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Stimulation of NPY Y_2 receptors by $PYY_{3–36}$ reveals divergent cardiovascular effects of endogenous NPY in rats on different dietary regimens

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Nordheim, Ulrich, and Karl G. Hofbauer. Stimulation of NPY Y_2 receptors by $PYY_{3–36}$ reveals divergent cardiovascular effects of endogenous NPY in rats on different dietary regimens. *Am J Physiol Regul Integr Comp Physiol* 286: R138–R142, 2004. First published October 9, 2003; 10.1152/ajpregu.00374.2003.—In the present experiments the gut hormone peptide $YY_{3–36}$ ($PYY_{3–36}$), which inhibits neuropeptide Y (NPY) release, was used as a tool to study the cardiovascular effects of endogenous NPY under different dietary regimens in rats instrumented with a telemetry transmitter. In a first experiment, rats were placed on a standard chow diet ad libitum and in a second experiment on a high-fat diet ad libitum. After 6 wk, $PYY_{3–36}$ (300 μg/kg) or vehicle was injected intraperitoneally. In a third experiment, $PYY_{3–36}$ or vehicle was administered after 14 days of 50% restriction of a standard chow diet. In food-restricted rats, $PYY_{3–36}$ increased mean arterial pressure (7 ± 1 mmHg, mean ± SE, $P < 0.001$ vs. saline, 1-way repeated-measures ANOVA with Bonferroni *t*-test) and heart rate (22 ± 4 beats/min, $P < 0.001$) during 3 h after administration. Conversely, $PYY_{3–36}$ did not influence mean arterial pressure (0 ± 1 mmHg) and heart rate (-8 ± 5 beats/min) significantly in rats on a high-fat diet. Rats fed standard chow diet ad libitum showed an intermediate response (mean arterial pressure 4 ± 1 mmHg, $P < 0.05$, and heart rate 5 ± 2 beats/min, not significant). Thus, in our studies, divergent cardiovascular responses to $PYY_{3–36}$ were observed in rats on different dietary regimens. These findings suggest that the cardiovascular effects of $PYY_{3–36}$ depend on the hypothalamic NPY release, which is increased after chronic food restriction and decreased during a high-fat diet.

blood pressure; heart rate; sympathetic nerve activity; neuropeptide Y; peptide YY

NEUROPEPTIDE Y (NPY) is one of the strongest endogenous stimulators of food intake (13) and is abundantly expressed in hypothalamic feeding centers such as the arcuate (ARC) and paraventricular nucleus (PVN; 6, 7). It has been demonstrated that the hypothalamic content of NPY varies with nutritional state probably due to different NPY release (25, 28). In addition to its role in appetite control, NPY also decreases blood pressure, heart rate (HR), and plasma norepinephrine levels after injection into the PVN (10, 26, 27) or the nucleus of the solitary tract (NTS) (8). Consequently, NPY-containing neurons that project from hypothalamic feeding centers (e.g., ARC, PVN) to cardiovascular centers of the brain stem (e.g., NTS) might be involved in both the regulation of energy balance and the regulation of cardiovascular function.

NPY and peptide YY (PYY) are closely related polypeptides, which are composed of 36 amino acids and share considerable homology (in rats: 67%) (19). While NPY acts as a neurotransmitter, the two endogenous forms of PYY ($PYY_{1–36}$ and $PYY_{3–36}$) are gut-derived hormones secreted by intestinal endocrine cells (L cells) into the circulation after a meal (1, 22). $PYY_{1–36}$ binds and activates at least three NPY receptor subtypes (Y_1, Y_2, and Y_5) in rats and humans, whereas $PYY_{3–36}$ is selective for the Y_2 receptor (15). In a recent study it was demonstrated that the gut hormone $PYY_{3–36}$ physiologically inhibits food intake (4). In the present experiments, we used $PYY_{3–36}$, which inhibits NPY release by activation of presynaptic NPY Y_2 receptors, as a tool to analyze the cardiovascular effects of endogenous NPY under different dietary regimens. NPY Y_2 receptors are highly expressed on NPY neurons in the ARC, which is a brain area directly accessible to circulating hormones. For that reason we assumed that the peripheral administration of $PYY_{3–36}$ might influence cardiovascular regulation by an ARC-PVN-NTS neuronal projection and that the magnitude of the cardiovascular $PYY_{3–36}$ effects depend on the prevailing central NPY tone. To test this hypothesis, conscious, unrestrained, normotensive rats were studied under two extremes of caloric intake, namely chronic food restriction (high central NPY tone) and overfeeding with a high-fat diet (low central NPY tone).

