Arginine and Asthma

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Recent studies suggest that alterations of the arginine metabolome and a dysregulation of nitric oxide (NO) homeostasis play a role in the pathogenesis of asthma. L-Arginine, a semi-essential amino acid is a common substrate for both the arginase and NO synthase (NOS) enzyme families. NO is an important vasodilator of the bronchial circulation, with both bronchodilatory and anti-inflammatory properties, and is synthesized from oxidation of its obligate substrate L-arginine, which is catalyzed by a family of NOS enzymes. Arginase is an essential enzyme in the urea cycle, responsible for the conversion of arginine to ornithine and urea. The NOS and arginase enzymes can be expressed simultaneously under a wide variety of inflammatory conditions, resulting in competition for their common substrate (fig. 1) [1].

Accumulating data show that low L-arginine bioavailability contributes to inflammation, airway hyperresponsiveness and remodeling of the asthmatic airway. Arginase plays an important role in this paradigm. Through substrate competition, arginase decreases bioavailability of L-arginine for NOS, thereby limiting NO production with subsequent effects on airway tone and inflammation. Arginine depletion may also contribute to NOS dysfunction by inducing the uncoupling of NOS and the formation of the proinflammatory oxidant peroxynitrite in the airways, further adding to the asthmatic milieu of oxidative stress. Finally, arginase can contribute to chronic airway remodeling through formation of L-ornithine with downstream production of polyamines and L-proline, which are involved in processes of cellular proliferation and collagen deposition. Ornithine and arginine also share the same intracellular cationic amino acid transporter. By shifting arginine metabolism away from NO towards ornithine, arginase can also impact intracellular transport.

Asymmetric dimethylarginine (ADMA) is an endogenous NOS inhibitor that competes with L-arginine for binding to NOS. It may also contribute to inflammation, collagen deposition, nitrosative stress and abnormal lung function in asthma. High levels of ADMA were recently demonstrated in both mouse and asthmatic human samples. Endogenous administration of nebulized inhaled ADMA to naive control mice, at
Fig. 1. Altered arginine metabolism in hemolysis: a path to pulmonary dysfunction. Dietary glutamine serves as a precursor for the de novo production of arginine through the citrulline-arginine pathway. Arginine is synthesized endogenously from citrulline primarily via the intestinal-renal axis. Arginase and NOS compete for arginine, their common substrate. In sickle cell disease (SCD) and thalassemia, bioavailability of arginine and NO are decreased by several mechanisms linked to hemolysis. The release of erythrocyte arginase during hemolysis increases plasma arginase levels and shifts arginine metabolism towards ornithine production, limiting the amount of substrate available for NO production. The bioavailability of arginine is further diminished by increased ornithine levels because ornithine and arginine compete for the same transporter system for cellular uptake. Despite an increase in NOS, NO bioavailability is low due to low substrate availability, NO scavenging by cell-free hemoglobin released during hemolysis, and through reactions with free radicals such as superoxide and other reactive NO species. Superoxide is elevated in SCD due to low superoxide dismutase activity, high xanthine oxidase activity and potentially as a result of coupled NOS in an environment of low arginine and/or tetrahydrobioppterin concentration or insufficient NADPH. Endothelial dysfunction resulting from NO depletion and increased levels of the downstream products of ornithine metabolism (polyamines and proline) likely contribute to the pathogenesis of lung injury, pulmonary hypertension and asthma in SCD. This model has implications for all hemolytic processes as well as pulmonary diseases associated with excess arginase production. This novel disease paradigm is now recognized as an important mechanism in the pathophysiology of SCD and thalassemia. Abnormal arginase activity emerges as a recurrent theme in the pathogenesis of a growing number of diverse pulmonary disorders. Regardless of the initiating trigger, excess arginase activity represents a common pathway in the pathogenesis of asthma and pulmonary hypertension. Reproduced with permission from the American Society of Hematology [1].
doses consistent with levels observed in the allergic inflamed lungs of the mouse model resulted in augmentation of the airway hyperreactivity in response to metacholine [2].

Numerous studies of allergic asthma in various animal models have demonstrated an increase in arginase activity in the inflamed airways. Studies in human asthma confirm the importance of arginase in the pathogenesis of experimental asthma. Increased arginase I activity, mRNA and protein expression have been demonstrated in inflammatory cells and airway epithelium from bronchial biopsies and bronchoalveolar lavage samples from asthmatic patients. Single nucleotide polymorphisms in both arginase 1 and arginase 2 have been associated with atopy and increased risk of childhood asthma. Increased arginase in the plasma of patients experiencing an acute asthma exacerbation has been demonstrated, while plasma L-arginine levels and the arginine/ornithine ratio (a biomarker that inversely correlates to arginase activity) were simultaneously reduced [3]. Clinical improvement in asthma symptoms corresponded temporally with reduction of arginase activity and increase in plasma L-arginine levels and the arginine/ornithine ratio [3]. The lung function of severe asthmatics correlates directly with L-arginine bioavailability, and inversely with serum arginase activity [4]. Furthermore, animal models of specific arginase inhibition have demonstrated prevention or reversal of airway hyperresponsiveness associated with allergen challenge [5]. The development and study of inhaled arginase inhibitors represents a promising area of research. L-arginine supplementation is another potential therapeutic method, although the results of limited human trials are less promising than animal studies.

Aberrant arginine catabolism represents a novel asthma paradigm that involves excess arginase activity, elevated levels of ADMA, altered intracellular arginine transport, and NOS dysfunction. Addressing the alterations in arginine metabolism may result in new strategies for treatment of asthma.

References