

Role of KCNQ2/3 channels in striatal response to dopamine and cocaine conditioned place preference

KCNQ currents are important for controlling neuronal excitability, serving as a brake against hyperexcitable states in neurons. As such, changes in KCNQ channel expression and activity have been implicated in several neuropsychiatric disorders including substance abuse. While KCNQ subunits are encoded by a family of genes (Kcnq1 - Kcnq5) that form tetrameric channels, most prior work has targeted these channels with pharmacological approaches that lack genetic specificity. Additionally, little is known about subunit-specific contributions to reward circuitry and drug-seeking behaviors. To better understand the function of KCNQ channels in the striatum, we engineered CRISPR sgRNAs targeting the promoters for Kcnq2 and Kcnq3 to permit subunit-specific CRISPR activation/interference strategies. To measure the role of KCNQ subunits on electrophysiological activity and dopamine response, we paired CRISPR manipulations with high-density multielectrode array recordings from striatal neurons. Notably, Kcnq3 knockdown selectively decreased action potential frequency, while overexpression increased frequency. Surprisingly, both overexpression and knockdown of Kcnq2 increased action potential burst frequency compared to non-targeting lacZ controls. Furthermore, Kcnq3 knockdown decreased firing rate following dopamine stimulation, suggesting a specific role for the Kcnq3 subunit in dopamine-induced activity. To assess whether KCNQ knockdown altered drug-seeking behavior, we used a cocaine conditioned place preference paradigm following targeted Kcnq2 or Kcnq3 knockdown in the adult rat nucleus accumbens. Though all animals showed a distinct preference for the cocaine paired chamber, we found no differences in preference between KCNQ sgRNAs and non-targeting lacZ controls. Taken together, these results demonstrate an important role for KCNQ channels in striatal cell function and dopamine stimulation. Ongoing studies are expanding these results to assess whether the effects of KCNQ channels on cocaine place preference are dose-dependent. These experiments continue to provide insight into how individual KCNQ subunits impact physiological and behavioral responses to dopamine stimulation and cocaine preference.

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