

## Melatonin and aging. A brief survey

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### **Abstract**

The relationship between the pineal gland and aging has been assumed already nearly a century ago. Recently, melatonin was considered by some authors as a "wonder drug." The present paper tries to summarize the relationship between melatonin and aging in three points. 1. Decline of melatonin production during aging. 2. The role of the pineal gland in the regulation of the ovarian cycle in aged females. 3. The antioxidant effect of melatonin and aging.

The age-related decline of pineal melatonin production is due to the degenerative changes of the neural structures (serotonergic and noradrenergic neuron systems) innervating the pineal gland and the suprachiasmatic nuclei rather than to the degeneration of the pineal tissue itself. The decreased melatonin production of the pineal gland precedes the destruction of ovarian cyclicity which can be partly counteracted by melatonin or by 5-hydroxytryptophane administration. The antioxidant effect of melatonin might explain its lifespan-prolonging effect, at least to a certain degree.

## Abbreviations in the text

CEA	constant estrous anovulatory state
DA	dopamine
5-HT	serotonin
5-HTP	5-hydroxytryptophane
LH	Luteinizing Hormone
NE	noradrenalin
SCN	suprachiasmatic nuclei

## Introduction

The multiple physiological role of the pineal gland can be subdivided quite arbitrarily into two main lines.

### *1. Functions acting throughout the entire life span.*

The major part of these functions show a decline with the progression of age: regulation of circadian rhythms, such as the sleep-wake cycle, feeding and drinking rhythms, some neuroendocrine rhythms or daily locomotor activity [1]. The circannual rhythm of sexual activity of the seasonal breeding species is limited to the period of sexual activity of the life; this is one of the most thoroughly investigated functions of the pineal gland [2]. Briefly mentioning only the most prominent further actions of this small gland, besides its oncostatic activity [3] and its effect played in the neuroimmunological regulation [4], the anti-oxidant (scavenger) effect of melatonin [5] belongs also to the permanent functions of the pineal.

### *2. Functions observed only in some special, so-called critical periods of life.*

Three such prominent critical periods of life can be distinguished when the pineal gland plays an important role in determining the hormonal profiles for a longer period of the life span. These three periods, the perinatal days, puberty and aging or senescence, were thoroughly investigated by several research laboratories. Among these critical phases, only the latter one belongs to our present task.

From this brief introduction, it becomes evident how a thin sector of the extended physiological role of the pineal gland is represented by our present subject. In spite of this fact, this problem became more and more intensively studied and came into the focus of attention of the researchers, not only of scientists involved in pineal research, but it also became the subject of general interest in society.

It has been always a great desire of the human being to prolong one's life span as far as possible. In

the medieval period, alchemists were looking for the "elixirum vitae" which could solve this problem in their epoch. In the last few decades, scientists have tried to reveal this secret in the little, "mysterious" organ, the pineal gland. Accordingly, in the last few years, several reports appeared in some newspapers—not scientific journals!—about melatonin as "wonder-drug" against several sorts of diseases, like an "elixirum vitae." Even books were published under a similar style with promising titles. Since authors of the present survey are very sceptic towards such types of publications, we do not intend to cite any of these reports by name or title.

In the spirit of a correct scientific criticism, the European Pineal Society accepted a statement at its 7<sup>th</sup> Colloquium in 1996, listing those effects of the pineal gland and its hormone melatonin, which could be considered as scientifically verified.

After these short critical remarks, in this review we try to summarize our own research data indicating the role of the pineal gland and melatonin played in the process of aging, compared to the results of the literature.

In this study, three main points will be surveyed.

## Evaluation of research data

### *1. Changes in melatonin production of the pineal gland during the progress of aging.*

Since melatonin production has a marked daily rhythm, generally the night time peak values are considered as basis of description. Data of Gupta [6] demonstrated that 2 significant declines occur in melatonin blood levels during the lifespan. The first decline appears in the period of puberty (at about 16 years of age), which is followed by a slight decrease in the adult ages, slowly, but continuously. Consequently, in the old age, over 80 years, melatonin levels are only about 1/5 of those observed in childhood. Several authors [7, 8, 9] reported similar changes.

