rodents influence the control of the estrous cycle, behavior, maintenance of pregnancy, fetal growth and lactation (Vasudevan et al., 2002). The deiodinases, proteins responsible for the activation of thyroid hormones present in human and rodent placentas rapidly metabolize maternal T4 to T3, which will be used by the fetus, with a significant amount of T4 also being transferred (Chan & Kilby, 2000). The placenta is freely permeable to iodine and thyrotropin releasing hormone (TRH), but not to TSH. We believe that maternal TRH transferred to the fetus may play an important role in the control of fetal thyroid function before complete maturation of the hypothalamic-pituitary-thyroid axis.

The authors reported that rat gestations induced to hypothyroidism is prolonged, lasting about 24 days, and generating on average nine pups per gestation, number
smaller than that of the control group average, which are usually of 12 pups. In addition, rats with low levels of thyroid hormones exhibit higher levels of progesterone at the end of gestation, as well as lower levels of estrogen and litters with lower weights when compared to data from control groups (Hapon et al., 2003). Another observed effect relating this dysfunction to gestation is the prolongation of corpus luteum function in pregnant rats (Hapon et al., 2007), where there is a reduction in the proliferation, apoptosis and expression of angiogenic factors in the corpus luteum of pregnant rats (Silva et al., 2014).

Induced hypothyroidism compromises the placental layers of the rat, and it increases glycogen cell population in the spongiotrophoblast layer relative to the cytrophoblastic cells, and interfere with the vascular development of the placental labyrinth, thus reducing proliferative activity and cellularity, and increasing the apoptotic rate of the three layers of the placental disc (Silva et al., 2012). This morphological alteration caused by such dysfunction may also cause low body weight of the litters of rats induced to hypothyroidism, this is because there is a reduction in the area occupied by fetal capillary in the placental labyrinth at 14 days of gestation, and may be insufficient to establish with maternal blood, causing low fetal weight (Silva et al., 2012).

Thus, a state of clinical or subclinical hypothyroidism may be worsened by the pregnancy state, and adequate function of the mammary glands may be impaired. The impact on mother and offspring is well documented, and one of its most pronounced consequences is delayed growth and delayed maturation of the newborn, causing mental retardation and subnormal height. Although most of these effects are attributed to the hypothyroid state of infants, any change in maternal metabolism that could lead to decreased milk production or excretion could further complicate offspring development (Hapon et al., 2003).

**Gonadal embryology**

Gonad development has two phases. The initial phase has the appearance of the so-called indifferent, bipotential gonad or genital crest, which is identical in males and females. The cell lines that compose it are bipotential, being indifferent to sex, and consists of an external cortex and a light yellow stain. It is transported through the placental disc (Silva et al., 2012). This morphology is maintained mainly by a significant increase in the tubular diameter between the PNDs 21 to 30 holds the maintenance of the medulla, as well as lower levels of estrogen and litters with lower weights when compared to data from control groups (Hapon et al., 2003). Another observed effect relating this dysfunction to gestation is the prolongation of corpus luteum function in pregnant rats (Hapon et al., 2007), where there is a reduction in the proliferation, apoptosis and expression of angiogenic factors in the corpus luteum of pregnant rats (Silva et al., 2014).

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In embryos with testes determining factors, the primitive sex chords proliferate and penetrate the medulla forming the testicular cords. Some of these cells differentiate into Sertoli cells, while the remaining form the seminiferous tubules. The testicular cords anastomose to form the rete testis, which becomes continuous with 15 to 20 persistent mesonephric tubules, the efferent duct. The testes determining factor also induces the differentiation of mesenchymal gonadal cells into interstitial Leydig cells (Mitchell & Sharma, 2009). We believe that Sertoli cells act as the organizing center of the male gonad, and orchestrate the differentiation of all other cell types (Wilhelm et al., 2007).

In PND 3, the testes consist of gonocyte-coated tubules and mitotically active Sertoli cells. In PND 15, spermatogonia are still mitotically active and spermatogonia reach the maximum density forming a thick pseudo-stratified layer with Sertoli cells. The mitotic rate in the population of spermatogonial cells decreases compared to that of the early childhood period (PND 3), and apoptotic spermatogonia are present in the center of the tubules. The period between the PNDs 21 to 30 holds the maintenance of the first wave of spermatogenesis in rounded spermatids, and mainly by a significant increase in the tubular diameter (Picut et al., 2015b).

