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Hyperphagia of hyperthyroidism: Is neuropeptide Y involved?

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Abstract

The possible role of neuropeptide Y (NPY) was studied in rats with hypermetabolism and hyperphagia induced by thyroxine (50–100–200 μg/day s.c. for 3–4 weeks). Both metabolic rate and body temperature increased quickly with thyroxine treatment, while hyperphagia started to develop only after 2 weeks of treatment. The weight gain rate progressively decreased or stopped. The NPY-induced hyperphagia was not altered significantly during thyroxine treatment (in severe thyrotoxicosis it was rather suppressed); the fasting-induced hyperphagia was smaller than in controls following 1 week of treatment, and it became enhanced only after 3 weeks, when the deficit in body weight indicated a certain level of starvation already prior to the food deprivation. The NPY-antagonist D-Tyr^{27,36},D-Thr^{32}-NPY(27,36) suppressed this fasting-induced hyperphagia, suggesting that endogenous NPY is involved in this late phase. In conclusion, hyperthyroidism per se does not increase the NPY activity, instead the quickly developing hyperthermia may inhibit the NPY actions; NPY may, however, be activated by a concurrent hypermetabolism-induced starvation.

Keywords: Thyroxine; Body weight; Food intake; Neuropeptide Y; Fasting; Body temperature

1. Introduction

As a chronic hypermetabolic state, hyperthyroidism is necessarily accompanied by increased food intake. Despite the hyperphagia, this state does not form a coordinated anabolic regulatory pattern of energy balance, since it is accompanied by hypermetabolism. It does not form a catabolic regulatory pattern either [1,2], but exhibits a compensatory change in consummatory behavior due to the primary metabolic processes. Nevertheless, the hyperphagia possibly involves the activity of some orexigenic/anabolic factors [3].

Neuropeptide Y (NPY) is the most powerful member of the relevant orexigenic/anabolic substances, and it is of great importance in the control of energy balance [1,2,4]. Upon central injection, NPY induces food intake [5–10]. Chronic application of this peptide causes lasting hyperphagia [11]. Fasting, in turn, enhances hypothalamic expression of NPY mRNA [12–14], induces an increase in the hypothalamic concentration of NPY [15] and in the expression of NPY receptors [16]. Besides, as an anabolic agent, NPY may also suppress metabolic rate and may cause hypothermia [6,17–19], in addition to the orexigenic effect [1,2,6]. The characteristic changes in energy balance elicited by fasting, i.e. the hypometabolism, hypothermia and hunger are regarded mostly as consequences of increased hypothalamic NPY activity [12,13], similarly to other forms of negative energy balance [14].

The possible role of NPY was analyzed in the present studies, during the development of hyperphagia induced by hyperthyroidism. Changes of body weight and spontaneous food intake, as well as responsiveness to exogenous NPY or to fasting (which involves activation of endogenous NPY) were investigated. It was presumed that in hyperthyroidism the central NPY-mechanisms should be activated to enhance feeding (and an NPY-dependent attempt to suppress excessive metabolic rate might also be advantageous, in face of the hypermetabolic effect of thyroxine). However, a feeding-related postprandial hyperthermia (whether or not feeding was induced by NPY), could be a complicating

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factor when superimposed on a hyperthyroidism-induced hyperthermia, and thus the action of any hyperphagic factor (including NPY) might possibly be antagonized. How may hyperphagia still develop?

The following experiments aimed to investigate a) the spontaneous daily food intake and weight gain rate during thyroxine treatment, together with b) the changes in resting metabolic rate and body temperature, and the experiments also aimed to analyze c) the re-feeding responses of hyperthyroid rats to previous food deprivation (with and without NPY-antagonist pretreatment), as well as d) their feeding responses to centrally applied NPY.

2. Materials and methods

2.1. Animals

Wistar rats of both sexes with initial body weight of 170–190 g were used from the animal house of the University. The room temperature was 22–26 °C (near-thermoneutral) and the lights were on between 06:00 and 18:00 h. The animals were kept individually in plastic home-cages with wood-chips bedding and with free access to standard laboratory chow and water (except on days when food was withdrawn for 24 h or 48 h to assess re-feeding behavior). All rats were accustomed to regular handling and to daily measurements of body weight. Some of them were also habituated to a confining-cage that was used later on at tests determining their metabolic rate; some others had a guide-cannula implanted into a lateral cerebral ventricle (i.c.v.).

