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Effects of Thyroid Hormone on the Renal Dopaminergic System

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This study determined the effects of thyroid hormone on the renal dopaminergic system. Surgical thyroidectomy (Tx) and treatment with 2-thiouracil (Thio) decreased renal cortex Na^+/K^+ ATPase activity and urinary volume. Tx also decreased urinary Na^+ and urinary L-DOPA without changing urinary excretion of Dopamine (DA). Thio treatment decreased slightly urinary L-DOPA and Na^+, but increased urinary excretion of DA. In both models of thyroid hormone deficiency, the ratio urinary DA/DOPA increased. Changes after Thio treatment were reversed after one month of drug withdrawal. Treatment with T_3 via osmotic minipump increased Na^+/K^+ ATPase activity and urinary L-DOPA, did not change urinary DA, and increased the ratio DA/DOPA.

To further analyze the effects of thyroid hormone deficiency, we administered selective DA_1 (SCH-23390), DA_2 (Sulpiride), and a non selective (Haloperidol) DA receptor antagonists to Thio treated and control animals. The DA_1 antagonist decreased diuresis, natriuresis and urinary L-DOPA in control, but had no effect in Thio treated rats. Sulpiride had no effect in either group. The combination of SCH-23390 plus Sulpiride decreased urinary L-DOPA and urinary volume only in Thio treated animals. Haloperidol decreased urinary volume in Thio treated animals, but had no effect in controls.

Our findings suggest that renal DA synthesis is to some extent dependent on thyroid hormone levels, and that the response of DA receptors is altered by thyroid hormone deficiency, indicating a role of this hormone in the regulation of the renal dopaminergic system.

Key Words: Thyroid hormone; renal dopamine; Na^+/K^+ ATPase; urinary dopamine; 2-thiouracil; dopamine antagonists; SCH-23390; sulpiride; haloperidol.

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Introduction

Besides their well known effects on metabolism, growth, and differentiation, thyroid hormones have significant effects on renal hemodynamics and tubular function. Thyroid hormone deficiency has been associated to decreased glomerular filtration rate and renal plasma flow. On the contrary, thyroid hormone excess is associated with increased glomerular filtration rate and renal plasma flow. This hormone also influences tubular membrane transport and electrolyte metabolism *(1–3)*. The effects of thyroid hormone on renal tubular function have been related to its effects on Na^+/K^+ ATPase, an enzyme playing a pivotal role in several tubular transport processes. This hormone induces *de novo* synthesis of both alpha and beta subunits of Na^+/K^+ ATPase in several tissues *(4–6)*, including the kidney *(7)*. Thyroid hormone excess results in increased renal tubular capacity for active transport, including an increase in Na^+/K^+ ATPase with consequent increases in sodium transport *(2,8)*. In contrast, thyroid hormone deficiency is associated with decreased tubular transport capacity, and the activity of Na^+/K^+ ATPase in the kidney is decreased, particularly in the proximal tubules, resulting in impaired Na^+ transport *(3–10)*.

Dopamine (DA) is known to modulate important vascular and renal functions such as blood pressure, and salt and water homeostasis. There is strong evidence suggesting that renal DA may play an important role in the regulation of Na^+ excretion *(11)*. It has been shown that circulating L-DOPA is filtered by the kidney, and that a major proportion of the DA in rat and human urine derives from decarboxylation of L-DOPA in proximal tubular cells. The inhibition of L-DOPA decarboxylation attenuates natriuretic responses *(12)*, decreases urinary excretion of DA *(13)*, and blunts DA excretory responses to volume changes *(12)*. The effects of DA produced in the tubules on Na^+ regulation have been related to inhibition of the activities of Na^+/K^+ ATPase *(14)*, and the Na^+/H^+ exchanger *(15)* in the proximal convoluted tubules of the kidney and other segments of the nephron *(16–18)*. Also, in vitro experiments using rat renal cortex slices have suggested that the synthesis of DA in the kidney is dependent on the concentration of sodium chloride in the medium, and sensitive to inhibition of the tubular transport of Na^+ *(19)*.

