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Exploring a Novel Mechanism of Vasoregulation Focusing Ion Channel-Coupling.

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Summary

Hypertension (high blood pressure) is a chronic condition with high prevalence in Japan. Because hypertension increases the risk of life-threatening cardiac diseases (angina, cardiac infarction) and cerebrovascular diseases (cerebral infarction, stroke), many antihypertensive drugs are used to control blood pressure within optimal levels. TRPV4 is a non-selective cation channel having sensitivity to warm temperatures and mechanical stimuli. In vascular endothelial cells of small resistant arteries, TRPV4 is activated downstream of mechanical stimuli including blood pressure and shear stress. Ca^{2+}-influx through TRPV4 leads following activation of Ca^{2+}-dependent K^+/Cl^- channels which contributes endothelia-dependent hyperpolarization to cause vasodilation. This study has focused on the functional coupling of TRPV4 and Ca^{2+}-dependent K^+/Cl^- channels on vascular endothelial cells, a potential target for antihypertensive drugs.

RT-PCR analysis has revealed the expression of TRPV4, Ca^{2+}-dependent K^+ (KCNN1-4) and Ca^{2+}-dependent Cl^- channel (TMEM16A) in the resistant artery (3rd order mesenteric artery) having important roles in blood pressure regulation. We aimed to establish the functional analysis of Ca^{2+}-dependent K^+/Cl^- channel activities following TRPV4 activation. HEK293T cell co-expressing TRPV4 and KCNN4 (Ca^{2+}-dependent K^+ channel) was used to record TRPV4 activator (GSK1016790A, 100nM)-induced KCNN4 current separately from TRPV4 current adapting selective KCNN4 inhibitor (TRAM-34, 1 mM) in whole-cell patch-clamp recordings. As a result, GSK1016790A-treatment caused substantial current activation, however, TRAM-34 failed to inhibit GSK1016790A-induced current in TRPV4/KCNN4-coexpressing cells. The results suggest that concentrations of GSK1016790A and TRAM-34 should be optimized in future studies.