Neurogenic Atherosclerosis Mediated by Neuropeptide Y
Hardening of the Evidence
Christopher G. Sobey

Atherosclerosis is a complex, progressive vascular disease that represents an enormous clinical problem, being the principal cause of myocardial infarction and stroke and responsible for 50% of all mortality in westernized societies.1 Multiple risk factors for atherosclerosis are known to exist, including hypertension, hyperlipidemia, obesity, and smoking. Treatment of occlusive coronary atherosclerotic plaques is limited to invasive surgical procedures such as angioplasty, stenting, or bypass surgery. Such procedures are effective in acutely restoring blood flow to normal, but restenosis often occurs. For example, in 30% to 40% of patients, restenosis occurs within just 6 months of stenting or angioplasty surgery.2 Restenosis is thought to involve generation of vascular smooth muscle growth factors stimulated by various risk factors in the presence of endothelial denudation or dysfunction. However, relatively little attention has been given to the growth-promoting role of nerve-derived factors, even though many vessels that are occluded by atherosclerotic plaques, such as coronary arteries, are richly innervated by sympathetic nerve fibers.

Endothelial Dysfunction and Neuroendocrine Activation

Endothelial cell dysfunction is widely regarded as a key early phenomenon in the process of atherogenesis.1 The endothelium normally functions to inhibit vascular cell proliferation by inhibiting platelet aggregation and the release of growth factors from the vascular wall. Endothelial injury therefore commonly results in neointima formation due to proliferating and migrating vascular smooth muscle cells and myofibroblasts. There has been recent interest in whether endothelial dysfunction, and indeed atherosclerosis, can result from activation of the sympathetic nervous system, for example during prolonged stress.3

Potential Importance of Sympathetic Nerves and Neuropeptide Y (NPY) in Atherogenesis

Activation of the sympathetic nervous system could indirectly contribute to atherosclerosis via increased vasoconstriction or by stimulating platelet aggregation or insulin resistance.3,4 Patients with hypertension and high sympathetic tone are at high risk for coronary disease, and this is not all attributable to blood pressure elevation.5 Interestingly, there is growing clinical and experimental evidence that acute and chronic forms of psychosocial stress might activate the sympathetic nervous system, thus contributing to the pathogenesis of atherosclerosis.3

Sympathetic neurotransmitters such as norepinephrine (NE), ATP, and NPY are known to have trophic effects on vascular smooth muscle. In particular, the mitogenic effects of NPY are very potent (starting at sub pmol/L concentrations) and are synergistic with those of both NE and ATP,6,7 making it a valid candidate as a stimulus for neurogenic atherosclerotic lesion development. NPY is a 36-amino acid peptide that is widely distributed across species in the central and peripheral nervous systems, and is coreleased with NE from sympathetic nerves. NPY is a vasoconstrictor in addition to its ability to stimulate growth of vascular smooth muscle and endothelium.8 In humans, NPY circulates in plasma and is released into the circulation during sympathetic activation by a number of stimuli, including exercise, cold exposure, and cigarette smoking.4 Marked elevation of plasma NPY occurs in severe or prolonged stress, and in patients with myocardial ischemia or congestive heart failure.9

In the cardiovascular system, NPY is not only contained in adventitial nerves, but it may be synthesized in endothelial10 and immune cells,11 and in megakaryocytes/platelets of rodents12 into which it may also be taken up from plasma. However, there is a closer correlation between plasma levels of NPY and NE than NPY and epinephrine, under physiological and pathological conditions, suggesting a largely neuronal source for plasma NPY.13 The effects of NPY are thought to be mediated by 5 different receptor subtypes, Y1 to Y5. Y1 receptors can mediate both the vasoconstrictor and mitogenic effects of NPY in vascular smooth muscle, whereas Y2 and Y5 receptors appear to mainly mediate angiogenic/endothelial effects. Recent epidemiological evidence that a common (6% to 14%) leucine7 to proline7 polymorphism in the peptide product of the NPY gene correlates highly with elevated total and LDL cholesterol levels, as well as increased thickening of the carotid artery, particularly in diabetes,14 provides evidence that the NPY signaling system may independently contribute to cardiovascular disease.

