Thyroid status influences baroreflex function and autonomic contributions to arterial pressure and heart rate

C. MICHAEL FOLEY,1 RICHARD M. McALLISTER,2 AND EILEEN M. HASSER1

1Department of Veterinary Biomedical Sciences and Dalton Cardiovascular Research Center, University of Missouri at Columbia, Columbia, Missouri 65211; and 2Department of Kinesiology and Department of Anatomy and Physiology, Kansas State University, Manhattan, Kansas 66506

Received 7 August 2000; accepted in final form 15 December 2000

Foley, C. Michael, Richard M. McAllister, and Eileen M. Hasser. Thyroid status influences baroreflex function and autonomic contributions to arterial pressure and heart rate. Am J Physiol Heart Circ Physiol 280: H2061–H2068, 2001.—The effect of thyroid status on arterial baroreflex function and autonomic contributions to resting blood pressure and heart rate (HR) were evaluated in conscious rats. Rats were rendered hyperthyroid (Hyper) or hypothyroid (Hypo) with triiodothyronine and propylthiouracil treatments, respectively. Euthyroid (Eut), Hyper, and Hypo rats were chronically instrumented to measure mean arterial pressure (MAP), HR, and lumbar sympathetic nerve activity (LSNA). Baroreflex function was evaluated with the use of a logistic function that relates LSNA or HR to MAP during infusion of phenylephrine and sodium nitroprusside. Contributions of the autonomic nervous system to resting MAP and HR were assessed by blocking autonomic outflow with trimethaphan. In Hypo rats, the arterial baroreflex curve for both LSNA and HR was shifted downward. Hypo animals exhibited blunted sympathoexcitatory and tachycardic responses to decreases in MAP. Furthermore, the data suggest that in Hypo rats, the sympathetic influence on HR was predominant and the autonomic contribution to resting MAP was greater than in Eut rats. In Hyper rats, arterial baroreflex function generally was similar to that in Eut rats. The autonomic contribution to resting MAP was not different between Hyper and Eut rats, but predominant parasympathetic influence on HR was exhibited in Hyper rats. The results demonstrate baroreflex control of LSNA and HR is attenuated in Hypo but not Hyper rats. Thyroid status alters the balance of sympathetic to parasympathetic tone in the heart, and the Hypo state increases the autonomic contributions to resting blood pressure.

hypothyroidism; hyperthyroidism; sympathetic nerve activity; ganglionic blockade; rats

VARIATIONS FROM EUTHYROID STATUS affect virtually all physiological systems, and effects on the cardiovascular system are particularly pronounced. Changes in thyroid status are associated with changes not only in cardiac and vascular function but also in autonomic regulation of the cardiovascular system (14). The clinical picture of hyperthyroidism is suggestive of increased sympathetic activity (1, 14), but assessments of sympathetic activity suggest that sympathetic outflow is either unchanged or reduced (5, 7, 13, 18). In contrast, whereas several clinical features of hypothyroidism are consistent with reduced sympathetic activity, indirect techniques suggest that sympathetic activity is elevated (4, 16, 23). Interestingly, in both hypo- and hyperthyroidism, the influence of the parasympathetic nervous system on heart rate (HR) seems to be reduced (3, 10, 11, 15). The mechanisms for the change in resting levels of sympathetic and parasympathetic outflow are unknown but could be due to a variety of mechanisms, including direct effects (excess or depletion) of thyroid hormone in central regions involved in autonomic regulation or changes in cardiovascular reflex systems that control the autonomic nervous system. Both hypo- and hyperthyroidism are associated with exercise intolerance (19). HR, blood pressure, and skeletal muscle blood flow responses to dynamic exercise suggest hypothyroid animals exhibit blunted activation of the sympathetic nervous system during dynamic exercise (20) and an exaggerated sympathetic response in hyperthyroidism (17, 21). The sympathetic nervous system activation that occurs in response to dynamic exercise requires, in part, participation of the arterial baroreflex (25). The arterial baroreflex tonically influences activity of both the sympathetic and parasympathetic nervous systems and buffers changes in arterial pressure on a beat-to-beat basis. The function of the arterial baroreflex is plastic and can be altered by numerous stimuli including circulating hormones. It is unknown whether arterial baroreflex function is altered by thyroid status. Changes in arterial baroreflex function during either hypo- or hyperthyroidism could potentially account for some of the change in autonomic outflow at rest and for the altered regulation of autonomic function in response to various stresses, including dynamic exercise.

