Regulation of Thyroid Hormones in the Secretion of Insulin and Gastric Inhibitory Polypeptide in Male Rats

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The effect of thyroid hormones on glucose-induced secretion of gastric inhibitory polypeptide (GIP) and insulin was studied. Male rats were thyroidectomized (Tx) or sham Tx. Sham Tx rats were injected with either propylthiouracil ([PTU] 20 mg/kg intraperitoneally) or saline for 2 weeks. In addition, thyroid-intact rats were injected intravenously with triiodothyronine ([T_3] 5 μg/kg) or saline 10 minutes before an oral glucose load (3.2 g/kg). Blood samples were collected from each animal via a jugular catheter at 0, 10, 20, 30, 45, 60, and 90 minutes following glucose ingestion. Plasma levels of GIP and insulin were measured by specific radioimmunoassays (RIAs). Thyroidectomy-induced hypothyroidism increased the basal level of plasma GIP, but decreased that of insulin. Insulin levels at 10, 20, and 30 minutes following oral glucose were lower in hypothyroid rats than in euthyroid rats. Conversely, GIP levels at 60 and 90 minutes following glucose ingestion in PTU-induced hypothyroid rats were higher than those in euthyroid rats. Furthermore, glucose-stimulated insulin secretion was unaltered by pretreatment with T_3, whereas the glucose-induced increase in plasma GIP was completely abolished by preinjection of T_3 in thyroid-intact rats. These results suggest that thyroid functions are involved in the regulation of insulin and GIP secretion in rats.

THYROTOXICOSIS or hyperthyroidism caused by thyroid hormones elicit normal[1-3] or elevated[4-9] plasma glucose and normal[7,10,11] or increased[1-6,8,9] plasma insulin levels in humans or rats under the fasted condition. Plasma glucose loads were higher[4-6,8] in hyperthyroid than in euthyroid conditions. However, the changes in basal and glucose-induced insulin secretion in hypothyroidism were not clear.

It is well known that gastric inhibitory polypeptide (GIP), an insulinotropic hormone originally isolated from the small intestine,[12,13] is increased after oral glucose loading[14] or administration of nutrients.[15] Since the secretion of insulin in response to glucose is enhanced by GIP,[16-20] it is of interest to delineate the role of thyroid hormones in regulating the glucose-dependent secretion of GIP.

Although neither hyperthyroidism[21] nor hypothyroidism[22] in humans alters the serum or plasma GIP level in response to oral glucose, we found that the increased secretion of GIP in male rats during aging seemed likely to be associated with hypothyroidism.[23]

To clarify the role of thyroid hormones in regulating the secretion of GIP and insulin, the present investigation was undertaken to examine basal and glucose-stimulated release of GIP and insulin in rats with hypothyroidism induced by thyroidectomy or administration of propylthiouracil (PTU) and rats with acute hyperthyroidism induced by intravenous injection of triiodothyronine (T_3).

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MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats weighing 250 to 300 g were housed in a temperature-controlled (22° ± 1°C) environment with 14 hours of artificial illumination daily (6 AM to 8 PM). All rats were given rat chow and tap water ad libitum.

Experiment 1

Rats were thyroidectomized (Tx) or sham Tx. Sham Tx rats were injected intraperitoneally with either PTU (20 mg/kg) or saline once daily for 2 weeks. One day before the oral glucose load, all rats were catheterized via the right jugular vein.[24,25] Glucose was administered after deprivation of food for 4 hours (from 6 AM to 10 AM) by applying 3.2 g/kg as a 40% solution into the esophagus via a plastic feeding tube. Blood samples (0.5 mL each) were collected at 0, 10, 20, 30, 45, 60, and 90 minutes following glucose ingestion. An equal volume of heparinized saline was injected immediately after each sampling.

Experiment 2

Intact male rats were used after deprivation of food for 4 hours (from 6 AM to 10 AM). They were injected intravenously with T_3 (5 μg/kg) or saline 10 minutes before an oral glucose load. Blood samples were collected using the method described in experiment 1.

