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Effect of melatonin supplementation on plasma vasopressin response to different conditions in rats with hyperthyroidism induced by L-thyroxine

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ABSTRACT

The present study was performed to determine how basal, isotonic, hypertonic and hypovolemic conditions affect fluid–electrolyte balance and plasma arginine vasopressin (AVP) levels in rats with experimental hyperthyroidism supplemented with melatonin.

The rats were divided into four groups of twenty-four subjects each kept under the following treatments during one month: (1) Controls; (2) treated with L-thyroxine; (3) treated with L-thyroxine and sham melatonin and (4) treated with L-thyroxine and melatonin. After this each group was further subdivided into subgroups that were subject to normal, isotonic, hypertonic and hypovolemic conditions.

The plasma AVP, total triiodothyronine (TT_3), total thyroxine (TT_4) and melatonin levels were measured in plasma by means of a Phoenix Pharmaceutical RIA test kit. Hematocrit and osmolality levels were also determined.

There were significant increases of total T3 and T4 levels in the L-thyroxine treated groups, $p<0.001$. The AVP levels were also increased in groups 2 and 3, but not so in the rats treated with melatonin ($p<0.001$), which also showed increased plasma melatonin levels ($p<0.001$).

These results indicate that treatment with L-thyroxine increases stimulated and non-stimulated AVP release that are inhibited by melatonin supplementation. It was also shown that AVP response to hypertonic and hypovolemic conditions was not affected by L-thyroxine treatment and/or L-thyroxine + melatonin treatment.

1. Introduction

Vasopressin release is mainly determined by changes in plasma osmolality [1,2] and by changes in blood volume [3]. The AVP response to hypertonic and hypovolemic conditions is also affected by the function of some endocrine organs [3,4].

Thyroid gland hormones affect liquid–electrolyte balance and general body metabolism [5–9]. In experimental studies, decreased AVP release and changes of normal control mechanisms were observed in hypothyroidism induced by propylthiouracil or thyroidectomy [10,11]. Deficiency of thyroid hormones resulted in a decrease of the AVP level [7]. It has been postulated that thyroid hormone deficiency directly alters vasopressin receptor biosynthesis in both liver and kidney, instead of acting via the depressed plasma vasopressin levels [7].

In a study performed on growing rats, it was found that treatment with L-thyroxine did not modulate vasopressin definition of the paraventricular nucleus in the hypothalamus [9]. A parallel study reported that hypo- and hyperthyroidism during pregnancy did not cause any significant changes in the neuropeptide content of fetal neural lobes [12]. Increased AVP levels were found in patients with hyperthyroidism [13,14]. These levels returned to values similar to those of healthy controls after normalization of thyroid gland function [14].

In vitro studies established that melatonin inhibited AVP release in suprachiasmatic nucleus through MT2 receptors [15,16]. There is MT1 melatonin receptor immunoreactivity in human hypothalamus and pituitary gland [17]. It has been reported that long-term melatonin administration had no effect on the AVP levels in the hypothalamus [18]. *In vitro* studies, however, showed that melatonin and its analogues stimulated AVP release and suppressed basal AVP levels [19].

Melatonin did not affect AVP release induced by metoclopramid AVP release in human subjects [20]. In another study AVP response to exercise had a 2.3-fold increase following administration of melatonin, while the increase was 3.6 times without melatonin [21]. The increase of plasma vasopressin was suppressed after administration of melatonin [22].

In the present study basal and isotonic, hypertonic and hypovolemic conditions were applied to learn how they influence fluid–electrolyte balance and plasma AVP levels in experimental hyperthyroidism in rats with and without supplementation with melatonin.

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Table 1
Body weight of rats in the four experimental groups and subgroups.

Subgroups[a]	C (g)	H (g)	H + S-Mel (g)	H + Mel (g)
Unstimulated	267.65 ± 5.05[b]	252.56 ± 3.94	251.85 ± 3.67	265.75 ± 2.67[b]
Isotonic-stimulated	268.75 ± 4.92[b]	252.46 ± 4.46	249.42 ± 4.35	265.45 ± 3.35[b]
Hypertonic-stimulated	268.12 ± 4.75[b]	251.55 ± 3.56	252.14 ± 4.57	266.34 ± 3.47[b]
Hypovolemic-stimulated	267.80 ± 5.44[b]	253.16 ± 4.44	253.33 ± 4.36	268.32 ± 3.26[b]

C: Controls, H: Hyperthyrodism, H + S-Mel: Hyperthyroidism + Sham Melatonin, H + Mel: Hyperthyroidism + Melatonin.
[a] $n = 6$ in each group.
[b] Compared to hyperthyroidism and hyperthyroidism plus-melatonin groups ($p < 0.05$).