The purpose of this study was to determine whether changes in thyroid status alter arterial baroreflex function. We used well-established rat models of hypo- and hyperthyroidism. Baroreflex responses in lumbar symp-
pathetic nerve activity (LSNA) and HR over a wide range of arterial pressures were evaluated in conscious rats. In addition, studies were conducted to estimate the contribution of the autonomic nervous system to the maintenance of arterial pressure and resting HR by pharmacologically blocking the autonomic nervous system with trimethaphan, a ganglionic blocking agent.

METHODS

Animals. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Missouri at Columbia. Male Sprague-Dawley rats (Sasco) weighing 175–200 g were housed two per cage under controlled conditions of temperature (20–21°C) and light (12:12-h light-dark cycle). Rats were randomly assigned to one of three groups: euthyroid control (Eut), hypothyroid (Hypo), and hyperthyroid (Hyper). Rats of the Hypo and Hyper groups consumed food ad libitum. Rats of the Eut group were food restricted such that bulk food intake was ~80% of normal to keep their body weights similar among groups.

Treatment. Rats were rendered hypothyroid by 2–3 mo of treatment with propylthiouracil (0.04 g/100 ml; Sigma) in the drinking water, as previously described (20). Hyperthyroidism was induced in rats by intraperitoneal administration of triiodothyronine (300 μg/kg in 0.50 mM NaOH; Sigma) on alternate days over 2–3 mo (21).

Determination of treatment efficacy. Establishment of altered thyroid status was confirmed by assessing left ventricular and soleus muscle oxidative capacity. The latter was estimated by determining activity of citrate synthase, a marker enzyme for oxidative metabolism, with the use of the colorimetric assay of Srere (28). It is well established that hypothyroidism induces a reduction in skeletal muscle citrate synthase activity (6, 9, 20). In contrast, hyperthyroidism is associated with an increase in muscle citrate synthase activity as well as left ventricular hypertrophy (6, 9, 21).

Surgical procedures. After the 2- to 3-mo treatment or control period, each rat was instrumented with catheters and nerve electrodes. All surgical procedures were performed using aseptic technique under halothane anesthesia. Catheters (polyethylene-10 fused to polyethylene-50) were inserted into the aorta and abdominal vena cava via the femoral artery and vein. Catheters were filled with heparinized saline (10 U/ml) and capped with an airtight plug. Through a midline abdominal incision, electrodes were implanted on the lumbar sympathetic chain caudal to the left kidney. Nerves and electrodes were covered with a polyvinylsloxane gel (Coltene President), which was allowed to harden before closure. The electrodes were manufactured using Teflon-insulated silver wires (0.005-in. diameter; Medwire) threaded through Silastic tubing (0.025-in. inner diameter). A ground wire was sewn to the surrounding muscle tissue. The catheters, electrodes, and ground wire were tunneled subcutaneously and exteriorized in the dorsal cervical region.

After the surgical procedures were completed, animals were given 30 ml of saline subcutaneously to aid in volume restoration. After animals had recovered from anesthesia, they were returned to their cage for a ~24-h recovery period before the start of any experimental procedures. By the end of the recovery period, the animals were grooming normally and displayed normal cage activity.

Experimental procedures. On the day of the experiment, the animal was placed in an experimental cage that was furnished with the animal’s own bedding. The experimental cage was placed within a Faraday cage. The arterial catheter was attached to a pressure transducer for recording arterial pressure. Mean arterial pressure (MAP) was derived electronically using a low-pass filter. HR was determined from pulsatile arterial pressure by a cardiogrometer. LSNA was amplified 1,000 times with the use of a preamplifier (Grass P511) and filtered using a high-pass frequency level of 30 Hz and a low-pass frequency level of 3 kHz. Action potentials were monitored with an oscilloscope (Tektronix) and an audio monitor (Grass M8). Nerve activity was rectified and integrated using a root-mean-square square converter with a time constant of 28 ms. The rectified integrated signal was averaged electronically. The background noise level of the nerve recording was determined as the minimum value during maximal elevation in arterial pressure. Audio and visual monitoring of nerve activity during this period was utilized to verify that sympathetic nerve activity bursts were eliminated. LSNA was defined as the amount of recorded nerve activity after subtraction of background noise.

