TRPM2

The transient receptor potential melastatin 2 (TRPM2) channel is associated with ischemia reperfusion injury, inflammation, cancer, and neurodegenerative diseases. However, the limit of specific inhibitors impedes the development of TRPM2-targeted therapeutic agents. To discover more potent and selective TRPM2 inhibitors, 59 N-(p-Amylcinnamoyl)anthranilic acid (ACA) derivatives were synthesized and evaluated using calcium imaging and electrophysiology approaches. Systematic structure-activity relationship studies resulted in some potent compounds inhibiting the TRPM2 channel with sub-micromolar half-maximal inhibitory concentration values. Among them, the preferred compound A23 exhibited TRPM2 selectivity over TRPM8 and TRPV1 channels as well as phospholipase A2 and showed neuroprotective activity in vitro. Following pharmacokinetic studies, A23 was further evaluated in a transient middle cerebral artery occlusion model in vivo, which significantly reduced cerebral infarction. These data indicate that A23 might serve as a useful tool for TRPM2-related research as well as a lead compound for the development of therapeutic agents for ischemic injury [1].

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cADPR is a well-recognized signaling molecule by modulating the RyRs, but considerable debate exists regarding whether cADPR can bind to and gate the TRPM2 channel, which mediates oxidative stress signaling in diverse physiological and pathological processes. Here, we show that purified cADPR evoked TRPM2 channel currents in both whole-cell and cell-free single-channel recordings and specific binding of cADPR to the purified NUDT9-H domain of TRPM2 by surface plasmon resonance. Furthermore, by combining computational modeling with electrophysiological recordings, we show that the TRPM2 channels carrying point mutations at H1346, T1347, L1379, S1391, E1409, and L1484 possess distinct sensitivity profiles for ADPR and cADPR. These results clearly indicate cADPR is a bona fide activator at the TRPM2 channel and clearly delineate the structural basis for cADPR binding, which not only lead to a better understanding in the gating mechanism of TRPM2 channel but also shed light on a cADPR-induced RyRs-independent Ca2+ signaling mechanism [2].

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2)
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