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Pathological and Therapeutic Usefulness of Lymphocyte K^+-Channels

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Summary

T lymphocytes predominantly express delayed rectifier K^+-channels (Kv1.3) in their plasma membranes. Patch-clamp studies revealed that the channels play crucial roles in facilitating calcium influx necessary to trigger the lymphocyte activation and proliferation. In addition to selective channel inhibitors that have been developed, we recently showed physiological evidence that the commonly-used drugs, such as non-steroidal anti-inflammatory drugs, antibiotics, anti-hypertensives and anti-cholesterol drugs, effectively suppress the channel currents in lymphocytes, and thus exert immunosuppressive effects.

Using experimental animal models, previous studies revealed the pathological relevance between the expression of ion channels and the progression of renal diseases. As an extension, we recently demonstrated that the overexpression of lymphocyte Kv1.3-channels contributed to the progression of chronic kidney disease (CKD) by promoting cellular proliferation and interstitial fibrosis. According to one of our patch-clamp studies, since benidipine, a long-acting 1,4-dihydropyridine Ca^{2+} channel blocker, or simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, were also highly potent as Kv1.3-channel inhibitors, they could exert therapeutic efficacy in the progression of CKD. Therefore, using a rat model with advanced stage chronic renal failure (advanced CRF), we examined the effects of benidipine or simvastatin on the histopathological features of the kidneys, cellular proliferation of leukocytes and the cortical expression of pro-inflammatory cytokines. In the cortical interstitium of advanced CRF rat kidneys, these drugs significantly ameliorated the progression of renal fibrosis. Simvastatin also ameliorated the progression of glomerular injury, but benidipine did not. Both drugs reduced the number of proliferating leukocytes with a significant decrease in the pro-inflammatory cytokine expression. Together with our *in vitro* evidence, the studies indicated the therapeutic potency of Kv1.3-channel inhibitors, such as benidipine and simvastatin, in the treatment or the prevention of CKD.