2. Materials and methods

2.1. Animals and their treatments

This study was performed at the Selcuk University Experimental Medicine Research and Application Center in strict adherence to the guidelines of the Selcuk University Ethics Committee.

Ninety-six 8-week old Sprague–Dawley male rats weighing 250–280 g each were used for the study. The animals were fed a standard rat chow and were kept in a room at 19–21 °C with a 12-h dark/light cycle. The rats were then divided into four groups of 24 rats each, as shown below:

1. *Controls*: Rats kept on a standard diet and tap water.
2. Given daily intraperitoneal injections (IP) of L-thyroxine (0.3 mg/kg/day, Sigma Chemical Co., Dorset, UK) for three weeks to induce hyperthyroidism [23].
3. In addition to L-thyroxine a sham-melatonin product was administered for two weeks.
4. Two weeks after inducing hyperthyroidism (see groups 2, and 3) the rats were supplemented with IP injections of 3 mg/kg/day melatonin. Melatonin was administered daily between 09.00 and 10.00 AM.

After four weeks the rats from all four groups were subdivided into 4 subgroups of six rats each just before sacrificing by decapitation for collection of samples, as follows:

a) *Controls*: The animals were decapitated without any application and blood samples were collected (no treatment).
b) *Isotonic subgroup*: Injected (IP, 1 ml/100 g body weight) with 0.9% NaCl 15 min before decapitation.
c) *Hypertonic subgroup*: Injected (IP, 1 ml/100 g body weight) with 1.5 M NaCl 15 min before decapitation.
d) *Hypovolemic subgroup*: Injected (IP, 2 ml/100 g body weight) with a solution prepared by dissolving 250 mg/ml polyethylene glycol (Sigma Chemical Co., Dorset, UK) in 0.15 M NaCl. The rats were decapitated 1 h later for collection of blood samples.

Considering the circadian release cycle of AVP, the blood samples were collected between 09.00 and 10.00 h in tubes containing EDTA. The plasma was separated by centrifugation and immediately frozen at −80 °C until needed for analysis. For determination of hematocrit the blood was drawn into heparin-treated capillaries, centrifuged for 5 min at 1000 rpm and read on a hematocrit scale. A Gonotec Osmomat 030 was used for determination of plasma osmolalities.

A Phoenix Pharmaceutical RIA test kit (RK-065-07) was used for AVP analysis. Melatonin was determined with a Biosource RIA test kit (KIPL0800). Total T_3 and T_4 levels were measured with Elisa test kits from Dialab, Austria, catalogue numbers Q00228 and Z01232, respectively.

The hematocrit levels were reported as %; plasma osmolality in mOsm/kg H_2O; vasopressin levels in pg/ml; Total T_3 in ng/dl and total T_4 in nmol/l.

2.2. Statistics

The statistical analysis was performed using the SPSS computer program. All values are reported as means ± SD. The Kruskal–Wallis variance analysis was used for comparison between groups and the Mann Whitney *U*-test was applied setting $p < 0.05$ as significance level.

3. Results

The body weights, hematocrit, osmolality, vasopressin, melatonin and thyroid hormone levels are shown in Tables 1–6.

Table 2
Hematocrit levels in subgroups subject to different conditions.

Subgroups	C (%)	H (%)	H + S-Mel (%)	H + Mel (%)
Unchallenged	40.80 ± 1.05	48.85 ± 1.67 *	48.42 ± 1.70 *	39.71 ± 0.37
Isotonic-stimulated	39.75 ± 0.92	47.42 ± 1.35 *	46.57 ± 1.52 *	38.42 ± 0.35
Hypertonic-stimulated	38.12 ± 0.75	47.14 ± 1.57 *	47.52 ± 1.39 *	39.71 ± 0.43
Hypovolemic-stimulated	47.80 ± 0.44a	53.33 ± 1.36 a*	52.28 ± 1.52 a*	48.287 ± 0.83 a

a: Hypovolemic groups have higher Hct levels compared to the other groups ($p < 0.001$).
*H and H + S-Mel groups were higher Hct levels compared to control (C) and Hyperthyroid-Melatonin Supplemented Groups (H + Mel) ($p < 0.001$).

