Biomedicine & Pharmacotherapy 93 (2017) 370–375

Available online at
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Review

Inducible nitric oxide synthase: Good or bad?

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ARTICLE INFO

Article history:
Received 22 March 2017
Received in revised form 29 May 2017
Accepted 12 June 2017

Keywords:
Nitric oxide synthase (NOS)
Inducible NOS (iNOS)
Endothelial NOS (eNOS)
Cyclooxygenase-2 (COX-2)
COX-2
Oxidative stress
Cardiovascular diseases

ABSTRACT

Nitric oxide synthases (NOS) are a family of isoforms responsible for the synthesis of the potent dilator nitric oxide (NO). Expression of inducible NOS (iNOS) occurs in conditions of inflammation, and produces large amounts of NO. In pathological conditions iNOS is regarded as a harmful enzyme and is proposed to be a major contributor to diseases of the cardiovascular system such as atherosclerosis. In this review, we address the notion that iNOS is a detrimental enzyme in disease and discuss its potentially beneficial roles. Additionally, we describe other molecules associated with iNOS in diseases such as atherosclerosis, and current research on therapeutic inhibitors tested to reduced pathology associated with cardiovascular diseases (CVD).

Contents

1. Introduction

Cardiovascular disease (CVD) is the broad term given to a group of diseases that affect the cardiac muscle and its associated vessels [1]. To date, CVD accounts for 1 in 3 deaths worldwide, particularly in developed countries. CVD is primarily caused by the inflammatory condition known as atherosclerosis, which is a chronic inflammatory disease of the arteries, by which the process of prolonged pathological changes occur [1].

Atherosclerosis is initiated by the subendothelial accumulation of low-density lipoproteins (LDL) altered by reactive oxidative species (ROS), causing the deposition of atherogenic or fibrofatty plaques which in turn results in the narrowing of lumen walls, reduces tissue perfusion and causes thickening and stiffening of vessel walls. The aforementioned processes provoke inflammation

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http://dx.doi.org/10.1016/j.biopha.2017.06.036
0753-3322/

ultimately leading to stenosis or thrombosis which may result in morbid events, where thrombosis can cause the rupture of fragile plaques, leading to stroke, heart attack and eventually death if left untreated [2].

Inflammation involves many complex chemical and cytological reactions that occur in response to injury caused by biological, physical or chemical insults. In healthy conditions, inflammation is a normal homeostatic response however, where inflammation persists chronically it shifts from being a protective mechanism to a harmful response and may lead to further damage [1]. Reduction in the inflammatory response may be a therapeutic target for diseases such as atherosclerosis. Extensive research has been conducted on pharmacological drugs for the treatment of inflammation, and have included common drugs such as the non-specific cyclooxygenase inhibitor, aspirin, which has been shown to be effective in reducing inflammation [3–5]. However, aspirin has been linked with adverse effects such as altered renal function and most commonly ulceration of the gastrointestinal tract [6]. As a result, researchers have sought other anti-inflammatory drugs such as selective cyclooxygenase-2 (COX-2) inhibitors in the hope that these drugs may provide the same efficacy as anti-inflammatory drugs, with less associated adverse effects.

2. Mechanisms of CVD

Endothelial dysfunction is the major pathway by which CVD develops, which is the imbalance between vasoconstricting and vasodilating substances acting on or produced within the endothelium [7]. Understanding the mechanisms associated with the development of endothelial dysfunction is complex, although it is known to involve the cross-communication of numerous physiological molecules and pathways, including pro-inflammatory pathways such as inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), such as superoxide (O_2—), peroxynitrite (ONOO-). Ultimately, endothelial dysfunction is understood to occur when nitric oxide (NO) as a free radical reacts with superoxide producing the highly reactive molecule ONOO— [8], which is considered an initial step in the atherosclerotic process [9].

