Inhibitory effects of central neuropeptide Y on the somatotropic and gonadotropic axes in male rats are independent of adrenal hormones

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Abstract

Neuropeptide Y (NPY) in the hypothalamus exerts multiple physiological functions including stimulation of adipogenic pathways such as feeding and insulin secretion as well as inhibition of the somatotropic and gonadotropic axes. Since hypothalamic NPY-ergic activity is increased by negative energy balance, NPY enables coordinated regulation of growth and reproduction in parallel with energy availability. Chronic pathological increases in central NPY-ergic activity contribute to obesity. Many of the adipogenic effects of NPY are specifically dependent on adrenal glucocorticoids. However, in the current study we show that central NPY does not require adrenal hormones to inhibit the somatotropic and gonadotropic axes in rats. Male adrenalectomized and sham-operated normal rats were intracerebroventricularly (ICV) infused with NPY (15 μg/day) or saline for 5–7 days, and plasma leptin, insulin-like growth factor (IGF-1) and testosterone were assayed, and epididymal white adipose tissue (WATe) was weighed. In normal intact rats, WATe weight and leptinemia were significantly increased by NPY, and these effects were prevented by adrenalectomy. In normal rats, NPY markedly reduced plasma IGF-1 levels (470 ± 40 versus 1260 ± 90 ng/ml) and testosterone (0.53 ± 0.28 versus 5.4 ± 0.80 nmol/l in saline-infused controls, $p < 0.0001$). Adrenalectomy decreased plasma IGF-1 concentrations to 290 ± 30 ($p < 0.0001$ versus normal rats), which were significantly reduced further by NPY. However, adrenalectomy had no significant effect on basal nor on NPY-induced plasma testosterone concentrations. In conclusion unlike the stimulatory effects of NPY on fat mass and leptinemia, NPY-induced inhibition of the somatotropic and gonadotropic axes in male rats do not require adrenal hormones.

1. Introduction

Neuropeptide Y (NPY) is one of several orexigenic neuropeptides involved in the regulation of energy homeostasis via actions within the hypothalamus [17]. Of all of these peptides however, NPY is one of the few which actually leads to the development of true obesity and insulin resistance when hypothalamic levels remain chronically elevated [3,28,30,33,40,46,47], as has been reported for various rodent genetic obesity syndromes [2,8,35,42]. The obesity syndrome which results from chronically elevated hypothalamic NPY levels in rodents [3,28,30,33,40,46,47] is still present even when NPY-induced hyperphagia is prevented [3,30,46], demonstrating that hyperphagia is not necessary for central NPY to produce its obesity-like effects.   NPY in the hypothalamus is also involved in the regulation of several other important physiological processes including growth [4,22,25], reproduction [4,5,25], and fluid balance [13]. For example,

intracerebroventricular (ICV) administration of NPY to rats has been shown to inhibit the somatotropic axis by reducing the pituitary content of growth hormone (GH) [4], abolishing the normal pulsate release of GH into the plasma [25], and consequently reducing the plasma concentrations of GH and its main effector in the periphery insulin-like growth factor I (IGF-1) [4,22,25]. Centrally infused NPY was also shown to inhibit several parameters of the gonadotropic axis of both male and female intact rats, such as the reduction of plasma sex hormone levels, resulting in reduced gonadal weight and impaired sexual function [4,5,25].

The diverse roles of NPY are mediated by several different Y-receptor subtypes, five of which have been cloned to date (Y1, Y2, Y4, Y5 and Y6). This has raised hope that specific antagonism of any of these receptors might specifically antagonize the various effects of NPY. However, anti-obesity drugs based on NPY-ergic antagonism will need to specifically target the adipogenic effects of NPY to avoid excessive side effects on other vital functions. The availability of only a few synthetic agonists and antagonists has strongly hampered the identification of the functional contributions of each of the different Y-receptor subtypes in different physiological processes, and the consequent development of specific therapeutics. Particularly, the receptor subtypes responsible for mediating NPY's massive feeding response and other hormono-metabolic changes that contribute to obesity have still not been clearly identified.

