

Cardiovascular Effects of Neuropeptide Y

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Neuropeptide Y (NPY) is present in the brain, the adrenal medulla, and peripheral sympathetic nerves. This peptide is released together with catecholamines during sympathoadrenal activation. It possesses direct vasoconstrictor properties that are not dependent on simultaneous adrenergic activation. Moreover, it potentiates the vascular effect of several stimulatory substances and may contribute to the modulation of blood pressure responsiveness under a number of circumstances. NPY may also

be indirectly involved in the control of blood pressure through regulating the release of hormones with well-established actions on the cardiovascular system. Am J Hypertens 1988;1:193-199

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Neuropeptide Y (NPY) is a 36 amino acid peptide first isolated from porcine brain.^{1,2} It has been found to be widely distributed throughout the central and peripheral nervous system of a variety of mammals including man (for review see references 3-6). This peptide is co-stored with norepinephrine in perivascular nerve fibers. It has also been localized to the adrenal medulla. NPY has been shown to induce vasoconstriction through a direct effect. In addition, it has been recognized to potentiate the contractile response evoked by stimulation of α -adrenoceptors.

The vasoactive properties of NPY have been extensively studied during the last few years. In the present work, we intend to focus on the evidence suggesting a role for this newly discovered peptide in the regulation of vascular tone.

CARDIOVASCULAR EFFECTS OF NPY

Central Effects Several observations support the view that NPY may actively participate in the central control of blood pressure. It is present in catecholamine-con-

taining neurons located in areas physiologically involved in the regulation of the cardiovascular system, particularly at the level of the nucleus tractus solitarius.^{7,8} One group of investigators has shown that intraventricular administration of NPY causes in conscious as well as in anesthetized rats a hypotension accompanied by a bradycardia.^{9,10} This type of hemodynamic response corresponds to what is expected to occur after central injection of α_2 -adrenergic agonists. It is therefore of interest that brain α_2 -adrenergic binding sites have been reported to increase in the presence of NPY.¹¹ It has been suggested that NPY stimulates presynaptic receptors on norepinephrine and/or epinephrine nerve terminals, which may enhance the presynaptic α_2 -adrenoceptor function to inhibit norepinephrine release.¹² The hypotension and bradycardia induced by intracisternal and intraventricular administration of NPY has however not been observed by all investigators.^{13,14} NPY may even be responsible in rats for a dose-dependent pressor response and a tachycardia.¹⁴ Such effects could be prevented by pretreating intravenously with α - and β -adrenoceptor blocking agents, suggesting that the cardiovascular response to centrally administered NPY is mediated by an activation of the sympathetic nervous system. Microinjection of NPY at a large dose into the nucleus tractus solitarius of rats decreases blood pressure and heart rate, whereas a pressor response can be obtained when a large dose is used.¹⁵ It is of note that a functional interaction between NPY and

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norepinephrine seems to exist at the central level, NPY potentiating the effect of the catecholamine.¹⁵ Furthermore, NPY seems to contribute to the regulation of central catecholamine turnover¹⁶ and to exert a negative feedback inhibitory effect on norepinephrine release at the presynaptic level.¹⁷ Whether the level of NPY in the brain is relevant to the development of some experimental forms of hypertension remains unclear. Strain- and age-related differences in NPY immunoreactivity occur in normotensive and genetically hypertensive rats.^{18,19} Concerning the mechanism of action of NPY at the cellular level, little was known until the recent report of a NPY-induced inhibition of adenylate cyclase activity;^{20,21} it is not yet known however if this action is common to all the reported effects of NPY.

