Neuropeptide Y–Induced Acceleration of Postangioplasty Occlusion of Rat Carotid Artery
Lijun Li, Edward W. Lee, Hong Ji, Zofia Zukowska

Objective—Attempts to restore blood flow through atherosclerotic vessels by angioplasty often result in restenosis. Because the role of nerves in this process is unclear, we investigated whether neuropeptide Y (NPY), a sympathetic cotransmitter with vascular mitogenic activities, contributes to postangioplasty restenosis.

Methods and Results—Carotid artery balloon angioplasty upregulated vascular expression of NPY and its processing enzyme (DPPIV/cd26) and receptors (Y1, Y2, Y5 mRNA and protein) within 6 to 24 hours and stimulated neointima formation and accumulation of NPY in platelets after 14 days. NPY pellets (1 to 10 µg/pellet for 14 days) inserted next to the injured artery elevated platelet and vascular NPY immunoreactivity to stress-like levels and dose-dependently augmented angioplasty-induced neointima. Strikingly, 10 µg NPY for 14 days led to vessel occlusion with an atherosclerotic-like lesion, with thrombus and neointima containing neo vessels, macrophages, matrix, and lipids. Y1 or Y5 receptor antagonist completely prevented the effect of NPY and reduced angioplasty-induced neointima by 50%.

Conclusions—Angioplasty upregulates platelet and vascular NPY systems, which then contribute to neointima formation via Y1 and Y5 receptor activation. Increasing NPY to high stress levels triggers formation of a thrombotic atherosclerotic-like lesion and vessel occlusion. Thus, NPY may be a risk factor for accelerated atherosclerosis, and NPY receptor antagonists may be a possible new treatment for restenosis. (Arterioscler Thromb Vasc Biol. 2003;23:1204-1210.)

Key Words: neuropeptide Y ■ NPY receptors ■ atherosclerosis ■ restenosis ■ neointima

Atherosclerosis is a multifactorial, pathological process and a leading cause of ischemic vascular diseases. Despite identification of multiple genetic and environmental risk factors such as hyperlipidemia, obesity, and smoking, it remains poorly manageable by conventional therapy. The most commonly used procedures are surgical vascular interventions such as percutaneous transluminal coronary angioplasty. Although effective acutely, they often, however, result in restenosis of occluded arteries.

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Multiple growth factors have been implicated in restenosis, most of them thought to derive from mesenchymal cells. Surprisingly, the role of perivascular sympathetic nerves that richly innervate these vessels is less known. Sympathetic activity has been believed to promote atherosclerosis indirectly, either by its vasoconstrictive effects or by stimulating platelet aggregation or insulin resistance. However, these views have been rapidly changing in recent years because both norepinephrine and its cotransmitter, ATP, have been found to exert direct trophic actions on vascular smooth muscle cells (VSMCs) both in vivo and in vitro.

NPY is also a sympathetic and central cotransmitter, mediating pleiotropic activities such as stimulation of appetite and anxiolysis by activating multiple G_{i/o}-coupled Y1-Y5 receptors. In the cardiovascular system, NPY cooperates with norepinephrine (NE) and causes, via Y1 receptors, a slow-onset, long-lasting vasoconstriction in many arteries, including coronary and cerebral. Plasma NPY levels are elevated by stress, such as cold exposure or treadmill exercise and, in patients with myocardial ischemia, congestive heart failure and hypertension. Recently, the vasoconstrictive Y1 receptor has also been identified as mediating proliferation of VSMCs in vitro.

In addition to neurogenic, extraneuronal NPY synthesis has been identified in endothelial and immune cells and megakaryocytes/platelets. Similar to VSMCs, NPY potently promotes growth of endothelial and immune cells, but specific receptor subtypes mediating its effects appear to differ. For example, the angiogenic activity of NPY seems to be mediated not by Y1 but by Y2/Y5 receptors. The switch from the Y1-receptor–mediated vasoconstriction and VSMC mitogenesis to non–Y1-receptor–mediated angiogenic actions of NPY is provided by DPPIV, which converts NPY1-36 to NPY3-36, a Y2/Y5-selective agonist. The latter is also the second major form of circulating NPY.

