

ADMA/NO Endothelial Pathway in Hypoxia Associated Chronic Respiratory Diseases

Abstract

Since its discovery, it is widely believed that Asymmetric Di Methyl Arginine (ADMA), as an inhibitor of Nitric Oxide (NO) synthesis, contributes to the pathogenesis of various diseases. This is especially evident in diseases of the cardiovascular system, where endothelial dysfunction leads to an imbalance between vasoconstriction and vasodilation. Although increased ADMA levels are strongly associated with endothelial dysfunction, several studies have pointed to a potentially beneficial effect of ADMA, primarily in the context of angiogenic diseases such as cancer and fibrosis chemical. The NO-independent anti proliferative properties of ADMA were identified in this setting. In particular, the regulation of ADMA by the degrading enzyme Dimethyl Arginine Dimethyl Amino Hydrolase (DDAH) has been the subject of many studies. DDAH is considered a promising therapeutic target for the indirect regulation of NO. In hypoxia-associated chronic respiratory disease, this controversial discussion of ADMA and DDAH is particularly clear-cut and is therefore the focus of this review. Endothelial-derived NO is known to be a major mediator of vasomotor tone regulation. NO is involved in a variety of mechanisms with regulatory functions, including inhibition of platelet adhesion and aggregation, monocyte adhesion, and smooth muscle cell proliferation. Therefore, NO plays an important role in vascular homeostasis. NO is produced by Nitric Oxide Synthase (NOS) enzymes. There are three distinct isomers that catalyze the formation of NO from the L-arginine and O₂ substrates, with L-citrulline being generated as a second product. The distinct isoforms differ in their tissue and cellular distribution and regulatory mechanisms. The three isoforms are neuronal NOS (NOS1, nNOS), inducible NOS (NOS2, iNOS) and endothelial NOS (NOS3, eNOS). Among others, nNOS is mainly expressed in the central and peripheral nervous system, kidney, pancreas, and skeletal muscle. The induced form of NOS was initially identified as a mediator of innate immunity and macrophages and can be induced in different cell types such as vascular smooth muscle cells, renal tubular epithelium, hepatocytes and mesenchymal cells. Expression of eNOS is mainly limited to vascular endothelial cells and mainly to medium and large sized arteries and arterioles.

Keywords: Endothelial • Hypoxia • Infections • Chronic Respiratory Diseases

Introduction

Not only is NO production dependent on oxygen, but NO also plays a very important role in the regulation of O₂ delivery through local vasomotor control and central cardiovascular and respiratory responses. O₂ is well known for its important function in cellular energy production. O₂ carrying capacity and blood flow saturation are the major determinants of tissue O₂ delivery. Therefore, NO plays a key role in the regulation of vascular tone and organ function during hypoxia. Paradoxically, hypoxic environments reduce eNOS expression and function, which suggests to us that considering NO as a vasopressor or blood pressure regulator is simply too simplistic. In recent years, the NO signaling cascade has been discussed as a “sensing-and-response” pathway to reduce O₂ bioavailability through interaction with the O₂ sensing pathway [1, 2].

Discussion

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Another example showing the complexity of the role of the L-arginine/NO pathway in hypoxia was shown. They were able to demonstrate that L-arginine supplementation promoted angiogenesis in the gas exchange region of the hypoxic lung and reduced the development of pulmonary hypertension in rats in a NOT independent manner. This suggests that in addition to the substrate function of NOS, L-arginine appears to have additional angiogenic properties, especially in the pulmonary circulation. N-guanidino-dimethylation of L-arginine residues in proteins by Protein-Arginine Methyl Transferases (PRMTs) and subsequent proteolysis leads to the release of free dimethylated L-arginine analogues in tissue and plasma. ADMA is known to inhibit all three forms of NOS isoforms. It competes with L-arginine for the binding site at the active site of NOS. Alternatively, ADMA can “uncouple” NOS by shifting the balance of NO generation to the side that produces superoxide. In vitro and in vivo studies demonstrate that an increase in ADMA can lead to a change in NO bioavailability as well as an increase in Reactive Oxygen Species (ROS) formation. Another dimethyl analogue of L-arginine is Symmetric Di Methyl Arginine (SDMA), but its role in the endothelial NO pathway remains unclear. Both SDMA and ADMA have the potential to interfere with NOS substrate availability by inhibiting the Cation L-Arginine (CAT) transmembrane transport system, but the IC₅₀ value is higher than the concentration value estimated indigenously of ADMA and SDMA. In a large number of prospective clinical studies, ADMA has been described as a predictor of major cardiovascular events and death in patients at low, intermediate, and high cardiovascular risk. Several recent studies have shown that SDMA is also associated with cardiovascular events and we have shown that SDMA, but not ADMA, has the potential to predict all-cause mortality in the following ischemic stroke [3-5].

Nearly 80% of ADMA is enzymatically hydrolysed by Dimethyl Arginine Di Methyl Amino Hydrolase (DDAH). DDAH is expressed in two isoforms, DDAH-1 and DDAH-2, which are characterized by distinct tissue distributions, are encoded by different genes, and can perform distinct functional roles. Overexpression of DDAH-1 or DDAH-2 saved mice from the adverse effects of ADMA infusion and improved recovery from vascular injury. Transient siRNA-mediated knockout experiments in mice reveal

specific functions of DDAH isoforms. Based on these experiments, it appears that DDAH-1 is the dominant form that regulates plasma ADMA levels, while DDAH-2 appears to be required for acetylcholine-dependent vasodilation [6, 7].

Conclusion

Indirect regulation of NO bioavailability by altering ADMA levels is discussed as a therapeutic option in various diseases. The ADMA concentration can be adjusted to varying degrees. An increase in ADMA formation due to increased PRMT activity can be observed in the context of various human cancers, suggesting a decrease in NO bioavailability. Increased PRMT activity can also be observed in various chronic respiratory diseases, leading to discussion that protein methylation could be a mechanism with therapeutic potential. The effect on NO formation due to the increase in ADMA concentration by decreasing the degradation of ADMA can recently be demonstrated by his colleagues. They identified a potent DDAH inhibitor that significantly increased intracellular ADMA levels and decreased lipopolysaccharide-induced NO production in endothelial cells. However, it is indisputable that increased concentrations of ADMA and SDMA in human tissues and plasma as well as in rodents are associated with an adverse course of various cardiovascular diseases with mortality increase. The mechanism behind ADMA is thought to inhibit NO production leading to endothelial dysfunction, but why SDMA is associated with adverse outcomes remains unclear. The correlation of ADMA and SDMA with cardiovascular disease is discussed elsewhere. This review will focus on the respiratory system and the effect of hypoxia on the endothelial ADMA/NO pathway. It is indisputable that in healthy lungs, NO plays a major role in maintaining adequate ventilation/perfusion in response to local hypoxia [8-10].

Acknowledgement

None

Conflict of Interest

None

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