ROS are reactive molecules that play a significant role in host-defence mechanisms of the body [10]. ROS within the vasculature can be derived from numerous sources, such as mitochondria, xanthine oxidases and peroxidases [11]. ROS are produced by a family of enzymes known as NOX, of which 7 catalytic isoforms so far have so far been identified, termed NOX1-5 and duel oxidase 1 and 2 (DUOX1 and DUOX2) [10,12]. NOX enzymes primarily function to provide cells with the localised release of ROS [13], and in healthy conditions are known to generate ROS needed for endothelial function and homeostasis of the cardiovascular system [14]. However, the inappropriate regulation of NOX has been implicated to contribute to inflammatory conditions such as atherosclerosis, where it encourages the nonspecific oxidative damage of cells contributing to disease [15,16]. When dysregulated these enzymes have been implicated to stimulate oxidative stress leading to endothelial dysfunction [14,17], with the NOX1, 2 and 4 isoforms having been implicated in disease such as atherosclerosis [10,13,18]. Thus, NOX enzymes as a therapeutic target for CVD has been of great interest to researchers and the pharmacological use of NOX inhibitor drugs which have been identified and are increasingly being explored in laboratory research.

To date a single origin or cause of the development of CVD is yet to be established; rather multifactorial risk factors such as hypertension, sedentary lifestyles, tobacco smoking, poor diet, gender and genetic susceptibility, facilitate the development of atherosclerosis. Interestingly, hyperhomocysteinemia (HHcy) has been regarded as an independent risk factor for atherosclerosis (see Fig. 1), especially in the initial stages [19,20]. Homocysteine (Hcy) is a non-protein, sulphur containing amino acid which is produced as a primary intermediate during the metabolism of methionine [19]. In healthy individuals Hcy is present in a normal range of 6–9 μM, whereas in diseased states this range has been found to increase to 10–100 μM and in severe cases can exceed this range [19,21,22].

HHcy elicits the development of atherosclerosis via increasing oxidative stress, reducing the bioavailability of NO (explained furtheron) and increasing the generation of ROS which may cause the uncoupling of NOS isoforms within the endothelium, causing a decrease in NO production and overproduction of O_2— [24], eventually leading to endothelial dysfunction.

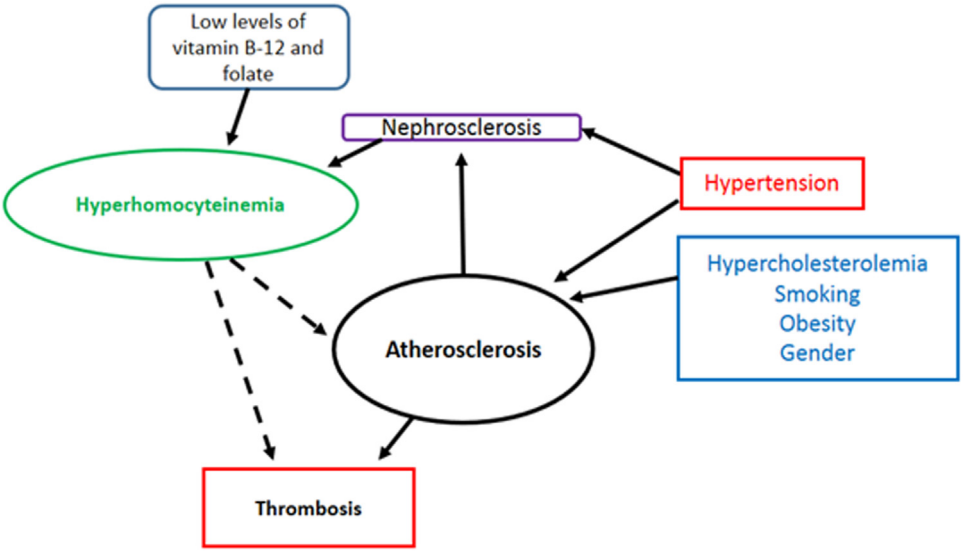

Fig. 1. The causative mechanisms of hyperhomocysteinemia and the association with atherosclerosis. Solid lines represent known mechanisms, and dashed lines represent proposed mechanisms of disease. Figure adapted from Brattstrom and Wilcken [23].