Role of the Thyroid Gland in the Development and Maintenance of Spontaneous Hypertension in Rats

F. Rioux and B.A. Berkowitz

SUMMARY We studied the vascular mechanisms involved in the prevention of the development of hypertension following thyroidectomy. Ablation of the thyroid gland of 4-week-old spontaneously hypertensive (SH) rats inhibited the development of hypertension and reduced the sensitivity of aortic strips to the vasoconstrictors phenylephrine, norepinephrine, and potassium chloride and the vasodilator isoproterenol. Daily injections of a replacement dose of L-thyroxine caused a complete recurrence of hypertension in these rats. This was accompanied by complete recovery of the aortic sensitivity to the vasoconstrictors and isoproterenol. In 10-week-old SH rats thyroidectomy prevented a further increase of blood pressure but did not reverse the hypertension. Here, the aortic sensitivity to vasoactive substances was reduced but to a lesser extent than in the SH rats thyroidectomized at 4 weeks of age. Hypertension was not obviously associated with hyperfunction of the thyroid gland. Furthermore, we found that at 4 weeks of age, during the prehypertensive period, SH rats have a significantly lower (42%) serum thyroxine level than age-matched normotensive Kyoto Wistar, American Wistar, and Sprague-Dawley rats. However, at 6 and 9 weeks, the serum thyroxine levels of SH rats are similar to those of the normotensive rats. In conclusion, we propose that the reduced sensitivity to endogenous vasoconstrictors in arteries of SH rats following juvenile ablation of the thyroid gland may prevent the development of hypertension in these rats. Moreover, the low serum thyroxine level in SH rats during the prehypertensive period may explain why young SH rats do not develop hypertension before 6 weeks of age.

THE ROLE of the thyroid gland in spontaneous hypertension has not yet been established. Aoki suggested that the thyroid gland is an essential organ for the development and maintenance of spontaneous hypertension in rats. The intraperitoneal injection of 1,000 μC of radioactive iodine to young rats not yet hypertensive was found to prevent completely the development of hypertension. Similar treatment progressively reduced the high blood pressure of adult spontaneously hypertensive (SH) rats toward the normotensive level. Oral administration of a thyroid powder to radiothyroidectomized SH rats caused a complete recurrence of hypertension. Yamabe reported both an increased uptake and rate of release of 131I from the thyroid gland of SH rats compared to control normotensive rats at 40–60 days and at 4–6, 12–14, and 18–20 months of age. The thyroid hormone secretion rate, measured by the indirect technique of Reinke and Singh, was also reported to be greater in SH rats than in control rats at the ages mentioned above. These results supported the hypothesis of Aoki that the thyroid activity of SH rats was increased.

Contradictory results recently were reported by Freely. The uptake of 131I by the thyroid gland of SH rats was found to be reduced compared to normotensive controls; the rate of release of thyroidal radioactivity also was reduced in SH rats, whereas the thyroid hormone secretion rate evaluated by the same method as that of Yamabe was greater in SH rats than in controls. Werner et al. observed a decreased serum thyroxine level in SH rats compared to age-matched normotensive Wistar rats. However, the serum thyroxine level of the SH rats was greater than that of the closely related normotensive Kyoto Wistar rats. From these results, it cannot be decided whether or not hypertension in SH rats is associated with hyperfunction of the thyroid gland.

In this study we have tried to better elucidate the role of the thyroid gland in spontaneous hypertension and particularly to study the vascular mechanism(s) involved in the prevention of the development of hypertension in SH rats following ablation of the thyroid gland.

