Arginine Metabolism in Asthma

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KEYWORDS

• Arginine metabolism • Nitric oxide synthase • Arginase • Agmatine • Citrulline • Ornithine • Polyamine • ADMA

KEY POINTS

- L-Arginine metabolism via the arginase and nitric oxide synthase pathways is important in maintenance of airways muscular tone.
- Imbalance in the L-arginine metabolism leading to nitric oxide deficiency and airway constriction can occur through increased arginase activity or by accumulation of endogenous nitric oxide synthase inhibitors such as asymmetric dimethylarginine (ADMA).
- ADMA may represent a novel therapeutic target in correcting the enhanced airways responsiveness in asthma.

INTRODUCTION

The semiessential amino acid, L-arginine, serves many functions in cellular and organ homeostasis. Of particular relevance to physiologic function is the production of nitric oxide (NO) from L-arginine by the nitric oxide synthase (NOS) family of isozymes, which serves to relax airway smooth muscle cells through direct interaction with the heme core of soluble guanylate cyclase. The production of NO can be modified in disease by increased competition between NOS and the arginase pathway, which produces urea and ornithine. The authors, and other investigators, have previously reported that the airways hypercontractility in animal models of asthma is at least in part related to imbalances in the production of NO by the neuronal NOS,[1] as well as increased competition for substrate L-arginine with the arginases.[2–4] It has more recently become appreciated that the production of the endogenous NOS inhibitor, asymmetric dimethylarginine (ADMA), as well as accumulation of the L-ornithine–derived

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polyamines, downstream of the arginase pathway, may also modify NO production and airway tone in asthma.[5,6]

ADMA in the Lung

Synthesis of ADMA (protein arginine methyltransferases)

The first step of arginine incorporation into proteins is through the attachment of arginine to the corresponding transfer RNA (tRNA) anticodon via aminoacyl tRNA synthetase. The arginine residue is inserted into the forming protein by the ribosomal complex and the formation of a peptide bond. Methyl groups are then added to the arginine residues in proteins by a family of protein arginine methyltransferases (PRMTs).[7] The 2 classes of PRMTs, type I and II, exhibit differential kinetics for the formation of asymmetric (ADMA) versus symmetric dimethylarginine (SDMA), respectively, in addition to synthesis of monomethyl arginine (MMA).[7] Yildirim and colleagues[8] (2006) reported that PRMTs are expressed in the mouse lung within the bronchiolar and alveolar epithelium and that PRMT2 can be induced by chronic hypoxia. Bulau and colleagues[9] subsequently reported a comprehensive expression profile of the PRMTs in mouse lung and demonstrated expression of both type I (PRMT1, PRMT3, PRMT4, PRMT6) and type II PRMTs (PRMT5, PRMT7). Although alterations in PRMT expression have not yet been demonstrated in human asthma, Ahmad and colleagues[10,11] reported increased expression of PRMT2 protein levels in bronchial epithelium from their mouse model of ovalbumin (OVA)-induced allergic airways inflammation. Sun and colleagues[12,13] also comprehensively examined PRMT expression in their rat OVA model of allergic airways inflammation and demonstrated significant upregulation of PRMT1, PRMT2, and PRMT3 and downregulation of PRMT4 in the lungs. PRMT1 expression was quantified in immunostained sections and shown to be upregulated in the bronchi and alveolar epithelial cells. They further demonstrated that administration of an arginine methyltransferase inhibitor (AM-1) before the OVA exposure led to a reduction in inflammation, as assessed by eosinophil cell counts from bronchoalveolar lavage (BAL) fluid, semiquantitative scoring of histologic sections of the lungs, interleukin 4 (IL-4) messenger RNA expression, and quantification of immunoglobulin (Ig) E and OVA-specific IgG1 in serum.[13] Given the timing of the AM-1 inhibitor administration, the investigators posited that IL-4 induced PRMT1 expression, which led to the expression of eotaxin in the inflamed airways. Given the complex interaction of PRMTs with arginine metabolism, it would be very interesting to examine the changes in ADMA and the pathophysiologic/functional impact of administration of AM-1 in established disease (ie, is PRMT a good candidate for therapeutic intervention in asthma?). The role of altered expression of PRMTs and the impact on protein and physiologic functions in asthma is clearly an area that requires further investigation.

ADMA, SDMA, and MMA are liberated on proteolytic cleavage of proteins, allowing access of these derivates to the intracellular milieu. SDMA has been reported to inhibit the cationic amino acid transporters (CAT1, *SLC7A1*; CAT2, *SLC7A2*), which are the primary means of cellular uptake of L-arginine.[14,15] In addition to competition at the cationic amino acid transporters, MMA and ADMA also act directly as competitive inhibitors of NOS.[16] The accumulation of these endogenous NOS inhibitors likely leads to impaired NOS function, despite the presence of "normal" levels of L-arginine; this has been described as the "arginine paradox".[16]

Degradation of ADMA

ADMA is metabolically degraded to L-citrulline and dimethylamine by dimethylarginine dimethylaminohydrolases (DDAH).[17,18] The 2 members of this family of enzymes, DDAH1 and DDAH2, are differentially expressed in tissues, including the kidney, liver,