Peripheral Actions

Vascular Distribution NPY has been identified by radioimmunochemical and immunocytochemical methods in perivascular nerve fibers of various organs, for instance at the level of cerebral, renal, coronary, mesenteric, and femoral arteries.³⁻⁶ NPY-containing nerve terminals are present with a much higher frequency around arteries than around veins.²² Most of the NPY-containing neurons are probably catecholaminergic, as it is possible to reduce the NPY content of perivascular nerve endings by performing either surgical or chemical sympathectomy.²³⁻²⁵

Effects of NPY in Isolated Vascular Preparations NPY possesses vasoconstrictor properties in isolated segments of arteries.²⁶⁻²⁹ The NPY-evoked contraction of vascular smooth muscle cells is not dependent on adrenergic mechanisms, as it cannot be antagonized by α -adrenoceptor blockade.^{30,31} However, an important vascular action of NPY appears to be the potentiation of the contractile response to norepinephrine^{26,28,32,33} and indeed to nerve stimulation.^{29,33} The NPY-mediated enhancement of vascular contraction is not limited to norepinephrine. The same effect has been observed with histamine,^{26,32} but the effect of NPY on the response to 5-hydroxytryptamine and K^+ requires clarification.^{26,33} The fact that the potentiating effect of NPY can be observed with different vasoconstrictors suggests a number of NPY-induced effects beyond the receptor of the vascular smooth muscle cell. However, NPY leads to a depolarization of the musculature of the rat tail artery,³³ and this effect may account to some extent for the potentiating action. By depolarizing the arterial smooth muscle it is indeed possible to increase the contractile responses to a variety of constrictor agonists.^{34,35} The entry of Ca^{2+} into the vascular smooth muscle cells seems to be important, although not absolutely necessary, for attainment of the direct constrictor effect of NPY.³¹ The potentiation of norepinephrine-induced vasoconstriction depends probably more on the Na^+

than the Ca^{2+} influx.²⁸ For this latter effect, an intracellular sequestered Ca^{2+} pool appears to play a key role.²⁸ It is relevant in this context that evidence for a NPY-induced inhibition of adenylate cyclase activity has also been found in blood vessels.³⁶ Recently, it has also been suggested that NPY modulates adrenergic neurotransmission by an endothelium-dependent mechanism.³⁷ Finally, it has to be stressed that the degree to which pre- and postjunctional effects of NPY are concerned in the process of sympathetic neurotransmission is still unclear. There is however good indication to suggest that the postjunctional contractile and facilitatory mechanisms prevail upon the prejunctional inhibitory action on norepinephrine release.³⁸

Effects of NPY in the Isolated Blood-Perfused Spleen NPY-like immunoreactivity has been detected within the adrenergic innervation of spleen tissue.^{39,40} Interestingly, the splenic vascular bed, unlike many isolated vessels,²⁶ is very sensitive to the direct vasoconstrictor action of NPY.⁴¹ Moreover, NPY is released into the venous drainage by sympathetic nerve stimulation.⁴² The increase in splenic arterial perfusion pressure evoked by electrical stimulation cannot be prevented by adrenoceptor antagonists at doses sufficient to abolish the response to norepinephrine.

Effects of NPY in the Isolated Heart and Cultured Atrial Cells The presence of NPY has been demonstrated in nerve fibers surrounding blood vessels and myocytes.^{22,43} In the isolated rabbit heart, NPY has been reported to reduce myocardial perfusion together with the force of contraction.^{44,45} Other studies failed however to detect a direct action of NPY on the heart muscle.^{46,47} The most striking cardiac effects of NPY observed using in vitro preparations appear to be a prejunctional suppression of stimulated norepinephrine release⁴⁷ and a contraction of the coronary vascular bed.^{46,48} The constrictor effect of NPY is not affected by α -adrenoceptor blockade but is likely to depend on extracellular calcium ions.⁴⁸ A new insight in the mode of action of NPY has emerged recently from studies performed on primary cultures of rat heart atria.⁴⁹ NPY was found to inhibit the stimulation of adenylate cyclase activity known to occur during activation of β -adrenoceptors. Pretreatment of the cells with pertussis toxin prevented this inhibitory effect. This observation suggests that NPY binds to its receptor at the surface of the cell to activate an inhibitory membrane protein called Gi, which then turns off the cyclic AMP pathway.