Methods

In the first series of experiments we used 36 male SH rats, 4–5 weeks old. At 2 and 4 weeks after surgical thyroidectomy (thyroparathyroidectomy) (TPX), weight, systolic blood pressure, and heart rate of sham-operated and TPX rats were measured. The effectiveness of thyroidectomy was assessed by comparing rectal body temperature and total serum thyroxine of sham-operated and TPX rats. At 40 days after surgery 10 of the TPX SH rats were divided in two groups: one group (five rats) received daily subcutaneous injection of 1-thyroxine (3 μg/100 g, Calbiochem) dissolved in 0.05 ml of peanut oil; the second group (five rats) received only peanut oil. The treatment was continued for 45 days. Weight, systolic blood pressure, and heart rate were recorded once a week during the treatment. At the end of this period SH rats of both groups were killed by a blow on the head and exsanguinated by cutting the carotid arteries. The thoracic aorta was removed, placed in Krebs' solution at 20°C, and cleared of fat, blood, and connective tissues. Spiral strips were cut from the aorta and prepared according to the method of Furchgott and Bhdarokam. Strips 3.0 cm in length and 1.0–1.5 mm wide were suspended in 10-ml organ baths,
TABLE 1  Effect of Thyroidectomy on Some Physiological Parameters of Young Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Time after surgery (days)</th>
<th>Sham-operated</th>
<th>Thyroidectomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>86.0 ± 4.3</td>
<td>132.0 ± 4.9</td>
</tr>
<tr>
<td>15</td>
<td>190.2 ± 6.6</td>
<td>81.0 ± 3.0</td>
</tr>
<tr>
<td>30</td>
<td>116.2 ± 3.2*</td>
<td>140.0 ± 3.6†</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125.0 ± 2.5</td>
<td>188.0 ± 3.2</td>
</tr>
<tr>
<td>0</td>
<td>196.2 ± 5.8</td>
<td>127.0 ± 4.2</td>
</tr>
<tr>
<td>15</td>
<td>145.0 ± 3.0†</td>
<td>147.0 ± 3.4†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>480.0 ± 10.2</td>
<td>459.0 ± 4.9</td>
<td>468.0 ± 9.3</td>
</tr>
<tr>
<td>0</td>
<td>490.0 ± 8.0</td>
<td>346.0 ± 10.2†</td>
</tr>
<tr>
<td>15</td>
<td>317.0 ± 4.8†</td>
<td></td>
</tr>
</tbody>
</table>

There were 18 rats in each group, 4-5 weeks old on the day of surgery. Results are expressed as mean ± SE.
* Statistically different from values of sham-operated rats (P < 0.02).
† Statistically different from values of sham-operated rats (P < 0.001).

TABLE 2  Effect of Thyroxine on the Weight, Blood Pressure, and Heart Rate of Thyroidectomized Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Period of treatment (days)</th>
<th>Sham-operated</th>
<th>Thyroidectomized</th>
<th>Thyroidectomized + thyroxine treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>216.0 ± 12.0</td>
<td>210.0 ± 11.0</td>
<td>200.0 ± 10.0</td>
</tr>
<tr>
<td>20</td>
<td>259.0 ± 12.0</td>
<td>251.0 ± 11.0</td>
<td>250.0 ± 10.0</td>
</tr>
<tr>
<td>45</td>
<td>311.0 ± 12.0</td>
<td>309.0 ± 11.0</td>
<td>309.0 ± 10.0</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>140.0 ± 6.0</td>
<td>140.0 ± 6.0</td>
<td>140.0 ± 6.0</td>
</tr>
<tr>
<td>0</td>
<td>141.0 ± 6.0</td>
<td>141.0 ± 6.0</td>
<td>141.0 ± 6.0</td>
</tr>
<tr>
<td>20</td>
<td>140.0 ± 7.0</td>
<td>140.0 ± 7.0</td>
<td>140.0 ± 7.0</td>
</tr>
<tr>
<td>45</td>
<td>133.0 ± 7.0</td>
<td>133.0 ± 7.0</td>
<td>133.0 ± 7.0</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>±12.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
</tr>
<tr>
<td>±12.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
</tr>
<tr>
<td>±12.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
</tr>
<tr>
<td>±12.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
<td>±14.0 ± 7.0</td>
</tr>
</tbody>
</table>

Five rats in each group received daily subcutaneous injections of thyroxine (3 μg/100 g of body weight). The treatment began 40 days after surgery. Results are expressed as mean ± SE.
* Statistically different from the values of thyroidectomized rats (P < 0.02).
† Statistically different from the values of thyroidectomized rats (P < 0.001).

