Cím:	INHIBITION OF Kv1.3 AND IKCa1 LYMPHOCYTE POTASSIUM CHANNELS AS A P AUTOIMMUNE DISORDERS
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Introduction: The transient increase of the cytoplasmic free calcium level is a key signal transduction mechanism in the process of lymphocyte activation. Voltage-sensitive Kv1.3 and calcium-dependent IKCa1 lymphocyte potassium channels have been implicated as important targets of selective immunomodulation in autoimmune disorders. The relationship between the influx of calcium through the cell membrane and the efflux of potassium makes the activation and cytokine production of T lymphocytes sensitive to pharmacological inhibition of Kv1.3 and IKCa1 channels. We aimed to characterize the effects of lymphocyte potassium channel inhibition on peripheral blood T lymphocyte activation in a number of immune-related disorders, such as rheumatoid arthritis, multiple sclerosis, type I diabetes and stroke induced immunosuppression compared to healthy individuals.

Methods: We determined calcium influx kinetics and its sensitivity to Kv1.3 and IKCa1 channel inhibition following PHA activation in CD4, Th1, Th2 and CD8 cells applying a novel flow cytometry approach.

Results: The time when the peak of calcium influx in T lymphocytes was reached decreased in autoimmune patients compared to healthy individuals, indicating that these cells are in a state of sustained reactivity due to the ongoing autoimmune reaction. In healthy controls the inhibition of the IKCa1 channel decreased calcium influx in Th2 and CD4 cells to a lower extent than in Th1 and CD8 cells. On the contrary, the inhibition of Kv1.3 channels resulted in a larger decrease of calcium entry in Th2 and CD4 than in Th1 and CD8 cells. In the investigated autoimmune patients a greater decrease of calcium influx upon the inhibition of the Kv1.3 channel than that of the IKCa1 channel was observed in Th1 cells. However, the selectivity of the investigated inhibitors was limited in our experiments. The inhibitory effect was present not only in disease-associated CD8 and Th1 cells, but also in the anti-inflammatory Th2 subset. The induced decrease in their function could lead to unwanted side-effects and in a setback of therapy in vivo.

Conclusions: Based on our results, a number of dominant features of T lymphocyte calcium influx and its sensitivity to the inhibition of potassium channels were identified that were present in the investigated autoimmune diseases. Further studies are needed on human samples and experimental models to judge the usefulness of this approach in the fight against autoreactive lymphocyte subsets and harmful cellular responses in autoimmune patients.