Because, as mentioned above, thyroid hormone affects tubular transport of Na^+, we designed this study to assess

the effects of thyroid hormone on the renal dopaminergic system. Urinary excretions of Na^+, L-DOPA, DA, the DA metabolite dihydroxyphenylacetic acid (DOPAC), and activity of Na^+/K^+ ATPase in the renal cortex were determined after surgical thyroidectomy, treatment with 2-thiouracil, and also after administration of T_3. Our results showed that thyroid hormone affects renal DA synthesis, suggesting increased DA synthesis in thyroid hormone deficient rats. To further assess the modifications induced in renal dopaminergic function in these animals, we studied the effects of the administration of different DA receptor blockers. We treated the animals with SCH-23390, a selective DA_1 antagonist that has an antidiuretic *(20)* and antinatriuretic effect *(21)* in normal rats, sulpiride, a selective DA_2 antagonist, and Haloperidol, a non-selective DA antagonist to determine modifications in diuresis, natriuresis, and urinary excretions of L-DOPA, DA and DOPAC.

Materials and Methods

Three month old male Wistar rats were used in these studies. All animals were bred in our laboratory, kept at 22ºC on a 12:12 h dark-light cycle and given free access to normal rat diet (protein content 25%) and tap water.

Effect of Thyroid Hormone Deficiency

Animals were surgically thyroidectomized at 45 day-old ($n = 14$) under light ether anesthesia. Another group of the same age was subjected to a sham operation ($n = 17$). Both groups were supplemented with 1% calcium lactate on tap water *ad libitum*. Forty five days after surgery, the animals were placed in metabolic cages and 24 h urine was collected.

Another group of animals (70 days old, $n = 14$) were given 2-thiouracil (4-hydroxy-2-mercaptopyrimidine, 500 mg/L) in their drinking water for 21 days. A control group was maintained on tap water ($n = 11$). On day 22, animals were placed in metabolic cages and 24 h urine was collected as described below. After the first urine collection, animals ($n = 7$) of each group were killed by decapitation, and plasma samples and kidneys were collected as described below. The remaining animals were transferred to their home cages and maintained on tap water for one month before a second 24 h urine collection (2-thiouracil treated $n = 7$; controls $n = 4$).

Effect of Thyroid Hormone Excess

To assess the effect of thyroid hormone excess, T_3 ($n = 9$) or vehicle ($n = 9$) were infused for 7 days via an osmotic minipump (model 2001, Alza Corporation, Palo Alto, CA) inserted under the skin in the interscapular region during light ether anesthesia. The T_3 dose was 10 µg/kg/day (infusion rate 22.5 µL/day; 125 µg/mL Sodium-liothironine). After treatment, animals were placed in metabolic cages and 24 h urine was collected.

Effect of Administration of Dopaminergic Antagonists to 2-Thiouracil Treated Animals

Control animals and rats treated with 2-thiouracil for 21 days were individually placed in metabolic cages on the morning of day one of the study. A basal 24 h urine sample was collected from each animal. Animals were then randomly assigned to one of the following treatments that started in the morning of day two: SCH-23390 (1 mg/kg/day sc: in two doses; $n = 6$ in each group–control or 2-thiouracil treated), a selective DA_1 antagonist; Sulpiride (6 mg/kg/day im; in two doses; $n = 9$ in each group), a selective DA_2 antagonist; SCH-23390 plus Sulpiride (same doses as before; $n = 7$ in each group), Haloperidol (300 µg/kg/day ip; in 4 doses; $n = 4$ in each group), a non-selective DA antagonist. 24 h urine samples were collected during the day of the study.

All urines were collected into 6N HCl. Urine content of Na^+ was determined by flame-photometry. Urinary concentrations of L-DOPA, DA and DOPAC were determined as described below. Plasma T_4 levels were measured by RIA using a commercially available kit (DPC, CA, USA). Kidneys were stored at −70ºC until assayed for the activity of Na^+/K^+ ATPase in cortex homogenates.

Assays

Catechols Determination

The catechols in 10 µL urine were determined as reported previously *(20)*. Briefly, catechols in the samples were partially purified by batch alumina extraction, separated by reverse-phase high-pressure liquid chromatography using a 4.6 × 250 mm ODS 5 µm column (Axxiom Chromatography Inc., USA), and quantified amperometrically by the current produced upon exposure of the column effluent to oxidizing and then reducing potentials in series using a triple-electrode system (ESA, Bedford, MA). Recovery through the alumina extraction step averaged 70–80% for catecholamines, 45–55% for L-DOPA and 40% for DOPAC. Catechol concentrations in each sample were corrected for recovery of an internal standard, dihydroxybenzylamine. Levels of L-DOPA, DA and DOPAC were further corrected for differences in recovery of the internal standard and of these catechols in a mixture of external standards. The limit of detection was about 15 pg/volume assayed for each catechol.

