Sympathetic nervous system activity in rat thyroid: potential role in goitrogenesis

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Young, James B., M. Elizabeth Bürgi-Saville, Ulrich Bürgi, and Lewis Landsberg. Sympathetic nervous system activity in rat thyroid: potential role in goitrogenesis. Am J Physiol Endocrinol Metab 288: E861–E867, 2005. First published December 7, 2004; doi:10.1152/ajpendo.00292.2004.—The role of sympathetic innervation in regulation of thyroid function is incompletely understood. We, therefore, carried out studies in rats utilizing techniques of norepinephrine turnover to assess thyroid sympathetic activity in vivo. Thyroidal sympathetic activity was increased 95% by exposure to cold (4°C), 42% by chronic ingestion of an iodine-deficient diet, and 32% in rats fed a goitrogenic diet (low-iodine diet supplemented with propylthiouracil). In addition, fasting for 2 days reduced sympathetic nervous system activity in thyroid by 38%. Thyroid growth and 125I uptake were also compared in intact and decentralized hemithyroids. These results suggest that sympathetic activity in thyroid contributes to gland enlargement and may modulate tissue responsiveness to TSH.

cold exposure; diet; fasting; iodine deficiency; pregnancy

THE THYROID GLAND IS RICHLY innervated by autonomic nerves. Although the potential importance of this innervation was recognized well over 100 years ago (17, 25), the precise roles played by the adrenergic, cholinergic, and peptidergic components of the thyroid innervation in the regulation of glandular function are unclear even today. Because nerve endings have been noted in proximity to thyroid follicles (37, 39), a neural role in thyroid regulation appears likely. In vitro studies have provided considerable information regarding tissue and cellular responses to diverse biogenic amines and neuropeptides (1), although the contributions of these agents in vivo are largely unknown. This lack of information arises, in part, from the following problem. Because the potential effects of thyroid nerves are inhibitory as well as stimulatory, changes in thyroid function after either disruption or excitation of efferent neural pathways cannot be attributed to specific neural events. Furthermore, the principal methods employed to assess the activity of thyroid nerves in any given setting have been based on functional differences observed between intact and denervated thyroid glands. Consequently, assignment of specific effects to thyroid nerves is largely inferential.

To circumvent this problem, we used a technique independent of glandular function to study thyroid neural physiology. Techniques of norepinephrine (NE) turnover assess the dynamic behavior of neuronal NE stores and provide a generally accepted index of the functional state of the sympathetic nervous system (SNS) in innervated tissues of unanesthetized, unrestrained experimental animals. This approach has been applied successfully in investigations of sympathetic nerves in heart, pancreas, liver, kidney, brown fat, skeletal muscle, and white adipose tissues, among others (8, 9, 46, 48, 49). Here, we show that NE turnover can be measured in rat thyroid and that sympathetic activity (NE turnover) in thyroid is susceptible to physiological manipulations known to affect thyroid function. Moreover, we provide evidence that increased activity of adrenergic nerves in thyroid may contribute to glandular enlargement under some circumstances.

METHODS

Animals. Sprague-Dawley rats were obtained from Zivic-Miller Laboratories (Zelienople, PA), and housed two or three per cage in a temperature-controlled room (21 ± 2°C) with a 12:12-h light-dark cycle. Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and with the approval of the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. Unless otherwise specified, all studies were carried out in male rats (150–175 g). Unilateral disruption of sympathetic innervation in rat hemithyroid (performed by the supplier) was accomplished by cutting the preganglionic nerve to the left superior cervical ganglion.