MATERIALS AND METHODS

Animals. Ten-week-old male Sprague-Dawley rats were obtained from Iffa Credo, L'Arbresle, France. The rats were housed in individual plastic cages in a room with controlled temperature (21–22°C) and a 12:12-h light-dark cycle (lights on from 0600 to 1800). The rats were allowed 1 wk to get accustomed to the new environment before the telemetry surgeries were performed. After a recovery period of 2 wk postsurgery the different diet regimens were started. In a first experiment, rats ($n = 7$) were placed on a standard chow diet (SCD) ad libitum (Nafag Ecosan, Switzerland, NAFAG 3432, 3.0 kcal/g, 61.6% of total calories from carbohydrate, 24.8% of total calories from protein, and 13.6% of total calories from fat) and in a second experiment ($n = 7$) on a high-fat diet (HFD) ad libitum (Research Diets, D12451, 4.7 kcal/g, 35% of total calories from carbohydrate, 20% from protein, and 45% from fat). After 6 wk, saline (2 ml/kg) or porcine $PYY_{3–36}$ (300 μg/kg) was injected intraperitoneally 1 h before the onset of the dark phase. In a third experiment, saline or $PYY_{3–36}$ was administered in SCD-fed rats after 14 days of 50% food restriction ($n = 7$). All experiments were performed in accordance with the Swiss regulations for animal experimentation.

Transmitter implantation. Rats were anesthetized by inhalation of isoflurane (2–3 vol% in medicinal oxygen). The operation area was shaved and sterilized with iodine, and a 4- to 5-cm midline abdominal

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Table 1. *Baseline values of MAP, HR, BT, and LA after different dietary regimens*

	Standard Chow Diet 50% Food Restriction (2 wk)		Standard Chow Diet ad libitum (6 wk)		High-Fat Diet ad libitum (6 wk)	
	Light	Dark	Light	Dark	Light	Dark
MAP, mmHg	101±3	103±3[a,d]	103±3	110±3	102±3	109±3
HR, beats/min	264±6[c,f]	294±4[c,f]	318±10	380±8	330±7	380±7
BT, °C	36.9±0.1[b,e]	37.7±0.1[b,d]	37.4±0.1	38.2±0.1	37.4±0.1	38.0±0.1
LA, counts/min	1.3±0.2	3.5±0.1[e]	1.3±0.2	4.0±0.4	2.1±0.4[g]	5.0±0.2

Values are means ± SE, $n = 7$ (each group), 1-way repeated measures ANOVA followed by Bonferroni *t*-test. MAP, mean arterial pressure; HR, heart rate; BT, body temperature; LA, locomotor activity. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$: food restriction (50%) vs. standard chow diet ad libitum. [d]$P < 0.05$, [e]$P < 0.01$, [f]$P < 0.001$: food restriction (50%) vs. high-fat diet ad libitum. [g]$P < 0.05$: high-fat diet ad libitum vs. standard chow diet ad libitum.

incision was made. The intestines were gently retracted with saline-soaked sterile gauze, permitting access to the abdominal aorta from the renal arteries to the iliac bifurcation. The abdominal aorta was separated from the vena cava distal to the renal arteries. To occlude temporarily the abdominal aorta, a vascular clamp (Fine Science Tools) was used. While the aorta was clamped, the catheter of the telemetry transmitter (TL11M2-C50-PXT, Data Sciences International) was inserted and secured with a single drop of tissue adhesive (Vetbond). The vascular clamp was removed and the catheter entry site was checked for leakage. The transmitter was sutured to the inside surface of the peritoneum, and the abdominal and skin incisions were closed with a nonabsorbable suture (Ethicon, silk 3–0 and Prolene 4–0, respectively). All procedures were performed aseptically and according to the recommendations of the manufacturer (Data Sciences International).