Experimental protocol. Baseline hemodynamic parameters were recorded for ~30 min to allow stabilization of MAP, HR, and LSNA before the start of the experimental protocol. The animals were resting quietly in their cages during the experimental procedures. Although the electrocardiogram was not recorded in these experiments, no signs of obvious arrhythmia were observed. Arterial baroreflex curves were generated by producing ramp changes in arterial pressure and recording the reflex changes in HR and LSNA. Ramp increases in arterial pressure were produced over 2–3 min by continuous intravenous infusion of the a1-adrenergic agonist phenylephrine (PE) at progressively increasing rates (2–25 μg·kg⁻¹·min⁻¹). Hemodynamic parameters were allowed to recover to within 10% of starting values (~20 min). Arterial pressure then was decreased (to ~40 mmHg) in a ramp fashion over 2–3 min by continuous intravenous infusion of sodium nitroprusside (SNP) at progressively increasing rates (10–100 μg·kg⁻¹·min⁻¹). The rate of change of arterial pressure was held constant by observing the pressure change and varying the infusion rate. The rate of change (~1–2 mmHg/s) was similar across all animals. This methodology was used to allow evaluation of both sympathetic and parasympathetic nerve activity effects and to prevent resetting of the arterial baroreflex (29). To minimize any potential effects of released humoral agents (e.g., angiotensin II, vasopressin, etc.) on baroreflex function, baroreceptors were activated (PE infusion) before being unloaded (SNP infusion).

After arterial baroreflex curves were generated, autonomic blockade studies were performed. Trimethaphan (15 mg/kg; Roche Laboratories), a ganglionic blocking agent, was administered intravenously to remove tonic autonomic outflow. Peak changes in MAP and HR in response to trimethaphan were recorded (within 0.5–2.0 min).

At the end of the experimental protocol, rats were deeply anesthetized with pentobarbital sodium. Soleus muscles were removed and frozen at −80°C for later analysis of citrate synthase activity. The rats were euthanized with an overdose of pentobarbital sodium. The heart was removed, and the left ventricle was isolated and weighed.

Data analysis. All data are expressed as means ± SE. LSNA was expressed and analyzed as a percentage of the control level of LSNA before changing arterial pressure (%Baseline). The control level of LSNA was defined as 100%. In addition, LSNA was analyzed relative to the maximum recorded level of LSNA during a decrease in MAP. In this case, the maximum recorded level of LSNA was defined as 100% (%Peak).

Arterial baroreflex curves were generated by relating HR and LSNA to MAP. The data were fit to a sigmoidal logistic
For each animal, the data were fit with the use of the logistic function, and the four parameters ($P_1$–$P_4$) and peak gain were determined. The parameters ($P_1$–$P_4$) and maximum gain were averaged within each group and compared among groups statistically using one-way analysis of variance (ANOVA). In addition, LSNA, HR, and $G_{MAP}$ values at 5-mmHg intervals were generated for each animal using each rat’s curve parameters. These LSNA, HR, and $G_{MAP}$ values at a given level of MAP were averaged and compared using two-way ANOVA with repeated measures. The MAP and HR values before and after trimethaphan in the Eut, Hypo, and Hyper groups were analyzed using two-way ANOVA with repeated measures. The peak changes in MAP and HR after trimethaphan between the three groups were analyzed by one-way ANOVA. When ANOVA indicated a significant interaction, differences between individual means were assessed by a least significant difference test (27). A probability of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SigmaStat for Windows (Jandel Scientific).

**RESULTS**

Treatment efficacy. Treatment with propylthiouracil was effective in establishing a hypothyroid state. Body weight, left ventricular weight, and soleus muscle citrate synthase activity were lower in Hypo rats compared with Eut rats (Table 1). Conversely, increased left ventricular weight, left ventricular-to-body weight ratio, and soleus muscle citrate synthase activity were exhibited by Hyper animals (Table 1). Food restriction of the Eut animals was effective in maintaining similar body weights between the Eut and Hyper rats. The Hypo rats failed to gain weight at the same rate as the Eut rats, which resulted in lower body weights in the Hypo animals.

Baseline MAP and HR values for the three groups of animals are presented in Table 1. Hypo rats had a reduced MAP at the start of the experimental procedures compared with the Eut and Hyper rats. Baseline HR values were not different among the groups.

Baroreflex control of LSNA. The effect of altered thyroid status on arterial baroreflex control of LSNA analyzed as a percentage of control LSNA (%Baseline) is presented in Fig. 2. As indicated in Table 1, Hypo rats had a lower baseline MAP compared with Eut or Hyper animals (Fig. 2A). The gain of the baroreflex curves as a function of MAP is presented in Fig. 2B. All groups exhibited reflex increases and decreases in LSNA in response to decreases and increases in MAP.

