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Small K channels: Big targets for treating alcoholism?

Hitoshi Morikawa and R. Adron Harris

Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin, Austin, TX 78712

Alcohol abuse and alcoholism represent major health problems in Western countries and are emerging as major concerns in many developing countries. Despite the large social and economic impact of excessive alcohol consumption, treatment options, particularly pharmacotherapies, are limited. This is, in part, due to a lack of a detailed understanding of the targets of alcohol action in brain that might be responsible for promoting excessive alcohol consumption. Accumulating evidence in recent years indicates important roles for calcium (Ca^{2+})-activated potassium (K^+) channels in behavioral responses to alcohol and the development of alcoholism (1). In this issue of *Biological Psychiatry*, two articles propose that small-conductance Ca^{2+} -activated K^+ (SK) channels may be novel therapeutic targets for alcohol dependence and excessive drinking associated with alcoholism (refs to the two papers here). Among ion channels expressed in the plasma membrane, SK channels are unique in that they are solely activated, or gated, by cytosolic Ca^{2+} and not directly by membrane potential (2). Thus, Ca^{2+} influx through Ca^{2+} -permeable ion channels, such as NMDA-type glutamate receptors or voltage-gated Ca^{2+} channels, elicits SK channel opening, resulting in negative feedback regulation of excitatory glutamatergic transmission and action potential firing (Figure 1).

In the first study, Mulholland et al. examined changes in SK channel function and expression following chronic ethanol exposure in the cornu ammonis 1 (CA1) region of the hippocampus, a brain area that is thought to be involved in withdrawal-induced seizures and in cognitive impairments observed in alcoholics. In CA1 pyramidal neurons, SK2 subtype SK channels are localized to dendritic spines, where they are tightly coupled to synaptically driven Ca^{2+} influx via NMDA receptors or voltage-gated Ca^{2+} channels (3). This synaptic activation of SK2 channels constitutes a Ca^{2+} -mediated negative feedback loop to dampen excitatory postsynaptic potentials (EPSPs) and spine Ca^{2+} signals that are critical for the induction of synaptic plasticity and glutamate-induced neurotoxicity. Indeed, blocking SK channels with the specific antagonist apamin facilitates hippocampal synaptic plasticity in brain slices and hippocampus-dependent memory encoding in behaving animals (2). Using organotypic slice preparations from Sprague Dawley rat pups, Mulholland et al. first show that chronic ethanol treatment (75 mmol/L for 7–9 days) results in 1) reduced SK channel function, assessed by measuring the apamin-sensitive component of depolarization-induced outward currents or that of glutamatergic EPSPs, in CA1 pyramidal neurons, and 2)

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Corresponding Author: R. Adron Harris, Ph.D., The University of Texas, Waggoner Center for Alcohol and Addiction Research, 2500 Speedway, MBB 1.124, Austin, TX 78712, 512 232-2514, 512 232-2525 (fax), harris@mail.utexas.edu.

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downregulation of membrane expression of SK2 channels in the hippocampus. They further find that SK2 expression is selectively decreased at synaptic sites in the hippocampus of adult C3H/He mice following continuous ethanol vapor inhalation for 64 hours, confirming that SK2 downregulation occurs after *in vivo* ethanol exposure. Importantly, enhancing SK channel function using the selective activator 1-ethyl-2-benzimidazolinone (1-EBIO) prevents neuronal hyperexcitability and neurotoxicity observed during ethanol withdrawal in rat organotypic slices and also reduces the severity of seizures in adult mice withdrawn from ethanol vapor inhalation.

In the second study, Hopf et al. tested the effect of chlorzoxazone (CZX), an SK channel activator that is FDA-approved as a centrally acting muscle relaxant, on alcohol intake after a history of chronic consumption using adult Wistar rats. In another report, this group has shown that long-term voluntary self-administration of alcohol, but not sucrose self-administration, causes reduced SK channel function and expression, leading to increased excitability, in neurons of the nucleus accumbens (NAcb) core, a brain area that is critical for motivated behaviors driven by cue-reward associations (4). This change is selective for the NAcb core and is not observed in the NAcb shell or the dorsal striatum. Accordingly, local infusion of 1-EBIO into the NAcb core, but not into the shell, reduces alcohol- but not sucrose-seeking behaviors. In the current study, Hopf et al. extend these findings by showing that systemic injection of CZX reduces alcohol intake after a prolonged history of intermittent access to alcohol (IAA; 24 hours/day, 3 days/week for 5–6 weeks followed by 3 hours/day, 3 days/week for 5–6 weeks) but not in rats that had continuous access to alcohol (CAA; 24 hour/day, 7 days/week for ~12 weeks). In support of this result, NAcb core neurons exhibit enhanced excitability and increased CZX inhibition of firing in brain slices prepared from IAA rats but not those from CAA rats.