Statistical analysis. Baseline values of mean arterial pressure (MAP), HR, body temperature (BT), and locomotor activity (LA) under different dietary regimens were registered by telemetry for 10 s every 30 min over 24 h. The time taken to change the cages and to determine body weight and food intake (usually 1 h) was excluded from analysis. Thus 11-h averages are shown for the light phase and 12-h averages for the dark phase. The values given in Table 1 represent a single 23-h period.

A higher sampling rate (i.e., 10 s every 10 min over 24 h) was chosen, when $PYY_{3–36}$ or vehicle was injected. Telemetry data were analyzed during 3 h (1800–2100) (Figs. 2 and 3) with the one-way repeated-measures ANOVA followed by Bonferroni *t*-test. Values are expressed as means ± SE.

Substances. Porcine $PYY_{3–36}$ (mol wt 3,980) was purchased from Neosystem (Strasbourg, France) and was dissolved in sterile saline immediately before intraperitoneal injection.

RESULTS

Effects of different dietary regimens. Body weight increased from 390 ± 6 to 491 ± 13 g ($P < 0.001$) in ad libitum SCD-fed rats during a 6-wk period and was significantly reduced after 2 wk of 50% food restriction (from 491 ± 13 to 418 ± 8 g, $P < 0.001$) (Fig. 1). In ad libitum HFD-fed rats, body weight increased from 389 ± 4 to 542 ± 12 g ($P < 0.001$). Thus an additional body weight increase of ~10% was observed in HFD-fed rats compared with SCD-fed controls. Daily food intake did not change throughout the experiment in SCD-fed controls (average over 6 wk: 86 ± 1 kcal/day). Rats on food restriction received 50% of their normal daily food intake (43 kcal/day). In rats on HFD, a strong increase of caloric intake was observed after the rats received the HFD (from 84 ± 2 kcal/day on *day 0* to 145 ± 9 kcal/day on *day 1*, $P < 0.001$). This effect was not maintained, but the daily caloric intake over 6 wk was still higher in rats on HFD compared with SCD-fed controls (99 ± 4 vs. 86 ± 1 kcal/day, $P < 0.01$).

Baseline values of MAP, HR, BT, and LA were significantly reduced after food restriction compared with ad libitum SCD-

