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Acute, subacute and chronic effects of central neuropeptide Y on energy balance in rats

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Abstract

Central neuropeptide Y (NPY) injection has been reported to cause hyperphagia and in some cases also hypometabolism or hypothermia. Chronic central administration induced a moderate rise of short duration in body weight, without consistent metabolic/thermal changes. In the present studies the acute and subsequent subacute ingestive and metabolic/thermal changes were studied following intracerebroventricular (i.c.v.) injections of NPY in cold-adapted and non-adapted rats, or the corresponding chronic changes following i.c.v. NPY infusion. Besides confirming basic earlier data, we demonstrated novel findings: a temporal relationship for the orexigenic and metabolic/thermal effects, and differences of coordination in acute/subacute/chronic phases or states. The acute phase (30–60 min after injection) was anabolic: coordinated hyperphagia and hypometabolism/hypothermia. NPY evoked a hypothermia by suppressing any (hyper)metabolism in excess of basal metabolic rate, without enhancing heat loss. Thus, acute hypothermia was observed in sub-thermoneutral but not thermoneutral environments. The subsequent subacute catabolic phase exhibited opposite effects: slight increase in metabolic rate, rise in body temperature, reaching a plateau within 3–4 h after injection – this was maintained for at least 24 h; meanwhile the food intake decreased and the normal daily weight gain stopped. This rebound is only indirectly related to NPY. Chronic (7-day long) i.c.v. NPY infusion induced an anabolic phase for 2–3 days, followed by a catabolic phase and fever, despite continued infusion. In cold-adaptation environment the primary metabolic effect of the infusion induced a moderate hypothermia with lower daytime nadirs and nocturnal peaks of the circadian temperature rhythm, while at near-thermoneutral environments in non-adapted rats the infusion attenuated only the nocturnal temperature rise by suppressing nighttime hypermetabolism. Further finding is that in cold-adapted animals, the early feeding effect of NPY-infusion was enhanced, whereas the early hypothermic effect in cold was limited by interference with competing thermoregulatory mechanisms.

Keywords: Neuropeptide Y; Food intake; Body weight; Energy balance; Body temperature; Cold adaptation; Circadian rhythms; Intracerebroventricular infusion; Anabolic effects; Catabolic effects

1. Introduction

For over two decades, neuropeptide Y (NPY) has been known as the most potent orexigenic peptide of the brain (Stanley and Leibowitz, 1984; Clark et al., 1985; reviews by Kalra et al., 1991, 1999; Williams et al., 2001; Kalra and Kalra, 2003). It is produced mainly in the arcuate nucleus, to be released primarily at nerve projections in the paraventricular, perifornical and ventromedial nuclei of the hypothalamus and the lateral hypothalamic area. During food deprivation the hypothalamic NPY mRNA expression (Grove et al., 2003), NPY level (Calzá et al., 1989), as well as the expression of NPY receptors (Xu et al., 1998) were found elevated. Such changes can probably account for the voracious appetite of fasting animals when food becomes accessible for them, or can at least contribute to the explanation of their feeding activity. In contrast, overfeeding

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suppressed hypothalamic NPY mRNA expression (McMinn et al., 1998). Despite that NPY knockout mice exhibited normal feeding patterns and also normal refeeding responses following food deprivation (Palmiter et al., 1998), an important role may still be ascribed to NPY in the regulation of food intake, particularly when the interaction of the peptide with leptin (Wang et al., 1997; Schwartz et al., 2000; Williams et al., 2001; Porte et al., 2002; Kalra and Kalra, 2003) is also considered.

NPY may, however, be more than just an orexigenic peptide. A detailed analysis of the effects of exogenous NPY may help to clarify some other properties of the peptide that are related to its orexigenic effects and its role in energy balance regulation. Since NPY has been shown also to suppress metabolic rate and/or body temperature (Billington et al., 1991; Egawa et al., 1991; Roscoe and Myers, 1991; Bing et al., 1997; Balaskó et al., 1999), it is presumably a rather complex regulator of energy balance and as such, it is better referred to as an anabolic substance (Székely et al., 2004). However, in order to confirm a complex anabolic character of the peptide, at least a temporal relationship should be demonstrated between its orexigenic vs. metabolic and thermal effects.

