The SK channel as a novel target for treating alcohol use disorders

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We recently described the SK-type potassium channel as a novel target for treatment of excessive alcohol intake.1 SK channel function is reduced in the nucleus accumbens (NAcb) core in rats consuming alcohol under intermittent (IAA) but not continuous (CAA) access, and the FDA-approved SK activator chlorzoxazone reduces the excessive alcohol intake in IAA rats but not the more moderate intake in CAA rats. Here, we discuss the implications of these and related findings for SK as a treatment for alcohol use disorders. In addition, we report that many NAcb core electrophysiological parameters related to action potential waveform or basal parameters were not altered in alcohol-drinking rats. These results are in strong contrast to those reported for cocaine, where several NAcb ion channels show adaptations after cocaine exposure. These results suggest that alcohol intake is associated with only limited ion channel neuro-adaptations in the NAcb relative to cocaine, and support the hypothesis that SK represents a selective and potent intervention to reduce excessive alcohol intake.

Introduction

There is great interest in identifying new pharmacological treatments for alcoholism, which has enormous and deleterious health, economic and societal consequences.2,3 Although there are several pharmacotherapies used for alcoholism, including naltrexone and acamprosate, these can be of moderate benefit or act only in a subset of alcoholics.4 We and other labs have used rodent models to identify alcohol-related neuro-adaptations in the brain which could facilitate alcohol intake and thus represent novel therapies to treat alcoholism. We focus in particular on the NAcb core, which is a critical regulator of many motivated and reward- and addiction-related behaviors.2,4-8

The SK Channel and Alcohol Exposure

Recent studies have identified alcohol-related changes in the SK-type calcium-activated potassium channels (SK) in several brain regions.1,6,9,10 We found that long-term, voluntary alcohol intake, either under operant conditions6 or under intermittent-access, home-cage, two-bottle choice (IAA),1 is associated with reduced SK function and increased excitability in neurons from the NAcb core. No NAcb core SK changes were observed in several control groups, including operant sucrose intake6 and in two-bottle choice rats with continuous access to alcohol (CAA).1 Interestingly, the FDA-approved SK activator chlorzoxazone, which has been used for decades as a centrally acting myorelaxant,11,12 reduces the excessive alcohol intake in IAA rats with no effect on the more moderate intake in CAA rats.1 Thus, chlorzoxazone may represent a potent and immediately accessible pharmacological treatment for human alcoholism. In addition, results from our two studies1,6 suggest that SK activators only reduce intake of rewards (including alcohol) under conditions where there is reduced SK function.

Other recent studies have linked alcohol exposure with SK adaptations in other brain areas. Chronic alcohol intake is associated with reduced SK channel function in the amygdala,13 and with reduced SK channel expression in the prefrontal cortex of chronic alcoholics,14-16 although the functional significance of these reductions is unclear.

Key words: SK channel, nucleus accumbens, alcohol use disorder, action potential, waveform

Submitted: 05/20/11
Accepted: 05/23/11
http://dx.doi.org/10.4161/chan.5.4.16577
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Commentary to: Hopf FW, Simms JA, Chang SJ, Seif T, Bartlett SE, Bonci A. Chlorzoxazone, an SK-type potassium channel activator used in humans, reduces excessive alcohol intake in rats. Biol Psychiatry 2011; 69:618–24; PMID:21195386; http://dx.doi.org/10.1016/j.biopsych.2010.11.011
exposure reduces hippocampal SK, which facilitates NMDA receptor (NMDAR) currents. Interestingly, hyperexcitability during alcohol withdrawal is reduced by NMDAR blocker(s) and also by the SK activator 1-EBIO. Further, repeated alcohol exposure reduces SK function in midbrain DA neurons, which increases NMDAR-induced burst firing and is associated with sensitized responses to cocaine. Thus, alcohol-related SK neuro-adaptations may occur in a number of brain regions and contribute to several different aspects of alcohol-related behaviors.

The molecular bases of these alcohol-related reductions in SK function are of interest, and could reflect decreased SK subunit protein levels, or instead decreased levels of the calcium required to activate SK channels or altered SK regulation by intracellular signalling molecules. However, operant alcohol intake reduces SK3 but not SK2 protein subunit levels in the NAc core, while alcohol exposure reduces hippocampal SK2 subunit levels. Although relatively little is known about the genetic regulation of these protein subunit levels, SK3 splice variants have been associated with schizophrenia. Thus, the genetic bases of the observed SK changes represent an interesting area for future studies.

Results

We originally focused on alcohol-related SK neuro-adaptations, which were determined using the SK antagonist apamin and by analyses of action potential (AP) firing and the slower afterhyperpolarization. Cocaine exposure alters the function of several NAc ion channels, including sodium, potassium, calcium, and SK, with a net decrease in NAc excitability. Since addiction to different substances could ultimately be expressed through a common mechanism, it is of great interest to understand whether alcohol exposure produces similar changes as cocaine. Here, we examined several AP waveform parameters and basal parameters which often accompany functional changes in different ion channels (see below). We averaged values for a given parameter for all NAc core neurons from a given rat, yielding results from n = 10, 9 and 7 alcohol-naive, CAA and IAA rats, respectively.

Sodium channels are a primary contributor to the AP upstroke, and cocaine-related changes in sodium channel function are associated with altered AP threshold and amplitude. Also, we find that low concentrations of the sodium channel blocker tetrodotoxin depolarizes the AP threshold and reduces the AP amplitude in adult striatal neurons. However, none of these parameters were altered in the NAc core by alcohol intake (Fig. 1), suggesting no changes in sodium channels.

Inwardly-rectifying K+ currents (IRK) play a major role in regulating depolarization from the resting potential, and cocaine-related IRK decreases in cortical neurons enhance AP firing, increase input resistance, and decrease rheobase, the minimum current required to generate an AP. However, there were no group differences in input resistance, rheobase, membrane time constant or resting membrane potential (Fig. 2A–D), suggesting no alcohol-related changes in IRK and/or K+ leak currents.

Finally, some studies have related changes in AP width and the peak magnitude of the afterhyperpolarization with potassium channels that underlie the fast AP repolarization. Again, these parameters were not different in NAc core neurons from IAA versus naive and CAA rats (Fig. 2E and F).

Materials and Methods

Materials and methods, including two-bottle intake and whole-cell electrophysiology, are described in Hopf et al. Resting membrane was measured just after breaking into a neuron, and then the neuron was brought to ~90 mV by passage of DC current through the patch amplifier. AP waveform parameters were determined at rheobase using custom software in Python 2.3 (www.python.org). AP threshold was the voltage where the rate of rise exceeded 2 V/s. AP amplitude and width were calculated relative to AP threshold. Input resistance was determined from the voltage change produced by a 33.3 pA hyperpolarizing pulse from a -90 mV resting potential. Membrane time constant was determined at rheobase by fitting a single exponential from initiation of the current step to 70 ms into the step. Voltage values were corrected for liquid junction potential.

Conclusion

Many ion channels contribute to AP firing. However, our analyses of basal and AP waveform parameters showed no
alcohol-related differences, suggesting that the alcohol-related enhancement of NAc core excitability primarily reflected decreased SK function. This hypothesis is supported by the observation that the SK channel blocker apamin produced a significantly greater enhancement in firing in control neurons, and that there were no differences in AP firing between alcohol-intake and control rats after exposure to apamin.1,6

Thus, alcohol-related reductions in SK function the NAc core,1,6 as well as the midbrain8 and hippocampus,10 may contribute to many alcohol-related behaviors, including self-administration, relapse and withdrawal, and represent a novel therapeutic target for alcoholism.

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