Table 1. Baseline hemodynamic parameters, body weights, heart weights, and soleus muscle citrate synthase activity

<table>
<thead>
<tr>
<th></th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>Body Weight, g</th>
<th>LV Weight, mg</th>
<th>LV/Body Weight, mg/g</th>
<th>Sol CS, $\mu$mol·min⁻¹·g⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eut</td>
<td>96 ± 3</td>
<td>293 ± 7</td>
<td>444 ± 19</td>
<td>853 ± 55</td>
<td>1.9 ± 0.1</td>
<td>26.3 ± 1.6</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hypo</td>
<td>84 ± 3†</td>
<td>281 ± 8</td>
<td>284 ± 6*†</td>
<td>525 ± 17†</td>
<td>1.8 ± 0.1†</td>
<td>11.9 ± 0.7*†</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hyper</td>
<td>94 ± 3</td>
<td>270 ± 10</td>
<td>474 ± 16</td>
<td>1,097 ± 46†</td>
<td>2.3 ± 0.0e</td>
<td>44.2 ± 1.2†</td>
</tr>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of rats. Eut, euthyroid; Hypo, hypothyroid; Hyper, hyperthyroid; MAP, mean arterial pressure; HR, heart rate; LV weight, left ventricle weight; Sol CS, soleus citrate synthase activity. *$P < 0.05$ vs. Eut rats; †$P < 0.05$ Hypo vs. Hyper rats.

The following equation was used to fit the data

\[ \text{SNA or HR} = (P_1 - P_4)/(1 + e^{P_3(MAP - P_5)}) + P_4 \quad (1) \]

The four parameters ($P_1$–$P_4$) were generated from the fit of the logistic curve to the data. These four parameters are used to describe the baroreflex function curve. $P_1$ is the upper plateau of the curve and is the maximum level of LSNA and heart rate (HR) in response to MAP; $P_2$ is the coefficient used to calculate the slope or gain at any given point on the curve; $P_3$, MAP that is associated with the midpoint of the curve; $P_4$, lower plateau of the curve and minimum level of LSNA or HR in response to an increase in MAP; %Baseline, percentage of control level of LSNA before changing arterial pressure.

A sigmoidal curve fit to the data points. The four parameters

\[ G_{MAP} = -(P_1 - P_4)P_2 \times e^{P_3(MAP - P_5)}[1 + e^{P_3(MAP - P_5)}] \quad (2) \]

Fig. 1. Example of a baroreflex curve relating lumbar sympathetic nerve activity (LSNA) and mean arterial pressure (MAP) from a euthyroid (Eut) control animal. Symbols, recorded data points; solid line, sigmoidal curve fit to the data points. The four parameters ($P_1$–$P_4$) determined from the logistic equation are illustrated and labeled on the graph. $P_1$, upper plateau of the curve and maximum level of LSNA and heart rate (HR) in response to MAP; $P_2$, coefficient used to calculate the slope or gain at any given point on the curve; $P_3$, MAP that is associated with the midpoint of the curve; $P_4$, lower plateau of the curve and minimum level of LSNA or HR in response to an increase in MAP; %Baseline, percentage of control level of LSNA before changing arterial pressure.
Baroreflex control of LSNA was also analyzed as a percentage of the maximum recorded level of LSNA in response to a decrease in MAP (%Peak). The curve parameters that describe baroreflex control of LSNA analyzed as %Peak are presented in Table 3. When baroreflex control of LSNA was analyzed this way, the four parameters in the Hypo and Hyper rats were not different from those in the Eut rats (Table 3). However, the level of LSNA at resting arterial pressure (calculated as a percentage of the peak) was significantly elevated in Hypo rats compared with either the Eut or Hyper rats (Table 3). These data indicate that, in Hypo rats, the ability to increase LSNA in response to decreases in MAP is reduced regardless of whether LSNA is calculated as %Baseline or as %Peak.