Diets. Animals received standard laboratory chow (Prolab R-M-H 3000, Agway, Syracuse, NY), unless otherwise noted. Food was removed from fasting animals 48 h before the start of the turnover measurement; animals were provided with 0.3% NaCl to drink during the fast. In the sucrose- and fat-feeding study, animals were fed diets containing 50% of energy as sucrose or fat and 50% chow for 4 days before turnover measurements were made; controls were fed the 50% chow ration alone. Thus nutrient-fed groups received twice the daily dietary energy of chow controls. The low-iodine diet (LID; Remington formula, Harlan Teklad, Madison, WI) was provided ad libitum either by itself or fortified with 0.15% propylthiouracil (PTU; Sigma Chemical, St. Louis, MO), as indicated. In experiments utilizing LID, control animals were also provided free access to iodide in the drinking water (as KI, 0.65 μg/ml; Sigma).

Pharmacological agents. α-Methyl-p-tyrosine (α-MPT as the methyl ester; Sigma) was dissolved in isotonic saline and injected intraperitoneally at time 0 in a dose of 250 mg/kg and again 3 h later in a dose of 125 mg/kg. Bovine TSH (Sigma) was dissolved in isotonic saline and injected subcutaneously in a dose of 1.5 U (in 0.3 ml) twice daily for either 3 or 8 days.

13H]NE turnover procedure. 1-[ring-2,5,6-3H]NE (40–60 Ci/mmol specific activity; Du Pont NEN Research Products, Boston, MA) was injected subcutaneously into an intact animal, and counts were then recorded in the thyroid gland. 

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MA) was purified before use by column chromatography with alumina; the labeled NE was adsorbed onto alumina at pH 8.6 and eluted in 0.2 N acetic acid. For each experiment, \(^{[3H]}\)NE was diluted to an appropriate concentration with 0.9% NaCl and injected intravenously into the tail veins of unanesthetized animals in a total volume of 1.0 ml. The dose of \(^{[3H]}\)NE used in these studies varied from 100 to 110 µCi/kg (~0.40–0.44 µg NE/kg). The rats were killed at preselected times. For each time point in the NE turnover studies, four to six animals were killed from each experimental group. The tissues were rapidly removed, frozen on dry ice, and stored at −20°C for later processing (usually within 2wk). In studies of behavior of \(^{[3H]}\)NE in rat thyroids, we analyzed tissues from thyroid glands that were attached to the underlying thyroid cartilage.

**Analysis of tissue catecholamines.** For NE analysis, the organs were homogenized in iced 0.2 N perchloric acid. After addition of the internal standard, 3,4-dihydroxybenzylamine (Sigma), catecholamines were isolated from the perchloric acid extract by adsorption onto alumina (Woelm neutral, ICN Nutritional Biochemicals) in the presence of 2 M Tris buffer (pH 8.7; Sigma) containing 2% EDTA. Catecholamines were eluted from the alumina with 0.2 N perchloric acid. We analyzed tissue catecholamines in the alumina eluates using the method of Eriksson and Persson (11) with slight modification. Unless otherwise specified, all chemicals were obtained from Fisher Scientific (Fair Lawn, NJ). Aliquots of the alumina eluates were counted for \(^{[3H]}\)NE by liquid scintillation spectrometry.

**Thyroid weight and \(^{125I}\) uptake.** Animals were injected with 5 µCi ip \(^{125I}\) in 0.3 ml of isotonic saline and were killed 4 h later. Hemithyroids were dissected free of supporting tissue and weighed. Tissue content of \(^{125I}\) was then determined by gamma scintillation spectrometry.

**Data analysis.** Data are displayed as means ± SE, unless otherwise noted. Statistical ANOVA and analysis of covariance (ANCOVA) were performed using Data Desk 6.1 statistical software (Data Description, Ithaca, NY) (40). For the analysis of tissue weight and \(^{125I}\) uptake, we used ANOVA incorporating a repeated measures design with two main factors: treatment and hemithyroid and an interaction term (treatment × hemithyroid) (40). For post hoc pairwise comparisons, we utilized Scheffe’s test (40).

