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Review

The role of neuropeptide Y in the pathophysiology of atherosclerotic cardiovascular disease☆

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ABSTRACT

With average life expectancy rising greatly, the incidence rate of arteriosclerotic cardiovascular disease (ASCVD) has significantly increased. The heart disease has now become the number one killer that threatens the global population health, the second is stroke. It will be of great significance to investigate the underlying pathophysiological mechanisms of ASCVD in order to promote effective prevention and treatment. The neuropeptide Y (NPY) has now been discovered for more than thirty years and is widely distributed in the central nervous system (CNS) and peripheral tissues. By combining with certain receptors, NPY performs a variety of physiological functions, including the regulation of food intake, cardiovascular effects, development, hormonal secretion, sexual behavior, biological rhythms, temperature and emotion. In ASCVD, increased peripheral NPY was involved in the pathophysiological process of atherosclerosis through affecting the vascular endothelial dysfunction, the formation of foam cells, the proliferation of vascular smooth muscle cells, the local inflammatory response of plaques and the activation and aggregation of platelets. Via central and/or the peripheral nervous system, increased NPY was associated with dyslipidemia, hypertension, obesity, diabetes, impaired glucose tolerance, and smoking which are all risk factors for ASCVD. In this review, we summarize the role of neuropeptide Y in the development of atherosclerotic cardiovascular disease.

1. Introduction

In 2013, the International Atherosclerosis Society first put forward that the reduction of ASCVD was the ultimate goal to manage lipid disorder in "global recommendations for the management of dyslipidemia" [1]. In the same year, ASCVD had its first appearance in international clinical guidelines. In this guideline, American Heart Association defined the clinical diagnosis of ASCVD as acute coronary syndrome, the medical history of myocardial infarction, stable or unstable angina, coronary revascularization, arteriosclerotic stroke, peripheral arterial disease or revascularization [2].

However, the pathogenesis of ASCVD remains unclear. In previous studies, the low-density lipoprotein cholesterol [3], insulin, leptin [4] and some microRNAs [5] were found to be associated with ASCVD. Meanwhile, it was also noted that a few clinical studies had suggested that the concentration of neuropeptide Y (NPY) was an independent predictor for coronary atherosclerotic heart disease [6–8] and ischemic stroke [9–11]. NPY plays a crucial role in blood lipid metabolism, glucose metabolism and blood pressure regulation, which are all risk factors for ASCVD. Thus, we hypothesize that NPY is closely related to ASCVD. In this review, we focus on the current understanding of the role of NPY in these processes, and particularly discuss if NPY is the potential risk factor to the ASCVD.

2. Molecular biological characteristics of NPY

Neuropeptide Y, a thirty-six amino acid peptide, was first isolated from the porcine brain by Tatemoto et al. in 1982. It widely distributes in the mammalian central and peripheral nervous systems [12]. Neuropeptides are small protein-like molecules produced by neurons,which are the most diverse class of signaling molecules in the brain engaged in many physiological functions. NPY is one of the neuropeptides. Through bonding to its receptors, NPY involved in many physiological processes, including cortical excitability, stress response, food intake and storage of energy as fat, circadian rhythms, reducing voluntary alcohol intake, lowering blood pressure, and controlling epileptic seizures. In the autonomic system it serves as a strong vasoconstrictor and also causes growth of fat tissue [13,14]. Until now, six kinds of mammalian NPY receptor subtypes have been identified, i.e. Y1–Y6 receptor

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subtypes belong to the G protein-coupled receptor family except for Y3 [15]. NPY not only works directly by combining with receptors of cells localized in the atherosclerotic lesion but also regulates the nervous system which extensively affects the ASCVD-associated risk factors to worsen atherosclerosis.

3. Peripheral NPY directly involved in atherosclerosis

The mechanisms underpinning the local atherosclerosis lesions includes: a) LDL translocates into the inter-space between endothelial cells, forming the oxidized low-density lipoprotein (Ox-LDL); b) monocytes and lymphocytes migrate into the artery intima then become macrophages, and then transform into foam cells after swallowing Ox-LDL, which leads to the secretion of growth factors and pro-inflammatory cytokines that facilitate the plaque growth and inflammation; c) the artery vascular smooth muscle cells (SMC) migrate into the intima, swallow lipid to form the myogenic foam cells and then proliferate and migrate to form the fibrous cap; d) the elevation of blood pressure and local vascular stenosis may cause the interruption of the artery intima and activate the process of thrombus formation from platelets. There is a number of sympathetic nerve endings where the peripheral NPY coexists with norepinephrine located in the arterial wall [16]. Immunohistochemistry methods have also verified that NPY and norepinephrine release together when the activity of sympathetic nerves is enhanced. In addition, when the sympathetic nerves are activated, the platelets secrete and release NPY. The relationship between peripheral NPY and the main factors involved in development of atherosclerosis will be presented in details below.

