Neuropeptide Y and $Y_1$-receptor agonists increase blood flow through arteriovenous anastomoses in rat tail

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Heath, Martha E. Neuropeptide Y and $Y_1$-receptor agonists increase blood flow through arteriovenous anastomoses in rat tail. J. Appl. Physiol. 85(1): 301–309, 1998.—The purpose of this study was to characterize neuropeptide Y (NPY)-induced vasodilation in the rat tail. Sterile surgical technique was used (with pentobarbital sodium anesthesia) to equip rats with a jugular catheter and a blind-ended thermocouple reentrant tube next to the carotid artery. Tail skin and core temperature were measured with thermocouples during experiments. Tail skin blood flow was monitored with a laser Doppler flowmeter, and tail total blood flow and volume were measured with plethysmography. After baseline data were collected, saline, NPY (16, 32, 64, and 128 µg/kg), [Leu$^{31}$ Pro$^{34}$]NPY (63.25 µg/kg), or NPY[13–36] (44.7 µg/kg) was administered intravenously. Tail total blood flow, volume, and tail skin temperature increased, whereas tail skin blood flow and core temperature decreased in response to both NPY- and the $Y_1$-receptor agonist [Leu$^{31}$ Pro$^{34}$]NPY but not in response to saline or NPY[13–36]. Studies conducted with the use of color microspheres demonstrated that arteriovenous anastomoses are involved in this NPY-induced vasodilation.

Neuropeptide Y (NPY) is a 36-amino acid peptide neurotransmitter that occurs, in separate vesicles, in the same sympathetic adrenergic fibers as does norepinephrine (NE) (8, 26). It also coexists with vasoactive intestinal peptide (VIP) in peripheral non-noradrenergic neurons (25), occurs in the adrenal medulla, and is one of the most abundant of all neuropeptides found in the brain (5, 39).

Six NPY-receptor subtypes have been identified (5, 40) thus far. Studies using C-terminal peptide fragments of NPY at the synaptic cleft revealed two receptor subtypes (39): $Y_1$ receptors, which were postsynaptic and occurred in the vascular smooth muscle, and $Y_2$ receptors, which were presynaptic and inhibited NE release (39). Whereas $Y_1$ and $Y_2$ receptors showed similar affinities for NPY and peptide YY (PYY), a third receptor ($Y_3$) (1) showed different affinities for these neuropeptides. Recently, several more receptors ($Y_4$, $Y_5$, and $Y_6$) have been identified through cloning methods (13–15).

NPY is highly vasoactive. Both peripheral and central administration alters cardiovascular function (39). Increased blood pressure and resistance in peripheral vascular beds and other tissues, as well as reduced heart rate, have been reported (see 5, 37). In vitro studies of the rat tail artery have shown that NPY caused a slow depolarization and concentration-dependent contraction via a direct effect on arterial smooth muscle cells (31). In vivo studies, in humans and other mammals, have demonstrated marked reduction in blood flow (BF) in the human forearm, and in brain, heart, kidney, pancreas, thyroid, spleen, skeletal muscle, and intestine in response to exogenous NPY (27, 39). NPY has been reported to cause constriction in both arteries (cerebral, coronary, skeletal muscle) and veins (iliac, femoral) in the guinea pig and rat (6).

In striking contrast to these previous reports, Heath and Thomas (22) demonstrated that NPY caused a pronounced increase in total BF (BF$_{tot}$), as measured in the rat tail by venous occlusion plethysmography (VOP). The NPY-induced increase in BF$_{tot}$ was accompanied by a marked increase in tail volume, an increase in tail skin temperature (T$_{sk}$), but a decrease in superficial skin microvascular BF (BF$_{sk}$).

