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INFLUENCES OF HYPERTONIC AND HYPOVOLEMIC TREATMENTS ON VASOPRESSIN RESPONSE IN PROPYLTHIOURACIL (PTU) INDUCED HYPOTHYROID RAT AND EFFECT ON SUPPLEMENTATION WITH L-THYROXINE

LEYLA AYDIN, R. MOGULKOC* and A. K. BALTACI

Department of Physiology, Meram Medical School, Selcuk University, Konya, Turkey

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This study was performed to investigate the effects of L-thyroxine treatment on plasma vasopressin (AVP) levels in rats with hypothyroidism induced by propylthiouracil (PTU). Animals were separated into three groups each having 6 rats: control, PTU, PTU+L-thyroxine groups. Then, the groups were further divided into 3 sub-groups including 6 rats (a; basal, b; hypertonic stimulated and c; hypovolemic stimulated). At the end of the experiments all rats were decapitated in order to obtain plasma samples for analysis in terms of Hct, osmolality, TT_3, TT_4 and vasopressin. Haematocrit (Hct) levels were the highest in hypovolemic stimulated sub-group ($P < 0.001$). Osmolality levels were higher in hypertonic stimulated sub-groups ($P < 0.001$). Total T_3 and T_4 values were the lowest in the PTU group and the highest in the L-thyroxine treated group ($P < 0.001$). Plasma AVP levels were reduced by hypothyroidism. However, L-thyroxine treatment after the hypothyroidism prevented this reduction ($P < 0.001$). Vasopressin responses to basal, hypovolemic and hypertonic stimulations were the lowest in the PTU group ($P < 0.001$). The results of the present study show that basal and stimulated plasma vasopressin levels are reduced in PTU-induced hypothyroidism. However, L-thyroxine treatment following hypothyroidism prevents this reduction.

Keywords: Hypothyroidism – thyroxine treatment – AVP – osmolality – rat

INTRODUCTION

Regulations of fluid-electrolyte balance are complex. Arginine vasopressin (AVP), angiotensin II, natriuretic peptides, vasoactive intestinal peptide, urotensin II and corticosteroid have roles in the control of water household and maintaining salt balance [17]. It has been shown that increase in the osmolality and reduction in the blood volume can increase AVP release [8]. Thyroid hormones can also affect fluid electrolyte balance [13]. Although increasing the AVP response, the capacity of a kidney to concentrate urine is not enough in congenital hypothyroid rat [1]. In thyroparathyroidectomized rats, glomerular filtration ratio, acid excretion and proximal tubular cell functions were reduced [13]. In another research on rats, propylthiouracil

*Corresponding author; e-mail: rasimmogulkoc@yahoo.com

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(PTU) treatment reduced plasma AVP levels and AVP receptor numbers in liver and kidney [2]. However, oral PTU treatment increased mRNA levels in hypothalamus supraoptic nucleus (SON) and paraventricular nucleus (PVN) [4].

In humans, however, it was reported that hypothyroidism had resulted in marked atrophy of renal tissue [18, 26] and in hyponatremia [22]. In hypothyroidism, AVP release was observed [5, 26]. However, limited research is available as to basal and stimulated AVP levels after the hypothyroidism plus thyroxine treatment.

The present study was carried out to investigate AVP levels in rats with hypothyroidism and hypothyroidism plus L-thyroxine treatment. AVP responses to hypertonic and hypovolemic stimulations were analyzed in hypothyroidism and/or hypothyroidism plus L-thyroxine treatment.

MATERIALS AND METHODS

The study was performed at the Department of Physiology, Medical Faculty, Firat University. Experimental procedure was approved by the local Ethics Committee. The study included total 54 Wistar-albino strain male rats, which were 6 months old and weighed 270–300 g.

Experimental animals were divided into three groups. They were kept at 19–21°C room temperature for 12 hours in dark/light cycle and fed with commercially available rat chew. Experiment animals were divided into three groups from the beginning of the study as follows:

1. General control group (C) (n = 18): Rats were fed with normal rat chew food and water. This group of animals received no treatment during the experiments.

2. PTU (6-n-propyl-2-thiouracil) group (n = 18): To induce hypothyroidism, PTU was given to rats 10mg/kg/day intraperitoneally for 3 weeks [19].

