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Cyclic GMP-dependent protein kinase regulation of airway smooth muscle in asthma

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The mechanisms regulating altered airway smooth muscle (ASM) cell tone and airway reactivity in asthma remain incompletely understood. For vascular smooth muscle (VSM), the most important endogenous relaxation pathway is the nitric oxide (NO)-guanylate cyclase-cyclic GMP-dependent protein kinase type I (PKGI) pathway in which endogenous NO from NO synthases or from exogenous nitrovasodilators activate guanylate cyclase, increasing cGMP levels, and activating PKGI. PKGI in turn targets specific VSM molecules that mediate smooth muscle relaxation. Recent evidence supports that in ASM, like in VSM, activators of guanylyl cyclases have significant cGMP-mediated relaxant and antiproliferative effects. PKGI is therefore a prime but unexplored candidate molecule to mediate ASM relaxation. Recently, we have used mice harbouring a mutation in the leucine zipper N-terminal interaction domain (LZM mice [1]) to test the hypothesis that PKGIα is a critical mediator of ASM relaxation that normally protects against airway hyperresponsivity via interactions with specific molecular targets, including ASM myosin phosphate and Rho/Rho-kinase, and that this regulatory system is perturbed in the setting of asthma. Using this knock-in mouse harboring a discrete mutation in the protein-protein interaction domain of PKGI, which disrupts NO-PKG-mediated smooth muscle relaxation by disrupting the PKGI-myosin phosphatase complex we have begun to explore the mechanism of PKGI-mediated ASM relaxation and the role of PKGI in models of asthma. Several asthma studies in LZM mice and WT littermates have now been performed and analyzed using both the acute and the chronic House Dust Mite (HDM) asthma model in WT and LZM mice. Endpoints examined include airway responsiveness to methacholine; quantification of inflammatory cell populations from Bronchoalveolar lavage (BAL); and studies of airway smooth muscle in the mice. In the LZM mice, there is a significant increase in bronchospasm noted in the airways of mutant mice in both acute and chronic asthma models. No differences between WT and LZM mice in the extent of increase in either total cells or in eosinophilia in BALF samples following HDM was noted in the either the acute or chronic models. The extent and volume of Airway SMC a-actin was also measured in the WT and LZM mice following HDM-induced asthma in the acute model. SMC labeling in the airways was quantified using immunohistochemistry and computerized morphometrics and for each measure, a significant increase in SMC number and total volume was noted in the LZM mice. Studies of PKG expression level and of SMC proliferation in the asthma models are underway. These experiments will provide better understanding of ASM relaxation at the molecular level and have the potential to identify novel gene targets for the development of new therapeutic approaches to bronchoconstriction in asthma.

References

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