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Reply to: "Arginase inhibitors: An alternative in treatment of obese asthma?"

We thank Dr Felix and Dr Kushnir for their interesting comment on our Recent Patents in Allergy/Immunology paper on the potential therapeutic use of arginase inhibitors in the treatment of asthma and allergic rhinitis.¹ In their comment, Drs Felix and Kushnir raise attention to the possible beneficial role of arginase inhibitors in a subset of patients with obese asthma, an area that was not covered by our paper. However, in a previous paper² we discussed the presence of a disturbed L-arginine homeostasis in various co-morbidities of asthma, including obesity and metabolic syndrome. Like Drs Felix and Kushnir, we concluded that treatment of airway symptoms with arginase inhibitors might be of particular interest in these cases indeed. However, this hypothesis still waits for experimental support.

Different phenotypes of obese asthma have been described,³ partially overlapping with the atopic phenotype described in our Recent Patents paper. However, a considerable subgroup has late-onset non-atopic disease with non-eosinophilic airway inflammation, low levels of expired fraction of nitric oxide and more severe asthma. In their comment, Drs Felix and Kushnir focus on increased levels of asymmetric dimethylarginine (ADMA) and a subsequently reduced L-arginine/ADMA ratio in this subgroup of patients.⁴ Surprisingly however, the authors do not refer to the increased arginase expression and activity in these patients,^{2,5} which seems to be an even more direct indication for the use of inhibitors of this enzyme.

The mechanism of enhanced arginase expression and activity in obese asthmatics is presently unknown. High-fat diets have shown to increase arginase 1 expression and activity in the airway epithelium in mice.⁶ In addition, neutrophilic airway inflammation—as is often observed in patients with obese asthma³—might play an important role, since azurophilic granules contain a high load of arginase 1 that is released upon activation of these cells.⁷ Moreover, using airway epithelial cells from obese asthmatics, Winnica et al⁵ recently demonstrated that increased L-arginine metabolism by arginase—presumably mitochondrial arginase 2—is involved in disturbed mitochondrial function and redox signalling, which are common mechanisms in obesity, metabolic syndrome and asthma. In this regard, the role of arginase 2 in different phenotypes of asthma is interesting and deserves further investigation.

Important questions remain to what extent changes in L-arginine metabolism in the lung affect systemic co-morbidities like obesity and metabolic syndrome and vice versa, as well as the impact of

arginase inhibition hereon. New complex animal models are warranted to investigate these questions. However, to prevent potential side effects of arginase inhibitors on other organs than those of interest, local treatment of the airways by inhaled arginase inhibitors may turn out to be the preferred way of administration for asthma.

CONFLICT OF INTEREST

The conflicts of interest have been stated in detail in our previous paper.¹

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