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THE EFFECT OF PINEALECTOMY ON PLASMA VASOPRESSIN RESPONSE TO ISOTONIC, HYPERTONIC AND HYPOVOLEMIC TREATMENTS IN RATS SUPPLEMENTED WITH L-THYROXINE

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The present study was conducted to determine the effects of basal, isotonic as well as hypertonic and hypovolemic treatments on fluid-electrolyte balance and plasma AVP levels in rats supplemented with L-thyroxine and pinealectomized L-thyroxine. The animals were initially separated into 4 groups: control (n = 24), L-thyroxine treated (n = 24); L-thyroxine + sham-pinealectomy (n = 24) treated and 4-L-thyroxine + pinealectomy (n = 24) treated. L-thyroxine was given for 4 weeks. At the end of the 4-week experimental period, the sub-groups were formed before decapitation, which were classified as unstimulated (n = 6), isotonic (n = 6), hypertonic (n = 6) and hypovolemic (n = 6) stimulation. Plasma AVP, total triiodothyronine (TT_3) and total thyroxine (TT_4) levels were examined in plasma by RIA. Hematocrit and osmolality levels were also determined. It was found that the TT_3 and TT_4 levels showed significant increases in L-thyroxine treated groups ($P < 0.001$). Also, plasma AVP levels increased in the group subjected to L-thyroxine treatment. However, this increase was depicted to be significantly more prominent in L-thyroxine + pinealectomy treated group ($P < 0.001$). The results of the present study indicate that L-thyroxine treatment increases the basal and stimulated AVP release, which became more significant in the pinealectomy plus L-thyroxine treatment group. Moreover, the results indicate that AVP response to hypertonic and hypovolemic stimulations does not undergo any change due to supplementation by L-thyroxine treatment and/or pinealectomy plus L-thyroxine.

Keywords: AVP – L-thyroxine treatment – pinealectomy – hypertonic and hypovolemic stimulation – osmolality – rat

INTRODUCTION

It has already been established that thyroid gland hormones have an effect on liquid-electrolyte balance [23, 27]. It has been reported that AVP levels reduce thyroid hormone deficiency [20, 21]. It was postulated that thyroid hormone deficiency directly

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alters vasopressin receptor biosynthesis in both the liver and the kidney, instead of acting via the depressed plasma vasopressin levels [1]. However, it has been demonstrated that thyroxine application did not modulate vasopressin gene definition in the paraventricular nucleus of the hypothalamus [9]. AVP levels were found to be higher than control levels whereas AVP levels were found to be similar to the control levels after normalization of thyroid gland at the end of the treatment in patients with hyperthyroidism [19].

It has been reported that normal AVP release rhythm and AVP response to hypovolemic and hypertonic stimulations change after pinealectomy [10, 11]. It was observed that pinealectomy increased plasma vasopressin levels but this increase was suppressed by melatonin application [15].

It was determined that melatonin inhibits AVP release in the suprachiasmatic nucleus through MT_2 receptors in the *in vitro* studies [13, 14]. It was reported that chronic melatonin application did not have any effect on AVP levels in the hypothalamus [18]. However, in an *in vitro* study it was observed that melatonin and its analog suppressed the basal and stimulated AVP release [30]. Melatonin application did not affect the basal or stimulated metoclopramid AVP release in human [7]. In another study which investigated the AVP response stimulated with exercise, it has been observed that AVP increase is 2.3 times in the presence of melatonin. On the contrary the manifestation of this increase is 3.6 times when melatonin is not applied [4].

The aim of the present study was to determine how basal, isotonic, hypertonic and hypovolemic stimulations affect fluid-electrolyte balance and plasma AVP levels rats treated with in L-thyroxine and/or pinealectomized L-thyroxine.

MATERIALS AND METHODS

Animals and their treatments

This study was performed in Selcuk University Experimental Medicine Research and Application Center and the study protocol was approved by the board of directors. 230–280 g, 8 weeks old, Sprague-Dawley strain male rats were used for the study. The animals were subjected to 19–21 °C room temperature and were kept for 12 hours in a dark/light cycle and fed with normal rat diet. The animals were separated into 4 groups before the initiation of the study as follows:

1 – Control group (n = 24); 2 – L-thyroxine (T) (n = 24) treated; 3 – L-thyroxine (T) + sham-pinealectomy (Sham-Pnx) (n = 24) treated; 4 – L-thyroxine (T) + pinealectomy (Pnx) group (n = 24) treated.