In studies of NE turnover, the data were plotted semilogarithmically. The method of least squares was used to calculate the slope of the regression line by examining externally studentized residuals. NE fractional turnover rates were assessed by ANOVA, and ANCOVA was used in comparison of hemithyroids from the same animals. Animals previously subjected to hemithyroidectomy were examined simultaneously in intact and decentralized hemithyroids. We evaluated goodness of fit for each regression line by examining externally studentized residuals. NE turnover was examined in thyroid, hemithyroids, and peripheral tissue and indicate that USCGD can effectively abolish sympathetic outflow to one hemithyroid without destroying the postganglionic sympathetic innervation.

**RESULTS**

**Effect of surgical decentralization on NE turnover in rat hemithyroid.** To determine whether changes in central sympathetic outflow were detectable in thyroid, NE turnover was examined simultaneously in intact and decentralized hemithyroids from the same animals. Animals previously subjected to unilateral (left-sided) superior cervical ganglion decentralization (USCGD) were injected with \(\alpha\)-MPT, a competitive inhibitor of tyrosine hydroxylase, and the decline over time in NE content in intact and USCGD hemithyroids was used as a measure of the activity of sympathetic nerves in the tissues (6). Data from this experiment are presented in Fig. 1. Surgery was performed 4 days before study, and all animals exhibited ptosis of the left upper eyelid at the time of study. NE content in intact and USCGD hemithyroids did not differ at baseline [12.6 ± 1.4 ng/hemithyroid in intact and 10.2 ± 1.5 ng/hemithyroid in USCGD animals, \(P = \) not significant (NS)]. After administration of \(\alpha\)-MPT, NE levels declined at a rate of 10.4 ± 2.4%/h in intact hemithyroids (\(P = 0.0003\)), whereas the rate of change in USCGD hemithyroids (2.4 ± 4.8%/h) did not differ from zero (\(P = \) NS). These data demonstrate that NE turnover, assessed after inhibition of NE biosynthesis, is dependent on an intact neural pathway from spinal cord to peripheral tissue and indicate that USCGD can effectively abolish sympathetic outflow to one hemithyroid without destroying the postganglionic sympathetic innervation.

**Effect of acute cold exposure on \(^{[3H]}\)NE turnover in rat thyroid.** Cold exposure is a well-recognized stimulus for activation of sympathetic nerves. The effect of acute exposure to an environmental temperature of 4°C on sympathetic activity in rat thyroid was examined and compared with \(^{[3H]}\)NE turnover rates seen in rats housed at 21°C. The results are illustrated in Fig. 2. Cold exposure accelerated fractional NE turnover in thyroid (from 7.8 ± 0.4 to 15.6 ± 1.1%/h, \(P < 0.0001\)). NE content in thyroid was unaffected by cold exposure (from 22.9 ± 0.9 in control to 22.1 ± 0.7 ng in the cold, \(P = \) NS). Consequently, total \(^{[3H]}\)NE turnover was 95% higher in thyroids of cold-exposed than in those of control rats (from 1.77 ± 0.17 to 3.46 ± 0.36 ng NE/h, \(P < 0.05\)). Measurement of cardiac \(^{[3H]}\)NE turnover in the same animals was 226% greater in the cold-exposed rats (from 26.0 ± 3.8 to 84.8 ± 9.8 ng NE/h, \(P < 0.05\)). Thus acute exposure to 4°C increases SNS activity in thyroid, as it does in heart, above that observed in rats at 21°C.

