

# Effects of melatonin and prolactin in reproduction: review of literature

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## SUMMARY

The pineal gland is responsible for producing a hormone called melatonin (MEL), and is accepted as the gland that regulates reproduction in mammals. Prolactin (PRL) also exhibits reproductive activity in animals in response to photoperiod. It is known that the concentrations of PRL are high in the summer and reduced during winter, the opposite of what is seen with melatonin in these seasons. In placental mammals, both prolactin and melatonin affect implantation, which is considered a critical point of pregnancy, since a successful pregnancy requires the development of a synchronous interaction between the endometrium and blastocyst for placental development. It is also known that PRL levels during pregnancy are essential for the maintenance of pregnancy, because this hormone induces the *corpus luteum* to produce progesterone, in addition to stimulating blastocyst implantation to maintain pregnancy and form the placenta. However, melatonin levels in plasma have also been shown to increase during pregnancy, peaking at the end of this period, which suggests that this hormone plays an important role in the maintenance of pregnancy. Thus, it is clear that treatment with prolactin or melatonin interferes with the processes responsible for the development and maintenance of pregnancy.

**Keywords:** pineal gland, pregnancy, progesterone, estrogens.

Study conducted at Universidade Federal Rural de Pernambuco, Recife, PE, Brazil

Article received: 5/11/2014

Accepted for publication: 6/15/2014

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<http://dx.doi.org/10.1590/1806-9282.61.03.269>

Conflict of interest: none

## PINEAL GLAND

The pineal gland develops from the roof of the diencephalon, behind the third ventricle, measuring approximately 8x4mm in adults, and weighing approximately 0.1 to 0.18g. It originates from an evagination from the roof of the diencephalon, acquires a cone-like shape, and is located in the epithalamic region between the posterior and habenular commissures. A small endymal recess from the third ventricle extends a short rod, which allows the connection of the pineal body to the roof of the diencephalon. It is almost completely surrounded by the *pia mater*.<sup>1</sup>

The pineal gland has a strong blood supply, and is the second organ (behind the kidney) with the highest blood flow in relation to tissue mass. The numerous capillaries within the parenchymal cells allow intense metabolic activity. The endothelium of the pineal is fenestrat-

ed. The blood supply is greater during the night, probably related to increased indole metabolism during these hours, that is, increased production of the hormone melatonin which is an indolamine. Removal of the superior cervical ganglion concomitantly decreases the metabolic activity of the gland and 2/3 of its normal blood flow. Most of this blood supply is provided by branches originating from the posterior choroidal arteries.<sup>2</sup>

The pineal differs from almost all of the brain by the absence of a blood-brain barrier, but resembles other periventricular glands, such as the median eminence, subfornical organ (SFO) and subcommissural organ (SCO), being derived from the endymal cells in the roof of the third ventricle.<sup>3</sup>

Histologically, its parenchyma consists of two types of cells: pinealocytes and neuroglia. The pinealocytes are predominant and are organized into strings resting on

the basal membrane, where they relate to the interstitial space. Two hormones are produced by pinealocytes: the indoleamines (predominantly melatonin – MLT) and peptides (such as arginine vasotocin). The latter hormone is a nonapeptide phylogenetically primitive and related to neurohypophyse hormones. Sympathetic innervation is essential for the regulation of the pineal function, consisting of noradrenergic fibers, originating in the sympathetic cervical ganglion and terminating in the interstitial space of the pineal gland or in the plasma membranes of the pinealocytes.<sup>1</sup>

The sympathetic nervous flow until the pineal gland is regulated, in turn, by impulses originating from the suprachiasmatic nucleus (SCN) of the anterior basal hypothalamus. This nucleus receives direct nerve stimulation from the retina (retinohypothalamic tract), which transmits information about light and darkness, regardless of conscious perception. Axons descend from the SCN that make synapses with autonomic neurons from the intermediolateral column of the upper thoracic spine. From there, the preganglionic axons leave the spinal cord, making synapses with the superior cervical ganglion neurons, where the postganglionic neurons that finally end in the pineal emerge.<sup>3</sup>