3. PTU + Thyroxine (T_4) (6-n-propyl-2-thiouracil + Thyroxine) group (n = 18): Firstly, PTU was applied for 2 weeks, and then L-thyroxine (obtained from Sigma Chemical Co., Dorset, UK) was given to animals 1.5 mg/kg/day for 1 week [27].

At the end of the application period just before decapitation, animals in all groups were further divided into 3 sub-groups each having 6 rats as follows:

a) Group with unchallenged (a) (n = 6): The animals were decapitated to take plasma.

b) Group with hypertonic stimulation (b) (n = 6): 1.5 mol · l^{-1} NaCl was applied intraperitoneally on the animals in this group as 1 ml/100 g of body weight to the animals were decapitated 15 min later [9].

c) Group with hypovolemic stimulation (c) (n = 6): 250 mg/ml Polyethylene glycol (obtained form Sigma Chemical Co., Dorset, UK) dissolved in 0.15 mol · l^{-1} NaCl was applied intraperitoneally as 2 ml/100 g body weight to the animals in this group before they were decapitated 1 h later in order to take blood samples [9].

All animals were decapitated between 09.00–10.00 a.m. considering the circadian rhythm of AVP release and blood samples were taken. Plasma of blood samples was put into tubes with EDTA and separated in a cooling centrifuge (3000 rev/min).

Derived plasmas were kept in –80 °C until the hormone analysis was made. Heparinized capillary tubes were used for Hct assessment. Derived blood samples were centrifuged for 5 minutes at 1000 rev/min and Hct levels were measured on Hct scale. Plasma osmolalities were read on a osmometer.

Analysis of parameters

HCT levels were given as percent, plasma osmolality levels mOsm/KgH_2O, vasopressin levels pg/ml, Total T_3 ng/dl, and Total T_4 nmol/l. Phoenix Pharmaceutical RIA test kit (catalogue no: RK-065-07) was used for AVP analysis, Elisa test kit was used for Total T_3 levels (Dialab, catalogue no: Q00228, Austria) and Elisa test kit was used for Total T_4 levels (Dialab, catalogue no: Z01232, Austria).

Statistics

Statistical analysis was done using SPSS statistics programme. 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 significance level at $P < 0.005$.

RESULTS

The body weight of rats was not different at the beginning of the study and at the end of the experiments. Hypovolemic stimulated group had the highest Hct levels ($P < 0.001$, Tables 1–3). In the basal groups (a groups), 2a was lower than groups 1a and 3a ($P < 0.001$, Table 4). Group 2b (hypertonic stimulated) was lower than group 1b ($P < 0.03$, Table 4). In hypovolemic stimulated groups, group 3 was higher than

Table 1
Parameters in control (C) group

	Group 1a	Group 1b	Group 1c
B. W. (g) (B. E.)	287.17 ± 6.71	292.00 ± 6.23	289.83 ± 9.00
B. W. (g) (Experiment)	294.00 ± 4.18	297.00 ± 6.71	295.00 ± 9.35
Haematocrit (%)	39.16 ± 1.72	40.50 ± 0.83	47.16 ± 1.16[a]
Osmolality (mOsm/KgH_2O)	279.33 ± 11.57	300.33 ± 11.76[b]	286.67 ± 7.76
TT_3 (ng/dl)	417.71 ± 29.42	416.17 ± 25.85	418.15 ± 27.84
TT_4 (nmol/L)	35.81 ± 3.86	39.45 ± 3.87	37.06 ± 1.84

B. W.: Body Weight (Before Experiment).
[a] $P < 0.001$ compared groups 1a and 1b.
[b] $P < 0.001$ compared groups 1a and 1c.

Table 2
Parameters in PTU group

	Group 1a	Group 1b	Group 1c
B. W. (g) (B. E.)	292.00 ± 4.83	291.50 ± 6.75	290.00 ± 6.03
B. W. (g) (Experiment)	296.00 ± 5.48	296.00 ± 7.42	295.00 ± 5.00
Haematocrit (%)	34.50 ± 0.54	37.33 ± 3.01	45.00 ± 1.41[a]
Osmolality (mOsm/KgH_2O)	268.50 ± 5.89	284.33 ± 7.84[b]	272.67 ± 5.24
TT_3 (ng/dl)	351.68 ± 12.91	326.64 ± 13.76	332.16 ± 19.56
TT_4 (nmol/L)	30.86 ± 1.50	30.76 ± 2.09	29.90 ± 2.85

[a] $P < 0.001$ compared groups 1a and 1b.
[b] $P < 0.001$ compared groups 1a and 1c.

