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Physiological and Pathophysiological Roles of Voltage-Gated and Ca^{2+}-Activated K^+ Channels

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Summary

There is a growing appreciation that ion channels encoded by the *ether-`a-go-go-related* gene family (ERG) have a functional impact in smooth muscle in addition to their accepted role in cardiacmyocytes and neurons. In isometric tension studies of non-pregnant myometrium, the ERG channel blockers dofetilide, E4031 and Be-KM1 increased spontaneous contractility and ERG activators inhibited spontaneous contractility. In contrast, neither ERG blockade nor activation had any effect on the inherent contractility inmyometrium from late pregnant animals. Moreover, dofetilide-sensitive K^+currents with distinctive 'hooked' kinetics were considerably smaller in uterine myocytes from late pregnant compared to non-pregnant animals. Expression of mERG1 isoforms did not alter throughout gestation or upon delivery, but the expression of genes encoding auxiliary subunits (KCNE) were up-regulated considerably. This study provides the first evidence for a regulation of ERG-encoded K^+channels as a precursor to late pregnancy physiological activity.

The intermediate-conductance Ca^{2+}-activated K^+ channel, $IK_{Ca}/K_{Ca}3.1$ is one of the major K^+ channels in T-lymphocytes, which regulate membrane potential and Ca^{2+} signaling, and are potential molecular targets for pharmacological intervention in autoimmune diseases. We identified novel spliced variants of $K_{Ca}3.1$ ($K_{Ca}3.1b$) from the human lymphoid tissues, which were lacking the N-terminal domains of the original $K_{Ca}3.1a$ as a result of alternative splicing events. $K_{Ca}3.1b$ suppressed the localization of $K_{Ca}3.1a$ to the plasma membrane and also IK_{Ca} channel activity of $K_{Ca}3.1a$ in a dominant-negative manner. The N-terminal domain of $K_{Ca}3.1$ is critical for channel trafficking to the plasma membrane, and that the fine tuning of IK_{Ca} channel activity modulated through alternative splicing events may be related to the control in physiological and pathophysiological conditions in T-lymphocytes. We further suggested that the increase in IK_{Ca} activity might contribute to differentiation of T-lymphocytes in auricle lymph node of delayed-type hypersensitivity (DTH) model and thereby cause inflammatory response of DTH in auricle.

Recently, a new experimental stromal hyperplasia BPH model corresponding to clinical benign prostatic hyperplasia (BPH) has established by Mori *et al.* (2009). We showed that $K_{Ca}3.1$ genes and proteins were highly expressed in implanted urogenital sinus (UGS), which is similar to human BPH tissues histologically, rather than those in the normal host prostate. In addition, the expression of two transcriptional regulators of $K_{Ca}3.1$, activator protein-1 (AP-1) and functional repressor element 1-silencing transcription factor (REST) were significantly increased and decreased in implanted UGS, respectively. Immunohistochemical examination showed that positive signals of $K_{Ca}3.1$ were detected exclusively in the stromal cells, whereas scarcely immunolocalized to the basal cells of the epithelium in implanted UGS. *In vivo* treatment with TRAM-34, a specific $K_{Ca}3.1$ inhibitor, significantly suppressed the increase in implanted UGS weights with the decrease in stromal cell components. These suggest that $K_{Ca}3.1$ blockers may be a novel treatment option for patients with BPH.