Renal and cardiac neuropeptide Y and NPY receptors in a rat model of congestive heart failure

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Callanan EY, Lee EW, Tilan JU, Winaver J, Haramati A, Mulroney SE, Zukowska Z. Renal and cardiac neuropeptide Y and NPY receptors in a rat model of congestive heart failure. Am J Physiol Renal Physiol 293: F1811–F1817, 2007. doi:10.1152/ajprenal.00191.2007.—Neuropeptide Y (NPY) is a 36-amino acid peptide that is released with norepinephrine and stimulates vasoconstriction, vascular and cardiomyocyte hypertrophy via Y1 receptors (R) and angiogenesis via Y2R. Although circulating NPY is elevated in heart failure, NPY’s role remains unclear. Activation of the NPY system was determined in Wistar rats with the aortocaval (A−V) fistula model of high-output heart failure. Plasma NPY levels were elevated in A−V fistula animals (115.7 ± 15.3 vs. 63.1 ± 17.4 pM in sham, P < 0.04). Animals either compensated [urinary Na+ excretion returning to normal with moderate disease (COMP)] or remained decompensated with severe cardiac and renal failure (urinary Na+ excretion <0.5 meq/day), increased heart weight, decreased mean arterial pressure and renal blood flow (RBF), and death within 5–7 days (DECOMP). Cardiac and renal tissue NPY decreased with heart failure, proportionate to the severity of renal complications. Cardiac and renal Y1R mRNA expression also decreased (1.5-fold, P < 0.005) in rats with heart failure. In contrast, Y2R expression increased up to 72-fold in the heart and 5.7-fold in the kidney (P < 0.001) proportionate to severity of heart failure and cardiomyopathy. Changes in receptor expression were confirmed since the Y1R agonist, [Leu31, Pro34]-NPY, had no effect on RBF, whereas the Y2R agonist (13–36)-NPY increased RBF to compensate for disease. Thus, in this model of heart failure, cardiac and renal NPY Y1 receptors decrease and Y2 receptors increase, suggesting an increased effect of NPY on the receptors involved in cardiac remodeling and angiogenesis, and highlighting an important regulatory role of NPY in congestive heart failure.

Y1 receptor; Y2 receptor; renal blood flow; cardiac hypertrophy

Neuropeptide Y (NPY) is a 36-amino acid peptide that is colocalized with norepinephrine (NE) in sympathetic nerves innervating the cardiovascular system and is one of the most abundant peptides in the brain and heart (37). It exerts pleiotropic activities, ranging from the regulation of cardiovascular and neuroendocrine functions to the stimulation of food intake and obesity, via the activation of multiple G/o protein-coupled receptors (Y1-Y5) (33). Its release is stimulated by severe and prolonged stress and in many pathological conditions (33). Congestive heart failure (CHF) is one of such conditions of severe and chronic stress activation of the sympathetic nervous and endocrine systems. Previous studies showed that NPY plasma levels are elevated in patients with CHF, regardless of the etiology (15, 16, 28). The increase in plasma NPY during CHF may be significant to the clinical course since NPY plasma concentration appears to be an independent marker for mortality in heart failure patients (27). However, since NPY has multiple effects on the cardiovascular system, the role of NPY in the pathophysiology of CHF is unclear.

Studies have demonstrated that the majority of the cardiovascular responses to NPY administration are due to the activation of peripheral Y1 and Y2 receptors. The Y1 receptor is primarily a vascular receptor located on the smooth muscle cells of arteries and veins (23). Y1 receptor activation is responsible for the vasoconstriction and smooth muscle cell proliferation associated with systemic/local NPY administration (34). Synergistic or additive potentiation of other vasoconstrictors like NE and angiotensin II (ANG II) is also mediated through the Y1 receptor (23, 29). Y2 receptors are primarily found presynaptically on sympathetic, parasympathetic, and sensory nerves (25), and when activated, inhibit neurotransmitter release. Recently, however, Y2 receptors have also been found to function postsynaptically as a main receptor for NPY-mediated angiogenesis in peripheral ischemic conditions (13) and in tumors (10).