**Effect of pregnancy on \(^{[3H]}\)NE turnover in rat thyroid.** Cardiac sympathetic activity is increased in the latter stages of rat pregnancy (7). In 20-day pregnant rats, \(^{[3H]}\)NE turnover was also measured in thyroid gland (Fig. 3). Pregnancy increased fractional NE turnover in thyroid from 8.6 ± 0.9 to 13.3 ± 1.3%/h (\(P = 0.0049\)). Because NE content in thyroid was slightly less in pregnant animals (16.7 ± 1.2 vs. 20.5 ± 1.2 ng, \(P = 0.0310\)), total \(^{[3H]}\)NE turnover was slightly, but not significantly higher in the pregnant rats (+26%, from 1.76 ± 0.28 ng NE/h in virgin controls to 2.23 ± 0.38 ng NE/h by 10.220.33 on September 20, 2017 http://ajpendo.physiology.org/ Downloaded from
Cardiac turnover in pregnant rats was 41\% greater in pregnant rats (from 40.9 ± 5.7 to 57.4 ± 8.9 ng NE/h, \( P < 0.05 \)). This sympathetic activity in thyroid is probably elevated in the late stages of rat pregnancy, although the effect is not as striking as in heart.

Effect of fasting on [\(^3\)H]NE turnover in rat thyroid. Fasting suppresses SNS activity in heart and other tissues (8, 43, 45, 46, 48). The effect of fasting on sympathetic activity in rat thyroid was examined, and the results are presented in Fig. 4.

Fasting for 2 days reduced fractional NE turnover in thyroids (from 10.2 ± 0.7 to 5.7 ± 0.7\%/h, \( P < 0.0001 \)). NE content in thyroid was slightly but not significantly increased in fasting rats (from 23.5 ± 0.7 ng in fed to 26.0 ± 1.1 ng in fasted, \( P = 0.065 \)). Consequently, total NE turnover was 38\% lower in thyroids of fasted rats (from 2.41 ± 0.23 ng/h to 1.49 ± 0.24, \( P < 0.05 \)). Cardiac NE turnover measured in the same animals was 32\% lower in hearts of fasted, compared with fed, animals (from 30.7 ± 3.6 to 20.8 ± 2.6 ng/h, \( P < 0.05 \)). Thus fasting decreases SNS activity in thyroid, as it does in heart.

Effect of nutrient intake on [\(^3\)H]NE turnover in rat thyroid. Dietary intake of carbohydrate and fat raises SNS activity in many peripheral tissues (32, 44, 46, 49). The effect of a 4-day exposure to diets containing 50\% of energy from either carbohydrates (sucrose) or fats (lard) on sympathetic activity in rat thyroid was assessed, and the results are illustrated in Fig. 5.

Fractional NE turnover in thyroid of sucrose-fed animals was greater than that in controls (from 6.6 ± 0.8 to 8.7 ± 0.5\%/h, \( P < 0.05 \)), whereas that in fat-fed rats was slightly but not significantly increased (8.6 ± 0.7\%/h, \( P = 0.067 \)). NE content in thyroid was slightly lower in both fat-fed and sucrose-fed rats than in controls (23.3 ± 0.8 ng in fat-fed rats, 23.7 ± 0.6 ng in sucrose-fed rats, and 26.5 ± 0.7 ng in controls, \( P < 0.005 \) overall). As a result, total NE turnover in thyroid was only 14\% greater than control in fat-fed rats (from 1.76 ± 0.26 in controls to 2.00 ± 0.23 ng/h, \( P = NS \)) and only 18\% higher in sucrose-fed animals (2.07 ± 0.18 ng/h, \( P = NS \)). In contrast, dietary fat increased cardiac NE turnover by 87\% (from 16.4 ± 3.0 in controls to 30.7 ± 4.8 ng/h, \( P < 0.05 \)) and dietary sucrose by 51\% (to 24.8 ± 3.8 ng/h, \( P < 0.05 \)). Thus, although...
dietary intake of fat or sucrose for 4 days clearly stimulates SNS activity in the heart, the effects in the thyroid are much less pronounced.

