ELSEVIER

Brain Research 821 (1999) 263–269

BRAIN RESEARCH

Research report

Increased NPY activity in the PVN contributes to food-restriction induced reductions in blood pressure in aortic coarctation hypertensive rats

J. Mark VanNess, Jamie E. DeMaria, J. Michael Overton *

Departments of Nutrition, Food and Exercise Sciences and Biological Sciences, and the Program in Neuroscience, Florida State University, Tallahassee, FL 32306-4340, USA

Accepted 15 December 1998

Abstract

We hypothesized that hypothalamic NPYergic mechanisms mediate the blood pressure lowering effect of caloric restriction in hypertensive rats. Aortic coarctation-induced (AC) hypertensive rats ($n = 25$) were assigned to either an ad libitum fed control group (AL) or food restricted group (FR; 60% of AL consumption) for 3 weeks. Rats were instrumented chronically with vascular catheters and bilateral guide cannulae directed at the paraventricular hypothalamic nuclei (PVN). Blood pressure (BP) and heart rate (HR) responses to bilateral PVN microinjection of saline (200 nl) or the putative NPY receptor antagonists [D-Trp^{32}]NPY$_{(1-36)}$ (3.3 μg/200 nl) and [D-Tyr^{27,36} Thr^{32}]NPY$_{(27-36)}$ (D-NPY$_{(27-36)}$; 3.3 μg/200 nl) were determined. The FR rats were then refed and cardiovascular responses to PVN injections of NPY receptor antagonists were again determined. FR rats had significantly reduced resting BP (159 ± 4 vs. 129 ± 4 mmHg) and HR (360 ± 11 vs. 326 ± 9 bpm) compared to AL controls. Refeeding restored BP and HR of FR rats to levels similar to AL (BP = 153 ± 4 mmHg, HR = 359 ± 11 bpm). PVN administration of [D-Trp^{32}]NPY produced foraging behavior and concurrent increases in BP and HR in FR, AL and Re-fed rats. The behavioral activation suggests that [D-Trp^{32}]NPY$_{(1-36)}$ produced activation of NPY receptors. In contrast, D-NPY $_{(27-36)}$ did not produce any behavioral response or affect BP or HR in AL or Re-fed rats. In FR rats, D-NPY $_{(27-36)}$ produced significant increases in BP (peak = 15 ± 3 mmHg) which partially reversed the effect of FR on BP. Thus, in FR rats with reduced BP, PVN administration of an NPY receptor antagonist increases BP. NPY blockade in the PVN accounted for about 50% of the BP effect of food restriction, thus other mechanisms are likely to be involved. These findings are consistent with the hypothesis that NPYergic mechanisms may contribute to the reduction of BP produced by food restriction.

Keywords: Hypertension; Energy balance; Hypothalamus; [D-Trp^{32}]NPY$_{(1-36)}$; [D-Tyr^{27,36} Thr^{32}]NPY$_{(27-36)}$

1. Introduction

Reduced caloric intake lowers blood pressure (BP) in hypertensive animals [11,20,25,38,39,41]. The mechanisms responsible for this observation have not been clarified; however, decreases in sympathetic nervous system activity frequently accompany reduced caloric intake. In the spontaneously hypertensive rat (SHR), fasting-induced reductions in BP are accompanied by reduced cardiac norepinephrine (NE) turnover [40] and reduced sympathetic support of BP [25]. Reduced plasma norepinephrine (NE) levels and decreased sympathetic support of BP have also been observed in the aortic coarctation-induced (AC) hypertensive rat during food restriction [39]. Thus, there is considerable evidence suggesting that reduced sympathetic activity is an important mechanism responsible for decreased BP resulting from reduced caloric intake. The mechanisms by which decreased caloric intake might produce reductions in sympathetic activity and BP are poorly understood.

Several lines of evidence suggest that neuropeptide Y (NPY)-containing neurons that project from the arcuate hypothalamic nuclei to the paraventricular nuclei (PVN) are important for the stimulation of appetite and the reduction in thermogenic sympathetic activity that accompany negative energy balance [5,17,32]. Interestingly, microinjections of NPY into PVN have also been shown to reduce plasma NE levels [37], heart rate [15,37], and BP [15]. Thus, increased activation of NPYergic activity in the hypothalamus could contribute to the sympathoinhibitory

* Corresponding author. 236 Biomedical Research Facility, Florida State University, Tallahassee FL 32306-4340, USA. Fax: +1-850-644-0989; E-mail: moverton@mailer.fsu.edu

0006-8993/99/$ - see front matter
PII: S0006-8993(99)01058-6

and hypotensive actions of reduced caloric intake. Furthermore, we have recently reported that lesions of the PVN markedly reduce the magnitude of reduction in BP produced by caloric restriction in AC hypertensive rats [38]. Therefore, we hypothesized that elevated NPYergic activity in the PVN could explain, at least in part, the reduced sympathetic activity and BP produced by caloric restriction.

