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BRIEF COMMUNICATION

Long-Term Effects of TRH Administration on Food Intake and Body Weight in the Rat[1]

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IGLESIAS, R., M. LLOBERA AND E. MONTOYA. *Long-term effects of TRH administration on food intake and body weight in the rat.* PHARMACOL BIOCHEM BEHAV 24(6) 1817–1819, 1986.—The effect of long-term TRH administration through drinking water (0.2 mg/ml) on food and water intake and body weight has been studied in three groups of female rats: (1) thyroidectomized, (2) thyroidectomized receiving daily 250 μg/kg of L-T_4, (3) sham-operated. Treatment with oral TRH for 30 days decreased body weight and increased food intake in sham-operated rats. No TRH effects on body weight or food consumption were observed in either of the other groups of thyroidectomized rats. TRH administration increased circulating T_3 levels in sham-operated animals, but had no effects in either hypo- or hyperthyroid, thyroidectomized rats. It can be concluded that the TRH-induced increase on food intake is mediated through the pituitary-thyroid axis.

Thyrotropin-releasing-hormone (TRH) Chronic TRH administration Food intake Drink

ACUTE TRH administration induces significant effects on the behavior of experimental animals and man [12]. These effects are independent of those observed on the pituitary-thyroid axis and are supposedly exerted directly on central nervous centers [1,12]. One of the most striking behavioral actions of TRH is its anorexigenic effect after the acute administration of high doses of the tripeptide [1, 4, 11]. Our present objective was to find out whether the acute anorexigenic action of TRH could be also observed in animals under long-term treatment. In addition, the possible permissive effects of thyroid hormone status as well as thyroid gland integrity on the effects of TRH on food consumption have been investigated.

METHOD

Just weaned Sprague-Dawley female rats (mean weight 50±2 g) were used. They were housed three per cage under a controlled temperature (20–23°C) and light cycle (on from 08:00 to 20:00). They were fed ad lib on laboratory rat chow (Sanders, Spain) and distilled water unless otherwise stated.

Three groups of animals were used: (1) thyroidectomized animals receiving daily saline injections (hypothyroid), (2) thyroidectomized animals receiving daily 250 μg of L-T_4 (Sigma)/kg body weight (this dose has been found to induce experimental hyperthyroidism with practically undetectable levels of TSH [3]) and (3) sham-operated rats, receiving daily saline injections (control). After 30 days of treatment each group was further divided into two subgroups which were put on distilled water (DW) or 0.2 mg TRH/ml (kindly provided by Prem, Spain) in distilled water. This dose has been found sufficient to produce a chronic thyrotroph stimulation when administered on a continuous basis [3].

The animals were weighed every day. The daily amounts of rat chow or drink ingested were measured during the 30 days of treatment. On days 3 and 15 blood samples were taken at 08:30, from the cut tip of the tail. Rats were killed by decapitation on day 30. Sera from all clotted blood samples were separated by centrifugation and stored at −20°C until measurement of T_3 and T_4 levels by radioimmunoassay [7].

The data were analyzed statistically using analysis of variance and a further comparison of main effects was done by Scheffe's S-method. Differences were considered significant at $p<0.05$.

RESULTS

In Fig. 1, the changes in body weight, as well as food and drink consumption data are shown. Growth was stopped in