Chemical Analysis

Blood glucose concentration was measured by a glucose analyzer (model 23A; Yellow Springs Instruments, Yellow Springs, OH). Plasma GIP concentration was measured by a radioimmunoassay (RIA) as described previously.[26,27] The limit of detection for this RIA was 15 pg per tube. Intraassay and interassay coefficients of variation were 5.1% (n = 10) and 8.3% (n = 10), respectively. Plasma insulin was determined by the RIA developed by Ho et al.[28] The level of thyrotropin (TSH) was measured by the RIA kit provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; Bethesda, MD). Rat TSH-I-8 and TSH-RP-2 were used for the iodination and standard, respectively.[29] Intraassay and interassay coefficients of variation were 2.0% and 5.4%, respectively. T_3 concentration in plasma samples was measured by a RIA kit purchased from Amersham International (Bucks, UK). Calcium concentration was determined by an atomic absorption method (model VIDEL 12; Instrumentation Laboratory, Andover, MA).

Statistical Analysis

For analyzing the Tx or PTU effect, the treatment mean at each sampling time was tested for homogeneity using a one-way ANOVA, and the difference between specific means was tested for significance using Duncan's multiple-range test.[30] The comparison between T_3- and saline-injected groups at each sampling time was analyzed by Student's unpaired *t* test. The effect of oral glucose was analyzed by Student's paired *t* test. A difference between two means was considered statistically significant when *P* was less than .05.

RESULTS

Effect of Hypothyroidism on Plasma T_3, TSH, and Calcium

Hypothyroidism resulted in decreased plasma T_3 and increased plasma TSH (Table 1). Administration of PTU did not affect plasma calcium, but calcium was decreased ($P < .01$) in Tx rats.

Effect of Hypothyroidism on Blood Glucose and Plasma Insulin and GIP

Basal blood glucose levels in hypothyroid rats (81 ± 5 mg/dL in Tx rats and 74 ± 5 mg/dL in PTU rats) were not significantly different from the levels in euthyroid rats (74 ± 4 mg/dL) (Fig 1). Blood glucose at 30 minutes following the oral glucose load was higher ($P < .05$) in PTU-injected rats (165 ± 12 mg/dL) than in sham Tx rats (126 ± 11 mg/dL). From 30 to 90 minutes after glucose ingestion, blood glucose in hypothyroid animals remained higher than the corresponding value in euthyroid animals (Fig 1).

Changes in plasma insulin concentration in euthyroid and hypothyroid rats are illustrated in Fig 2. Basal plasma insulin levels were lower ($P < .01$) in all hypothyroid rats (13.6 ± 1.6 μU/mL in Tx rats and 12.0 ± 1.0 μU/mL in PTU rats) compared with sham Tx rats (26.7 ± 2.7 μU/mL). Plasma insulin increased by 1.9- to 2.2-fold at 10, 20, and 30 minutes following the oral glucose load in all rats. However, the glucose-induced increase in insulin was significantly lower ($P < .01$) in hypothyroid rats than in euthyroid rats. Thirty minutes after glucose stimulation, plasma insulin declined gradually in all rats, and remained at a lower value in hypothyroid rats compared with intact animals.

In contrast, the basal plasma GIP level was significantly ($P < .05$) higher in Tx rats (0.66 ± 0.09 ng/mL) than in euthyroid rats (0.36 ± 0.08 ng/mL) (Fig 3). Administration of PTU did not alter the basal level of plasma GIP (0.48 ± 0.07 ng/mL). The oral glucose load elicited an increase in GIP secretion that peaked (twofold) at 20 minutes following glucose ingestion in euthyroid rats. In Tx and PTU rats, circulating GIP (0.70 ± 0.06 to 0.77 ± 0.06 ng/mL) remained higher throughout the 45- to 90-minute period compared with the level in euthyroid rats (0.44 ± 0.06 to 0.52 ± 0.06 ng/mL), although in Tx rats there was no peak response to glucose ingestion.

Table 1. Plasma T_3, TSH, and Calcium in Euthyroid and Hypothryoid Male Rats

Treatment	No. of Rats	T_3 (ng/dL)	TSH (ng/mL)	Calcium (μg/mL)
Sham Tx	9	15.7 ± 3.9	1.4 ± 0.4	84.0 ± 2.8
Tx	9	3.9 ± 1.7*	9.2 ± 0.8*	46.7 ± 2.1*
PTU	9	2.3 ± 0.9*	8.6 ± 1.2*	87.3 ± 2.6

NOTE. Results are the mean ± SEM.
*$P < .01$ *v* sham Tx.

