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Review

Aging in blood vessels. Medicinal agents FOR systemic arterial hypertension in the elderly

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ABSTRACT

Aging impairs blood vessel function and leads to cardiovascular disease. The mechanisms underlying the age-related endothelial, smooth muscle and extracellular matrix vascular dysfunction are discussed. Vascular dysfunction is caused by: (1) Oxidative stress enhancement. (2) Reduction of nitric oxide (NO) bioavailability, by diminished NO synthesis and/or augmented NO scavenging. (3) Production of vasoconstrictor/vasodilator factor imbalances. (4) Low-grade pro-inflammatory environment. (5) Impaired angiogenesis. (6) Endothelial cell senescence. The aging process in vascular smooth muscle is characterized by: (1) Altered replicating potential. (2) Change in cellular phenotype. (3) Changes in responsiveness to contracting and relaxing mediators. (4) Changes in intracellular signaling functions.

Systemic arterial hypertension is an age-dependent disorder, and almost half of the elderly human population is hypertensive. The influence of hypertension on the aging cardiovascular system has been studied in models of hypertensive rats. Treatment for hypertension is recommended in the elderly. Lifestyle modifications, natural compounds and hormone therapies are useful for initial stages and as supporting treatment with medication but evidence from clinical trials in this population is needed. Since all antihypertensive agents can lower blood pressure in the elderly, therapy should be based on its potential side effects and drug interactions.

Contents

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1. Introduction

Aging can be defined as a progressive deterioration of biological functions after the organism has attained its maximal reproductive competence (Guarner-Lans and Rubio-Ruiz, 2012). Aging is associated to an impairment of blood vessel function, which is a very early and important event leading to cardiovascular disease (El Assar et al., 2012). Dominant aspects of vascular aging include increased arterial stiffness, dilation of central elastic arteries and endothelial dysfunction (Kotsis et al., 2011).

Vascular aging is associated with both structural and functional changes that take place at the level of the endothelium, vascular smooth muscle cells (VSMC) and the extracellular matrix of blood vessels. There are few studies on the aging of vascular contraction and relaxation responses. Age-related vascular changes may differ from one species to another and in blood vessels supplying individual organs.

Therapies geared to retard the vascular aging process are of great clinical importance. In fact, there are numerous studies in process, aiming at determining the etiology of cardiovascular aging, as well as the prevention of its more noxious aspects.

2. The aging endothelium

The mechanisms underlying the age-related endothelial vascular dysfunction are as follows.

2.1. The enhancement of oxidative stress

Reactive oxygen and nitrogen species are essential signaling molecules, regulating vascular homeostasis, and relevant changes related to age in the vascular wall are driven by them (Bachschmid et al., 2012). There are several main systems proposed to be the sources for the reactive oxygen species (ROS) increased production in the human vasculature, namely NADPH oxidase, xantine oxidase, uncoupled nitric oxide synthase and the mitochondrial respiratory chain (Brandes et al., 2005; Lassegue and Griendling, 2010; Cau et al., 2012).

The age-dependent increase in free radical formation causes deterioration of the nitric oxide (NO) signaling cascade, alters and activates prostaglandin metabolism, and promotes novel oxidative posttranslational protein modifications that interfere with vascular and cell signaling pathways. As a result, vascular dysfunction manifests itself. Compensatory mechanisms are initially activated to cope with age-induced oxidative stress, but become futile, which results in irreversible oxidative modifications of biological macromolecules (Bachschmid et al., 2012; van der Loo et al., 2002).

Several lines of evidence in experimental animal models indicate the central role of mitochondria both in lifespan determination and in cardiovascular aging. In aging, there is a reduction in the number of mitochondria and an increase in the generation of dysfunctional proteins, which leads to a depletion in the energy supply and even to an increase in the superoxide production (Pang et al., 2008). Mitochondrial oxidative stress, mitochondrial damage and biogenesis, as well as the crosstalk between mitochondria and cellular signaling, play a central role in cardiac and vascular aging (Dai et al., 2012).

2.2. The reduction of NO bioavailability

This can be caused by diminished NO synthesis and/or by augmented NO scavenging due to oxidative stress, leading to peroxynitrite formation ($ONOO^-$) (El Assar et al., 2012). NO is synthesized from L-arginine through the action of the NO synthases, particularly the endothelial synthase (eNOS), in the case of the vessels (Loscalzo, 2013). Reduced NO production may be due to: (1) a deficiency in NOS substrates and cofactors; (2) the presence of endogenous eNOS inhibitors; and (3) a lower expression and/or activity of eNOS. Enhanced NO degradation may be mostly due to excessive amounts of ROS such as superoxide anions that quench NO diminishing its functional activities. The lower availability of L-arginine with aging could be related to an increased expression and/or activity of arginase, the enzyme that degrades L-arginine (Santhanam et al., 2008). The synthesis of NO is blocked by the inhibition of the NOS active site with guanidine-substituted analogs of L-arginine such as asymmetric dimethylarginine (ADMA), which is a naturally occurring amino acid found in plasma and various tissues (Yamagishi and Matsui, 2011). There is a positive correlation between the plasmatic levels of ADMA and age (Schulze et al., 2005). Tetrahydrobiopterin (BH_4) is an essential cofactor for NO synthesis by eNOS and an inadequate availability of BH_4 results in 'uncoupling' of eNOS and synthesis of superoxide anion instead of NO (Landmesser et al., 2003). There is a reduction in BH_4 bioactivity with aging; however, the mechanism responsible for this reduction is unclear (Seals et al., 2011).

Studies in experimental models and even humans reveal that constitutive production of NO is reduced with aging and this circumstance may be relevant to a number of diseases that plague the aging population (Torregrossa et al., 2011). NO is one of the most important signaling molecules in our body, and loss of NO function is one of the earliest indicators or markers of disease. Clinical studies provide evidence that insufficient NO production is associated with all major cardiovascular risk factors, such as hyperlipidemia, diabetes, hypertension (Torregrossa et al., 2011).

Paradoxically, in rats the expression of eNOS in blood vessels increases significantly with age, but the levels of NO diminish, suggesting that this reduction is due to the rapid conversion of NO to peroxynitrates, through the action of superoxide radicals (Sun et al., 2004). Vascular and renal mRNA for inducible NO