To test this hypothesis, we determined the BP responses to PVN administration of putative NPY antagonists in ad libitum and food restricted hypertensive rats. We predicted that blockade of NPY receptors would elevate BP and sympathetic activity in food restricted rats, while having minimal cardiovascular effects in normally fed animals. Because the receptors within the PVN that may mediate the NPYergic stimulation of appetite and reductions in sympathetic activity have not been clearly determined [2], the BP response of two different putative NPY receptor antagonists were examined. We hypothesized that blocking NPYergic receptors within the PVN would significantly increase BP of hypertensive rats that were in negative energy balance.

2. Materials and methods

2.1. Treatment conditions

All experiments were approved by the Institutional Animal Care and Use Committee at Florida State University. Male Sprague–Dawley rats (6–7 weeks old, 151–175 g; $n = 25$), were individually housed in standard wire rack cages. They were given free access to rat chow (Laboratory Rodent Diet 5001; PMI Feeds; St. Louis, MO; NaCl content = 0.96%) and demineralized water for a 2-week acclimatization period prior to any intervention. The animal quarters were maintained at a temperature of 22–23°C, and kept on a 12-h light:dark cycle (lights off: 1700–0500 h).

To produce hypertension by partial aortic coarctation, animals were anesthetized with ketamine/acepromazine maleate (100/1.1 mg/kg, i.p.) for placement of a suprarenal abdominal aortic constricting ligature as described previously [38]. The animals were allowed to recover for 7 days before being randomly assigned to either an ad libitum fed control group (AL) or a food restricted (FR) group.

Food consumption was measured weekly in the AL group. The animals in the FR group received 60% of the food consumed by AL rats. FR rats received their daily allotment of food between 1600 and 1700 h. Feeding was within 1 h of 'lights off' so that the corticosterone rhythm that becomes entrained to restricted daily feeding coincides with the normal circadian peak of corticosterone just after the beginning of the dark phase of the 24 h light:dark cycle [18].

2.2. Surgery

Two weeks prior to cardiovascular data collection, all rats were anesthetized (ketamine/acepromazine) and placed into a stereotaxic device (David Kopf; Tujunga, CA) with the incisor bar approximately −3 mm so the skull was level. Guide cannula (26-gauge) (Plastics One, Roanoke, VA) were positioned 12° from vertical and directed bilaterally toward the PVN using coordinates from Paxinos and Watson [27]. Cannulae were secured in position with stainless steel screws and dental adhesive, and closed with 33-gauge internal 'dummy' cannulae.

One week later, an intravascular catheter was inserted into the left carotid artery of all rats while under halothane anesthesia as described previously [39]. Catheters were flushed daily with heparinized saline (100 U/ml) to maintain patency. The week following catheterization, animals continued to receive either the ad libitum or restricted diet and were acclimatized to round opaque testing cages (diameter = 30 cm; height = 39 cm) used for data collection. Each acclimatization session (2–3 sessions/rat) lasted 2–3 h during which no food or water was available.

2.3. Protocols

A tygon extension line was attached to the vascular catheters for measurement of pulsatile BP. Thirty-three gauge internal injection cannulae, that extend 1.0 mm beyond the PVN-directed guide cannulae, were attached to extension lines and back-filled with 200 nl of either [D-Trp^{32}]NPY$_{(1-36)}$ (3.3 μg/200 nl/side), [D-Tyr^{27,36} Thr^{32}]NPY$_{(27-36)}$ (D-NPY$_{(27-36)}$; 3.3 μg/200 nl/side) or saline vehicle (SAL; 200 nl/side). The dose of D-NPY$_{(27-36)}$ has been shown to successfully blunt NPY- and fasting-induced feeding when injected into PVN [24]. The dose of [D-Trp^{32}]NPY$_{(1-36)}$ has been shown to significantly blunt NPY-induced feeding [3]. The injection stylets were inserted into the guide cannulae and treatments were microinjected using a 1 μl Hamilton syringe over a period of 1 min/side without disturbing the animal. BP was monitored before, and for 2 h following injections. In order to avoid potential confounding effects of feeding on BP, no food or water was available during the period of time the animals were in testing cages for central microinjection studies.

PVN treatments were administered bilaterally on a different day, in a random order within AL and FR groups. Treatments were separated by 24–48 h. After completion of the treatments, the FR group was given food ad libitum for three days and the protocol was repeated for these animals in the refed state ($n = 11$). [D-Trp^{32}]NPY$_{(1-36)}$ and [D-Tyr^{27,36} Thr^{32}]NPY$_{(27-36)}$ were purchased from Bachem, Torrance, CA.

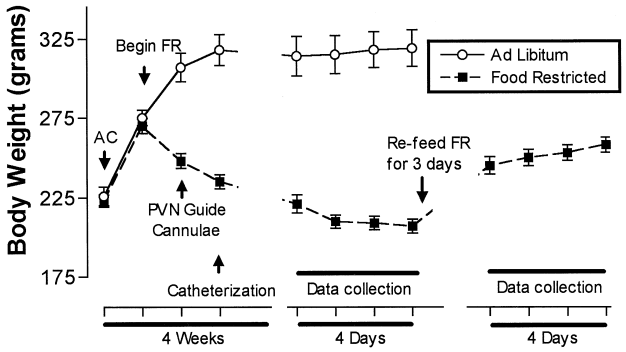

Fig. 1. Effects of treatments on body weight. Body weight was not different between ad libitum (AL) and food restricted rats at induction of aortic coarctation hypertension (AC) or at the beginning of 60% food restriction (FR). Thereafter, food restricted rats weighed significantly less than AL rats. Body weights of Refed food restricted rats remained significantly below AL rats.