containing an oxygenated (95% O₂-5% CO₂) Krebs’ solution at 37°C. A tension of 1 g was applied to each strip. A 2-hour equilibration period with several washes was allowed before adding drugs to the bath. Changes of tension were recorded with an isometric force displacement transducer (Grass FT 03) coupled to a Grass polygraph. Dose-response curves to phenylephrine hydrochloride (Sigma), norepinephrine (Sigma), and potassium chloride (Fisher) were obtained by cumulative additions of the compounds. Intervals of 60 minutes were allowed between each dose-response curve. Only one dose-response curve to each agonist was obtained on each tissue. Dose-response curves to isoproterenol hydrochloride (Winthrop) and nitroglycerin (Lilly) were obtained by cumulative addition of each compound to strips half-maximally contracted with KCl. Possible effects of isoproterenol on α-adrenergic receptors were prevented by pretreating the tissues with phentolamine hydrochloride (Ciba) (9.0 × 10⁻⁶ M) for 20 minutes. The length of the tissues was measured at the end of the 2-hour equilibration period. At the end of the experiments the tissues were blotted carefully and weighed. Changes in tension were expressed as grams per cross-

![Figure 1](image1.png)  
**Figure 1**  Dose-response curves for phenylephrine on aortic strips removed from sham-operated spontaneously hypertensive (SH) rats (A), thyroidectomized SH rats (B), and thyroxine-treated thyroidectomized SH rats (C). The thyroidectomy was performed on 4-week-old SH rats. Each point is the mean ± SE of five experiments. Asterisks indicate a significant difference between thyroidectomized SH rats and each of the two other groups (P < 0.001).

![Figure 2](image2.png)  
**Figure 2**  Dose-response curves for potassium chloride on aortic strips removed from the same groups of spontaneously hypertensive rats as in Figure 1.
sectional area. Results obtained with isoproterenol and nitroglycerin were expressed in percent of the maximal relaxation; maximal relaxation is referred to the distance between plateau of contraction and initial baseline level.

In the second series of experiments we used 10-week-old SH rats. Weight, systolic blood pressure, and heart rate were measured on days 0, 15, 30, and 45 after surgical thyroidectomy. Some of the rats received daily subcutaneous injections of l-thyroxine (3 μg/100 g of body weight) during the first 15 days after the surgery. TPX SH rats were given CaCl₂·2H₂O, 0.7%. On day 46, rectal body temperature and serum thyroxine level were determined. Aortic strips from sham-operated and TPX SH rats were used as before.

In the third series of experiments we used 4-, 6-, and 9-week-old Kyoto Wistar and SH rats provided by Hoffman-LaRoche. Age-matched American Wistar and Sprague-Dawley rats (purchased from Charles River Breeding Laboratories) were also used for comparison. All of these rats were male. They were given Purina rat chow and tap water except phenylephrine and isoproterenol, which were dissolved in saline. There were five rats in each group, thyroidectomized at 4 weeks of age. The treatment with thyroxine was started 40 days after the operation and lasted for 45 days. Results are expressed as the mean ± SEM of ED₅₀ values.

![](https://image.pollinations.ai/prompt/3D illustration of a graph showing dose-response curves for isoproterenol on aortic strips removed from the same rats as in Figure 2. The relaxant effect of isoproterenol was measured on tissues half-maximally contracted with potassium chloride. Same as in Figure 1.)

### Table 3 Effect of Thyroidectomy and Thyroxine Treatment on the Sensitivity of Aortic Strips of Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Sham-operated</th>
<th>Thyroidectomized</th>
<th>Thyroidectomized + thyroxine treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine (× 10⁻⁶ M)</td>
<td>6.3 ± 1.6*</td>
<td>62.0 ± 8.0</td>
<td>4.6 ± 0.2*</td>
</tr>
<tr>
<td>Potassium chloride (× 10⁻⁴ M)</td>
<td>6.3 ± 0.8*</td>
<td>23.1 ± 0.2</td>
<td>5.9 ± 0.8*</td>
</tr>
</tbody>
</table>

* Statistically different from values of thyroidectomized rats (P < 0.001).