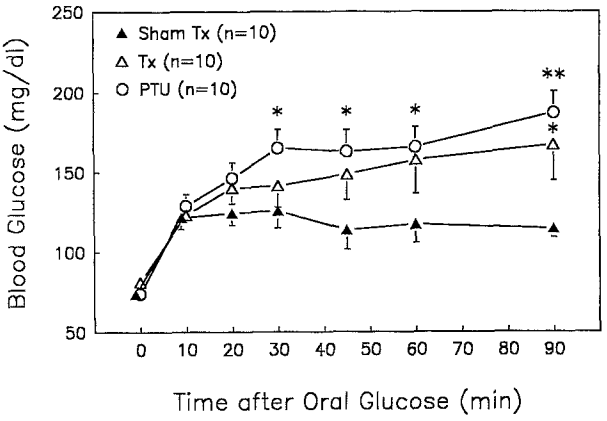

Fig 1. Blood glucose levels in euthyroid and hypothyroid rats. *$P < .05$, **$P < .01$: *v* sham Tx.

Effect of Acute T_3 Injection on Blood Glucose and Plasma Insulin and GIP

Intravenous injection of T_3 in male rats resulted in a 10- to 24-fold increase of plasma T_3 within 60 minutes (from 0.05 ± 0.01 to 1.17 ± 0.11 and then 0.53 ± 0.04 μg/dL). Plasma T_3 concentration was not altered by the oral glucose load.

The basal blood glucose level (69 ± 2 *v* 67 ± 4 mg/dL) was not altered by intravenous injection of T_3, whereas blood glucose at 20 minutes after glucose ingestion was significantly higher ($P < .01$) in T_3-treated rats (129 ± 11 mg/dL) than in saline-injected rats (99 ± 3 mg/dL) (Fig 4). There was no statistical difference in the blood glucose level between hyperthyroid and euthyroid rats at 30, 45, and 60 minutes following the oral glucose load.

Oral glucose increased plasma insulin levels in both euthyroid rats (from 31 ± 2 to 94 ± 12 μU/mL) and hyperthyroid rats (from 51 ± 12 to 179 ± 51 μU/mL) (Fig 5). Although neither spontaneous nor glucose-stimulated secretion of insulin was significantly altered by administration of T_3, the mean

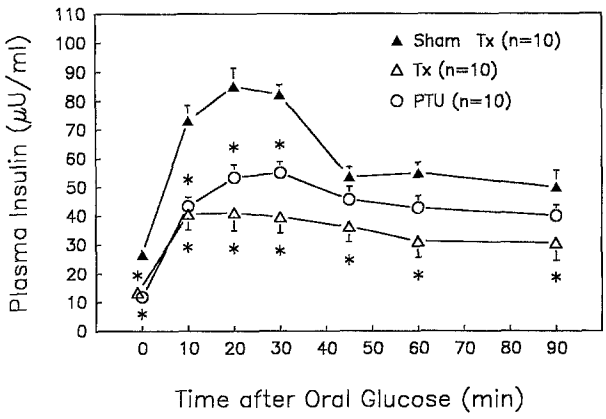

Fig 2. Plasma insulin levels in euthyroid and hypothyroid rats. *$P < .05$ *v* sham Tx.

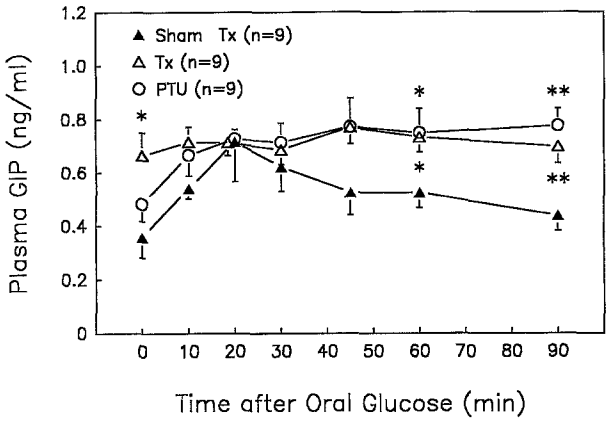

Fig 3. Plasma GIP levels in euthyroid and hypothyroid rats. *$P < .05$, **$P < .01$: *v* sham Tx.

