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Identification of Ginsenoside Interaction Site in Human Kv1.4 Channel

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ABSTRACT

Voltage-gated K+ (Kv) channels play critical roles in a wide variety of physiological processes in peripheral and central nervous systems and heart. Due to their primary role in repolarization following action potentials, Kv channels have been targets for many drugs/toxins for their therapeutic applications. We previously demonstrated that 20(S)-ginsenoside Rg3 (Rg3) inhibits human Kv1.4 (hKv1.4) channel activity. However, the cellular mechanism on hKv1.4 channel regulations by Rg3 is poorly understood. In the present study, we further identified Rg3 interaction site of hKv1.4 channel. We used wild-type and mutant hKv1.4 channels expressed in Xenopus laevis oocytes using the two-microelectrode voltage-clamp technique. Rg3-induced inhibitions of hKv1.4 channel currents were concentration-dependent and reversible manners. Raising extracellular [K+]o enhanced outward hKv1.4 channel currents (K+ activation) and abolished Rg3 effects on hKv1.4 channels. Rg3 treatment caused a significant change in EC50 values for K+ activation. In hKv1.4 channel, amino acid residue K531 is a K+ activation site and forms part of external tetraethylammonium (TEA) binding site. Based on this information, we further examined the TEA effect on Rg3-induced regulation of wild-type hKv1.4 channel and vice versa in K531Y mutant channel. We found that K531 residue might be an overlapping site for Rg3 and external TEA binding site. In addition, the docked modeling study using wild-type and K531Y mutant channels revealed that K531 residue plays a key role in forming hydrogen bonds in interactions between Rg3 and hKv1.4 channel. These results indicate that Rg3 is a novel hKv1.4 channel regulator through interacting with K531 residue.