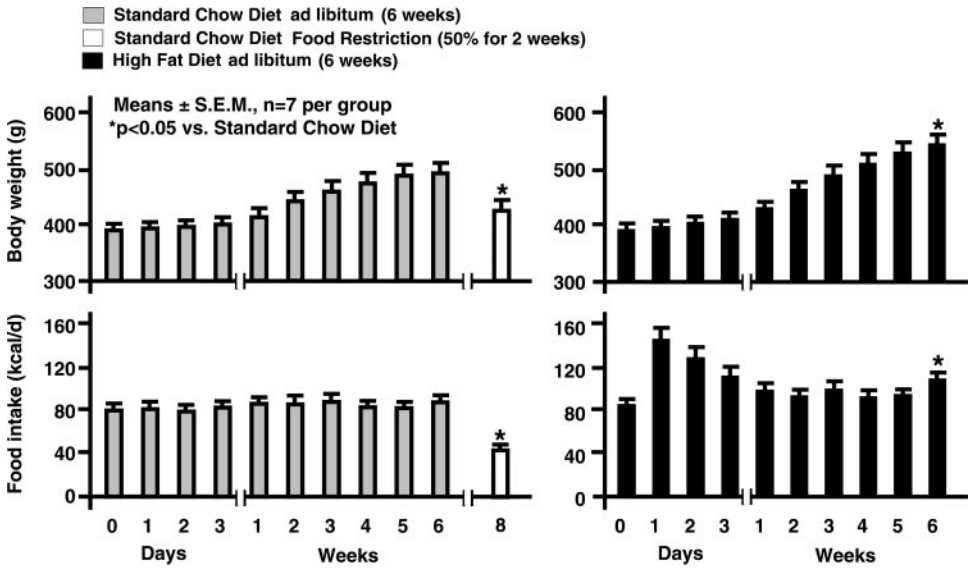

Fig. 1. Influence of a standard chow diet (SCD) ad libitum, 50% restriction of an SCD, and a high-fat diet ad libitum on body weight and 24-h food intake in male Sprague-Dawley rats ($n = 7$, each group). Values are means ± SE. *$P < 0.05$ vs. SCD ad libitum.

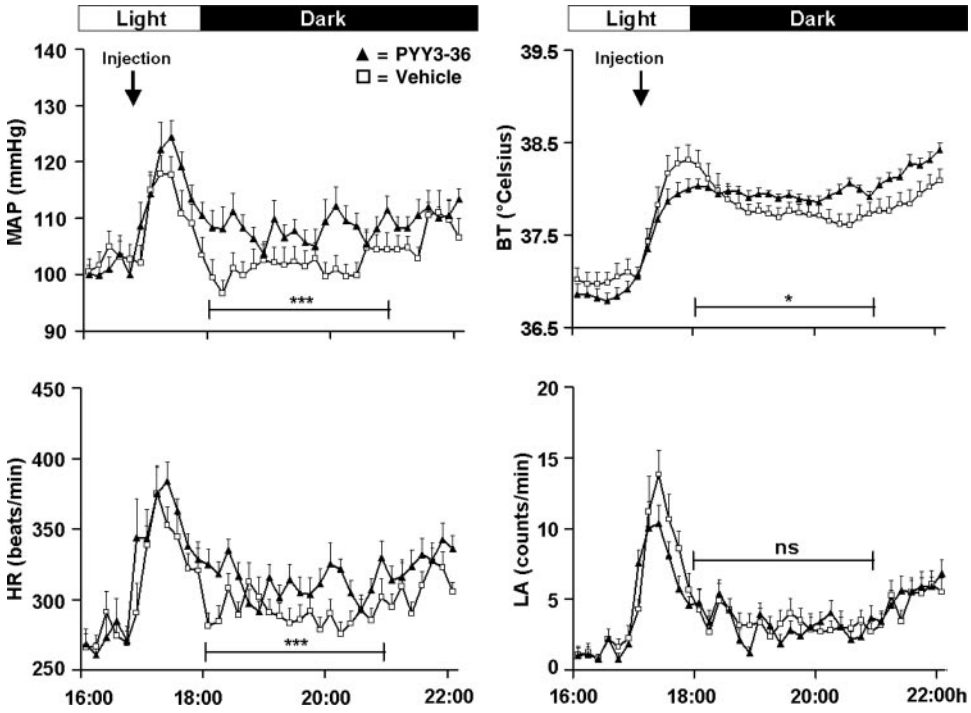

Fig. 2. Influence of intraperitoneal injection of peptide YY $(PYY)_{3–36}$ (300 μg/kg, ▲) or vehicle (saline, 2 ml/kg, □) on mean arterial pressure (MAP), heart rate (HR), body temperature (BT), and locomotor activity (LA) in SCD rats after 14 days of 50% food restriction. Values are means ± SE. Arrows indicate injection time (1700). Statistical evaluation of 3-h intervals (1800–2100, horizontal line) was performed by using the 1-way repeated-measures ANOVA followed by Bonferroni *t*-test. $*P < 0.05$, $***P < 0.001$, ns (not significant): $PYY_{3–36}$ vs. saline.

fed animals (Table 1). Changes of MAP, HR, BT, and LA were more pronounced during the dark phase (−7 ± 1 mmHg, −86 ± 6 beats/min, −0.5 ± 0.1°C, and −0.5 ± 0.4 counts/min; food restriction vs. SCD ad libitum) than during the light phase (−2 ± 1 mmHg, −54 ± 5 beats/min, −0.5 ± 0.1°C, and −0.0 ± 0.2 counts/min; food restriction vs. SCD ad libitum). Overfeeding with an HFD for 6 wk did not change baseline values of MAP, HR, and BT compared with SCD-fed controls, whereas LA tended to increase.

