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“Drugs of abuse can produce long-term changes in the electrical activity of neurons in the brain. Recently, we have been researching a new role for GIRK potassium channels—proteins that control the movement of potassium ions in the brain—in drug addiction. Our studies may provide new insights into the cellular mechanisms of drug addiction as well as some mental disorders, such as schizophrenia and attention deficit hyperactivity disorder (ADHD).”

Alcohol’s inebriating effects are familiar to everyone. But despite its long history and the widespread use of ethanol—the alcohol in intoxicating beverages—when it comes to alcohol’s impact on brain activity on a molecular level, it remains among the least understood of psychoactive drugs. Although alcohols had previously been shown to lead to the opening of GIRK (short for G-protein-activated inwardly rectifying potassium) channels, it was not known whether this was a direct effect or byproduct of other molecular changes in the cell.

When Slesinger and collaborators determined the three-dimensional structure of GIRK channels at high resolution, they discovered a molecular pocket that resembled confirmed alcohol-binding sites found in two other proteins (alcohol dehydrogenase, the enzyme that breaks down alcohol in the body, and LUSH, a fruit fly protein that senses alcohol in the environment). This finding allowed them to address the puzzle of how alcohol activates GIRK channels.

When they systematically introduced amino acid substitutions that denied alcohol molecules access to the potential interaction site, alcohol could no longer efficiently activate the channel, confirming that they had hit upon an important regulatory site for alcohol. The team further established that this pocket is a trigger point for channel activation since G protein activation was also altered. They believe that alcohol hijacks the intrinsic activation mechanism of GIRK channels and stabilizes the opening of the channel, perhaps by “lubricating” the channel’s activation “gears.”

A better understanding of how GIRK channels are activated could point to new strategies for treating human diseases. Using the protein structure as a starting point, for example, it may be possible to develop a drug that antagonizes the actions of alcohol to treat alcohol dependence. Alternatively, if a novel drug is identified that fits the alcohol-binding site and activates GIRK channels, this could dampen overall neuronal excitability in the brain and perhaps provide a novel pharmacological tool for treating epilepsy.

For more information, please visit
salk.edu/faculty/slesinger.html



Left to right:

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