NPY and the Adrenal Medulla The presence of NPY has been established in adrenal medullary cells⁵⁰⁻⁵³ and adrenal medullary pheochromocytoma tissue.^{52,54-57} Interestingly, the content of NPY in the tumors is generally increased in comparison with normal adrenals. Some pheochromocytoma appear to synthesize and se-

crete enough of this peptide to raise circulating NPY levels.^{54,56,57} Whether determination of plasma NPY levels is of practical use in the diagnosis of pheochromocytoma needs to be further explored.⁵⁷ It remains also a matter of speculation whether the elevation of plasma NPY levels found in some patients with pheochromocytoma is sufficient to contribute to the hypertensive state.

A key question is whether NPY is released into the circulation upon sympathetic activation. This seems to be really the case since both reflex sympathetic activation and electrical nerve stimulation of the adrenal have been shown recently to cause a marked increase in NPY and catecholamine output.⁵⁸ In the intact animal, however, there is evidence suggesting that the sympathetic nerves contribute to the largest extent to the increase in plasma NPY concentrations after activation of the sympathoadrenal system.⁵⁹ In basal conditions, conscious normotensive rats exhibit similar circulating levels of NPY independently of the presence or the absence of adrenal medulla (personal observation).

Effects of NPY in Intact Animals In pithed rats, NPY infusion in a dose that does not affect blood pressure per se enhances the pressor response to α_1 -adrenoceptor stimulation with phenylephrine as well as to electrical stimulation of the sympathetic outflow.⁶⁰ In these rats, a direct pressor effect of NPY can be obtained by raising the dose of the peptide.⁶⁰ Potentiation of the blood pressure effect of α -adrenoceptor stimulation has also been observed in conscious rats infused with a nonpressor dose of NPY.⁶¹ This was shown utilizing not only norepinephrine, but also the indirectly acting sympathomimetic agent tyramine (personal observation). Interestingly, the blood pressure response to angiotensin II was also clearly increased by this low dose of NPY which given alone was devoid of pressor effects. In contrast, NPY did not alter the response to vasopressin. Several studies have confirmed that the NPY-induced pressor effect is not attenuated by α -adrenoceptor blockade.⁶⁰⁻⁶⁴

The vasoconstrictor activity of NPY *in vivo* seems to be Ca^{2+} -dependent, as it can be reduced by calcium entry blockade.^{60,62,64} It is possible to trigger the release of NPY into systemic circulation by splanchnic nerve stimulation.⁶⁵ Evidence has been provided from studies in pithed guinea pigs that clonidine, an α_2 -adrenoceptor agonist, reduces the increase in plasma NPY concentration resulting from electrical nerve stimulation.⁶⁶ This points to a role of presynaptic α_2 -adrenoceptors in the modulation of NPY release by nerve terminals. The importance of sympathetic outflow in determining circulating levels of NPY is strongly suggested by the fact that the ganglion blocker pentolinium, at the same time as reducing blood pressure, markedly reduces in acute experiments the peptide concentration in the plasma.⁶⁷

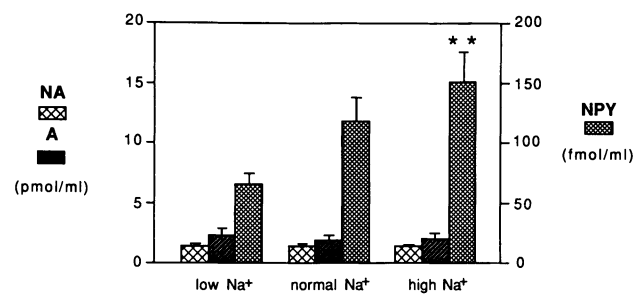


FIGURE 1. Comparison of plasma concentrations of NPY with catecholamines in rats kept on low ($n = 10$), normal ($n = 12$), and high ($n = 14$) sodium diets. Plasma noradrenaline, adrenaline, and NPY concentrations are shown in the left, middle, and right columns, respectively, for the three different sodium intakes. The NPY concentration was significantly higher (** $P < 0.02$) in the group receiving a high sodium diet when compared to rats on a low sodium diet (from reference 75).

