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REVIEW ARTICLE

Melatonin and the thyroid gland

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Abstract

This review briefly summarizes the published data on relationships observed between melatonin – the main pineal hormone, and the thyroid gland. The prevailing part of the survey is devoted to thyroid growth processes and function. A large experimental evidence exists suggesting the inhibitory action of melatonin on thyroid growth and function; this effect has been revealed by using different experimental models: by chronic and short-term melatonin administration *in vivo*, by light restriction, which is known to increase the activity of the pineal gland, by pinealectomy, etc., as well as by employing the *in vitro* conditions. Thus, much information has been accumulated, indicating – in experimental conditions – a mutual relationship between the pineal gland and the thyroid. The confirmation of these relations in clinical studies in humans meets numerous difficulties, resulting – among others – from the fact that, nowadays, human beings, as well as certain animal species, used in experimental studies, have been living far away from their natural and original habitat. It makes almost impossible to compare the results obtained in particular studies performed in different species, on the pineal-thyroid interrelationship.

Abbreviations

Ado	adenosine
AK	adenosine kinase
AMP	adenosine monophosphate
dado	deoxyadenosine
damp	deoxyadenosine monophosphate
dThdPase	thymidine phosphorylase
NAS	*N*-acetylserotonin
PD-ECGF	platelet-derived endothelial cell growth factor
T_3	triiodothyronine
T_4	thyroxine
TK	thymidine kinase
TSH	thyrotropin

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) – the main secretory product of the pineal gland – displays several functions in living organisms. It is known for its role in seasonal reproductive physiology, circadian rhythmicity and sleep processes and for its ability to reduce the "jet lag" symptoms in humans [1]. Additionally, melatonin has been shown to modulate immune functions, growth processes and cancerogenesis, and oxidative processes [2–6].

The existing relationship between the pineal and the thyroid gland has been evidenced in result of numerous experimental studies. Several questions, however, still arise, namely:

1) to what extent is the relationship in question a direct one?;
2) are there any intermediate substances or factors involved in this regulation?;
3) is there a local (autocrine?) regulation of thyroid hormone secretion by melatonin in the thyroid gland?;
4) does melatonin participate in the control of thyroxine (T_4) monodeiodination reaction, leading to triiodothyronine (T_3) formation in peripheral tissues?;
5) are there any cells in the body capable to produce both thyroid hormones and melatonin?; etc.

Whereas it is generally accepted that T_4 – under physiological conditions – is exclusively produced in the thyroid gland and peripherally metabolized into more active hormon – T_3 (80% of the entire amount of T_3 present in the body is a product of T_4-monodeiodination reaction), there are probably different sources of melatonin. It is already known that, beside the pineal gland, other organs, tissues or cells serve as the site of melatonin production [7, 8]. Among others, positive immunostaining with antibodies against melatonin has been described with respect to C cells of the thyroid gland [7, 9]. Unfortunately, no studies have yet been performed to reveal a possible presence of melatonin in thyroid follicular cells. Thus, not only typical endocrine but, at least, paracrine (if not autocrine) regulation should be considered between melatonin and thyroid hormones.

Melatonin and thyroid growth processes

Numerous data indicate a suppressive effect of melatonin on thyroid growth processes.

In very early experiments it was shown that pinealectomy, i.e. an elimination of the main source of melatonin, resulted in increased thyroid weight in rats [10] and mice [11]. That finding was confirmed in numerous subsequent experiments, using different parameters of growth processes; several of them were performed at our laboratory.

