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Targeting arginase and nitric oxide metabolism in chronic airway diseases and their co-morbidities

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In the airways, arginase and NOS compete for the common substrate L-arginine. In chronic airway diseases, such as asthma and COPD, elevated arginase expression contributes to airway contractility, hyperresponsiveness, inflammation and remodeling. The disrupted L-arginine homeostasis, through changes in arginase and NOS expression and activity, does not only play a central role in the development of various airways diseases such as asthma or COPD. It possibly also affects L-arginine homeostasis throughout the body contributing to the emergence of co-morbidities. This review focusses on the role of arginase, NOS and ADMA in co-morbidities of asthma and COPD and speculates on their possible connection.

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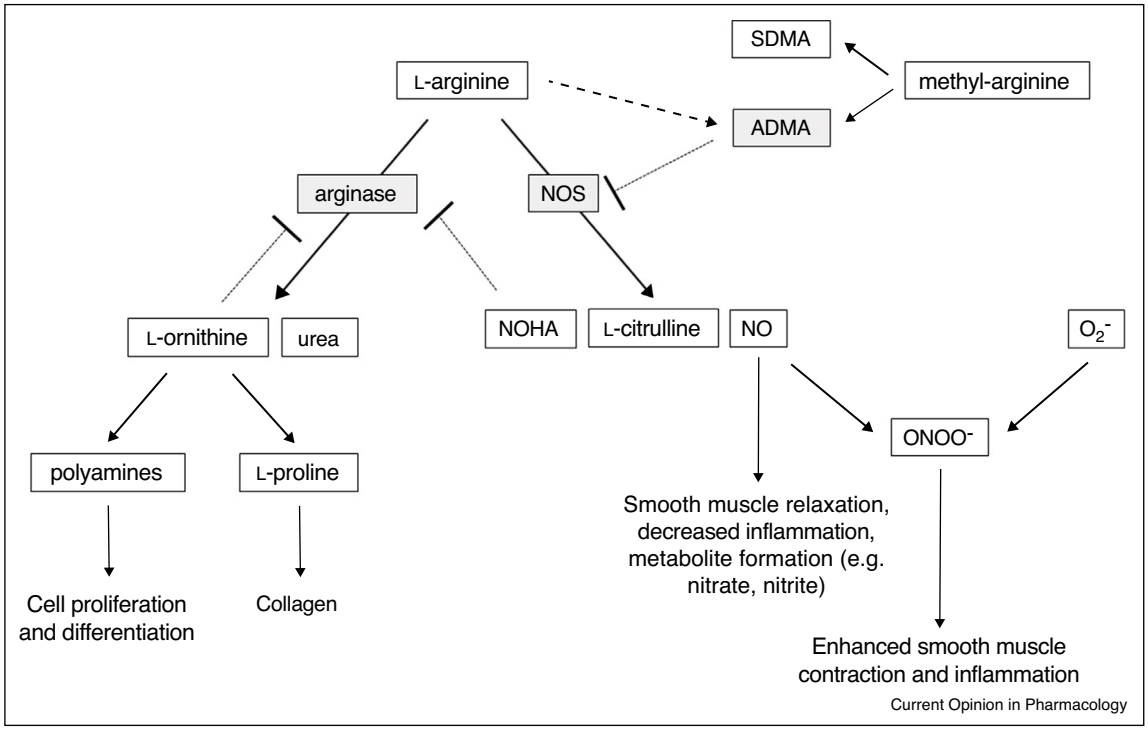
Introduction

Arginase catalyzes the reaction in which L-arginine is converted to L-ornithine and urea. In humans, two arginase isoenzymes have been identified, arginase 1 and arginase 2, that differ in cellular location and tissue distribution [1]. Both arginase enzymes are constitutively expressed in the airways. The cytosolic arginase 1 and mitochondrial arginase 2 can particularly be found in airway endothelial cells, epithelial cells, fibroblasts and macrophages [2]. Furthermore, the expression of both enzymes can be induced in airway smooth muscle cells [3,4].