These observations suggest, for the following reasons, the hypothesis that arteriovenous anastomoses (AVAs) participate in the NPY-induced increase in BF$_{tot}$. AVAs, which are abundant in the rat tail skin (12), are relatively large-diameter connections between arteries and veins that allow an increase in nonnutrient “thermoregulatory” BF in the skin (12). When AVAs in the skin open, there are increases in the diameter of blood (22), in total BF$_{sk}$, and in T$_{sk}$, because more heat is brought to the skin by the greater volume of blood flowing through it. There is also often a reduction in the microvascular BF through capillaries, as blood flows by another path of lesser resistance (20, 22). These are exactly the changes observed in the rat tail in response to NPY (22).

AVA BF is important in thermoregulatory mechanisms, such as cold-induced vasodilation and peripheral vasoconstriction during heat stress; these are potentially important to medical conditions such as non-freezing cold injury, heat syncope, and heat stroke. Therefore, further study of NPY-induced increase in BF$_{tot}$ in the rat tail is warranted. The specific aims of this study were to 1) document the dose-response relationship for tail BF (BF$_{tot}$ and BF$_{sk}$), 2) test the hypothesis that AVAs participate in the NPY-induced vasodilation, and 3) assess the NPY-receptor subtypes involved in the vasodilatory response through the use of the $Y_1$- and $Y_2$-receptor antagonists ([Leu$^{31}$ Pro$^{34}$]NPY, and NPY[13–36], respectively).

METHODS

Animals and surgical preparation. Twenty-one male Long-Evans rats (weighing 290–310 g) were studied. All rats were equipped with a cannula (S-26, ITT, Life Science) in a jugular vein, and some were equipped with a blind-ended reentrant tube sutured to the muscle adjacent to the carotid artery. A thermocouple was inserted into the reentrant tube for measurement of body core temperature (T$_c$). These sterile surgical...
procedures were done while the rats were fully anesthetized with ~50 mg/kg pentobarbital sodium.

Measurements. The temperature of the air (Ta), Tc, and Tsk was measured using 40-gauge thermocouples. Tail BFtot was measured in the tail by VOP. A mercury-in-Silastic strain gauge (model EC-4; D.E. Hokanson, see Ref. 21) connected to an electronic plethysmograph (model BFM 403A; TSI Laserflo; see Ref. 21). So that hair would not interfere with laser Doppler, VOP BF, or Tsk measurements, the hair was removed from the tail by using a depilatory.

Preparation for experiments. Rats were anesthetized with ~50 mg/kg pentobarbital sodium and were gently introduced into a cylindrical Plexiglas rat restrainer. The restrainer allowed free access to the hind legs and tail and to the end of the cannula and reentrant tube located between the shoulders. Tail BFtot is measured by using a pneumatic venous occlusion cuff, which must be positioned at the base of the tail, and a mercury-in-Silastic strain gauge that measures changes in volume of the tail during the periodic occlusions. The latter had to be positioned midway along the tail (e.g., 7–10 cm from base of the tail) to avoid artifacts either from being too close to the cuff or from being in a region (tail tip) where the radius is too small. A laser Doppler flow probe and a thermocouple were positioned on the skin adjacent to each other and as near to the strain gauge as possible (e.g., 6–8 cm from the base of tail). A BFsk reading of 5 ml·min⁻¹·100 ml tissue⁻¹ was used as the minimum acceptable baseline value. If BFsk was lower than this, then the laser Doppler probe was repositioned until an acceptable reading was obtained. All instrumentation was connected to an IBM-compatible computer via an analog-to-digital converter (Keithley). Thermocouple and laser Doppler channels were sampled at 1-s intervals and averaged for 20 s. The VOP measure of tail BFtot was done at 20-s intervals. The occlusion cuff was inflated to 50–55 mmHg for 5 s, and tail BFtot was assessed between the 2nd and 4th s of the cuff inflation.