**Melatonin**

The pineal gland produces and secretes melatonin and other peptides still poorly defined, through the release of noradrenaline (NE) by intraparenchymal nerve fibers, where this release and activity of the pineal gland are activated in dark environment and inhibited by light (Maganin et al., 2009; Junqueira & Carneiro, 2013). Also known as N-acetyl-S-methoxytryptamine, melatonin derives from the serotonin that has tryptophan as the precursor, and is the main product of the pineal, exhibiting high solubility and a light yellow stain. It is transported through the plasma connected to proteins such as albumin (Sumaya et al., 2005; Maganin et al., 2008).

With specific receptors in cell membranes (MT1 and MT2), melatonin has several functions as modulating the circadian cycle of antioxidant enzymes, bone metabolism, growth of ovarian follicles, ovulation, luteinizing hormone, fertilization and implantation (Tamura et al., 2009; 2014; Sharma et al., 2015). This hormone can also exert antioxidant functions, due to its small molecular size and its lipolipid properties, being able to cross all cell membranes and reach intracellular compartments, as well as the nucleus and mitochondria, organelles with high concentrations (León et al., 2005; Waseem et al., 2017), preventing damage to DNA (Sousa Coelho et al., 2018). The reduction in the occurrence and growth of tumors causes melatonin to be the most important natural oncostatic hormone in the human body (Reiter, 2004; Cabrera et al., 2010). We also believe that melatonin plays an important role during the life cycle, acting in growth, development, maturation and aging, decreasing its plasma concentration with the individual’s age (Tamura et al., 2009; 2014).
Melatonin is cited in several studies as an important part of the neuroendocrine system, influencing the control of circadian rhythms and controlling various physiological processes (Ferreira et al., 2010). The sites in which the interaction between melatonin and the endocrine system occur are still unclear. We believe that the activity of this hormone involves the hypothalamus, the pituitary, the gonads, and the pineal gland, the main one responsible for its production (Reiter, 1995).

**Melatonin and the gonads**

Melatonin is a broad-spectrum functional hormone responsible for regulating internal hormonal changes in response to variations according to periods of light and darkness (Mukherjee & Haldar, 2014). In photoperiodic species, melatonin secretion by the pineal gland is responsible for the effects of day length on the seasonal reproduction cycle (Maldonado et al., 2012). In these species, melatonin has a pro-gonadotrophic effect, increasing follicle-stimulating hormone (FSH) and luteinizing hormone (LH) peak concentrations, probably by blocking the inhibitory effects of sex steroids on ovulation (Rocha et al., 2011).

In species with non-seasonal reproduction, that is, non-photoperiodic, pre-ovulatory release of gonadotrophins is controlled by a circadian cycle. These species present a daily circadian rhythm of melatonin release (Claustrat et al., 2005). There are melatonin receptors, MT1 and MT2, in both male and female gonads of these species (Maganin et al., 2008; Mukherjee & Haldar, 2014), thus reaffirming its antigonadotropic properties, such as inhibition of gonadal development, spermatogenesis and androgen production in males and absence of follicles, corpus luteum and proliferation of interstitial tissue in females (Soares Jr et al., 2003).

Melatonin plays a significant role in fetal programming, since the follicular fluid has high concentrations of it, suggesting its direct participation in oocyte maturation and embryo development, due to its ability to reduce oxidative stress in the ovarian follicles and to protect these oocytes of free radical damage (Nelissen et al., 2011; Brzezinski et al., 1987). Melatonin levels in maternal plasma may increase during pregnancy, however, in compromised pregnancies, this hormone in the mother and fetus may be affected (Chen et al., 2013).

As for female gonads, the mechanisms that control folliculogenesis are still unclear; however, hormones and several growth factors are involved (Escames et al., 2012). Studies have demonstrated the presence of melatonin receptors (MT1 and MT2) in the ovarian follicles, thus supporting the hypothesis of its performance in ovarian physiology (Soares Jr et al., 2003; Lee et al., 2014). Regarding the male gonads, melatonin plays a protective role in testicular development both in vitro and in vivo, as well as regulates it by controlling the secretion of neurohormones (particularly GnRH) and testosterone (Li & Zhou, 2015).