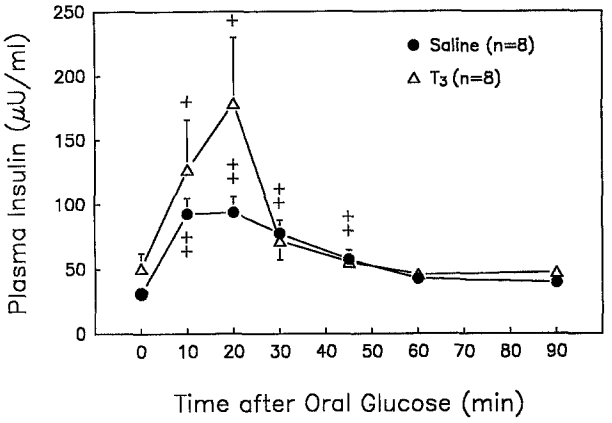

Fig 5. Acute effects of T_3 on plasma insulin levels after an oral glucose load in male rats. $^{+}P < .05$, $^{++}P < .01$: *v* value at 0 minutes by Student's paired *t* test.

plasma insulin level was maintained higher in T_3-treated than in saline-treated rats.

The basal plasma GIP level (0.18 ± 0.11 ng/mL) in T_3-injected rats was nonsignificantly different ($P > .05$) from that in saline-injected rats (0.67 ± 0.22 ng/mL) (Fig 6). However, the increase (31% to 94%, $P < .05$ or $P < .01$) in GIP secretion in response to the oral glucose load in rats treated with saline was completely abolished in animals treated with T_3.

DISCUSSION

The present study demonstrated that (1) hypothyroidism reduced spontaneous and glucose-stimulated insulin secretion, (2) thyroidectomy increased basal GIP secretion and PTU-induced hypothyroidism increased glucose-stimulated GIP secretion in food-deprived rats, and (3) administration of T_3 increased the peak values of blood glucose but inhibited the response of GIP to an oral glucose load in rats.

It has been shown that hyperthyroidism caused by T_3 elicits significantly elevated basal and oral glucose–stimulated plasma levels of insulin and glucose.[8] Administration of thyroxine in rats increases plasma insulin,[3,5] whereas blood glucose is either normal[3] or increased.[5] Our data indicated that basal levels of neither blood glucose nor plasma insulin were significantly altered by pretreatment with T_3. Although T_3 caused an increase in blood glucose at 20 minutes following oral glucose, plasma insulin in response to oral glucose was unchanged by T_3. Apparently, acute administration of T_3 does not affect basal and glucose-stimulated insulin secretion.

It has been demonstrated that GIP secretion can be increased by an oral glucose load.[14,31] However, we found that the stimulatory effect of oral glucose on GIP secretion was abolished in rats treated with T_3. These results showed that T_3 treatment may modify the secretory pattern of insulin and GIP via different mechanisms. Whether T_3 inhibits the secretion of GIP in response to oral glucose by a direct action on secretory cells in the gastrointestinal tract is not yet known.

Changes in blood glucose and plasma insulin and GIP in Tx and PTU rats after an oral glucose load should be mainly due to the absence of thyroid hormones rather than to the plasma calcium level. This is because thyroidectomy and PTU treatment caused different effects on plasma calcium levels but elicited similar plasma glucose, insulin, and GIP levels. The hyperglycemia caused by hypothyroidism in rats following oral glucose is apparently due to the insufficiency of insulin secretion. Since GIP stimulates the release of somatostatin,[18,19,32-34] we speculate that the hypoinsulinemia that occurred

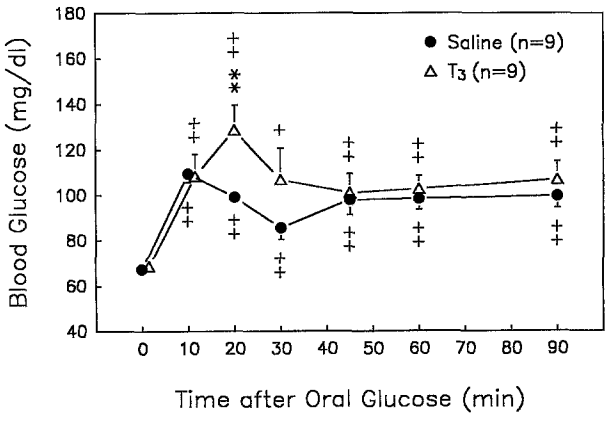

Fig 4. Acute effects of T_3 on blood glucose levels after an oral glucose load in male rats. **$P < .01$ *v* saline by Student's unpaired *t* test. $^{+}P < .05$, $^{++}P < .01$: *v* value at 0 minutes by Student's paired *t* test.