Night time peak values of melatonin rapidly decreased in adults compared to prepubertal children [10, 11, 12]. An even more rapid fall is evidenced in senescence [13]. When monitoring blood melatonin levels throughout the day in young adults (20–27 years) and in old (67–84 years) individuals, Arendt et al. [14] demonstrated a dramatic decrease in the nocturnal melatonin peak values in aged subjects. The authors added, however, in spite of their data, the following remarks: "There was little direct evidence in humans that melatonin supplements could attenuate or reverse age-related changes in health."

For a better understanding of the causes and consequences of the progressive decline in melatonin

secretion with advanced age, it seems reasonable to briefly survey the most important regulatory mechanisms influencing melatonin production.

As demonstrated by neuroanatomical [15, 16] and neurophysiological [17] studies, light impulses regulating pineal melatonin production arrive to the gland through the retinohypothalamic pathway, involving the suprachiasmatic nuclei (SCN) which are generally considered as a rhythm-generating pacemaker ("biological clock") for the pineal gland and for several other neuroendocrine rhythms [18, 19].

According to neurochemical [20] and immunohistochemical [21] results, supported by our own physiological data [22, 23, 24], the SCN receive many afferents from different brain neuronal systems [25]. The most important afferent inputs terminating in the SCN are the serotonergic (5-HT) pathways originating from the raphe nuclei of the brain stem [26]. Besides 5-HT fibers, SCN also receive terminals from catecholaminergic [27] fibers of the brain stem.

On the other hand, the presence of melatonin receptors in the SCN [28] furnished evidence for the possibility that melatonin may also directly influence the SCN, besides its action exerted on the brain areas giving rise to the 5-HT and noradrenergic (NE) fibers ascending to the circadian pacemaker area of SCN (Fig. 1). Therefore, a multiple and complicated reciprocal feed-forward and feed-back regulatory mechanism appears to act between the SCN and pineal gland [29].

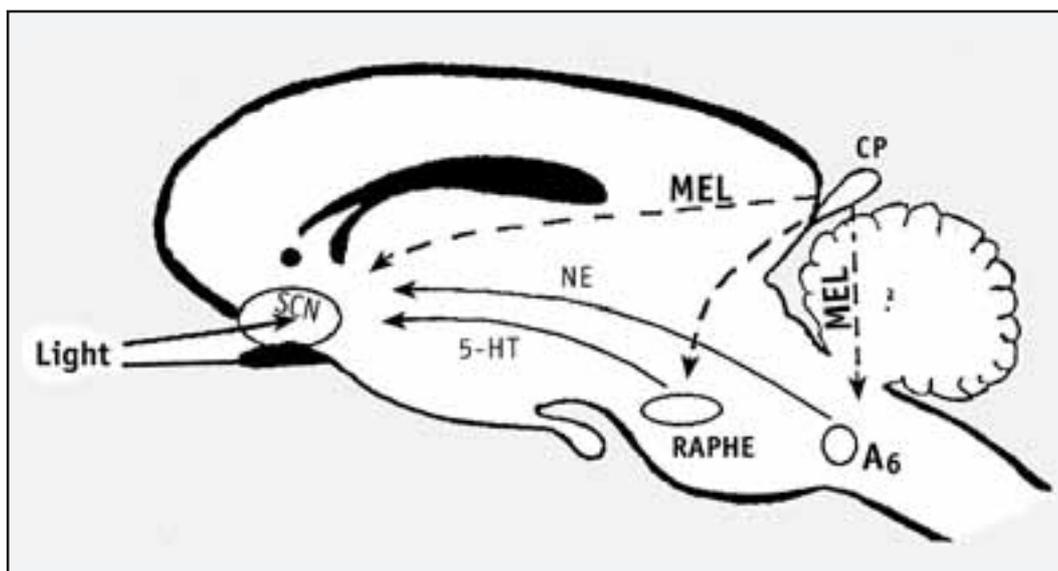
Several reports evidenced the degeneration of monoaminergic neurons in the aging brain [30, 31].