Effect of iodine deficiency on \([^3]H\)NE turnover in rat thyroid. Iodine deficiency was induced by placing rats on LID and giving them only distilled water to drink. Control rats received KI in drinking water in addition to the LID. After 31 days, \([^3]H\)NE turnover was measured in both groups. The results in thyroid are presented in Fig. 6. Body weights did not differ between the two groups. In thyroids from iodine-deficient animals, tissue NE levels were higher (from 44.0 ± 2.0 to 50.3 ± 1.7 ng, \(P = 0.0206\)) and fractional NE turnover rates were increased (9.4 ± 0.6 in controls to 11.7 ± 0.7 %/h in iodine-deficient rats, \(P = 0.0224\)). Consequently, total NE turnover was 42% greater in the iodine-deficient group (from 4.14 ± 0.46 to 5.87 ± 0.56 ng/h, \(P < 0.05\)). By contrast, total NE turnover was unchanged in hearts of the iodine-deficient rats, being 85.9 ± 12.2 ng NE/h in iodine-deficient rats and 84.6 ± 10.5 ng NE/h in controls, \((P = \text{NS})\). Thus sympathetic activity in thyroid, but not in heart, is increased by iodine deficiency.

Effect of LID ± PTU on \([^3]H\)NE turnover in rat thyroid. One method commonly used to induce a goitrogenic response is chronic exposure of rats to LID supplemented with an antithyroid agent such as PTU. The effects of ingestion of this goitrogenic diet for 47 days on \([^3]H\)NE turnover in rat thyroid is shown in Fig. 7. Animals fed the LID + PTU regimen ate only one-third to one-half the amount of food consumed by the control animals when measured over two 3-day periods and gained significantly less weight. At time of study, LID + PTU-fed rats weighed 173 ± 4 g and controls weighed 343 ± 5 g \((P < 0.0001)\). NE content in thyroid was reduced in the LID + PTU-fed rats, from 38.6 ± 1.1 to 29.5 ± 1.4 ng \((P < 0.0001)\), although fractional NE turnover was increased from 14.6 ± 1.2 in controls to 25.2 ± 2.0 %/h in the LID + PTU group \((P < 0.0001)\). Consequently, overall \([^3]H\)NE turnover was 32% higher in thyroids from animals fed the LID + PTU diet (from 5.64 ± 0.62 to 7.42 ± 0.96 ng NE/h, \(P < 0.05\)). Concurrent measurements of \([^3]H\)NE turnover in heart showed a 63% increase in the LID + PTU-fed animals (from 76.1 ± 13.2 to 123.8 ± 19.0 ng NE/h, \(P < 0.05\)). Thus sympathetic activity in thyroid, as well as in heart, is increased in animals consuming the goitrogenic diet.

Effect of LID ± PTU on tissue weight and \(125\text{I}\) uptake in rat thyroid. To examine the potential contribution of the sympathetic innervation in thyroid to the goitrogenic response, thyroid weight and uptake of \(125\text{I}\) were compared in intact and decentralized hemithyroids from the same animals fed either the LID + PTU or control diet for 21 days. The results from two separate studies are summarized in Table 1. In both experiments, the LID + PTU regimen increased thyroid weight three- to fourfold and thyroid \(125\text{I}\) uptake by 60–130%. Moreover, in both studies, USCGD hemithyroids weighed less and took up less \(125\text{I}\) than intact hemithyroidis. Although the impact of the USCGD procedure on thyroid weight appeared slightly greater in LID + PTU rats than in controls, the interaction term between treatment and innervation (hemithyroid) in the ANOVA was not statistically significant for either tissue weight or \(125\text{I}\) uptake whether analyzed with untransformed or log-transformed data. Thus, in two experiments, the USCGD procedure decreased thyroid weight and \(125\text{I}\) uptake in rats fed either the control or LID + PTU diets, although these effects were not demonstrably different in the two dietary groups.

