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Identification of IQM-266, a novel DREAM ligand that modulates K_V4 currents.

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Downstream Regulatory Element Antagonist Modulator (DREAM)/KChIP3/calsenilin is a neuronal calcium sensor (NCS) with multiple functions, including the regulation of A-type outward potassium currents (I_A). This effect is mediated by the interaction between DREAM and K_V4 potassium channels and it has been shown that small molecules that bind to DREAM modify channel function. A-type outward potassium current (I_A) is responsible of the fast repolarization of neuron action potentials and frequency of firing. Using surface plasmon resonance (SPR) assays and electrophysiological recordings of $K_V4.3$/DREAM channels, we have identified IQM-266 as a DREAM ligand. IQM-266 inhibited the $K_V4.3$/DREAM current in a concentration-, voltage-, and time-dependent-manner. By decreasing the peak current and slowing the inactivation kinetics, IQM-266 led to an increase in the transmembrane charge ($QK_V4.3$=DREAM) at a certain range of concentrations. The slowing of the recovery process and the increase of the inactivation from the closed-state inactivation degree are consistent with a preferential binding of IQM-266 to a pre-activated closed state of $K_V4.3$/DREAM channels. Finally, in rat dorsal root ganglion neurons, IQM-266 inhibited the peak amplitude and slowed the inactivation of I_A. Overall, the results presented here identify IQM-266 as a new chemical tool that might allow a better understanding of DREAM physiological role as well as modulation of neuronal I_A in pathological processes.

Keywords: $K_V4.3$ channels; DREAM; DREAM ligands; KChIP; A-type current; Alzheimer.

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