No interference was made on the animals in general control group during the 4 weeks experiment. However, isotonic, hypertonic and hypovolemic stimulations were carried out before decapitation.

In the L-thyroxine treated groups, intraperitoneal L-thyroxine (0.3 mg/kg/day) was injected for 4 weeks (Sigma Chemical Co., Dorset, UK).

In sham-pinealectomized and L-thyroxine treated groups, initially sham-pinealectomy was applied on animals under general anesthesia. The animals were anaesthetized by a combination of Xylazine hydrochloride (Rompun, Bayer) 5 mg/kg and Ketamine (Eczacibasi, Istanbul) 60 mg/kg. After 4 weeks recovery period following the operation, the animals were supplemented L-thyroxine intraperitoneally (0.3 mg/kg) for 4 week.

In the first phase, the pineal glands of the animals in pinealectomized group were taken away under general anesthesia [12]. The skulls of the rats were placed in a stereotaxic device. Rats in the sham group were subjected to the same pinealectomy procedures as under general anesthesia, but their pineal glands were not removed, which was followed by injection of L-thyroxine (4 weeks), after the recovery period (30 days).

At the end of the experimental period just before the decapitation, animals in all the groups were separated into 4 sub-groups including 6 rats each.

(a) Group without Stimulation (n = 6): The animals were decapitated without any application and their plasma was taken.

(b) Group with Isotonic Stimulation (n = 6): 0.9% NaCl 1 ml/100 g was administered intraperitoneally 15 minutes before decapitation of the animals [10].

(c) Group with Hypertonic Stimulation (n = 6): Intraperitoneal 1.5 M NaCl 1 ml/100 g was given to the animals in this group 15 minutes before decapitation of the animals [10].

(d) Group with Hypovolemic Stimulation (n = 6): Polyethylene glycol (Sigma Chemical Co., Dorset, UK) was resolved as 250 mg/ml in 0.15 M NaCl on the animals in this group before decapitation of the animals and their blood samples (2 ml/100 g) were taken 1 hour after intraperitoneal administration [10].

All the animals were decapitated between at 09.00–10.00 in the morning, considering the circadian release rhythm of AVP and about 5.5–6 ml blood samples were taken. Blood samples were put into tubes with EDTA and decomposed in a cool centrifuge (3000 r.p.m.). Plasma was kept in –80 °C until the hormone analysis.

Determination of hematocrit and plasma osmolality levels

Heparinized capillary tubes were used for hematocrit assessment. Derived blood samples were centrifuged for 5 minutes at 10,000 r.p.m. and hematocrit levels were read on the hematocrit scale. Plasma osmolalities were read on osmometer. Hematocrit levels were given as percentage, whereas plasma osmolality levels as mOsm/kg H_2O.

Analysis of hormones

The hormone levels were determined in plasma. Phoenix Pharmaceutical RIA test kit was used for AVP analysis (Catalog No: RK-065-07), Elisa test kit was used for Total T_3 levels (DIALAB, Catalog No: Q00228, Austria) and Total T_4 levels (DIALAB,

Catalog No: Z01232, Austria). Moreover, BioSource RIA test kit was used to determine melatonin levels (Catalog No: KIPL0800). Vasopressin levels as pg/ml, Total T_3 as ng/dl, Total T_4 as nmol /l, and melatonin was given as pg/ml.

Statistics

Statistical analysis was done using SPSS statistics programmer. Results were given as mean ± standard deviation. Kruskal-Wallis variance analysis was used for comparison between the group and Mann Whitney *U* test was applied for maintaining significance level at $P < 0.005$.

Table 1
Hematocrit levels in study groups (%)

Sub-groups	Control	T	T + Sham-Pnx	T + Pnx
Unstimulated (n = 6)	40.80 ± 1.05	47.45 ± 1.67[b]*	47.50 ± 0.12[b]*	48.50 ± 0.51[b]*
Isotonic stimulated (n = 6)	39.75 ± 0.92	46.42 ± 1.35[b]*	46.12 ± 0.45[b]*	47.00 ± 0.29[b]*
Hypertonic stimulated (n = 6)	38.12 ± 0.75	44.18 ± 1.57[b]*	44.04 ± 0.25[b]*	45.33 ± 0.71[b]*
Hypovolemic stimulated (n = 6)	47.80 ± 0.44[a]*	51.32 ± 1.36[a]*	51.80 ± 0.21[a]*	52.12 ± 0.35[a]*

T: L-thyroxine treatment.
T + Sham-Pnx: Treatment + Sham-Pinealectomy.
T + Pnx: Treatment + Pinealectomy.
[a]*compared to unstimulated, isotonic stimulated and hypertonic-stimulated groups.
[b]*compared to control group ($P < 0.001$).