It is via this neural pathway that external light regulates pineal activity. Typically, during the day, light inhibits the production of the main hormone produced by the pineal, i.e. melatonin. Conversely, the production of melatonin is stimulated at night. Sectioning of the sympathetic innervation or the use of  $\alpha$ -adrenergic blockers inhibits the metabolic activity of the pineal cells.<sup>4</sup> Furthermore, the pineal also contains a series of biologically active substances that it either synthesizes or simply stores, and which will exercise their primary activities at a distance after being secreted. These include biogenic amines (norepinephrine, serotonin, histamine, melatonin and related indoleamines, dopamine and octopamine), peptides (luteinizing hormone-releasing hormone – LHRH, thyrotropin-releasing hormone – TRH, somatostatin and vasotocin) and gamma-aminobutyric acid (GABA).<sup>5</sup>

The most studied of these substances is melatonin. Sympathetic nerve endings in the superior cervical ganglion release norepinephrine in accordance with a circadian rhythm, which is related to the light-dark cycle in the environment, increasing secretion of the neurotransmitter during the dark phase. In melatonin biosynthesis, tryptophan is first converted by tryptophan hydroxylase into 5-hydroxytryptophan, which is decarboxylated into serotonin. Serotonin is acetylated into N-acetylserotonin, which is O-methylated, resulting in melatonin. The en-

zymes responsible for these two phases are arylalkylamine N-acetyltransferase (NAT) and hydroxyindole-O-methyltransferase (HIOMT).<sup>6</sup>

The NAT enzyme exhibits a robust daily rhythm, reaching concentrations 100 times higher than in the dark phase compared to daylight hours. The rhythm of the second enzyme is less evident, but HIMOT participates in seasonal regulation of melatonin production. This daily variation in the NAT enzyme causes reduced levels of serotonin in the dark phase to be accompanied by an increase in N-acetylserotonin and melatonin concentrations. Norepinephrine acts on Alpha1 and Beta1 receptors in the pineal gland, causing the activation of the key enzyme arylalkylamine N-acetyltransferase (or serotonin N-acetyltransferase), which determines the circadian production of melatonin.<sup>7</sup>

The two main metabolic pathways of melatonin occur in the liver and brain. Hydroxylation of melatonin takes place in the liver forming 6-hydroxymelatonin, followed by conjugation with sulphate or glucuronate, and subsequently being excreted in the urine. In brain tissue, melatonin is converted into N-gamma-Acetyl-N-2-formyl-5-methoxykynurenamine, suffering immediate degradation into N-acetyl-5-methoxytryptamine. Other minor metabolic pathways include the formation of N-Acetylserotonin and cyclic 2-Hydroxymelatonin, occurring in various cells. Although melatonin synthesis has been reported in other locations, such as intestines, uterus, ovary, brain, and blood cells, the study of the synthesis route in different species has been performed in the retina and pineal.<sup>8</sup>

Plasma melatonin reflects the melatonin synthesized in the pineal, while melatonin synthesized in the retina has a local action. Melatonin synthesis, both in the pineal and in the retina can be controlled by light.<sup>9</sup> In humans, melatonin secretion increases soon after the onset of darkness, with peaks in the middle of the night (between two and four in the morning), and gradually falls during the second half of the night. There are daily and seasonal modulations of a number of physiological processes which are related to melatonin. *Serum* concentrations of melatonin also vary considerably according to age.<sup>1</sup> It is maximal in the first years of life, falling immediately preceding puberty and becoming minimal with old age. Thus, it is postulated that melatonin also has an important role in determining the physiological changes associated with life cycle (growth, maturation and aging).<sup>9</sup>

It is known that in addition to the day/night light cycle, melatonin levels may also be affected by the pinealectomy process, which modifies the rate of secretion by abruptly suppressing its production. Exposure to pine-

alectomy inhibits the secretion of melatonin, and the process may be reversed when the animals are submitted to treatment with melatonin.<sup>9</sup>