NPY, NE, [Leu³¹ Pro³⁴]NPY, and NPY[13–36] protocols. In preliminary studies, doses of 32 and 64 µg/kg of NPY were shown to result in plasma levels of 2.0–2.5 pmol/ml of NPY in 300-g rats. The range of plasma levels observed in rats is 0.3–0.4 pmol/ml in baseline (control) conditions, and 1.2–1.5 pmol/ml in conditions of cold stress induced by 300-g rats. The range of plasma levels observed in rats is preliminary studies, doses of 32 and 64 µg/kg of NPY were equimolar to 64 µg/kg of NPY (4). NE (5), 32 (5), and 64 (n = 7), or 128 (n = 7) µg/kg NPY were, therefore, used in the present study to generate plasma levels similar to those found during stress in rats. The doses of [Leu³¹ Pro³⁴]NPY (63.25 µg/kg) and NPY[13–36] (44.7 µg/kg) administered were equimolar to 64 µg/kg of NPY (n = 4). NE (n = 2) was delivered in a dose of 400 µg/kg, a dose known to invoke its normal vasoconstrictive effect.

Fully instrumented rats rested in the restrainer for 15–30 min before the intravenous administration of NPY (16, 32, 64 or 128 µg/kg), NE (400 µg/kg), the Y₁-receptor agonist [Leu³¹ Pro³⁴]NPY (63.25 µg/kg), the Y₂-receptor agonist NPY[13–36] (44.7 µg/kg), or saline control. The volume of all injections was 300 µl, and injections were delivered over a 2-min period. Baseline recording was begun 5 min preceding the injection, and measurements were continued for at least 35 min postinjection. All experiments were done at Ta of 24–26°C.

Use of color microspheres to assess NPY effect on AVAs. Color microspheres (Interactive Medical Technologies, Los Angeles, CA) of 15-µm diameter were used to assess whether AVAs in the rat tail are involved in the NPY-induced increase in BFtot. Microspheres of this diameter can pass through AVAs but will be caught in the smaller diameter capillaries. Thus microspheres infused into the blood supply of the tail will end up in one of two places. Either they pass through AVAs in the rat tail and, after passing through the heart, end up in the capillaries of the lungs, or they will be caught in the capillaries of the tail tissues.

For these experiments, a second cannula was surgically introduced into the arterial blood supply to the tail, in the distal region of the descending aorta, well distal to the major blood supply to the hindlimbs, and just proximal to the caudal artery. Most microspheres infused via this cannula must flow into the caudal artery. The only other possibility is the very few vessels feeding the skin and muscle tissues of caudalmost region of the body, in which case the microspheres would either be trapped in those capillary beds or pass through AVAs and be trapped in the lungs. Successful experiments were completed on eight rats. Approximately 0.5 million color microspheres of 15-µm diameter were infused in the arterial cannula 1–2 min after administration of saline (300 µl iv; red microspheres; control) and 1–2 min after a subsequent administration of NPY (64 µg/kg in 300 µl iv; violet microspheres). The rats were killed 10 min after completion of the injection protocol. Tissue samples of the lung and skin midway along the tail (a section from 4–10 cm from base of tail) were taken immediately and sent to Interactive Medical Technologies. The number of microspheres of each color present in the tissue samples was counted by and reported by Interactive Medical Technologies.

Data presentation and statistical analysis. The data collected at 1-min intervals are provided from one representative experiment in which NPY, NE, [Leu³¹ Pro³⁴]NPY, and NPY[13–36] were administered. To summarize the BFtot and BFsk responses to NPY, the mean values for each 5-min period, including baseline and up to 40 min postadministration, were calculated for each experiment. The mean ± SD of the responses for each dose of NPY and for physiological saline were then calculated. Analysis of variance (not repeated measures) and Dunnett’s multiple-comparison test were used to assess whether the BFtot and BFsk responses to different doses of NPY were significantly different from responses to saline (control) administration. Dunnett’s test is appropriately used when one data group is the control (saline) to which all other groups are compared. Paired t-tests were used to assess whether there were more microspheres in the lung than in the tail skin tissue after saline and NPY administration (n = 8).