$PYY_{3–36}$ and food intake. Peripheral administration of $PYY_{3–36}$ (300 μg/kg ip) resulted in a slight reduction of 24-h food intake in ad libitum-fed SCD rats (79 ± 2 vs. 88 ± 2 kcal/day in saline-treated controls, $P < 0.05$, paired *t*-test) and ad libitum HFD-fed rats (91 ± 3 vs. 102 ± 5 kcal/day in saline-treated controls, $P < 0.05$). There was no difference in the 24-h food intake in food-restricted SCD-fed rats after $PYY_{3–36}$ administration because these rats always consumed all of the food that was offered to them.

Cardiovascular, temperature, and locomotor responses to $PYY_{3–36}$. Figure 2 shows the effects of $PYY_{3–36}$ after 2 wk of 50% food restriction, the group in which the strongest responses to $PYY_{3–36}$ were observed. During the last hour before injection, values for MAP, HR, BT, and LA were similar in the respective $PYY_{3–36}$- and vehicle-treated groups. Immediately after injection (1700), a strong transient rise in MAP, HR, BT, and LA occurred in all rats, which disappeared within 1 h (injection artifact). In the following stable period, MAP, HR, and BT were significantly elevated in $PYY_{3–36}$-treated rats compared with vehicle-treated controls. $PYY_{3–36}$ increased MAP by 7 ± 1 mmHg during the 3 h after administration ($P < 0.001$, 1-way repeated-measures ANOVA followed by Bonferroni *t*-test), HR by 22 ± 4 beats/min ($P < 0.001$), and BT by 0.2 ± 0.0°C ($P < 0.05$; Fig. 2). The cardiovascular and temperature responses occurred in the absence of any change in locomotor activity.

Figure 3 shows a summary of the cardiovascular, tempera-

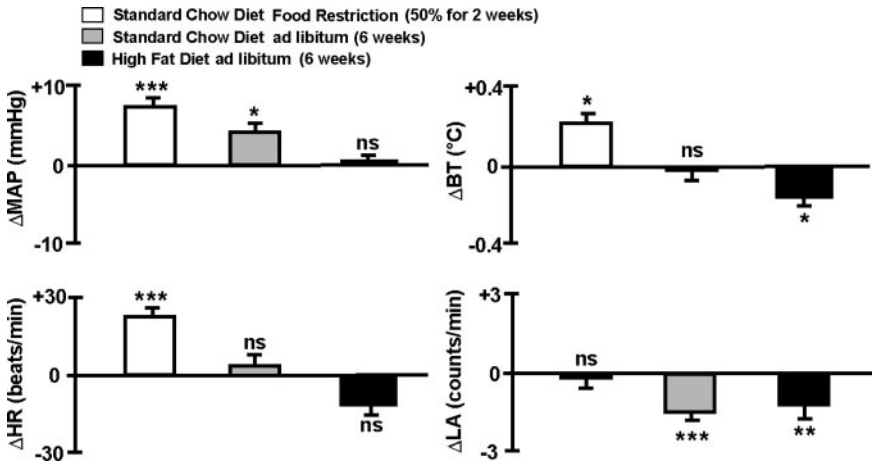

Fig. 3. Summary of the cardiovascular, temperature, and locomotor responses of $PYY_{3–36}$ after different dietary regimens. Delta (Δ) represents the difference between the response to vehicle and $PYY_{3–36}$ injections. After intraperitoneal administration of $PYY_{3–36}$ (300 μg/kg) or vehicle (saline, 2 ml/kg) 3-h intervals (1800–2100) were analyzed by using the 1-way repeated-measures ANOVA followed by Bonferroni *t*-test. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, ns: $PYY_{3–36}$ vs. saline.

ture, and locomotor responses of $PYY_{3–36}$ during different dietary regimens. In contrast to increased MAP, HR, and BT in food-restricted rats, $PYY_{3–36}$ did not change MAP (0 ± 1 mmHg) and HR (−8 ± 5 beats/min) in rats on an HFD. Rats on an SCD ad libitum showed an intermediate response (MAP 4 ± 1 mmHg, $P < 0.05$ and HR +5 ± 2 beats/min, not significant).