There is evidence that through its secretions the pineal gland can interact with the hypophysis, modulating the release of its hormones. Some early studies have shown that stimulation of the activity of the pineal *in situ* inhibits the proliferation of hypophysary cells.<sup>4</sup> On the other hand, it has also been shown that hypophysectomy leads to atrophic changes in the pineal gland, suggesting a regulatory feedback of effect of hypophysis on the development and function of the pineal.<sup>8</sup> Most studies that correlate this gland relate to the development of sexual function, as well as the effects on the gonads, the pineal appears to interfere with the secretion of growth hormone and thyroid and adrenal functions through the hypothalamic-hypophysis-thyroid axis.<sup>10</sup>

## MELATONIN AND REPRODUCTION

Melatonin plays a major role in a variety of physiological functions, including regulation of circadian rhythms associated with visual, reproductive activities, cerebrovascular, neuroendocrine and neuroimmune actions.<sup>1</sup>

This hormone plays a critical role in reproductive activity and blastocyst implantation in a number of different mammalian species, including sheep, ferrets, horses, hamsters and rats.<sup>11,12</sup> Furthermore, maternal transfer of melatonin in mammals indicates that the daily photoperiod perceived by the mother during pregnancy or lactation is transferred to the fetus through the placenta or the milk.<sup>13</sup>

It is speculated that melatonin has the requisites to be considered an anti-estrogen drug, due to its interference with estrogen receptors. Furthermore, it acts in the synthesis of estrogen by inhibiting the aromatase enzyme that controls its interconversion from its androgenic precursors, altering the whole blastocyst implantation process and development of the follicle.<sup>14</sup>

Experimentally, melatonin prevents the growth and promotion of spontaneous or chemically induced mammary tumors in rodents. This effect has also been observed in cell cultures (*in vitro*). This hormone also inhibits the proliferation and invasiveness of cells during the blastocyst implantation process.<sup>15</sup>

Experimental studies with female rats and hamsters reported that removal of the pineal gland leads to a decrease in melatonin levels with consequent premature vaginal opening, ovarian hypertrophy, increased cornification of vaginal cells and chronic anovulation, effect that can be reversed after administration of melatonin.<sup>16,17</sup>

In contrast, according to Murcia-García et al., treatment with melatonin reduces the weight of ovaries and delays sexual maturation in rats.<sup>18</sup> Melatonin replacement is capable of reversing continuous and transitional anovulatory estrous cycle in rats caused by exposure to continuous light or due to the removal of the pineal. The reduction of melatonin can decrease embryo implantation, as well as interfere with pregnancy when rats are subjected to short photoperiods (8L: 16D – eight hours of light: sixteen hours of dark), showing an increase in melatonin levels accompanied by depressions in follicle stimulating hormone (FSH) and reduction in follicle development, becoming anestrus.<sup>19</sup>

According to Woo et al.,<sup>20</sup> the expression of receptors for melatonin MT1 and MT2 has been identified in human reproductive tissues, including the mammary epithelium, myometrium, ovary and granulosa-luteal cells. Furthermore, melatonin causes seasonal variation changes in the rates of fertilization, embryo quality, sperm concentration and chromatin condensation in sperm.<sup>21</sup> In females, the influence of melatonin on the reproductive function can be inferred from studies that indicate that high levels of melatonin cause amenorrhea,<sup>14</sup> decrease in gonadotropin secretion and the secretion of prolactin in response to the photoperiod.<sup>22</sup>

Melatonin also causes changes in the secretion of FSH and LH hormones which regulate gonadal function and activity,<sup>14</sup> as when pregnant ewes were maintained in constant light for 138 days (146 gestation days) there was a decrease in melatonin levels and increased metabolic activity in the reproductive organs. Moreover, pinealectomy associated with melatonin treatment in pregnant ewes changed the daily pattern of fetal breathing movements, suggesting that photoperiodic information provides the fetus with circadian variations through maternal melatonin.<sup>23</sup>

Studies have suggested that melatonin has a role in ovarian physiology, given that high concentrations of melatonin have been detected in follicular fluid.<sup>24</sup> Additionally, the presence of melatonin receptors in the follicular cells of rats and mice<sup>25,26</sup> suggests possible melatonin production in the ovary.<sup>27</sup> Its well-documented role as an antioxidant may be associated with follicular development and oocyte quality, interfering in processes such as oocyte maturation and ovulation.<sup>23</sup>