Table 2
Plasma osmolalities in groups (mOsm/kg H_2O)

Sub-groups	Control	T	T + Sham-Pnx	T + Pnx
Unstimulated (n = 6)	297.80 ± 4.05[b]	296.66 ± 3.94[b]	300.85 ± 3.47[b]	302.75 ± 3.42[b]
Isotonic stimulated (n = 6)	295.45 ± 3.42[b]	295.36 ± 3.66[b]	297.52 ± 3.55[b]	298.42 ± 3.45[b]
Hypertonic stimulated (n = 6)	308.22 ± 2.45[a]	311.45 ± 3.46[a]	317.24 ± 2.77[a]	318.24 ± 3.77[a]
Hypovolemic stimulated (n = 6)	302.80 ± 2.74[b]	300.26 ± 3.24[b]	313.43 ± 2.36[b]	314.33 ± 3.56[b]

T: L-thyroxine treatment.
T + Sham-Pnx: Treatment + Sham-Pinealectomy.
T + Pnx: Treatment + Pinealectomy.
* Different letters in same column are significant ($P < 0.05$).

RESULTS

Hematocrit, osmolality, melatonin and thyroid hormone levels are given in the Tables. Hematocrit (HCT) values were given in Table 1. L-thyroxine treatment increased hematocrit levels ($P < 0.001$). Pinealectomy in addition to L-thyroxine treatment increased this level, although not statistically. Hypovolemic stimulation significantly increased hematocrit levels in all groups when compared to other sub-groups (without stimulation, isotonic and hypertonic stimulation groups) ($P < 0.001$). When the plasma osmolality was examined, it was found that these parameters increased hypertonic stimulation in proportion to the other sub-groups (Table 1, $P < 0.001$).

Plasma vasopressin levels of unstimulated groups were 6.93 ± 0.74, 9.46 ± 0.64, 9.42 ± 0.16, 12.26 ± 0.51 in control, T, T + Sham-Pnx and T + Pnx groups, respectively (Fig. 1). AVP levels in isotonic stimulated groups were 6.82 ± 0.44, 8.23 ± 0.36, 8.33 ± 0.45 and 11.74 ± 0.29 in control, T, T + Sham-Pnx and T + Pnx groups, respectively (Fig. 1). Plasma AVP levels in hypertonic stimulated groups were 12.81 ± 0.56, 15.65 ± 0.72, 15.04 ± 0.25, 17.57 ± 0.71 in control, T, T + Sham-Pnx and T + Pnx groups (Fig. 1). AVP levels in hypovolemic sub-groups were 12.11 ± 0.44, 14.82 ± 0.56, 14.98 ± 0.21 and 17.46 ± 0.35 in control, T, T + Sham-Pnx and T + Pnx groups, respectively (Fig. 2).

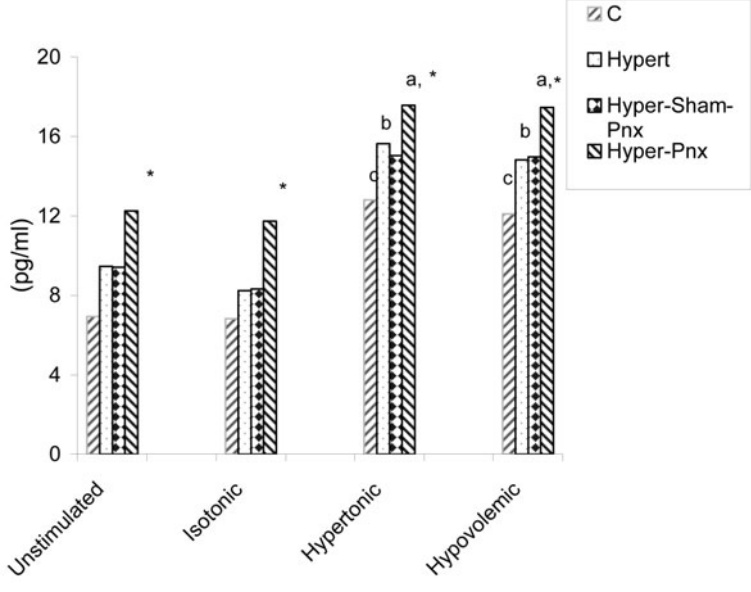

Fig. 1. Plasma AVP levels in groups (C: control, Hypert: L-thyroxine, Hyper-Sham-Pnx: L-thyroxine-sham-pinealectomy, Hyper-Pnx: L-thyroxine-pinealectomy). [a,b,c] Significant compared to unstimulated and isotonic stimulated sub-groups ($P < 0.001$, $n = 6$, for each group). * compared to control, hyperty-roidism, hypertyroidism-sham-pinealectomy