New Evidence for Proatherosclerotic Effects of NPY

Consistent with the concept that sympathetic neurotransmitters may play a role in the development of atherosclerosis, the
article by Li et al.15 in this issue reports compelling new evidence for a major role of NPY in the formation of occlusive neointimal lesions following experimental balloon angioplasty. In this pharmacologically based study, the authors tested the hypothesis that NPY has proatherosclerotic activity and that NPY receptors known to mediate cellular proliferation (ie, Y1, Y2, and Y5) are activated by vascular injury and mediate the vascular smooth muscle proliferation and restenosis in this model. Several major new findings are reported regarding the role of NPY in experimental atherogenesis.

First, the authors found that at 14 days after angioplasty of the rat carotid artery, platelet NPY content was profoundly increased to levels similar to those achieved by sympathetic nervous system activation during exposure to cold stress. It seems conceivable that the NPY in plasma of angioplasty-treated rats largely originated in sympathetic nerves of the injured vessel segment. Angioplasty also increased expression of Y1, Y2, and Y5 receptor mRNA and protein in the injured arterial segments. It is interesting to consider that NPY levels would have been further concentrated in the injured vascular segment due to adherence of NPY-containing platelets at the site of endothelial disruption. However, given that rat platelets are particularly enriched with NPY, the relevance of this in the human situation is difficult to ascertain.

Second, the significant neointima formation and medial thickening which occurred in the angioplasty-injured arteries over 14 days could be effectively inhibited by intravenous treatment with Y1 or Y5 receptor antagonists, confirming that actions of NPY were essential for these structural changes in the injured artery wall.

Third, and perhaps most striking, was the finding that if angioplasty-injured vessels were directly and continuously exposed to higher, “pathophysiological-like” concentrations of NPY delivered from a slow-release pellet implanted in the adjacent perivascular space, complete vessel occlusion by an atherosclerotic lesion occurred within 14 days. Intravenous Y1 or Y5 receptor antagonist administration also prevented development of the NPY-induced occlusive lesions. Notably, these advanced plaques occurred in the absence of elevated plasma cholesterol levels and appeared in several aspects to be similar to lesions which occur over many years in humans. For example, these occlusive lesions contained vascularized neointima, thrombus, extracellular matrix, macrophages, and lipids. Such lesions are typically very difficult to reproduce in animals without previous genetic or dietary modification of lipid metabolism, and this model should therefore represent a valuable new approach for studies of atherosclerotic plaque formation. It remains to be determined whether the rapidity of the plaque formation in this model is actually a limitation for improving our understanding of much more slowly developing human lesions.

Limitations and Implications

In summary, the report by Li et al.15 is the first description of an animal model of rapid vascular occlusion with human-like atherosclerotic lesions in normal rats (a species normally resistant to atherosclerosis), and the data suggest a key role for the sympathetic neurotransmitter NPY as a major mediator. The actual source of NPY and its cellular targets in the angioplasty-induced lesion formation remain to be identified, as does the relative importance of Y1 and Y5 receptors. The authors do not report whether blood pressure was increased in these animals in association with the elevated plasma NPY levels, but if a pressor effect did occur, interpreting the major actions of NPY may be further complicated. Moreover, the conclusions regarding the role of NPY and its receptors in lesion formation are partially dependent on data using pharmacological receptor antagonists which could potentially have limited selectivity, and are therefore still somewhat indirect. Hence, it would be interesting to perform similar experiments in mice deficient in NPY, Y1, or Y5 receptors, which are now available,16 to provide more direct evidence that this sympathetic neurotransmitter does indeed accelerate atherosclerosis and mediate restenosis following vascular interventions. If so, inhibitors of NPY receptors could perhaps be a new approach to prevent restenosis and ischemic cardiovascular disease following angioplasty or stenting, especially in patients suffering from chronic stress and/or sympathetic nervous system hyperactivity. If NPY does play a role in human atherogenesis, it will be of great interest to evaluate its importance relative to previously identified and established clinical risk factors.

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References


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