SPHINGOSINE-1-PHOSPHATE/SPHINGOSINE KINASE PATHWAY IS INVOLVED IN MOUSE AIRWAY HYPER-RESPONSIVENESS

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Sphingosine-1-phosphate (S1P) has been shown to regulate numerous and diverse cell functions, including smooth muscle contraction. Here we assessed the role of S1P/Sphingosine kinase (SPK) pathway in regulation of bronchial tone. *Objectives*: to determine using an integrated pharmacological and molecular approach i) the role of S1P as endogenous modulator of the bronchial tone ii) the linkage between S1P pathway and bronchial hyperresponsiveness. *Methods*: we evaluated S1P effects on isolated bronchi and whole lungs, harvested from Balb/c mice sensitised to ovalbumin versus vehicle treated mice, by measuring bronchial reactivity and lung resistance. *Main results*: S1P administration on non-sensitized mouse bronchi does not cause any direct effect on bronchial tone, while a significant increase in Ach-induced contraction occurs following S1P challenge. Conversely, in ova-sensitized mice S1P/SPK pathway triggers airway hyperesponsiveness. Indeed, S1P causes a dose dependent contraction of isolated bronchi. Similarly in the whole lung system S1P increased airway resistance only in ova sensitized mice. The action on bronchi of S1P is coupled to an enhanced expression of SPK_1 and SPK_2 as well as of $S1P_2$ and $S1P_3$ receptors. In these experiments the key role for S1P/SPK in hyperreactivity has been confirmed by pharmacological modulation of SPKs. *Conclusions*: S1P/SPK pathway does not seem to play a major role in physiological conditions, while it may become critical in pathological conditions. These results open new windows for therapeutic strategies in diseases like asthma.