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Central NPY-Y5 receptors activation plays a major role in fasting-induced pituitary–thyroid axis suppression in adult rat

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ABSTRACT

Neuropeptide Y (NPY) inhibits TRH neurons in fed state, and hypothalamic NPY higher expression during fasting has been proposed to be involved in fasting-induced suppression of the hypothalamus-pituitary–thyroid (HPT) axis. We investigated the role of central Y5 receptors in the control of thyrotropin (TSH) and thyroid hormone (TH) secretion. Fed and fasting rats received twice daily central injections (3rd ventricle) of Y5 receptor antagonist (CGP71683; 15 nmol/rat) for 72 h. Fasted rats also received a single central injection of CGP71683 (15 nmol/rat) at the end of 72 h of fasting. In fed rats, Y5 receptor blockade reduced total food intake by 32% and body mass by almost 10% ($p<0.01$), corroborating the role of this receptor in food intake control. 72 h-fasted rats exhibited a 4-fold increase in serum TSH ($p<0.001$), 1 h after a single injection of Y5 antagonist. Also with multiple injections during 72 h of fasting, Y5 blockade resulted in activation of thyroid axis, as demonstrated by a 3-times rise in serum T4 ($p<0.001$), accompanied by unchanged TSH and T3. In fed rats, the chronic central administration of CGP71683 resulted in reduced total serum T4 without changes in free T4 and TSH. Serum leptin and PYY were not altered by the NPY central blockade in both fed and fasted rats, suggesting no role of these hormones in the alterations observed. Therefore, the inhibition of central Y5 neurotransmission resulted in activation of thyroid axis during fasting suggesting that NPY-Y5 receptors contribute to fasting-induced TSH and TH suppression.

1. Introduction

Fasting-induced hypothalamus-pituitary–thyroid (HPT) axis suppression is believed to represent an adaptive response to energy deprivation [1–3]. In rodents, prolonged fasting results in decreased preproTRH expression in neurons of hypothalamic paraventricular nucleus (PVN) accompanied by low or inappropriately normal serum thyrotropin (TSH) and reduction of serum thyroid hormone concentrations [4,5]. Peripheral metabolic signals may play a role in this phenomenon, but the precise related mechanisms remain unknown.

Since circulating levels of leptin are reduced in fasted animals and its administration increases both preproTRH expression and serum TSH, it has been proposed a role for this hormone in the control of HPT axis activity [6–8]. Effects of leptin on TRH neurons of the PVN may be direct and indirect. The indirect pathway is related to increased CREB phosphorylation and may result from the action of leptin on hypothalamic arcuate nucleus (ARC) [9], where leptin has the ability to revert the fasting-induced changes in expression of many genes, including NPY, which expression is increased during fasting [10,11].

It has been demonstrated that NPY neurons innervate hypophysiotropic TRH neurons of the PVN [12] and that ARC is a major source of these NPY neurons projecting to TRH neurons [13]. In addition, NPY-containing axon terminals of medulla origin innervate TRH neurons in the PVN. These medulla NPY neurons co-localize with cathecholamine [12,14,15] and, therefore NPY is co-released with cathecolamines and may potentially modulate their actions on hypophysiotropic TRH neurons. Previous reports have shown that central NPY administration promotes suppression of HPT axis in fed rats [16,17], and that central administration of either Y1 or Y5 receptors agonists reduced proTRH mRNA expression in the PVN of fed rats, as well as their thyroid hormone serum levels in the presence of low or inappropriately normal TSH [18]. Thus, increased Y receptors activation and, consequently, inhibition of the cAMP-CREB signalling pathway, may contribute to suppressed preproTRH expression that occurs during fasting. Therefore, as proposed before [16–18], increased NPY neurotransmission to TRH neurons could play a major role in fasting-induced HPT axis suppression [16], an effect possibly mediated by Y1 and Y5 receptor activation.

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In the present study we addressed the question of the role of NPY action through Y5 receptors in the control of pituitary–thyroid axis during fasting, employing a pharmacological central blockade approach. Although Y1 blockade was also performed, most of the animals exhibited the barrel rolling behaviour and thus, the results were not reliable. Therefore, here we report the effects of the central Y5 blockade on thyrotropin and thyroid hormones secretion of animals in fed and fasted state.

2. Materials and methods

2.1. Animals

Experiments were performed on 3 months old male Wistar rats, kept in individual cages under a 12:12 h light/dark cycle (lights on at 7:00) at 23–25 °C. All protocols were approved by the Institutional Animal Care and Use Committee of Biophysics Institute Carlos Chagas Filho.