There are several reports linking NPY to CHF. Millar et al. (20) demonstrated that NPY stimulates hypertrophy of cardiomyocytes. In contrast, studies done by Allen et al. (1) showed beneficial effects of NPY on the kidneys; a diuretic and natriuretic action, even in the face of reduced renal perfusion. This finding has been supported by others showing that NPY administration decreases plasma renin activity in high-renin conditions like CHF and some forms of hypertension (22, 26, 31). Taken as a whole, these studies suggest that instead of potentiating the effects of vasoconstrictive agents like ANG II and NE, NPY may be acting to modulate excessive vasoconstriction and sodium retention seen in CHF, possibly through the Y2 receptor.

The objective of this study was to elucidate the changes in the NPY system in heart failure using an experimental model of high-output CHF. We examined the changes in plasma NPY, as well as the concentration of NPY in several different sympathecetically innervated tissues during the course of CHF. We also determined the expression of the Y1 and Y2 receptor genes, and whether this pattern of expression might account for differences in cardiac and renal NPY function in heart failure.

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METHODS

**Creation of an aortocaval fistula.** Male Wistar rats (250–350 g) were anesthetized with 25 mg/kg ip injection of tribromoethanol. An abdominal midline incision was made to visualize the abdominal aorta and vena cava. Aortocaval (A-V) fistulas were placed below the level of the renal arteries by the method established by Garcia and Diebold (7). Briefly, a 2-cm section of the vessels distal to the origin of the renal arteries was temporarily occluded (~30 s) with a pair of mini-clamps. At the midpoint between the two clamps, an 18-gauge needle was inserted through the wall of the aorta, advanced into the vena cava through the common wall between the vessels, and manipulated from side to side to widen the opening between the aorta and vena cava. The needle was then withdrawn, the aortic puncture was sealed with cyanoacrylate glue, clamps were removed, and abdominal incisions were closed. After the surgical procedure was completed (~10 min), the rats were given 0.2 ml of 40,000 U/ml penicillin and placed under a heat lamp until they recovered. The rats were then placed in metabolic cages to measure sodium balance for the remainder of the study. An age- and weight-matched group of rats underwent sham operations (the same procedure except for the needle puncture) and served as controls. All protocols were approved by the Animal Care and Use Committees of Georgetown University and in accordance with National Institutes of Health (NIH) guidelines.

**Chronic metabolic balance studies.** Rats housed in metabolic cages had their food intake, water intake, urine output, and fecal weight measured daily. Sodium intake was calculated by multiplying the concentration of the electrolytes in the rat chow by the total amount of food eaten per day. Urinary sodium was determined by flame photometer (IL-943, Instrumentation Labs). Daily fluid balance was determined by subtracting the daily urine volume from the amount of water the rats drank per day. Animals were monitored for 6–8 days to determine the severity of CHF. Rats with A-V fistula, which also demonstrated physical signs of CHF (i.e., lethargy and dyspnea) and had sodium excretion below 0.50 meq/day, were considered to be in decompensated (severe) heart failure. Rats excreting more than 0.50 meq/day of sodium were considered to be in compensated (moderate) heart failure. At the end of the 6- to 8-day period, the three groups were anesthetized, blood samples were taken via aortic puncture for determination of plasma NPY concentration, and a variety of sympathetically innervated organs (heart, spleen, adrenal medulla, kidneys) were removed and weighed for analysis of tissue NPY.

**Drug infusion studies.** In a separate experimental group, rats underwent either A-V fistula or sham surgery. The rats were then placed in metabolic balance and monitored for 5 days. At the end of the observation period, rats were anesthetized and prepared for acute studies. Rats in severe heart failure did not tolerate acute surgery and thus, the drug infusion studies were only performed on COMP A-V fistula rats. Male control (n = 5) and A-V fistula (n = 15) rats were anesthetized with 100 mg/kg ip inactin and a tube was inserted into the trachea to promote spontaneous breathing. Catheters (PE-50) were placed in the carotid artery (for blood pressure measurement), jugular vein (for infusion of 2% inulin), femoral vein (for saline, NPY, Y1 agonist, or Y2 agonist infusion), and bladder (for urine collection). The renal artery and vein were carefully separated without affecting the renal nerves and a Doppler flow probe (Valpey-Fisher) was placed around the renal artery for renal blood flow (RBF) measurement using a pulsed Doppler flowmeter (Department of Bioengineering, University of Iowa) (35). Inulin (2% in isotonic saline) was infused throughout the study at 0.20±0.05 ml/hr to replace fluid lost due to surgical manipulations and to ensure adequate urine production. Rats were allowed to equilibrate for 60 min before the experiment. Baseline mean arterial pressure (MAP) and RBF were measured and normal saline (through femoral catheter) was infused for 30 min. Following the saline, either NPY (200 or 400 ng/min), Y1 agonist [[Leu31, Pro34]-NPY, 200 or 400 ng/min], or Y2 agonist [NPY (3–36), 700 or 1,400 μg/min iv] was infused for 30 min. RBF was recorded every 5 min, and average RBF was calculated for the 30-min period with values printed out using the Buxco system (Buxco Biosystem XA version 2.10, Buxco Electronics, Wilmington, NC).