RESULTS

Effect of NPY on BF and body temperatures. Figure 1 (left) illustrates the effects of 64 µg/kg exogenous NPY on (top to bottom) BFtot, BFsk, and Tsk, in the rat tail in one experiment. The effect of NPY has an immediate pronounced dynamic phase that is of short duration and is followed by a prolonged and less pronounced static phase. The dynamic phase included an immediately marked increase in tail BFtot and tail volume that peaked within 1–3 min. Concurrent with the increase in BFtot is an increase in tail Tsk, and a consistent 1–3% increase in total tail volume (not shown) is observed as a pronounced upward shift in the baseline of the analog and digitized plethysmographic record. In contrast, BFsk in the tail declined to <50% of baseline within 1–3 min, and Tc declined by up to 1.5°C. This dynamic
Fig. 1. Representative experiments in which neuropeptide Y (NPY; left) and norepinephrine (NE; right) were administered to rats. NPY causes marked increase in total tail blood flow (BF

\[ \text{BF}_{\text{tot}} \text{ (BT)} \], and skin temperature (\( T_{\text{tail skin}} \)), and a decrease in skin blood flow (BF

\[ \text{BF}_{\text{sk}} \]). Dotted line, mean baseline (BL); \( T_{\text{core}} \), core body temperature. In contrast, NE causes an immediate decrease in all measures of blood flow.
phase ended as the values of all parameters moved toward baseline levels, albeit without fully achieving them. In the subsequent static phase, that continued throughout the rest of the experiment, BF$_{tot}$ remained somewhat elevated and BF$_{sk}$ remained somewhat depressed.

The effect of exogenous NE (400 µg/kg) on these same variables is presented in Fig. 1 (right) for comparison. NE invokes marked reductions in both BF$_{tot}$ and BF$_{sk}$ due to vasoconstriction and has no effect on tail T$_{sk}$. In comparison, the marked increase in BF$_{tot}$ after NPY administration suggests that NPY dilates some vessels in the tail. However, the reduction in BF$_{sk}$ at the same time indicates that this increase in BF does not involve the cutaneous microvascular bed.

Dose-response relationships. Figure 2A illustrates the dose-response relationship, including the time component, for NPY and BF$_{tot}$. Each bar represents the mean BF during a 5-min period of the experiment. The results represent the means ± SD from five (16 and 32 µg/kg) and seven rats (saline, 64 µg/kg), respectively. In the saline control experiments, there was normally a slight rise in BF$_{tot}$ as the experiment progressed. Although a dose of 16 µg/kg caused an elevation in BF$_{tot}$ during the dynamic phase (minutes 5–10), neither it nor the level during the static phase (compared at minutes 20–25) was significantly different from saline control (P > 0.05). Doses of 32 and 64 µg/kg caused larger, significant increases in BF$_{tot}$ in both the dynamic (minutes 5–10; P < 0.05) and static phases (minutes 20–25; P < 0.05) of the response. A dose of 128 µg/kg (not shown) did not further increase BF$_{tot}$ above that observed for 64 µg/kg.

Figure 2B illustrates the dose-response relationship between NPY and BF$_{sk}$. NPY caused a clear and marked reduction in BF$_{sk}$, the magnitude of which was dose dependent. The reduction in BF$_{sk}$ was not significant for 16 µg/kg (P > 0.05) but was significant for both 32 and 64 µg/kg (P < 0.01) when values were compared at minutes 20–25 of the experiment. It should be noted

![Fig. 2. Dose-response relationship for NPY and BF$_{tot}$ (A) and BF$_{sk}$ (B). Each bar represents average response during 5 min. Effect of dose on both short-term dynamic phase and more prolonged static phase of NPY is demonstrated.](http://jap.physiology.org/)

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that the laser Doppler flowmeter used for measuring microvascular BF is limited to making that measurement at only one small area. However, given the consistency of the response during multiple experiments, this measurement is likely to be representative of what is occurring throughout the skin.