Under conditions of light restriction, associated with an increased activity of the pineal gland, suppression of the thyroid growth was found in male mice [12]. Melatonin inhibited the basal and thyrotropin (TSH)-stimulated mitotic activity of the thyroid follicular cells *in vivo*, when administered to mice in late-afternoon s.c. injections for 10 days, and in organ culture [13]. The indoleamine prevented the pinealectomy-induced increase of mitotic indices in the rat thyroid gland [14]. The effect of short-term s.c. administration of melatonin (5 days) on ^{3}H-thymidine incorporation into DNA of rat thyroid lobes, transferred, after collecting, into incubation *in vitro*, was dose-dependent; melatonin, in dose of 25 μg/daily, effectively reduced ^{3}H-thymidine incorporation, when used in dose of 50 μg/daily – melatonin produced no effect, however, the indoleamine, applied in the highest dose – 100 μg/daily, brought about an increase of ^{3}H-thymidine uptake [15]. Melatonin applied *in vitro* was less effective than in *in vivo* conditions; only in the concentration of 10^{-9}M, did the indole reduce ^{3}H-thymidine incorporation into DNA of rat thyroid lobes [16]. Melatonin, released from s.c. pellets, prevented the inhibitory effect of late-afternoon melatonin injections on growth processes in rat thyroid [17, 18]; those results suggest a counter-antithyroid action of melatonin released from pellets on the growth-inhibiting response of the gland, following melatonin injection. Melatonin and, to a lesser extent, another indoleamine – 5-methoxytryptamine, decreased the mean nuclear volume of thyroid follicular cells in Syrian hamsters [19]. Melatonin and its precursor – N-acetylserotonin (NAS), administered to male rats, decreased the mitotic activity in the thyroid gland [20]. The inhibitory effect of short photoperiod on the thyroid growth processes was shown in mice [12] and in Indian palm squirrels (*Funambulus pennanti)* [21]. It is to be stressed that the pineal gland involvement in the photoperiodic response of the thyroid cannot be excluded, since parallel changes of melatonin concentrations were observed, following a short photoperiod exposure [21]. Moreover, much experimental evidence, derived either from our [13, 22] or from other [23,24] laboratories, speak in favour of direct melatonin influence on thyroid follicular cells. This hypothesis is further confirmed by the finding that the pituitary is not necessary to demonstrate the increase in thyroid weight after pinealectomy in mice [11, 25].

Measurements of some enzyme activities, related to growth processes, have been performed in our laboratory; these are the following enzymes: thymidine kinase, thymidine phosphorylase and adenosine kinase. Additionally, we have examined the effect of indoleamines on cyclic AMP generation in rat thyroids *in vitro*.

Thymidine kinase (TK: thymidine 5'-phosphotransferase, EC 2.7.1.21) is an enzyme responsible for catalyzing the phosphorylation of thymidine, functioning as a part of the pyrimidine salvage pathway involved in DNA synthesis and being closely correlated with ^{3}H-thymidine

incorporation and mitosis [26]. Adenosine kinase (AK; EC 2.7.1.20) is an enzyme which catalyses the phosphorylation of adenosine (Ado) and deoxyadenosine (dAdo) to adenosine monophosphate (AMP) and deoxyadenosine monophosphate (dAMP), respectively. Adenosine kinase functions as a part of the purine metabolic pathway involved in DNA synthesis and is the key enzyme regulating the Ado content. Thymidine phosphorylase (dThdPase, EC 2.4.2.4) is an enzyme catalyzing the reversible phosphorolysis of thymidine, deoxyuridine and their analogues to the respective bases and to 2-deoxyribose-1-phosphate. This enzyme has been proved to be identical to the platelet-derived endothelial cell growth factor (PD-ECGF), which is involved in the process of angiogenesis.

We have shown that melatonin and NAS decreased the concentration of cyclic AMP [27] and reduced the activity of TK [28] in rat thyroid lobes incubated *in vitro*. It seems that the influence of melatonin on TK activity in the thyroids depends on the age of animals; when the employed thyroid tissue had been collected from rats much younger than those applied in the previous experiment [28], melatonin, added to the incubation medium, increased TK activity in thyroids collected from intact, sham-operated and hemithyroidectomized animals [29].

In another study, hemithyroidectomy increased dThdPase activity in the remaining thyroid lobe. Melatonin, applied *in vitro*, decreased the dThdPase activity in thyroid lobes collected from intact animals, sham-operated animals and hemithyroidectomized rats [30]. The results suggest an involvement of melatonin in the regulation of thyroid growth, hypothetically – by an impairment of the process of angiogenesis.

Hemithyroidectomy decreased AK activity in the remaining thyroid lobe; melatonin, used *in vitro*, increased the AK activity in thyroid lobes collected from intact and sham-operated rats, but it did not change AK activity in the remaining thyroid lobes after hemithyroidectomy [29]. The results suggest a certain role of AK in the regulation of (patho)physiological processes in the thyroid gland after hemithyroidectomy.