Baroreflex control of HR. The effect of altered thyroid status on arterial baroreflex control of HR is presented in Fig. 3. As indicated in Table 1, resting MAP was lower in Hypo rats compared with Eut or Hyper animals, but baseline HR was similar among groups (Fig. 3A). All groups exhibited reflex increases and decreases in HR in response to changes in MAP (Fig. 3A). The gain of the baroreflex curves as a function of MAP is presented in Fig. 3B. Baroreflex control of HR in Hyper rats was similar to that in Eut rats over the range of arterial pressures evaluated. In addition, the gain of the baroreflex curve in the Hyper animals was not significantly different from that of the Eut rats. The maximum HR, minimum HR, pressure at the midpoint of the curve, or peak gain were not different between the Hyper and Eut rats (Table 4). In contrast, Hypo rats exhibited a markedly altered baroreflex control of HR. In Hypo rats, HR was reduced over the complete range of pressures, resulting in a downward shift in baroreflex control of HR (Fig. 3A). The resting

Table 2. Curve parameters describing baroreflex control of LSNA expressed as a percentage of baseline

<table>
<thead>
<tr>
<th></th>
<th>( n )</th>
<th>( P_1 ), %Baseline</th>
<th>( P_2 ), 1/mmHg</th>
<th>( P_3 ), mmHg</th>
<th>( P_4 ), %Baseline</th>
<th>Peak Gain, %Baseline/mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eut</td>
<td>6</td>
<td>230 ± 22</td>
<td>0.062 ± 0.011</td>
<td>94 ± 6</td>
<td>18 ± 6</td>
<td>-3.4 ± 0.8</td>
</tr>
<tr>
<td>Hypo</td>
<td>8</td>
<td>157 ± 16†</td>
<td>0.077 ± 0.008</td>
<td>93 ± 4</td>
<td>27 ± 4</td>
<td>-2.5 ± 0.4†</td>
</tr>
<tr>
<td>Hyper</td>
<td>7</td>
<td>249 ± 23</td>
<td>0.091 ± 0.014</td>
<td>85 ± 3</td>
<td>15 ± 6</td>
<td>-5.0 ± 0.6</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n \), number of rats. \( P_1 \), upper plateau of the curve and maximum level of lumbar sympathetic nerve activity (LSNA) in response to a decrease in MAP; \( P_2 \), coefficient used to calculate slope or gain at any given point on the curve; \( P_3 \), MAP associated with the midpoint of the curve; \( P_4 \), lower plateau of the curve and minimum level of LSNA in response to an increase in MAP. *\( P < 0.05 \) vs. Eut rats; †\( P < 0.05 \) Hypo vs. Hyper rats.
HR of the Hypo rats was close to the maximum HR of their baroreflex curve, demonstrating that the Hypo rats had a limited ability to increase HR when arterial pressure was decreased. In the Hypo rats, both the maximum and the minimum HR were decreased compared with Eut and Hyper groups (Table 4). Neither the midpoint of the curves nor the peak gain were different among the three groups (Table 4). The gain of baroreflex control of HR in Hypo rats was blunted significantly compared with that in the Eut animals over a pressure range of 60–85 mmHg but was enhanced through pressures of 100–115 mmHg (Fig. 3B).

Response to autonomic blockade. The average MAP and HR values before and after autonomic blockade with trimethaphan in Eut, Hypo, and Hyper rats are presented in Fig. 4. The maximum changes in MAP and HR in response to trimethaphan are presented in Fig. 5. Before autonomic blockade, baseline MAP and HR in the Hypo and Hyper groups were not different from the Eut group, although MAP in the Hypo group tended to be lower (Fig. 4, open bars). Autonomic blockade by intravenous administration of trimethaphan decreased MAP in all groups (Figs. 4A and 5A). The absolute level of MAP after autonomic blockade was similar in Eut and Hyper animals; however, pressure was lower in the Hypo rats compared with the Eut or Hyper animals (Fig. 4A, solid bars). In a similar fashion, the reduction in MAP in response to ganglionic blockade (Fig. 5A) was similar in Eut and Hyper animals. However, the depressor response to trimethaphan was greater in the Hypo group compared with the other groups. The greater depressor response in Hypo animals occurred despite a lower baseline MAP in the Hypo animals.

The effects of autonomic blockade on HR varied among the different groups. The level of HR after removal of tonic autonomic input to the heart (intrinsic HR) was reduced in the Hypo animals and greater in the Hyper animals compared with the Eut animals (Fig. 4B, solid bars). As indicated in Fig. 5B, administration of trimethaphan produced no change in HR in the Eut rats, a decrease in HR in the Hypo rats, and an increase in HR in the Hyper rats.

