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CELL SIGNAL CONTROL OF MUSCARINIC ACTIVATION OF CARDIAC POTASSIUM CHANNEL

Yoshihisa Kurachi

Division of Molecular and Cellular Pharmacology, Department of Pharmacology, Graduate School of Medicine, Osaka University, Osaka, Japan

Upon application of acetylcholine, a cardiac potassium channel is activated to decelerate the heart beat. Activation of the potassium channel is mediated by the $\beta\gamma$-subunits of PTX-sensitive G proteins (K_G) that are coupled to m2- or A1-receptors in cardiac cell membrane. This system is also utilized by various receptors including GABA, opiate and dopamine for formation of slow inhibitory postsynaptic potential in neurons and endocrine cells. This system is subject to further functional and spatial controls. In the functional aspect, we recently found that the activity of K_G is regulated by RGS proteins in an apparent voltage-dependent manner, which forms the relaxation behavior of K_G current. The RGS proteins are inactivated with binding of PIP3 in the resting state. Ca^{2+}/CaM complex that is formed by depolarization-induced Ca^{2+} influx across cell membrane binds to RGS in a competitive manner against PIP3. This causes de-inhibition of RGS activity. The re-activated RGS stimulates GTPase activity of $G\alpha$, resulting in the decrease in free [$G\beta\gamma$] and thus activity of K_G at depolarized potentials. With this understanding of the mechanism for relaxation-behavior of K_G, we could have quantitatively estimated the physiological dynamics of receptor-G protein cycle. This allows us modeling of the kinetic behavior of K_G channel activity. With the model, we will be able to obtain further insights in the mechanisms for temporal and also voltage-dependent behavior of K_G. On the other hand, for the spatial control, we found that isoforms of GIRK2 are responsible for control of dendritic localization of K_G in neuron. It was also found that cardiac type of K_G channels (GIRK1/GIRK4) expressed in pituitary thyrotrophs distribute exclusively on the cytosolic vesicles. The K_G channel system is recruited to the cell membrane upon application of a secretagogue, TRH. Thus, this turns out to be a novel negative feedback mechanism for hormone-secretion. In conclusion, temporal and spatial controls should play mandatory roles in determining the physiological roles of "receptor-G protein-ion channel system" in various tissues. Further studies are needed to elucidate them.