Table 3
Plasma melatonin levels in groups (pg/ml)

Sub-groups	Control	T	T + Sham-Pnx	T + Pnx
Unstimulated (n = 6)	17.62 ± 0.84	14.60 ± 0.84	14.41 ± 0.84	2.79 ± 0.27*
Isotonic stimulated (n = 6)	16.41 ± 0.44	14.48 ± 0.44	14.38 ± 0.44	2.63 ± 0.29*
Hypertonic stimulated (n = 6)	17.26 ± 0.56	15.26 ± 0.56	14.26 ± 0.56	2.68 ± 0.25*
Hypovolemic stimulated (n = 6)	16.92 ± 0.44	15.84 ± 0.45	15.74 ± 0.45	2.74 ± 0.24*

T: L-thyroxine treatment.
T + Sham-Pnx: Treatment + Sham-Pinealectomy.
T + Pnx: Treatment + Pinealectomy.
* Compared to the other groups ($P < 0.001$).

Table 4
Plasma total T_3 levels in groups (ng/dl)

Sub-groups	Control	T	T + Sham-Pnx	T + Pnx
Unstimulated (n = 6)	74.34 ± 2.38^c	86.52 ± 2.12^b	85.83 ± 2.25^b	94.60 ± 2.75^a
Isotonic stimulated (n = 6)	74.42 ± 2.69^c	85.20 ± 2.75^b	85.42 ± 2.44^b	94.16 ± 2.29^a
Hypertonic stimulated (n = 6)	73.18 ± 3.45^c	85.83 ± 2.28^b	86.20 ± 2.75^b	94.92 ± 2.32^a
Hypovolemic stimulated (n = 6)	74.40 ± 2.77^c	86.02 ± 2.30^b	86.80 ± 3.12^b	94.25 ± 2.82^a

T: L-thyroxine treatment.
T + Sham-Pnx: Treatment + Sham-Pinealectomy.
T + Pnx: Treatment + Pinealectomy.
Different letters in same line are significant ($P < 0.001$) ($a > b > c$).

AVP levels significantly increased in all experimental groups when the hypertonic and hypovolemic stimulations compared to unstimulated and isotonic stimulated groups ($P < 0.001$). Also, in the comparison of the main groups (control, T, T + Sham-Pnx and T + Pnx groups), it was observed that L-thyroxine and L-thyroxine + sham-Pnx and L-thyroxine-Pnx group had higher plasma AVP levels than the control group ($P < 0.001$). L-thyroxine + Pnx group presented the highest plasma AVP levels than all the other groups ($P < 0.001$). This increase occurred in all the sub-groups, too (unstimulated, isotonic, hypertonic and hypovolemic-stimulated groups) (Fig. 1).

Table 5
Plasma total T_4 levels in groups (nmol/l)

Sub-groups	Control	T	T + Sham-Pnx	T + Pnx
Unstimulated (n = 6)	41.80 ± 1.95[c]	74.46 ± 1.67[b]	74.44 ± 2.12[b]	85.44 ± 2.12[a]
Isotonic stimulated (n = 6)	40.05 ± 2.18[c]	73.65 ± 1.35[b]	74.64 ± 2.45[b]	84.64 ± 2.45[a]
Hypertonic stimulated (n = 6)	41.12 ± 1.88[c]	75.12 ± 1.57[b]	75.32 ± 2.25[b]	85.42 ± 2.25[a]
Hypovolemic stimulated (n = 6)	41.43 ± 2.02[c]	75.98 ± 1.36[b]	76.25 ± 2.21[b]	86.15 ± 2.21[a]

T: L-thyroxine treatment.
T + Sham-Pnx: Treatment + Sham-Pinealectomy.
T + Pnx: Treatment + Pinealectomy.
* Different letters in same line are significant ($P < 0.001$) (a > b > c).

Plasma melatonin levels of are presented in Table 3. Melatonin values were lower in L-thyroxine and L-thyroxine + Sham-Pnx groups than in the control group ($P < 0.001$). L-thyroxine + Pnx group had the lowest values ($P < 0.001$).