Table 3
Plasma osmolalities in subgroups under different stimuli.

Subgroups	C (mOsm/kg H_2O)	H (mOsm/kg H_2O)	H + S-Mel (mOsm/kg H_2O)	H + Mel (mOsm/kg H_2O)
Unstimulated	287.80 ± 2.04 b	291.66 ± 3.94 b*	290.85 ± 3.47 b*	285.45 ± 3.42 b
Isotonic-Stimulated	285.45 ± 3.12 b	290.36 ± 3.62 b*	289.52 ± 3.45 b*	284.32 ± 3.40 b
Hypertonic-stimulated	298.23 ± 3.45 a	305.45 ± 2.46 a *	304.24 ± 2.77 a*	297.24 ± 3.35 a
Hypovolemic-stimulated	290.80 ± 2.44 b	297.26 ± 3.24 b*	296.43 ± 2.36 b*	293.30 ± 4.42 b

a,b: Hypertonic-stimulated groups have higher than the other subgroups ($p < 0.05$) (a > b).
* Statistical significance was determined compared to C and H + Mel groups ($p < 0.05$).

Table 4
Plasma melatonin levels in groups and subgroups.

Subgroups	C (pg/ml)	H (pg/ml)	H + S-Mel (pg/ml)	H + Mel (pg/ml)
Unchallenged	18.62 ± 0.84 b	14.60 ± 0.84 c	14.92 ± 0.56 c	65.50 ± 0.37 a
Isotonic-stimulated	18.41 ± 0.44 b	14.48 ± 0.44 c	14.89 ± 0.73 c	64.52 ± 0.35 a
Hypertonic-stimulated	18.26 ± 0.56 b	15.26 ± 0.56 c	13.94 ± 0.42 c	65.11 ± 0.43 a
Hypovolemic-stimulated	18.92 ± 0.44 b	15.84 ± 0.45 c	14.02 ± 0.74 c	64.47 ± 0.83 a

a: H + Mel group has the highest melatonin levels compared to the other groups ($p<0.001$) (a>b>c).
b: Control group (C) has the higher melatonin levels compared to the H andH + S-Mel groups ($p<0.001$) (b>c).

Table 5
Total T_3 levels in experiment groups.

Subgroups	C (ng/dl)	H (ng/dl)	H + S-Mel (ng/dl)	H + Mel (ng/dl)
Unchallenged	74.34 ± 2.38 c	86.52 ± 2.12 a	86.42 ± 2.40 a	79.53 ± 2.55 b
Isotonic-stimulated	74.42 ± 2.69 c	85.20 ± 2.75 a	85.62 ± 2.52 a	80.39 ± 2.35 b
Hypertonic-stimulated	73.18 ± 3.45 c	85.83 ± 2.28 a	85.72 ± 2.39 a	80.15 ± 2.43 b
Hypovolemic-stimulated	74.40 ± 2.77 c	86.02 ± 2.30 a	86.65 ± 2.32 a	80.22 ± 2.30 b

a: Hypertroid and Hyperthyroid-Sham-Melatonin groups have the highest TT_3 levels compared to C and H + Mel groups ($p<0.001$) (a>b and c).
b: H + Mel group has the higher compared to C group ($p<0.001$) (b>c).

As a result of hyperthyroidism, there was a decrease of body weight of the rats in groups 2 and 3, Table 1 ($p<0.05$) and increases of hematocrit levels, Table 2 ($p<0.001$). Under hypovolemic conditions all experimental subgroups showed increased hematocrit levels, Table 2 ($p<0.001$). The subgroup under hypertonic condition presented increases in osmolality in comparison to all other subgroups, Table 3 ($p<0.001$). The rats in groups 2 and 3 had higher osmolalities than controls and melatonin-treated rats.

As seen in Fig. 1, the plasma AVP levels were 6.90 ± 0.94 pg/ml (controls); 9.36 ± 0.64 pg/ml (L-thyroxine); 9.19 ± 0.15 pg/ml (L-thyroxine plus sham melatonin) and 8.45 ± 0.37 pg/ml (L-thyroxine plus melatonin) in unstimulated groups. In the same order, the plasma AVP levels of isotonic subgroups were 6.81 ± 0.44, 8.03 ± 0.36, 8.30 ± 0.52, and 7.49 ± 0.35 pg/ml.