Microsphere studies. Microspheres were used to test the hypothesis that AVAs dilate and participate in the NPY-induced increased BFtot. Figure 3 shows the number (mean ± SD) of microspheres/g tissue reaching the tail skin (left) and lung (right) after normal administration of saline (300 µl iv; control) or 64 µg/kg NPY in a 300-µl injection. After saline, 14,080 ± 10,420 microspheres/g tissue were found in the lung. Significantly more microspheres (40,571 ± 26,790/g tissue; P < 0.01) were found in the lung after administration of NPY. Furthermore, the number of microspheres trapped in the tail skin tissue is actually higher (P < 0.005) after saline (2,988 ± 2,010/g tissue) than after NPY (1,496 ± 1,223/g tissue) administration. This is as expected, considering the reduced microvascular BFtot measured by laser Doppler flowmeters. These results demonstrate the participation of AVAs in the NPY-induced increase in rat tail BFtot.

Effect of [Leu31 Pro34]NPY and NPY[13–36] on BF and body temperatures. Figure 4 illustrates the effects of [Leu31 Pro34]NPY (the Y1-receptor agonist) and of NPY[13–36] (the Y2-receptor agonist), respectively, on tail BFtot and BFsk in the tail. Clearly, the Y1-receptor agonist has a similar effect to that of NPY (compare with Fig. 1). In marked contrast, the Y2-receptor agonist has no effect on either tail BFtot or BFsk in the tail. These results suggest that Y1 receptors, or receptors responsive to Y1 agonist, participate in the NPY-induced increase in BFtot and concurrent decreases in BFsk. The results also indicate that Y2 receptors are not involved in this increased BF.

DISCUSSION

The results of these studies demonstrate that exogenous NPY, administered at physiological levels, consistently invokes in the rat tail an increase in BFtot, tail blood volume, and tail Tsk, and a decrease in tail BFsk. It is further demonstrated that there is a dose-response relationship for both BFtot and BFsk and that the increase in BFtot is caused by a pronounced vasodilation in which AVAs play a role. Finally, this NPY-induced vasodilation is also invoked by the Y1-receptor agonist, [Leu31 Pro34]NPY, but not by a Y2-receptor agonist, NPY[13–36]. The discussion that follows examines these observations and conclusions in some detail.

Clear evidence of NPY-induced increase in BFtot. The present study provides unrefutable evidence that physiological levels of NPY induce increases in BFtot in the rat tail. This is because the method used to measure BFtot (VOP) is a direct, quantitative, and frequently used measure that cannot provide a false indication of such increases in BFtot. The observation is supported further by the concurrent increase in tail (blood) volume and tail Tsk, notwithstanding the reduction in superficial microvascular tail BFsk. It should be noted that such decreases in microvascular or capillary BF have often been observed when blood flows by another path of lesser resistance (20, 22). The conclusion that some vessels in the tail dilate in response to exogenous NPY is supported by the observed simultaneous increase in tail blood volume and BFtot.

AVAs. AVAs are relatively large-diameter connections between arteries and veins that allow an increase in non-nutrient thermoregulatory BF through the skin (12). They are opened during heat stress (19). They are also thought to open, periodically, during exposure to extreme cold to prevent tissue freezing (commonly referred to as cold-induced vasodilation) (10).

AVAs are the most likely vascular tissue to be involved in the NPY-induced increase in BFtot, because of the several reasons already enumerated in the introduction and the following additional reasons. The possibility that the dilation occurs in arteries, arterioles, venules, and veins is rejected, because the subsequent flow through capillaries would be a limiting factor and because it has already been demonstrated that capillary BF in the skin is reduced rather than increased. The observed increase in blood volume could be explained by pooling of blood in compliant veins, but that cannot explain the increased tail BF. AVAs are known to occur in large numbers in the rat tail (12). In addition, the rat tail is the only one of many peripheral tissues studied where NPY causes increases in BFtot associated with vasodilation, and it is the only one of these tissues that is known to have abundant AVAs.