Recently, a common (6% to 14%) polymorphism of the signal peptide of the NPY gene with leucine(7)-to-proline(7)

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substitution has been discovered in the European population.\textsuperscript{22} Interestingly, the mutation correlates highly with elevated total and LDL cholesterol levels\textsuperscript{22} and increased carotid artery intima-media thickening.\textsuperscript{23} Our experimental data, together with these human findings, led us to hypothesize that NPY exerts proatherosclerotic activity; its proliferative receptors are activated by vascular injury, which then results in VSMC proliferation and restenosis.

**Methods**

**Rat Carotid Artery Angioplasty**

Angioplasty was performed as described.\textsuperscript{24} In male anesthetized Wistar rats (350 to 375 g), a 2F Fogarty balloon catheter was inserted into the left common carotid artery, and angioplasty was performed by retracting the balloon catheter 3 times. On catheter removal, the left external carotid artery was ligated, and blood flow was restored. As controls, intact unoperated and sham-operated (tying off the external carotid artery, and angioplasty was performed by retracting the balloon into the left common carotid artery through the left external carotid artery (or contralateral vessels in some rats) and secured in place with a neighboring muscle.

**Drugs**

The Y1 (H409/22 acetate) and Y5 (CGP71683A) antagonists (60 mg/mL each, gifts from AstraZeneca, structures identical to BIBP3223\textsuperscript{23} and the Novartis compound,\textsuperscript{26} respectively, with established specificity\textsuperscript{25–27}) or vehicle (60% PEG-400) were delivered at 0.02 \( \mu \text{mol/kg} \) per min for 14 days into the right jugular vein via osmotic minipumps. These concentrations (0.1 \( \mu \text{mol/L} \)) of Y1 and Y5 antagonists blocked proliferation of rat aortic VSMC in response to 0.01 \( \mu \text{mol/L} \) NPY in vitro.\textsuperscript{14} NPY-containing (1 to 10 \( \mu \text{g/pellet} \) for 14 days) or placebo-containing pellets (Innovative Research of America) were placed during angioplasty at the site of the left carotid artery (or contralateral vessels in some rats) and secured in place with a neighboring muscle.

**Morphometry**

After 14 days, in reanesthetized and artificially resired rats, both common carotid arteries were harvested and fixed. Tissues were paraffin-embedded and stained with H&E or Masson’s trichrome for morphometry. Intima was calculated as the area luminal from the internal lamina, and media as area between external and internal lamina (averaged from 15 arterial sections and imaged) (Optimax-Nikon computer with NIH image) (additional information available online on http://atvb.ahajournals.org).

**Histocytochemistry and Immunocytochemistry**

Tissue sections were deparaffinized and stained with primary antibodies against the endothelial markers, cd31 and von Willebrand factor (vWF), the macrophage scavenger receptor (cd68), and hyaluronan, a marker for matrix deposition (HA).\textsuperscript{28} Additionally, sections were stained with Oil Red O to identify lipid deposition and Masson’s Trichrome to identify matrix and neovascularization (additional information online).

**Reverse Transcriptase–Polymerase Chain Reaction**

Both common carotid arteries were harvested, samples were immediately snap frozen, and total RNA was isolated using TRI-Reagent. cDNA was synthesized with random hexamer and MMLV reverse transcriptase, and 18s rRNA served as an internal control. NPY, DPP IV, and NPY-Y1-Y5 receptor primer sequences\textsuperscript{16} are provided online. Polymerase chain reaction (PCR) was performed using Taq DNA polymerase (Promega) as described.\textsuperscript{16} After electrophoresis, the products were visualized by ethidium bromide staining.