Measurement of Na^+/K^+ ATPase Activity

Slices of renal cortex were homogenized in 25 mM phosphate buffer pH 7.4. Homogenates were centrifuged at 2000 rpm for 10 min. Supernatants were centrifuged at 12000 rpm for 30 min and pellets resuspended in the original volume of the same buffer. Na^+/K^+ ATPase activity in a membrane suspension was measured as described *(21)* in a buffer pH 7.4 containing (in mM) 120 NaCl, 5 KCl, 10 $MgCl_2$, 1 EDTA, 100 Tris-HCl, 10 Na_2ATP and [γ-^{32}P]ATP (2-5 Ci/mmol) in tracer amounts, using a 15 min incubation time at 37ºC in

Table 1
Plasma Levels of T_4, T_3, TSH, Body Weight, Urinary Volume, Na^+ Excretion, Urinary DOPAC, Plasma L-DOPA and the Activity of Na^+/K^+ ATPase in Renal Cortex Homogenates in Control, Thyroidectomized (Tx) and Rats Treated for 21 Days with 2-Thiouracil (Thio), One Month after Withdrawal of 2-Thiouracil Treatment (Thio Withdrawal) and Rats Treated with T_3 for 7 Days

	Control	Tx	Thio	Thio withdrawal	T3 treatment
Plasma T_4 (mg/dL)	3.34 ± 0.29	1.29 ± 0.15#	0.77 ± 0.12#	4.02 ± 0.44	
Plasma T_3 (mg/dL)	5.84 ± 0.40				7.00 ± 0.40#
Plasmatic TSH (mg/mL)	4 ± 1	51 ± 6*			
Body Weight (gr)	358 ± 16	210 ± 9#	307 ± 11#	341 ± 25	334 ± 20
Urinary Volume (mL/24 h)	12.25 ± 1.20	4.13 ± 0.44*	8.50 ± 0.29*	13.50 ± 1.50	13.00 ± 1.40
Urinary Sodium (mEq/24 h)	1.05 ± 0.11	0.55 ± 0.06#	0.98 ± 0.13	1.02 ± 0.17	1.15 ± 0.15
Na^+/K^+ ATPase (μmol Pi/mg prot/h)	9.28 ± 1.26	3.94 ± 0.72#	2.17 ± 0.90*	7.52 ± 0.84	13.60 ± 1.60*
Plasma L-DOPA (pg/mL)	360 ± 72	399 ± 87#			
Urinary DOPAC (ng/24 h)	15242 ± 2072	3136 ± 554#	20584 ± 2096	16449 ± 2257	16895 ± 1500

Values are mean ± SEM. #$p < 0.04$; *$p < 0.005$ vs Control.

the absence or presence of 4 mM ouabain. When ouabain was present, NaCl and KCl were ommitted from the incubation medium. The phosphate liberated by hydrolysis of [γ-^{32}P]ATP was separated by centrifugation after adsorption of unhydrolyzed nucleotide on activated charcoal. Radioactivity was measured in a liquid scintillation spectrometer. Na^+/K^+ ATPase activity was calculated as the difference between the means of determinations performed in the presence and in the absence of ouabain, and expressed as μmol of ^{32}P hydrolyzed per mg protein per hour.

Data Analysis

Data are means ± SE. Independent means t-test or one-way ANOVA were used to assess the significance of differences between treated and control animals. A paired t-test was used to assess the differences in groups before and after treatment with dopaminergic antagonists. Linear regression analysis was used to calculate correlation between variables. $p < 0.05$ defined statistical significance.

Results

Effect of Thyroid Hormones Deficiency and Excess

Table 1 shows plasma levels of thyroid hormones and L-DOPA, body weight, urinary volume, urinary sodium, urinary DOPAC, and renal Na^+/K^+ ATPase activity, in surgically thyroidectomized (Tx), 2- thiouracil treated, T_3 treated and control animals.

Thyroidectomy and 2-thiouracil treatment significantly reduced T_4 plasma levels. Neither group gained weight as the control group did. At the time of the urine collection, body weight was significantly lower in both thyroidectomized and 2-thiouracil treated animals than in the control group. Urinary volume was also significantly lower than in controls in both Tx animals and 2-thiouracil treated, while the urinary excretion of Na^+ was lower in the Tx group than in controls but similar to controls in the 2-thiouracil treated group. The activity of Na^+/K^+ ATPase in membranes from renal cortex was reduced significantly in both models of thyroid deficiency. Plasma L-DOPA was similar in control and thyroidectomized animals. Treatment with T_3 via an osmotic mini-pump raised plasma levels of T_3, and increased the activity of Na^+/K^+ ATPase in renal cortex, but had no significant effect on body weight, urinary volume or urinary excretion of Na^+ (Table 1).

