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Congenital Abnormality of Pituitary-Thyroid Axis in Spontaneously Hypertensive Rats (SHR) and Stroke-Prone Rats (SPR) (39081)

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Our previous study (1) has shown that the plasma TSH level was elevated in a substrain of spontaneously hypertensive rats (SHR), in spite of normal plasma triiodothyronine (T_3) concentration. Although this unexpected finding provided a new aspect of abnormality in SHR, an exact relationship between the development of hypertension and the elevation of plasma TSH was not well analyzed in our previous paper (1). Since the development of hypertension is genetically determined in SHR (2), it is possible that an abnormal pituitary–thyroid axis is also genetically determined in this strain. However, it is equally possible that an elevation of TSH is produced after the development of hypertension for unknown reasons. To shed some light on this subject, we have repeatedly measured plasma concentrations of TSH, prolactin, thyroxine (T_4), and T_3 in rats at intervals of 1 to 3 months. Control rats, SHR, and stroke-prone rats (SPR) (3) were the animals used to measure hormone concentrations. The data indicated that abnormal pituitary–thyroid interplay did appear earlier than the development of hypertension in SHR and SPR.

Materials and methods. All rats used were bred at Kyoto University. Only male animals were used for the experiments. The animals were fed laboratory chow and water *ad lib*. Two groups of animals were used, the 15-day-old group, and a second group of five control rats, five SHR, and five SPR, which were transferred from Kyoto University to Shinshu University at the age of 1 month and were used for the subsequent experiments. Blood was obtained by cardiac puncture at the age of 15 days, 1 month, 2 months, 3 months and 6 months. Plasma was separated and kept at −20°C until use. Plasma T_4, T_3, TSH, and prolactin were measured as reported previously (1, 4). Blood pressure was measured by tail pulse pickup in unanesthetized rats. The data were analyzed for statistical significance by the Student t test; a P value of less than 0.05 was considered statistically significant.

Results. At the age of 15 days, blood was obtained from five controls, five SHR and five SPR by opening the thorax. Plasma T_3 concentrations of SPR and SHR were less than those of the controls (Table I). On the other hand, the plasma TSH concentrations of SHR were significantly more than those of the controls and of the SPR.

In 1-month-old rats, blood pressure was normal in the controls, SHR and SPR. At this time, however, the plasma T_3 concentration was the same in the controls and SPR, but was significantly less in SHR than in those two groups. As compared to the controls, plasma TSH concentration was significantly elevated in SHR and SPR, but the increase was more in SHR than in SPR. Also, plasma prolactin concentration was raised in SPR.

In 2-month-old rats, hypertension was not observed in any of the groups. As was found in 1-month-old groups, plasma T_3 concentration was the same in the controls and SPR, but was significantly less in SHR. Again, plasma TSH concentration was significantly more in SHR and SPR than in the controls. On the other hand, plasma prolactin concentration was the same in the three groups.

In 3-month-old rats, hypertension was still not observed in any of the groups. As observed in 2-month-old groups, plasma TSH concentration was more in SHR and SPR than in the controls.

In 6-month-old rats, hypertension was noticed in SHR and SPR. At this stage,

TABLE I. ALTERATIONS OF PLASMA CONCENTRATIONS OF THYROXINE, TRIIODOTHYRONINE, TSH AND PROLACTIN WITH AGE IN SHR AND SPR

Age and group	Body weight g	Blood pressure mm Hg	Plasma concentration of hormone			
			T_4 μg/100 ml	T_3 ng/100 ml	TSH μU/ml	Prolactin ng/100 ml
15-day-old[a]						
SPR (5) (5)	18 ± 3			81.5 ± 9.8[b]	31.3 ± 3.0	
SHR (5) (5)	17 ± 4			64.0[c]	60.0 ± 9.6	
Control (5)	20 ± 3			114.7 ± 13.8	21.2 ± 4.0	
1-month-old[d]						
SPR (5)	84 ± 3	123 ± 6		107.0 ± 15.9	27.3 ± 1.6	3.7 ± 0.58
SHR (5)	64 ± 3	118 ± 4		79.0 ± 13.0	44.9 ± 9.2	2.8 ± 0.72
Control (5)	74 ± 3	110 ± 7		127.0 ± 12.0	21.5 ± 1.9	1.8 ± 0.29
2-month-old[e]						
SPR (5)	193 ± 13	130 ± 5		100.1 ± 6.9	40.8 ± 7.4	6.8 ± 1.7
SHR (5)	190 ± 11	120 ± 7		81.4 ± 6.0	47.8 ± 6.7	8.4 ± 1.6
Control (5)	200 ± 7	116 ± 5		128.0 ± 14.0	23.3 ± 3.1	5.3 ± 1.7
3-month-old[f]						
SPR (5)	250 ± 10	135 ± 15			40.7 ± 6.6	
SHR (5)	224 ± 10	123 ± 6			49.9 ± 4.7	
Control (5)	252 ± 12	115 ± 5			21.7 ± 4.5	
6-month-old[g]						
SPR (5)	343 ± 5	208 ± 2	4.3 ± 0.2	84.1 ± 1.0	60.3 ± 5.8	9.5 ± 5.1
SHR (5)	383 ± 7	188 ± 3	1.3 ± 0.2	34.8 ± 2.0	85.4 ± 7.1	12.6 ± 4.8
Control (5)	412 ± 10	121 ± 7	4.6 ± 0.2	89.1 ± 2.0	35.2 ± 8.4	10.0 ± 1.6

[a] TSH: SPR vs Control, $P < 0.05$; SHR vs Control $P < 0.001$; SHR vs SPR, $P < 0.005$.