**Plasma and tissue processing for determination of NPY immunoreactivity.** Tissue (~50 mg) and plasma samples from the sham, compensated (COMP), and decompensated (DECOMP) rats were placed in Eppendorf tubes containing 2 ml of 1 M acetic acid, placed in a 100°C water bath for 20 min, and then sonicated. Ten microliters of the tissue/acetic acid solution were removed from each sample to determine protein concentration and the remainder was spun at 20,000 g for 60 min. The supernatant was removed and placed in (12×75 mm) polypropylene tubes while the pellet was washed with 500 μl of 1 M acetic acid and resupined for 20 min. The second supernatant was added to the first; the samples were dried in a high-speed vacuum and stored at 4°C until used for NPY radioimmunoassay.

**Northern blot analysis.** Tissue samples (0.5 g) were homogenized in a guanidine isothiocyanate/β-mercaptoethanol solution and RNA was purified by overnight ultracentrifugation in CsCl at 32,000 rpm at 24°C. The RNA pellet was suspended in a 0.3 M sodium acetate solution, precipitated overnight using cold ethanol, and resuspended in Tris-EDTA (ethylenediaminetetraacetic acid) (TE) buffer.

Ten micrograms of total RNA were separated by electrophoresis on a 1.2% denaturing agarose gel with formaldehyde, transferred to a positively charged nylon membrane by capillary blotting, and fixed by exposure to UV light for 1 min. The membranes were prehybridized in buffer containing 50% formamide, 5× SSC, 5× Denhart’s solution, 1% SDS, 100 μg/ml of salmon sperm DNA, and 5% Dextran sulfate at 42°C for 1 h. Hybridization was carried out at 42°C overnight in prehybridization buffer supplemented with cDNA probe labeled with [32P] using Prime-a-Gene labeling kit (Promega). The Y1 receptor probe, provided by Dr. D. Larhammar, was a 1.4-kb Xhol-EcoRI fragment of human Y1 receptor cDNA containing part of the COOH-terminal coding region and 3′-untranslated region (11). The Y2 receptor mRNA was detected using cDNA probe containing the entire reading frame of the human Y2 receptor (24). After hybridization, membranes were washed and exposed to the Kodak X-ray film overnight at ~70°C. Northern blots were scanned using a digital camera and density of the bands was quantified using NIH Image software.

**Statistical analysis.** The SigmaStat and one-way repeated-measures ANOVA with post hoc Dunnett’s t-test were used for all statistical analysis (P ≤ 0.05 was considered significant). Data are means ± SE for indicated number of n, and graphed using SigmaStat, Microsoft Excel, GraphPad Prism, and Origin 5.0.

RESULTS

**Daily sodium excretion.** Daily urinary sodium excretion is depicted in Fig. 1A. Sham-operated controls (n = 5) demonstrated a postsurgical reduction in sodium excretion for 1 day and were back excreting presurgical levels of sodium by postoperative day 2. In rats with compensated heart failure (n = 9), urinary sodium excretion was significantly reduced for several days following A-V fistula surgery (average Na+ excretion days 1–4: COMP: 1.10 ± 0.29 vs. sham: 2.07 ± 0.23 meq/day, D = 0.04); however, by postsurgical day 5, COMP rats were excreting levels similar to the sham-operated controls (average Na+ excretion days 5–8: COMP: 2.52 ± 0.16 vs. sham: 2.35 ± 0.05 meq/day, D = 0.37). In contrast, sodium excretion was significantly reduced in rats with decompensated heart failure (n = 6) as daily sodium excretion never increased over 0.25 ± 0.22 meq/day throughout the experimental period (P < 0.001 vs. sham and COMP).

