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The hypothalamo-neurohypophysial response to melatonin

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Abstract The present paper reviews the findings accumulated on the role of pineal gland and its hormone – melatonin – in regulation of the hypothalamo-neurohypophysial system activity. Effects of modified photoperiod, pinealectomy or treatment with melatonin on the vasopressin and oxytocin biosynthesis and/or secretion have been described. Taken together, the *in vivo* and *in vitro* data suggest that the effect of melatonin on the vasopressin and oxytocin secretion depends on this pineal hormone concentration and experimental conditions.

Introduction

Vasopressin (AVP) and oxytocin (OT) content in the hypothalamo-neurohypophysial system represents a net result of several processes, i.e., AVP/OT synthesis by magnocellular neurones situated in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus, infundibular transport of the hormone towards the neural lobe of the pituitary, and finally the secretion of OT and AVP into the blood. Several stimuli (both physiological and pathological) were reported to influence the AVP and OT biosynthesis and/or secretion. Moreover, the release of neurohypophysial hormones exhibits diurnal changes, which are presumably related to the effects of environmental light. Indeed, diurnal variations in the concentration of OT and AVP in the hypothalamus, neurohypophysis and plasma were described in the rat [1–5] as well as in human blood plasma [6, 7]. Daily rhythms in electrical activity of the magnocellular neurones secreting OT and AVP have also been found to depend on the presence of intact pineal [8].

A cycle of melatonin production in the pineal gland and retina with peak and nadir levels during dark and light hours, respectively, was reported to exist in several species [9–11]. Information as to lighting conditions reaches the pineal gland via two groups of neural pathways. The first originates from the retina and involves the retinohypothalamic tract, hypothalamic suprachiasmatic (SCN) and PVN nuclei, also the spinal cord and superior cervical ganglion [12]. Another group of neural pathways converging in the pineal is connected with afferentation of central origin [13]. Namely, the SCN neurons project directly to the SON [14] as well as the PVN [15], and some nerve fibres of the latter have been demonstrated in the rat pineal gland [16]. Environmental light affects, therefore, melatonin synthesis rhythm as well as its diurnal excretion into the blood. Taking together data as to the diurnal rhythm of melatonin [11, 17] and neurohypophysial hormones [2, 3] secretion, it is postulated that diurnal variations in the AVP and OT production and/or secretion may be mediated, at least in part, by the pineal gland and its hormone – melatonin [see: 18]. This paper reviews the findings accumulated on the role of melatonin in regulation of the hypothalamo-neurohypophysial system activity.

The effect of pinealectomy on the vasopressin and oxytocin synthesis and/or release

As early as thirty years ago, the pineal gland was found to affect function of the hypothalamic magnocellular neurones. Namely, pinealectomy resulted in a diminution of the neurosecretory activity in the SON [19] and PVN [20] neurones; this effect could be reversed by pineal implantation into the hypothalamus [21]. The neurosecretory activity of the PVN neurones is also modified by melatonin [22].

Within the last two decades, a great number of data were accumulated as to the role of pineal in the regulation of the neurohypophysial hormones secretion. Namely, in 1980 pinealectomy was reported to decrease the AVP storage in the rat neurohypophysis [23]. Later experiments showed that pineal removal results not only in a diminution of the neurohypophysial vasopressinergic activity, but the OT content in the hypothalamo-neurohypophysial system was also decreased after pinealectomy [24–30]. Moreover, the influence of modified α- and/or β-adrenergic transmission (as brought about by desmethylimipramine-DMI, phenoxybenzamine-POB or propranolol) on the hypothalamic and neurohypophysial AVP/OT content in normal and pinealectomized rats has been reported [26–28, 31]. A single intracerebroventricular (icv) injection of DMI decreased the AVP and OT content in the neurohypophysis of rats with intact pineal gland, while pretreatment with POB attenuated the effect of DMI on the OT storage [26]. Following pineal removal, DMI intensified the pinealectomy-induced decrease of the neurohypophysial OT but not AVP content, while icv α-adrenergic blockade was ineffective in modifying the response in question [26, 31]. Repeated treatment with DMI resulted in a distinct increase of the hypothalamic and neurohypophysial AVP/OT content in both intact and pinealectomized rats [28, 31]. Treatment with propranolol reversed the pinealectomy-induced diminution of the AVP and OT levels in the hypothalamus and neurohypophysis; in pineal-intact animals, however, no effect of propranolol on either hypothalamo-neurohypophysial OT storage or hypothalamic AVP content was noted [27].