Evidence supporting the hypothesis that AVAs participate in the NPY-induced increase in BFtot in the rat tail. That AVAs are involved in the NPY-induced increase in BFtot in the rat tail is convincingly demonstrated by the results of the experiments using color microspheres (Fig. 3). Blood flowing through the arterial vessels of the tail will end up in the veins by passing either
through capillaries that are 2–3 µm in diameter or through AVAs that are 20–50 µm in diameter. Whereas 15-µm-diameter microspheres easily pass through AVAs, they are trapped in the capillary beds. The fact that the number of microspheres ending up in the lung tissue is severalfold greater after NPY administration than after the administration of saline clearly indicates that AVAs participate in the NPY-induced increase in BF<br><br>tot in the rat tail. Furthermore, the decline in the number of color microspheres trapped in the capillaries of the tail skin after NPY administration, compared with after saline administration, reaffirms the decline in microcirculatory BF<br><br>sk after NPY administration, as measured locally by the laser Doppler flowmeter.

Y1-receptor agonist invokes NPY-induced vasodilation. The protocol used for observing the effects of NPY was repeated with [Leu31 Pro34]NPY (a Y1-receptor agonist) and NPY[13–36] (a Y2-receptor agonist). Figure 4 presents and compares the effects in the tail of [Leu31 Pro34]NPY and NPY[13–36] on BF<br><br>tot and BF<br><br>sk. The Y1-receptor agonist (Fig. 4, left) has an effect that is essentially identical to that of NPY (compare with Fig. 1, left). In marked contrast, the Y2-receptor agonist (Fig. 4, right) has no apparent effect on tail BF<br><br>tot or BF<br><br>sk. Thus the present study eliminates the possible involvement of Y2 and related receptors and implicates the involvement of Y1 or [Leu31 Pro34]NPY-responsive receptors. It should be noted that Y2 receptors show a similar level of affinity for [Leu31 Pro34]NPY as Y1 receptors (5) and thus could potentially be involved in the response. In contrast, Y4 and Y5 receptors show much lesser affinity (1/8 and 1/50) for [Leu31 Pro34]NPY than do Y1 receptors (13). Because NPY and [Leu31 Pro34]NPY in equimolar doses had similar effects on BF<br><br>tot, it is unlikely that Y4 and Y5 receptors are involved.

Finding an NPY-induced increase in BF<br><br>tot in the rat tail was initially unexpected in light of the numerous reports that NPY causes either vasoconstriction or no change in vascular tone in blood vessels and that NPY reduced BF in the organs and tissues heretofore studied (8, 11, 34). NPY has also been shown to cause systemic hypertension (7). Thus one plausible explanation for the increased BF<br><br>tot is that it is due to an elevation in blood pressure that is caused by vasoconstriction in other tissues. Although the present study did not measure blood pressure, two observations con-
Conflict with this explanation. First, microvascular BFsk should have increased rather than decreased with elevations in blood pressure. Second, although an increase in blood pressure can increase BF through vessels, it cannot increase BF through AVAs unless the AVAs are already open. Thus we return to the conclusion that NPY, either directly or indirectly, is affecting AVA tone. In addition, it should be noted that high doses (>3 nM/kg) of NPY are reported to decrease mean arterial pressure because of release of histamine from mast cells (17). The timing of the reported hypotension response (1- to 12-min postinjection) correlates well with the timing of the increased tail BFtot observed in the present study.