In addition to NPY receptor antagonists, glucocorticoid antagonists may also be of potential therapeutic use in obesity management, since glucocorticoids are known to stimulate the NPY-ergic system and are permissive for the adipogenic effects of NPY. In rats, excessive glucocorticoids promote body fat gain [7,11,26,44], hyperinsulinemia [7,12,26,44], and also increase expression of NPY and Y- receptors within the hypothalamus [1,6,18,20,41]. It has been demonstrated that adrenalectomy largely prevents the obesity syndrome induced by chronic central NPY infusion in normal rats. This included complete blockade of chronic NPY-induced weight gain, hyperphagia, basal and glucose-induced hyperinsulinemia, hyperleptinemia, hypertriglyceridemia, and muscle insulin resistance [29,31,45]. These effects were restored by specific glucocorticoid replacement [31,34,45]. Other studies showed that adrenalectomy or administration of type II adrenal steroid receptor antagonists significantly attenuated or abolished the hyperphagia induced by acute central NPY injection in rats [16,23,34,37], although this was not consistent in all studies [43].

All of these observations indicate that glucocorticoids have a regulatory role in long-term central NPY signalling. However, whether adrenal glucocorticoids are specifically required for the adipogenic effects of central NPY, or whether glucocorticoids are required in a mechanism common to all of the central effects of NPY is currently unknown. If the former is true, glucocorticoid antagonists may be of value for the specific pharmacological treatment of obesity. Alternatively, possible differences in glucocorticoid regulation of different NPY-ergic functions could point to differences in cellular mechanisms, providing additional targets besides NPY receptors for selective drug therapy.

Therefore, in this study we investigated the impact of adrenalectomy on the known ability of central NPY administration to inhibit the somatotropic and gonadotropic axis in rats. Here we show the effects of ICV NPY infusion on plasma IGF-1 and testosterone levels

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in adrenalectomized compared to sham-operated male rats, which demonstrate that, unlike the adipogenic effects of central NPY, adrenal hormones are not necessary for NPY to exert its inhibitory effect on the somatotropic and gonadotropic axes in rats.

2. Materials and methods

Animals and surgery. Procedures were approved by the Animal Experimentation Ethics Committee of the Garvan Institute and St Vincent's Hospital, and are in keeping with the National Health and Medical Research Council of Australia's guidelines on animal experimentation. Male Wistar rats (Animal Resources Centre, Perth, Australia) were housed under conditions of controlled temperature (23°C) and illumination (6.00 –18.00 h) on pelleted paper bedding. They were allowed ad libitum access to standard laboratory chow (Norco Stockfeeds, South Lismore, Australia) and water, unless otherwise stated.

Rats were anaesthetised with intraperitoneal ketamine and xylazine (60 mg/kg and 10 mg/kg, Parke-Davis, Australia, and Bayer AG, Leverkusen, Switzerland) and were bilaterally adrenalectomized or sham operated at 10–11 weeks of age (body weight 378 ± 3 g, $n = 30$). Drinking water of adrenalectomized rats was supplemented with 0.9% NaCl. Upon recovery (7–10 days), the right lateral cerebral ventricle [27] and right jugular vein were cannulated. Animals were left to recover pre-surgery weights (7–10 days) in individual cages, with daily handling. The drinking response to ICV injection of angiotensin II (25 ng in 5 µl saline, Auspep, Melbourne, Australia) was tested. Only rats that drank ~8 mls or more in the 30 minutes after injection (~90% of the animals) were used for further studies. Blood samples were taken from adrenalectomized animals 10 days post-surgery, and only rats with negligible plasma corticosterone levels (<25 ng/ml) were used.

Chronic ICV infusions. Osmotic minipumps (model 2001, Alza Corporation, Palo Alto, CA) were subcutaneously implanted [27] under halothane anaesthesia for ICV infusion of porcine NPY (15 µg/day, Auspep, Melbourne, Australia) or saline vehicle. To prevent NPY-induced hyperphagia, all animals were presented with and consumed 32 g/day of chow, an amount equivalent to their spontaneous food intake measured prior to infusion. After 5–7 days of ICV infusion, a blood sample was taken from the jugular catheter (2–3 hours post-prandial) and stored at -20°C until plasma leptin, IGF-1 and testosterone assay (radioimmunoassay kits from Linco Re- search Inc, St Louis, MO, Bioclone, Marrickville, Australia, and ICN Biomedicals, Costa Mesa, CA, respectively). Animals were euthanased with ketamine/xylazine, and the right epididymal fat pad was removed and weighed.