When the thyroid glands are removed surgically a problem most investigators face is the possibility that the parathyroid glands also are removed or damaged. Accordingly, the surgery is considered a thyroparathyroidectomy (TPX) and CaCl₂·2H₂O, 0.7%, is given to the rats to drink instead of tap water in order to avoid parathyroid tetany. Surgery and sham-operations (incision and probing of glands but no ablation of tissue) were performed under sodium pentobarbital (Abbott) anesthesia (50 mg/kg, ip).

The SH rats which we utilized were derived from the original Okamoto-Aoki colony and bred at Hoffman-LaRoche. The systolic blood pressures and heart rates of unanesthetized SH rats were recorded with a photoelectric transducer coupled to a Carworth rat blood pressure monitor and to a Gould recorder and amplifier. The cuff inflation was done with an automatic Narco cuff pump.

The composition of the Krebs' solution was (millimolar): NaCl, 118.2; KCl, 4.6; KH₂PO₄, 1.2; MgSO₄·7H₂O, 1.2; CaCl₂·2H₂O, 2.5; NaHCO₃, 25.0; glucose, 10.0; and the disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA), 0.03. All drugs were dissolved in saline except phenylephrine and isoproterenol, which were dissolved in 0.01 N HCl. Fresh stock solutions were made daily. Concentrations of all drugs are expressed as molar.

All the results were expressed as the mean ± SEM. The differences between means were compared by Student's t-test and those with P values of 0.05 or less were considered to be significant.

### Results

The effect of thyroidectomy on the weight, systolic blood pressure, and heart rate of 4- to 5-week-old SH rats is shown in Table 1. At 15 days after the surgery the weights, blood pressures, and heart rates of TPX SH rats were significantly reduced compared to those of sham-operated SH rats. Similar results were obtained 30 days after the surgery. At the end of this 4-week period the body temperature of TPX SH rats was significantly lower (P < 0.001) than that of sham-operated SH rats (37.0 ± 0.2°C, n = 10, for TPX SH rats and 38.5 ± 0.2°C, n = 10, for sham-operated SH rats). The serum thyroxine level was 0.3 ± 0.1 μg/100 ml, n = 10, in TPX SH rats and 5.5 ± 0.2 μg/100 ml, n = 10, in sham-operated SH rats. The difference in serum thyroxine level was significant (P < 0.001).

At 40 days after surgery, daily subcutaneous injections of thyroxine (3 μg/100 g of body weight) were given to a group of five TPX SH rats. The effect of this treatment on the growth, systolic blood pressure, and heart rate of young SH rats is illustrated in Table 2.
treatment both weight and heart rate of TPX SH rats receiving treatment were significantly higher than those of untreated TPX SH rats. However, the blood pressure was not significantly different between these two groups. After 45 days of treatment the blood pressure of thyroxine-treated TPX SH rats was restored to hypertensive level.

Assuming that the high blood pressure level of SH rats is maintained by an increased vascular resistance, we tested the hypothesis that thyroidectomy prevented the development of hypertension in young SH rats by decreasing the sensitivity of arteries to vasoconstrictors. To investigate this question we compared the sensitivity to vasoconstrictors and vasodilators of aortic strips removed from sham-operated, TPX, and thyroxine-treated TPX SH rats (Figs. 1 and 2).

The sensitivity to phenylephrine and KCl of aortic strips removed from TPX SH rats was found significantly lower than that of aortic strips removed from sham-operated rats. Similar results were obtained with norepinephrine as the agonist. Thyroxine restored completely the sensitivity to vasoconstrictors of aortic strips removed from TPX SH rats. Doses of phenylephrine or KCl required to cause 50% of the maximal effect (ED₅₀) in strips of aorta of the different groups of rats are summarized in Table 3. The ratio of ED₅₀ values for phenylephrine-contrasted strips in TPX and sham-operated SH rats was 2 times greater than the ratio of ED₅₀ values for KCl-contrasted strips of the same group of rats. Thyroidectomy was also found to reduce significantly the ability of isoproterenol, a β-adrenergic stimulant, to relax aortic strips of young TPX SH rats. This is illustrated in Figure 3. Thyroxine treatment restored completely the vasodilator property of isoproterenol. Nitroglycerin-induced relaxation of aortic strips removed from young SH rats was not affected by thyroidectomy or thyroxine treatment.