Figure 1 shows that thyroidectomy and 2-thiouracil treatment reduced urinary excretion of L-DOPA, although the reduction in the later group did not reach statistical significance, while treatment with T_3 increased urinary DOPA. Urinary DA was increased in 2-thiouracil treated animals, but was similar to controls in Tx and T_3 treated rats. As a result, the ratio urinary DA to L-DOPA was significantly increased in Tx as well as in 2-thiouracil treated rats, and significantly decreased in T_3 treated animals. Conversely, urinary DOPAC was significantly lower in the Tx rats but was similar in 2-thiouracil treated, T_3 treated, and control animals (Table 1).

One month after withdrawal of 2-thiouracil treatment, the effects of the treatment on plasma T_4, body weight, urinary volume, and renal cortex Na^+/K^+ATPase activity (Table 1) as well as on urinary excretions of L-DOPA, DA, and the DA/DOPA ratio (Fig. 1) were completely abolished.

Effect of Administration of DA Antagonists to 2-Thiouracil Treated Animals

Administration of SCH-23390, a selective DA_1 antagonist, significantly decreased diuresis (68 ± 13%, $p < 0.05$) in control animals, but did not produce any significant modification in 2-thiouracil treated rats. Administration of sulpiride, a selective DA_2 antagonist, had no effect on urinary volume in any of the groups. Administration of SCH-23390

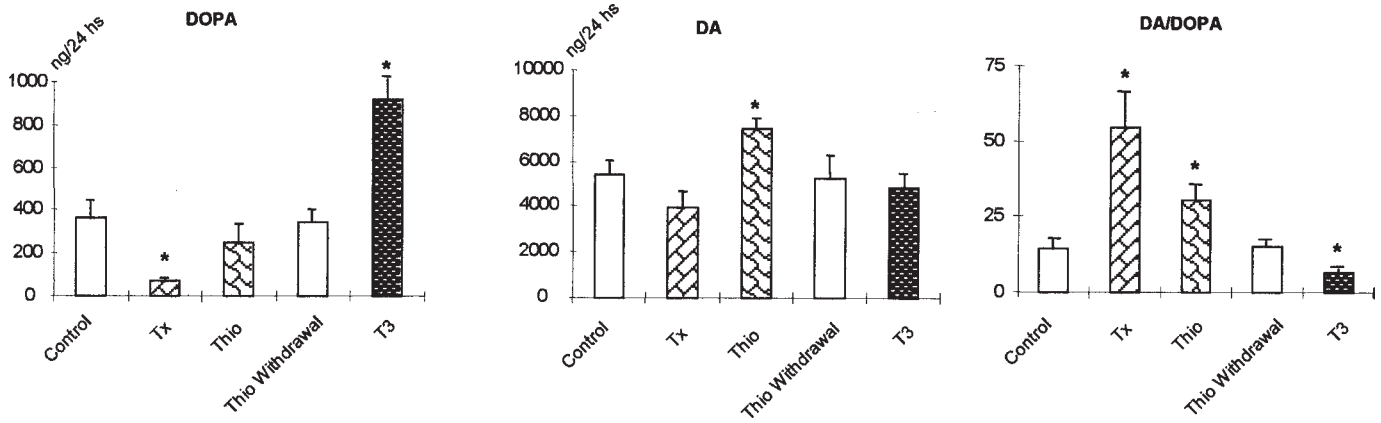

Fig. 1. Urinary excretion of L-DOPA, Dopamine (DA), and the ratio urinary DA/L-DOPA in control, thyroidectomized (Tx), animals treated for 21 days with 2-thiouracil (Thio), one month after withdrawal of 2-thiouracil (Thio withdrawal), and rats treated with T_3 for 7 days. *$p < 0.02$.