Rats with decompensated heart failure experienced many of the symptoms commonly associated with CHF, such as dys-
pneumonia, lethargy, pallor in the extremities, and a reduction in appetite. As mentioned above, rats in decompensated heart failure ate significantly less on a daily basis than either sham or compensated rats. To ensure that differences seen in the sodium excretion of the DECOMP group were not due to reduced food intake, a separate group of sham-operated rats was fed the daily food intake of the decompensated rats. Pair-fed sham (PFS) rats excreted less sodium than either compensated or nonpair-fed sham rats. However, they excreted significantly more sodium per day compared with decompensated rats (PFS: 50% in the hearts of rats with A-V fistula compared with sham controls; P < 0.05; Fig. 2A). In contrast to what was seen with the NPY-Y1 receptor, the heart and kidney tissues taken from rats with A-V fistula demonstrated a dramatic increase in NPY-Y2 receptor mRNA expres-
sion, depending on severity of CHF. Compared with sham, NPY-Y2 receptor mRNA was increased 30- and 75-fold over control levels in COMP and DECOMP rats, respectively (P < 0.05; Fig. 4A). Similar results were found in the kidney tissue, with significant 2.5- and 6-fold increases in COMP and DECOMP rats, respectively (P < 0.05 vs. sham; Fig. 4B).

Effect of NPY, Y1 agonist, and Y2 agonist on RBF. As mentioned above, the acute studies were only able to be performed in the COMP A-V fistula animals. Therefore, the following results apply only to the COMP state of heart failure. Infusions of low concentration (200 ng/min) of NPY, Y1 {[Leu31, Pro34]-NPY}, or Y2 (NPY 3–36) agonist did not significantly affect RBF (data not shown). Figure 5A illustrates the change in RBF in sham and A-V fistula group (COMP only) in response to the Y1 agonist [Leu31, Pro34]-NPY (400 ng/min) compared with saline infusion. In sham rats, RBF decreased during infusion of [Leu31, Pro34]-NPY (P < 0.001 vs. saline). RBF was not affected by the Y1 agonist in the A-V fistula group.

In response to the Y2 agonist (NPY 3–36) (400 ng/min), RBF was increased 10% in both sham and A-V fistula rats compared with saline control period (P < 0.05 vs. saline in each group; Fig. 5B).

The effects of NPY on RBF are depicted in Fig. 5C. NPY significantly reduced RBF in both sham (P < 0.001 vs. saline) and the A-V fistula group (P < 0.001 vs. saline).

DISCUSSION

Numerous studies have reported that the actions of NPY are altered in both animal models and in humans with CHF (15, 16, 28, 32). In healthy subjects and in animals, NPY via Y1 receptors acts as a vasoconstrictor, potentiating the effects of other like agents, such as NE and ANG II (4, 19, 21). In heart failure, NPY’s vasoconstrictive properties were found to be attenuated and the natriuretic/afterload reducing actions enhanced (1). In contrast, in healthy individuals and animals, Y2 receptors act primarily as inhibitory presynaptic receptors, inhibiting NE and NPY release (9); or as a stimulatory angio- genetic postsynaptic receptor (36). Its role in CHF has never been addressed. Our present study demonstrates that in the high-output heart failure model, the NPY system and its Y1 and Y2 receptors in the heart and the kidneys are differentially regulated and appear to play a compensatory role.

The A-V fistula model of CHF exhibits cardiomegaly, depressed MAP and RBF, and produces both moderate (COMP, compensate and excrete sodium) and severe (DECOMP, retain sodium and expire) disease. The high-output CHF model used in this set of experiments revealed the changes in the NPY system, similar to those reported in human studies (15). Our analysis began with a characterization of this model of heart failure. As expected, two forms of disease were demonstrated, differentiated by the level of urinary Na⁺ excretion.
In general, rats subjected to an A-V fistula demonstrated an increase in total heart weight, a decrease in MAP and RBF (Fig. 1, C–E), an increase in plasma NPY concentrations, and a decrease in peptide levels in almost all major sympathetically innervated organs (Fig. 2). This, most likely, reflected a marked overall increase in sympathetic activity, known to accompany CHF (17). As hypothesized with heart failure, the discrepancy in NPY levels in plasma and tissue may be attributed to the potential exhaustion in NPY-producing capabilities in each organ, which may have released their NPY into the systemic circulation as a result of sympathetic hyperactivity (18). This resulted in a high plasma NPY levels compared with decreased NPY concentrations in all organs including adrenal glands.

