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Review

Nitric oxide bioavailability dysfunction involves in atherosclerosis

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ABSTRACT

The pathological characteristics of atherosclerosis (AS) include lipid accumulation, fibrosis formation and atherosclerotic plaque produced in artery intima, which leads to vascular sclerosis, lumen stenosis and irritates the ischemic changes of corresponding organs. Endothelial dysfunction was closely associated with AS. Nitric oxide (NO) is a multifunctional signaling molecule involved in the maintenance of metabolic and cardiovascular homeostasis. NO is also a potent endogenous vasodilator and enters for the key processes that suppresses the formation vascular lesion even AS. NO bioavailability indicates the production and utilization of endothelial NO in organisms, its decrease is related to oxidative stress, lipid infiltration, the expressions of some inflammatory factors and the alteration of vascular tone, which plays an important role in endothelial dysfunction. The enhancement of arginase activity and the increase in asymmetric dimethylarginine and hyperhomocysteinemia levels all contribute to AS by intervening NO bioavailability in human beings. Diabetes mellitus, obesity, chronic kidney disease and smoking, etc., also participate in AS by influencing NO bioavailability and NO level. Here, we reviewed the relationship between NO bioavailability and AS according the newest literatures.

1. The way of NO production and its functions

NO is an endothelium derived relaxing factor produced in the vascular endothelial cell (VEC) wherein nitric oxide synthase (NOS) catalyzed the oxidation of L-arginine (L-arg) and oxygen to produce NO. This process involves in some cofactors such as nicotinamide adenine dinucleotide phosphate-II (NADPH-II), calcium (Ca^{2+})/calmodulin (CaM), flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD) and tetrahydrobiopterin (BH_4) [1]. NO plays an important role in regulating vascular tone, lowering lipid levels, and inhibiting the expressions of adhesion molecules, platelet aggregation as well as vascular smooth muscle cell (VSMC) proliferation [2]. NOS is the only rate-limiting enzyme during NO synthesis from L-arginine. There are 3 NOS isoforms: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS), Under physiological state, nNOS and eNOS is more inclined to express, but under pathological state inducible NOS (iNOS) is more likely to express [3]. The synthesis of NO can be triggered by receptor-dependent agonists such as acetylcholine (Ach) and bradykinin (BK), non-receptor-dependent agonists such as Ca^{2+} ionophore, and blood flow alteration (Table 1) [4]. In addition, NO can be generated from nitrate (NO_3^-)/nitrite (NO_2^-) and s-nitrosothiols catalyzed by the diverse enzymes under the different conditions [5]. Under aerobic conditions, the stable metabolic products of NO are mainly NO_3^- and $NO_2^-\cdot$ which produce NO and increase NO bioavailability in vascular wall [6]. It has been reported that leafy vegetables, which is rich in NO_3^- have some positive regulating effects on the glycolipid metabolism, insulin resistance, inflammation and endothelial dysfunction in mice [7].

2. The relationship between NO bioavailability and AS

AS is described as a chronic progressive disorder characterized by vascular sclerosis and lumen stenosis due to accumulation of lipid, VSMC, and platelet that triggered by lipid peroxidation, endothelial dysfunction, inflammatory mediators released by activated macrophage, and the migration and proliferation of VSMC in tunica intima of artery. At intimal site, monocytes differentiate into macrophages and engulf oxidized low-density lipoproteins (ox-LDL), leading to the formation of inflammatory foam cells. Atherosclerotic lesion goes along with exacerbated macrophage accumulation and the excessive or prolonged release of inflammatory mediators followed by VSMC migration and proliferation from the media to the intima [8].

The abnormal alteration of the endothelial function is often triggered by an imbalance between the endothelial vasoprotective factors such as NO, endothelium-dependent hyperpolarization, the enhanced oxidative stress state, and the generated vasoconstrictors [9]. The

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Table 1
The mechanisms that NO bioavailability dysfunction related to atherosclerosis