In the hypertonic subgroups derived from groups 2 and 3 the AVP level were 15.95 ± 0.72 and 13.42 ± 0.39 pg/ml, respectively, higher than that of groups 1 and 4: 12.82 ± 0.56 and 11.71 ± 0.43 pg/ml, respectively (Fig. 1).

The AVP levels in the hypovolemic subgroups were, in the same order as above, 11.22 ± 0.44, 14.82 ± 0.56, 13.07 ± 0.52 and 11.25 ± 0.83 pg/ml (Fig. 1). In all subgroups, those derived from the two groups of rats with hyperthyroidism the AVP levels were significantly higher than those of controls and rats treated with melatonin, $p<0.001$, Fig. 1.

The plasma melatonin levels are presented in Table 4. As expected, these were higher in group 4 than in all other groups ($p<0.001$) and those of controls higher than the two groups with hyperthyroidism ($p<0.001$).

Tables 5 and 6 give the total plasma T_3 and T_4 levels of all groups. These parameters were higher in the hyperthyroidism and hyperthyroidism plus sham-melatonin groups than in the other two groups, $p<0.001$. The melatonin supplemented group had higher levels of T_3 and T_4 than the controls ($p<0.001$).

4. Discussion

In all cases the responses were as expected, such as decreases of body weight and increases of hormone levels in the rats with hyperthyroidism, or the increase of melatonin in the group that received it in addition to L-thyroxine. The same can be said of the experimental subgroups where osmolality increased due to hypertonic stimulation and the hematocrit did increase under hypovolemic conditions [24].

The most relevant observation is that plasma AVP increased as a result of hyperthyroidism and that the increase was prevented by supplementation with melatonin.

Triiodothyronine and L-thyroxine participate on regulation of liquid–electrolyte balance [7,8]. There are conflicting results in the relationship of these thyroid hormones and vasopressin and its mechanism is not yet fully understood.

Salomez-Garnier et al. analyzed arginine vasopressin in twenty-six patients with peripheral hyperthyroidism. No significant differences were found in comparison to healthy controls, but in four patients with severe mixed edema and low osmolality the AVP levels were elevated [25].

In another research performed on pregnant mothers hypo- and hyperthyroidism did not cause a significant change in the AVP levels of babies [9].

In a previous research we found significant decreases in plasma AVP levels under basal, hypertonic and hypovolemic conditions in rats with hypothyroidism induced by propylthiouracil or thyroidectomy [10,11] or its increase in hyperthyroid rats [26]. Other studies reported increased vasopressin levels in hypothyroidism induced by thyroidectomy [27]. Similarly, Tohei et al. found increased AVP release from median eminence in experimental hypothyroidism [28].

In a study performed on patients with hyperthyroidism, AVP levels were found to be higher than controls until normalization of thyroid

Table 6
Total T_4 levels in groups.

Subgroups	C (nmol/l)	H (nmol/l)	H + S-Mel (nmol/l)	H + Mel (nmol/l)
Unchallenged	41.80 ± 1.95 c	74.46 ± 1.67 a	73.42 ± 1.70 a	48.82 ± 1.37 b
Isotonic-stimulated	40.05 ± 2.18 c	73.65 ± 1.35 a	73.57 ± 1.52 a	49.77 ± 1.35 b
Hypertonic-stimulated	41.12 ± 1.88 c	75.12 ± 1.57 a	74.52 ± 1.39 a	50.19 ± 1.43 b
Hypovolemic-stimulated	41.43 ± 2.02 c	75.98 ± 1.36 a	75.28 ± 1.52 a	50.64 ± 1.83 b

a: Hypertroid and Hyperthyroid-Sham-Melatonin groups have the highest TT_3 levels compared to C and H + Mel groups ($p<0.001$) (a>b and c).
b: H + Mel group has the higher compared to C group ($p<0.001$) (b>c).