Statistical analysis. Results were assessed by ANOVA followed by Fisher's post-hoc tests, using StatView version 4.5 (Abacus Concepts Inc, CA). Data on plasma hormone levels were Log10 transformed prior to ANOVA due to large to achieve normal distribution of data. For all statistical analyses, $p < 0.05$ was accepted as being statistically significant.

3. Results

There was no significant difference in body weight among the four groups of rats (normal or adrenalectomized, ADX ± NPY) during ICV infusion. Body weight after 6 days of infusion: Normal + ICV vehicle, 407 ± 8 g; Normal + ICV NPY, 382 ± 7 g; ADX + ICV vehicle, 385 ± 13 g; ADX + ICV NPY, 421 ± 15 g, $n = 4$–11 rats per group, NS. This is consistent with data showing that, whereas chronic central NPY infusion significantly increases body weight in ad

libitum-fed rats, no such increase is observed when NPY-induced hyperphagia is prevented by pair-feeding with vehicle-infused controls [30,46].

In sham-operated normal rats, 7-day central NPY infusion (15 μg/day in 24 μl) increased adiposity, as shown by the significant increases in epididymal white adipose tissue (WATe) weight (Fig. 1A) and plasma leptin concentrations (Fig. 1B). Compared with normal controls, adrenalectomy per se significantly reduced white adipose tissue mass and plasma leptin levels (Fig. 1). Central NPY administration to adrenalectomized rats restored these measures of adiposity to values not significantly different from normal control rats, although this was not a significant increase in comparison with adrenalectomized controls (Fig. 1).
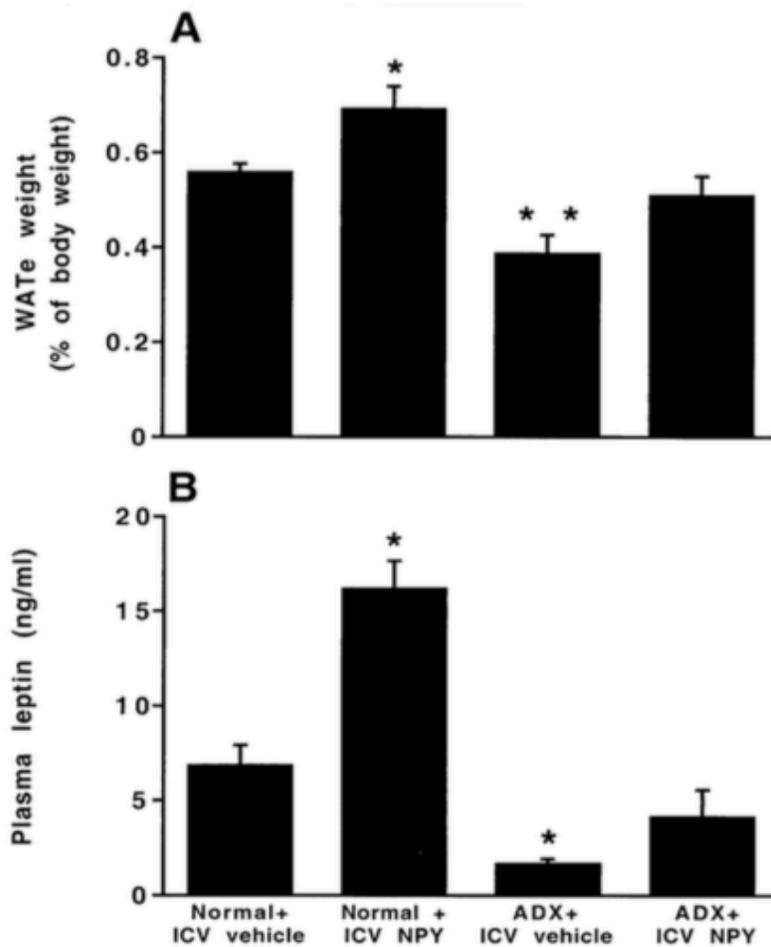

Fig. 1. Weight of epididymal white adipose tissue (WATe) as a percent of body weight (A), and plasma leptin concentrations (B) of normal and adrenalectomized (ADX) rats intracerebroventricularly (ICV) infused with NPY (15 μg/day for 7 days), compared to ICV vehicle-infused normal or ADX rats. Plotted values are means $\pm$ SEM of 4–7 rats per group. * $p <$ 0.05; ** $p < 0.01$ versus Normal + ICV vehicle.