Collectively, these studies raise an exciting possibility that CZX and other SK channel activators may be used to alleviate alcohol withdrawal symptoms and reduce alcohol drinking in alcoholics. However, several concerns/questions need to be considered before enthusiastically embracing the therapeutic potential of SK activators. First, SK channels are expressed in wide range of neurons in diverse brain areas subserving different behavioral and cognitive functions (2). Therefore, global enhancement of SK channel function may cause unwanted side effects. For example, SK channels critically regulate the firing of neurons in the basal ganglia structures important for controlling locomotor activity. The locomotor depressing effect of CZX observed in the study by Hopf et al., although statistically non-significant at a low dosage (10 mg/kg), might turn out to be disturbing in human patients. Furthermore, enhancement of SK function in the hippocampus may actually aggravate cognitive impairments associated with alcoholism. Indeed, transgenic SK channel overexpression or SK channel upregulation during aging have been associated with deficits in hippocampal synaptic plasticity and hippocampus-dependent learning tasks (2). On the other hand, enhancement of SK function in other brain areas might improve alcohol-related symptoms not addressed in the two studies. For example, it has been shown that CZX improves motor performance in a mouse model of cerebellar ataxia (5), suggesting that it may ameliorate motor incoordination during acute alcohol intoxication. Furthermore, enhancement of SK function in the amygdala may act to reduce anxiety symptoms that drive compulsive alcohol intake.

Second, it would be important to determine the extent of SK channel changes in different brain areas and the SK subtype (SK1–3) selectivity of these changes. In this regard, it is of note that SK3, but not SK2, channels are downregulated in NAcb core neurons after long-term alcohol intake (4). Although neither 1-EBIO nor CZX are specific for different SK subtypes, development of subtype selective activators might enable targeting of SK channels in specific brain areas/neurons.

Third, is the intermittent drinking model, where CZX decreased drinking, a good model of alcohol dependence or even excessive drinking in humans? CZX did not reduce alcohol consumption in the continuous access model and it will be important to determine effects of CZX on other animal models that emulate human alcohol consumption (6).

Fourth, what are the cellular and molecular mechanisms causing downregulation of SK channels during long-term alcohol exposure? Does protein kinase A-mediated internalization of SK channels play a role in removal of these channels from the plasma membrane (2)? It is surprising that such a diversity of treatments and alcohol concentrations all change the expression and/or function of SK channels. For example, Mulholland et al. used continuous exposure to a relatively high (75 mM) concentration of ethanol for the *in vitro* experiments, whereas the rat operant self-administration paradigm would result in much lower ethanol concentrations in brain for a short period of time each day (4). This raises the question of whether different mechanisms are responsible for the actions of these different alcohol treatments. Elucidating these mechanisms might enable actual reversal, or even prevention, of SK channel downregulation, thus “curing” this form of alcohol-induced neuroadaptation.

Finally, another key mechanistic question is whether there are changes in expression of genes coding for SK channels (Kcnn genes) in animals treated with alcohol or human alcoholics. There are extensive brain gene expression databases in the alcohol field and a site such as the Ethanol-Related Gene Resource (ERGR, <http://bioinfo.mc.vanderbilt.edu/ERGR/index.php>) can be queried. A search of ERGR finds that operant self-administration of alcohol in rats increases the expression of Kcnn2 (SK2) (7). Examination of databases comparing gene expression in alcoholic and nonalcoholic human brain shows that Kcnn mRNAs were not reliably detected in those studies (8). An important goal for the future is to determine if there are changes in Kcnn gene expression or SK function in human alcoholics.

Despite these potential concerns and remaining questions, the two studies clearly open a new line of investigation that may provide novel treatment options for alcohol dependence. In light of the fact that CZX is an FDA-approved drug, small K channels may offer big hope to researchers, physicians, and patients battling alcoholism.

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Figure 1.

Schematic diagram illustrating how SK channels are activated during excitatory glutamatergic transmission or action potential firing. NMDA-type glutamate receptors are activated by synaptically released glutamate, while voltage-gated Ca^{2+} channels are activated by membrane depolarizations associated with excitatory postsynaptic potentials (EPSPs) or action potentials. Ca^{2+} influx through NMDA receptors or voltage-gated Ca^{2+} channels causes increases in intracellular Ca^{2+} levels. Ca^{2+} binding to SK channels triggers opening of SK channels and efflux of K^{+} ions, resulting in membrane hyperpolarization, dampening of EPSPs, and a decrease in action potential firing. SK channel activators used in the two studies increase Ca^{2+} sensitivity of SK channels, thereby strengthening SK channel-mediated negative feedback regulation of EPSPs and action potential firing.