Targeting calcium channels specifically expressed by Th2 cells prevents experimental allergic asthma

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Allergic asthma is a chronic inflammatory disease of the lungs which prevalence and severity are both increasing. T helper (Th) lymphocytes include T-cell subsets that exert different functions. Among them, Th1 and Th2-cells produce interferon gamma and interleukin (IL-)4 respectively. Asthma arises from aberrant $CD4^+$ T-cell-mediated immune responses, with a Th2-cell phenotype. Ca^{2+} signalling in Th2-cells is responsible for the production of IL-4, IL-5 and IL-13 that are all deleterious in asthma. Signalling pathways and especially calcium regulation differ between Th1 and Th2-cells with little being known in Th2-cells. Our aim was to investigate the steps controlling the calcium response in Th2 lymphocytes. We demonstrated that dihydropyridine receptors (DHPR) were expressed in Th2 but not in Th1 murine cells, and that they were involved in TCR-dependent calcium response. Moreover, DHPR controlled Th2-cytokine production (IL-4, IL-5, IL-10 and IL-13). Th2 cell differentiation was associated with an up-regulation of DHPR and these channels were identified at the molecular level as calcium channels related to those expressed by excitable cells. A DHPR antagonist or antisense oligonucleotides directed against these channels suppressed both calcium response and Th2 cytokine production without any effect on Th1 cells. In a murine model of allergic asthma, we showed that lung-infiltrating $CD4^+$ T-cells expressed DHPR. DHPR antagonist or specific antisense oligonucleotides prevented all the features of allergic asthma by abrogating Th2-mediated inflammation in an active model of allergic asthma and following adoptive transfer of effector Th2-cells. However, nicardipine did not prevent lung inflammation consecutive to Th1-cell transfer, emphasizing Th2-cell specific targeting. Th2-cells transfected with antisense oligonucleotides also showed an impaired capacity to trigger asthma when compared to control transfected Th2-cells. Altogether these data indicate that these Ca^{2+} channels are crucial in Th2 but not in Th1-cell signalling and that they could be a target to prevent allergic asthma.