The effect of thyroidectomy on the weight, blood pressure, and heart rate of 10-week-old SH rats is presented in Table 4. At 15 days after the surgery there was a loss of weight and an apparent reduced rate of growth in the TPX SH rats compared to sham-operated SH rats. Daily subcu-

### Table 4  Effect of Thyroidectomy and of Thyroidectomy plus Thyroxine Treatment on the Weight, Blood Pressure, and Heart Rate of Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Time after surgery (days)</th>
<th>Sham-operated</th>
<th>Thyroidectomized</th>
<th>Thyroidectomized + thyroxine treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>243.0 ± 7.0</td>
<td>198.0 ± 6.3*</td>
<td>265.0 ± 5.2</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>190.0 ± 4.1</td>
<td>230.0 ± 12.0</td>
<td>200.0 ± 8.2*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>465.0 ± 14.5</td>
<td>357.0 ± 17.1*</td>
<td>372.0 ± 8.0*</td>
</tr>
</tbody>
</table>

There were 12 rats in each group. The surgery was performed when the rats were 10 weeks old and the thyroxine treatment (3 μg/100 g of body weight) was started the day of the surgery. Results are expressed as mean ± se.

* Statistically different from the values of sham-operated rats (P < 0.001).
† Statistically different from the values of thyroxine-treated rats (P < 0.005).
‡ Statistically different from the values of sham-operated rats (P < 0.02).
§ Statistically different from the values of thyroxine-treated rats (P < 0.001).

There were 12 rats in each group. The surgery was performed when the rats were 10 weeks old and the thyroxine treatment (3 μg/100 g of body weight) was started the day of the surgery. Results are expressed as mean ± se.

* Statistically different from the values of sham-operated rats (P < 0.001).
† Statistically different from the values of thyroxine-treated rats (P < 0.005).
‡ Statistically different from the values of sham-operated rats (P < 0.02).
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† Statistically different from the values of thyroxine-treated rats (P < 0.005).
‡ Statistically different from the values of sham-operated rats (P < 0.02).
§ Statistically different from the values of thyroxine-treated rats (P < 0.001).
taneous injections of thyroxine (3 μg/100 g of body weight) almost completely prevented this fall in body weight. Thyroidectomy also prevented further increases in blood pressure in SH rats. However, the systolic blood pressure of TPX SH rats never reached normotensive levels during the 45 days of observation. Heart rate of TPX SH rats was significantly reduced when compared to sham-operated or thyroxine-treated TPX SH rats. At 45 days after the surgery, body temperature of TPX SH rats was 37.0 ± 0.2°C, n = 6, compared to 38.8 ± 0.3°C, n = 6, for sham-operated SH rats. The difference was significant (P < 0.001). Serum thyroxine levels were 0.1 ± 0.03 μg/100 ml, n = 6, in TPX SH rats and 4.2 ± 0.3 μg/100 ml, n = 6, for sham-operated SH rats. This difference was significant (P < 0.001).

The mechanism by which thyroidectomy prevented further increases in blood pressure of 10-week-old SH rats was investigated by comparing the sensitivity to phenylephrine and KCl of aortic strips removed from sham-operated and TPX SH rats. The dose-response curves to phenylephrine and KCl on aortic strips removed from these rats are shown in Figures 4 and 5. Thyroidectomy clearly reduced the sensitivity of aortic strips to these two agonists. The maximum effect of both agonists was not altered by thyroidectomy. ED50 values of both compounds were significantly increased after thyroidectomy. The ratio of ED50 values for phenylephrine-contracted strips removed from sham-operated and thyroidectomized SH rats was 2 times greater than that of KCl-contracted strips (Table 5).

Thyroidectomy in 10-week-old SH rats was without any measurable effect on the isoproterenol-induced relaxation of aortic strip pretreated with KCl. The results are shown in Figure 6. The maximal relaxation to isoproterenol of aortic strips removed from sham-operated and TPX SH rats was found significantly reduced (P < 0.01) as compared to that of SH rats sham-operated at 4 weeks of age (Fig. 3). Nitroglycerin-induced relaxation of aortic strips of SH rats thyroidectomized at 10-weeks of age was not different from that observed in strips from sham-operated rats.