DISCUSSION

Adaptation to an HFD and food restriction. Caloric intake was higher in HFD than in SCD rats (total difference: +546 kcal after 6 wk), which explains the additional rise of body weight in HFD rats (51 g after 6 wk, 1 g fat = 7.7 kcal) and suggests that metabolism was increased in HFD-fed rats probably due to increased LA. Overfeeding with an HFD for 6 wk did not change MAP and HR significantly compared with SCD-fed controls. These results are consistent with a previous observation (24) that diets with an increased amount of fat do not significantly raise blood pressure and HR after 6 wk in conscious, unrestrained normotensive rats and suggest that overfeeding with an HFD is only associated with a small stimulation of cardiovascular sympathetic tone. Overfeeding with an HFD did not change BT either. However, during the dark phase, BT tended to decrease in HFD-fed rats compared with SCD-fed controls, which might be ascribed to the fact that lipids, a main constituent of the HFD, are less thermogenic than carbohydrates, a main constituent of the SCD (3). Most of the daily food intake occurs during the dark phase, which could explain why the slightly reduced BT values were only observed during this period.

The significant decrease in body weight after 2 wk of 50% food restriction was associated with strong reductions in MAP, HR, BT, and LA. Suppression of the sympathetic nervous system is the most likely explanation (30). The observation that these changes were stronger during the dark phase than during the light phase probably reflects high sympathetic nerve activity (SNA) during the dark phase and low SNA during the light phase. The different effects of sympathetic withdrawal during the dark and light phase resulted in blunted circadian rhythms in food-restricted rats.

$PYY_{3–36}$ and cardiovascular regulation. The primary new finding of the present study is that Y_2 receptor stimulation by $PYY_{3–36}$ exerted cardiovascular effects in conscious, unrestrained normotensive rats and that the magnitude of these cardiovascular effects differed depending on the dietary regimen. In food-restricted SCD-fed rats, $PYY_{3–36}$ increased MAP and HR, whereas in ad libitum HFD-fed rats, $PYY_{3–36}$ did not affect MAP and HR. We assume that this difference corresponds to increased hypothalamic NPY release after food restriction and decreased hypothalamic NPY release during overfeeding with an HFD (5, 6).

The different pattern of $PYY_{3–36}$ in food-restricted rats and rats on an HFD suggests opposite effects of central and peripheral NPY Y_2 receptor stimulation. In food-restricted rats (with high endogenous NPY tone), the central effects of NPY Y_2 receptor stimulation dominated, which resulted in an increase of MAP and HR. Conversely, the peripheral effects of NPY Y_2 receptor stimulation dominated in HFD-fed rats (with low central NPY tone), which tended to decrease HR probably due to presynaptic inhibition of sympathetic neurotransmitters such as norepinephrine (16, 18, 23). The fact that blood pressure did not decrease after $PYY_{3–36}$ in HFD-fed rats, which probably had an increased sympathetic tone, could be due to regionally selective vascular effects of Y_2 receptor stimulation. It has been shown that blood pressure was hardly affected after peripheral administration of the Y_2 receptor agonist $NPY_{13–36}$ in anesthetized rats (11), whereas cutaneous microvascular blood flow substantially increased. This observation could explain why $PYY_{3–36}$ injection induced a fall in BT in the HFD-fed rats (probably a consequence of an increase in cutaneous blood flow) while blood pressure remained unchanged.