2.2. Stereotaxic surgery

Rats underwent third ventricular cannulation (i.c.v.) 7 to 10 days prior to the experiment. Briefly, a stainless steel guide cannula (0.6 mm o.d.; Acerionx, São Paulo, Brazil) for microinjection was implanted 0.5 mm posterior to bregma and 8.0–8.5 mm ventral to skull [19–21], under ketamine + xylazine anesthesia. Verification of correct cannula placement was made by the observation of fluid-filled column (attached to guide cannula) displacement, as described before [21,22].

2.3. Protocols

The Y5 receptor antagonist, CGP71683 (Tocris, MO, USA), was dissolved in 30% DMSO and kept frozen at −20 °C until the experiment. Each microinjection consisted of 2 μL of either vehicle (30% DMSO) or CGP71683 (7.5 nmol/μL; 15 nmol/rat) [23] injected during 30–60 s through the guide cannula, as the following protocols: I – rats with free access to chow received 6 microinjections (15 nmol/rat, 10–14 h interval between each one) and were killed 1 h after the last injection, between 9 and 10 a.m. Food intake was estimated by the reduction in chow mass (g), evaluated daily, immediately before each icv injection. II – 72 h-fasted rats received a single microinjection of vehicle or CGP71683 (15 nmol/rat) and sacrificed 1 h latter. III – during a period of 72 h of fasting, rats were treated with multiple injections of vehicle or CGP71683 with the same protocol used for fed animals, and the fasting period started 10 h before the first microinjection. At the end of experimental protocols, rats were decapitated and serum was obtained from trunk blood for the measurement of the concentrations of hormones.

2.4. Hormone measurements

Serum TSH concentrations were measured by specific RIA, employing reagents supplied by National Hormone and Peptide Program (Torrance, CA, USA) as previously described [24], and it was expressed in terms of the reference preparation 3 (RP3). Minimum assay detection value was 0.18 ng/ml and intra-assay variation coefficient was less than 8% in all assays. Free serum T4, total serum T4 and T3 were measured by RIA commercial kits (Mab-ICN Pharmaceuticals, Costa Mesa, CA, USA). Minimum assay detection value was 0.15 ng/dL for free T4, 25 ng/dl for total T3 and 1 μg/dl for total T4. The intra-assay variations were 1.2%, 1.8% and 3.7%, respectively. Samples of the same experiment were measured within the same assay.

Serum leptin and PYY were determined by specific rodents radioimmunoassay kits (Linco Research, MA, USA) in accordance with the recommendations of manufacturers. The minimum detection value was 0.5 ng/mL and 15.6 pg/mL for leptin (4.6% of intra-assay variation) and PYY (1.8% of intra-assay variation), respectively. All samples to be compared were measured within the same assay.

2.5. Statistics

Data are reported as means ± S.E.M. Serum TSH was analyzed employing Mann–Whitney test and for temporal food intake analysis we employed two-way ANOVA, followed by Bonferroni post test. All other results were analyzed by unpaired t test. Null hypothesis was discarded when $p<0.05$.

3. Results

3.1. Central Y5 receptors blockade and food consumption and body weight of fed animals

Previous studies have shown that CGP71683, a Y5 receptor inhibitor, has the ability to reduce food intake, and in order to test the effectiveness of the present treatment protocol with the Y5 antagonist, CGP71683, we tested food ingestion and body weight. Twice daily intracerebroventricular (icv) injections of the Y5 receptor antagonist, CGP71683, for 72 h reduced total food intake by 32% ($p=0.014$ – Fig. 1B). The anorexigenic effect of CGP71683 was more evident during the dark phase after the first injection (Fig. 1A), when food ingestion was reduced by almost 50% ($p<0.01$). In addition, at the end of the treatment the CGP71683-treated rats had lost almost 10% of total body mass ($p<0.001$ – Fig. 1C).

3.2. Central Y5 blockade and thyroid axis function of fasted animals

3.2.1. Single icv administration

Rats treated with a single icv dose of CGP71683 after being fasted for 72 h, and sacrificed 1 h later, showed a 4-times increase in serum TSH concentration ($p<0.001$), without significant change in total or free T4 and in total T3 concentration as compared to fasted controls ($p=0.195$, $p=0.4$ and $p=0.085$ – Fig. 2).