The differences between the weights, systolic blood pressures, heart rates, body temperatures, hematocrits, and total serum thyroxine levels of SH, Kyoto Wistar, American Wistar, and Sprague-Dawley rats are illustrated in Table 5. The systolic blood pressures of SH rats were significantly greater than those of American Wistar and Sprague-Dawley rats at 4, 6, and 9 weeks of age. This difference was also observed between SH rats and Kyoto Wistar rats but only at 6 and 9 weeks of age. The heart rates of SH rats were greater than those of Kyoto Wistar rats at the ages of 4 and 9 weeks and greater than those of American Wistar rats at 6 and 9 weeks. The heart rates of SH rats were consistently more elevated than those of Sprague-Dawley rats at all three ages. Obviously, SH rats become hypertensive between the 4th and 6th weeks of age. An interesting observation was that the body temperatures of SH rats were significantly higher than those of the three other strains of normotensive rats, at all ages. Hematocrits of SH rats were not different from those of Kyoto Wistar and American Wistar rats; at 4 and 6 weeks of age Sprague-Dawley rats had higher hematocrits than SH rats.

The serum thyroxine levels of SH rats were significantly lower than those of Kyoto Wistar, American Wistar, and Sprague-Dawley rats at 4 weeks of age; there were no differences at 6 weeks of age, but at 9 weeks SH rats had higher serum thyroxine levels than American Wistar rats but not Kyoto Wistar and Sprague-Dawley rats. The increase in serum thyroxine level between the 4th and 6th weeks in all four strains of rats is illustrated in Figure 7. A 120% increase in serum thyroxine level of SH rats between the 4th and 6th weeks has to be compared with a 233% increase in serum thyroxine level of Kyoto Wistar rats during the same period of time; the increase in serum thyroxine level of American Wistar and Sprague-Dawley rats was 20% and 12%, respectively, during that period. This 12% increase was not significant.

The total serum triiodothyronine levels of 4-week-old SH and Kyoto Wistar rats were, respectively, 145.0 ± 9.0 ng/100 ml (n = 10) and 142.0 ± 4.0 ng/100 ml (n = 5). At 6 weeks of age, the serum triiodothyronine level of SH and Kyoto Wistar rats were, respectively, 166.0 ± 8.0 ng/100 ml (n = 5) and 186.0 ± 14.0 ng/100 ml (n = 5).

### Discussion

Surgical thyroidectomy performed on 4- to 5-week-old SH rats significantly inhibited the development of hypertension. This confirms a previous report by Aoki. In his experiment, radiothyroidectomy performed in the prehypertensive period prevented the development of hypertension in young SH rats. He also reported that daily administration of a thyroid powder (30 mg/100 g of body weight)
restored completely the hypertension in young TPX SH rats. The present report shows that the daily subcutaneous injections of a replacement dose of L-thyroxine restores growth, heart rate, and hypertension in young TPX SH rats.

The mechanism by which thyroidectomy prevents, and thyroxine restores, hypertension in SH rats was investigated. Thyroidectomy performed in the prehypertensive period of SH rats was found to depress the sensitivity of aortic strips to phenylephrine, an α-adrenergic receptor stimulant, and KCl, a nonspecific agonist. On the other hand, thyroidectomy reduced significantly the β-relaxant effect of isoproterenol without modifying the nonspecific vasodilation induced by nitroglycerin. Thyroxine administration to TPX SH rats restored completely the sensitivity of aortic strips to phenylephrine, KCl, and isoproterenol. Additional studies with other blood vessels will be of importance because if the reduced sensitivity to vasoconstrictors observed in aortic strips of SH rats after thyroidectomy also occurs in the resistance vessels, this would contribute significantly to the prevention of hypertension in TPX SH rats.