[b] Mean ± SE.

[c] Pooled plasma.

[d] Determination for 1–6 months old were made in the same group of animals.

T_3: SHR vs Control, $P < 0.05$. TSH: SHR vs Control, $P < 0.001$; SPR vs Control, $P < 0.05$; SHR vs SPR, $P < 0.01$. Prolactin: SPR vs Control, $P < 0.05$.

[e] T_3: SHR vs Control, $P < 0.05$. TSH: SHR vs Control, $P < 0.01$; SPR vs Control, $P < 0.01$.

[f] TSH: SHR vs Control, $P < 0.01$; SPR vs Control, $P < 0.01$.

[g] Blood pressure: SHR vs Control, $P < 0.01$; SPR vs Control, $P < 0.01$. T_4: SHR vs Control, $P < 0.05$; SHR vs SPR, $P < 0.05$. T_3: SHR vs Control, $P < 0.001$; SHR vs SPR, $P < 0.005$. TSH: SHR vs Control, $P < 0.005$; SPR vs Control, $P < 0.005$; SHR vs SPR, $P < 0.05$.

plasma T_4 concentration was the same in the controls and SPR, but was significantly less in SHR. Similarly, plasma T_3 concentration was the same in the controls and SPR, but was significantly less in SHR. On the other hand, plasma TSH concentration was increased in SHR and SPR, but the increase was more in SHR than in SPR. No difference in plasma prolactin concentration was found among the three groups.

Discussion. In SHR and SPR used in this experiment, hypertension appeared at the age of 6 months but not at the age of 3 months. Since hypertension usually appeared at the age of 10 to 15 weeks (5), occurrence of hypertension was delayed somewhat in our experiment. The exact reason for this delay is not known. At any rate, it was found that plasma T_4 and T_3 concentrations were decreased significantly and that the plasma TSH level, conversely, was elevated in 6-month-old-SHR, the results being similar to those of our previous study (1). Furthermore, our present study indicated that adult SPR did show an increase of plasma TSH despite normal T_4 and T_3 concentrations. Since hypothyroid patients sometimes did show an elevated prolactin concentration in the plasma (6), we have further measured plasma prolactin concentration in three groups of adult animals, but failed to detect any differences among the three groups.

Therefore, we conclude that hypertensive rats (SHR and SPR) have elevated plasma TSH concentrations regardless of their plasma T_4 and T_3 concentrations.

A possible abnormality in pituitary–thyroid axis was then studied in young rats in which hypertension did not yet appear. At the ages of 1 and 2 months, SHR did have a low plasma T_3 concentration on one hand, and an elevated TSH concentration on the other hand. Furthermore, normal T_3 concentration and elevated TSH level were found in 1 and 2-month-old SPR. Thus, the endocrine changes found in rats without hypertension were very similar to those found in adult rats with hypertension. This suggested that TSH abnormality was genetically determined in SHR and SPR. In support of this concept, 15-day-old SHR did have a low plasma T_3 concentration and a high plasma TSH level.

Based on the data of thyroidectomized, T_4-maintained rats, our previous study (1) suggesged that the pituitary thermostat (7) for thyroid hormone was set at a higher level in SHR because of some abnormalities in the pituitary, hypothalamus, or both. Since catecholamine metabolism in the brain is abnormal in SHR (8, 9), and since catecholamine is involved in the secretion of TRH (10), an increased secretion of TSH may be in some way related to an increase of TSH synthesis or release. To test this hypothesis, further experiments are in progress in our laboratory. Quite interestingly, plasma prolactin concentration was slightly more in 1-month-old SHR and SPR. However, since this increase subsided gradually with age, the measurement in younger animals is required to establish the concept that prolactin secretion is also abnormal in SHR and SPR.

Summary. In an attempt to study whether TSH abnormality was genetically determined in SHR and SPR, plasma T_4, T_3, TSH and prolactin concentrations were measured in the animals with intervals of 1 to 3 months. Hypertension was found in 6-month-old SHR and SPR, but it was not found in younger animals. In contrast, a decrease of plasma T_3 and an increase of plasma TSH were found in 15-day-old SHR. Also, an increase of TSH was found in 1-month-old SPR in spite of normal plasma T_3 concentration. These abnormalities in SHR and SPR increased progressively with age. It is suggested that thyroid–pituitary abnormality was genetically determined in SHR and SPR.

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