Alterations in the metabolism of brain monoaminergic neurotransmitters [32] were also demonstrated. Changes in the density of 5-HT and of NE nerve terminals in the SCN were detected histochemically [30] and by physiological approach [33]. Besides brain monoamines, degeneration of opioi-dergic fibers [34] and a rapid fall of Metenkephalin content of the SCN [35] were also reported in the aging rats.

On the base of the data, briefly summarized here, it seems to be correct to infer that decline in melatonin production during aging might be a consequence of the age-related alterations of the brain neuronal systems regulating pineal activity. This latter aspect was the subject of our studies in connection with the age-related dysfunction of the reproductive cyclicality in the female rat.

## *2. The role of the pineal gland in the regulation of the ovarian cycle in the aging female rat*

It is well known that the regular 4-day ovarian cycle of the female albino rat is abolished over two years of age. The earlier stage of this period is characterized by constant vaginal estrus in the vaginal smears. After a further few months, constant vaginal diestrus will develop indicating the complete ceasing of ovarian function. The constant vaginal cornification (estrus) was considered to be the sign of senescence in our experiments. In our investigations, we attempted to counteract the development of this anovulatory state or to restore the normal vaginal cyclicality by interventions affecting pineal activity.



**Fig. 1.** Postulated role of brain monoaminergic neurotransmitters by which melatonin influences the activity of the suprachiasmatic nuclei.

*Abbreviations* – SCN: suprachiasmatic nuclei; MEL: melatonin; A<sub>6</sub>: noradrenergic cell group; CP: pineal body; NE: noradrenergic tract; 5-HT: serotonergic tract

Twenty-two month old female rats showing constant vaginal estrus (CEA rats) received 10 µg melatonin in the form of daily subcutaneous injection; parallel groups of CEA rats were treated with 5-hydroxytryptophane (5-HTP), precursor of serotonin, (25 mg/kg daily dose).

After a few days (4–5 days) of treatment, proestrus and diestrus phases reappeared in the vaginal smears. Within 10–14 days, reinstatement of an irregular cyclicity was observed in both groups of the treated rats. Although it was not a regular 4-day cycle characteristic for the control group of young animals, still an irregular, but consequent periods of cyclicity were restored due to the applied treatments. 5-HTP proved to be more efficient in this respect than melatonin: rats treated with 5-HTP exhibited restored vaginal cycles in a higher percent than rats of the melatonin-treated group (Fig. 2).

For explanation of this latter phenomenon, we assumed that 5-HTP restored vaginal cyclicity acting on the SCN which are involved also in the organization of the female reproductive cycle, besides many other cyclic events [36]. Experiments of Walker [37] appeared to be in favor of this hypothesis. In his studies, lack of ovulation with constant vaginal estrus (CEA state) was induced by daily estrogen administration in young animals. CEA syndrome elicited in this manner was counteracted by local microinjections of 5-HTP into the SCN leading to restoration of the preovulatory LH peak. Consequently, the ovulation was restored. This experiment clearly indicates that serotonin—and probably, also melatonin—might act at the level of the SCN involved in the regulation of ovarian cyclicity.

In the aging animals, the serotonergic mechanism is degenerating, at least partly. This will result in disturbances of the function of the rhythm generating system, leading to abolished ovarian cyclicity.

A crucial point remained to be discussed. Was the dramatic decrease in melatonin production, observed in old subjects, the result of the degeneration of the monoaminergic nerve terminals in the SCN and in the pineal gland? Or, according to another possibility, might the pinealocytes also lose—at least partly—their melatonin-secreting capacity in aging?

In order to answer these questions, in our further experiments, we compared melatonin release from the pineal tissue of young and aged rats in response to noradrenergic (NE) infusions. Results of these series are demonstrated in Fig. 3.

In the *in vitro* perfusion system, developed for pineal studies in our laboratory [38, 39], pineal tissue has a low basal secretion rate of melatonin. Following a single 1 min infusion of NE, high melatonin peak was registered in both young and aged groups. These results demonstrated that pineal tissue of the aging rats was able to react with a similar peak of melatonin release to the same dose of NE than of young adults. However, we have to add that repeating this experiment after a few hours on the same tissue sample somewhat lowered melatonin release was detected from pineals of aged animals compared to the young pineal tissue.