**Western Blotting**

Carotid arteries were homogenized in RIPA buffer and centrifuged, and supernatants were collected. Protein samples were resolved on a Tris-Glycine gel and transferred onto a nitrocellulose membrane, and blots were blocked with nonfat milk in TBST buffer and incubated with rabbit polyclonal anti-human Y1, Y2, or Y5 antibodies (AstraZeneca). The membranes were then washed with TBST buffer, incubated with horseradish peroxidase-conjugated anti-rabbit IgG antibody (Amersham Pharmacia Biotech). Signal was detected using ECL reagents (Amersham Pharmacia Biotech) and visualized by autoradiography (additional information online).

**NPY Immunoreactivity**

NPY immunoreactivity (NPY-ir) was measured using ELISA\textsuperscript{12,18} in platelet-poor plasma (PPP) and platelet-rich plasma (PRP), carotid arteries, and neighboring skeletal muscle from intact, angioplasty-subjected (with and without NPY pellet), and stressed rats (placement in 1 cm ice-cold water for 2 hours).\textsuperscript{12} Tissues were harvested after clearing of blood to eliminate platelet-derived NPY and deproteinized by boiling in 1 mol/L acetic acid.\textsuperscript{12,18} Blood was collected from the femoral artery, and PRP and PPP were prepared by sequential centrifugation.\textsuperscript{18}

**Statistical Analysis**

Results were analyzed by one- and two-way ANOVA, and, where appropriate, a post hoc Dunnett’s \( t \)-test was used. Data are presented as mean±SEM for indicated number of repetitions and were considered significant at \( P<0.05 \).

**Results**

**NPY-ir Levels in Plasma and Carotid Artery**

Fourteen days after angioplasty, plasma NPY-ir levels in PPP remained unchanged compared with intact rats (Figure 1A). In PRP, however, plasma NPY-ir levels were significantly increased in the rats treated with angioplasty+placebo compared with the unoperated rats (\( P<0.01 \), Figure 1B). This increase tended to be even greater in the angioplasty+NPY-treated rats (\( P<0.01 \) compared with intact, Figure 1A).
NPY-ir levels in PRP in angioplasty + NPY-treated rats were comparable to those attained during 2-hour 4°C cold water stress (Figure 1A). Stress, unlike angioplasty, also increased NPY-ir levels in PPP (Figure 1A).

Angioplasty in the placebo-treated rats did not affect NPY-ir levels in the carotid artery compared with the contralateral uninjured vessels from the same rats. However, angioplasty-injured NPY-treated carotid arteries had significantly elevated NPY-ir levels ($P<0.01$, Figure 1B) compared with intact arteries. NPY-ir content in the muscle around the NPY-treated (0.00427±0.00082 ng/mg), but not placebo-treated, angioplasty-injured artery was significantly higher ($P<0.01$) than in their contralateral muscle surrounding the uninjured right carotid artery (0.00280±0.00081 ng/mg).

**NPY-Induced Neointima Formation and Media Thickening**

Fourteen days after angioplasty, there was a significant neointima formation in the carotid artery, whereas no changes were seen in the contralateral uninjured vessel (Figures 2A and 2B). NPY (1 to 10 μg for 14 days) dose-dependently increased neointima formation in the angioplasty-injured artery (from 0.048±0.002 mm² with placebo to 0.112±0.008 mm² with 1 μg of NPY, $P<0.05$, or 0.347±0.015 mm² with 10 μg of NPY, $P<0.01$, Figures 2B through 2D). Unlike in the angioplasty + placebo group, the NPY-induced neointima was not laminar, and at the lower NPY dose, neointima grew into the lumen and divided vessels into 2 (Figure 2C).

Angioplasty in the placebo-treated rats also significantly increased media thickness of the injured (0.074±0.003 mm²) compared with those of the contralateral uninjured arteries from the same rats (0.050±0.002 mm², $P<0.01$) or intact vessels of the sham-operated rats (0.048±0.001 mm², $P<0.01$). NPY treatment of the uninjured arteries also caused significant media thickening (0.084±0.005 mm²) compared with the untreated vessels (0.050±0.002 mm², $P<0.01$).

