SK channel activation for alcoholism

By Lauren Martz, Staff Writer

Researchers at the **Ernest Gallo Clinic and Research Center at University of California, San Francisco** have found that activating small conductance calcium-activated potassium channels in the nucleus accumbens region of the brain could help treat alcohol addiction.¹ The team is planning to repurpose the generic SK activator chlorzoxazone for this indication, although concerns about liver toxicity need to be resolved.

Frederic Woody Hopf, associate investigator at the Ernest Gallo Center, told *SciBX* that “existing pharmacotherapies for alcoholism, including naltrexone and acamprosate, have moderate but mixed effectiveness in humans, perhaps reflecting effectiveness in particular subpopulations. Thus, there is considerable interest in identifying novel therapies for human alcoholism.”

Hopf also noted that the marketed alcoholism drugs are generally used to reduce levels of continuous drinking. He and colleagues are taking a different approach by looking for compounds that specifically reduce drug-seeking behavior during withdrawal to prevent relapse.

Alkermes Inc. markets Vivitrol naltrexone, a sustained-release injectable formulation of naltrexone, to treat alcohol dependence. **Forest Laboratories Inc.** and **Merck KGaA** market Campral acamprosate calcium to treat alcohol addiction.

In previous studies by Hopf's group, rats abstaining from alcohol exhibited greater motivation to seek alcohol than rats not forced to abstain.² Now, the team has determined the molecular and neurologic effects associated with abstinence and increased alcohol seeking.

The group analyzed brain slices from rats that self-administered alcohol for 42–50 days and then were forced to abstain for 3–5 weeks. In the brain slices, neurons of the nucleus accumbens core had greater action potential firing than neurons from age-matched, naïve controls or neurons from animals abstaining from sucrose. Sucrose is routinely used as a control substance because the animals are motivated to learn the same methods for self-administration and experience some of the same short-term neurological changes with sucrose as a reward as they do with alcohol.

There was no change in the firing of neurons in other brain regions such as the nucleus accumbens shell or the dorsal lateral striatum, suggesting that the alterations brought on by alcohol withdrawal were specific to the nucleus accumbens core.

To determine the effects of preventing the excessive neuronal firing upon alcohol withdrawal, the team treated the brain slices of alcohol-abstaining rats with a small conductance calcium-activated potassium channel (KCNN; SK) activator. SKs work by lengthening the period of time between a neuron's firings.

Indeed, the SK activator decreased firing of neurons more in the nucleus accumbens core of alcohol-abstaining rats than in the core of naïve or sucrose-abstaining rats. The findings suggest that blocking SK currents can prevent the neurological processes that cause alcohol-seeking behavior.

In rats, intracranial injection of the SK activator into the nucleus accumbens core decreased self-administration of alcohol following abstinence compared with injection of vehicle, showing less motivation to obtain alcohol.

Clinical testing

Based on the results in the *Neuron* paper, the Gallo team wants to run a clinical trial of an SK activator for alcohol dependency.

“We are planning clinical trials to examine whether drinking in alcoholics can be reduced by the FDA-approved drug chlorzoxazone,” said Hopf. Chlorzoxazone is approved as a muscle relaxant.

If the results are positive, “the use of SK activators to reduce motivation for alcohol would strongly complement existing pharmacological and behavioral strategies for alcoholism,” which are focused on reducing drinking, he said. “SK activators could represent an acute

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But Daniel Deaver, VP of nonclinical R&D at Alkermes, thinks chlorzoxazone may not be well suited for studies in alcoholics. “The concern is that chlorzoxazone is a compound that causes liver toxicity,” he said.

“If you consider the patient population, thinking that this drug could safely have an effect is really a leap of faith. Serious health issues in the population in question include liver cirrhosis,” Deaver added. “So it's not as simple as ‘this is already approved, let's use it’. It is very possible that the dose at which chlorzoxazone would be used could be inappropriate for alcoholic patients.”

He also cautioned: “The regulatory approval of the drug was so long ago that it might be hard to get it into a clinical trial. They really need to prove safety of the appropriate dose.”

Hopf acknowledged the potential toxicity issue and said his group is “also interested in research that identifies other novel SK

activators that might offer fewer side effects than chlorzoxazone.”

In terms of safety precautions for clinical testing of chlorzoxazone, Hopf said that only alcoholics with healthy livers would be included in the trial. He added that “other drugs are prescribed that have adverse events in the liver, such as acetaminophen. In the case of chlorzoxazone, adverse liver events are severe but they are rare.”

Chlorzoxazone is approved to treat acute, painful musculoskeletal conditions at an oral dose of 500 mg 3–4 times daily. Hopf said that based on studies in rats, the dose for acute treatment in alcoholics could be as low as 200 mg, taken as needed.

Regardless of the specific SK activator used, Deaver thinks delivering the molecule could be a challenge, as it would have to both cross the blood brain barrier (BBB) and target a specific part of the brain.

“The advantage of targeting the ion channel is that it is potentially a very selective target in a very focused brain region. The disadvantage is that you have to be able to target that area,” he said. “It has been found to be very difficult to target discrete brain regions.”

Without a way to target the nucleus accumbens core, “the biggest caveat is that potassium channels are widely distributed throughout the body, so off-target action is a concern,” said Deaver. Although the risks of peripheral side effects have not been extensively studied, they could include disrupted intestinal motility and disrupted parasympathetic regulation of cardiac and visceral functions.^{3,4}

Hopf suggested that simply getting an SK activator into the brain would likely work, even without specific targeting.

“Reduced SK function at the cellular level developed after long-term alcohol intake but not sucrose intake. Similarly, SK activators

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—Daniel Deaver, Alkermes Inc.

reduced alcohol intake but had no effect on sucrose intake, suggesting that SK activators can only alter reward seeking under conditions where SK is altered. The specificity of this effect should limit side effects on motivation for more natural rewards,” he said.

Hopf added that he is not particularly concerned about off-target effects of SK-activating drugs outside of the brain. He said that high levels of SKs do occur in the smooth muscles of the blood vessels and that SK activators can have a muscle-relaxing effect. However, he added that as a muscle relaxant, chlorzoxazone is only effective in a subset of patients, suggesting that musculoskeletal side effects wouldn't be an issue for all patients.

Hopf told *SciBX* that his team's work has not been patented and is unavailable for licensing.

Martz, L. *SciBX* 3(12); doi:10.1038/scibx.2010.363

Published online March 25, 2010

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