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An Elevation of Plasma TSH Concentration in Spontaneously Hypertensive Rats (SHR) (38874)

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Thyroidal radioiodine uptake and release varied somewhat from strain to strain in rats, but no abnormal elevation or depression has been reported in rats (1). Okamoto (2) isolated a new strain from Wistar rats with spontaneous hypertension and noticed that this strain of rats had bigger thyroids, adrenals, and pituitaries than those of the control strain. Since coincidence of an increase of pituitary and thyroid weights suggests an increased production and release of TSH by the anterior pituitary, the present experiment was undertaken to study TSH concentrations of the anterior pituitary and circulating blood and to measure thyroid activity in response to an increase of blood TSH. The data indicated that spontaneously hypertensive rats (SHR) had not only high blood pressure but also an abnormal increase of blood TSH.

Materials and Methods. Control rats and SHR were obtained from two different sources. One substrain of SHR was obtained from NN Laboratory, and the other substrain of SHR was bred in Kyoto University. Only male rats were used for the experiments. The animals were fed laboratory chow and water ad lib. unless otherwise stated. In experiment 2, animals were fed low-iodine diets beginning 10 days before radioiodine injection. Radioiodine (1.7 μCi of ^{131}I) was injected intraperitoneally, and autopsy was performed 24 hr later. At autopsy, blood was obtained by cardiac puncture, using heparinized syringes. Plasmas were separated and kept at $-20°$ until use. The pituitary, thyroid, and adrenal were cleanly dissected out and weighed on a torsion balance. Thyroid and adrenal weights were expressed as mg/100 g body wt. In experiment 3, 2 μg T_4 was injected intraperitoneally daily for 7 days beginning 3 days after thyroidectomy. Bloods were drawn 24 hr after the last dose of T_4. Pituitary and plasma TSH concentrations were measured as reported previously (3). Plasma thyroxine (T_4) concentration was measured by competitive binding assay. Plasma triiodothyronine (T_3) concentration was measured by radioimmunoassay. To rule out the error associated with measurements of T_4, T_3 and TSH, pooled plasma was always used as the standard. Plasma PB^{131}I was measured as reported previously (4). Blood pressures were measured by tail-pulse pickup in unanesthetized rats. The data were analyzed for statistical significance by the Student *t* test.

Results. Experiment 1. Serum thyroxine, triiodothyronine, and TSH levels, and pituitary contents of TSH. In the first step of this experiment, rats were obtained from NN Laboratory Blood pressure of SHR was 185 $\pm$ 7 mm Hg (mean $\pm$ SE), while it was 135 $\pm$ 6 mm Hg (mean $\pm$ SE) in the controls. Plasma T_4 was slightly but significantly less in SHR than in the controls. Plasma T_3 concentration was the same in both SHR and control groups (Table I). However, plasma TSH concentration was significantly elevated in SHR. Also, pituitary content of TSH increased significantly in SHR.

In the second part of this experiment, rats were obtained from Kyoto University. Blood pressure of SHR was 194 $\pm$ 7 mm Hg, while it was 137 $\pm$ 6 mm Hg in the controls. Plasma T_4 and T_3 concentrations decreased significantly in SHR.

Experiment 2. Thyroid activity and adrenal weight in SHR. Rats were obtained from NN Laboratory. Blood pressure of SHR was 192 $\pm$ 8 mm Hg, while it was 130 $\pm$ 4 mm

TABLE I. PLASMA THYROXINE, TRIIODOTHYRONINE, AND TSH LEVELS, AND PITUITARY CONTENT OF TSH.

Group	No. of animals	Body wt (g)	Plasma T_4 (μg/100 ml)	Plasma T_3 (ng/100 ml)	Plasma TSH (μU/ml)	Pituitary TSH (mU/pituitary)
Control (NN)	5	285±6[a]	5.0±0.4	82±8.2	34.2±3.2	212±18
SHR (NN)	5	274±8	3.5±0.2	90±8.8	61.0±14.1	409±12
P value		NS	<0.05	NS	<0.02	<0.02
Control (Kyoto)	5	280±7	4.6±0.2	89±2.0	35.2±8.4	
SHR (Kyoto)	5	275±6	1.3±0.2	34±2.0	85.4±17.1	
P value		NS	<0.01	<0.01	<0.05	

[a] Mean ± SE. Control (NN), control rats were obtained from NN Laboratory, SHR (NN), spontaneously hypertensive rats were obtained from NN Laboratory.