**NPY-Induced Formation of an Atherosclerotic-Like Lesion**

In addition to neointima, NPY also stimulated formation of thrombus (Figures 2D, 3A, and 3B). NPY-induced lesion was additionally characterized using cell-specific markers and histocytochemistry. Continuous, vWf-positive (endothelial) staining was found in the endothelial layer of the uninjured vessels (Figure 3A). In contrast, in the angioplasty + placebo-treated vessels, vWf-positive staining was patchy, indicating noncontinuous regenerated endothelium (Figure 3A). In response to NPY, massive vWf-positive staining and numerous cd31-positive microvessels were identified within the neointimal lesion and thrombus (Figures 3A and 3C), indicating neovascularization. This was confirmed in Masson’s trichrome staining, which visualized the presence of red blood cell–containing microvessels (red-stained cells, Figure 3B) within neointima of the NPY-treated but not placebo-treated injured arteries. Masson’s trichrome staining also revealed increased matrix deposition (blue staining, Figure 3B), also indicated by increased hyaluronan staining in the NPY-treated but not placebo-treated injured vessels (Figure 3D).

Accumulation of macrophages and lipids in human atherosclerotic plaques has been a key marker for atherosclerosis. Figure 3E shows a significant increase in cd68-positive staining for macrophages in the neointimal lesion of the NPY-treated, but not in placebo-treated, injured or uninjured vessels. In the same lesion area, in NPY-treated vessels, there was also a marked increase in the Oil Red O staining, indicating lipid deposition absent in vessels from other groups (Figure 3F).

**NPY Receptor Expression**

Intact rat carotid arteries showed low Y1 receptor expression by reverse transcriptase–PCR and Western blot analysis and also expressed NPY itself and DPPIV mRNA (Figures 4A and 4B). Six and 24 hours after angioplasty, the Y1, Y2, and, to a lesser extent, Y5 receptor mRNAs and proteins became...
upregulated, as compared with sham-operated or intact carotid arteries (Figures 4A and 4B). In contrast, at the same time (6 to 24 hours), DPPIV mRNA became downregulated in the angioplasty-injured placebo-treated arteries (Figure 4A). Expression of Y1 and Y5, but not Y2, receptor expression persisted in the injured vessels until 14 days after angioplasty when, additionally, vessels regained expression of DPPIV mRNA (Figure 4A).

Administration of the NPY pellet did not change the pattern of the NPY receptor and DPPIV expression except that the Y5 mRNA at 6 (not shown) and 24 hours after angioplasty and DPPIV mRNA at 14 days after angioplasty appeared stronger than in the placebo-treated rats (Figure 4A).

Effects of Y1 and Y5 Receptor Antagonist on Neointima and Media Thickening

Angioplasty-induced neointima formation was reduced by 50% by the Y1 receptor antagonist (H409/22 acetate, 0.02 μmol/kg per min for 14 days, IV, P<0.01, Figure 5) and by 40% by the Y5 antagonist (CGP71683A, 0.02 μmol/kg per min for 14 days, IV, P<0.01, Figure 5). These same receptor antagonists, alone or combined, completely prevented the NPY-induced vessel occlusion and neointimal thickening, although the Y1 antagonist was significantly more effective than the Y5 antagonist (P<0.05, Figure 5). Also, only the Y1 receptor antagonist reduced media thickening in the injured vessels in the placebo-treated group (from 0.074±0.003 to 0.046±0.002 mm², P<0.01).

Discussion

This is the first report that balloon angioplasty causes early and persistent activation of the NPY growth-promoting receptor system in injured rat carotid arteries as well as peptide accumulation in platelets. To our knowledge, our study also provides the first description of an animal model leading to rapid vascular occlusion with an atherosclerotic-like lesion in normal rats without prior genetic or dietary modification of lipid metabolism. The mechanism of NPY-induced formation of this occlusive atherosclerotic-like lesion seems to be multifactorial.