In the present experiments we administered $PYY_{3–36}$ systemically, because it has been demonstrated that after peripheral administration $PYY_{3–36}$ acts on the ARC to stimulate presynaptic Y_2 receptors (4). This is probably due to the fact that the blood-brain barrier is absent or leaky in this brain region (13). The intracerebroventricular administration of $PYY_{3–36}$ does not appear to be a suitable approach to differentiate between the central and the peripheral cardiovascular actions of $PYY_{3–36}$, because it may lead to a different pattern of NPY receptor activation in the brain. This assumption is based on the observation that intracerebroventricular administration of $PYY_{3–36}$ in mice increases food intake (12, 14), an effect opposite to that observed after peripheral administration (4). These divergent responses of food intake to $PYY_{3–36}$ are probably due to the fact that after intracerebroventricular administration, $PYY_{3–36}$ penetrates more widely into the brain and may then act on Y_2 receptors in other brain regions and also on Y_5 receptors, for which $PYY_{3–36}$ exhibits a lower affinity (15). A different pattern of NPY receptor activation may not only elicit a different feeding response but also a different pattern of cardiovascular effects.

In SCD-fed controls, MAP was slightly elevated without a change of HR, which is consistent with a previous observation that intracerebroventricular injection of the Y_2 receptor-preferring agonist $NPY_{13–36}$ produces an increase in blood pressure without effect on HR in conscious rats (2). Moreover, central NPY Y_2 receptor stimulation via $NPY_{24–36}$ significantly increased blood pressure in anesthetized dogs (20) and mean arterial pressure tended to be lower in Y_2 receptor knockout mice (21).

The magnitude of the changes in MAP and HR observed in our studies might seem small but still be of clinical relevance. They are equal to those seen after food restriction or regular physical exercise in human subjects (29). Moreover, prospective clinical studies have demonstrated that even small blood pressure changes over a long period of time are associated with a considerable risk for cardiovascular diseases (17).

$PYY_{3–36}$ and BT. Intracerebroventricular administration of NPY or microinjection directly into the PVN have been shown to suppress the thermogenic SNA as demonstrated by direct measurement of the SNA to brown adipose tissue (9). Thus administration of $PYY_{3–36}$, which acts in the central nervous system to inhibit NPY release, should be associated with elevated thermogenic SNA and increased BT. In fact, we observed higher BT values after $PYY_{3–36}$ administration in our experiments, but only in food-restricted rats, which have a high central NPY tone. In ad libitum SCD-fed rats, this stimulatory effect on BT was not seen.

NPY Y_1 and Y_2 receptors in the peripheral nervous system are also involved in thermoregulation, because they modulate

vascular tone. It has been demonstrated that the activation of presynaptic Y_2 receptors in the periphery produces cutaneous vasodilation due to presynaptic inhibition of norepinephrine at blood vessels of the skin and superseded the postsynaptic Y_1 receptor-mediated vasoconstriction (11). The subsequent heat loss evoked by cutaneous vasodilation might explain the decrease of BT observed in HFD-fed rats after $PYY_{3–36}$ administration.

$PYY_{3–36}$ and locomotor activity. $PYY_{3–36}$ did not change LA in food-restricted SCD-fed rats but reduced LA significantly in ad libitum SCD- and HFD-fed rats. These findings indicate that the locomotor response did not contribute to increased MAP, HR, and BT observed in food-restricted SCD-fed rats after $PYY_{3–36}$ administration. Conversely, it may be that the LA after $PYY_{3–36}$ is related to the changes in food intake. LA was reduced when food intake was lowered by $PYY_{3–36}$ administration in the ad libitum SCD- and HFD-fed groups, whereas it remained unchanged in SCD-fed rats on food restriction.

In summary, divergent cardiovascular responses to $PYY_{3–36}$ were observed in rats on different dietary regimens. These findings suggest that the cardiovascular effects of $PYY_{3–36}$ depend on the preexisting hypothalamic NPY release and that central NPY has a tonic influence on blood pressure and HR, which becomes prominent during caloric deprivation.

GRANTS

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