EFFECT OF THYROID HORMONES ON DISTENSION-INDUCED GASTRIC ACID AND PEPSIN SECRETIONS IN RATS

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Background: Thyroid hormones are known to influence acid and pepsin secretion, though the exact mechanism is not fully understood. In this study, distension-stimulated acid and pepsin secretions in hypo- and hyperthyroid rats were compared with controls.

Materials and Methods: Each group consisted of 8 N-mari rats of both sexes, weighing 246.6±9.2 g. Hypo- and hyperthyroid states were induced by administration of methimazole (500 mg/L H_2O) and thyroxin (200 µg/L H_2O) respectively, in drinking water. All animals were deprived of food, but not of water 24 hours before the experiments. After anesthetization with sodium thiopental (50 mg/kg body weight, ip), tracheotomy and laparatomy, gastric secretions were collected through a cannula introduced via the duodenum. Gastric distension was induced by the injection of Ringer solution in stomach (1.5 cm^3/100 g body weight).

Results: Acid secretions, which were measured by automatic titrator in the hypothyroid, hyperthyroid and control groups were 8±0.2, 14.6±1.9 and 10.2±0.1 µmol/15 min, respectively. Pepsin secretions were 4.4±0.5, 9.09 ±0.4 and 6.1±0.1 mg/15 min. in respective groups. There were statistically significant differences in both series between control and the other two groups.

Conclusion: The results from the measurements of thyroid-stimulating hormones and T_4 hormones showed that increased or decreased thyroid function can significantly affect gastric distension-induced acid and pepsin secretion.

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Key Words: Thyroid hormones, gastric acid secretion, gastric pepsin secretion, gastric distention, rat.

Thyroid hormones affect the function of some body organs including cardiovascular[1-3] and nervous systems,[4-6] liver,[7] development and reproductive systems and growth process.[8,9] There is evidence that they also affect gastric acid and pepsin secretions.[10,11] In a study by Kayode and Michael, it was shown that thyroid hormones influence total parietal cell mass, so that thyroidectomy reduces, while administration of thyroid hormones increases parietal cell mass. The study also showed that thyroid hormones trigger biochemical signals relating to cell growth, and in mice taking thyroxin, mitotic activity increases in the gastrointestinal (GI) tract epithelial cells, especially in crypts, and it is probable that parietal cells also increase their proliferative activity. These increases in cell mass causes an increase in acid secretion. On the other hand, thyroidectomy inhibits parietal cell mitotic activity and decreases acid output.[12]

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Another study by Tseng et al. also showed the effects of thyroxin on gastric development.[13] Weigert et al. studied co-effects of thyroxin and corticosterone on gastric acid and pepsin secretion in rats, and noticed that thyroxin injection increases acid/pepsin output, but adrenalectomy significantly lowers pepsinogen and acid output. Once again, administration of corticosterone to those animals restored acid/pepsin secretion.[13,14]

lt has been observed that coadministration of thyroxin and corticosterone has a remarkable effect on acid/pepsin secretion.The lowering of thyroxine level in rats by the adminstration of propyl-thiuracil decreases acid/pepsin secretion.

Gastric distention triggers acid/pepsin secretion by a vaso-vagal reflex.[15,16] Paintal has shown that afferent fibers in vagus nerves can be activated by gastric distention and increased acid/pepsin output.[17] ln addition to vagus nerve, acetylcholine is released from local cholinergic nerve fibers, acts directly on its receptors on chief cells and parietal cells and increases acid/pepsin outputs.[18]

Vaso-vagal reflex and local nerve fibers that are stimulated by distention can also release gastrin and histamine locally, which have a strong effect on acid output but only a weak effect on pepsin secretion. Cholinergic

agents increase and atropine inhibits this effect.[19] In the present study, we tried to elucidate the effects of thyroid hormones on gastric distention-induced acid and pepsin secretions in rats.

