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MEETING ABSTRACT

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Role of prostaglandin D_2 in equine allergic diseases

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Background: Similar to humans, horses develop skin and respiratory symptoms that are attributed to allergies. Thus, horses are a natural disease model, as they share similar immune response mechanisms with humans. Furthermore, there is a growing need for additional treatment options for allergic equine diseases, because of their widespread usage as domestic animals and their commitment in sport. Equine insect bite hypersensitivity (IBH)—an allergic disease of the skin—and heaves, also known as RAO (recurrent airway obstruction)—an allergic airway disease—are the most studied atopic diseases in horses and their prevalence has distinctly increased in the last decades. Lipid mediators play a crucial role in the pathogenesis of human allergic diseases and antagonism of leukotriene and prostaglandin (PG) D_2 receptors has been shown to be effective in the treatment of asthmatic and allergic patients. However, thus far, little is known about their therapeutic value in veterinary medicine. Our main goal was to explore the role of PGD_2 and its receptors CRTH2 and DP_1 in leukocytes of allergic (IBH and RAO) and non-allergic horses. We aimed to address the crucial questions if (i) the PGD_2/CRTH2-DP_1 axis represents a potential target for new therapeutic approaches, and if (ii) alterations in the PGD_2/CRTH2-DP_1 axis may serve as a new class of biomarkers.

Methods: Assays were performed in whole blood or polymorphonuclear cells were isolated from whole blood of allergic and non-allergic horses by density gradient centrifugation. The impact of PGD_2 on eosinophil and neutrophil responsiveness was evaluated in well-established assays of shape change and chemotaxis. In some experiments, cells were pretreated with selective antagonists for DP_1 (MK-0524; 1 µM) and CRTH2 (OC000459; 300 nM). Expression pattern of the PGD_2 receptors DP_1 and CRTH2 were characterized by flow cytometry. Differential blood count was performed with a standard hematology analyzer for human and veterinary use.

Results: The DP_1 receptor is expressed on equine eosinophils and neutrophils at a basal level and enhanced expression of DP_1 was found on eosinophils from allergic horses. While CRTH2 expression was generally found at higher basal levels, both neutrophils and eosinophils from allergic horses showed an increased expression. Eosinophils and neutrophils from allergic and non-allergic horses showed no difference in their shape-change capacity in response to PGD_2 (0.1–30 nM), but showed a distinct migratory activity towards this lipid mediator. Neutrophils and eosinophils from allergic horses showed an increased chemotactic response towards PGD_2 (30 nM) and an increased expression of PGD_2 receptors. In presence of the selective CRTH2 antagonists MK-0524 and OC000459 chemotaxis mediated by PGD_2 and the selective CRTH2 agonist 13,14-dihydro-15-keto-PGD_2 (DK-PGD_2) was attenuated. Generally, neutrophils of allergic horses exhibited a hyper-migratory phenotype also in response to other chemoattractants such as interleukin-8 and leukotriene B_4.

Discussion: The increased expression of DP_1 and CRTH2 and the enhanced response of eosinophils and neutrophils to PGD_2 in allergic horses suggest that the PGD_2/CRTH2-DP_1 activation axis has a pivotal role in mediating equine allergic responses and thus may represent a potential novel therapeutic and diagnostic target.

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