Pineal removal has been described to affect the secretion of neurohypophysial hormones under conditions of both equilibrated and disturbed (due to dehydration, haemorrhage or hyperosmotic stimulation) water balance. Namely, pinealectomy was found to increase circulating OT levels in euhydrated [30, 32] or dehydrated [33] rats. Also the rate of response of vasopressinergic and oxytocinergic neurones to bleeding was augmented after pineal removal [29]. In other experiments, however, pinealectomy attenuated the effect of both hypovolaemia and plasma hyperosmolality on the secretion of AVP [34]. Moreover, a reduced Fos (a protein product of the immediate early gene c-fos) production in the SON neurones was found to accompany the pinealectomy-induced diminution of the neurohypophysial hormones secre-

tion into the blood in response to hyperosmotic stimulation [35].

The influence of pinealectomy on the AVP and OT synthesis in the hypothalamus is not clear so far. Namely, pinealectomy was reported to increase the ^{3}H-leucine uptake by the hypothalamic magnocellular SON and PVN neurones [36], but to lower the fos protein production within the rat SON [35]. Other studies showed that neither pinealectomy nor treatment with melatonin were able to affect the OT mRNA production in the hamster hypothalamus [37]. On the other hand, the biosynthesis rate of AVP in the rat hypothalamus was recently shown (by using the colchicine method) to be higher two weeks after pinealectomy, but reduced eight weeks after the surgery, as compared with sham operated animals [38]. However, the biosynthesis of OT in the hypothalamus was not affected two weeks after pineal removal, while eight weeks after the surgery it was significantly elevated [39]. These recently reported data seem to suggest that the effect of pinealectomy on the AVP and/or OT biosynthesis rate changes with time after the surgery.

The vasopressin and oxytocin synthesis and/or secretion as influenced by different photoperiod.

The response of oxytocinergic and vasopressinergic neurons to modified photoperiod (i.e., continuous lighting, long or short photoperiod) was found to alter with time of exposure to such conditions [32, 37, 40]. Exposure of pinealectomized animals to constant light for eight days resulted in a diminution of the neurohypophysial AVP and OT content, but it did not change the hypothalamic and plasma levels of both hormones. When, however, animals with intact pineal gland were exposed to such lighting conditions, the AVP/OT contents in the hypothalamus and neurohypophysis were diminished whereas their plasma levels were increased [32]. Exposure of rats to constant light for two or ten days influences the AVP and OT storage in the hypothalamo-neurohypophysial system as well as these hormones secretion into the blood [2]. It also affects the diurnal hormonal rhythms; following ten days exposure to constant lighting, plasma AVP and OT rhythms showed a phase shift [2].

The ability of long or short photoperiod to affect the neurohypophysial hormones synthesis and/or secretion has been studied in male Syrian hamsters. In long day (LD)-exposed hamsters, pinealectomy induced a decrease in the posterior pituitary AVP and OT content, whereas plasma hormone levels were unchanged; in such animals melatonin was not able to prevent the effects of pinealectomy [37, 40]. Exposure to short day (SD) for ten weeks (but not for one week) led to the increase in the neurohypophysial AVP and OT storage, but again there were no corresponding changes in circulating hormone concentrations; the hypothalamic OT mRNA levels were also not altered by SD exposure [37]. The influence of SD on the neurohypophysial AVP and OT storage was apparently dependent on the presence of intact pineal gland, since pinealectomy blocked whereas melatonin injections mimicked the effects of SD on the response in question [37, 40].

