# The mu opioid receptor genotype may be a marker for those who drink for alcohol's rewarding effects

December 14 2012

Previous research had identified an individual's subjective response to alcohol as a marker of alcoholism risk. The A118G single nucleotide polymorphism (SNP) of the mu opioid receptor (OPRM1) gene had also been previously associated with subjective response to alcohol in heavy drinkers. A new study extends this research, showing that the OPRM1 genotype seems to moderate the pleasant and stimulating effects to alcohol among alcohol-dependent (AD) individuals but not its unpleasant and sedative effects.

Results will be published in a special online issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"People's response to drugs of abuse, including alcohol, varies dramatically," said Lara A. Ray, assistant professor in the department of psychology at the University of California, Los Angeles as well as corresponding author for the study. "Some research has suggested that the quality and intensity of a person's response to alcohol can predict whether they develop problems with alcohol. For example, individuals who experience stronger stimulant and rewarding effects from alcohol are more likely to drink heavily, thus increasing their chances of developing an alcohol use disorder.

"We have known for a long time that alcoholism runs in families, which implies a genetic risk," said Dr. Raymond F. Anton, Distinguished

Professor and director of the Center for Drug and Alcohol Programs at the Medical University of South Carolina. "There is currently great interest in how medications work in different people based on their individual genetic makeup, which is called 'personalized medicine.' If you think about it, alcohol is a pharmacological agent that works on the brain in certain defined ways which we know about. So it would make sense that it would work differently in different people, most of which is likely based on genetic differences."

"The opioid system has been shown to be partially responsible for the rewarding effects of alcohol," added Ray. "We were interested in whether a mutation in this system, specifically in the OPRM1gene, would change the way AD individuals respond to alcohol in the lab. We knew that as alcoholism progresses, the rewarding effects of alcohol become less salient; AD patients tell us they mostly drink to feel normal as opposed to drinking to feel good."

Ray and her colleagues recruited 295 non-treatment seeking problem drinkers (217 males, 78 females) from the Los Angeles community through print and online advertisements. Participants were between 21 and 65 years of age, had self-identified problems with alcohol, and were consuming a minimum of 48 standard drinks per month. Of these, 43 individuals with AD, balanced for the genotype of interest (23 A-allele carriers and 20 G-allele carriers), completed two sessions of either intravenous alcohol (0.06 g/dl) or saline. Subjective responses were measured during the alcohol and saline sessions.

"AD carriers of the G-allele of the OPRM1 gene showed a greater response to alcohol in terms of stimulation, vigor, and positive mood, as compared to A-allele homozygotes," said Ray. "However the increased response was selective, such that carriers of the G allele did not differ in terms of their sedative response or craving during the alcohol administration. We also observed a trend-level effect such that those

participants who were more severely AD had a greater reduction in tension in response to the alcohol compared to less-severe participants. Together, we believe these findings help connect genetics and neuroscience of alcoholism by demonstrating a role for disease severity in clinical samples."

"This variant of the opiate receptor gene is the exact same one that predicts naltrexone response," said Anton, "and which exists in about 25 percent of Caucasians. The data support the idea that alcohol might work through the brain opiate system to hypothetically increase dopamine and thereby lead to perceived positive aspects of alcohol consumption. It would also provide a reason as to why naltrexone – which blocks this effect – might break the link between alcohol-induced stimulation and further drinking as shown by myself and others. So what we have is a better understanding of a biological process that makes sense clinically and therapeutically."

"The gene we investigated, OPRM1, has received considerable attention in the alcohol research field both in terms of risk for alcoholism and for responsiveness to treatment with naltrexone," noted Ray. "This study is the first to have tested the effects of this gene on response to alcohol in AD individuals. Furthermore, the finding that more severely AD patients exhibited greater reduction in tension in response to alcohol supports the theory that as alcoholism progresses, people are driven to drink primarily for negative reinforcement, namely, alleviation of negative mood or aversive physiological states from abstinence. On a related note, patients in the early stages of alcoholism or who report drinking for reward, or to 'feel good,' may be especially good candidates for an opioid blocker such as naltrexone or possible nalmefeme."

"What these data show, and something I have been talking about for a long time, is the need for the research field to invest heavily in understanding alcohol by gene interactions," added Anton. "There should

be a large-scale national study to evaluate thousands of individuals like the ones studied here. We have the genetic tools and the clinical research methods to make the link between individual differences and alcohol response/effects – which lies at the root cause of why some people become dependent/addicted and others do not."

Provided by Alcoholism: Clinical & Experimental Research