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KCNE1-Dependent Sumoylation of K_v7.1 Subunits Determines the Voltage-Dependence of Cardiac I_{Ks} Channels

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K_v7.1 and KCNE1 subunits assemble to form I_{Ks} channels, which are fundamental to cardiac repolarization. Here, we identify SUMOylation of I_{Ks} channels as a fundamental regulatory pathway in the heart. A report (Qi et al. Neuron. 2014) that partial deficiency of SENP2 deSUMOylase in mice produced sei-zures, bradycardia and sudden death in association with hyperSUMOylation of M-current channels (K_v7.2/K_v7.3) led us to study I_{Ks} currents in neonatal mice. We found intracellular application of SENP2 to increase I_{Ks} current due to a -20 mV shift in the voltage-dependence of activation ($V_{1/2}$); in contrast, SUMO2 application decreased the current due to a +20 mV shift in $V_{1/2}$. A 40 mV excursion in $V_{1/2}$ between the deSUMOylating and SUMOylating conditions was seen also when mouse or human K_v7.1 and KCNE1 subunits were expressed in Chinese hamster ovary (CHO) cells. Förster resonance energy transfer (FRET) confirmed co-assembly of YFP-SUMO2 and I_{Ks} channels formed with K_v7.1-CFP. Consistent with SUMOylation, mutation of a single target residue in K_v7.1 abolished FRET and the effects of SENP2 or SUMO2 on I_{Ks} current density. To count the number of SUMO2 subunits in I_{Ks} complexes, total internal reflection fluorescence (TIRF) microscopy with simultaneous two-color photobleaching was used. I_{Ks} channels carry a maximum of four SUMO2s, one on each K_v7.1 subunit. Unexpectedly, K_v7.1 channels studied in the absence of KCNE1 carry at most two SUMO2s despite having four available K_v7.1 SUMO-sites. Modification of both K_v7.1 channels and I_{Ks} channels by two SUMO2s produced a 20 mV shift in $V_{1/2}$ while four SUMO2s produced a 40 mV shift in I_{Ks} channels. We propose that KCNE1-dependent SUMOylation of K_v7.1 is required to yield the native biophysical attributes observed for I_{Ks} channels in mammalian cardiac myocytes. underlying this unique inactivation and its modulation by KCNE1 remain elusive. Recently, we have shown that the KCNQ1 channel opens during voltage sensor movements to both the intermediate and fully activated states, resulting in intermediate open (IO) and activated open (AO) states. In this study, we found that the previously called the open and inactivated states of