Table 3
Parameters in PTU+T_4 group

	Group 1a	Group 1b	Group 1c
B. W. (g) (B. E.)	289.83 ± 6.24	288.83 ± 7.36	288.67 ± 6.98
B. W. (g) (Experiment)	286.00 ± 6.52	285.20 ± 7.43	287.00 ± 5.70
Haematocrit (%)	38.14 ± 2.26	39.42 ± 0.97	49.42 ± 1.71[a]
Osmolality (mOsm/KgH_2O)	283.50 ± 8.69	302.67 ± 6.65[b]	285.83 ± 5.33
TT_3 (ng/dl)	502.10 ± 23.15	462.07 ± 16.85	477.40 ± 54.88
TT_4 (nmol/L)	44.45 ± 5.01	38.75 ± 4.14	37.16 ± 0.77

[a] $P < 0.001$ compared groups 1a and 1b.
[b] $P < 0.001$ compared groups 1a and 1c.

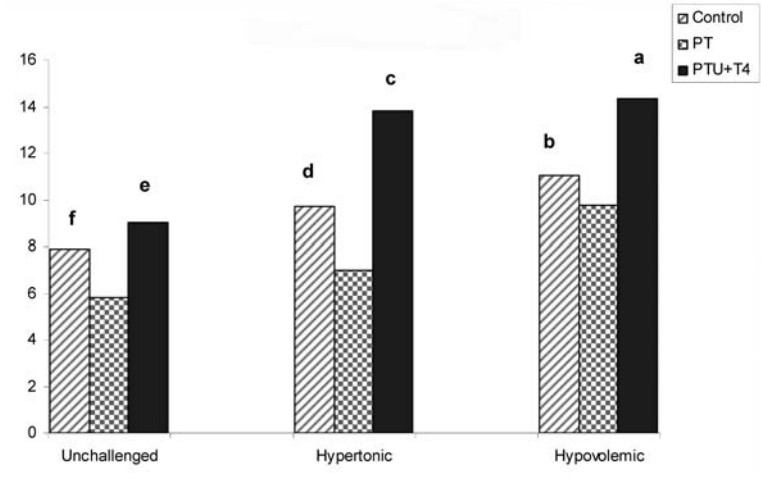

Fig. 1. Plasma AVP levels to unchallenged, hypertonic and hypervolemic stimulations. a – $P < 0.001$, compared to C and PTU hypovolemic; b – $P < 0.001$, compared to PTU hypovolemic; c – $P < 0.001$, compared to C and PTU hypertonic; d – $P < 0.001$, compared PTU hypertonic; e – $P < 0.001$, compared to C and PTU unchallenged; f – $P < 0.001$, compared to PTU unchallenged

group 2 ($P < 0.001$, Table 4). When the osmolality levels were examined, it was seen that group 1b was significantly higher than groups 1a and 1c ($P < 0.001$, Table 1). In groups 2 and 3, b sub-group was significant than other groups ($P < 0.001$, Tables 2–4). The 3b was higher than 2b ($P < 0.01$, Table 4). In hypovolemic sub-groups (c groups), 2c was lower than 1c and 3c ($P < 0.002$, Table 4). Total T_3 levels were not different in the sub-groups of groups 1, 2 and 3. In basal groups, group 3 was the highest, and group 1 was higher than group 2 and lower than group 3 ($P < 0.001$,

Table 4
Parameters in all experiment groups
(Unchallenged, hypertonic and hypovolemic subgroups)