2.4. Behavioral responses

Microinjections of [D-Trp^{32}]NPY$_{(1-36)}$ into PVN elicited a vigorous behavioral response characteristic of feeding. To quantify this response, activity in the testing cages was assessed on the following scale: 0 = no movement, asleep or sitting quietly; 1 = small head movements, walking intermittently, no grooming; 2 = mild grooming/movements, no burrowing, no rearing on hind legs; 3 = walking, intermittent circling, occasional short periods of rearing on hind legs; 4 = some burrowing, continuous grooming, rearing, continuous circling; 5 = continuous and vigorous grooming, burrowing or rearing.

2.5. Plasma NE

In pilot studies it was noted that PVN directed microinjections of D-NPY$_{(27-36)}$ increased BP in FR rats. To determine if sympathetic activity was also increased, a blood sample was collected 30 min post injection of D-NPY$_{(27-36)}$ and saline for determination of plasma NE levels using HPLC as described previously [38].

2.6. Histology

At the conclusion of cardiovascular data collection, rats were deeply anesthetized with sodium pentobarbital (30 mg/kg, i.v.). Dye (5% fast green; 200 nl) was injected in the same manner as all other PVN injections. Rats were then perfused, the brain removed and first placed in 10% formalin for 3 days, then transferred to a 30% sucrose solution for at least 2 days. Brains were sectioned on a freezing cryostat. Sections (25-μm slices) were thaw-mounted onto gelatin coated slides. To determine the placement of cannulae, every other section was stained with cresyl violet, and compared to dye markings seen on unstained sections. Placement of injections was assessed by visual comparison to the atlas of Paxinos and Watson [27].

2.7. Data analysis

A two-factor ANOVA (diet treatment groups × time) was used to determine the effect of diet treatment on BP, HR and behavioral response data for each central injection. A one-way ANOVA was used to compare plasma NE between groups. Tukey's post-hoc test was used to determine differences between means when a significant main effect or interaction was detected. A value of $P < 0.05$ was used to determine significance.

3. Results

3.1. Body weight

Body weights were not different between groups at the time of AC, or prior to assignment to diet treatment (Fig. 1). Food restricted rats lost weight during the study, whereas AL rats gained weight. Refeeding of FR rats for three days significantly increased body weight, but not to levels of AL animals.

3.2. Pretreatment BP and HR (Table 1)

Food restriction (60% of AL consumption) produced significant reductions in BP and HR compared to AL. Three days of refeeding restored BP and HR to levels similar to those seen in AL animals.

3.3. BP, HR and behavioral effects of PVN treatments

Saline injected into the PVN produced no changes in BP, HR or behavior in AL, FR or Refed groups (Fig. 2). Injection of [D-Trp^{32}]NPY$_{(1-36)}$ into the PVN produced foraging behavior (Fig. 3C) and associated increases in HR (Fig. 3B) and BP (Fig. 3A). The temporal relationship

Table 1
Resting arterial BP and HR of groups prior to PVN microinjections

		AL	FR	Refed
SAL	BP	159 ± 4	129 ± 5 *	153 ± 4
	HR	360 ± 11	326 ± 9 *	359 ± 11
	n	11	14	9
Trp32	BP	157 ± 5	136 ± 4 *	154 ± 5
	HR	359 ± 16	321 ± 14 *	365 ± 11
	n	5	6	6
DNPY	BP	158 ± 3	129 ± 4 *	157 ± 4
	HR	356 ± 8	331 ± 7 *	357 ± 8
	n	11	14	11

Resting mean arterial blood pressure (BP) and heart rate (HR) in ad libitum fed (AL), food restricted (FR; 60% AL consumption) and following 3–7 days refeeding of FR rats (Refed).
Values were taken prior to PVN injection of saline (SAL; 200 nl/side), [D-Trp^{32}]NPY$_{(1-36)}$ (Trp32; 3.3 μg/200 nl/side) or [D-Tyr^{27,36} Thr^{32}]NPY$_{(27-36)}$. (DNPY; 3.3 μg/200 nl/side).
*: Indicates $P < 0.05$ vs. AL.