First, NPY has been shown before by us and others to stimulate VSMC proliferation. In vitro, NPY is a potent mitogen—its activity for rat and human VSMC starts at sub-pM concentrations—and elicits a bimodal response by activating multiple receptors, Y1 and Y5, which seem to exist in high- and low-affinity states. The sensitivity of VSMCs to the proliferative effects of NPY is augmented by intense β-adrenergic receptor activation. Reciprocally, NPY cooperates synergistically with other sympathetic neurotransmitters, norepinephrine, and ATP, all of which were shown in vitro to potentiate each other’s actions.

In the present study, we used a slow-release pellet to administer NPY at the injury site. The 1- to 10-μg pellets,
delivering NPY over 14 days, increased NPY-ir levels in the vessel wall and neighboring muscle (used to support the pellet) 2.5-fold and without altering circulating peptide levels in PPP. In contrast, angioplasty alone or with NPY markedly elevated NPY-ir in PRP to levels similar to those yielded by high-intensity cold stress in unoperated rats. A rise of NPY-ir in platelet-rich, but not platelet-poor, plasma suggests accumulation of NPY in platelets adhering at the site of endothelial injury. The latter is known to augment platelet aggregation attributable to removal of antiaggregatory factors, such as nitric oxide and prostacyclin, and platelet uptake of other circulating peptides, ie, cardiac natriuretic peptide, has also been reported.

Alternatively, the angioplasty-induced rise in platelet NPY may be attributable to upregulation of de novo peptide synthesis in megakaryocytes. Earlier, we and others reported that in rats and some strains of mice, NPY is synthesized in megakaryocytes and released from platelets during secondary aggregation. NPY may be proaggregatory, because it potentiated aggregation to subthreshold doses of collagen in rat platelets, and higher platelet NPY levels were found to associate with greater aggregability in spontaneously hypertensive rats. Because levels similar to those in spontaneously hypertensive rats were found in our study, this may suggest that increased platelet NPY augments platelet aggregability, which in turn promotes thrombus formation.

Thrombus formation per se may additionally accelerate neointima formation by platelet secretion of vascular mitogens such as platelet-derived growth factor. Conceivably, NPY could also act indirectly to promote thrombus formation by changing vessel rheology. However, this mechanism appears insufficient, because thrombus did not form in vessels treated with 1 μg NPY, even though they were more obstructed than the placebo-treated injured vessels. Furthermore, a direct proaggregatory effect of NPY is suggested by the massive secretion of vWF in vessels treated with 10 μg NPY. vWF facilitates binding of platelet surface glycoprotein Ibα to collagen and mediates platelet adhesion to injured vascular wall, and its elevated levels have been linked to atherosclerosis. Thus, NPY-mediated stimulation of vWF expression and thrombus formation within the injured vessel...
may represent an additional proatherosclerotic mechanism of the peptide.

In addition to stimulating VSMC growth, NPY seems to augment neointima formation by activating its neovascularization, a phenomenon normally absent in vessels subjected to angioplasty alone. We have previously reported the potent angiogenic activity of NPY in multiple in vitro and in vivo models. Along with angiogenesis, NPY activates DPPIV, a peptidase which is not only the converting enzyme of NPY but is also involved in matrix remodeling. In our study, the ability of NPY to stimulate matrix deposition was indicated by marked hyaluronic immunostaining in neointima from the NPY- but not placebo-treated vessels. Formation of matrix, which is a major factor contributing to vascular occlusion in both experimental and human atherosclerosis, could represent another mechanism for NPY-induced atherosclerotic-like lesion.