In normal rats, chronic ICV NPY infusion significantly reduced plasma IGF-1 levels to values less than 40% of ICV vehicle-infused normal controls (Fig. 2). Adrenalectomy per se caused a marked decrease in plasma IGF-1 levels compared to normal control rats (Fig. 2). However, central NPY infusion induced a still greater and significant decrease in the plasma IGF-1 levels of adrenalectomized rats, to values 60% of adrenalectomized controls (Fig. 2).
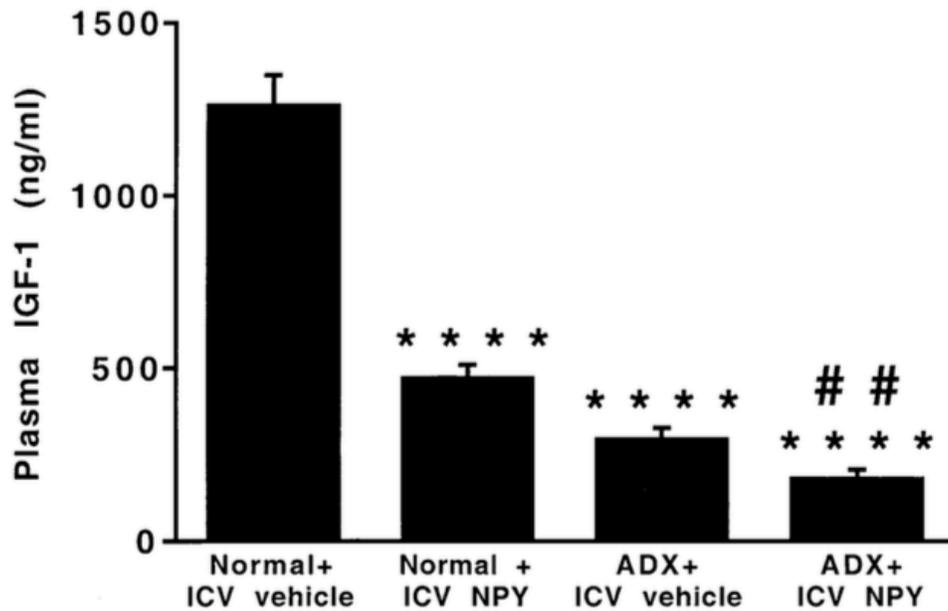

Fig. 2. Plasma IGF-1 concentrations of normal and adrenalectomized (ADX) rats intracerebroventricularly (ICV) infused with NPY (15 μg/day for 5–7 days), compared to ICV vehicle-infused normal or ADX controls. Plotted values are means ± SEM of 4–7 rats per group. **** $p < 0.0001$ versus Normal + ICV vehicle. ## $p < 0.01$ versus ADX + ICV vehicle.

Fig. 3 shows plasma testosterone concentrations in the four groups of rats. ICV NPY infusion for 5–7 days resulted in a significant, 10 to 15-fold decrease in plasma testosterone concentrations in both normal and adrenalectomized rats. However, adrenalectomy per se had no significant effect on plasma testosterone levels.
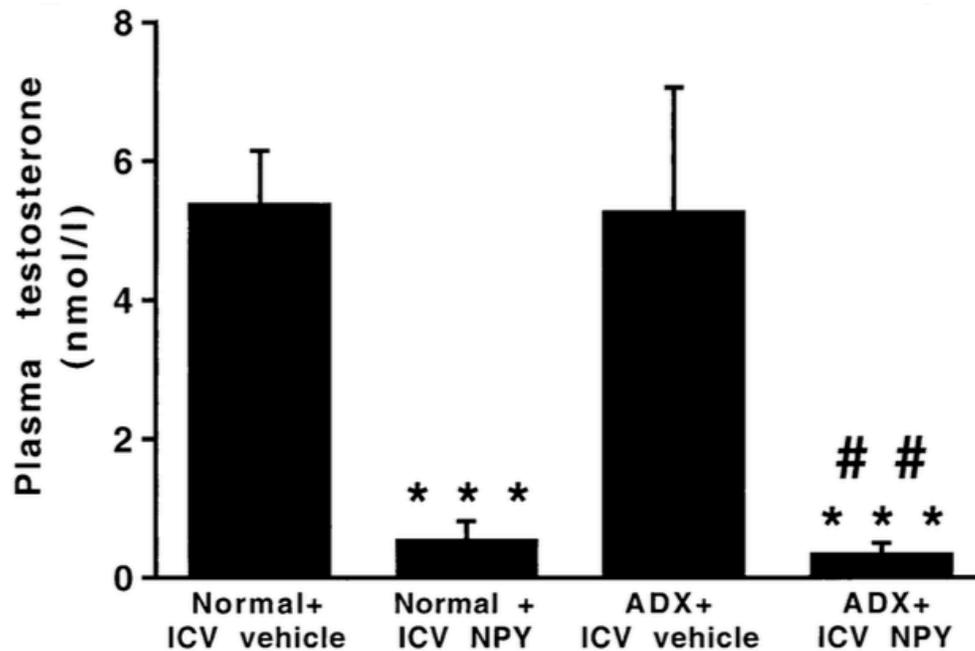
Fig. 3. Plasma testosterone concentrations of normal and adrenalectomized (ADX) rats intracerebroventricularly (ICV) infused with NPY (15 μg/day for 5–7 days), compared to ICV vehicle-infused normal or ADX rats. Plotted values are means $\pm$ SEM of 4–11 rats per group. *** $p < 0.001$ versus Normal + ICV vehicle. ## $p < 0.01$ versus ADX + ICV vehicle.

