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Review

Innervation of the arterial wall and its modification in atherosclerosis

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ABSTRACT

The autonomic nervous system (ANS) plays an essential role in the regulation of vascular tone. Sympathetic neurotransmitters epinephrine and norepinephrine are released from the terminals of perivascular nerves and suppress endothelial production of nitric oxide (NO), an important vasodilator. Sympathetic nerves also release neuropeptide Y, a co-transmitter that stimulates vasoconstriction and proliferation of vascular smooth muscle cells. Parasympathetic nerves release acetylcholine, which leads to vascular contraction when NO production is inhibited. The ANS produces a variety of other vasoactive substances including ATP, calcitonin gene-related peptide, dopamine, and serotonin. On the other hand, the vascular system can reciprocally influence ANS activity through the release of NO, reactive oxygen species (ROS), angiotensin II, and other mechanisms. In pathological conditions such as atherosclerosis, hyperactivation of sympathetic neural activity has pro-atherogenic effects on the vascular function by increasing vasoconstriction, accumulation of modified lipoproteins in the vascular wall, induction of endothelial dysfunction, and stimulation of oxidative stress and vascular remodeling. Indeed, suppression of the sympathetic ANS should be beneficial for the treatment of cardiovascular diseases.

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Contents

1. Introduction

The pathogenesis of atherosclerosis is associated with marked structural and functional changes in the arterial wall including those affecting endothelial cells (ECs), vascular smooth muscle cells (VSMCs), resident macrophages, pericyte-like cells and other cell types. The major route of the pro-atherogenic action of metabolic and proinflammatory stress factors, which impair normal vascular function, is from the arterial lumen. These include serum lipoprotein and lipid modification and accumulation in the intima, oxidative stress, pro-inflammatory and prothrombotic stimuli driven by cytokines, chemokines, and other biologically active mediators, and infiltration of the subendothelial space with inflammatory immune cells (Ross, 1999). However, vascular function can also be impaired from the outside of vessels. Alterations in the autonomic nervous system (ANS) that are involved in the control of vascular tone could contribute to endothelial dysfunction and

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atherogenesis (Amiya et al., 2014). In this review, we consider how impaired interactions between the ANS and integral structural constituents of the vascular wall could contribute to the pathogenic mechanisms of atherosclerosis.

2. Autonomic nervous system neurotransmitters and their vascular effects

The sympathetic and parasympathetic nervous systems innervate vascular walls and regulate wall contractility and tension. ECs of large vessels are not directly innervated by the ANS whereas the endothelium of the microvasculature does receive direct contacts from nerve endings (Burnstock, 1990). Nerve terminals do not form synapses with vascular cells but release transmitters that can reach target cells (Hirst et al., 1992). The terminals are varicose and mobile and there is no structural post-junctional specialization on effector cells, rather the receptors for neurotransmitters accumulate on cell membranes at close junctions (Burnstock, 2008). Neurotransmitters such as adenosine triphosphate (ATP) could be released from nerve terminal varicosities and act on the endothelial P2Y receptors to mediate hyperpolarization of VSMCs (Draid et al., 2005) through release of the endothelial-derived factor (Fig. 1) (Thapaliya et al., 1999).

Cholinergic nerve endings are present in the muscular and endothelial layers of the vascular wall, whereas adrenergic nerve endings of the sympathetic nerve system can be found only in the muscular layer (Amiya et al., 2014). Arterial ECs have muscarinic M3 receptors that are involved in the regulation of production of nitric oxide (NO), a molecule that causes vasorelaxation (Hamel, 2004). Acetylcholine acts upon VSMCs *via* M2 and M3 receptors and causes their contraction when NO production is suppressed (Bolton and Lim, 1991).

Sympathetic stimulation leads to blocking of the endothelial-dependent and blood flow-mediated NO release *via* an α-adrenergic mechanism (Iemitsu et al., 2000; Hijmering et al., 2002). In animal models, blockage of perivascular vasomotor nerves results in seriously impaired endothelial function (Burnstock, 1990). In hypertensive patients, treatment with monoxidine, an α_2-adrenoreceptor agonist, has been shown to have beneficial effects on endothelial function (Topal et al., 2006; Derosa et al., 2007). Therefore, sympathetic nerves could influence endothelial function involved in the regulation of vascular tone.