DISCUSSION

These studies evaluated the effect of thyroid status on arterial baroreflex control of LSNA and HR in conscious rats. The major findings of this study are that Hypo rats exhibit blunted baroreflex mediated increases in LSNA and HR and a downward shift in baroreflex control of HR compared with Eut rats. In contrast, baroreflex function generally was similar in Hyper and Eut rats. These studies also evaluated the autonomic contributions to resting arterial pressure and HR. In Hyper and Eut rats, autonomic blockade produced a similar decrease in MAP, but Hyper rats had a greater increase in HR than Eut rats. Hypo rats exhibited a greater fall in both MAP and HR than Eut rats after autonomic blockade. Taken together, the data indicate that Hypo rats have depressed arterial

Table 3. Curve parameters describing baroreflex control of LSNA as a percentage of maximum

<table>
<thead>
<tr>
<th></th>
<th>$P_1$, %Peak</th>
<th>$P_2$, 1/mmHg</th>
<th>$P_3$, mmHg</th>
<th>$P_4$, %Peak</th>
<th>Peak Gain, %Peak/mmHg</th>
<th>Resting MAP, %Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eut</td>
<td>101 ± 1</td>
<td>0.063 ± 0.011</td>
<td>94 ± 6</td>
<td>9 ± 2</td>
<td>−1.4 ± 0.2</td>
<td>46 ± 4</td>
</tr>
<tr>
<td>Hypo</td>
<td>102 ± 1</td>
<td>0.076 ± 0.008</td>
<td>96 ± 4</td>
<td>18 ± 3†</td>
<td>−1.6 ± 0.1</td>
<td>68 ± 6†</td>
</tr>
<tr>
<td>Hyper</td>
<td>101 ± 1</td>
<td>0.091 ± 0.013</td>
<td>85 ± 3</td>
<td>6 ± 2</td>
<td>−2.2 ± 0.3</td>
<td>46 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n$, number of rats. *$P < 0.05$ vs. Eut rats; †$P < 0.05$ Hypo vs. Hyper rats.
baroreflex function and elevated dependence on resting sympathetic tone to both the heart and vasculature. Hyper rats exhibit normal baroreflex function and normal sympathetic tone to the vasculature.

**Evidence of altered thyroid state.** Propylthiouracil treatment and administration of triiodothyronine in rats has been utilized previously by numerous laboratories to induce a hypothyroid and hyperthyroid state, respectively (6, 20, 21, 24). In this study, Hypo rats had reduced weight gain, left ventricular weight, soleus muscle citrate synthase activity, and a decrease in intrinsic HR, which indicated that propylthiouracil was effective in producing hypothyroidism. In contrast, regular administration of triiodothyronine produced cardiac hypertrophy, increased soleus muscle citrate synthase activity, and an increase in intrinsic HR. These changes are consistent with reported effects of altered thyroid status in rats (6, 20–22) and suggest that the Hypo and Hyper rats in this study were hypothyroid and hyperthyroid, respectively.

**Effect of thyroid status on arterial baroreflex function.** In this study, several significant changes in arterial baroreflex function were observed in Hypo rats compared with Eut rats. Hypo rats exhibited a blunted sympathoexcitatory response to low arterial pressures. This reduced capacity to reflexly increase LSNA was demonstrated whether the curve relating LSNA to MAP was determined before or after autonomic blockade by intravenous administration of trimethaphan (15 mg/kg). The residual MAP after removal of tonic activity of the autonomic nervous system was lower in Hypo rats compared with either Eut or Hyper rats. Also, in Hyper rats, the intrinsic HR was greater than in Eut rats. These changes are consistent with reported effects of altered thyroid status in rats (6, 20–22) and suggest that the Hypo and Hyper rats in this study were hypothyroid and hyperthyroid, respectively.

![Fig. 4. MAP (A) and HR (B) under control conditions (open bars) and after autonomic blockade by intravenous administration of trimethaphan (15 mg/kg, gray bars) in Eut (n = 5), Hypo (n = 7), and Hyper rats (n = 5). The residual MAP after removal of tonic activity of the autonomic nervous system was lower in Hypo rats compared with either Eut or Hyper rats. Also, the intrinsic HR (HR after trimethaphan) was lower in Hypo rats and greater in Hyper rats compared with that in Eut rats. *Statistical difference between baseline and peak response of Eut rats, †statistically different from peak response of Hypo rats, and ‡statistical difference between peak response of Hypo and Hyper rats at P < 0.05.