In the second study, an additional group of animals fed the control diet was treated with twice daily injections of TSH for either 3 or 8 days before injection of \(125\text{I}\). The effects of TSH treatment on thyroid weight and \(125\text{I}\) uptake in intact and USCGD hemithyroids are presented in Table 2. As in experiment 2 in Table 1, surgery occurred 24 days before study. The two TSH treatment groups did not differ from one another in tissue weight, although in rats treated with TSH for 8 days thyroid weight was slightly greater \((P = 0.05)\) than in control rats from this experiment \(\text{experiment 2, Table 1}\). Thyroid weight, however, did not differ between intact and USCGD hemithyroids. \(125\text{I}\) uptake was markedly increased by TSH treatment \((P < 0.0001)\), although uptake did not differ between rats treated with TSH for 3 or for 8 days. Uptake also was significantly less in the USCGD group than in intact hemithyroid group \((P = 0.0186 \text{in TSH-treated rats, } P = 0.0013 \text{ if nontreated, control rats are also included in the analysis})\). Thus surgical decentralized of the thyroid limits iodine uptake,

Fig. 6. Effects of iodine deficiency on \([^3]H\)NE turnover in thyroid. Male rats were fed the low-iodine diet (LID) for 31 days before study. Control rats were also fed LID but received iodide in the drinking water. Data are plotted as means ± SE for natural log of NE specific activity from 3–5 animals in each group at each time point. ●, Control animals; ▲, iodine-deficient animals.

Fig. 7. Effects of ingestion of LID plus propylthiouracil (PTU) on \([^3]H\)NE turnover in rat thyroid. Male rats were fed LID for 47 days before study. Control animals received LID plus iodide in the drinking water. Data are plotted as means ± SE for natural log of NE specific activity from 3–5 animals in each group at each time point. ●, Control animals; ▲, LID + PTU-fed animals.
an impairment that persists despite treatment with exogenous TSH.

**DISCUSSION**

One of the goals of our investigation was to apply the techniques of NE turnover to the assessment of sympathetic activity in rat thyroid. Although previous attempts to evaluate the role of the SNS in thyroid function have used methods that were largely inferential, this study combined measurements of NE turnover in thyroid gland with comparative studies of thyroid function in intact and centrally isolated (following ganglion decentralization). *Although the interaction term between treatment (Rx) and hemithyroid was included in the ANOVA model, it was not statistically significant for any variable.

**Table 1. Effects of LID + PTU in intact and decentralized rat hemithyroids**

<table>
<thead>
<tr>
<th></th>
<th>Control (Intact)</th>
<th>LID + PTU (USCGD)</th>
<th>P*</th>
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<tbody>
<tr>
<td>Tissue wt, mg</td>
<td>9.2 ± 0.7</td>
<td>8.7 ± 0.5</td>
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<tr>
<td>Log (tissue wt)</td>
<td>0.955 ± 0.031</td>
<td>0.933 ± 0.026</td>
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<tr>
<td>125I uptake, counts/min</td>
<td>30,867 ± 3,281</td>
<td>26,965 ± 2,915</td>
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<tr>
<td>Log (uptake)</td>
<td>4.470 ± 0.047</td>
<td>4.410 ± 0.048</td>
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**Experiment 1**

<table>
<thead>
<tr>
<th></th>
<th>Control (Intact)</th>
<th>LID + PTU (USCGD)</th>
<th>P*</th>
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</thead>
<tbody>
<tr>
<td>Tissue wt, mg</td>
<td>9.4 ± 0.7</td>
<td>8.5 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Log (tissue wt)</td>
<td>0.961 ± 0.031</td>
<td>0.921 ± 0.029</td>
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<tr>
<td>125I uptake, counts/min</td>
<td>44,623 ± 4,968</td>
<td>40,729 ± 3,184</td>
<td></td>
</tr>
<tr>
<td>Log (uptake)</td>
<td>4.630 ± 0.042</td>
<td>4.598 ± 0.033</td>
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**Experiment 2**

Values are means ± SE; For experiment 1, n = 9 rats for control and for low-iodine diet (LID) + propylthiouracil (PTU) groups; for experiment 2, n = 10 for control group and n = 9 for LID + PTU group. 125I uptake was measured 4 h after intraperitoneal injection of 125I. USCGD, unilateral superior cervical ganglion decentralization. *Although the interaction term between treatment (Rx) and hemithyroid was included in the ANOVA model, it was not statistically significant for any variable.