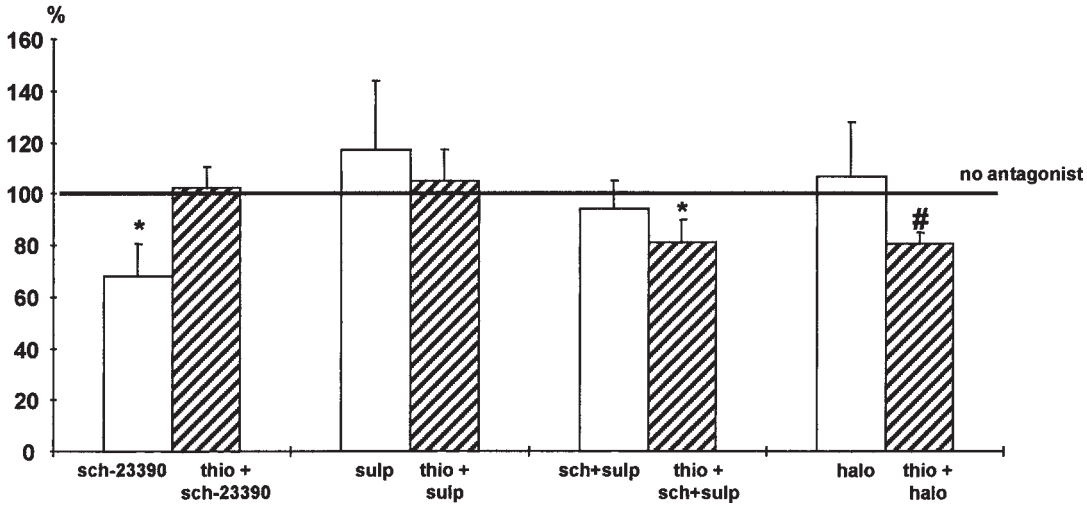

Fig. 2. Urinary volume in control (white bars) and animals treated for 21 days with 2-thiouracil rats (dashed bars), after treatment with different DA antagonists (SCH-23390, Sulpiride or Haloperidol), in percentage compared with the same group before antagonist treatment. The line in 100% represents the basal urinary volume for each group. *$p < 0.05$; #$p < 0.02$.

plus sulpiride, or haloperidol decreased further the diuresis (SCH + Sulpiride: 81 ± 12%; $p < 0.05$, haloperidol: 80 ± 4%, $p < 0.02$) in animals treated with 2-thiouracil, but had no effect in control rats (Fig. 2).

Administration of SCH-23390 decreased Na^+ excretion (52 ± 17%, $p < 0.05$, Fig. 3) in control animals but had no effect in 2-thiouracil treated rats. Administration of sulpiride had no significant effect in any of the groups. Administration of SCH-23390 plus sulpiride, or haloperidol did not affect Na^+ excretion in either control or treated animals.

Administration of SCH-23390 significantly decreased L-DOPA (82 ± 12 vs 212 ± 30 ng/24 h, $p < 0.01$, Table 2) in control animals, and also decreased, although not significantly, DOPAC excretion, but had no affect on the increased DA excretion observed in 2-thiouracil treated rats. Treatment with Sulpiride did not effect urinary excretions of L-DOPA, DA, or DOPAC in either group. Administration of SCH-23390 plus Sulpiride did not significantly affect urinary catechols in control animals but significantly decreased L-DOPA excretion in 2-thiouracil treated rats (114 ± 20 vs 241 ± 69 ng/24 h, $p < 0.05$). Treatment with haloperidol significantly decreased the increased excretion of DA (5780 ± 260 vs 7650 ± 870 ng/24 h, $p < 0.05$), and not significantly those of L-DOPA and DOPAC in 2-thiouracil treated animals, but was without significant effect in control rats.

Discussion

This study shows that thyroid hormone deficit and excess are associated with alterations in the renal dopaminergic system.

In thyroidectomized animals, hypothyroidism was confirmed by decreased levels of plasma T_4, increased levels