3.2.2. Multiple icv administration

Twice daily icv administration of CGP71683 for 72 h resulted in 3-times higher serum total T4 and 37% increase in free T4 in the fasted group treated with CGP71683 than in fasting controls treated with vehicle ($p<0.001$). Serum TSH and T3 concentrations remained statistically undistinguished between groups (Fig. 2). Body mass loss was also higher in CGP71683-treated group (17.32 ± 0.38 *vs.* 15.29 ± 0.43%, CGP71683 *vs.* vehicle respectively; $p=0.002$). CGP71683 treatment did not change either PYY or leptin concentration of fasted rats (Table 1).

3.3. Central Y5 blockade and thyroid axis function of fed animals

We also tested the effect of multiple icv injections on central Y5 blockade on pituitary thyroid axis of fed rats (Fig. 3). Total serum T4 was reduced by 62% as compared to control levels, but not free serum T4 that was similar between groups. Total T3 was slightly reduced by 18% ($p=0.033$). There was no significant difference in serum TSH ($p=0.34$). Circulating leptin and PYY did not differ significantly between groups (Table 1).

4. Discussion

The present study demonstrates for the first time that the pharmacological blockade of Y5 receptors results in activation of the pituitary–thyroid axis during fasting. This finding strongly supports the previous concept that the higher NPY expression is a physiological phenomenon that contributes importantly to the axis suppression during fasting [16–18,25].

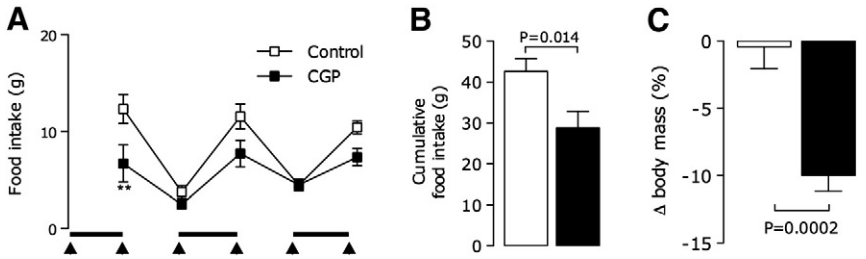

Fig. 1. Effect of multiple central (3rd ventricle) administration of Y5 antagonist (CGP71683; 15 nmol/rat, twice daily, during 72 h) on fed rats. (A) Food intake: arrows indicate the time of microinjection and black/white bars correspond to dark/light periods respectively. $^{**}p<0.01$; (B) Cumulative food intake; (C) Change in total body mass relative to pre-injection. Data are presented as mean ± S.E.M. $n = 10$ rats per group.

According to current concepts, the reduced thyroid hormone levels observed during fasting result, mainly, from the suppression of the stimulatory action of the hypothalamus-pituitary axis on thyroid function [1–5,26]. Based on previous studies showing that an Y5 agonist was able to suppress preproTRH expression [15] in fed rats, central Y5 receptor blockade would increase TRH synthesis and release, resulting