	Unchallenged		
	C	PTU	PTU+T_4
B. W. (g) (B. E.)	287.17 ± 6.71	292.00 ± 4.83	289.83 ± 6.24
B. W. (g) (Experiment)	294.00 ± 4.18	296.00 ± 5.48	286.00 ± 6.52
Haematocrit (%)	39.16 ± 1.72	34.50 ± 0.5[a]	38.14 ± 2.26
Osmolality (mOsm/KgH_2O)	279.33 ± 11.57	268.50 ± 5.8[b]	283.50 ± 8.69
TT_3 (ng/dl)	417.71 ± 29.4[d]	351.68 ± 52.91	502.10 ± 23.1[c]
TT_4 (nmol/L)	35.81 ± 3.86	30.86 ± 1.50[e]	44.45 ± 5.01
	Hypertonic		
	C	PTU	PTU+T_4
B. W. (g) (B. E.)	292.00 ± 6.23	291.50 ± 6.75	288.83 ± 7.36
B. W. (g) (Experiment)	297.00 ± 6.71	296.00 ± 7.42	285.20 ± 7.43
Haematocrit (%)	40.50 ± 0.83	37.33 ± 3.01[a]	39.42 ± 0.97
Osmolality (mOsm/KgH_2O)	300.33 ± 11.76	284.33 ± 7.8[b]	302.67 ± 6.65
TT_3 (ng/dl)	416.17 ± 25.85[d]	326.64 ± 13.76	462.07 ± 16.85[c]
TT_4 (nmol/L)	39.45 ± 3.87	30.76 ± 2.09[e]	38.75 ± 4.14
	Hypovolemic		
	C	PTU	PTU+T_4
B. W. (g) (B. E.)	289.83 ± 9.00	290.00 ± 6.03	288.67 ± 6.98
B. W. (g) (Experiment)	295.00 ± 9.35	295.00 ± 5.00	287.00 ± 5.70
Haematocrit (%)	47.16 ± 1.16	45.00 ± 1.41[a]	49.42 ± 1.71
Osmolality (mOsm/KgH_2O)	286.67 ± 7.76	272.67 ± 5.24[b]	285.83 ± 5.33
TT_3 (ng/dl)	418.15 ± 27.84[d]	332.16 ± 19.56	477.40 ± 54.88[c]
TT_4 (nmol/L)	37.06 ± 1.84	29.90 ± 2.85[e]	37.16 ± 0.77

[a] $P < 0.001$, compared to C and PTU+T_4
[b] $P < 0.001$, compared to C and PTU+T_4
[c] $P < 0.001$, compared to C and PTU.
[d] $P < 0.001$, compared PTU.
[e] $P < 0.001$, compared PTU and PTU+T_4

Table 4). Similar findings were seen for hypertonic and hypovolemic sub-groups ($P < 0.001$, Table 4). For Total T_4 levels, groups 1 and 3 were not different, group 2 was lower than the other two groups ($P < 0.003$, Table 4). In the control group, AVP levels were 7.89 ± 0.45, 9.72 ± 0.73 and 11.06 ± 1.10 (for basal, hypertonic and hypovolemic sub-groups, respectively). In the PTU group, these levels were: 5.83 ± 0.42, 7.00 ± 0.29 and 9.75 ± 0.69, respectively. In the third group (PTU+T_4), AVP levels were 9.03 ± 0.74, 13.80 ± 0.82 and 14.36 ± 0.87, respectively. On examining the AVP levels in all groups, it was seen that in groups 1 and 2, b and c sub-groups were higher than the sub-group. C sub-group was higher than b sub-group ($P < 0.001$, Table 4, Fig. 1). In PTU + T_4 group, b and c sub-groups were not different from each other, but higher than a sub-group ($P < 0.001$, Table 4, Fig. 1). In basal sub-groups (groups a), AVP levels were significantly different from each other. The 2a was the lowest, and 3a was the highest. However, 1a was higher than 2a and lower than 3a ($P < 0.001$, Table 4, Fig. 1). In b sub-groups (hypertonic stimulated), PTU group was lower than control (C) and PTU + T_4 groups. PTU + T_4 group was higher than group 1 (C) ($P < 0.001$, Table 4, Fig. 1). In hypovolemic stimulated sub-groups (groups c), 3c sub-group (PTU + T_4) was significantly higher than sub-groups 1c and 2c ($P < 0.001$, Table 4, Fig. 1). Although control group was higher than PTU group, there was no statistical difference.