![Fig. 5. Peak changes in MAP (A) and HR (B) in response to autonomic blockade by intravenous administration of trimethaphan (15 mg/kg) in Eut (open bars; n = 5), Hypo (solid bars; n = 7), and Hyper rats (gray bars; n = 5). Removal of tonic activity of the autonomic nervous system produced a greater fall in MAP and HR in Hypo rats compared with either Eut or Hyper rats. Also, Hyper rats demonstrated a tachycardia in response to trimethaphan compared with Eut rats. *Statistical difference among groups indicated by horizontal bars at P < 0.05.

### Table 4. Curve parameters describing baroreflex control of HR

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>P1, beats/min</th>
<th>P2, 1/mmHg</th>
<th>P3, mmHg</th>
<th>P4, beats/min</th>
<th>Peak Gain, beats·min⁻¹·mmHg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eut</td>
<td>6</td>
<td>386 ± 26</td>
<td>0.054 ± 0.007</td>
<td>100 ± 6</td>
<td>198 ± 10</td>
<td>−2.5 ± 0.4</td>
</tr>
<tr>
<td>Hypo</td>
<td>8</td>
<td>306 ± 9†</td>
<td>0.110 ± 0.017</td>
<td>105 ± 4</td>
<td>154 ± 12†</td>
<td>−4.2 ± 0.8</td>
</tr>
<tr>
<td>Hyper</td>
<td>7</td>
<td>382 ± 35</td>
<td>0.105 ± 0.034</td>
<td>88 ± 5</td>
<td>227 ± 13</td>
<td>−3.6 ± 0.8</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of rats. *P < 0.05 vs. Eut rats; †P < 0.05 hyp vs. hyper rats.
MAP was calculated as a percentage of baseline or of maximum LSNA. In addition, baroreflex control of HR was shifted downward, and resting HR in Hypo rats was near the upper plateau of the curve. Thus the Hypo rats were limited in their ability to increase HR and LSNA in response to decreases in MAP. These changes in baroreflex control of LSNA and HR occurred in the absence of any shifts in the midpoint of the curves, suggesting that there was no significant pressure resetting of the baroreflex in the Hypo rats. Conversely, Hypo rats responded to increases in arterial pressure with similar sympathoinhibitory and bradycardic responses compared with Eut rats. Although the peak gain of either the LSNA or HR baroreflex curve was not different, the Hypo rats exhibited a decreased gain close to resting arterial pressures compared with the baroreflex gain of the Eut rats. These data suggest that Hypo rats have a blunted arterial baroreflex; specifically, they exhibit impaired ability to increase sympathetic activity and HR to hypotensive challenges.

In Hyper rats, the major indexes (maximum, midpoint, minimum, and peak gain) used in this study to describe arterial baroreflex function were not altered. Hyper rats did exhibit a slightly enhanced gain compared with Eut rats only over a specific segment of the range of MAP (75–95 mmHg) used to generate the LSNA baroreflex curve. Taken together, these data suggest that Hypo rats generally have similar arterial baroreflex function compared with Eut rats.

It has been demonstrated that extreme food restriction in middle-aged Fischer 344 rats enhances baroreflex control of HR and produces a substantial resting bradycardia (8). The major change in the reflex control of HR was a greater tachycardic response to decreases in arterial pressure. In these Fischer rats, body weight was reduced ~45% compared with the control group by the 10–12 mo of reduced calorie diet (~60% of control group). Furthermore, excessive calorie intake has been shown to blunt arterial baroreflex function (2). In the current study, the Eut rats were food restricted ~20% for the 2- to 3-mo treatment protocol, which kept the body weights of the Eut and Hyper rats similar. It is possible that this level of food restriction would alter arterial baroreflex function; however, this seems unlikely because the magnitude and duration of the food restriction was much less than previously studied (8).

Autonomic contributions to arterial pressure and HR. In this study, Hypo rats had a greater autonomic contribution to resting MAP compared with Eut rats. Also in Hypo rats HR decreased in response to ganglionic blockade, suggesting a predominant sympathetic influence on HR at rest. The lower residual MAP after ganglionic blockade could be due to a variety of mechanisms in the Hypo rats including reduced resting tone of resistance vessels, lower cardiac output, or lower circulating levels of vasoconstrictor hormones, including angiotensin II or vasopressin. The enhanced autonomic contribution to MAP is consistent with enhanced dependency on sympathetic tone to the vasculature and heart. However, the data from this study do not directly address this concept. It is difficult to directly compare resting levels of sympathetic outflow between different groups of animals. Keeping this technical limitation in mind, the concept of increased sympathetic outflow is consistent with previous studies (4, 13, 16) that measured plasma catecholamines and norepinephrine turnover rates in hypothyroidism. In the Hypo rats, the sympathetic influence on resting HR compensated for the lower intrinsic HR of the Hypo rats (22) and normalized the resting HR to a similar rate as the Eut rats. In contrast, the increased autonomic contributions to resting MAP in the Hypo rats were not able to fully compensate, and MAP was decreased compared with the Eut rats.