Various neurotransmitters are known to have effects on endothelial function. For example, a sympathetic co-transmitter neuropeptide Y (NPY), which is released upon nerve activation and ischemia, stimulates vessel constriction and proliferation of VSMCs (Fig. 1) (Lundberg et al., 1984). ECs are able to express NPY, its receptors, and dipeptidyl peptidase IV, an enzyme which cleaves NPY, thereby inactivating the peptide and producing NPY3-36, an agonist of the PY2 receptor that displays pro-angiogenic properties (Abdel-Samad et al., 2012). Therefore, NPY induces the autocrine signaling mechanism in ECs that could regulate formation of new vessels and vascular regeneration in tissue damage (Lee et al., 2003).

Dopamine binds to D2 dopamine receptors in ECs in a process that leads to down-regulation of endothelial permeability induced by vascular endothelial growth factor (VEGF) through the stimulation of the production of vascular permeability factor (VPF) (Bhattacharya et al., 2008). Dopamine induces endocytosis of the VEGF receptor II and therefore restricts its bioavailability, as well as preventing the interaction between VPF and VEGF and the activation of VEGF-dependent signaling (Basu et al., 2001).

Calcitonin gene-related peptide (CGRP) induces vasodilation by binding to its receptor on the endothelial surface (Kawasaki et al., 1988; Hagner et al., 2001). CGRP exists in two forms, α-CGRP and β-CGRP. The α-form comprises 37 amino acids and is translated from the transcript alternatively spliced from the calcitonin/CGRP gene (Emeson et al., 1989). The β-form of human CGRP is produced from the distinct gene located in the vicinity to the calcitonin/CGRP gene and differs from the α-form in three amino acids (Rezaeian et al., 2009). The CGRP receptor is a heterodimer consisting of calcitonin receptor-like receptor (CALCRL), a G protein-coupled receptor and receptor activity-modifying protein (RAMP1) (Poyner et al., 2002).

CGRP can also cause vascular relaxation in an endothelium-independent manner with involvement of cyclic adenosine monophosphate (cAMP), activation of potassium ATP-dependent (KATP) channels or BKCa channels (at a lower concentration, Deng and Li, 2005). The CGRPergic vasorelaxation system and sympathetic

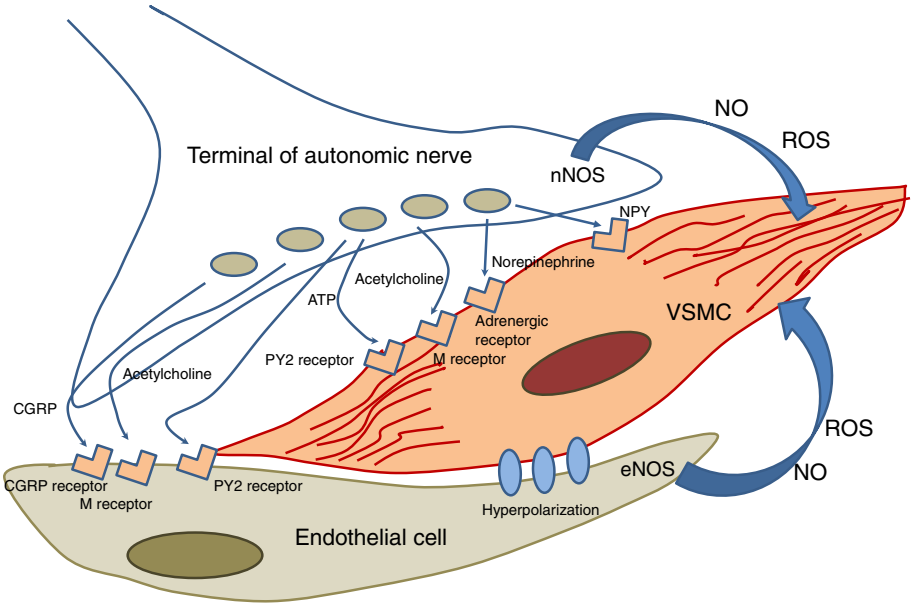

Fig. 1. The mechanisms by which the perivascular autonomous nervous system (ANS) influences vascular function. Perivascular terminals of autonomic nerves contain vesicles loaded with various neurotransmitters and vasoactive substances that could be released by activated nerves into the intercellular cells and diffuse to the target cells (endothelial cells and vascular smooth muscle cells (VSMCs)). The effector cells contain various receptors each of which specifically interact with a certain vasoactive factor released by nerves. Endothelial cells and vasomotor nerve terminals contain endothelial (eNOS) and neuronal (nNOS) nitric oxide (NO) synthase that produce a potent vasodilator NO and reactive oxygen species (ROS) modulating VSMC function. Adenosine triphosphate (ATP) released from nerve terminal varicosities acts *via* the endothelial P2Y receptors to mediate hyperpolarization of VSMCs through release of the endothelial-derived factor. CGRP, calcitonin gene-related peptide; NPY, neuropeptide Y.

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