Subjects and Methods

The experiments conformed to national guidelines for conducting animal studies. N-Mari rats of both sexes with a median weight of 246±5.1 gm, kept in 25±2°C temperature, with a 12-hour light/dark cycle and fed with a standard diet were chosen for the study. There were three groups of eight rats: hypothyroid, hyperthyroid and control. Hypothyroidism was induced by giving metimazole (Loghman Co.) 500 μg/L of drinking water for 20 days, and hyperthyroidism was induced by adminstration of 200 μg/L thyroxine (Iran Hormone Co.) in a liter of drinking water for 35 days.[12] The control group had access to normal tap water. Each animal had an average of 30 mL of water per day. Rats were deprived of food but not of water for 24 hours before the experiments.[21] Anesthesia was induced by intraperitoneal injection 50 mg/kg of thiopental (Biochemie GmbH, Vienna, Austria) and after tracheostomy, cervical esophagus was ligated.[21] A midline incision was made on abdomen and a silicone tube 2.5 mm in external diameter was introduced in the stomach via duodenum. Residual gastric secretions were removed by performing lavage several times with 1-2 mL of Ringer solution at 37°C, and allowed for 30 minutes to reach a steady state.[22]

To measure basal acid output, 1 mL of Ringer solution was introduced in the stomach and repeated 15 minutes later. The gastric contents were removed and 1 mL of sample was titrated by TTT80 (Radiometer Co, Denmark).[23] After measuring the pH, titration was continued up to pH=7 by adding 0.1 N sodium hydroxide. Titratable acid was calculated and reported as micromole acid per 15 minutes. Basal acid output was measured twice in 15 and 30 minutes. By injecting 1.5 mL of Ringer solution per 100 gm of body weight every 15 minutes up to 75 minutes, gastric distention was induced.[24] Gastric contents were removed every 15 minutes and a volume of each sample was titrated as described before.

Pepsin measurements of the samples were performed by the Anson method.[25] In this method, pepsin acted on the substrate (hemoglobin) and the final product of reaction was measured by UV spectrophotometer. Standard curves were drawn by using pure pepsin and hemoglobin (both from Sigma Co.). Venous blood samples were taken just before and after inducing hypo- and hyperthyroid states in all animals. Their sera were kept at -20°C and T4 and thyroid-stimulating hormone (TSH) values were measured by radioimmunoassay to confirm their thyroid states. ln each group, the mean ± SE quantities of acid and pepsin secretion were calculated. Test results were compared by analysis of variance and *t*-test and a $P<0.05$ was considered significant.

TABLE 1. *Thyroxine and TSH levels in the three study groups of rats.*

Group	Mean±SE T4 (μg/dL) Pre-treatment	T4 (μg/dL) Post-treatment	TSH (μu/mL) Pre-treatment	TSH (μu/mL) Post-treatment
Control Euthyroid (n=8)	1.9±0.5	1.9±0.5	0.18±0.006	0.18±0.006
Hypothyroid (n=8)	2.4±0.3	0.01±0.001**	0.17±0.005	1.9±0.3*
Hyperthyroid (n=8)	2.1±0.4	11.5±2.6*	0.18±0.003	0.15±0.001**

*$P<0.05$; **$P<0.001$.

Results

Results showed that thyroxin level decreased significantly in the hypothyroid group in comparison to its level before metimazole treatment ($P<0.001$), and in the hyperthyroid group, thyroxin levels increased significantly after thyroxin administration ($P<0.05$). Similarly, TSH levels showed significant rise ($P<0.05$) and fall ($P<0.001$) in the hypothyroid and hyperthyroid groups, respectively (Table 1). In the hypothyroid group, basal acid output decreased significantly in the minutes of 15 and 30 (3.3±0.2 and 3.3±0.3 micromole per 15 minutes), in comparison to the control group (4.5±0.1 and 4.6±0.1 micromole per 15 minutes) ($P<0.0001$).