Also, the present observations seem to be in direct conflict with the finding by Neild (31) that NPY causes vasoconstriction in the isolated-vessel preparations of the rat tail artery. There are, however, several plausible reasons why the vasoconstriction observed in that isolated rat tail artery preparation was not observed in the present study and why those results should not be extrapolated to the whole animal. First, the plasma levels of NPY (1.5–2.5 pmol/kg) used in the present study were much lower than the 20–30 nM doses used to perfuse the isolated rat tail artery (31) and may not, therefore, have been great enough to cause constriction in the artery. Second, it should be understood that, although isolated vessel preparations can provide much insight about the pharmacology of a given vessel, such preparations do not fully mimic the conditions in the whole animal. Third, the vasculature of the rat tail is complex, with not just one, but several, arteries traversing its length, and there are numerous anastomoses between those arteries (31). Thus the actual route of arterial BF can be shifted between different arteries. It is possible that the ventral medial artery studied by Neild (31) responds differently to NPY than do the several lateral or collateral arteries or the anastomose connecting them. Finally, because AVAs are involved and because they are highly specialized vascular structures, unlike any of the other vascular tissues in which the response to NPY has been studied, it is not surprising that would have unique responses to NPY or other pharmacological agents. Indeed, AVAs could not perform their unique function of altering the route of BF to increase both the flow and volume of blood in the skin in response to the specific conditions of heat stress if they were pharmacologically identical to arteries. The pharmacological mechanism involved in the control of BF through AVAs is not fully understood, although one report suggests the involvement of α1-adrenergic receptors in pig AVAs (4).

The most obvious explanation for the observed increase in BFtot via AVAs in response to NPY is that NPY acts at the presynaptic level to inhibit NE release, which subsequently results in relaxation of AVA tone. This conclusion is based on the following several observations. First, there is evidence that AVA tone is maintained by the sympathetic nervous system via action of NE (19, 30) on adrenergic receptors, as demonstrated in studies on dogs and sheep (18, 23). In addition, a more recent study has more specifically implicated the involvement of α1-adrenergic receptors in regulating BF through AVAs in pigs (4). Second, NPY has been shown both to inhibit NE release by its presynaptic action on Y2 receptors and also to postsynaptically potentiate the vasoconstriction induced by NE by action on Y1 receptors (34). One problem with this hypothesis is that our results indicate that NPY acts on Y2 receptors, which were previously reported to be postsynaptic (38), rather than Y1 receptors, which were reported to be presynaptic (38). However, more recent studies have demonstrated that Y1 receptors occur presynaptically and that Y2 receptors occur postsynaptically (16, 29). Thus it is possible that Y1 receptors could be presynaptic in a specialized tissue, such as AVAs, where NPY causes dilation rather than vasoconstriction.

In more recent studies, it was shown that both Y1 and Y2 receptors occur in arterioles in intestinal submucosa of guinea pigs (32) and in the microvascular tree in the hamster cheek pouch (2). Neild and Lewis (32) observed that a Y1-receptor agonist caused a greater potentiation of a vasoconstriction response to short pulses of K+ than to NPY per se, and, furthermore, that a Y2-receptor agonist reduced the magnitude of vasoconstriction. This differs from the inhibition of NE release presynaptically. Rather, the Y2 agonist PYY-(13–36) is acting on Y2 receptors on the smooth muscle to modulate the opening of the Ca2+ channels, just as they do in nerve terminals (9).

Clearly, further study is needed to characterize definitively the receptors involved, to ascertain whether they are presynaptic or postsynaptic, and to understand the pharmacological mechanism responsible for the observed NPY-induced increase in tail BFtot. On the basis of other reports in the literature, the possibility clearly remains that other receptor types and vasoactive substances are involved in the pharmacology of this mechanism. For example, NPY has also been found to be costored with ACh in parasympathetic nerves (35) and possibly to modulate ACh secretion (24). This is relevant, because ACh is a known vasodilator substance. Also, as mentioned above, larger doses of NPY have caused release of histamine from mast cells, which, due to the vasodilatory effects of histamine, resulted in hypotension (17). Finally, the potentiation of the vasoconstriction response induced by NE (34) is dependent on both endothelium and Ca2+ (3) and independent of adrenergic receptors (28). This opens the possible involvement of Ca2+ channels and endothelium-derived relaxing factor, which some investigators believe is nitric oxide (33) or nitrosothiol (41). Thus there are several plausible mechanisms by which NPY could invoke vasodilation in the rat tail, and it is clear that other neurotransmitters in addition to NPY and other receptors in addition to Y1 receptors could be involved in this response.

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REFERENCES