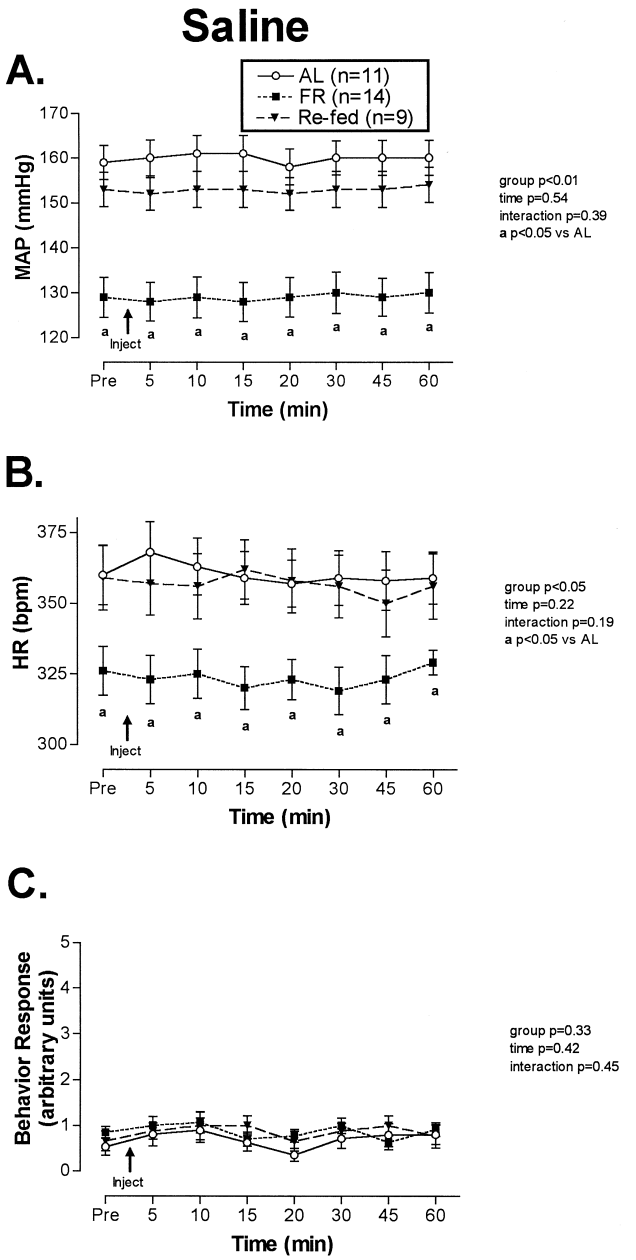

Fig. 2. Responses to bilateral injections of saline (200 nl) into PVN of conscious, unrestrained AC rats fed ad libitum, food restricted (60% AL for 3 weeks), and Refed rats. (A) Mean blood pressure, (B) heart rate and (C) behavior response. For HR and MAP: control value (Pre) represents a 20-min average, all others are 5-min averages.

between the cardiovascular and behavioral responses suggests that the observed BP and HR increases may be due to the increase in physical activity.

Microinjections of the NPY antagonist D-NPY$_{(27-36)}$ into the PVN did not significantly affect BP, HR or behavior in AL or Refed rats (Fig. 4A–C). In FR rats, D-NPY$_{(27-36)}$, caused an increase in BP that reached statistical significance between 10 and 75 min post injection (15 ± 3 mmHg at 15 min post). HR also appeared to increase in the FR group after D-NPY$_{(27-36)}$ injection. ANOVA indicated a significant interaction for HR, although post-hoc analysis did not reveal significant increases from pre-injection value. Importantly, there was no increase in activity associated with D-NPY$_{(27-36)}$-induced BP responses (Fig. 4C). The small peak in activity 45 min post injection is due to re-infusion of donor blood after blood collection.

3.4. Plasma NE

Plasma NE levels 30 min after PVN injection of SAL indicate that FR rats had significantly lower plasma NE (230 ± 73 pg/ml) compared to AL (696 ± 73 pg/ml) and