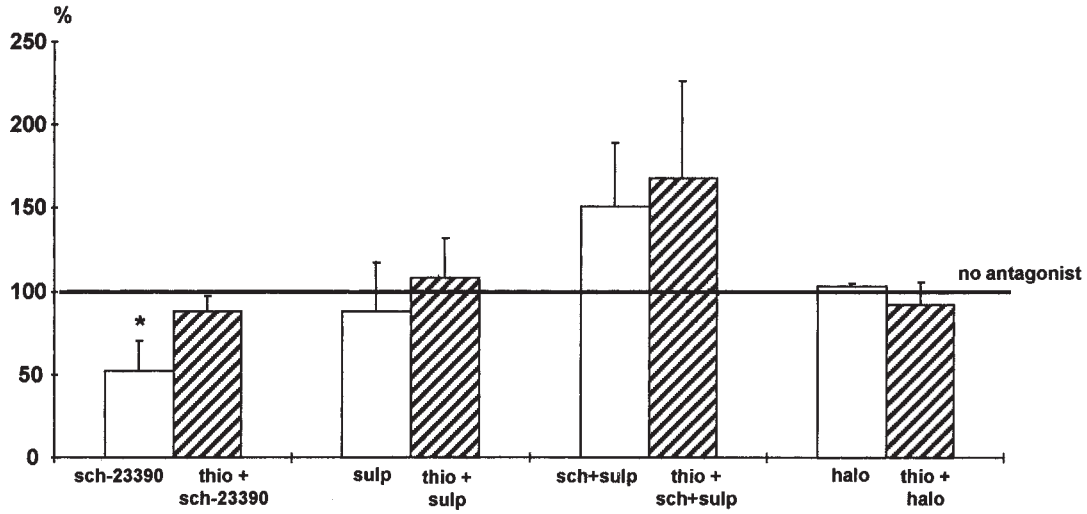

Fig. 3. Urinary excretion of sodium in control (white bars) and animals treated for 21 days with 2-thiouracil rats (dashed bars), after treatment with different DA antagonists (SCH-23390, Sulpiride or Haloperidol), in percentage compared with the same group before antagonist treatment. The line in 100% represents the basal urinary excretion of sodium for each group. *$p < 0.05$.

Table 2
Urinary Levels of L-DOPA, DA, and DOPAC in Control and 2-Thiouracil-treated Animals after Different DA Antagonists Treatments

	Control animals			2-Thiouracil-treated animals		
Treatment	L-DOPA	DA	DOPAC	L-DOPA	DA	DOPAC
SCH-23390	42 ± 09#	98 ± 15	84 ± 20	78 ± 16	102 ± 10	83 ± 11
Sulpiride	105 ± 21	117 ± 14	101 ± 21	141 ± 44	174 ± 34	140 ± 30
SCH + Sulpiride	102 ± 29	103 ± 10	89 ± 13	65 ± 17*	107 ± 13	161 ± 33
Haloperidol	151 ± 74	132 ± 25	174 ± 49	84 ± 33	77 ± 06*	70 ± 10

SCH-23390 ($n = 6$), Sulpiride ($n = 9$), SCH and Sulpiride ($n = 7$) and Haloperidol ($n = 4$) results (mean ± SEM) are expressed as percent of the urinary excretion on day 1. *$p < 0.05$, #$p < 0.01$ vs urinary excretion on day 1.

of plasma TSH, and difference in weight gain after treatment. After treatment for 21 days with 2-thiouracil, rats had decreased levels of plasma T_4 and decreased weight gain. Also, hypothyroid animals had a marked decrease in renal cortex Na^+/K^+ ATPase activity in line with that previously described in kidney *(5)* and other organs *(2–4)*. Conversely, rats treated with T_3 had increased plasma levels of the hormone and increased renal cortex Na^+/K^+ ATPase, in line with previous reports *(22)*.

Urinary L-DOPA was decreased in thyroidectomized rats and increased in T_3 treated animals. Urinary L-DOPA derives from L-DOPA filtered from the plasma and not reabsorbed in the tubules *(23)*. Thus, changes in urinary L-DOPA may result from changes in plasma levels of L-DOPA. However, this change seems not to be the cause of decreased urinary L-DOPA in thyroidectomized animals, since plasma levels of L-DOPA in this group were similar to those in control animals. Changes in urinary L-DOPA may also result from overall changes in tubular reabsorption. However, changes in tubular reabsorption described in both hypothyroid and hyperthyroid animals are opposite to the changes that would explain urinary L-DOPA differences in our study. Decreased urinary L-DOPA may result from increased tubular reabsorption, but in hypothyroid animals, tubular reabsorption has been found to decrease *(3)*. It is possible that changes in excretion of L-DOPA are derived from changes in renal plasma flow, since thyroid hormones deficiency is associated with decreased and excess thyroid hormones with increased renal plasma flow *(3)*.

The finding of increased urinary DA in 2-thiouracil treated animals and unchanged urinary DA in the presence of decreased excretion of L-DOPA in thyroidectomized animals reflects an increased DA/DOPA ratio in both groups of thyroid deficient animals suggesting an increased renal

production or decreased degradation of DA relative to L-DOPA in hypothyroidism. On the contrary, excess thyroid hormone was associated with increased excretion of L-DOPA, unchanged urinary DA, and decreased DA/DOPA ratio suggesting decreased renal DA production or increased degradation. A significant fraction of urinary DOPAC derives from the metabolization of renal DA *(25)*. In 2-thiouracil treated rats, urinary DOPAC was similar to that in control animals, thus the increased urinary DA most likely reflects increased renal production of the amine. Similarly, in T_3 treated animals, unchanged urinary DOPAC suggests decreased renal DA production rather than increased degradation. Because in thyroidectomized animals urinary DOPAC was decreased, increased urinary DA in these animals may also result from decreased degradation of the amine.

