Studies Offer Clues About How Alcoholic Behavior is 'Switched' On

May 9 2005

As part of an ongoing effort to understand the biochemical basis of alcohol abuse, scientists at the U.S. Department of Energy's Brookhaven National Laboratory have published two studies on how modulating receptors for dopamine - a chemical "signaler" in the brain's reward circuits - affects drinking behavior in mice and rats.

"Stopping alcohol abuse will never be as simple as turning on or off a 'switch,' but finding ways to modulate the brain's reward circuits could play a role in developing successful treatments," said Brookhaven's Panayotis (Peter) Thanos, lead author of both studies. The studies appear in the May 27, 2005, issue of Life Sciences and the June 2005 issue of Pharmacology Biochemistry and Behavior, both now available online.

In the first study, the scientists increased the number of dopamine "D2" receptors in strains of mice with genetically varying levels of D2 receptors. Earlier Brookhaven studies have shown that "up-regulating" D2 receptors by delivering the D2 gene directly to the brain's reward center decreased drinking behavior in rats trained or genetically predisposed to drink large quantities of alcohol.

The Life Sciences study demonstrates this same "alcoholism-quenching" effect of D2 "gene therapy" in mice with normal to moderately low levels of D2s, supporting the idea that receptor up-regulation could play a role in the treatment of alcoholism.

Also in that study, however, so-called "knockout" mice, which initially

had no D2s, drank more in response to D2 up-regulation. “This suggests that there may be a threshold level of D2 receptors needed for animals to respond to the reinforcing effects of alcohol,” Thanos said.

“When we up-regulated D2 levels in the knockout mice, we may have approached or obtained D2 levels close to this threshold, thus producing the reinforcement and an increase in ethanol intake,” Thanos said. But, he added, this doesn’t mean that D2 up-regulation would turn non-drinkers into alcoholics. “We could speculate that further increases in D2, above this threshold, would result in a decrease in ethanol consumption in this group as well,” he said.

In the second study, Thanos’ group tested the idea that blocking the activity of another kind of dopamine receptor, known as D3, might reduce alcohol consumption. They tested their hypothesis in rats with a genetic predisposition to prefer alcohol when given a choice between a 10 percent ethanol solution and pure water, comparing them with rats that had no prior preference for alcohol. Both sets of animals were treated with varying doses of “SB-277011-A,” a known D3 receptor “antagonist” — a chemical that binds to the receptor thus blocking dopamine’s ability to bind and send its pleasure/reward signal.

The two higher doses of the antagonist (10 and 30 milligrams per kilogram body weight) reduced drinking behavior in the alcohol-preferring rats; the highest dose decreased drinking (though less dramatically) in the non-preferring group, which drank less to begin with. The lowest dose (3mg/kg) had no effect in either group. None of the doses caused any side effects.

“Recent studies have demonstrated that SB-277011-A is a highly selective D3-blocker and also reduces cocaine-seeking behavior, as well as behavior involving other drugs of abuse, such as nicotine and heroin,” Thanos said.

While it is well known that brain circuits modulated by other neurotransmitters (such as glutamate and serotonin) also play a role in alcohol intake, Thanos said, “these two studies provide further insight into the complex roles of dopamine — and may help us better understand the mechanism(s) of alcohol abuse and assist in the development of specific, molecular-based treatments.”

The Life Sciences study was funded by the Office of Biological and Environmental Research (OBER) with the U.S. Department of Energy's Office of Science and by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Mental Health, and the National Institute on Drug Abuse (NIDA). Collaborators at Oregon Health and Science University, the University of Buenos Aires, and the University of Nagoya School of Medicine are co-authors on this paper.

The Pharmacology, Biochemistry and Behavior study was funded by DOE's OBER and NIAAA. Researchers at St. John's University, NIDA, GlaxoSmithKline Pharmaceuticals, and NIAAA collaborated on this study.

Source: Brookhaven National Laboratory