Downstream metabolism of L-ornithine leads to the formation of polyamines and L-proline, which are involved in cell proliferation and differentiation, and collagen production, respectively [1,5•]. Next to the effects of metabolic products of arginases, many biological effects of the enzymes are related to their competition with nitric oxide synthases (NOS) for the common substrate L-arginine. Three distinct NOS enzymes are expressed in mammals; endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). As eNOS and nNOS are constitutively expressed in the airway epithelium, in inhibitory nonadrenergic noncholinergic neurons (nNOS) and airway vascular endothelial cells (eNOS), they are also referred to as constitutive NOS (cNOS). All NOS isoenzymes use L-arginine for the formation of nitric oxide (NO) and L-citrulline. Increases in intracellular calcium concentrations, through the action of agonists or membrane depolarization, trigger cNOS to produce relatively low amounts of NO. iNOS is particularly expressed in epithelial cells and macrophages during inflammation. In contrast to cNOS, iNOS produces large amounts of NO and enzyme activation is dependent on changes gene expression, among others induced by proinflammatory cytokines [6]. Furthermore, when L-arginine levels are low, for example due to elevated arginase activity, NOS is uncoupled and superoxide is formed. Superoxide rapidly reacts with NO to form peroxynitrite, often leading to detrimental effects in the tissue by nitration of tyrosine residues [7].

The arginase and NOS pathways may interact at different levels (Figure 1). This could be through competition for L-arginine, inhibition of arginase by the intermediate NOS metabolite Nω-hydroxy-L-arginine and through L-ornithine that causes feedback inhibition of arginase and inhibition of L-arginine uptake by cells producing NO. Next to arginase, NOS and their metabolic products, also methylated arginines such as the arginine derivatives asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) can greatly influence L-arginine homeostasis [8]. ADMA and its inactive stereoisomer SDMA are primarily formed as byproducts during the degradation of methylated arginine containing residues. Furthermore, small amounts of ADMA may be produced from free arginine directly [9]. Whereas ADMA serves as an endogenous competitive inhibitor of NOS, SDMA influences NO synthesis by competing with arginine and other methylated arginines for cellular transport [8].

Figure 1



The interactive role of arginase, NOS and ADMA in L-arginine homeostasis. Arginase and NOS compete for their common substrate L-arginine. Arginase converts L-arginine to urea and L-ornithine. Downstream conversion of L-ornithine leads to the production of polyamines and L-proline, that contribute to cell proliferation and differentiation, and collagen formation, respectively. Also, L-ornithine inhibits arginase activity. During conversion of L-arginine to NO and L-citrulline by NOS, the endogenous arginase inhibitor NOHA is formed. NO induces smooth muscle relaxation, a decrease in inflammation and forms metabolites in the airway. At low L-arginine levels, NOS is uncoupled and O_2^- is formed, which reacts rapidly with NO to form $ONOO^-$. AMDA and SDMA are formed by degradation of methylated arginine containing proteins. ADMA may also be formed from free L-arginine. ADMA serves as an endogenous antagonist of NOS. ADMA, asymmetric dimethylarginine; NO, nitric oxide; NOHA, Nω-hydroxy-L-arginine; NOS, nitric oxide synthases; O_2^-, superoxide; $ONOO^-$, peroxynitrite; SDMA, symmetric dimethylarginine.

We and others previously showed that an increased arginase activity in the airway contributes to airway obstruction and hyperresponsiveness, by reducing the available substrate for cNOS and iNOS [10]. As a result, production of bronchodilatory NO is decreased and superoxides are formed, which react with NO to form peroxynitrite, thereby enhancing airway contraction and inflammation. Furthermore, elevated airway arginase activity leads to increased L-ornithine production. Which potentially contributes to airway remodeling by increased cell proliferation and collagen formation [10,11]. The disrupted L-arginine homeostasis, through changes in arginase and NOS expression and activity, does not only play a central role in the development of various airways diseases such as asthma or COPD. It possibly also affects L-arginine homeostasis throughout the body contributing to the emergence of co-morbidities. This review focusses on the role of arginase and NOS in co-morbidities of asthma and COPD (Table 1) and speculates on their possible connection.

Asthma

The chronic airway inflammatory disease asthma is associated with enhanced levels of exhaled NO generated by iNOS in the airway epithelium [12]. In asthmatic patients local and systemic changes in iNOS, peroxynitrite, arginase, ADMA and arginine levels have been observed and are associated with i.a. lung function and asthma severity [5•,10,13]. In support, gene association studies in asthmatic patients [14] and different animal models of allergic asthma [15•,16] show a key role for arginase in different aspects of the disease.

Allergic rhinitis is a frequent co-morbidity of asthma [17]. Allergic rhinitis patients show increased nasal arginase and iNOS expression [18,19], and changes in nitrite/nitrate and nitrite serum levels during symptomatic periods [20,21]. Furthermore, peroxynitrite plays a likely role in nasal blockage after allergen encounter [22]. Interestingly, the role of arginase in allergic rhinitis has not much been studied. Treatment of allergic rhinitis patients with