Pathogenesis	eNOS uncoupling	Ser1177/Thr495 phosphorylation	signaling pathway	iNOS/eNOS/NO level	NO bioavailability	AS	Reference
ox-LDL	↑	Ser1177↓	NADPH↑ ROS↑ eNOS-Akt-HSP90↓ ADMA↑ ArgII↑ $O_2.^-$↑ $ONOO^-$↑ NF-κB↑	eNOS↓ iNOS↑ NO↓	↓	↑	[11] [12] [5] [3] [27]
HDL	↓		ox-LDL↓	eNOS↑ NO↑	↑	↓	[12]
oxidative stress	↑		NADPH↑ ROS↑ $ONOO^-$↑ BH_4↓$O_2.^-$↑ ox-LDL↑	eNOS↓ iNOS↑ NO↓	↓	↑	[18,19] [20] [22]
Inflammation	↑	Ser1177↓ Thr495↑	NF-κB↑ eNOS-Akt-HSP90↓ ADMA↑ ROS↑ $O_2.^-$↑	eNOS↓ iNOS↑ NO↓	↓	↑	[23,24] [28] [29] [28,34]
vasodilatation	↓		Ca^{2+}↑ cGMP↑ s-nitrosylation↑	eNOS↑ NO↑	↑	↓	[35,36] [10]
Vasoconstriction	↑		cGMP↓cIMP↑ ET-1↑ AngII↑ NADPH↑ ArgII↑	iNOS↑ NO↓	↓	↑	[1] [30,31] [28,38]
Arginase	↑		L-arg↓ $O_2.^-$↑ BH_4↓ROS↑ ADMA↑	eNOS↓ NO↓	↓	↑	[39,40] [11]
ADMA	↑		L-arg↓ $O_2.^-$↑	eNOS↓ NO↓	↓	↑	[43] [29]
homocysteine (Hcy)	↑	Ser1177↓ Thr495↑	$O_2.^-$↑$ONOO^-$↑ s-nitrosylation↑ BH_4↓ADMA↑ROS↑ VEGF/Akt/eNOS↓	eNOS↓ NO↓	↓	↑	[32] [46] [47] [45]
Diabetes (hyperglycaemia)	↑	Ser1177↓	NADPH↑$ONOO^-$↑ROS↑ AGEs↑ BH_4↓ L-arg↓ DDAH↓ ADMA↑	eNOS↓ iNOS↑ NO↓	↓	↑	[48,49] [50] [11] [47]
Obesity	↑	Ser1177↓	eNOS-Akt-HSP90↓ BH_4↓ ADMA↑ ROS↑ L-arg↓ AngII↑ ET-1↑	eNOS↓ iNOS↑ NO↓	↓	↑	[53] [54] [55] [37,56]
Chronic kidney disease	↑		NADPH↑ROS↑$ONOO^-$↑ L-arg↓ ADMA↑	eNOS↓ iNOS↑ NO↓	↓	↑	[57] [58,59]
Smoking	↑		ox-LDL↑ AGEs↑ ROS↑	eNOS↓ NO↓	↓	↑	[59] [5,33]

markedly decreased NO bioavailability may result from lipid peroxidation, oxidative stress, inflammatory responses and angiotasis changes in cardiovascular systems, which has been regarded by more and more scholars as one of the pivotal causes in endothelial injury and AS.

2.1. Lipid infiltration and oxidative modification cause endothelial dysfunction to exacerbate AS by decreasing NO bioavailability

Ox-LDL is the primary reason for which hyperlipidemia triggers AS (Fig. 1). Ox-LDL brings about endothelial dysfunction via eNOS uncoupling which results in an increase in superoxide anions ($O_2.^-$) production but a decrease in NO level. The activity of eNOS is upregulated by the phosphorylation of serine residue 1177 (Ser1177, human numbering corresponding to S1176 in mice). This phosphorylation activating is involved in the serine/threonine protein kinase Akt (i.e. protein kinase B, PKB) and heat shock protein 90 (Hsp90) [10]. After ox-LDL conjoining with its lectin like oxidized low density lipoprotein receptor 1 (LOX-1), it stimulates NADPH oxidase to generate ROS, restrains Akt-mediated eNOS Ser1177 phosphorylation, destroys the combination of eNOS-Akt and HSP90, upregulates the expression of caveolin (the main coat protein of caveolae, a negative regulator of eNOS), elevates serous asymmetric dimethylarginine (ADMA) level and activates arginaseII, all of which attenuate the eNOS activity and the NO bioavailability [2,5,11,12]. In addition, iNOS binds to calmodulin even at a negligible concentration of Ca^{2+} and produces extensive amount of $O_2.^-$, which spontaneously react with NO to form peroxynitrite anion ($ONOO^-$, a highly reactive and cytotoxic radical), inducing lipid peroxidation and vascular endothelial dysfunction [3]. It has been reported that at low concentration (< 10 μg/mL), ox-LDL can activate phosphoinositide 3-kinase (PI3K)/Akt/eNOS pathway, which then are mediated by p38 MAPK- and SAPK/JNK-related pathways to contribute to the formation of new vessels and NO [13,14]. The inhibition of iNOS-dependent NO production caused by ox-LDL promotes the proliferation of macrophage, which might be an additional significant pathophysiological mechanism of AS. Furthermore, NO donor could cut down macrophage proliferation induced by ox-LDL [15].

Atherosclerotic plaque is related to the accumulation of cholesterol in vascular wall. High density lipoprotein (HDL) is involved in the reverse transport of cholesterol and increases the cholesterol efflux of macrophage. HDL-C can also resist the inhibition of ox-LDL on eNOS and can restrain oxidative stress as well as inflammation, exerting its