Review

Atherosclerosis and angiogenesis: what do nerves have to do with it?

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Abstract:
Neuropeptide Y (NPY) is a sympathetic neurotransmitter and a stress mediator with pleiotropic activities mediated by multiple receptors, Y1-Y5. Originally known as an appetite stimulant and a vasoconstrictor, NPY has recently emerged as a growth factor for a variety of cells from vascular smooth muscle to neural precursors – implicating the peptide in atherosclerosis and tissue remodeling. NPY is also potently angiogenic, and was hailed as a potential candidate for a nerve-driven ischemic revascularization.

To determine if the latter, beneficial activity of the peptide can be separated from its deleterious pro-atherosclerotic action – receptor specificity and mechanisms of this “Janus phenomenon” were studied. Expression of Y2 receptors on the endothelium, and Y1 receptors on vascular smooth muscle, were required for angiogenic and pro-atherosclerotic activities, respectively. Amplification of both activities was provided by co-expression of Y5 receptors. In rodent models, limb ischemia up-regulated the NPY-Y2 system, which contributed to post-ischemic revascularization; exogenous NPY further augmented it and nearly normalized blood flow and function of ischemic tissues. NPY-induced angiogenesis was also dependent on nitric oxide and endothelial dipeptidyl peptidase IV (DPPIV, which converts NPY to Y2/Y5-selective agonist), but resistant to Y1 receptor blockade. Conversely, vascular angioplasty up-regulated the NPY-Y1 system and promoted atherosclerosis and hyperplastic remodeling, and these activities were blocked by Y1 receptor antagonist and augmented by DPPIV inhibitors. Thus, drugs targeting specific NPY receptors may become new therapeutics against atherosclerosis/restenosis (Y1-selective antagonists) or for ischemic revascularization (Y2-selective agonists). Such drugs may be particularly beneficial for patients with elevated circulating NPY levels e.g. by chronic stress.

Key words:
nepotipeptide Y, NPY receptors, dipeptidyl peptidase IV, endothelium, ischemia, angioplasty, restenosis

Abbreviations:

Introduction

Vascular remodeling has become a popular topic of research, as it appears to underlie an increasing number of diseases. Many cardiovascular diseases such as hypertension, heart disease and stroke are due to hyperplastic and hypertrophic changes in the muscular vessel wall and/or atherosclerosis. In other conditions, such as tumors or retinopathy, the major change in vessel geometry is formation of new vessels, or angiogenesis. In physiological states, both processes, hypertrophy/hyperplasia of vascular smooth muscle cells and angiogenesis co-exist and are required for development of a functional circulation, to provide adequate blood flow in changing circum-