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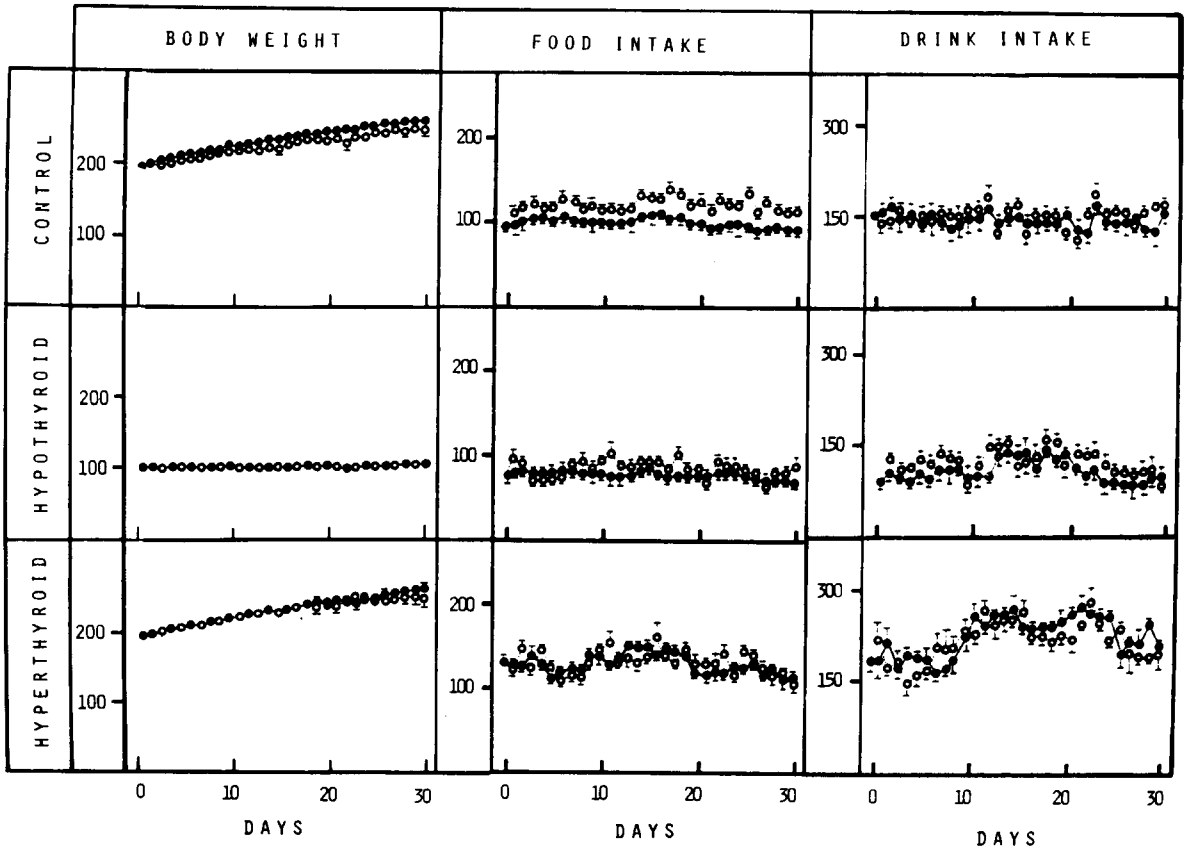

FIG. 1. Body weight changes and food and drink intake in control, hypothyroid and hyperthyroid animals on TRH or distilled water as drinking solution. Daily treatment of the animals with saline (control and hypothyroid groups) or L-T_4 (hyperthyroid) started 30 days before the beginning of the experiment. On day 0 these groups were divided into two subgroups each, one receiving TRH as drinking solution (TRH group, white dots) and the other distilled water (DW group, black dots). Body weight data (g) represent the mean±s.e.m. of 12 animals per group. Food and drink are expressed as g and ml respectively consumed per kg of body weight. Data are expressed as means±s.e.m. of four different cages, each containing 3 rats. Where data from animals on DW or TRH coincide, they are represented with either white or black dots, for easier visualization of the graphs.

TABLE 1

EFFECT OF CHRONIC TRH ADMINISTRATION ON THE BLOOD CONCENTRATION OF THYROID HORMONES IN CONTROL AND HYPERTHYROID RATS

	Days of Treatment					
	Day 3		Day 15		Day 30	
	DW*	TRH†	DW	TRH	DW	TRH
Control						
T_3 ($nM \cdot l^{-1}$)	0.991± 0.047	1.524± 0.077	0.912± 0.074	1.426± 0.105	0.791± 0.066	1.292± 0.095
T_4 ($nM \cdot l^{-1}$)	50.28 ± 3.38	66.70 ± 3.19	46.64 ± 1.96	50.17 ± 2.07	43.31 ± 3.42	48.61 ± 3.27
T_3/T_4 ratio ($\times 10^3$)	20.15 ± 1.43	22.24 ± 1.43	21.12 ± 2.08	28.87 ± 1.59	17.35 ± 1.07	25.53 ± 2.56
Hyperthyroid						
T_3 ($nM \cdot l^{-1}$)	1.555± 0.123	1.052± 0.129	0.945± 0.111	0.863± 0.082	0.766± 0.158	1.055± 0.110
T_4 ($nM \cdot l^{-1}$)	142.13 ±19.34	110.36 ±13.09	146.53 ±14.78	115.46 ±14.05	108.61 ±13.81	122.96 ±12.37
T_3/T_4 ratio ($\times 10^3$)	9.38 ± 0.62	8.97 ± 0.83	6.64 ± 0.47	6.96 ± 0.52	6.97 ± 0.93	8.09 ± 1.07

All values are mean±s.e.m. of 12 animals.

*DW: distilled water control treatment. †TRH: administration of TRH in drinking water.