Plasma TT_3 and TT_4 levels are given in Tables 4 and 5, respectively. When these parameters were examined, it was found that there were important increases in these levels due to L-thyroxine injection ($P < 0.001$). These levels were higher in L-thyroxine and L-thyroxine + Sham-Pnx groups than in the control group ($P < 0.001$) and that the T + Pnx group had higher levels than all other groups.

DISCUSSION

When the findings of the present study were evaluated, it became clear that results were obtained as expected. The increased thyroid hormones levels are due to L-thyroxine injection for 4 weeks. Besides this, the purpose was to achieve a significant decrease in plasma melatonin levels of these groups due to pinealectomy, and to increase plasma osmolalities through hypertonic applications and increases in hematocrit after hypovolemic stimulation.

It has been accepted that thyroid gland hormones, triiodothyronine and thyroxine are effective on liquid-electrolyte balance and its regulation as they are effective on general metabolism [23, 27]. Different results were obtained in the studies, which aimed to print out the relation of vasopressin and thyroid hormone and these mechanisms could not certainly be revealed. Salomez-Granier et al. [24] examined AVP levels in 26 patients with peripheral hypothyroidism. They observed that AVP levels did not show a significant change in the majority of these patients when compared to the control group. However, AVP levels in four patients increased despite severe myxoedema and low osmolality. In our previous studies, we found significant

decreases in plasma AVP levels due to different stimulations like basal, hypertonic and hypovolemic stimulations as a result of hypothyroidism induced with propylthiouracil or thyroidectomy [20, 21] or due to increase in hyperthyroid rats [22]. On the contrary, it has been shown that vasopressin levels increased in hypothyroidism due to thyroidectomy [30]. It has been demonstrated that AVP release from median eminence increased in hypothyroidism [25]. In a study carried out on patients with hyperthyroidism, AVP levels were found to be higher than control levels. However, AVP levels were found to be similar to control levels after normalization of thyroid gland at the end of the treatment [19]. In our present study, we defined an increase in AVP levels of both basal (unstimulated group) and stimulated (hypertonic and hypovolemic) groups at the end of 4-week L-thyroxine injection. This situation shows that L-thyroxine treatment increases basal and stimulated AVP release. Similar findings were stated in other studies, as well [19, 26]. Ciosek [5] found that intravenous administration of TRH in different doses indicated different effects depending on the dose. However, it has been reported that neurohypophyseal AVP content was raised. Plasma AVP levels were changed in hyperthyroid and simultaneously dehydrated or salt-loaded rats [6]. One of the important findings of our experiments was the increase in hematocrit percentage in the treated groups. Remarkably, there was no decrease in AVP levels despite the increase in hematocrit levels.

This present situation highlights a difference in AVP release mechanisms. It has been reported that AVP release can be induced with mechanisms other than the change in liquid volume [8]. It is also possible that there might be an increase in AVP level as a response to vasodilatation in the periphery due to L-thyroxine treatment.

In the second part of our study, treatment and pinealectomy was investigated in order to determine the AVP release in basal and stimulated conditions. There were significant increases in AVP level due to treatment after pinealectomy. This situation indicates that pinealectomy significantly stimulates basal and stimulated AVP release in L-thyroxine treatment. It was determined that normal AVP release rhythm and AVP response to hypovolemic and hypertonic stimulations change after pinealectomy [10, 11]. It was also reported that plasma vasopressin levels increased in pinealectomized rats, which was inhibited by melatonin application [15]. The findings are parallel to the findings of the previous studies. However, it was reported that vasopressin levels decreased as a response to osmotic stimulation following pinealectomy [28]. It was determined that this mechanism was induced by a decrease in the response of central osmoreceptors due to pinealectomy and that melatonin affected magnocellular system activation. However, in an other study, melatonin support in pinealectomy did not affect the response of vasopressinergic and oxytocinergic neurons to hemorrhage [16]. It was reported that pinealectomy suppressed basal and potassium stimulated vasopressin release from neurointermediate lobe [17]. In our study, as we did not induce melatonin support to the animals in the group after pinealectomy, we cannot comment on whether it may have caused any modulation on the response in pinealectomy. However, it is possible that vasopressin release might have increased by two different mechanisms; both direct increases in AVP release due to pinealectomy. Pinealectomy exhibits an increasing effect on thyroid

hormones. Indeed, an inverse relation was reported between pineal gland and thyroid hormones [2, 3].

The results of the present study indicate that hyperthyroidism modified AVP response to different treatments. Hyperthyroidism induced by L-thyroxine significantly increases both basal and stimulated AVP releases. However, the increase is much more pronounced in the pinealectomized L-thyroxine treated group.

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