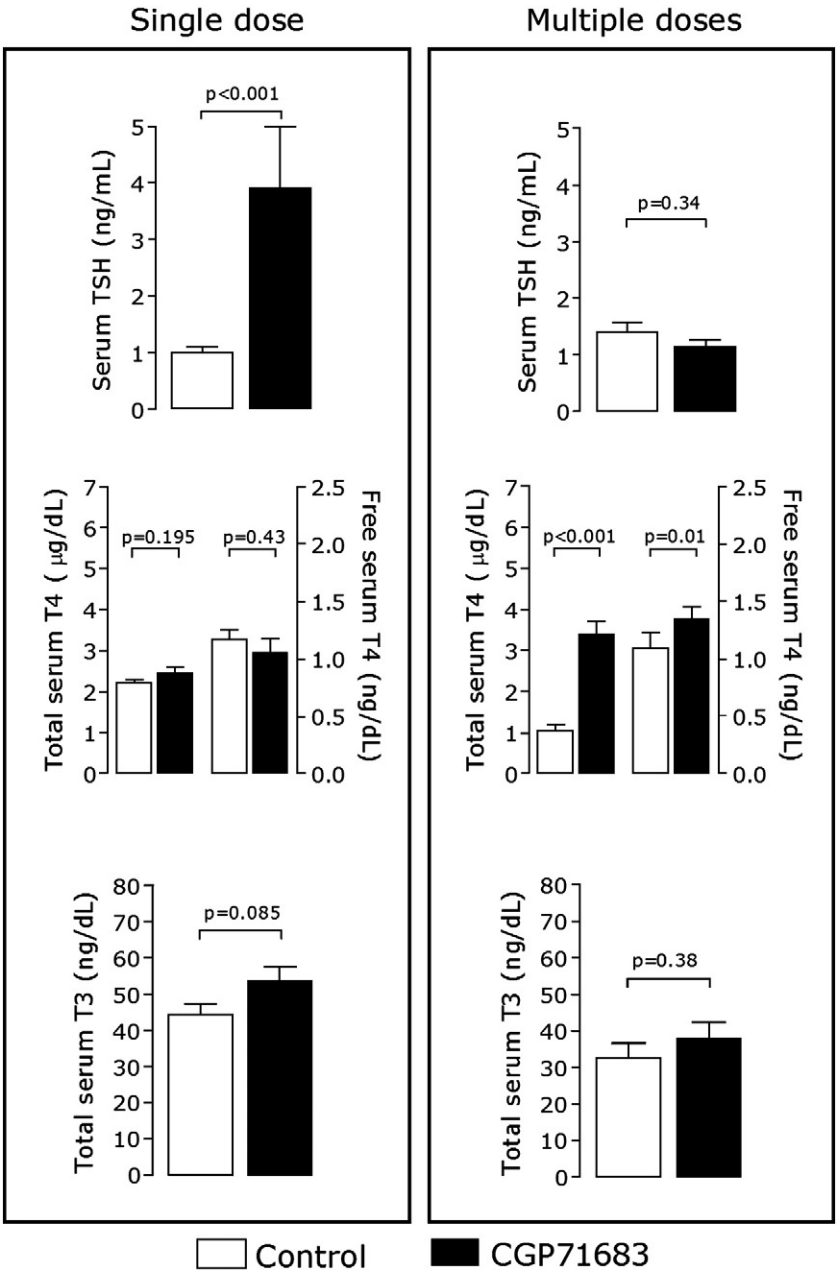

Fig. 2. Effect of a single (first column) and multiple (second column) central (3rd ventricle) administration of Y5 antagonist (CGP71683; 15 mol/rat, single administration 1 h before sacrifice or multiple administration twice daily during 72 h) on serum TSH, total and free T4 and total T3 of fasted rats. Data are presented as mean ± S.E.M $n = 10$–11 rats per group.

Table 1
Serum leptin and PYY of fed and fasted animals after multiple intracerebroventricular injections of NPY-Y5 antagonist (CGP71683).

Group		Leptin (ng/mL)	*P*	PYY (pg/mL)	*P*
Fed	Control	3.09 ± 0.35	0.95	110.7 ± 9.6	0.94
	CGP	3.13 ± 0.48		109.6 ± 10.8	
Fasted	Control	1.10 ± 0.19	0.54	106.9 ± 12.2	0.53
	CGP	1.39 ± 0.41		118.7 ± 13.9	

$n = 10$–11animals/group.

in stimulation of thyrotropes and increased thyrotropin (TSH) secretion. This is in agreement with our acute experiment, when a single intracerebroventricular dose of the Y5 antagonist (CGP71683) resulted in a rapid increase in serum TSH of fasted animals. In addition, the chronic blockade of central Y5 receptors during fasting also activated the thyroid axis, as indicated by the higher serum total and free T4 of the animals treated with the antagonist during 03 days. In those rats, serum TSH had returned to similar levels of the fasting controls, probably due to the feedback of T4, counteracting the stimulatory effect of TRH on TSH release. However, the higher serum T4 in the presence of the same level of TSH of fasting controls also suggests that TSH of the antagonist-treated group presented a higher biological activity. This argues in favour of the hypothesis of an increased TRH production since an important action of TRH is to increase TSH biological activity, by regulation of the appropriate glycosylation of the hormone [27].

Even though fasting Y5 antagonist-treated rats exhibited increased serum T4, their serum T3 remained statistically similar to controls. These data raise the possibility that the Y5 antagonist caused a decrease in the conversion of T4 to T3, catalyzed by 5′ deiodinases. The possibility that Y5 receptors are involved in the regulation of 5´dediodinase activity was suggested before in a previous study showing that an Y5 agonist, administered centrally to rats, was able to increase the 5´dediodinase activity of brown adipose tissue [18]. However, more specific studies will have to address this question.