Melatonin and the neurohypophysial hormones synthesis and/or release

Early findings as to the effects of pineal extracts and/or melatonin injections on activity of the hypothalamo-neurohypophysial system have been described by Guzek [41]. In 1973, Orsi et al. observed that melatonin diminished the protein synthesis in the rat hypothalamus and hypophysis [42]. Two years later, pineal extracts were reported to have no effect on the AVP biosynthesis in the hypothalamo-neurohypophysial complex in organ culture [43]. More recently, melatonin was shown to be without significant effect on the hypothalamic OT mRNA levels in Syrian hamsters [37]; it was also not able to modify the OT biosynthesis rate in sham operated or pinealectomized rats [44]. On the other hand, however, melatonin strongly inhibited the rise in the rat hypothalamic AVP biosynthesis rate due to pinealectomy [45].

The role of melatonin in regulation of the AVP and OT secretion has been studied both under physiological (i.e., normal) and some pathological conditions (i.e., dehydration, haemorrhage, hyperosmotic stimulation and/or stress, which are all known to stimulate the neurohypophysial hormones release). Melatonin was found to modify the AVP and/or OT secretion from the hypothalamo-neurohypophysial system both *in vivo* [25, 40, 46–53] and *in vitro* [54–59].

The effect of melatonin on the vasopressin and oxytocin secretion *in vivo*.

First data from our laboratory, as to the effects of melatonin on the release of neurohypophysial hormones, showed that in pineal-intact rats melatonin, administered at the end of light phase, decreased the AVP and OT storage in the hypothalamus and neurohypophysis [25, 46]. In pinealectomized animals, however, similar treatment with melatonin did not affect the pinealectomy-induced depletion of AVP and OT levels in the neurohypophysis [25]. Results of further studies have indicated existence of both stimulatory and inhibitory actions of this pineal hormone, depending mostly on a dose applied and experimental conditions. Namely, repeated subcutaneous (sc) or intraperitoneal (ip) injections of melatonin stimu-

lated both AVP and OT release when administered at a dose level of 100 μg melatonin/100 b.w. [46], but were ineffective at a dose of 25 μg melatonin per animal [37, 40, 48]. When administered intravenously [53] or icv [52], higher doses of melatonin stimulated, whereas lower doses inhibited the release of AVP from the male rat neurohypophysis. Similarly, when lactating female rats were used for the studies, the suckling-induced OT release was inhibited by icv injected melatonin at a dose level of 1 ng/ml, while lower dose (10 pg/ml) and two higher doses (100 ng/ml or 10 μg/ml) of melatonin did not modify the response in question [51]. The latter results suggest that melatonin inhibits the OT secretion, as induced by suckling, from the posterior pituitary only at the concentration which is relatively close to its physiological level in the blood.

Melatonin influence on the regulation of AVP and OT secretion under pathological conditions seems to depend on the experimental situation. Indeed, under conditions of normal water balance, treatment with melatonin was followed by a decrease in the neurohypophysial AVP and OT content [25, 40, 46, 47, 50]. However, melatonin did not modify the depletion of neurohypophysial AVP and OT storage noted in rats deprived of water for two or four days [46] as well as it did not further affect the posterior pituitary hormone levels as decreased following haemorrhage [47], pinealectomy [25] or both haemorrhage and pinealectomy [29]. On the other hand, it augmented the diminution in the neurohypophysial AVP/OT storage in response to some stressful stimuli such as hypertonic saline ip injection [40] or immobilization [49, 50]. Melatonin also facilitated the neurohypophysial hormones secretion into the blood due to hypertonic saline administration [48] as well as increased these hormones secretion in pinealectomized and immobilized rats [49, 50].