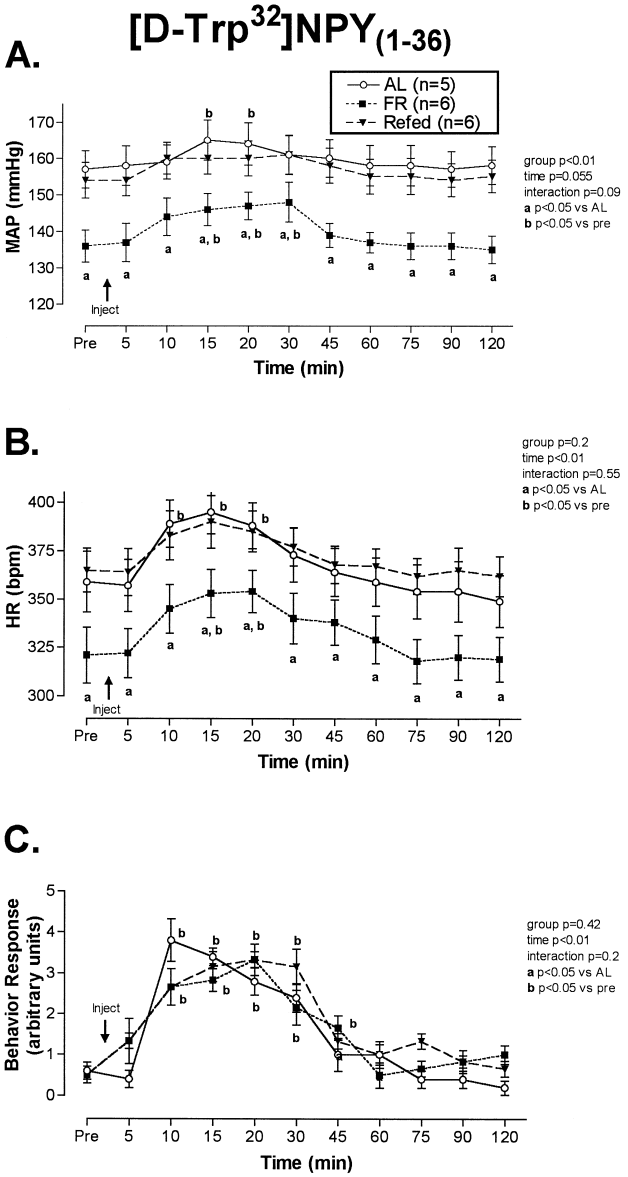

Fig. 3. Responses to bilateral injections of the putative NPY receptor antagonist [D-Trp^{32}]NPY$_{(1-36)}$ (3.3 (μg/200 nl/side) into PVN of conscious, unrestrained AC rats fed ad libitum, food restricted (60% AL for 3 weeks), and Refed rats. (A) Mean blood pressure, (B) heart rate and (C) behavior response. For HR and MAP: control value (Pre) represents a 20-min average, all others are 5-min averages.

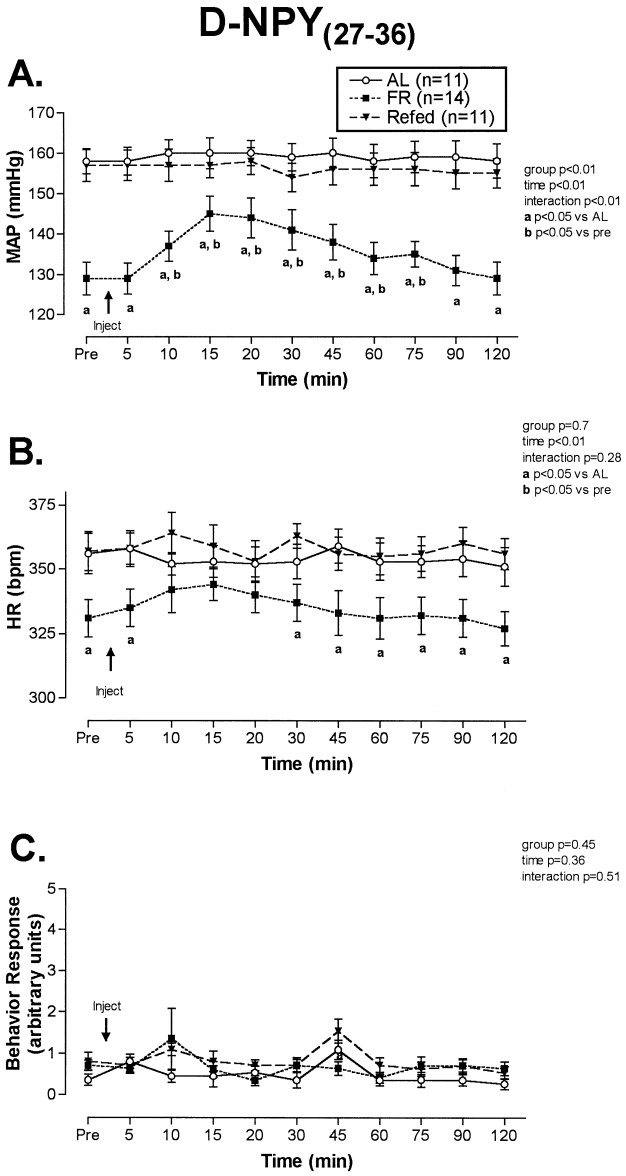

Fig. 4. Responses to bilateral injections of the putative NPY receptor antagonist [D-Tyr^{27,36}, Thr^{32}]NPY$_{(27-36)}$ (D-NPY$_{(27-36)}$; 3.3 (μg/200 nl/side) into PVN of conscious, unrestrained AC rats fed ad libitum, food restricted (60% AL for 3 weeks), and Refed rats. (A) Mean blood pressure, (B) heart rate and (C) behavior response. For HR and MAP: control value (Pre) represents a 20-min average, all others are 5-min averages.

Refed rats (716 ± 72 pg/ml). ANOVA indicated a main effect for NE levels to be elevated 30 min after PVN injection of D-NPY (FR $= 320 \pm 73$, AL $= 742 \pm 73$, Refed $= 760 \pm 76$ pg/ml); however, post hoc analysis did not detect differences vs. SAL injection within any group.

4. Discussion

The major new finding reported herein is that PVN administration of the NPY receptor antagonist D-NPY$_{(27-36)}$ significantly increases BP in food restricted AC hypertensive rats, but has no effect on BP in normally fed or refed rats. Furthermore, the increase in BP produced by PVN administration of D-NPY$_{(27-36)}$ was observed in the absence of any behavioral response. Although we did not see similar effects with another putative NPY receptor antagonist ([D-Trp^{32}]NPY$_{(1-36)}$), we will point out below that our findings are consistent with recent reports indicating that the compound produces NPY receptor agonist activity. The finding that PVN administration of D-NPY $_{(27-36)}$ elevates BP specifically in FR rats supports the hypothesis that increased hypothalamic NPY activity may be partially responsible for the reductions in BP produced by reduced caloric intake.