The first phase of this experiment allowed a conclusion that the pineal gland still remains capable of responding with melatonin release to the neural inputs, especially to noradrenergic stimuli, also in aged subjects.

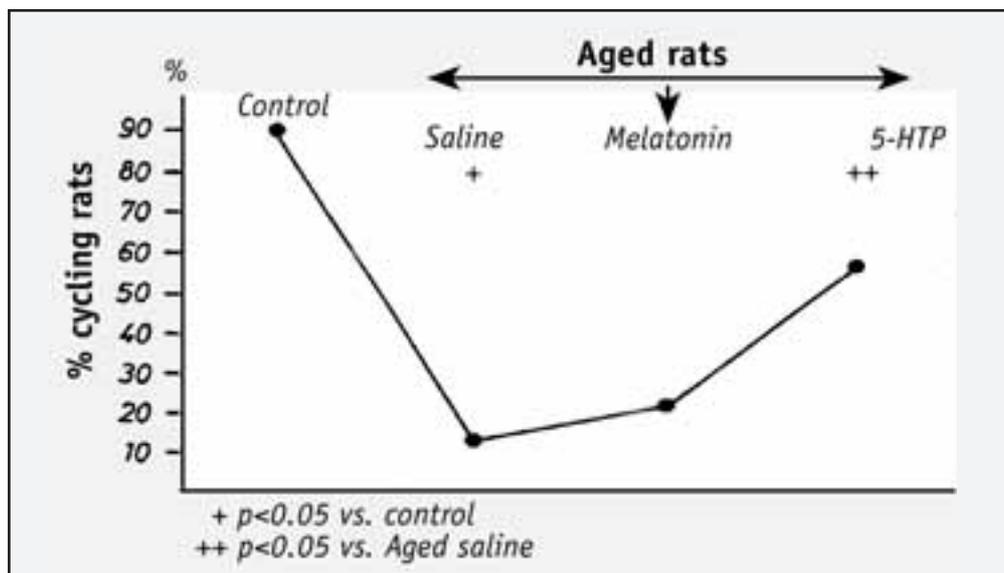
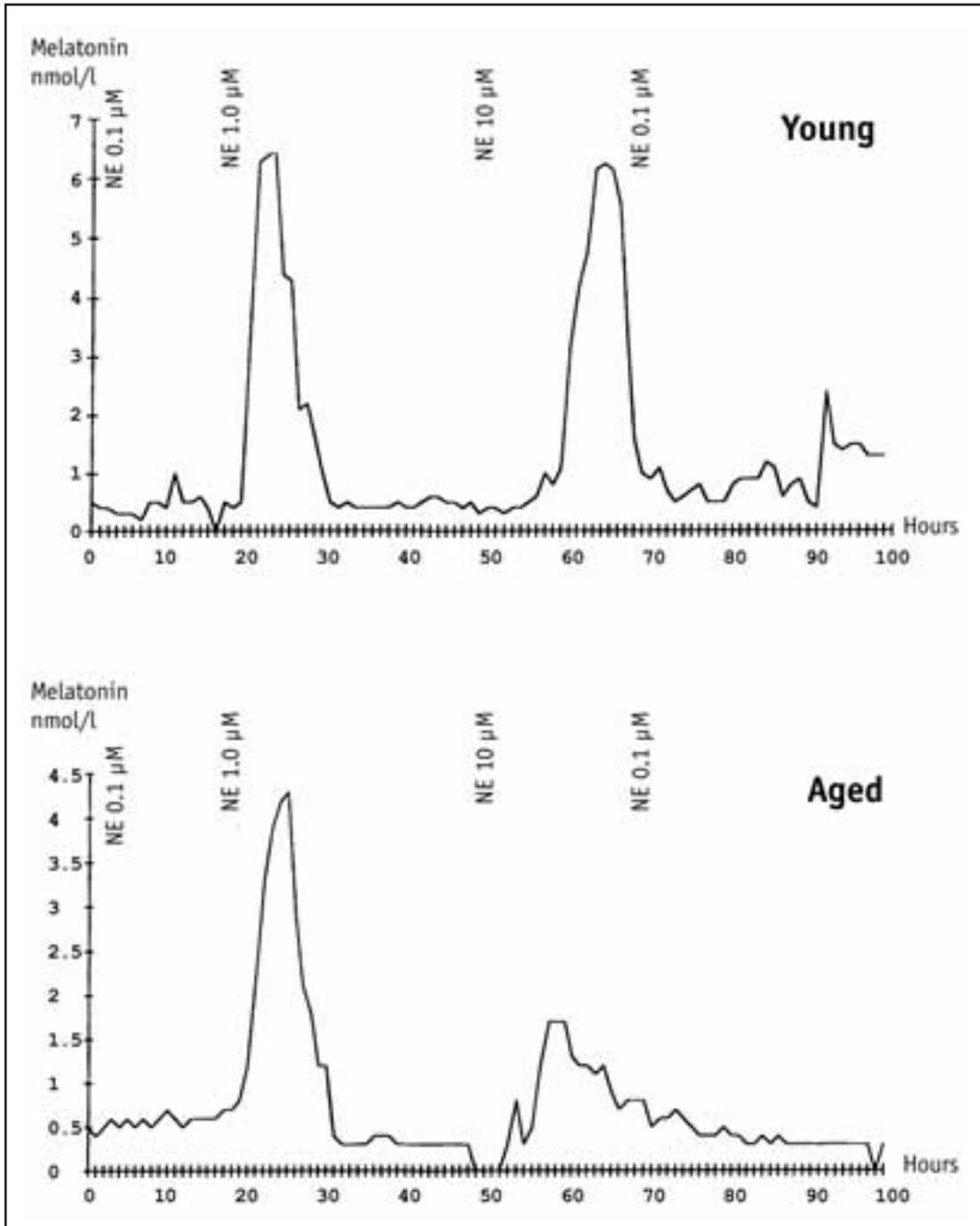


