

Gene therapy can reduce long-term drinking among rodents

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“An ‘experiment of nature’ is observed in some individuals of East Asian origin, who are 66 to 99 percent protected against alcoholism,” explained Yedy Israel, professor of pharmacological and toxicological chemistry at the Universidad de Chile, and adjunct professor of pathology, anatomy and cell biology at Thomas Jefferson University in Philadelphia.

“These individuals carry a genetic mutation that inactivates the aldehyde dehydrogenase-2 enzyme, which is needed to eliminate products of alcohol metabolism. When they drink, they experience nausea, facial redness and a pounding heart.” Israel, past president of the U.S. Research Society on Alcoholism, is the study’s corresponding author.

Israel added that although gene therapy is predominantly associated with helping “bubble babies” – children who must live in a sterile bubble because they lack all immunity and may die of infections – there are presently 1,300 clinical gene-therapy trials for different conditions worldwide.

“Gene therapy is a technique that has been proposed for a number of human conditions, mostly to correct inborn errors that lead to severe conditions,” noted Richard Deitrich, Professor Emeritus at the University of Colorado School of Medicine. “In terms of alcohol research, however, this is certainly ‘cutting edge.’ The goal here is to silence a gene or at least impair its function, thereby mimicking a genetic condition that some Asian individuals normally have that protects them from developing alcoholism.”

Researchers used rats that were initially bred as heavy alcohol drinkers, and then further rendered alcohol dependent through a two-month period of unlimited, voluntary intake of the equivalent of premium beer, followed by withdrawal, followed by a one-hour “happy hour” each day. During this hour, the animals drank 10 times more alcohol than what is normally consumed. An anti-Aldh2 antisense gene was then intravenously administered, with the intent of “shutting off” ALDH2 activity.

“Animals that were given a single intravenous injection of the antisense gene therapy reduced their consumption by one half, for a full month, which was the duration of the study,” said Israel. “This would appear to have implications for a social-drinking pattern, and the notion of ‘harm reduction,’ where full abstinence is not the only acceptable goal.”

“These findings are a long way from being applied to humans,” cautioned Deitrich. “There are both practical and theoretical issues that need to be addressed. For example, does the antisense gene get into the brain” Presumably not, but that needs to be shown. Is there any crossover of the antisense gene into reproductive organs, such as sperm or eggs” Again, presumably not, but that also needs to be shown. Can they target the liver specifically” What is the duration of the effect” This study went out to 34 days, but the treatment will not be feasible if it requires once-a-month treatment.”

On a more theoretical level, Deitrich wondered about the treatment applications of gene therapy for alcoholism. “For example, should it be reserved to treat individuals who are already dependent or should it also be offered to individuals not yet alcohol dependent but drinking heavily” What would be the effect on the individual who takes the treatment but continues to drink, as do some of the heterozygous individuals” These individuals have a higher incidence of cancers of the throat and upper respiratory tract. However, the authors point out that if they can target

the liver with the antisense therapy, other tissues would retain their ability to remove acetaldehyde. This is not the case for East Asians in whom ALDH is inactive in all tissues.”

Despite the questions that remain, Deitrich added, “this is a remarkable paper and, even if these studies are never translated to humans, it is an important addition to the alcohol- research field.”

Israel and his colleagues are planning to examine methods by which they can deliver genes through a single treatment that can last for a period of one year to a lifetime. “Given that the main problem in the pharmacological treatment of alcoholism is that patients do not adhere to the treatment, and that the effect of most recent medications is only moderate at best, gene therapy shows great potential value for the treatment of alcoholism,” Israel said. “A rapid transfer of gene-therapy possibilities into the clinic will depend on how these new studies proceed.”

Source: University of Colorado Health Science Center at Fitzsimons

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