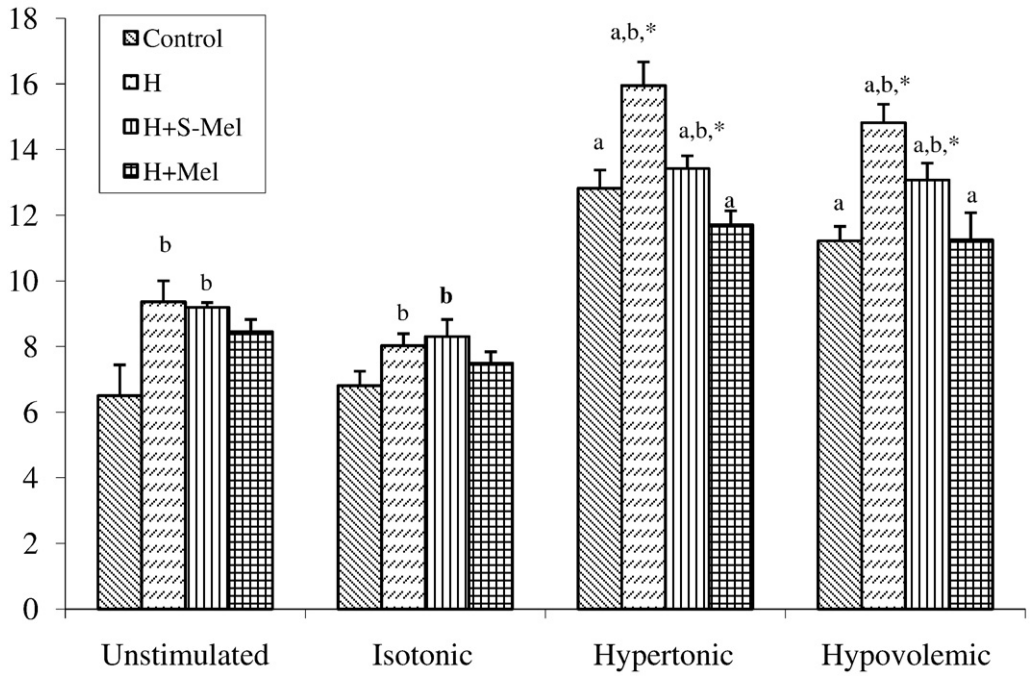

Fig. 1. Plasma vasopresin (AVP) levels (pg/ml) in all groups and subgroups. [a]Hypertonic and hypovolemic groups had higher AVP levels compared to unstimulated and isotonic-stimulated groups ($p<0.001$). [b,*] H (L-thyroxine) and H + S-Mel (L-thyroxine plus sham melatonin) groups have higher AVP levels compared to controls (C) and H + Mel (L-thyroxine plus melatonin) groups ($p<0.001$).

gland function [14]. In agreement with other studies [14,29], we found increased AVP levels in both basal (without stimulation) and stimulated (hypertonic and hypovolemic) groups following hyperthyroidism induced by L-thyroxine.

In addition, it was postulated that the increase of AVP levels could be the result of an increase in renin–angiotensin system activity (RAS) due to hyperthyroidism [30]. Another reason for the increase in plasma AVP in hyperthyroidism may be the reflex response to maintain normal blood pressure [31,32].

One of the important findings of our experiments is that the increase in hematocrit levels is not accompanied by decreases of AVP in the hyperthyroid groups.

In the second part of the study, the relationship between L-thyroxine-induced hyperthyroidism and melatonin supplementation was explored to determine the AVP release level in basal and stimulated conditions. Treatment with melatonin resulted in a significant reduction of the AVP level in basal and stimulated conditions. This result is consistent with studies where it was found that plasma vasopressin levels increased in pinealectomized rats, which were suppressed by melatonin [22].

On the other hand, it was reported that vasopressin levels decreased in response to osmotic stimulation following pinealectomy [33]. It was suggested that this mechanism was induced by the decrease in the response of central osmoreceptors following pinealectomy and that melatonin affected magnocellular system activation.

It is possible that vasopressin release might be reduced due to two different mechanisms. One such mechanism would be inhibition of thyroid hormones release by melatonin. For example, it has been reported that there is an inverse relationship between pineal gland and thyroid hormones levels [33,34,35]. Another mechanism would be the inhibition of basal or stimulated AVP release by melatonin. It was reported that melatonin affected vasopressin release [19] and supplementation with melatonin suppressed basal and stimulated AVP release in *in vivo* and *in vitro*, depending on dose and experimental conditions [36].

5. Conclusions

We have shown that L-thyroxine increases unstimulated and stimulated AVP release under different conditions and that such an increase is inhibited by melatonin supplementation.

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