As in most cases of surgical thyroidectomy, we cannot eliminate entirely the possible effects of parathyroidectomy. However, our observation that thyroidectomy prevents hypertension in young SH rats is in agreement with Aoki’s studies in which rats were thyroidectomized with 131I, a procedure which would not destroy the parathyroid glands. Moreover, we observed that following surgery thyroxine administration is sufficient to restore both the hypertension and aortic reactivity. These findings indicate that we need not invoke altered parathyroid hormone levels to explain the present data.

The β-receptor function in aortic strips of SH rats also was decreased after thyroidectomy. Since the β-receptors in arteries mediate relaxation, a decrease in their function should favor vasoconstriction. However, the net result that we observed was a prevention of the development of hypertension in TPX SH rats, clearly showing that the present data indicate that we need not invoke altered parathyroid hormone levels to explain the present data.

Although it was tempting to relate the decreased heart rate to the absence of development of hypertension in the young SH rats after thyroidectomy, it became obvious that the heart rate may be completely restored by thyroxine at a time when the blood pressure level of TPX SH rats was not significantly higher than that of sham-operated SH rats.
rats. Moreover, we showed that the heart rate may be severely reduced without restoring normotension in 10-week-old TPX SH rats. These results suggest that the high heart rate of SH rats is not responsible, by itself, for the development or the maintenance of hypertension in SH rats.

Surgical thyroidectomy performed in 10-week-old SH rats prevented the further increase of blood pressure observed in sham-operated SH rats. In spite of the absence of thyroxine in the blood, the blood pressure of SH rats thyroidectomized at 10-weeks of age remained high during the 6 weeks after surgery. Thus, thyroidectomy is more effective in preventing hypertension than in reversing established hypertension. That thyroidectomy in the adult SH rats prevented the further development of hypertension but did not markedly reduce the hypertension already present may be explained by several factors. First, in the young SH rats, thyroidectomy was about twice as effective in reducing sensitivity of aortic strips to vasoconstrictors as it was in 10-week-old SH rats. Second, following the development of hypertension, the blood pressure may be maintained by increased blood vessel wall thickness and increased vascular collagen synthesis which decrease the lumen size of the arteries. These structural modifications may be more easily prevented than reversed. Aoki's ability to reverse hypertension in 15- to 30-week-old female SH rats by thyroidectomy. However, in 15- to 30-week-old male SH rats, hypertension appears to be only partially reversed even 10 weeks after the destruction of the thyroid gland. This result suggests that the effect of thyroidectomy in adult SH rats may be dependent on the sex of the rats and, possibly, on the duration of the hypertension. Third, it cannot be excluded that as a result of thyroidectomy, there is an increased activity of the sympathetic nervous system in the adult SH rats which maintains the hypertension to a greater extent than in the young SH rats. This possibility is supported by several reports showing an increased activity of the sympathetic nervous system in rats following thyroidectomy.

In comparing the total serum thyroxine level of 4-, 6-, and 9-week-old SH rats with that of age-matched Kyoto Wistar, American Wistar, and Sprague-Dawley rats, it was found that SH rats were unique in showing a low serum thyroxine level at 4 weeks of age. However, there were no differences between the total serum triiodothyronine levels of 4-week-old SH and Kyoto Wistar rats, nor was the oxygen consumption different in these rats (F. Rioux and B. Berkowitz, unpublished results). The total serum thyroxine level of 6- and 9-week-old SH rats was similar to that of age-matched Kyoto Wistar, American Wistar, and Sprague-Dawley rats. These results do not support the hypothesis that spontaneous hypertension is associated with a hypofunction of the thyroid gland.

In summary, a major finding in this study was that the decreased vascular sensitivity to vasoconstrictor substances may be important in the prevention of hypertension following juvenile thyroidectomy in SH rats. In the SH rat there is a low serum thyroxine level at 4 weeks of age. Between the 4th and 6th weeks of age in the SH rats, two events take place: there is a rapid increase in serum thyroxine level from low to normal level and, at the same time, there is an increase in blood pressure from normotensive to hypertensive level. A direct relationship between these two events is far from certain. However, if the expression of the sympathetic nervous system activity requires a normal circulating level of thyroxine, the low serum thyroxine level found in 4-week-old SH rats may provide an explanation as to why a young SH rat may have a significant increase in the activity of the sympathetic nervous system and not yet be hypertensive.

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