Chronic peripheral administration of serotonin inhibits thyroid function in the rat

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Summary
We studied the effect of chronic intraperitoneal (ip) administration of serotonin (5-HT) and thyroid function. We injected daily intraperitoneally for 10 days different doses of 5-HT, and measured plasma thyroid hormones and TSH levels. There was a decrease in the plasma levels of T3 and T4 with medium doses of 5-HT (0.2 and 0.4 mg/Kg bw for T3, and 0.2 for T4). No effects were evidenced on the plasma levels of TSH. In normal environmental conditions, the site action of 5-HT outside the blood-brain barrier is active when the 5-HT is injected at defined doses. This is probably a result of down-regulation independent of the hypothalamus-pituitary-thyroid axis.

Key words: serotonin/deiodinase activity/thyroid hormone/brown adipose tissue/thermogenesis /rat organs.

Introduction

The role of serotonin (5-HT) in the regulation of TRH-TSH secretion is still controversial. 5-HT inhibits TSH production at hypothalamic level, modulating TRH secretion (1,2,3). Intracerebroventricular injections (ic) of 5-HT produced contrasting results. Some authors (4,5) reported an increase of plasma TSH at low and high doses of 5-HT, while others reported a non dose-dependent increase in TSH only when 5-HT was injected in the third ventricle (6,7). On the other hand, ic or intraperitoneal (ip) injection of 5-HT and of agonists of 5-HT receptors (quipazine or fenfluramine) induces a decrease of plasma TSH and of TSH-cold response (6,8). The effect of administration of 5-hydroxytryptophan (5-HTP) is also unclear, although its addition to the diet for two weeks in high concentrations showed decrease in plasma TSH and a lower TSH-cold response (9).
These observations point towards an inhibitory serotoninergic site both within and without the blood-brain barrier. The presence of serotoninergic site of action without the blood-brain barrier is shown by the observation that, when 5-HT agonists were given subcutaneously and ip, TSH-cold response was lowered in a dose-dependent manner (6,10).
In rats with lesions of the hypothalamic paraventricular nucleus, TSH-cold response is decreased, while the effect of 5-HT was only partially abolished when 5-HT was injected in the cerebral ventricle (11).
Other experiments show that the administration of T3 decreases the function of 5-HT1A and 5-HT1B receptors, but increases 5-HT2-mediated response, enhancing the synthesis and turnover of 5-HT in the brain of mice (12). Administration of T4 for seven days induced a 38% decrease in 5-HT concentration in low-platelet blood plasma, and experimentally-induced hypothyrodism caused a 24% increase of 5-HT (13).
The metabolism of thyroid hormones may have links with the metabolism of biogenic amines. T4 treated rats show increased plasma concentration of 5-HT, istamine, glutamate, and decrease in gamma-aminobutyric acid (GABA), monoamine oxidase (MAO) and histaminase (14). 5-HT levels are also increased in the cerebral cortex, but not in the hippocampus, after both acute and chronic T3 administration (15). All these observations suggest a functional link between serotoninergic system, thyroid function and behavioural changes. The existence of a circadian rhythm in TSH secretion can explain in part the contrasting results reported. However, on the whole there seems to be an inhibitory effect of 5-HT in the regulation of TSH secretion (5,16).
This investigation studied the relationship between 5-HT and thyroid function in rats injected ip daily for 10 days with different doses of 5-HT.

Materials and Methods

All procedures were carried out according to the policy statement of the American College of Medicine after approval of the Ethics Committee of the Second University of Naples, Faculty of Medicine and Surgery.

Animals

Male Wistar rats weighing 220-270 g., were kept in a animal room at a temperature of 22-24°C, at 50% relative humidity with an artificial cycle of light and darkness

Table 1. T3, T4, and TSH plasmatic level in rats injected intraperitoneally with different doses of serotonin or saline (control) for 10 days.

Variable	Control	0.1 mg/kg bw	0.2 mg/kg bw	0.4 mg/kg bw	0.8 mg/kg bw	1.6 mg/kg bw
T3 (ng/dl)	52.3±2.4	58±2.6	34.4±3.2*	39.2±2.5*	60.3±2.4	57.9±2.8
T4 (mg/dl)	5.78±0.33	5.49±0.42	4.08±1.21°	5.43±2.46	6.32±1.04	5.9±0.98
TSH (ng/dl)	0.98±0.12	0.88±0.23	1.07±0.10	0.86±0.22	0.99±0.08	0.96±0.14

*p < 0.01 ; °p < 0.05

(06:00-18:00). They were given laboratory standard pellets and water ad libitum.

Procedure

Thirty rats, divided in 6 groups of five rats each, received the following treatment:

Controls: animals injected ip daily for 10 days with 0.5 ml of sterile apirogen saline.

Treated (5 groups): animals injected ip daily for 10 days with different doses of 5-HT in a final volume of 0.5 ml. The doses used for each group were: 1.6, 0.8, 0.4, 0.2, 0.1 mg/kg of body weight (bw).

24 hours after the last injection blood samples were drawn by intracardiac puncture, and plasmatic thyroid hormones levels and TSH are measured by radioimmunoassay (RIA). All blood samples were taken between 11:00 and 12:00 hours to minimise circadian differences in TSH secretion.

Statistical analysis

All values are presented as mean ± standard error. Statistical analysis was performed using a one way analysis of variance with statistical significance set at p <= 0.05. Where significance was found, a Newman-Keul *post hoc* test was applied to determine differences between means.

Results

Intraperitoneal injection of different doses of 5-HT for 10 consecutive days induced changes in the plasma concentrations of T3 and T4 (Table 1). 5-HT exerts an inhibitory effect on T3 plasma level at 0.2 and 0.4 mg/kg bw dosage (p< 0.01), and on T4, at 0.2 mg/kg dosage (p< 0.05). The effects of higher or lower doses are, for both hormones, within the range found in control rats. No significant differences were found for TSH level both in control and in treated rats.

Discussion

The results of our study suggest that 5-HT has sites of action outwith the blood brain barrier, so that 5-HT is able to modify thyroid hormone levels in normal environmental conditions at medium doses (0.2 and 0.4 mg/kg bw). This non-dose dependent effect of 5-HT could be related to down regulation of 5-HT receptors. This effect evidences that 5-HT administered by injected in a chronic fashion at the above doses induce lower plasma levels of thyroid hormones, and can influence the mechanisms regulating the energy expenditure, in which the modifications of 5'-monodeiodinase activity in several organs, and especially in the brown adipose tissue, have a main role. We were not able to ascertain a significant effect on TSH concentration, in agreement previous work Mattila et al. (1981) and Krulich et al. (1979) found an increase of TSH only when the injection was carried out in the third ventricle, again in a non dose-dependent effect (6,7). Therefore, the effects of 5-HT on thyroid hormones level is not dependent on its action on the hypothalamus-pituitary-thyroid axis when administrated peripherally.

Chronic treatment with T3 may decrease the function of 5-HT1A and 5-HT1B receptors, but increases 5-HT2-mediated response, enhancing synthesis and turnover of 5-HT in the mouse brain (12). On the other hand, T4 administration for 7 days induced a 38% decrease in 5-HT concentration in low-platelet blood plasma, while experimentally induced hypothyroidism caused a 24% 5-HT increase (13).

Conclusions

The results of this study shed further light on the possible role of 5-HT in controlling heat production and energy expenditure. 5-HT, together with its effect on thyroid function, exerts a modulating action on food intake, decreasing it, and on food choice, inducing a diet containing more proteins and less carbohydrates. 5-HT may also act peripherally directly on the thyroid, thus controlling energy expenditure through heat production.

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