Karyometric investigations present another field of our interest. Karyometry has been proved to be a useful method of assessment of various tissue and organ activities (mainly secretory but not only). An increased volume of cell nuclei may either result from enhanced DNA synthesis or it may emerge from a stimulated functional activity (the increased protein synthesis). In the previous studies, we examined the influence of melatonin and TSH on karyometric parameters of rat thyrocytes [31]. We found that a short-photoperiod exposure, associated with a stimulation of the pineal gland, resulted in a decrease of the mean volume of thyrocyte nuclei in male gerbils [32]. Additionally, we observed that melatonin, administered in late-afternoon injections, decreased the mean nuclear volume of thyrocytes in male Syrian hamsters [19], and, when used *in vitro*, the indole significantly decreased the mean nuclear volume and the nuclear intersection area of thyrocytes [31].

Growth processes are undoubtedly involved in the complex process of carcinogenesis. The protective effects of melatonin against cancer is a subject of an intensive research [4–6]. Because of the potential role of ionizing radiation in the pathogenesis of thyroid cancer, the studies on protective effects of melatonin against radiation-induced oxidative stress and cancer of the thyroid gland seem to be of special value. There has, hovewer, been a scarcity of data in the literature concerning this issue. It has been found that histoenzymological changes in rat thyroid gland, caused by an exposure to 8 Gy of γ-radiation, were partially reversed by pretreatment with melatonin [33]. In another study, when using morphometric parameters, melatonin was shown to decrease the height of thyroid follicular cells and the nuclear volume of the cells from rats exposed to 8 Gy-radiation [34].

The potential protective effect of melatonin against thyroid cancer will unquestionably be a subject of future studies.

Melatonin and thyroid function

Several data suggest that the inhibitory effect of melatonin on the thyroid concerns not only growth processes but also the function of this gland. Consequently, we present several pieces of evidence concerning such effects, obtained at our and other laboratories.

Late afternoon s.c. injections of melatonin decreased circulating thyroid hormone concentrations in adult Syrian hamsters of both sexes (melatonin – 25μg/daily) [35] and in male Wistar rats (melatonin – 50 μg/daily) [36].

Pinealectomy performed in male Wistar rats, resulted in an increase in serum thyroxine (T_4) concentrations 10 weeks after pinealectomy, that process being prevented by melatonin administration; the concentrations of triiodothyronine (T_3) remained unchanged in the pinealectomized rats [37].

However, an opposite effect was observed when melatonin was chronically released from s.c. pellets, implanted to male Wistar rats; the indoleamine increased both T_3 and T_4 levels after 10 days and also, however to a lesser degree, after 10 weeks; this effect may be called the "prothyroid" action of melatonin [36]. On the other hand, the joint effect of late-afternoon melatonin injections and melatonin-implants caused no changes in thyroid hormone concentrations [36].

Not only may chronic melatonin availability, but also a short-term treatment with the hormone, result in a "prothyroid" action under certain conditions. Unexpectedly, when melatonin is injected at a dose of 25 μg/daily to rats for 5 consecutive days in the late light phase, it increases serum T_3 concentration and reveals a slight tendency towards rising serum T_4 [38]. In the same study, also a 5-day treatment with NAS resulted in the "prothyroid" effect, concerning thyroid secretory processes.

Some more recent studies still confirm the inhibitory effects of melatonin on thyroid secretion. In the experiment *in vitro*, melatonin was shown to directly inhibit T_4 secretion by thyroids from both tadpoles and frogs [39]. The decrease in plasma T_4 levels in turtles, due to melatonin administration, was accompanied by reduced the thyroid gland weight, follicular epithelial cell height and a decreased activity of thyroid peroxidase [40]. Under conditions of constant darkness, the reduced plasma T_4