Gastric distention-induced acid output began after 30 minutes and continued up to 75 minutes, but in 45 minutes did not significantly alter in hypothyroid group compared with the control group. However, in the minutes of 60 and 75, it was significantly less than the control group (8.1±0.2 and 8±0.2 micromole per 15 minutes vs. 10.3±0.2 and 10.2±0.1 micromole per 15 minutes) ($P<0.0001$). Basal acid output was significantly higher in the hyperthyroid group in the minutes of 15 and 30 (6.02±0.1 and 6.07±0.1 micromole per 15 minutes) than the control group (4.5±0.1 and 4.6±0.1 micromole per 15 minutes)($P<0.0001$). After distention, acid output increased significantly in the minutes of 45, 60 and 75 in the hyperthyroid group (14.6±1.9 and 14.7±1.9 and 14.8±1.9 micromole per 15 minutes) compared with the control group (10.3±0.1, 10.2±0.1 and 9.5±0.6 micromole per 15 minutes) ($P<0.05$) (Figure 1). lt is evident in Figure 2 that basal pepsin levels in the minutes of 15 and 30 were not significantly different in the hypothyroid and control groups. But after gastric distention, pepsin levels rose in the minutes of 45 and remained high up to the minutes of 75 in all three groups, and the differences were significant between the hypothyroid group (4.4±0.5, 4.3±0.5 and 3.8±0.5 μg/15 min) and the control group (6.1±0.1,5.9±0.1 and 5.5±0.2 μg/min) ($P<0.05$). Basal pepsin secretion in the minutes of 15 and 30 was significantly higher in the hyperthyroid group (3±0.4 and 3.3±0.4 μg/15 min) than the control group (1.6±0.09 and 1.8±0.07 μg/15 min) ($P<0.05$). Similarly after gastric distention, the hyperthyroid group had higher pepsin outputs in the minutes of 45, 60 and 75 (9±0.4,

FIGURE 1. Mean variation of basal and distention-induced acid output in rats.

FIGURE 2. Mean variation of basal and distention-induced pepsin output in rats.

8.1±0.4 and 8.3±0.4 μg/15 min) than the control group (6.1±0.1, 5.9+0.1 and 5.5±0.2 μg/15 min) (P<0.001).

Discussion

It is evident that hypo- and hyperthyroid states were appropriately induced in the study groups, by measuring their serum TSH and thyroxin levels (Table 1). ln this study, gastric acid/pepsin outputs were measured in basal state and in response to distention in hypo- and hyperthyroid rats. ln the hypothyroid group, although distention increased both acid and pepsin outputs in comparison to the basal state, this increase was significantly less than that observed in the control group (Figure 1 and 2). This response to distention was stronger in the hyperthyroid group, and the difference with the control group was also statistically significant. Gastric distention presumably increases acid and pepsin secretions via vaso-vagal and local cholinergic reflexes.[10,16,17] Grossman has observed that gastric distention activates local cholinergic gastric, pylorofundic and pyloropyloric reflexes and the latter increases gastrin, thereby increases acid and pepsin secretions. These local reflexes were probably effective in increasing acid/pepsin outputs in the present study. But it is still unclear how thyroid hormones affect acid/pepsin secretions. ln some organs like the heart, thyroid hormones increase beta-adrenergic receptors,[2] while in the liver and smooth muscle cells of vessel walls, alpha-adrenergic receptors are increased by thyroid hormones.[1,7] lt is probable that thyroid hormones increase cholinergic, histaminic and gastrin receptors in chief cells and parietal cells of stomach. Kayode et al. have observed that thyroxin increases mitotic activity of crypt cells of digestive tract in rats.[12] This mechanism may also have been evident in our study, changing the number of secretory cells in accordance with thyroid hormone levels. A third possibility is that thyroid hormones induce their effects in acid/pepsin secretions by changes in cellular metabolism and ATP generation.[9] Increased thyroid hormones in the hyperthyroid group may also increase sensitivity and response of gastric parietal and chief cells to locally released acetyl-choline and gastrin and causes acid/pepsin outputs increase as a result. There is no evidence that metimazole has any direct inhibitory effect on gastric acid/pepsin secretions. Other effects of thyroid hormones on gastric secretory cells, if any, should be further studied.

In comparison to the euthyroid (control) group, gastric acid output was increased and decreased in hyperthyroid and hypothyroid rats, respectively. This may have clinical implications as hyper- and hypo-acidity may cause acid-peptic diseases or maldigestion. Therefore, it is recommended that acid and pepsin content of gastric juice be measured in hyper- and hypothyroid patients.

There is no other report on the effects of thyroid hormones on gastric distention-induced acid/pepsin outputs to compare the results of the present study with. Our results show that thyroid hormones have a direct effect on gastric distention-induced acid/pepsin secretion. But further histological and histochemical studies are needed to elucidate the mechanism of this effect.

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