The effect of melatonin on the vasopressin and oxytocin secretion *in vitro*

Growing number of evidence suggests that the *in vitro* effect of melatonin on the AVP and OT secretion from the hypothalamo-neurohypophysial system depends on the concentration of the hormone, time of day and species of animals used as donors of a tissue for the studies. In 1979 melatonin was reported to stimulate the AVP secretion from the rat neurohypophysis in a dose dependent manner [54]. Later *in vitro* studies have shown that melatonin was able to stimulate the release of both AVP and OT from isolated posterior pituitary of sham-operated (i.e., not pinealectomized) or pinealectomized rats when used at relatively high concentrations (10^{-6} M and 10^{-3} M), but at the concentration of 10^{-7} M it was ineffective [55]. In contrast to these observations, Yasin et al. [57] showed that melatonin had an inhibitory effect on both basal and K^+-evoked AVP and OT release from the isolated rat hypothalamus, with maximal inhibition at 10^{-7} M. In addition, the effect of melatonin on these hormones secretion was found to depend on the light:dark cycle and could be seen only during the day [58].

When Syrian hamsters were used as donors of a tissue, the inhibitory effect of melatonin on the AVP and OT secretion from isolated posterior pituitary was also noted, but the three concentrations of melatonin used (10^{-11} M, 10^{-9} M and 10^{-7} M) induced effects of similar magnitude [56]. In the case of K^+-stimulation, however, only dose of 10^{-9} M melatonin was effective in inhibiting the AVP and OT release from the hamster posterior pituitary *in vitro*; the other two doses of melatonin showed no significant difference from the control [56]. Lack of the effect of 10^{-11} M and 10^{-7} M doses of melatonin (which are lower or higher, respectively, than its physiological circulating level) has suggested that under conditions of K^+-evoked stimulation, melatonin was effective in modifying the AVP and OT secretion from the posterior pituitary *in vitro* only when used at the concentration which is relatively close to its physiological level in the blood.

General conclusions

The question as to the possible mechanisms underlying modulation of the neurohypophysial hormones synthesis and secretion by melatonin has not been adequately answered, yet. However, exogenous melatonin may modify the AVP and/or OT synthesis and release *via* specific membrane receptors which have been demonstrated in several brain areas with high levels of binding over the SCN and pars tuberalis of the pituitary [60, 61]. Another possibility is that melatonin modifies activity of the vasopressinergic and oxytocinergic neurons by a direct action on a genome without interaction with specific membrane receptor. Indeed, after systemic administration melatonin crosses the blood-brain barrier and accumulates in the anterior pituitary as well as in the hypothalamus, both in cytosolic and nuclear fractions [11, 62]. Due to its lipophilicity (and, therefore, its ability to pass through cell membrane) melatonin modulates a number of cellular functions as well as releases the genomic activation [63] probably *via* the brain-specific nuclear receptors RZR, both α- and β-subtype [64].

Melatonin alters the metabolism of some catecholamines in the hypothalamus and neurointermediate lobe [65–67]. Therefore, by its direct influence on the hypothalamic neurons and/or indirect, i.e., by modified neurotransmission in the brain, mel-

atonin could affect the synthesis and/or release of AVP and OT. In fact, acetylcholine, dopamine and prostaglandins were found to be involved in melatonin-mediated inhibition of the neurohypophysial hormones secretion both *in vivo* [53] and *in vitro* [59]. As yet, however, the way of melatonin action on the hypothalamic SON and PVN magnocellular neurons requires further investigations.

In summary, it is concluded: 1) The response of vasopressinergic and oxytocinergic neurons to modified photoperiod changes with time of exposure to such conditions; it apparently depends on the presence of intact pineal gland, but is not mediated by melatonin. 2) The pineal gland seems to exert an inhibitory impact on the biosynthesis of AVP (but not that of OT), the effect being attributed to melatonin. 3) Melatonin inhibits the AVP and OT secretion from the posterior pituitary (both *in vivo* and *in vitro*) when used at the concentration regarded to be in the range of the physiological level. 4) Melatonin augments the AVP and OT response to some pathological stimuli, such as volume and/or hyperosmotic stimulation or immobilization stress. 4) The response of vasopressinergic and oxytocinergic neurons to stress depends on the presence of intact pineal gland; the role of melatonin in the respective mechanism(s) is suggested. 5) Mechanisms related to melatonin effect on vasopressinergic neuron activity are – at least partly – different from those related to melatonin influence on oxytocinergic neuron function under similar conditions.

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