Receptor variant influences dopamine response to alcohol

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A genetic variant of a receptor in the brain's reward circuitry plays an important role in determining whether the neurotransmitter dopamine is released in the brain following alcohol intake, according to a study led by researchers at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), part of the National Institutes of Health. Dopamine is involved in transmitting the euphoria and other positive subjective effects produced by alcohol.

A report of the findings, which help explain the diverse genetic susceptibility for alcohol use disorders, will appear online in Molecular Psychiatry on May 18, 2010.

"By advancing our understanding of the neurobiology that underlies the addictive properties of alcohol, this finding helps us understand why alcohol affects people in very different ways," says NIAAA Acting Director Kenneth R. Warren, Ph.D. "This kind of information also aids the development of personalized medications for alcohol problems."

Receptors for brain molecules known as opioid peptides help initiate the neurochemical reactions that underlie the positive effects produced by alcohol. Activation of the mu-subtype of opioid receptor following alcohol consumption triggers the release of dopamine from the forebrain.

"But there is much variation in alcohol-induced responses that are thought to be related to dopamine," explains Markus Heilig, M.D.,

Ph.D., NIAAA clinical director and the study's senior author. "Previous studies by our group and others suggest that variants of opioid genes may contribute to the observed variation, possibly through effects on alcohol-induced dopamine release."

He notes, for example, that people who carry the mu-opioid receptor variant designated as 118G report increased euphoria following alcohol consumption. Dr. Heilig's group has reported that a similar mu-opioid receptor variant in monkeys heightened the stimulating effects of alcohol and increased their alcohol consumption.

In the current study, first author Vijay A. Ramchandani, Ph.D., an investigator in NIAAA's Laboratory of Clinical and Translational Studies, Dr. Heilig, and their colleagues explored whether the 118G mu-opioid receptor variant influences dopamine release from a forebrain region called the ventral striatum in response to alcohol.

Using human positron emission tomography (PET), an imaging technique that allowed the researchers to analyze dopamine activity in the brain, they compared dopamine release in two groups of people that had been given a dose of alcohol. The groups consisted of those who carried a copy of the gene for the 118G mu-opioid receptor variant, and those who carried only genes for the more common 118A variant. They found that only people with the 118G variant had a dopamine response to alcohol - no such response happened in subjects with the 118A receptor variant.

In a separate experiment, they inserted genes for the human 118G or 118A mu-opioid receptor variants into mice and then directly measured the animals' dopamine response to a dose of alcohol. Mice with the 118G variant showed a fourfold higher peak dopamine response to the alcohol challenge compared to mice with the 118A variant.

"Taken together, our data strongly support a causal role of the 118G variant of the mu-opioid receptor to confer a more vigorous dopamine response to alcohol in the ventral striatum," says Dr. Ramchandani. "The findings add further support to the notion that individuals who possess this receptor variant may experience enhanced pleasurable effects from alcohol that could increase their risk for developing alcohol abuse and dependence. It may also explain why these individuals, once addicted, benefit more from treatment with blockers of endogenous opioids."

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