TABLE II. THYROID ACTIVITY AND ADRENAL WEIGHT.

Group	No. of animals	Body wt (g)	Thyroid wt (mg/100 g body wt)	Thyroidal ^{131}I uptake	Plasma $PB^{131}I$ (cpm)	Adrenal wt (mg/100 g body wt)
Control (NN)	6	180±6[a]	6.6±0.5	39.5±3.2	176±31	11.4±0.4
SHR (NN)	6	172±9	8.5±0.8	58.0±3.1	129±10	16.8±1.0
P value		NS	<0.02	<0.02	NS	<0.02

[a] Mean ± SE. Abbreviations are the same as in Table I.

TABLE III. PLASMA THYROXINE, TRIIODOTHYRONINE, AND TSH LEVELS, AND PITUITARY TSH CONTENT IN THYROIDECTOMIZED RATS INJECTED WITH 2 μg THYROXINE DAILY FOR 7 DAYS.

Group	No. of animals	Body wt (g)	Plasma T_4 (μg/100 ml)	Plasma T_3 (ng/100 ml)	Plasma TSH (μU/ml)	Pituitary TSH (mU/pituitary)
Control (NN)	5	210±8[a]	2.8±0.5	26±3.9	52.8±11.4	203±36
SHR (NN)	5	198±5	2.7±0.3	24±6.2	109.0±11.9	385±51
P value		NS	NS	NS	<0.01	<0.02

[a] Mean ± SE. Abbreviations are the same as in Table I.

Hg in the controls. As shown in Table II, thyroid and adrenal weights were increased significantly in SHR. The average thyroidal radioiodine uptake at 24 hr was significantly more in SHR than in the controls. On the other hand, plasma $PB^{131}I$ was the same in both groups.

Experiment 3. Plasma thyroxine, triiodothyronine, and TSH levels, and pituitary TSH content in thyroidectomized rats injected with thyroxine daily for 7 days. Rats were obtained from NN Laboratory. Blood pressure of SHR was 190 ± 6 mm Hg, while it was 133 ± 5 mm Hg in the controls. Serum T_4 and T_3 levels were the same in both control and SHR groups. In spite of these findings, plasma TSH concentrations were elevated significantly in SHR. Pituitary TSH content was significantly more in SHR than in the control group (Table III).

Discussion. In SHR, thyroid activity varied somewhat from substrain to substrain, but a consistent finding was that plasma TSH concentration was elevated significantly regardless of which substrain of SHR was used. It is, therefore, concluded that the anterior pituitary of SHR is synthesizing and secreting supernormal amounts of TSH because of unknown reasons. In order to study this subject, we measured plasma T_4 and T_3 concentrations in two substrains of SHR. Plasma T_4 and T_3 concentrations were significantly depressed in Kyoto substrain of SHR, suggesting that hypothyroid-

ism was the cause of increased TSH secretion. In contrast, NN substrain of SHR was apparently euthyroid as evidenced by normal plasma T_3 levels, but had an elevated TSH concentration. This suggested that there were some individual variations from subgroup to subgroup in terms of thyroid activity. The most likely explanation to account for the results obtained from the NN substrain is that the pituitary "hormostat" (5) is set at a higher level. This hypothesis is further supported by an additional experiment in which thyroidectomized NN substrain rats were injected with 2 μg T_4 daily for 7 days. As shown in Table III, plasma T_4 and T_3 concentrations were the same in SHR and control groups, suggesting that peripheral metabolism of thyroid hormones was not altered in SHR. Nevertheless, the pituitary content of TSH increased significantly under this experimental condition. On the basis of these findings, it can be concluded that the pituitary is synthesizing and secreting an excess of TSH under normal concentration of circulating thyroid hormones. Thus, an exact site of abnormality should be in the anterior pituitary, hypothalamus, or both.

Although hypertension and increased secretion of TSH are present in both substrains of SHR, the exact causal relation between TSH and hypertension is not known at present.

Summary. Thyroid activity was tested in two substrains of SHR. Plasma level and pituitary content of TSH increased significantly in both substrains of SHR. As a result, the thyroid weight and thyroidal radioiodine uptake increased significantly. Plasma T_3 concentration was decreased in Kyoto substrain but was normal in NN substrain, while plasma T_4 concentration decreased significantly in both substrains. Since the pituitary content and plasma level of TSH were significantly higher in spite of the normal concentration of plasma T_3, it is concluded that the pituitary "hormostat" is set at a higher level at least in the NN substrain of SHR.

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