Medical Xpress

Understanding alcohol's damaging effects on the brain

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While alcohol has a wide range of pharmacological effects on the body, the brain is a primary target. However, the molecular mechanisms by which alcohol alters neuronal activity in the brain are poorly understood. Participants in a symposium at the June 2010 annual meeting of the Research Society on Alcoholism in San Antonio, Texas addressed recent findings concerning the interactions of alcohol with prototype brain proteins thought to underlie alcohol actions in the brain.

Proceedings will be published in the September 2011 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"Alcohol is the most common drug in the world, has been used by diverse human communities longer than recorded history, yet our understanding of its effects on the brain is limited when compared to other drugs," said Rebecca J. Howard, a postdoctoral fellow at The University of Texas at Austin Waggoner Center for Alcohol & Addiction Research and corresponding author for this study.

Howard explained that neuroscientists have discovered how marijuana, cocaine, and heroin each bind to a special type of protein on the surface of brain cells, fitting like a key into a lock to change that protein's normal function. Yet alcohol has special properties that make it difficult to characterize its lock-and-key binding in detail, for example, alcohol is much smaller than other drugs, and appears to interact with several different types of proteins.

"The adverse effects of alcohol abuse are devastating on a personal level and on a societal level," added Gregg Homanics, a professor of anesthesiology and pharmacology & chemical biology at the University of Pittsburgh. "Alcohol abuse costs our society more than the costs of all illegal drug abuse combined. For many years, most investigators thought that alcohol exerted nonspecific effects on the brain and simply perturbed neuronal function by dissolving in the membranes of nerve cells. However, our understanding of alcohol action has dramatically shifted in the last 10 to 15 years or so. There is now solid experimental evidence that alcohol binds in a very specific manner to key protein targets in the brain to cause the drug's well known behavioral effects. This review summarizes some of the most recent research."

Some of the key points were:

- Combining X-ray crystallography, structural modeling, and site-directed mutagenesis may be better suited to studying alcohol's low-affinity interactions than traditional techniques such as radioligand binding or spectroscopy.

  "One major problem in studying alcohol binding to brain proteins is that the alcohol key does not fit very tightly into any particular protein lock," said Howard. "That is, alcohol has a 'low affinity' for proteins, compared to how other drugs interact with their own protein targets. We think this is one reason it takes such a large quantity of alcohol to affect the brain: whereas users of cocaine or heroin may consume just a few milligrams at a time, a person drinking a shot of strong liquor consumes about 1,000 times that much alcohol (several grams). The low affinity of alcohol for its protein targets [also] makes it difficult to study by traditional methods that rely on detecting stable drug-protein complexes over a long period of time."

- Some common themes are beginning to emerge from a review of diverse proteins such as inwardly rectifying potassium, transient receptor potential, and neurotransmitter-gated ion channels, as well as protein kinase C epsilon.

  "It is now very clear that hydrophobic pockets exist in the structure of various brain proteins and alcohols can enter those pockets," said Homanics. "Alcohols interact with specific amino acids that line those pockets in a very specific manner."

- In particular, evidence is emerging that supports characteristic, discrete alcohol binding sites on protein targets.

"Different drugs bind to different types of proteins on the surface of brain cells, each fitting like a key, or drug, into a lock, or binding site, on a protein to change its normal function," explained Howard. "Understanding the exact shape of that lock and key helps us to understand how individuals with special mutations may be affected differently by drugs, and can help scientists design new medicines to help people with drug abuse or other problems."

"I feel that there is now overwhelming evidence that specific alcohol binding sites exist on a variety of brain protein targets," added Homanics. "This is significant because we can now focus on defining these sites in greater detail, ultimately at the level of each atom involved. This will allow for, one, a more complete understanding of the molecular pharmacology of alcohol action, two, the discovery of similar sites on other important brain proteins, and three, the rational design of drugs that can selectively target these binding sites."

"Our review summarizes very recent advances in understanding the molecular details of alcohol binding sites, which now include human brain targets, not just metabolic enzymes and receptors from other species," said Howard. "This information will give researchers new opportunities to characterize human mutations and design new medicines. Furthermore, common themes emerging about alcohol binding sites may help scientists identify important binding sites in other important brain proteins."

"In other words," said Homanics, "alcohol exerts its effects via binding sites on target molecules just like all other drugs we know about. There is now solid evidence from several different putative alcohol targets using several different techniques that alcohol interacts with specific brain targets in a highly selective manner. This is particularly important for more senior clinicians and researchers that were trained years ago when the predominant theory of alcohol action was via nonspecific effects on the nervous system." Both Howard and Homanics are hopeful that this research will aid the development of therapies and treatments for individuals with alcohol problems.

"Great progress is being made in understanding how alcohol exerts its effects on the brain at the molecular level," noted Homanics. "Understanding how alcohol affects brain proteins on a molecular level is essential if we are to effectively develop rational treatments to combat alcohol use disorders."

Provided by Alcoholism: Clinical & Experimental Research