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Genes influence impulsive behavior, preceding the development of alcoholism

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Numerous studies have shown that highly impulsive behavior - defined as the tendency to choose small, immediate rewards over larger, delayed rewards - is more prevalent in drug addicts and alcoholics compared to individuals without addictions. A new study using mice has found that genes influence impulsivity, which may then contribute to the risk for developing alcoholism.

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

"There is increasing evidence that the character trait of impulsivity predisposes towards addiction in all its forms, such as drugs, alcohol, gambling," said Nicholas J. Grahame, associate professor of psychology at Indiana University-Purdue University at Indianapolis. "Data from the National Epidemiologic Survey on Alcoholism and Related Conditions suggest that a variety of disorders that increase impulsivity - from bipolar disorder, to conduct disorder, and antisocial personality disorder (ASPD) - are associated with an increase in risk for alcoholism."

"The relationship between high impulsivity and drug use raises many questions," added Suzanne H. Mitchell, associate professor in behavioral neuroscience at Oregon Health & Science University. "For example, is an impulsive individual more likely to experiment with drugs, and then develop a problem? If such a relationship was found, identifying children or adolescents with high levels of impulsivity might, in theory, allow us to identify individuals at risk for developing a substance-use

disorder like alcoholism."

Grahame and his colleagues tested several selected lines of alcohol-nad′ve mice: offspring of High Alcohol Preferring (HAP) mice, HAP1 and HAP2; offspring of Low Alcohol Preferring (LAP) mice, LAP2; as well as offspring of low-drinking progenitor (HS/Ibg) mice. All of the mice were tested on a delay-discounting task, which employs two levers to provide subjects with a choice between a small, immediate or a large, delayed saccharin reward.

"We first used selective breeding to obtain mice genetically predisposed to drink alcohol," said Grahame. "The experiment was to create lines of animals that differ in genes related to alcohol drinking, and the central question was: 'Are any of the genes affected by this manipulation related to impulsivity?' To study this, we used a task that is widely used in both human and animal studies, which was to give a choice between an immediate but small reward and a delayed but large reward. The mice that had the genes to drink, the HAP1 and HAP2 mice, were more impulsive than their low-drinking counterparts, the LAP2 and HS/IBG mice."

"Given that these differences in impulsivity were present in alcohol-nad′ve animals," added Mitchell, "neural changes brought about by alcohol consumption could not be responsible for the differences between the two groups of mice."

"I think these data can clearly be extrapolated to humans," said Grahame, "because the same task can be used in a variety of species, including humans, to assess ability to plan for the future. The data suggest that if humans are like mice, their differences in impulsive behavior may also be affected by their genes, and these differences in impulsivity could confer some of the familial risk for alcoholism that we already know about."

Mitchell agreed. "The results imply that a subset of individuals who are 'family-history-positive' for alcoholism behave more impulsively," she said. "However, the results do not mean that individuals with high levels of impulsivity are doomed to a life of substance use, just as having genes associated with alcoholism does not destine you for a life of alcoholism. The interaction between genes and environment is critical. However, the study supports other work indicating that there is a genetic component to impulsivity. Future work could shed light on which genes are important in impulsive decision making, and which genes are shared with the propensity to develop a substance-use disorder."

"I think that the quality of impulsivity we are assessing here resonates with many folk stories about "fools" and their poor decision making," said Grahame. "I think of Jack of beanstalk fame who trades his cow for three magic beans, the grasshopper who has fun now while the ant plans for the future, and the pig that works hard to build the brick house that can survive the wolf. We try to inculcate low impulsivity in our children, because it is such an important survival trait for many reasons."

While the natural impulsivity of children tends to diminish as they mature, added Grahame, a decrease in heavy drinking that occurs for many during their teen years may be absent for those who have other problems, causing them to remain impulsive well into their adult years.

"Our data suggest that impulsivity contributes to high alcohol drinking and, consequently, the diagnosis of any disorder associated with life-long impulsivity - for example, ASPD, bipolar disorder, borderline personality disorder, and attention-deficit disorder - is grounds for serious concern about later problems with alcoholism and drug abuse, which can aggravate the severity of the disorders I just mentioned," said Grahame. "We already know this from human studies, but I think that the mouse data make us more certain about the causal direction, and genetic mediation, of some of these associations."

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