4.1. BP, sympathetic activity, and negative energy balance

The effects of chronic food restriction on sympathetic activity and BP in the present study are consistent with those previously shown in AC rats [36,38,39]. Reductions in BP produced by chronic food restriction in the AC rat are associated with reduced sympathetic support of BP [39] and reduced plasma NE [38]. Acute and chronic food restriction also lowers sympathetic support of BP in the SHR [20,25,41]. Refeeding rapidly reverses the BP effects of fasting in the SHR [20,41]. Similarly, we discovered in the current study that three days of ad libitum feeding by chronically food restricted AC hypertensive rats fully restored hypertension (Table 1) and elevated plasma NE levels. This re-establishment of elevated sympathetic activity and BP was observed after short term refeeding even though body weight had not reached that of AL rats (Fig. 1). These results support the idea that negative energy balance, rather than reductions in body weight per se, produce reductions in sympathetic activity and concomitant decreases in BP in the SHR and AC hypertensive rats.

We speculate that plasma leptin levels, which are clearly involved in afferent signaling of the hypothalamus concerning the status of energy balance [6,12], were elevated upon refeeding and may have been involved in the return of elevated sympathetic activity in refed rats. Exogenous leptin administration activates hypothalamic neurons [9,10], increases sympathetic activity [16], and increases arterial pressure [7,34]. Further experiments will be required to test this hypothesis.

The AC model of hypertension was selected for this study because its etiology is characterized by high sympathetic activity. Two to three weeks following AC, plasma NE levels are elevated, cardiac NE turnover is increased and tissue NE levels are depleted [35,38]. Because the elevations in BP due to AC hypertension are related to enhanced sympathetic activity, this model is ideal for studying the effects of food restriction on reducing sympathetic activity and BP. In the AC rat, the PVN is important in maintaining BP and sympathetic support of BP [38]. PVN lesions dramatically reduce BP and sympathetic ac-

tivity in AC rats. Furthermore, food restriction attenuates the cardiovascular and sympathetic responses produced by PVN lesions. Thus, the PVN may therefore be an important central site for homeostatic reductions in sympathetic activity during food restriction.

4.2. Negative energy balance and neuropeptide Y

Within the mediobasal hypothalamus, negative energy balance produces rapid increases in preproNPY mRNA and increased NPY delivery from the arcuate nuclei to the PVN [4,30]. This increase in hypothalamic NPY promotes positive energy balance by stimulating food intake and by reducing thermogenic sympathetic activity [5,17,32]. Previous studies have indicated that injections of NPY into the PVN reduces sympathetic activity as indicated by plasma NE levels [37], and reduced directly measured sympathetic activity to brown adipose tissue [8]. Interestingly, NPY also has significant cardiovascular effects in the CNS. Several studies have shown that both i.c.v. [1,14,21,31,33] and PVN [15,37] administration of NPY decreases BP and HR. Therefore, we hypothesized that NPY may be involved in the reductions in sympathetic support of BP that occurs during negative energy balance. Based on this hypothesis, we predicted that blockade of NPY receptors in the PVN would partially reverse the reductions in BP and heart rate that are normally seen during caloric restriction.

There are multiple endogenous receptors that produce the peripheral and central physiologic effects of NPY [2]. Within the hypothalamus, the specific receptors involved in mediating NPY-induced effects on feeding and sympathetic activity have not yet been clarified. However, two recent reports indicate possible roles for the Y1 and Y5 receptors. NPY-Y1 receptor knockout mice displayed a reduced feeding response to fasting [28], while NPY-Y5 receptor knockout mice have a reduced feeding response to exogenous NPY administration [22]. Thus, increased NPY activity at Y1 receptors may be involved in the compensatory hyperphagia that follows reduced caloric intake. It is not yet clear why the NPY knockout mice displays normal refeeding responses [26], while the Y1 receptor knockout demonstrates depressed refeeding.

We utilized two putative NPY antagonists selected for this study that have been shown to attenuate NPY-induced feeding. Hypothalamic administration of [D-Trp^{32}]-NPY$_{(1-36)}$ was shown to attenuate the feeding activation produced by co-administered NPY [3]. However, recent evidence suggests that [D-Trp^{32}]NPY$_{(1-36)}$ stimulates Y5 receptors [13,19] produces similar neurochemical and behavioral effects analogous to NPY [13,23]. Similarly, we also observed substantial behavioral activation characteristic of foraging, suggesting activation of NPY receptors.

PVN administration of [D-Tyr^{27,36} Thr^{32}]NPY$_{(27-36)}$ has been shown to suppress compensatory hyperphagia following fasting and NPY-stimulated feeding [24]. In the present study, a similar dose of D-NPY$_{(27-36)}$ did not alter BP, HR or behavior in AL or refed rats. This finding is consistent with a recent report showing i.c.v. administration of D-NPY$_{(27-36)}$ does not influence BP in ad lib fed animals [29]. However, when administered into PVN of food restricted rats, D-NPY$_{(27-36)}$ produced significant increases in BP. This increase in BP was not associated with any behavioral response. Furthermore, increases in BP in FR rats were not associated with reflex bradycardia, but rather an increase in HR to levels seen in ad lib fed animals. In order to determine if the BP response was associated with increases in sympathetic activity, plasma NE levels were assessed. Although plasma NE tended to be increased following D-NPY$_{(27-36)}$ treatment, this result was not statistically significant. Unfortunately, blood was collected more than 30 min post PVN injection, while the peak BP was seen at 15 min post. Given that NE has a very short half-life, it is possible that we did not detect the maximum effect produced by PVN administration of D-NPY$_{(27-36)}$. Therefore, mechanisms of D-NPY$_{(27-36)}$-induced increases in BP will require further study.