3.1. NPY and vascular endothelial cells

Endothelial cells serve as a barrier between the blood vessel wall and blood. The endothelial dysfunction is the initiating factor for atherosclerosis via increasing the permeability of endothelium, enhancing the adhesion of leukocytes and changing the expression of genes in endothelial cells. The endothelial dysfunction may result in the aggregation of lipids, inflammatory cells, blood clotting substances, proliferation of vascular smooth muscle cells, and angiogenesis to facilitating the formation of atherosclerotic plaques. Present studies have demonstrated that NPY–Y1, Y2 and Y5 receptors are distributed on the endothelial cells. Under pathological condition, NPY binds to Y1 receptor to perform a vasoconstrictor effect, enhance the norepinephrine vasoconstriction [17], which leads to the elevation of blood pressure, local vascular stenosis and spasm, then promotes the retraction and discontinuity of endothelial cells. Moreover, the binding of NPY with Y1 receptor on endothelial cells promotes the mitosis of endothelial cells, which plays a key role in the process of intima thickening [18,19]. Although endothelial cells secrete a small amount of dipeptidyl peptidase IV (DPPIV) in physiological conditions, DPPIV significantly increase in ischemia, inflammation or injury [20]. DPPIV cleave NPY_{1-36} to NPY_{3-36}, increasing the affinity between NPY and Y2, Y5 receptors. NPY binds to receptor Y2 on endothelial cells, promoting the vascular endothelial cells to secret NO and VEGF, reducing the generation of its endothelin-1 [21] and angiostatin, facilitating the proliferation and migration of endothelial cells, all of which accelerate angiogenesis [22]. Consequently, the excessive new vessels in atherosclerotic plaque not only accelerate the growth of the plaque but also increase the risk of rupture and hemorrhage.

3.2. NPY and macrophages

The formation of foam cells in the atherosclerotic plaques and the chronic inflammation of plaque underpin the main processes of atherosclerosis. Macrophages are the key to both actions. In the model of rat carotid arteries with balloon injury, numerous macrophages with Y1, Y2 and Y5 receptors of NPY on their surface gathered at the atheromatous plaque lesions after administration of NPY to local injury regions of carotid artery [18]. Further study found that the level of NPY expression in the atherosclerotic plaque dramatically increased. A large number of macrophages were prone to assemble into foam cells, then participated in the further development of atherosclerotic plaque [23]. Furthermore, NPY–Y1 and NYP–Y2/Y5 receptors contributed to this process [24,25]. In addition, Zhou et al. found that after NPY binding to Y1 receptor, it could promote the macrophages to synthesize and release the high mobility group protein B1 through the protein kinase C/extracellular signal-regulated kinase (PKC/ERK) pathway, which is extensively involved in the inflammatory response and may contribute to damaging the integrity of the endothelial cells barrier [26].

3.3. NPY and vascular smooth muscle cells

Vascular smooth muscle cells are a critical part of the arteria media. Its pathophysiologic changes are extremely important in the formation of atherosclerosis, and NPY impacts VSMC in various aspects. Firstly, NPY has been proven to promote the proliferation of vascular smooth muscle cells in vitro and in vivo experiments. In vitro experiments of human or rat vascular smooth muscle cells, NPY accelerated the proliferation of VSMC. NPY activated the Y1 receptor and synergistic Y5 receptor in VSMC, increasing the concentration of Ca^{2+} in VSMC cytoplasm, activating the protein kinase C, promoting mitosis, which consequently leads to atherosclerosis [27]. In the apo-E rat carotid arteries balloon injury model, when NPY was delivered to the injured part of rat carotid artery, the injured part formed apparent atherosclerotic plaque lesions and the VSMC significantly increased in the plaques. It was also found that the expression of NPY–Y1/Y5 receptor in plaques significantly increased and suggests that the NPY–Y1/Y5 receptor inhibitor may alleviate vascular wall injury caused by vulnerable plaques rupture [28]. In addition, NPY can directly bind to the Y1 receptor in VSMC to play a role in vasoconstriction [13]. NPY binding to the Y2 receptor in VSMC [29] promoted migration and proliferation of VSMC, which contributed to the formation of new vessels in plaques [29].

3.4. NPY and platelets

Platelets in the peripheral blood circulation play an important role in the synthesis and storage of NPY. The activation of platelets is the key factor in the early stages of atherosclerosis formation. In a healthy state, platelets barely secrete NPY. However, when the vascular endothelium is injured, platelets will be activated and the generation and release of NPY will be increased. In turn, the platelets will adhere and aggregate to the injured vascular regions. Myers et al. found that when the collagen in the injured regions of the rat artery were exposed, the same process would happen, numerous formations of thrombus would appear, the gene expression in platelets would increase significantly, and the NPY–Y1/Y5 receptor expression would greatly increase [18,30]. Ruohonen et al. found that in the balloon injury model of rat carotid arteries, after NPY was delivered to the local injury part of carotid artery, the area of plaque lesion increased by 50%. In addition, there was significant increase of platelets aggregation in plaques, and it was also identified that the Y1/Y5 receptor expression was significantly elevated [30]. This suggested that the NPY–Y1/Y5 receptor might also be involved in the process of aggregation and adhesion of platelets, thus intensifying the formation of atherosclerotic plaques.

As described above, NPY synthesized and secreted from sympathetic ganglia and platelets has a wide range of interactions with endothelial cells, phagocytes, vascular smooth muscle cells and platelets in the pathophysiologic process and formation of atherosclerotic plaque formation (Fig. 1). Furthermore, combining with atherosclerosis, the strong vasoconstrictor effect of NPY can directly lead to the spasm of stenosis lesions, which induces ASCVD.