Although the data unequivocally show that central NPY administration induces food intake, the orexigenic effects of acute or chronic treatments may not be identical. Whereas an acute hyperphagia following central NPY injection may be thought to induce some subacute compensatory suppression of feeding activity (a rebound effect) once the acute orexigenic action is over, the expected chronic hyperphagic effect of central infusion of the peptide may not be so easily compensated. Indeed, NPY infusions were reported to cause sustained hyperphagia and enhanced weight gain or to cause obesity (Beck et al., 1992; Raposinho et al., 2001; Baran et al., 2002). However, neither the hyperphagia, nor the weight gain was excessive. Although chronic NPY over-activity in leptin-defective animals is probably a causative factor in the severe obesity of such animals (Bing et al., 1997; Schwartz et al., 2000), it is possible that in animals with uncompromised leptin actions (and with normal function of catabolic factors) a chronic elevation of NPY-activity can still be compensated by the help of some counter-regulatory mechanisms and thus, the hyperphagia does not necessarily remain apparent for a long time. It also needs to be clarified whether or not a sustained hypothermia develops during NPY infusion – this could be tested in chronically cold-exposed animals.

In the state of special energy balance seen in cold-adaptation, a continuous hyperphagia is indispensable for compensating the high metabolic rate. This hyperphagia might be presumed to necessitate a chronic elevation of endogenous NPY-activity (resembling NPY infusion), but this could be unfavorable because of an NPY-induced simultaneous suppression of metabolic rate and a consequent danger of life-threatening hypothermia. Accordingly, if NPY plays any role in this hyperphagia, its orexigenic and metabolic actions may be dissociated and the anabolic pattern presumed for NPY actions may be modified (Bing et al., 1998) because of competing homeostatic drives. The actions of NPY may therefore vary with the thermal-adaptation status and the mechanisms of NPY-action may be better understood if the thermal adaptation status is also taken into account.

In the present studies, we analyzed in rats (1) the acute or subacute changes in food intake following a central injection of NPY; (2) the mechanisms of acute or subacute thermal responses to central NPY injection (which responses, as many other thermoregulatory reactions, may depend on the prevailing environmental temperatures); (3) the temporal relationship between NPY-induced acute or subacute changes in food intake vs. metabolic rate and body temperature; (4) the changes of body temperature and body weight in the course of chronic central infusions of the peptide; (5) the differences of these NPY effects in animals of dissimilar states of energy balance, namely the differences observed between cold-adapted and non-adapted animals.

2. Materials and methods

2.1. Animals

Female Wistar rats of 210–250 g initial body weight were either maintained in a room of the Department's animal-house at a high temperature of 23–26 °C (up to 27–28 °C in the nest, near thermoneutrality), or were adapted to a cold chamber of 4–5 °C for a minimum of 4 weeks. The lights were on between 06:00 and 18:00 h at both sites. Each rat was kept individually in a plastic home-cage with wood-chips bedding and each had continuous access to standard laboratory chow and water. Four groups were formed: groups 1 vs. 2 were non-adapted vs. cold-adapted rats to be used in studies with acute intracerebroventricular (i.c.v.) injection of NPY or 0.9% NaCl (pyrogen-free saline, PFS), while groups 3 vs. 4 were non-adapted vs. cold-adapted rats to be used in studies with central infusion of NPY or PFS. Animals of groups 1 and 2 were accustomed to regular handling and to daily body weight measurements, and were familiarized with semi-restraining cages that were used later on when measuring body temperature and metabolic rate. Rats of groups 3 and 4 were only weighed on a daily basis. The daily food consumption was occasionally assessed before treatments. Most animals of groups 1 and 2 were used repeatedly for central injections of NPY or PFS when investigating their acute/subacute feeding or thermoregulatory responses,