Investigating separate and joint effects of alcohol and tobacco on the nucleus accumbens

May 4 2010

The brain's nucleus accumbens (NAC) is a core region of the mesocorticolimbic dopaminergic system and is interconnected with the ventral tegmental area (VTA) and the prefrontal cortex. The mesocorticolimbic system is thought to be central to the reinforcing effects of many drugs and plays an important role in addiction. A new study has found that alcohol abuse elevated the expression of a distinct set of genes in the NAC and VTA, while nicotine blunted this effect in the VTA.

Results will be published in the July 2010 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"In spite of their differences in pharmacology, alcohol and tobacco consumption are often intimately linked," said Traute Flatscher-Bader, a postdoctoral research fellow at The University of Queensland and corresponding author for the study. "Nonetheless, the molecular mechanisms that underlie alcohol and nicotine abuse, and particularly their co-abuse, are still incompletely understood."

"One thing that researchers have encountered is that it is often difficult to find 'pure' alcoholics, that is, alcoholics that only abuse alcohol and nothing else," agreed Simon Worrall, director of postgraduate coursework programs in molecular biology at The University of Queensland. "Many alcoholics are poly-drug abusers, with the most

common other drug being nicotine. Thus, many studies which have studied the effects of alcohol on the brain and other organs have been compromised because they have not taken account of the effects of nicotine addiction which is often superimposed on the effects of alcohol addiction."

In the first part of the current study, Flatscher-Bader and her colleagues used DNA microarray technique to study the expression of many thousands of genes in the brains of non-smoking and smoking alcoholics and non-drinking smokers.

"We examined the impact of alcoholism and smoking on gene expression in the NAC in 20 chronic alcohol abusers and controls with and without recent smoking history," said Flatscher-Bader. "The results revealed that in this brain region, the abuse of alcohol and nicotine had distinct effects on the expression of genes. In addition, altered expression of a number of genes was associated with both alcohol and nicotine abuse. Within the latter group was a set of genes which play a crucial role in a molecular pathway regulating cell structure."

The researchers then went on to investigate in more detail the altered expression of six selected genes within the pathway regulating cell structure in two brain regions, using 30 cases comprised again of smoking and non-smoking controls and alcohol abusers. For this part of the study they used the method called "real time polymerase chain reaction."

"This expanded investigation revealed that one of the genes, called RHOA, was elevated by alcohol abuse and its highest expression was evident in the smoking alcoholics in both brain regions," said Flatscher-Bader. "The RHOA gene had previously been implicated in the initiation of tobacco smoking. In the NAC, the expression of a further four of the six selected genes was increased by alcohol abuse. Interestingly, the

highest expression for each of the genes in the NAC was in the smoking alcoholics. In the other brain region called the VTA, alcohol abuse had a similar effect and elevated the expression of all six selected genes. In contrast to the NAC, however, concurrent smoking dampened the induction of five of these alcohol-sensitive genes in the VTA."

"Many studies have analyzed the changes in gene expression in this brain system to try to untangle the molecular pathology of alcohol addiction," said Worrall, "but this is amongst the first to take into account the effect of co-administration of nicotine with alcohol.

Flatscher-Bader stressed that there are several cell types in the brain and there are several steps between gene expression and impact on cell structure and function. "It has to be emphasized that our study is important as a first step in identifying molecular pathways underlying the effects of alcohol abuse and smoking and their co-joint abuse on the human NAC and VTA, "she said. "It now needs to be tested if our findings are, indeed, associated with changes to neuronal structure and function."

"A better understanding of the molecular basis of withdrawal may help in the development of new treatments to ameliorate the symptoms," added Dr Worrall. "Not many previous studies took into account the potential effects of nicotine addiction that may be superimposed on top of those from alcohol, so these results may help clinicians better use present therapy/drugs to treat patients abusing both alcohol and/or nicotine and may also lead to the development of new drugs."

Provided by Alcoholism: Clinical & Experimental Research