Two groups were formed when the rats reached the body weight of 220–260 g: in the experimental group the animals were given daily subcutaneous (s.c.) injections of thyroxine for 22 or 28 days in a dose of 50 or 100 μg (hyperthyroid rats), or in some cases 200 μg (thyrotoxic rats), while some animals of the control group were treated s.c. with 0.9% NaCl (half of the controls in Figs. 1 and 2) but – since this was without effect – other controls were untreated. Most control animals and some rats from the experimental group were used for checking the rate of daily weight gain and spontaneous daily food intake. The rest of the rats from both groups were divided into three subgroups, which underwent different procedures before thyroxine treatment (serving as "controls" for later stages of treatment), at the end of the first and also after the third week of treatment (5–8 days and 22–26 days, respectively): resting metabolic rate and the corresponding core body temperature (T_c) were measured (procedure #1); the acute re-feeding activity was observed in animals that had fasted for a period of 24 h (some "controls" fasted for 48 h: their fasting state, judged by the weight loss, was thought to be of comparable severity as the fasting state of hypermetabolic–hyperthyroid rats that were food deprived for 24 h, see Section 2.3) (procedure #2); while the rest of the rats had an i.c.v. cannula preimplanted, and was given NPY through this cannula to evoke an acute increase of food intake (or an NPY-antagonist to attenuate the re-feeding hyperphagia) (procedure #3).

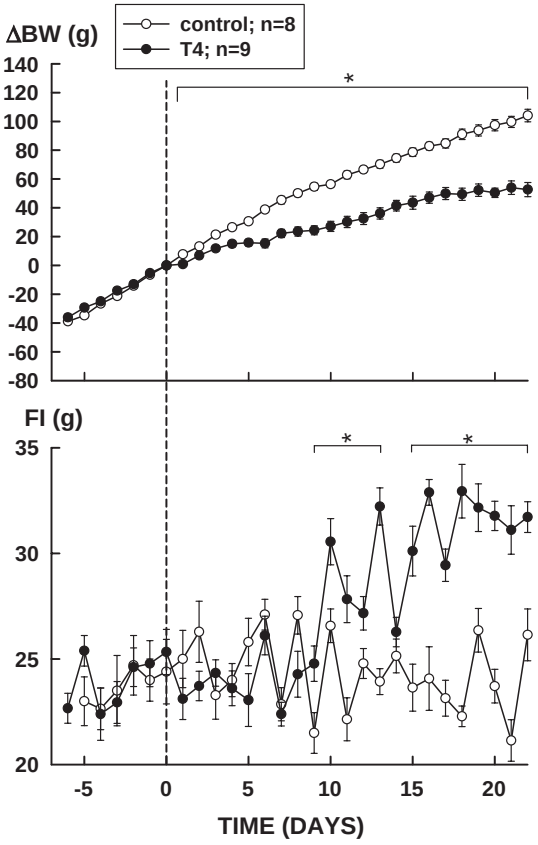

Fig. 1. Spontaneous weight gain rate (upper panel) and daily food intake (lower panel) in male control untreated rats (○) and in male rats treated with daily 50 μg s.c. thyroxine injections (●) for 22 days (body weights at day 0: 235±6 g and 246±10 g, respectively). *Denotes significant differences between $p<0.05$ and $p<0.001$.

Male and female rats exhibited different growth rates and food intake values: both were greater in males than in females. Male animals were used for fine analysis of these changes following small (daily 50 μg) thyroxine doses, whereas (as in our earlier studies [6,20,21]) the metabolic/thermal changes, the re-feeding activity and the effects of NPY or its antagonist (procedures #1–3) were analyzed in less quickly growing female rats which, in the present studies, were treated with more effective doses of thyroxine for 28 days (usually daily 100 μg, or in a few cases 200 μg).

After finishing the experimental sessions, all rats were euthanized by an overdose of intraperitoneal (i.p.) urethane. The location of the i.c.v. cannula was checked macroscopically at post-mortem examination. For these studies we obtained the approval of the University of Pécs Ethical Committee for the Protection of Animals in Research, which was in accordance with national standards (BA 02/2000–20/2001) — in all experimental procedures and interventions the general rules of handling and treating animals were strictly observed.