Responses of thyroid sympathetic nerves to various physiological manipulations are consistent with known effects of these conditions on SNS activity in other tissues. Cold exposure is a well-known stimulus of SNS activity in many but not all peripheral tissues (4, 8, 46, 48). The cold-induced acceleration in thyroidal NE turnover was qualitatively similar to that in heart (Fig. 3) and also consistent with indirect evidence of sympathetic activation in thyroid, since sympatholytic agents antagonize the cold-induced increase in colloid droplet formation in thyroid follicular cells in vivo (13). The findings from our present experiment probably underestimate the impact of cold temperature because the controls were housed at 21°C, which is below the thermoneutral range for these animals (30). Pregnancy is also associated with tissue-specific changes in SNS function (7), and its impact in the thyroid was again qualitatively similar to that in heart (Fig. 4). Consumption of a goitrogenic diet (LID supplemented with PTU) increased NE turnover in thyroid as well as heart. The stimulus for these responses likely represents a combination of both iodine deficiency and hypothyroidism, since hypothyroidism is widely recognized to stimulate sympathetic activity in human subjects (12, 29) and in peripheral tissues of experimental animals (2, 21, 36, 38).

These studies also indicate that alterations in dietary intake affect thyroidal SNS activity. Fasting suppressed SNS activity in thyroid, a response similar to that shown previously in heart and other tissues (8, 43, 45, 46). Although the role of local sympathetic innervation in the regulation of thyroid function is incompletely understood, it is likely that the reduction in thyroidal SNS activity (Fig. 4) contributes to the overall

**Table 2. Effects of TSH in intact and decentralized rat hemithyroids**

<table>
<thead>
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<th>TSH × 3 days</th>
<th>TSH × 8 days</th>
<th>P*</th>
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<tr>
<td>Tissue wt, mg</td>
<td>10.8 ± 1.6</td>
<td>9.9 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>125I uptake, counts/min</td>
<td>116,411 ± 13,516</td>
<td>102,108 ± 13,113</td>
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</tbody>
</table>

Values are means ± SE; n = 4 rats in TSH × 3 days group and n = 3 rats in TSH × 8 days group. 125I was measured 4 h after intraperitoneal injection of 125I. *Although the interaction term between Rx and hemithyroid was included in the ANOVA model, it was not statistically significant for any variable.
suppression in thyroid function during fasting (42). On the other hand, diet may also stimulate SNS activity in thyroid. Although the effects of dietary fat and sucrose (Fig. 5) were quantitatively less in thyroid than in heart, the impact of iodine deficiency was much more pronounced. Given the importance of an intact sympathetic innervation for thyroidal responses to TSH (Table 2), the increase in SNS activity in thyroids of iodine-deficient animals (Fig. 6) raises the possibility that the SNS may participate in the augmentation of TSH responses noted in iodine deficiency (5). Thus dietary manipulations appear to alter SNS activity in rat thyroid, and the changes induced may, in turn, contribute to physiological alterations in thyroid function.

The changes in NE turnover noted in these experiments provide information regarding the activity only of the postganglionic, noradrenergic fibers in thyroid. Because neuropeptide Y is localized predominantly but not exclusively within NE-containing thyroid nerves (16), heightened activity of the noradrenergic fibers may also indicate enhanced neuronal release of neuropeptide Y. Measurements of NE turnover, however, provide no information regarding the functional state of cholinergic or nonadrenergic peptidergic fibers for which no techniques presently exist for selective estimation of the activity of these nerves in vivo.