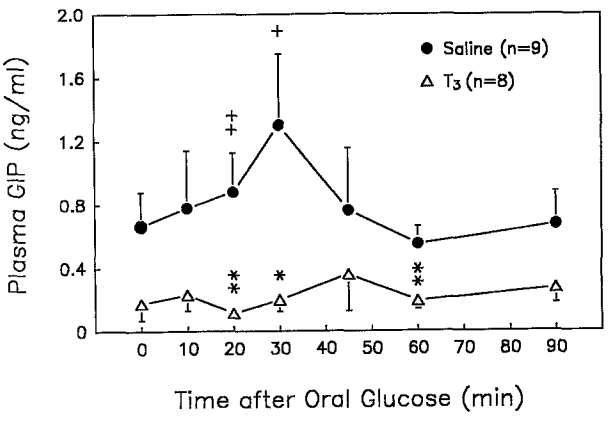

Fig 6. Acute effect of T_3 on plasma GIP levels after an oral glucose load in male rats. *$P < .05$, **$P < .01$: *v* saline by Student's unpaired *t* test. $^{+}P < .05$, $^{++}P < .01$: *v* value at 0 minutes by Student's paired *t* test.

in Tx and PTU hypothyroid rats might be, at least in part, due to an increase of pancreatic or intestinal somatostatin secretion stimulated by the higher plasma GIP levels. Although the increment of plasma GIP was not observed in Tx rats after the oral glucose load, basal and 60- to 90-minute postglucose GIP levels were significantly higher in Tx rats than in euthyroid animals. The reason that PTU did not induce a significantly higher basal plasma GIP level is not clear.

Compared with euthyroid animals, the higher GIP levels in hypothyroid rats and the disappearance of the GIP response to oral glucose in T_3-treated rats showed that thyroid hormones play an inhibitory role in regulating the secretion of GIP in rats. It has been shown that in vitro release of GIP from a preparation of canine intestinal cells is increased by addition of the calcium ionophor, A-23187, or the adenylate cyclase activator, forskolin.[35] Although the mechanisms for the action of thyroid hormones on GIP secretion are unknown, it is probably associated with the production of 3′,5′-cyclic adenosine monophosphate and influx of extracellular calcium in GIP-producing cells.

The increase of blood glucose in response to oral glucose in hypothyroid rats should be due to the decrease of glucose utilization caused by the decreased insulin response to glucose ingestion. However, the increase of the peak value for blood glucose in response to oral glucose in T_3-injected rats might be due to an increase of basal hepatic glucose production,[36] an increase in the rate of intestinal glucose absorption,[37] and/or hyperglucagonemia.[2,7]

The responses of serum glucose, insulin, and GIP following oral glucose have been studied in hyperthyroid patients with Graves' disease[21] and hypothyroid subjects with thyroid carcinoma.[22] Although serum glucose levels are higher in Graves' disease patients[21] and normal in carcinoma patients,[22] basal insulin remains normal and glucose-stimulated serum insulin levels are higher in both groups compared with euthyroid controls. Furthermore, neither hyperthyroid patients with Graves' disease[21] nor hypothyroid subjects with thyroid carcinoma[22] show an alteration in the GIP response to oral glucose. The reasons for the difference between rats and humans remain unknown, but may be attributed to the different causes of thyroid dysfunction and/or different age ranges.

In addition, the adrenergic regulation associated with thyroid hormones on GIP secretion could not be excluded. Epinephrine results in hyperinsulinemia in hyperthyroid rats[9,38] and humans[7] more markedly than in euthyroid rats and humans. But no hyperinsulinemia can be induced in hypothyroid rats.[7] It is well known that thyroid hormones can increase the number and affinity of β-adrenergic receptors in the heart and possibly in other tissues.[39] Although there is no direct evidence at the present time, epinephrine may play a specific role in regulating the effect of thyroid hormones on GIP secretion.

In summary, the present investigation indicates that the T_3-inhibited GIP response to hyperglycemia and hypothyroidism resulted in a decrease of insulin secretion but an increase of GIP secretion in male rats.

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