![Fig. 3. NPY Y1 receptor expression in heart failure. A: NPY Y1 receptor mRNA in the heart. Both COMP (n = 9) and DECOMP (n = 6) rats demonstrated a significant decrease in expression of Y1 mRNA compared with sham (n = 5). *P < 0.05 vs. sham. B: NPY Y1 receptor mRNA in the kidney. Both COMP (n = 9) and DECOMP (n = 6) rats demonstrated a significant decrease in expression of Y1 mRNA compared with sham (n = 5). *P < 0.05.](image)

![Fig. 4. NPY Y2 receptor expression in heart failure. A: NPY Y2 receptor mRNA in the heart. Both COMP (n = 9) and DECOMP (n = 6) rats demonstrate a significant increase in expression of Y2 mRNA, with DECOMP rats increasing expression beyond COMP rats. *P < 0.05 vs. sham (n = 5). #P < 0.05 vs. COMP. B: NPY Y2 receptor mRNA in kidneys. Both COMP (n = 9) and DECOMP (n = 6) rats demonstrate a significant increase in expression of Y2 mRNA, with DECOMP rats increasing expression beyond COMP rats. *P < 0.05 vs. sham (n = 5). #P < 0.05 vs. COMP.](image)

![Fig. 5. Effect of NPY, Y1R, and Y2R agonists on RBF in control and A-V fistula rats. A: effect of Y1 agonist on RBF. High-dose (400 ng/min) infusion of the Y1 agonist reduced RBF in the sham (n = 5) group but did not alter RBF in A-V fistula rats (COMP only, n = 15). *P < 0.05 vs. saline. B: effects of Y2 agonist on RBF. High-dose (400 ml/min) infusion of the Y2 agonist enhanced RBF in both sham (n = 5) and A-V fistula rats (COMP only, n = 15) compared with saline. *P < 0.05 vs. saline. #P < 0.0001 vs. saline. C: effects of NPY on RBF. High-dose (400 ml/min) infusion of NPY reduced RBF in both sham (n = 5) and A-V fistula rats (COMP only, n = 15). #P < 0.0001 vs. saline.](image)
The present studies confirmed and extended previous reports by demonstrating a differential pattern of expression of NPY and its major receptors, Y1 and Y2, which may have important implications in the progression of CHF. Interestingly, only the DECOMP group displayed a decrease in ventricular NPY levels (Fig. 2D), consistent with what was reported for CHF patients (2, 15, 16): this was also observed in the kidney (Fig. 2G). In addition, our study demonstrated a negative association between cardiac NPY concentration and the severity of heart failure (Fig. 2, C and D). Unlike previously reported observations, however, our studies included an examination of renal NPY content in healthy and CHF animals.

With regard to the kidney, high renin levels have been associated with the development of severe CHF. Interestingly, only rats in severe heart failure demonstrated a reduction in kidney NPY concentration (Fig. 2G). Since renal NPY depletion, like that in the heart, may indicate excessive NPY release from hyperactive sympathetic nerves, these data suggest that renal NPY may contribute to the severity of heart failure in these rats. However, previous studies showed NPY to reduce the release of renin in high-renin states like CHF (22, 31). Furthermore, Winaver et al. (30) showed that rats in severe heart failure display markedly increased plasma renin-angiotensin levels, while rats in moderate heart failure do not. Thus we hypothesize that while increased release of NPY in the kidneys may be beneficial, rats that exhausted their renal stores of NPY are unable to inhibit renin release, allowing for increased ANG II to further impair cardiovascular function.