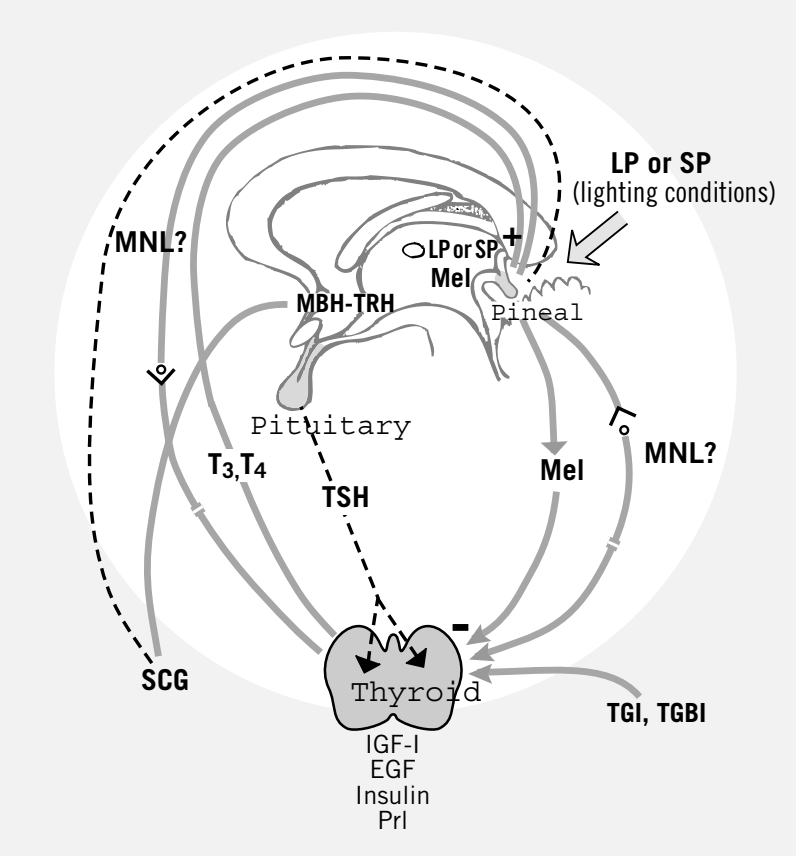

Fig. 1. General model of possible reciprocal relationships between the pineal gland, the superior cervical ganglia and the thyroid, involved in the control of thyroid growth. EGF – epidermal growth factor, GH – growth hormone, PRL – prolactin, LP – long photoperiod, SP – short photoperiod, MBH – medio-basal hypothalamus, MEL – melatonin, MNL – multineuronal link, SCG – superior cervical ganglion, TGI – thyroid growth-stimulating immunoglobulins, TGBI – thyroid growth-blocking immunoglobulins, TSH –thyrotropin, TRH – thyrotropin releasing hormone, T_3 – triiodothyronine, T_4 – thyroxine.

concentration and lower thyroid weight in *Funambulus pennanti* were found; in contrast – pinealectomy resulted in an enhanced thyroid function [41]. Melatonin injection reduced T_4 concentration in control rats, and T_3 concentration in rats with transplanted anterior pituitary [42].

The influence of melatonin on thyroid hormone secretion could either be direct or indirect one. It was recently shown that injections of melatonin caused a decrease in both blood TSH and thyroid hormone concentrations in rats, and the reduced TSH and thyroid hormone concentrations correlated with melatonin blood concentration [43]. On the other hand, it has been shown that melatonin stimulates, whereas pinealectomy decreases TSH accumulation in the unique thyroid hormone-immunoreactive cells in rat pars tuberalis [44].

It is worth considering whether melatonin influences activities of monodeiodinases – enzymes participating in thyroid hormone metabolism in peripheral tissues. It was previously shown that melatonin, released from s.c. pellets for 15 days, enhanced type II thyroxine 5'-monodeiodinase in brown adipose tissue of Syrian hamsters, without changing of serum thyroid hormone concentrations [45]. Similarly, activation of cerebrocortical type II 5'-deiodinase activity in Syrian hamsters, kept under short photoperiod or subjected to the indoleamine liberated from s.c. pellets, was observed [46]. It has been shown in the recent studies that treatment with melatonin results in an increased activity of type I 5'-monodeiodinase in the liver and kidney and of type II 5'-monodeiodinase in adipose tissue of newborn rabbits, the changes in enzyme activities being accompanied by increased concentrations of serum T_4, T_3, and reverse T_3 [47].

Aging is strictly connected with a gradual decrease in the production of several hormones, among others, melatonin and thyroid hormones. Therefore, an assessment of the relationship between decreased production and secretion of these hormones is of a great interest.