The Hyper rats had similar autonomic contributions to resting MAP as the Eut rats. These data are supported by previous studies (5, 7, 13) that directly or indirectly measured sympathetic outflow. In Hyper rats, ganglionic blockade increased HR, suggesting a predominant parasympathetic influence on resting HR that apparently balanced the elevated intrinsic HR in Hyper rats. The increase in intrinsic HR likely is due to direct effects of thyroid hormone on the heart (13, 22, 26, 30). The specific mechanism for increases in vagal influence on HR is unknown and could be due to an increase in vagal nerve activity, an increase in acetylcholine release, enhanced muscarinic receptor/signaling pathway, or a combination of any of these possibilities.

Perspectives. The specific physiological consequences of blunted arterial baroreflex function in Hypo rats are unknown. It would be predicted that Hypo rats would have a reduced capacity to maintain blood pressure in situations that require reflex activation of the sympathetic nervous system such as hemorrhagic stress, orthostatic stress, and dynamic exercise. It is well documented that hypothyroidism results in exercise intolerance with decreases in both maximal oxygen uptake and endurance (19). The mechanisms that account for the reduced exercise tolerance are multifactorial, but the alteration in baroreflex function may be a contributing factor. It has been suggested that inadequate cardiovascular support accounts for a majority of the exercise intolerance in hypothyroidism (19). Although direct changes in cardiac and vascular function due to the deficiency in thyroid hormone must play a role in the exercise intolerance, the effects of sympathetic nervous system activation during dynamic exercise in hypothyroidism also are reduced compared with the euthyroid state (19). Because the normal sympathoexcitatory response to dynamic exercise is dependent at least in part on arterial baroreflex function (25), one possibility is that the blunted baroreflex function in Hypo rats accounts for part of the inadequate cardiovascular response during dynamic exercise. Hyperthyroidism also is associated with a decrease in exercise tolerance. In contrast to the inadequate cardiovascular support observed in hypothyroidism, altered energy metabolism within the exercising muscle accounts for the majority of the reduced exercise tolerance in hyperthyroidism (19). The sympathetic response to dynamic exercise is appropriate or potentially enhanced in hyperthyroidism (7, 19). The relatively
unchanged baroreflex function in Hyper rats is consistent with the sympathetic response to dynamic exercise in the hyperthyroid state. Future studies that evaluate baroreflex function during exercise in hyperthyroidism and hypothyroidism are necessary to test these ideas directly.

In conclusion, Hypo rats exhibit altered arterial baroreflex function and, specifically, have a reduced capacity to increase LSNA and HR in response to decreases in arterial pressure. In addition, Hypo rats have a greater dependence on autonomic contributions to resting blood pressure and HR, consistent with an elevation in baseline sympathetic tone. The intrinsic HR of Hypo rats was reduced compared with that in Eut rats. In contrast, baroreflex control of LSNA and HR generally was similar between Hyper and Eut rats. The autonomic contribution to resting MAP was also similar between Hyper and Eut rats, but the Hyper rats appeared to have a predominant vagal influence on HR that counterbalanced the increase in intrinsic HR seen with hyperthyroidism. Taken together, these data suggest that hypothyroidism in rats blunts the arterial baroreflex and alters the relative contribution of systems that maintain resting blood pressure and HR. In contrast, hyperthyroidism in rats produces few quantitative effects on the baroreflex and on the contribution of the autonomic nervous system to the maintenance of resting arterial pressure.

The authors thank Sarah A. Friskey and Jodie A. Smith for excellent technical assistance in performing the surgical preparations and experimental procedures. The authors also thank Tammy Srawn for performing the citrate synthase activity assays.

This research was supported by National Heart, Lung, and Blood Institute Grants HL-55306, HL-36088, and HL-57226, by the Missouri Affiliate of the American Heart Association, and by the University of Missouri Research Board.

REFERENCES