5. Conclusions

Chronic food restriction produces dramatic reductions in BP and plasma NE of male AC hypertensive rats. Food restriction-induced reductions in BP and plasma NE are abolished by three days of refeeding. PVN injection of the NPY antagonist [D-Tyr^{27,36} Thr^{32}]NPY$_{(27-36)}$ increases BP in food restricted rats toward the levels seen in ad libitum fed animals. These results provide the first evidence that NPYergic mechanisms within the PVN may suppress BP during food restriction in hypertensive rats.

Acknowledgements

This work was supported in part by AHA 9601436 (Fl. Affiliate) and NIH RO1 HL56732.

References

[1] J.A. Aguirre, K. Fuxe, L.F. Agnati, G. von Euler, Centrally injected neuropeptide Y (13–36) produces vasopressor effects and antagonizes the vasodepressor action of neuropeptide Y (1–36) in the awake male rat, Neurosci. Lett. 118 (1990) 5–8.

[2] A. Balasubramaniam, Neuropeptide Y family of hormones: receptor subtypes and antagonists, Peptides 18 (1997) 445–457.

[3] A. Balasubramaniam, S. Sheriff, M.E. Johnson, M. Prabhakaran, Y. Huang, J.E. Fischer, W.T. Chance, [D-Trp32] Neuropeptide Y: a competitive antagonist of NPY in rat hypothalamus, J. Med. Chem. 37 (1994) 811–815.

[4] B. Beck, M. Jhanwar-Uniyal, A. Burlet, M. Chapleur-Chateau, S.F. Leibowitz, C. Burlet, Rapid and localized alterations of neuropeptide

