Exploring the in vitro and ex vivo efficacy of novel arginase inhibitors for the treatment of allergic asthma

Van den Berg, M. P.M.; Kurhade, S. H.; Lunev, S.; van Faassen, H J ; Bos, I. S.; Zuidhof, A. B.; Groves, M.; Kema, I P; Domling, A. S.; Meurs, H.

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The In Vitro and Ex Vivo Efficacy of Novel Arginase Inhibitors for the Treatment of Allergic Asthma

M. P. van den Berg[1], S. H. Kurhade[2], S. Lunev[2], H. J. van Faassen[3], I. S. Bos[1], A. B. Zuidhof[1], M. Groves[2], I. P. Kema[3], A. Dömling[2], H. Meurs[1], R. Gosens[1]; [1]Molecular Pharmacology, University of Groningen, Groningen, Netherlands, [2]Drug Design, University of Groningen, Groningen, Netherlands, [3]Laboratory Medicine, University Medical Centre Groningen, Groningen, Netherlands.

Corresponding author's email: m.p.m.van.den.berg@rug.nl

Rationale: Studies in asthma patients and animal models have shown a key role for arginase isozymes in allergic airway inflammation, obstruction, hyper responsiveness and remodeling. Therefore, arginase represents a potential target for asthma treatment. The currently available arginase inhibitors are not optimal for clinical development as they lack subtype selectivity, and show limited uptake by cells and tissues due to the hydrophilic nature of the compounds. In this study, we synthesized and pharmacologically evaluated the efficacy of a novel class of arginase inhibitors. Methods: A colorimetric biochemical urea inhibition assay was used to generate IC50-values of the novel compounds for inhibiting recombinant human arginase 1 and 2 isotypes. Precision-cut lung slices of ovalbumin sensitized male guinea pigs were treated for 30 minutes with the novel arginase inhibitors (1, 10 and 100 µM), or reference compounds Amino-2-Borono-6-Hexanoic Acid (ABH) or SHK145 (1 µM). Slices were used to establish ovalbumin dose response curves to examine the effect on airway narrowing. Furthermore, to examine the effect of arginase inhibition on allergen induced histamine release, the ABH treated slices were stimulated with different doses of ovalbumin for 5 minutes. Slices were homogenized and histamine levels of both homogenized tissue and supernatant were determined by HPLC-MS/MS. Results: IC50 determination for ABH, SHK145, SHK081-2, SHK081-5 and SHK186-8 showed IC50-values of 1.5, 15, 19, 25 and 0.19 µM for recombinant human arginase 1 and 2.5, 10, 20, 85 and 0.24 for arginase 2 respectively. Treatment of lung slices with 1 µM ABH resulted in a significant decrease in ovalbumin induced airway narrowing, decreased E_{max} and increased EC_{50}, compared to control. The efficacy of 1, 10 and 100 µM SHK081-2, SHK081-5 and SHK186-8 was comparable to that of ABH. Interestingly, slices pretreated with 1 µM SHK145 showed a significant increase in E_{max}, but not EC_{50} or ovalbumin induced airway narrowing, compared to slices pretreated with 1 µM ABH ($p < 0.05$). Experiments to determine histamine levels after ovalbumin challenge show a reduction in histamine release after treatment with 1 µM ABH compared to control. Conclusions: We have shown that the novel compounds are able to inhibit the arginase enzymes in vitro and ex vivo in a similar fashion as ABH. Furthermore, we show that arginase regulates allergic airway narrowing by influencing histamine release by mast cells. These findings bring us a step closer to the development of novel arginase inhibitors for the treatment of allergic asthma.

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