Melatonin treatment in middle-aged rats did not influence T_3 concentration, which – comparing to the effects observed in young animals – was much lower [48]. However, when examining this relationship in humans, melatonin reveals a recovery effect of thyroid function towards a more juvenile pattern of regulation; melatonin treatment for 3–6 months in elder patients (aged 42–62 years) with initial low level of blood melatonin resulted in a significant increase in thyroid hormone concentrations [49]; it is not excluded that the described effect is a direct one because a similar treatment with melatonin in aging patients did not result in any changes of TSH concentration [50].

Melatonin as antioxidant in the thyroid

Several thyroid disorders are accompanied by enhanced oxidative stress. In experimental model of hyperthyroidism, L-T_4-tretament resulted in an increased level of Schiff bases – a parameter of oxidative stress – in lung, brain and kidney homogenates; melatonin decreased both basal and elevated Schiff bases concentrations, due to L-T_4 treatment [51]. The same tendency has been shown for others parameters: malondialdehyde and conjugated dienes [52, 53].

Pineal-thyroid relationship in humans

The clinical data on the pineal-thyroid relationship are scarce. Whereas no changes have been observed by some others [54] in melatonin levels in either hypothyroidism or hyperthyroidism of human subjects, others investigators found the increase in nocturnal melatonin concentrations in hypothyroid patients [55]. A decreased nocturnal melatonin concentration was observed in patients subjected to surgical treatment because of the effects exerted by recurrent non-toxic nodular goiter, when compared to controls [56].

Blood concentrations of melatonin were evaluated in patients with very large non-

toxic nodular goitre before and after thyreoidectomy; unexpectedly, nocturnal melatonin concentrations were significantly higher after than before the operation [57]. The authors have drawn a conclusion that the goitre of a very large size can – possibly – compress the superior cervical ganglia, and – in consequence – alter indirectly the Mel synthesis. According to the current views, however, melatonin could be actively taken up by enlarged thyroid with subsequent decrease in blood concentration of the indoleamine.

Thyroid hormone-stimulation of pineal function or growth processes

The stimulatory effect of the thyroid hormones on the pineal gland is supported by many morphological, biochemical and clinical findings. Peschke (58–60) reported that T_4 significantly increased the surface area of nuclei cross sections of rat pinealocytes in vivo; Thyroidectomy (TX) and/or methylthiouracil (MTU) treatment caused a significant decrease of the surface area in question. Also the results of our studies speak in favor of thyroid stimulation of pineal growth; thyroid hormones increased the MNV of pinealocytes in organ culture, as well as slightly increased the MMAR of pinealocytes [61]. In turn, Milcou et al. [62] have found a significantly increased amount of DNA in rat pineals, following the administration of T_4 to culture medium. A further support for our hypothesis has been provided by the results of Nir and Hirschman [63] who showed that both thyroid hormones (T_4 and T_3) enhanced melatonin concentration and induced an increase of norepinephrine-stimulated Nac-5HT content in cultured rat pineals. In studies *in vivo*, treatment with T_4 resulted in the increase in the night peak of melatonin in rats [64].

Concluding remarks

All the above mentioned results, while proving the inhibition of thyroid growth and/or thyroid function by the pineal [65], as well as the reports on the stimulation of the pineal gland activity and growth processes by the thyroid hormones [61, 63, 64, 66], have prompted us to formulate a hypothesis on the existence of a reciprocal relationship between the thyroid and the pineal [65, 67] (Fig. 1). In agreement with this hypothesis, melatonin could act directly on thyroid follicular cells, inhibiting their proliferation. Accordingly, it is possible that plasma concentrations of thyroid hormones are direct modulators of the pineal function and growth.

This review is the fourth one after previous three published before [65, 68, 69]. Because numerous studies are expected to be performed in a near future on melatonin and thyroid gland, especially with respect to oxidative stress and molecular mechanisms of interactions in question, a subsequent survey will be necessary to update the issue of melatonin-thyroid relationship.

The experimental and clinical evidence, as presented in our survey, indicates an undoubtable role of melatonin in physiological and pathological processes of the thyroid gland, providing "a green light" for the use of this indoleamine under certain clinical conditions in humans.

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