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Nitrergic system and plasmatic methylarginines: Evidence of their role in the perinatal programming of cardiovascular diseases

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ABSTRACT

Atherosclerosis, in turn preceded by endothelial dysfunction, underlies a series of important cardiovascular diseases. Reduced bioavailability of endothelial nitric oxide, by increasing vascular tone and promoting platelet aggregation, leukocyte adhesion, and smooth muscle cell proliferation, plays a key role in the onset of the majority of cardiovascular diseases. In addition, high blood levels of asymmetric dimethylarginine, a potent inhibitor of nitric oxide synthesis, are associated with future development of adverse cardiovascular events and cardiac death. Recent reports have demonstrated that another methylarginine, i.e., symmetric dimethylarginine, is also involved in the onset of endothelial dysfunction and hypertension. Almost a decade ago, prematurity at birth and intrauterine growth retardation were first associated with a potential negative influence on the cardiovascular apparatus, thus constituting risk factors or leading to early onset of cardiovascular diseases. This condition is referred to as cardiovascular perinatal programming. Accordingly, cardiovascular morbidity and mortality are higher among former preterm adults than in those born at term. The aim of this paper was to undertake a comprehensive literature review focusing on cellular and biochemical mechanisms resulting in both reduced nitric oxide bioavailability and increased methylarginine levels in subjects born preterm. Evidence of the involvement of these compounds in the perinatal programming of cardiovascular risk are also discussed.

1. Introduction

Almost a decade ago, prematurity at birth and intrauterine growth retardation were first reported to exert a negative influence on cardiovascular apparatus, being risk factors or leading to an increased risk of cardiovascular disease in childhood as well as in adulthood. This condition is referred to as cardiovascular perinatal programming [1,2]. For example, coronary artery disease mortality rate in adult males and females is higher among subjects born preterm and/or with low birth weight than in those born full term [3,4]. In mammals, nitric oxide (NO) is an important cellular signaling compound implicated in a series of physiological and pathological processes [5]. NO is released by the endothelium of blood vessels and inhibits vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium, originating in vasodilation and increasing blood flow [6]. Patients affected by atherosclerosis display a reduced bioavailability of endothelial NO [7]. Specifically, endothelium damage induced by atherosclerosis elicits a decrease in bioactivity of the enzyme endothelial nitrix oxide synthase (NOS), with subsequent impaired release of NO coupled with enhanced local degradation. Taken together, these processes result in an increased generation of reactive oxygen species and consequent cascade of oxidation-sensitive mechanisms in the arterial wall [6]. Hematic asymmetric dimethylarginine (ADMA) is a peptide derived from the continuous protein turnover of all the cells in the body. Normally present in blood, ADMA is a potent inhibitor of NO synthesis, thus representing an early marker of endothelial dysfunction, i.e., the first stage of the atherosclerotic process in blood vessels [8,9]. Indeed, previous reports have demonstrated an association between high levels of ADMA and multiple pathological conditions such as high cholesterol, smoking, diabetes, hypertension, heart failure, chronic renal failure, erectile dysfunction, preeclampsia, and liver failure [10–18]. All these conditions are characterized by endothelial damage and by the development of typical atherosclerotic plaques. The detection of high plasma ADMA levels is associated with future onset of adverse cardiovascular events and cardiac death, suggesting the predictive power of ADMA [19,20]. Based on these assumptions, it was hypothesized that fetal and maternal NO and ADMA may play an early role in influencing future development of the cardiovascular apparatus. It should moreover be underlined that NO is the main vasodilator compound present in the placenta and is involved in the regulation of feto-placental vascular reactivity, placental bed vascular resistance,

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trophoblast invasion and apoptosis, and platelet adhesion/aggregation in the intervillous space [21–23]. Placental vascular development plays a pivotal role in ensuring adequate fetal development [24]. Intrauterine growth restriction is a condition known to interfere with NO release and subsequently produce placental vascular dysfunction [25]. (See Box 1.)

The aim of this paper was to undertake a comprehensive literature review focused on cellular and biochemical mechanisms resulting in both reduced NO bioavailability and increased methylargine levels in subjects born preterm. Evidence supporting the involvement of these compounds in the perinatal programming of cardiovascular risk are also discussed.

2. Materials and methods

2.1. Search strategy

A PubMed/Medline search has been conducted using the MeSH terms: nitric oxide (NO), nitrergic system, enzyme NOS, methylarginines, asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), dimethylarginine-dimethylaminohydrolase (DDAH), reactive oxygen species (ROS), pregnancy, placenta, fetus, preeclampsia, delivery, birth, offspring, sons, prematurity at birth, preterm, birth weight, intrauterine growth restriction, endothelial dysfunction, atherosclerosis, perinatal programming, cardiovascular risk, and their combinations. Articles identified in this manner were retrieved, and the reference lists searched for additional relevant articles. The search was limited to English-language publications, but no other restrictions were applied. The PubMed/Medline database was searched from its inception to July 2014. The papers of key importance are reported in this review.