In addition to determining the NPY content in different tissues, this study also examined the mRNA expression of NPY-Y1 and NPY-Y2 receptors in the hearts and kidneys of rats with moderate and severe heart failure. mRNA of both the Y1 and Y2 receptor was altered in rats with CHF. Y1 mRNA was significantly reduced in both the hearts and kidneys of COMP and DECOMP rats, dependent on severity of CHF (Fig. 3). This was similar to what is known to occur with \( \beta_1 \)-adrenergic receptor mRNA in patients with CHF (3), suggesting that both may reflect receptor downregulation due to enhanced release of sympathetic neurotransmitters during CHF-induced sympathetic activation. Conversely, the expression of Y2 receptor mRNA was markedly increased in the heart and kidney of rats with CHF (Fig. 4). This suggests that while the effects of Y1 receptors are attenuated in both the heart and the kidney, at the same time, the effects of Y2 receptors are enhanced. Subsequently, we investigated whether these changes in receptor mRNA expression were associated with alterations in kidney function.

In a separate group of CHF rats, we studied the renal blood responses to specific NPY-Y1 and -Y2 receptor agonists. Animals that underwent an A-V fistula, whose basal RBF was lower than in control rats, exhibited an attenuated response to the RBF-lowering effects of Y1 agonist, [Leu31, Pro34]-NPY (Fig. 5A), presumably due to a downregulation of Y1 receptors. In contrast, the Y2 agonist (NPY3–36) tended to increase RBF (Fig. 5B) in CHF as well as in sham, suggesting functional Y2 receptors.

The differential changes in Y1 and Y2 receptor expression may be an important counterregulatory response to limit the excessive vasoconstriction seen in CHF by 1) a reduction in Y1 receptor-mediated vasoconstriction, direct and indirect via other vasoconstrictors such as NE or ANG II, 2) enhancement of the angiogenic effects of NPY via postsynaptic endothelial Y2 receptors (36) in peripheral and coronary vasculatures, and 3) an anti-adrenergic effect of NPY via presynaptic Y2 receptors to reduce NE release and hence, limit its deleterious activity in CHF. Although the expression of mRNA and protein level can be used as preliminary indicators of NPY receptor’s functionality in CHF, further studies are needed to investigate NPY signaling pathways and functional consequences in CHF.

It is interesting to note that NPY itself decreased RBF in CHF kidney (Fig. 5C), even in the presence of increased Y2 receptor expression. A likely explanation for this is the involvement of another receptor type, the Y5 receptor. As reported by our group (14, 23), the Y5 receptor, which is induced by tissue ischemia and injury (12), has amplifying effects on Y1 receptor-mediated mitogenic effects of the peptide (23). Vascular hypertrophy has previously been shown to increase responsiveness of the vessels to vasoconstrictors via purely structural reasons (Folkov’s theory) (5). Therefore, when NPY, a nonselective Y1, Y2, and Y5 agonist, was infused, it might have been still effective in reducing RBF in CHF kidney by utilizing its Y5 receptors, despite the significant decrease in Y1 receptor expression. Thus, an overall effect of NPY in the renal circulation in CHF may be a net effect of enhanced vasoconstriction, vascular hypertrophy, and increased blood flow via Y2 receptors, either due to vasodilation and increased angiogenesis.

An alternative or additional possibility is that the changes in NPY receptor populations in this model of CHF are also associated with alterations in NPY metabolizing enzymes, specifically dipeptidyl peptidase IV (DPPIV). It has been shown that NPY (3–36), the end product following cleavage of NPY by DPPIV, is an endogenous Y2/Y5 receptor-prefering ligand (8). If this enzyme is upregulated along with the Y2 receptors, as we previously showed in other ischemic states (13), then subjects with CHF would have an innate mechanism for controlling excessive NE and renin release. Overall, characterizing the role of DPPIV and other NPY receptors in CHF would be useful to determine NPY’s role in CHF.

The heart failure-induced differential regulation of the NPY system suggests that NPY is an important neurovascular modulator in the development of CHF-related pathology. Further studies are needed to determine the factors contributing to whether NPY acts to compensate or exacerbate the development of the disease; as it is capable of deteriorating the conditions with excessive vasoconstriction and cardiac hypertrophy via Y1 receptors and enhancing the cardiovascular compensatory mechanisms, such as angiogenesis via Y2 receptors.

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