Although organized, vascularized thrombus is a hallmark of advanced atherosclerosis, transmigration of monocytes/macrophages, lipid deposition, and foam cell formation are prerequisites for its early stages. In humans, development of advanced atherosclerotic plaques usually occurs over many years of life, and to be reproduced in animals, major dietary or genetic modifications of lipid transport systems such as apolipoprotein E or LDL receptors are required. To our knowledge, no animal model has been described in which atherosclerotic lesions were formed within normolipemic environment. Surprisingly, neointimal lesion induced by NPY, but not angioplasty alone, was highly positive for cd68-immunostaining, indicating macrophage infiltration. At similar locations, NPY-treated angioplasty-injured vessels also showed marked lipid deposition, indicating formation of foam cells. The mechanisms of the effects of NPY on macrophages and lipid deposition remain to be determined. Previously, however, NPY was shown to activate monocyte migration and phagocytosis and also to promote lipid storage in adipocytes. The latter action is not only of central origin but results from the strong antilipolytic action of NPY in adipocytes.

Supporting the activities of NPY, the endogenous vascular NPY receptor system was found to be activated by angioplasty. Expression of Y1, Y2, and Y5 receptors increased as early as 6 to 24 hours after angioplasty (both mRNAs and proteins), whereas expression of DPPIV became downregulated. Because DPPIV is constitutively expressed in endothelium, its disappearance suggests successful deendothelization induced by angioplasty. DPPIV converts NPY1-36 to NPY3-36, which is inactive at Y1 but activates Y2/Y5 receptors. Loss of DPPIV may then augment NPY-Y1 receptor–mediated VSMC proliferative activities. These changes, both DPPIV and Y5 mRNA expression, appeared stronger after NPY treatment, although semiquantitative RT-PCR did not allow for real quantification.

By 14 days after angioplasty, DPPIV mRNA expression was regained by injured vessels, suggesting reendothelization of angioplasty-injured vessels, also indicated by partial restoration of vWF-positive cells of the innermost layer of the neointima. Finally, angioplasty-induced upregulation of Y2 receptors and DPPIV, particularly strong in the context of NPY, may contribute to neointima formation by promoting NPY-mediated neovascularization.

Alone or combined, Y1 and Y5 receptor antagonists (H409/22 acetate and CGP71683A, respectively), which block NPY-mediated VSMC proliferation in vitro, reduced the angioplasty-induced neointima formation by 40% to 50%. Even more remarkably, the effect of NPY was entirely prevented when treated with either Y1 or Y5 receptor antagonist. The Y1 antagonist was more effective than the Y5 antagonist in inhibiting NPY-induced neointima and was the only one to prevent media thickening. The latter findings support previous reports of NPY-Y1 receptor involvement in medial hypertrophy in hypertension. Thus, it seems that the Y1 receptor plays a major role in medial VSMC growth but both Y1 and Y5 receptors cooperate in NPY-induced neointima formation.

Why the antagonists of either receptor similarly inhibit angioplasty-induced neointima formation but their effect was not additive remains to be determined. One possibility is receptor heterodimerization, as shown for an increasing number of G-protein–coupled receptors, for example angiotensin receptors. All of the NPY receptors are G, coupled and share similar signaling, including inhibition of adenyl cyclase activity and phosphorylation of mitogen-activated protein kinase. NPY receptor heterodimerization is presently being investigated.

In summary, angioplasty of the rat carotid artery increases the platelet content of NPY and activates the vascular NPY-Y1/Y5 receptor system, which then contributes to 50% of neointima formation. Increasing NPY vascular content within a pathophysiological range such as yielded by intense stress rapidly occludes angioplasty-injured vessels with an atherosclerotic-like lesion containing vascularized neointima, thrombus, matrix, macrophages, and lipids. Thus, NPY, a neurotransmitter from the sympathetic nerves, is a new factor that can accelerate atherosclerosis and mediate restenosis after vascular interventions. Inhibitors of NPY-Y1 and -Y5 receptors may, therefore, be potential new ways to treat restenosis and ischemic cardiovascular diseases. Such a treatment may particularly benefit patients with elevated NPY levels subjected to chronic stress or carriers of the NPY signal peptide polymorphism, which apparently makes the peptide more releasable and is associated with accelerated atherosclerosis.

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