When infused for 30 minutes at a dose lacking any effect on systemic pressure, NPY does not modify heart rate and cardiac output in conscious rats. Furthermore, it does not produce major changes in regional blood flow distribution.⁶⁸ In anesthetized rats infused only briefly with NPY (2 minutes), blood flow increased in several tissues (notably the kidney and the heart) in the absence of a generalized effect on hemodynamics.⁶⁹ A potentially important function of NPY appears to be an inhibitory action on the response of the cardiac vagus to sympathetic stimulation.^{70,71}

A number of interesting findings have been obtained by studying the relationship between blood pressure responsiveness and NPY in states where responses to vasoconstrictor agents are altered. Endotoxemia is one condition in which vascular responsiveness to pressor agonists has been shown to be markedly suppressed, both in hypotensive and nonhypotensive states.^{72,73} It is therefore noteworthy that NPY infused at a nonpressor dose can reverse this abnormality.⁶¹ It is perhaps through this mechanism that NPY prevents the blood pressure fall induced by endotoxin in rats subjected to adrenal medullectomy.⁷⁴

NPY may also be involved in the modulation of blood pressure responsiveness during changes in sodium balance.⁷⁵ Thus, circulating levels of NPY were higher in rats maintained for 3 weeks on a high sodium intake than in animals kept for the same period on a salt-deficient diet. Intermediate values were obtained in rats fed with a regular sodium intake (Figure 1). It has to be stressed that plasma norepinephrine and epinephrine achieved similar levels in the three different study groups. Sodium loading is known to enhance blood pressure responsiveness to norepinephrine and to favor the development of hypertension. It is therefore conceivable that an excess of sodium influences blood pressure regulation to some extent via an increase in circu-

lating NPY levels, which in turn potentiate the vasoconstrictor effect of α -adrenoceptor stimulation.

Some of the cardiovascular effects of NPY may be related to an action of the peptide on the secretion of hormones physiologically involved in blood pressure control. For instance, NPY suppresses renin release,^{76,77} most likely by inhibiting adenylate cyclase activity in renin-producing cells through a pathway involving the protein Gi.⁷⁷ NPY has also been shown to increase the release of the atrial natriuretic factor;⁷⁸ the significance of this finding is less clear but it could lead to diuresis and natriuresis.

Effects of NPY in Man NPY infused intravenously at a dose that slightly increases blood pressure is well tolerated by normal subjects.^{79,80} Recently, NPY has been administered directly into a coronary artery of patients with typical angina but no significant abnormality at the arteriogram.⁸¹ Half of the patients developed a transient myocardial ischemia during infusion of the peptide.

Results obtained in man suggest that NPY is released together with catecholamines when the sympathoadrenal system is activated. This has been shown during physical exercise,⁸²⁻⁸⁴ in response of the cold pressor test,⁸³ as well as during thoracotomy and surgery for cardiopulmonary bypass.⁸⁵ In two studies,^{82,85} there was a significant correlation between plasma levels of NPY and norepinephrine, but not between plasma levels of NPY and epinephrine. This was taken as an indication for a release of neural rather than adrenal origin.

CONCLUSIONS

Interest in the field of research on NPY has been growing rapidly during recent years. This peptide is widely distributed within the central and peripheral nervous system. The property of NPY that seems to be of major physiologic importance is the action on vascular smooth muscle cells. Indeed, NPY can cause blood vessels to constrict through both direct and indirect mechanisms. NPY may therefore be implicated in cardiovascular homeostasis by modulating blood pressure responsiveness to different pressor stimuli. In addition, there is now some evidence suggesting that NPY influences the secretion of hormones known to play a role in body fluid and blood pressure control.

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