DISCUSSION

Rats having same body weight were used in these groups, because this can affect the examined parameters. Hct levels were reduced in hypothyroidism but L-thyroxine treatment prevented these reductions. Our finding is supported by a previous study [15]. However, present findings show that hypovolemic stimulation is important for the AVP release. Similar findings were seen for osmolalities which showed that hypertonic stimulations were effective. However, plasma osmolality levels were reduced in hypothyroidism group. A previous study showed that hypothyroidism caused hyponatremia [22]. It has been postulated that disturbances in water and salt balance mechanisms observed in hypothyroidism were due to thyroid hormone deficiency and reduced AVP levels [3]. Thus, reduced osmolality levels seen in hypothyroidism supported our results [13, 24, 28]. Efficiency of PTU treatment to induce hypothyroidism and L-thyroxine treatment was evaluated as marked decreases and normalization, respectively. Similar findings had been reported previously [23, 28]. However, it has also been reported that AVP response increased due to hypertonic and hypovolemic stimulations [14, 31]. Thyroid hormones are effective for maintaining liquid-electrolyte balance and its regulation due to their effects on overall body metabolism [6, 7]. Different findings were reported in studies which explored relation between thyroid hormones and the AVP release. Salomez-Granier et al. [25] had reported that plasma AVP levels were not different in control vs. hyperthyroidism groups. However, they reported that AVP increase was seen even in mixed edema and low osmolalities. Another study reported that babies had not been affected from

hypo- or hyperthyroid mothers [7]. Zimmerman et al. [32] reported that in hypothyroidism induced by thyroidectomy, AVP levels increased. On the contrary, we have previously found that AVP levels were reduced by thyroidectomy [20]. It was proposed that plasma AVP levels decrease in primary hypothyroidism [11]. Mogulkoc et al. [19] showed that, in hypothyroidism induced by PTU injection for 2 weeks, AVP levels were reduced both in basal and stimulated conditions. In the present study, PTU treatment for 3 weeks caused reduced AVP levels not only in basal but also hypertonic and hypovolemic stimulations. Moreover, in our present study, we determined that both plasma osmolalities and AVP levels were reduced after PTU treatment. Vargas et al. [29] have reported that urinary AVP excretion increased in hyperthyroidism while vasopressin release decreased under different stimulations. Mogulkoc et al. [19, 20] found that AVP response to hypertonic and hypovolemic stimulations was reduced in hypothyroidism induced by PTU treatment or thyroidectomy. It has been postulated that impaired AVP release affects renal functions by two different mechanisms. Firstly, adenylate cyclase activity in renal medulla is reduced which affects stimulation of AVP receptors. Secondly, AVP receptor biosynthesis is impaired due to thyroid hormone deficiency. Therefore, it has been generally accepted that due to impairment of these mechanisms, AVP levels decrease in hypothyroidism [2, 3, 13]. In the second section of the study, basal and stimulated AVP responses were studied under high dose L-thyroxine treatment by a week of hormone substitution after hypothyroidism. Present findings showed that L-thyroxine treatment corrected the impaired AVP responses to different stimulations and even increases in thyroid hormones elevated plasma AVP levels. These results support the previous study. Stempniak et al. [28] reported that reduced AVP release in hypothyroidism was increased following L-thyroxine treatment. Once again, Marcisz et al. [16] determined that increased AVP release was normalized after the correction of thyroid function. We found that AVP response to hypovolemic stimulation is more significant as compored to other stimulations. Though some studies do not support our findings [12], a number of studies are in parallel with ours and show that hypovolemic stimulation increases AVP response [9, 10, 20]. It is postulated that deterioration of thyroid function can occur through the renin-angiotensin system. Similar findings have been reported previously [21]. In a study that searched through the relation between vasopressin release and aquaporins, an increase of AVP release due to elevated aquaporins in renal medulla and cortex was reported [5]. However, it has been shown that although L-thyroxine treatment could correct increased AVP levels in thyrotoxicosis, it could not reduce aquaporins [30].

The results of the present study show that basal and stimulated plasma AVP levels are reduced in hypothyroidism. However, L-thyroxine treatment following hypothyroidism prevents these reductions. On the other hand, the results show that vasopressin response to hypertonic and hypovolemic stimulations is not changed in thyroid dysfunction.

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