ANOVA tests showed the following significant differences: T_3 levels: factor days of treatment, $F(3,138)=4.81$, $p<0.01$; control-DW compared to control-TRH, $F(3,138)=2.73$, $p<0.05$. T_4 levels: control compared to hyperthyroid, $F(3,138)=3.29$, $p<0.025$. T_3/T_4 ratio: control compared to hyperthyroid, $F(3,138)=2.71$, $p<0.05$.

hypothyroid rats, $F(5,1980)=1794.6$, $p<0.005$, compared with sham-operated controls. No differences in the growth pattern were observed between controls and hyperthyroid animals. The oral treatment with TRH decreased the body weight of controls receiving TRH compared with those on DW, $F(5,1980)=5.56$, $p<0.005$. There were no significant differences between the corresponding TRH and DW groups in either hypothyroid or hyperthyroid animals.

Daily food intake was significantly lower in the hypothyroid group compared with controls, $F(5,685)=20.53$, $p<0.005$. Hyperthyroid animals had a higher daily food intake than controls, $F(5,685)=56.80$, $p<0.005$. The amount of drink consumed every day showed the same relationships and statistical significance as did the food ingested, $F(5,540)=6.18$, $p<0.005$, in hypothyroid versus controls; $F(5,540)=124.87$, $p<0.005$, in hyperthyroid versus controls.

In controls, chronic treatment with oral TRH resulted in increased food but not drink consumption, $F(5,685)=12.4$, $p<0.005$. No significant differences were found in these parameters in both altered thyroid states. The average daily intake of TRH during the treatment was 28 ± 1, 23 ± 2 and 43 ± 2 mg per kg of body weight in control, hypothyroid and hyperthyroid groups respectively.

In Table 1, serum T_3 and T_4 levels are shown. Values of hypothyroid rats are not depicted since they were undetectable (lower than 0.2 nM/l for T_3 and 3.8 nM/l for T_4). T_3 values decreased with age in all groups, $F(3,138)=4.81$, $p<0.01$. In hyperthyroid animals T_4 levels were higher than those of controls, $F(3,138)=3.29$, $p<0.025$, while T_3 levels were higher on day 3 but later became indistinguishable from those of controls. T_3/T_4 ratio were lower in hyperthyroid animals than in controls, $F(3,138)=2.71$, $p<0.05$.

Treatment with TRH induced increases in the circulating T_3 levels in controls, $F(3,138)=2.73$, $p<0.05$. The T_3/T_4 ratios in TRH-treated controls were higher than those of untreated rats. The administration of TRH to hyperthyroid rats resulted in a transient decrease—on day 3—in both T_3 and T_4 without changing the T_3/T_4 ratio.

DISCUSSION

Long term oral administration of TRH to control rats resulted in a significant decrease in body weight coupled with increased food consumption and unchanged water ingestion. This effect was not observed in thyroidectomized animals, either with or without daily T_4 injections. It can be assumed thus, that the full functional presence of the thyroid gland is needed for chronic TRH treatment action of food utilization efficiency.

As confirmed in the present report, repeated administration of TRH to control rats induced higher T_3 levels. This increase leads to increased food consumption and body weight loss, since T_3 increases the metabolic rate [6]. Higher circulating T_3 would then result in weight loss, and an increase in food consumption as a compensatory mechanism.

Acute intraventricular or parenteral administration of TRH has been reported to decrease food and water intake in deprived and stressed rats [4, 10, 11]. This effect was observed in control as well as in hypophysectomized rats, suggesting that the anorexigenic effect of TRH was independent of the hypothalamic-pituitary-thyroid axis [4].

The apparently different effects of chronic versus acute TRH administration on food consumption can be tentatively explained on the basis of the inhibitory effects of high doses of TRH on eating at the central nervous system level. In our experimental setup, TRH was administered through a high number of small doses depending on the drinking pattern of the rat. Thus, it can be assumed that this treatment would stimulate the pituitary-thyroid axis in a rather continuous way as shown by the raised T_3 levels. However, blood TRH levels, because of its fast turnover [9], would probably not reach the threshold beyond which it has an effect on food ingestion through the central nervous system. Thus, this explanation does not preclude the possible anorexigenic effects of TRH at higher doses; this effect could be mediated through the active—and longer lasting—TRH catabolite cyclo His-Pro [8] that can inhibit food ingestion in the rat when injected into the brain [5]. The use of high doses of TRH has been postulated for the treatment of some degenerative nervous diseases, such as amyotrophic lateral sclerosis [2], even though the chronic TRH stimulation of the pituitary-thyroid axis should also be taken into account, as is shown in this study.

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