Thyroid enlargement commonly occurs during pregnancy and in the presence of iodine deficiency with or without added PTU. The demonstration of heightened SNS activity in thyroid in these conditions suggests that sympathetic nerves might play a role in these goitrogenic responses. Whether the sympathetic effects involve changes in blood flow or in thyroid cell number or function are presently unknown. On the other hand, the increase in thyroidal SNS activity during cold exposure implies that sympathetic activation per se is not sufficient for goitrogenesis.

Two experiments were performed, however, to test the hypothesis that the increase in thyroidal SNS activity in iodine-deficient, PTU-treated rats contributes to goiter formation. The studies compared tissue weight and 125I uptake in animals subjected to unilateral disruption of the preganglionic fibers to the superior cervical ganglion (USCGD), the sympathetic ganglion from which the adrenergic innervation of the thyroid originates (34). After 21–24 days of exposure to the iodine-deficient, PTU-containing diet (LID + PTU), tissue weight and 125I uptake were less overall in USCGD than in intact hemithyroids (Tables 1 and 2). The proportional effects of surgical decentralization to reduce tissue weight and 125I uptake were not statistically distinguishable in control and LID + PTU-fed animals. These findings indicate that sympathetic “tone” in thyroid actively promotes tissue growth and uptake of 125I and does so both in control and in LID + PTU-fed animals.

The conclusions drawn from these experiments are at odds with previous reports from Cardinali and coworkers (23) who advanced the thesis that thyroid sympathetic nerves suppress the goitrogenic response. The differences between our work and theirs are largely, if not entirely, methodological in nature. In their studies, they examined various thyroid responses within several days after unilateral superior cervical ganglionectionomy (27, 28, 31). Ganglionectionomy, unlike decentralization, destroys the postganglionic sympathetic innervation; in contrast, decentralization leaves the postganglionic innervation intact but abolishes delivery of efferent impulses (see Fig. 1).

In other tissues, superior cervical ganglionectionomy elicits denervation supersensitivity (33) and, over time, neuronal ingrowth from the contralateral innervation (24), although neither of these phenomena has been reported in the thyroid. Direct comparisons between the effects of two similar adrenergic lesions have been carried out in the pineal gland, another midline endocrine organ that receives bilateral adrenergic innervation from the superior cervical ganglia (3). After unilateral sectioning of the postganglionic adrenergic fibers to the pineal, sprouting develops from the contralateral innervation (24). Consequently, the functional capacity of the pineal, which declines acutely after initial denervation, returns to normal within a few days (20). In contrast, unilateral decentralization does not elicit a sprouting response, and the glandular function remains permanently depressed (20). These studies in the pineal gland and the differences between our present findings and those previously reported by Cardinali and coworkers argue strongly that, in future investigations of the role of thyroid sympathetic nerves in the regulation of glandular function, superior cervical ganglion decentralization should be the procedure of choice for selective disruption of efferent sympathetic pathways.

Perspectives

All peripheral endocrine organs are innervated by postganglionic sympathetic nerves (47), although the contribution of this innervation to regulation of glandular function is unclear. In ovary, testis, and adrenal gland, sympathetic nerves contribute to compensatory growth of the remaining gland after surgical removal of one gland (14, 15, 18), a response analogous to the contribution of sympathetic innervation to goitrogenesis reported here. In addition, sympathetic nerves increase the sensitivity of target organs to trophic stimulation. Adrenal cortical responses to ACTH are, in part, dependent on the integrity of the sympathetic innervation (10), and the acquisition of adult response characteristics for both ovary and adrenal is influenced by development of sympathetic innervation (22, 41). Similarly, the blunted increase in 125I uptake in decentralized hemithyroids of TSH-treated rats (Table 2) implies that thyroid gland responses to TSH are also partially dependent on local SNS activity. Although the importance of sympathetic and other autonomic nerves to regulation of endocrine function is not precisely defined, current data suggest that this innervation may serve to modulate glandular responses to trophic stimulation and that such “fine tuning” may be susceptible to physiological regulation, effects that may underlie circadian rhythmicity of thyroid hormone levels in rats (19).

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GRANTS

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