Both in vivo and in vitro studies have suggested that the synthesis of DA in proximal tubular cells is influenced by extracellular concentrations of Na^+ *(23)*. Other studies have suggested this synthesis is dependent on Na^+/K^+ ATPase activity *(19)*. Experiments performed in rat renal cortex slices have shown that the synthesis of DA in the kidney is dependent on the concentration of sodium chloride in the medium, and sensitive to inhibition of the tubular transport of Na^+ *(19)*. In our study the decrease in Na^+/K^+ ATPase activity brought about by thyroid hormone deficiency was associated with increased rather than decreased DA production and increased pump activity after T_3 treatment was associated with decreased rather than increased DA production, suggesting that in these models, renal DA synthesis is not directly dependent on the activity of the pump.

In order to clarify the effects of increased renal DA synthesis in 2-thiouracil treated animals, we studied the effects of administration of DA antagonists. The results of these studies suggested impaired renal dopaminergic function in thyroid hormone deficient animals. Administration of a DA_1 antagonist had a clear antidiuretic and antinatriuretic effect in control animals, but had no such effect in those thyroid deficient. In control animals, SCH-23390 has been shown to attenuate the diuretic effect of high salt diet *(20)*, and to produce antinatriuresis when infused in the renal artery *(21)*. It has also been shown to attenuate the diuretic and natriuretic responses to acute sodium loading without altering the increase in urinary dopamine *(11,26)*. Both the effects on diuresis and natriuresis have been reported to be related to the blockade of renal tubular dopaminergic receptors, since no clear modification in renal hemodynamics was present *(11,21)*. In this study, however, SCH-23390 administered systemically also decreased L-DOPA excretion, suggesting that it may have also affected renal hemodynamics resulting in decreased filtered load of L-DOPA. SCH-23390 had no effect in animals with thyroid hormone deficiencies similar to that reported in spontaneously hypertensive rats *(21)*, which also have increased urinary DA or DA responses *(27,28)*. Blockade of both DA_1 and DA_2 receptors either by administration of the combination of SCH-23390 and sulpiride, or by haloperidol produced a clear modification in diuresis in hypothyroid animals, suggesting an alteration in the regulation of renal hemodynamics in these animals. Sodium excretion was not modified by administration of any of the DA antagonists, suggesting that Na^+ balance is independent of renal dopaminergic activity in animals with thyroid deficiency. Our findings point to an altered dopaminergic activity in hypothyroid animals. Such an alteration has been reported in striatal dopaminergic function in the neonatal hypothyroid rat *(29)*, and adult hypothyroid animals *(30)*.

In conclusion, our findings suggest that renal DA synthesis is to some extent dependent on thyroid hormone levels, and that the response of DA receptors is altered by thyroid hormone deficiency, indicating a role of this hormone in the regulation of the renal dopaminergic system. In thyroid deficient animals, changes in renal uptake and/or decarboxylation of L-DOPA may represent a compensatory mechanism, contributing to preservation of urinary sodium excretion, similar to what has been suggested in patients with asymptomatic left ventricular systolic dysfunction *(24)*.

It remains to be established to what extent these alterations participate in the changes in glomerular filtration rate and renal plasma flow associated with alterations in thyroid hormones levels *(31,3)*.

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References

1. Katz, A. I., Emmanouel, D. S., and Lindheimer, M. D. (1975). *Nephron* **15,** 223–249.
2. Moses, A. and Scheinman, S. (1996). In: *Werner and Ingbar's The Thyroid*, 7th ed. Braverman, Lewis, E. and Utiger, R. D. (eds.). Lippincott-Raven Publishers: Philadelphia, PA, pp. 628–631.
3. Moses, A. and Scheinman, S. (1996). In: *Werner and Ingbar's The Thyroid*, 7th ed. Braverman, Lewis, E. and Utiger, R. D. (eds.). Lippincott-Raven Publishers: Philadelphia, PA, pp. 812–815.
4. Desai-Yaknik, V., Zeng, J., Omori, K., Sherman, J., and Morimoto, T. (1995). *Endocrinology* **136,** 629–639.
5. Heguvary, C. (1977). *Res. Com. Chem. Path.* **17(4),** 689–702.
6. Mc Bride, B. and Early, R. (1989). *Br. J. Nutr.* **62(3),** 673–682.
7. Mc Donough, A. A., Brown, T. A., and Horowitz, B. (1988). *Am. J. Physiol.* **254,** C323–C329.
8. Cutler, R. E., Glatte, H., and Dowling, J. T. (1967). *J. Clin. Endocr. Metab.* **27,** 453–460.
9. Kinsella, J. and Sacktor, B. (1985). *Proc. Natl. Acad. Sci. USA* **82,** 3606.