4. Discussion

Our study demonstrates that, whereas the effects of central NPY infusion to increase body fat content are dependent on the presence of adrenal glands, the inhibitory effects of central NPY on the somatotropic and gonadotropic axes of male rats do not require adrenal hormones.

Central NPY infusion in normal rats significantly increased white adipose tissue mass and plasma leptin concentrations, a known index of total percent body fat [10]. These increases occurred despite the fact that NPY-infused rats were prevented from overeating by pair-feeding with controls, and that there was no increase in body weight. Adrenalectomy abolished these NPY effects, in keeping with studies showing that other adipogenic effects of NPY are completely prevented or significantly attenuated by prior adrenalectomy in rats [16,23,29,31,34,37,43,45], and restored by specific glucocorticoid replacement [31,34,45].

In adrenalectomized rats, despite significantly reduced basal plasma IGF-1 levels, central NPY infusion was still able to inhibit the somatotropic axis, indicated by further reductions in plasma IGF-1. Adrenal insufficiency in animals and in man is associated with low plasma GH or IGF-1 concentrations [14,36]. This is in keeping with findings that acute administration of glucocorticoids stimulate basal and growth hormone releasing hormone-induced GH secretion, and reduce the potency of IGF-1 mediated negative feedback [38]. Central NPY is known to inhibit several parameters of the somatotropic axis in rats [4,22,25], most probably via stimulation of somatostatin secretion from neurons in the periventricular nucleus [22]. Since adrenalectomy and central NPY administration have additive inhibitory effects on plasma IGF-1 levels, these interventions probably inhibit the somatotropic axis via divergent pathways.

During long-term central NPY infusion in normal male rats, plasma testosterone levels were markedly decreased. This is in agreement with the original findings of Pierroz et al showing also significant reductions in plasma levels of leutenizing hormone (LH) and follicle stimulating hormone (FSH), and decreases in seminal vesicle and testis weights after ICV NPY infusion [25]. We further showed that adrenalectomy affected neither the basal plasma testosterone levels, nor the inhibitory effect of central NPY administration on the gonadotropic axis in male rats. This finding indicates that adrenal hormones are not major regulators of the hypothalamo-pituitary-testicular axis in rats. Although a few studies have shown inhibitory effects of adrenalectomy on pituitary-testicular hormone release [15,19,39], many functions of this axis were unaffected by adrenalectomy. This includes plasma levels of LH, FSH and testosterone [9,32], testosterone- and prolactin-induced inhibition of LH and FSH release [21,24], and the release of LH in response to leutenizing hormone releasing hormone [24].

Although adrenal insufficiency produced an overall decrease in plasma IGF-1 levels, our study has shown that adrenal hormones are not necessary for central NPY to inhibit he somatotropic and gonadotropic axes in male rats. Further understanding of central NPY-ergic pathways that are dependent or not on adrenal hormones, including glucocorticoids, will contribute to our understanding of how NPY specifically regulates energy balance, growth and reproduction.

Acknowledgments

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