One of the hormonal factors thought to regulate follicular development is melatonin. Studies demonstrating the presence of its receptors (MT1 and MT2) in the follicle support the hypothesis of its role in ovarian physiology. However, there are still insufficient studies regarding the action of melatonin on folliculogenesis and little information about its activity in the initial, pre-antral phase.<sup>25,26</sup>

Adriaens et al.<sup>28</sup> observed that the use of 100  $\mu\text{M}$  of melatonin increased the production of androstenedione (A4) in the secondary follicles (100-130  $\mu\text{m}$  in diameter) of mice cultivated for 12 days, whereas the addition of higher doses of this hormone (2mM) was toxic to the follicle, reducing follicular viability.

In contrast, in a study aimed to evaluate the radioprotective ability of melatonin to prevent follicular atresia caused by  $\gamma$ -radiation,<sup>29</sup> using exogenous melatonin (100  $\mu\text{g}$ ) in mice, found a higher proportion of follicles in early stages of development (primordial and primary) compared to the irradiated group. The presence of melatonin in follicular fluid of pre-ovulatory human follicles has been detected at concentrations higher than those in serum.<sup>24</sup>

Thus, studies have shown that rats exposed to continuous light stimulation or pinealectomized present a drop in the amount of melatonin produced, leading to changes in the estrous cycle that prolong the estrous phase. However, the exogenous administration of melatonin in rats that were pinealectomized or exposed to continuous light regularized the cycle. In addition, a decrease has been observed in the level of follicle stimulating hormone (FSH) after pinealectomy with subsequent melatonin treatment, leading to impairment of follicular function and ovarian hormone production.<sup>30</sup>

## PROLACTIN AND REPRODUCTION

Prolactin (PRL) is a pleiotropic hypophysary hormone, best known for its luteotrophic actions in rodents. It is a 23-kD peptide synthesized and segregated by adenohypophysis lactotropic cells, and several other organs including uterine and placental decidual cells, lymphocytes and epithelial breast cancer cells. The gene encoding PRL is located on chromosome 6 and its expression is influenced by dopamine, estrogen and TRH (thyrotropin-releasing hormone).<sup>31</sup>

Prolactin is characterized by influencing and participating in reproductive activities such as stimulation of mammary gland development during pregnancy and regulation of postpartum lactation, and it may also influence the normal activity of glands like the prostate and the lacrimal gland, and provide proliferative stimulus for breast and prostate tumors.<sup>32</sup>

It is known that in addition to these functions, prolactin also governs the regulation of gonadal function, participating in steroidogenesis, *corpus luteum* formation and modulation of the effects of gonadotropins.<sup>33</sup> It has an anti-apoptotic effect in a number of cells including lymphomas and mammary epithelial cells, participates

in the transport of water through the fetal membrane, as well as the production and immunoregulation of ovarian steroids. Prolactin stimulates the production of milk during the postpartum period, stimulates the growth, development and metabolism of the fetus, and it is important for the degradation of the *corpus luteum* and decrease in levels of sex steroids during the menstrual cycle. In addition, prolactin stimulates the process of ovulation, implantation and placental development.<sup>34</sup>

It has recently been shown that prolactin may regulate genes in multiple ovarian events such as follicular development, since prolactin gene knockout mice showed smaller follicles and consequent reduction in ovulation, delayed release of the oocyte and impaired oocyte maturation.<sup>35</sup>

It is also known that there is a directly proportional relationship between prolactin and progesterone during gestation, with the cause of sterility in prolactin gene knockout mice being attributed, particularly, to the absence of sufficient progesterone for implantation, support and subsequent placental development and maintenance.<sup>36</sup>

The highest concentration of prolactin is detected in amniotic fluid, 10 to 100 times higher than the maternal or fetal serum. Probably the biggest source of prolactin into the amniotic fluid is the *decidua*. During lactation, prolactin levels should not exceed 200 ng/mL. If this occurs, other causes of hyperprolactinemia should be sought. These prolactin levels may remain high as long as the child is suckling.<sup>31</sup>