3. Results

3.1. NO and methylarginase metabolism: Established knowledge

Endothelial NO is synthesized with the contribution of the calcium-calmodulin-controlled isoenzymes NOS. Three NOS isoforms have been identified: neuronal (nNOS), inducible (iNOS), and endothelial (eNOS). The essential amino acid L-arginine, which enters the endothelial intracellular environment from plasma by means of specific membrane transport carriers, is converted into NO by the NOS family in the presence of both oxygen and cofactor tetrahydrobiopterin, resulting in the production of L-citrulline. NO released by endothelial cells relaxes vascular smooth muscles via the cyclic guanosine monophosphate-dependent pathway, thus exerting a strong vasodilatory effect [26,27].

Box 1
Main biological functions of ADMA and SDMA.

Asymmetric dimethylarginine (ADMA)

- It interferes with nitric oxide formation by inhibiting the enzyme nitric oxide synthase, thereby causing endothelial dysfunction. The latter is the first step of the atherosclerotic process.
- ADMA is a predictor of cardiovascular events and mortality in a number of different populations.

Symmetric dimethylarginine (SDMA)

- It interferes with nitric oxide generation by inhibiting the L-arginine uptake within the cell, thereby causing endothelial dysfunction.
- SDMA is a novel marker for kidney function and an independent predictor of all-cause mortality after acute ischemic stroke, irrespective of kidney function.

ADMA is produced when arginine residues are methylated through the action of types I and II protein arginine methyltransferases. ADMA is a competitive inhibitor of L-arginine for all the three NOS isoforms. Approximately 20% ADMA is excreted through the kidney, whereas the remaining 80% is metabolized to L-citrulline and dimethylamine by the specific enzyme dimethylarginine-dimethylaminohydrolase (DDAH), which is widely expressed in human tissues, primarily in the liver and in the kidney. Two DDAH isoforms exist: DDAH1, mainly in the kidney and brain, and DDAH2, predominantly in the heart and the kidney [28–30]. Symmetric dimethylarginine (SDMA) is a structural isomer of ADMA. The ADMA/SDMA ratio is a marker of ADMA catabolism and excretion, an indirect indicator of DDAH activity. A high ADMA/SDMA ratio is suggestive of reduced DDAH activity, and vice versa [31]. Inhibition of DDAH activity causes methylarginines accumulation together with the stoppage of NO synthesis and subsequent vasoconstriction. The critical role of DDAH activity in regulating NO synthesis in vivo has been demonstrated in a transgenic DDAH mouse model. This model exhibited an increased DDAH activity, and plasma ADMA levels reduced by 50%. Reduction in plasma ADMA is associated with a significant increase in NO activity, resulting in increased plasma and urine nitrate levels until doubled. In the transgenic mouse, the increase in NO activity leads to a reduction in systolic blood pressure of 15 mm Hg. This result provides evidence of the importance of DDAH activity and plasma ADMA levels in the regulation of NO synthesis [32]. The system of carriers, known as cationic amino acid transporters (CATs), is responsible for ADMA uptake from an extracellular to intracellular environment [26]. An increase in intracellular ADMA inhibits CATs, thus blocking NOS activity, and limiting cellular uptake of L-arginine, thereby contributing to oxidative stress and further NO biogenesis inhibition. NO and ADMA synthesis and metabolism pathways are summarized in Fig. 1.

3.2. Involvement of the nitrergic system in placental development

During pregnancy, the placenta acts as an interface between the mother and the fetus and strongly influences fetal programming by directly regulating blood flow, transporter activity, fetal nutrient supply and growth [33,34]. Placental nutrient transport is dependent on vascular development, which in turn determines blood flow to the placenta. NO regulates placental blood flow, while high ADMA levels are associated with uterine artery flow disturbances, underlining how, during placental maturation and development, epigenetic mechanisms, such as NO/ADMA imbalance, may play a key role in epigenetic fetal programming [35]. The placenta originates from trophoblasts that subsequently differentiate into cytotrophoblasts and syncytiotrophoblasts (primary villi). Cytotrophoblasts anchor the fetus to the mother and establish blood flow to the placenta. Conversely, syncytiotrophoblasts act as a placental transporting epithelium and contain a series of transporter proteins located in the plasma membranes of both the mother and the fetus. These carriers are responsible for delivering nutrients to the fetus. Placental nutrient transport is dependent on vascular development, which, in turn, is regulated by NO release. NOS isoform expression increases throughout pregnancy, reaches a peak around mid-gestation, and it is implicated in tissue remodeling, immunosuppression, and vasoregulation [36–41]. NO plays also a supportive role in promoting embryo survival [42]. In a ewe model, circulating NO and its metabolites were higher in pregnancies with multiple fetuses in comparison with singletons [43]. Increased plasma NO levels have been also reported in human pregnancy [44]. In an animal model involving pregnant sheep, endothelium-dependent relaxation of the uterine arteries largely involves the up-regulation of NO release that, in turn, results in a decrease in smooth muscle intracellular calcium concentration [45]. Autonomic innervation is lacking in the human feto-placental vasculature, and NO directly regulates feto-placental blood flow. Accordingly, NO is the main placental vasodilator involved not only in the regulation of feto-placental vascular reactivity but also in platelet adhesion/aggregation

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