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Alcohol may elevate the expression of two enzymes called CYP2E1 and CYP2U1

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The prefrontal cortex (PFC) and amygdala (AMG) are brain regions that not only referee cognitive functions and emotional states, but also contribute to the reinforcing effects of alcohol and tobacco. Researchers already knew that alcohol and tobacco use can modulate cytochrome P450 expression in the liver and other tissues, but little is known about the effects of alcohol and tobacco on P450s in the human AMG. A new study focusing on two CYP2 enzymes that metabolize drugs and endogenous compounds has found that chronic drinking is associated with higher CYP2E1 and CYP2U1 protein expression in both brain regions, particularly the AMG.

Results will be published in the May 2015 online-only issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"The basolateral AMG, the specific amygdalar region analyzed in this study, seems to mediate the triggering of drug cravings by drug-related cues, such the sight of a lighter for a smoker, or the sight of a drink for an alcoholic," explained Francesca Toselli, a postdoctoral fellow in pharmacology and toxicology at the University of Toronto. "The PFC, on the other hand, mediates a relapse into drug use triggered by re-exposure to the drug itself, such as having a cigarette or a drink again after a period of abstinence."

P450 enzymes from the CYP2 family, Toselli added, are major contributors to the clearance of drugs that target the brain. Animal work

has shown that this can occur directly in the brain and in living animals. Furthermore, nicotine appears to be able to alter the activity of some relevant CYP2 enzymes in the brain and other tissues.

Toselli and her colleagues examined 28 frozen human autopsy brain-tissue samples previously collected by qualified pathologists from 20 human subjects; the majority were male, only one sample was from a female subject - an alcoholic non-smoker. They analyzed and compared the expression of CYP2A6, CYP2B6, CYP2D6, CYP2E1, CYP2J2, CYP2S1, CYP2U1 and CYP2W1 proteins in PFC and AMG samples from alcoholic smokers, alcoholic non-smokers, non-alcoholic smokers, and non-alcoholic non-smokers in order to assess the effects of alcohol use and smoking on expression of these proteins.

"Our study shows that alcohol and cigarette smoke may increase the expression of two important drug- and endogenous compound-metabolizing enzymes in two brain areas that modulate drug addiction and affective behavior," said Toselli. She noted that this could lead to interactions between metabolism of drugs and endogenous substrates such as neurotransmitters which, in turn, could alter drug response and brain physiology.

"Both alcohol and cigarette smoke were associated with higher CYP2U1 expression in the PFC, and its expression was particularly elevated in subjects with a concurrent drinking and smoking history," she said. "Alcohol was also associated with higher CYP2U1 expression in the AMG. Furthermore, chronic drinking was associated with higher CYP2E1 expression in both brain regions analyzed, particularly in the AMG, and to a higher extent than what was observed for CYP2U1."

Toselli added that one of the major findings from her group's study is the potential effect of alcohol on the expression of CYP2U1 in the brain. "CYP2U1 is an enzyme that metabolizes, among other compounds, fatty

acids and the tryptophan derivative, indole," she explained. "The major indole metabolite generated by CYP2U1 is oxindole, which is thought to contribute to the central nervous system depression associated with liver failure, such as hepatic encephalopathy. Our results could thus suggest a potential new research angle on the mechanisms underlying this disease."

Provided by Alcoholism: Clinical & Experimental Research