

Arginase inhibitors: An alternative in treatment of obese asthma?

With great interest and pleasure, we read the article by Meurs and coworkers¹ concerning the use of arginase inhibitors in the treatment of asthma and allergic rhinitis. Their patent is focused on arginase as a new drug target, using an arginase inhibitor in the prophylactic treatment of patients with asthma and allergic rhinitis.¹ They discussed some studies in animal models and asthmatic patients showing pathways of L-arginine metabolism and their relationship to allergen-induced airway obstruction, inflammation, hyperresponsiveness, and remodeling.¹

Another area that was not covered by the article and deserves attention is the potential therapeutic role of arginase inhibitors in a specific phenotype of asthma, the obese asthma. This subgroup of patients usually has late-onset, nonatopic disease with noneosinophilic airway inflammation, low levels of expired fraction of nitric oxide (FENO), and few sputum eosinophils.² L-arginine is a semi-essential amino acid, which is substrate of various enzymatic pathways, including the synthesis of nitric oxide (NO), creatine, agmatine, ornithine, glutamate, proline, polyamine, and dimethylarginines, including asymmetric dimethylarginine (ADMA).³ It was demonstrated that ADMA, which is an endogenous inhibitor of all isoforms of nitric oxide synthases (NOS), may modify NO synthesis and airway tone.⁴

Obesity, metabolic syndrome, cardiovascular diseases, and asthma were associated with increased levels of ADMA.⁴ Endothelial NOS (eNOS) is important for local vasodilatation, and its inhibition by ADMA may lead to endothelial dysfunction, increased risk of atherosclerosis, and other cardiovascular diseases.⁵ In addition, elevated ADMA may direct NOS to form superoxide rather than NO and cause oxidative stress, damage, and mitochondrial dysfunction⁵ (Figure 1).

Mitochondrial dysfunction has been suggested as a common pathogenic mechanism to obesity, metabolic syndrome, and asthma.⁶ On the other hand, the restoration of mitochondrial number and function may lead to the recovery of normal bioenergy with improvement of these conditions.⁶ In obese individuals, excess calories and reduced physical activity overload the mitochondria, leading to overproduction of reactive oxygen species, damage to mitochondrial components, and loss of mitochondria.⁶ Mitochondrial dysfunction results in incomplete oxidation of fatty acids and increased circulating lipids. Some circulating lipids inhibit insulin signaling and may promote insulin resistance.⁶ Thus, it forms the basis for the triad of obesity, dyslipidemia, and hyperglycemia, resulting in metabolic syndrome.

Asthma is associated with oxidative stress, which may be partially derived from mitochondrial dysfunction, but may also accelerate this dysfunction.⁵ Inducible NOS (iNOS) can synthesize high levels of NO which, in the presence of reactive oxygen species, leads to generation of more toxic reactive nitrogen species. Oxo-nitrosative stress leads to covalent modification and inhibition of various cellular proteins.⁶ These changes are observed in metabolic syndrome, and are associated with organelle dysfunction such as the endoplasmic reticulum and mitochondria, causing injury and cell death.⁶ Still in this context, Holguin et al⁷ showed that in subjects with late-onset asthma, a lower L-arginine/ADMA ratio was inversely related to body mass index (BMI), what could explain the inverse relationship between BMI and FENO found. In addition, these lower L-arginine/ADMA ratios were associated with lower IgE levels, increased respiratory symptoms, reduced lung function, and worse asthma quality of life. Arginase inhibitors could act in these patients by increasing the L-arginine/ADMA ratio with L-arginine competing with shared enzymes (Figure 1). However, increased L-arginine could also be substrate for more formation of ADMA, via protein arginine methyltransferases (PRMTs).⁷

Recently, our group demonstrated that severe asthma was significantly associated with metabolic syndrome in a representative sample of Brazilian adolescents.⁸ In addition, significant associations were observed between severe asthma and obesity, increased waist circumference, hyperglycemia, and hyperinsulinemia.⁸ Asthmatic obese patients usually have a more severe condition, greater difficulty in controlling symptoms and resistance to inhaled corticosteroids.⁹ Therefore, treatment for the obese-asthma phenotype needs to be multidisciplinary and involve strategies other than usual asthma control therapy, including weight reduction, dietary changes, and sometimes alternative medications.

Meurs et al¹ concluded that arginase inhibitors may be effective in the treatment of asthma and allergic rhinitis, due to their anti-allergic, bronchoprotective, anti-inflammatory, and anti-remodeling effects. But they may also be particularly beneficial for asthma associated with obesity and/or metabolic syndrome, as they can act on the pulmonary and cardiovascular aspects of this phenotype mitigating mitochondrial dysfunction, among other actions. A better understanding of the phenotypic characteristics of asthma associated with obesity and its underlying pathophysiological mechanisms will allow the development of more effective and personalized treatments for these patients.

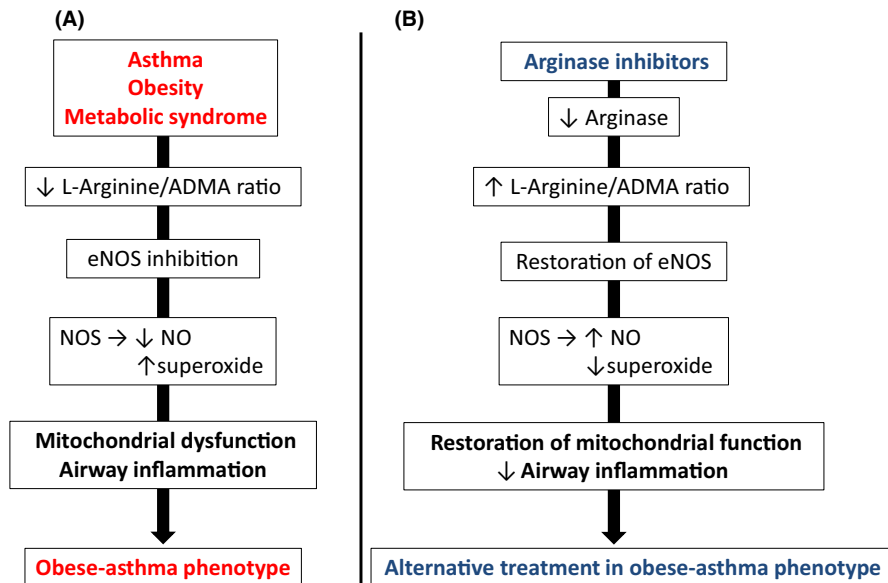


FIGURE 1 Mechanism of action of arginase inhibitors in relation to ADMA and L-arginine. A, Asthma, obesity, and metabolic syndrome are associated with increased levels of ADMA, which is an endogenous inhibitor of all isoforms of NOS. Elevated ADMA may direct NOS to form superoxide rather than NO, by inhibition of eNOS. Collectively, these processes may exacerbate airway inflammation and mitochondrial dysfunction leading to more severe asthma, as observed in obese-asthma phenotype. B, Arginase inhibitors could act in this context by increasing the L-arginine/ADMA ratio. Reduced ADMA may direct NOS to form NO, restoring endothelial and mitochondrial function. These effects may restore mitochondrial function and decrease airway inflammation. ADMA, asymmetric dimethylarginine; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; and NOS, nitric oxide synthase

KEYWORDS

asthma, asthma treatment, basic mechanisms, pharmacogenomics, pharmacology

CONFLICT OF INTEREST

The authors have no conflict of interest in relation to this work.

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