Y in discrete hypothalamic nuclei with feeding status, Brain Res. 528 (1990) 245–249.
[5] C.J. Billington, J.E. Briggs, S. Harker, M. Grace, A.S. Levine, Neuropeptide Y in hypothalamic paraventricular nucleus: a center coordinating energy metabolism, Am. J. Physiol. 266 (1994) R1765–70.
[6] J.F. Caro, M.K. Sinha, J.W. Kolaczynski, P.L. Zhang, R.V. Considine, Leptin: the tale of an obesity gene, Diabetes 45 (1996) 1455–1462.
[7] R.M. Casto, J.M. VanNess, J.M. Overton, Effects of central leptin administration on blood pressure in normotensive rats, Neurosci. Lett. 246 (1998) 29–32.
[8] M. Egawa, H. Yoshimatsu, G.A. Bray, Neuropeptide Y suppresses sympathetic activity to interscapular brown adipose tissue in rats, Am. J. Physiol 260 (1991) R328–R334.
[9] J.K. Elmquist, R.S. Ahima, C.F. Elias, J.S. Flier, C.B. Saper, Leptin activates distinct projections from the dorsomedial and ventromedial hypothalamic nuclei, Proc. Natl. Acad. Sci. USA 95 (1998) 741–746.
[10] J.K. Elmquist, R.S. Ahima, E. Maratos-Flier, J.S. Flier, C.B. Saper, Leptin activates neurons in ventrobasal hypothalamus and brainstem, Endocrinology 138 (1997) 839–842.
[11] P. Ernsberger, D.O. Nelson, Effects of fasting and refeeding on blood pressure are determined by nutritional state, not by body weight change, Am. J. Hypertens. 1 (1988) 153S–157S.
[12] J.S. Flier, E. Maratos-Flier, Obesity and the hypothalamus: novel peptides for new pathways, Cell 92 (1998) 437–440.
[13] C. Gerald, M.W. Walker, L. Criscione, E.L. Gustafson, C. Batzl-Hartmann, K.E. Smith, P. Vaysse, M.M. Durkin, T.M. Laz, D.L. Linemeyer, A.O. Schaffhauser, S. Whitebread, K.G. Hofbauer, R.I. Taber, T.A. Branchek, R.L. Weinshank, A receptor subtype involved in neuropeptide-Y-induced food intake, Nature 382 (1996) 168–171.
[14] A. Harfstrand, Intraventricular administration of neuropeptide Y (NPY) induces hypotension, bradycardia and bradypnea in the awake unrestrained male rat. Counteraction by NPY-induced feeding behaviour, Acta Physiol. Scand. 128 (1986) 121–123.
[15] D. Harland, T. Bennett, S.M. Gardiner, Cardiovascular actions of neuropeptide Y in the hypothalamic paraventricular nucleus of conscious Long Evans and Brattleboro rats, Neurosci. Lett. 85 (1988) 239–243.
[16] W.G. Haynes, W.I. Sivitz, D.A. Morgan, S.A. Walsh, A.L. Mark, Sympathetic and cardiorenal actions of leptin, Hypertension 30 (1997) 619–623.
[17] S.C. Heinrichs, F. Menzaghi, G.F. Koob, Neuropeptide Y-induced feeding and its control, Vitam Horm 54 (1998) 51–66.
[18] K.I. Honma, S. Honma, T. Hiroshige, Critical role of food amount for prefeeding corticosterone peak in rats, Am. J. Physiol. 245 (1983) R339–44.
[19] Y. Hu, B.T. Bloomquist, L.J. Cornfield, L.B. DeCarr, J.R. Flores-Riveros, L. Friedman, P. Jiang, L. Lewis-Higgins, Y. Sadlowski, J. Schaefer, N. Velazquez, M.L. McCaleb, Identification of a novel hypothalamic neuropeptide Y receptor associated with feeding behavior, J. Biol. Chem. 271 (1996) 26315–26319.
[20] M.A. Jones, J.M. VanNess, R.M. Casto, J.M. Overton, Influence of food deprivation on sympathetic support of blood pressure in the spontaneously hypertensive rat, Nutrition Res. 15 (1998) 1581–1594.
[21] H. Klemfuss, S. Southerland, K.T. Britton, Cardiovascular actions of neuropeptide Y and social stress, Peptides 19 (1998) 85–92.
[22] D.J. Marsh, G. Hollopeter, K.E. Kafer, R.D. Palmiter, Role of the Y5 neuropeptide Y receptor in feeding and obesity, Nat. Med. 4 (1998) 718–721.
[23] F.F. Matos, V. Guss, C. Korpinen, Effects of neuropeptide Y (NPY) and [D-Trp32]NPY on monoamine and metabolite levels in dialysates from rat hypothalamus during feeding behavior, Neuropeptides 30 (1996) 391–398.
[24] R.D. Myers, M.H. Wooten, C.D. Ames, J.W. Nyce, Anorexic action of a new potential neuropeptide Y antagonist [D-Tyr27, 36, D-Thr32]-NPY (27–36) infused into the hypothalamus of the rat, Brain Res. Bull. 37 (1995) 237–245.
[25] J.M. Overton, J.M. VanNess, R.M. Casto, Food restriction reduces sympathetic support of blood pressure in spontaneously hypertensive rats, J. Nutr. 127 (1997) 655–660.
[26] R.D. Palmiter, J.C. Erickson, G. Hollopeter, S.C. Baraban, M.W. Schwartz, Life without neuropeptide Y, Recent Prog. Horm Res. 53 (1998) 163–199.
[27] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, 2nd edn., Academic Press, Sydney, 1986.
[28] T. Pedrazzini, J. Seydoux, P. Kunstner, J.F. Aubert, E. Grouzmann, F. Beermann, H.R. Brunner, Cardiovascular response, feeding behavior and locomotor activity in mice lacking the NPY Y1 receptor, Nat. Med. 4 (1998) 722–726.
[29] A.K. Roscoe, S.M. Leach, J.W. Nyce, W.R. Wooles, Hypotensive effects of [D-Tyr27, 36, D-Thr32]-NPY-(27–36), Peptides 8 (1995) 1411–1415.
[30] A. Sahu, P.S. Kalra, S.P. Kalra, Food deprivation and ingestion induce reciprocal changes in neuropeptide Y concentrations in the paraventricular nucleus, Peptides 9 (1988) 83–86.
[31] K. Sato, J.T. Crofton, Y.X. Wang, L. Share, Effects of gender on the central actions of neuropeptide Y and norepinephrine on vasopressin and blood pressure in the rat, Brain Res. 689 (1995) 71–78.
[32] M.W. Schwartz, M.F. Dallman, S.C. Woods, Hypothalamic response to starvation: implications for the study of wasting disorders, Am. J. Physiol. 269 (1995) R949–R957.
[33] N.A. Scott, V. Webb, J.H. Boublik, J. Rivier, M.R. Brown, The cardiovascular actions of centrally administered NPY, Regul. Pept. 25 (1989) 247–258.
[34] E. Shek, M. Brands, J. Hall, Chronic leptin infusion increases arterial pressure, Hypertension 31 (part 2) (1998) 409–414.
[35] F.M. Siri, Sympathetic changes during development of cardiac hypertrophy in aortic-constricted rats, Am. J. Physiol. 255 (1988) H452–H457.
[36] S.J. Swoap, P. Boddell, K.M. Baldwin, Interaction of hypertension and caloric restriction on cardiac mass and isomyosin expression, Am. J. Physiol. 268 (1995) R33–R39.
[37] G. Van Dijk, A.E. Bottone, J.H. Strubbe, A.B. Steffens, Hormonal and metabolic effects of paraventricular hypothalamic administration of neuropeptide Y during rest and feeding, Brain Res. 660 (1994) 96–103.
[38] J.M. VanNess, R.M. Casto, J.E. DeMaria, J.M. Overton, Food restriction attenuates the blood pressure response to paraventricular hypothalamic nuclei lesions in aortic coarctation hypertension, Brain Res. 792 (1998) 237–245.
[39] J.M. VanNess, R.M. Casto, J.M. Overton, Antihypertensive effects of food-intake restriction in aortic coarctation hypertension, J. Hypertens. 15 (1997) 1253–1262.
[40] J.B. Young, L. Landsberg, Suppression of sympathetic nervous system by fasting, Science 196 (1977) 1473–1475.
[41] J.B. Young, D. Mullin, L. Landsberg, Caloric restriction lowers blood pressure in the spontaneously hypertensive rat, Metabolism 27 (1978) 1711–1714.