According to Gholami et al. (2013), melatonin may improve the structure of testicular tissue. Such researchers have observed that this hormone can induce cell proliferation in normal cells and induce apoptosis in damaged cells (Gholami et al., 2014) (Niu et al. 2016); however, its addition to the spermatogenic stem cell (SSCs) culture medium could increase SSC proliferation by stimulating glial-derived neurethropilic factor (GDNF) production in the Sertoli cells. Furthermore, low levels of melatonin during pregnancy and lactation matrix results in an involution of the uterine offspring, indicating that their levels during pre and postnatal development interfere with testicular growth (Tuthill et al., 2005). We also know that pinealcystomy increases testicular weight, while administration of exogenous melatonin decreases the above-mentioned weight in non-pinealecotomized rats (Kuş et al., 2000; Akosman et al., 2013).

**Melatonin and thyroid**

There is a significant relationship between the thyroid and pineal glands, suggesting that deficiencies in thyroid function may alter the release of melatonin (Rom-Bogoslavskaja & Bondarenko, 1984). Hypothyroidism causes a significant decrease in plasma melatonin levels, when we compare rodents induced to it to healthy rodents. Rats induced to hyperthyroidism have higher levels of this indoleamine in plasma, suggesting a relationship between the thyroid disorders and the pineal gland (Belviranli & Baltaci, 2008; Baltaci & Mogulkoc, 2017; 2018). Likewise, Bondarenko et al. (2011) demonstrated that signs of hypothyroidism in rats with low levels of melatonin due to exposure to constant light were reversed with their exogenous application. Laskar et al. (2015) investigated the presence of receptors of this hormone in the thyroid gland, and reported that exogenous application of melatonin increased T4 levels in female rats. Their results were also found by Skipor et al. (2010) that, through the exogenous application of this indolamine, found a prevention in the decay of serum T3 levels and a control in the decay of T4 levels.

**Effects of hypothyroidism on morphometry and cell proliferation**

There are several studies showing that thyroid hormones affect spermatogenesis by promoting changes in basal metabolic activity and cellular respiration of the testes (Oppenheimer et al., 1987; Mutvel & Nelson, 1989; Fadalla et al., 2017), or by affecting Leydig cells, resulting in the reduction of testosterone secretion (Zirkin et al., 1980; Mendis-Handagama et al., 1991). In addition, in hypothyroid rats, testicular morphology is also affected, where there is a modification in the relation of the testicular-lumen epithelium, causing changes in lumen size (Ai et al., 2007).

Previous studies have shown that such a thyroid disorder can also affect ovarian morphology by altering the number of ovarian follicles (Meng et al., 2017). The transition from the primary to the secondary follicle (pre-antral stage) is controlled by intra-ovarian factors such as GDF-9 (Differentiation Factor and Growth-9) (McGrath et al., 1995; Onisaka et al., 2006). We know that the thyroid influences this mitogenic factor, although the mechanism is still not fully understood (Dong et al., 1996; Hayashi et al., 1999).

Along with morphological changes, we know that during pregnancy, in humans and rodents, the uterus undergoes a series of morphofunctional changes in order to accommodate the growing embryo, but the hypothyroid state decreases the proliferative rate of epithelial cells, stroma and myometrium by reducing the response of uterine cells to estrogen (Kirkland et al., 1981). In addition to this organ, hypothyroidism may also cause a decrease in the expression of proliferative antigens in placentas and testes of rats (Silva et al., 2012; Fadalla et al., 2017), thus showing the anti-proliferative effect of hypothyroidism.

**CONCLUSION**

This selective literature review supports the proposition that maternal hypothyroidism affects the development of the embryo, focusing specially on their gonads. As it is apparent from the studies hereby mentioned, melatonin may play a role in the protection of the effects of hypothyroidism in both mothers and their offspring, by preventing the decrease in thyroid hormone levels in rats, and reversing signs of hypothyroidism in rats. Additionally,
melatonin seems to interfere directly in the embryogenesis of both gonads, since there are receptors for this hormone in ovaries and testicles. In addition, it is still unclear how melatonin affects the ovaries. We know that in testicles, melatonin plays a protective role by stimulating normal cell proliferation, but it induces apoptosis on damaged cells. We hope that because of this paper the interest in the effects of hypothyroidism in the embryology of fetuses from hypothyroid mothers will increase, giving relevance to a disease that affects a growing number of females in reproductive ages, since studies on this topic are scarce.

CONFLICT OF INTERESTS
The authors declare that there are no conflicts of interest.

Corresponding author:
Yuri Mateus Lima de Albuquerque
Departamento de Morfologia e Fisiologia Animal
Universidade Federal Rural de Pernambuco
PE, Brazil.
E-mail: yuri.lima-de-albuquerque@insa-lyon.fr

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