10. Garg, L. C. and Tisher, C. C. (1985). *J. Lab. Clin. Med.* **106(5),** 568.
11. Hedge, S. S. and Lockhandwala, M. F. (1990). *Am. J. Hypertens.* **3,** 78S–81S.
12. Sowers, J. R., Crane, P. D., Beck, F. W. J., McClanahan, M., King, M. E., and Mohanty, P. K. (1984). *Endocrinology* **115,** 2085–2090.
13. Ball, S. G. and Lee, M. R. (1977). *Br. J. Clin. Pharmacol.* **4,** 115–119.
14. Aperia, A., Bertorello, A., and Seri, I. (1987). *Am. J. Physiol.* **252,** F39–F45.
15. Felder, C. C., Campbell, F., Albrecht, F., and Jose, P. A. (1990). *Am. J. Physiol.* **259,** F297–F303.
16. Bertorello, A. M. and Katz, A. I. (1993). *Am. J. Physiol.* **265,** F743–F755.
17. Grider, J., Kilpatrick, E., Ott, C., and Jackson, B. (1998). *Eur. J. Pharmacol.* **342(2–3),** 281–284.
18. Satoh, T., Cohen, H. T., and Katz, A. I. (1993). *Am. J. Physiol.* **265,** F399–F405.
19. Soares-Da-Silva, P. and Fernandes, M. H. (1992). *Br. J. Pharmacol.* **105,** 811–816.
20. Eisenhofer, G., Goldtein, D. S., Stull, R., Keiser, H. R., Sunderland, T., Murphy, D. L., and Kopin, I. J. (1986). *Clin. Chem.* **32,** 2030–2033.
21. Armando, I., Nowicki, S., Aguirre, J. A., and Barontini, M. (1995). *Am. J. Physiol.* **268,** F1087–F1092.
22. Kinsella, J. and Sacktor, B. (1985). *Proc. Natl. Acad. Sci. USA* **82,** 3606–3611.
23. Lee, M. R. (1993). *Clin. Sci. (Lond)* **84,** 357–375,
24. Ferreira, A., Bettencourt, P., Pestana, M., Oliveira, N., Serrao, P., Maciel, M. J., Cerqueira-Gomes, M., and Soares-Da-Silva, P. (2000). *Clin. Sci. (Colch)* Sep 1;**99(3),** 195–200.
25. Wolfovitz, E., Grossman, E., Folio, C. I., Keiser, H. R., Kopin, I. J., and Goldstein, D. S. (1993). *Clin. Sci.* **84,** 549–557.
20. Sharif, N. A., Nunes, J. L., Lake, K. D., McClelland, D. L., Corkins, S. F., Lakatos, I., Rosenkranz, R. P., Whitting, R. L., and Eglen, R. M. (1995). *Gen. Pharmacol.* **26,** 717–735.
21. Felder, R. A., Seikaly, M. G., Cody, P., Eisner, G. M., and Jose, P. A. (1990). *Hypertension* **15,** 560–569.
26. Hansell, P. and Fasching, A. (1991). *Kidney Int.* **39,** 253–258.
27. Stier, C. T. Jr., Itskovitz, H. D., and Chen, Y. H. (1993). *Clin. Exp. Hypertens.* **15(1),** 105–123.
28. Racz, K., Kuchel, O., Buu, N. T., and Tenneson, S. (1985). *Circ. Res.* **57(6),** 889–897.
29. Vaccari, A., Rossetti, Z. L., de Montis, G., Stefanini, E., Martino, E., and Gessa, G. L. (1990). *Neuroscience* **35(3),** 699–706.
30. Crocker, A. D., Overstreet, D. H., and Crocker, J. M. (1986). *Pharmacol. Biochem. Behav.* **24(6),** 1593–1597.
31. Vaamonde, C. A., Sebastianelli, M. J., Vaamonde, L. S., Pellegrini, E. L., Watts, R. S., Klinger, E. L. Jr., and Papper, S. (1975). *J. Lab. Clin. Med.* **85,** 451–466.