Fig. 2. Occurrence of cyclicity in aging CEA rats treated with melatonin or with drugs acting on central serotonergic neurons.



**Fig. 3.** Effect of norepinephrine (NE) on melatonin release in perfusion system from pineal gland of young (11 months old) and aging rats.

This finding indicates that the primary cause of the sharp decrease of melatonin secretion in the aging individuals is the degeneration of noradrenergic terminals in the pineal gland rather than the age-related destruction of pineal tissue itself, as it was demonstrated by some authors [40]. However, the second phase of this experiment indicates also the possible role of age-related diminution of the secretory capacity of the pineal tissue [41].

All these data, concerning the relationship between the pineal gland and decline of reproductive ability

in the advanced ages, confirm the existence of the “melatonin deficiency syndrome” raised by Rosenzwaig [13]. In several species, including the human being, the decline in nighttime peak levels of melatonin are earlier detectable than the disorders in the ovarian cycle. Decline in melatonin levels during aging can be considered a signal, which indicates the expected approaching disorganization of the ovarian function.

Therefore, the onset of lowered melatonin levels in the presenile age might be considered as a marker of the forthcoming disorders in the sexual cycle.

### *3. The role of the antioxidant effect of melatonin in the retardation of aging*

Our working group was not engaged in research of the antioxidant (“scavenger”) effect of melatonin. However, dealing with the relationship between melatonin and aging, molecular biological aspects of pineal hormonal effects cannot be omitted. Reiter and coworkers [5] proposed this action as one of the most important aspects of pineal functions. The destruction caused by oxidative stress and free radicals is considered to be responsible for degenerative, age-related disorders such as heart diseases, damage of blood vessels, etc. Joints might also be injured by such free radicals. This explains the intensive research work dealing with the scavenger effect of melatonin which provides a promising way for the application of melatonin as a cytoprotective drug.

### **Conclusion**

The antioxidant and cytoprotective effect of melatonin, besides its described antitumor activity and immunomodulatory action attributed to its “scavenger” effect [4, 5], might give an explanation in the future to the highly desired but not unequivocally verified lifespan-prolongating effect of the pineal gland. This way, melatonin could really contribute to prolong life span in spite of the fact that it never should be considered as an “elixirum vitae.”

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