Interestingly, CGP71683-treated fasted rats lost more weight than vehicle-treated fasted rats, supporting an involvement of Y5 receptors in energy expenditure independent of food consumption. Other studies have proposed that NPY via Y5 receptors decreases energy expenditure by affecting thermogenesis in brown and white adipose tissue [28,29].

Present data also support an important role for Y5 receptors in the control of food intake, as previously described by others [28–30]. In free-fed rats, the icv administration of the Y5 receptor antagonist induced a reduction in total food intake during the 72 h of the treatment, without modifying light phase food intake and with a marked effect during the dark phase after the first injection, corroborating previous studies [30]. The decrease in food intake is the major determinant of the body weight lost. These animals exhibited serum TSH that did not differ from controls, reduced total serum T4, but normal free T4, This suggests a reduction in the serum thyroid binding proteins, which is known to occur in nutritional deprivation [31], and thus, may be correlated to the body weight reduction caused by chronic central CGP treatment. Nevertheless, it is clear that a persistent stimulation of pituitary–thyroid axis by chronic Y5 blockade occurs only during fasting. This may be related to the higher NPY input to TRH neurons that is possibly occurring in the fasting state [10,11].

Leptin stimulates the HPT axis, acting directly and indirectly at TRH neurons [9] and PYY3-36 has been shown to be able to acutely stimulate TSH secretion in fasted rats [32]. However, the effects of central Y5 blockade on the pituitary–thyroid axis observed in the present study were independent of changes in serum leptin or PYY, both in fed and fasted states. This reinforces the conclusion that the effects observed were the result of Y5 receptors blockade directly at the central nervous system. However, the precise mechanisms involved in the stimulation of pituitary–thyroid axis by Y5 central blockade in fasting are still unclear. In addition to a possible direct antagonism of Y5 receptors in TRH neurons, another important potential mechanism is a blockade of the inhibitory effects of NPY on the melanocortin system, which inactivation during fasting contributes to the decrease in TRH synthesis [33]. It also should be considered that, even though not predominant, NPY innervation to TRH neurons also arises from cathecolaminergic neurons in the medullae. Thus, NPY-Y5 receptor antagonism may also reflect consequences of the action of NPY as a sympathetic co-transmitter that potentially could modulate the influence of adrenergic fibers on TRH neurons [12,14,15].

Previous study [18] had demonstrated the involvement of Y1 receptors in the inhibition of HPT axis exerted by NPY neurotransmission. As mentioned before, we have tested an Y1 receptor antagonist (BIBP3226), however the results were inconclusive because the drug induced the barrel rolling behaviour in most of the animals. The same behaviour was observed by others using either a different Y1 antagonist [34] or an antibody against NPY microinjected into ventrolateral thalamic area [35].

In conclusion, blockade of Y5 receptors within the central nervous system of fasted rats stimulated the pituitary–thyroid axis, suggesting that increased NPY neurotransmission, via Y5 receptors activation, is an important energy sparing response activated during prolonged fasting.

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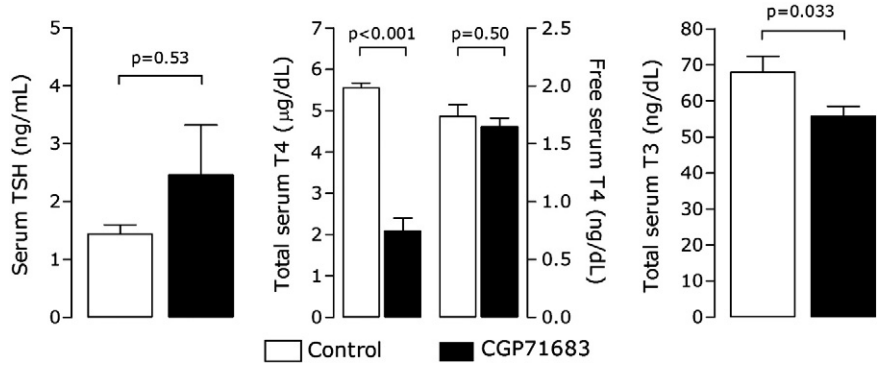

Fig. 3. Effect of multiple central (3rd ventricle) administration of Y5 antagonist (CGP71683; 15 nmol/rat, twice daily, during 72 h) on serum TSH , total and free T4 and total T3 of fed rats. Data are presented as mean ± S.E.M $n = 10$ rats per group.

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