During fetal life and in newborns up to one week old, serum prolactin levels are greater than 200 ng/mL. Some children may have mammary secretions after birth, popularly called "witch's milk." This is due to loss of the inhibitory effect of estrogen and maternal progesterone. And the lactogenic effect of prolactin is exercised at its fullness. However, after a few weeks, this secretion disappears, and basal prolactin secretion decreases, reaching levels of 5 to 20 ng/mL by adulthood.<sup>35</sup>

In non-pregnant uteri, PRL synthesis has been detected at the peak of secretory and menstrual phases, coinciding with the first histological signs of decidualization. If pregnancy occurs, the number of differentiated decidual cells and the synthesis of decidual PRL increase after implantation, reaching a peak between 20 and 25 weeks, and stopping close to term.<sup>17</sup> Jabbour and Critchley<sup>37</sup> confirmed the expression of the PRL receptor (PRL-R) in the endometrium and *decidua*. Immunohistochemical and *in situ* hybridization methods have revealed that PRL-R is expressed strongly by the glandular epithelium and the stromal cells of the decidualized endometrium. It is minimally expressed or absent in proliferative and initial secretory phases.<sup>38</sup>

Stewart et al.<sup>39</sup> studied PRL-R in the endometrium of sheep during the estrous cycle, and concluded that endometrial PRL secretion stimulates the development and function of the endometrial glands during pregnancy, to facilitate the implantation and placentation of the conceptus.

Negami and Tominaga<sup>40</sup> reported the effects of PRL in cultured human endometrial cells (stromal and epithelial cells) and discussed their role in implantation. In summary, they reported that PRL at low concentrations (3 to 30 ng/mL) increases the binding to its receptors and the growth of endometrial cells.

Rossi et al.<sup>32</sup> showed that mice subjected to hyperprolactinemia, provided that they continued presenting estrous cycles, presented the most proliferated and thickened endometrium in the morphological analysis during the diestrus phase. However, Pazan et al.<sup>41</sup> showed that hyperprolactinemia causes a decrease in progesterone production and the number of pinopods in the endometrium adult rats. They also verified that there was a decrease in the number of embryonic implantations in rats with hyperprolactinemia. Possibly, in both cases, prolactin could determine cell proliferation by gene activation or blocking the cell signal of cell differentiation.

## CONCLUSION

Thus, it is clear that treatment with prolactin or melatonin interferes with the processes responsible for the development and maintenance of pregnancy.

## RESUMO

Efeitos da melatonina e da prolactina na reprodução: revisão de literatura.

A glândula pineal é responsável pela produção do hormônio melatonina (MEL), sendo aceita como a glândula reguladora da reprodução em mamíferos. A prolactina (PRL) também exibe atividade reprodutiva em animais, em resposta ao fotoperíodo. Sabe-se que as concentrações de PRL são elevadas durante o verão e baixam durante o inverno, ocorrendo o oposto com os níveis do hormônio melatonina nessas estações. Nos mamíferos placentários, tanto a melatonina quanto a prolactina influenciam a implantação, que é considerada o ponto crítico da gravidez, pois o sucesso da gestação requer o desenvolvimento de uma interação sincronizada entre o endométrio e o blastocisto para o desenvolvimento da placenta. Sabe-se ainda que os níveis de PRL durante a gestação são essenciais para a manutenção da gravidez, pois esse hormônio induz o corpo lúteo a produzir progesterona, além

de estimular a implantação do blastocisto, mantendo a prenhez e o desenvolvimento placentário. Em contrapartida, tem-se demonstrado também que os níveis de melatonina no plasma aumentam durante a gestação, atingindo valores elevados no fim desse período, sugerindo que esse hormônio desempenhe um importante papel na manutenção da gestação. Dessa forma, fica claro que o tratamento com prolactina ou melatonina interfere nos processos responsáveis pelo desenvolvimento e pela manutenção da gestação.

**Palavras-chave:** glândula pineal, gravidez, progesterona, estrogênios.

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