Brain Data Fuel Alcoholism Gene Clash

Alcoholics fall into two groups, depending on whether their brains exhibit a dramatically lower or slightly elevated flow of dopamine, a chemical that helps regulate pleasurable emotions during eating, drinking, and sex, a new study finds. Controversial studies suggesting that a substantial minority of alcoholics inherit a gene associated with depressed dopamine transmission appear to be on the right track, the new study's authors hold.

Nonviolent alcoholics have many fewer and less widely distributed dopamine reuptake sites—cellular gateways for recovering and recycling dopamine at key nerve junctions—than do nonalcoholics, asserts a team of Finnish scientists led by Jari Tiihonen, a psychiatrist at the University of Kuopio. These reuptake sites prove slightly more extensive in highly violent alcoholics than in nonalcoholics, the researchers report in the July NATURE MEDICINE.

The findings fit with evidence associating one form of the D2 dopamine receptor gene, known as the A1 allele, with reduced numbers of dopamine receptors in the brain (SN: 11/14/92, p.332). People with fewer receptors have a greater likelihood of developing severe alcoholism or other types of drug abuse, some investigators theorize. The receptor disparity between violent and nonviolent alcoholics is not due to alcohol-induced changes in blood flow or shrinkage of brain tissue, withdrawal effects, or poor nutrition, the Finnish scientists argue.

Earlier studies lumped violent and nonviolent alcoholics together, which "might be one reason for the previous controversial findings concerning the association between alcoholism and [dopamine] abnormalities," Tiihonen's team writes.

But controversy permeates all aspects of these studies, and the genetic significance of the new data has already become a matter of dispute.

The Finnish researchers studied 19 habitually violent alcoholics (who had committed murders or other violent crimes), 10 nonviolent alcoholics, and 19 nonalcoholic adults. Each volunteer received an injection of a minute amount of a radioactive substance that attaches to dopamine reuptake sites. An imaging device then translated radioactive emissions into data on the number and extent of dopamine receptors in brain areas thought to regulate pleasurable sensations.

A separate brain imaging study, reported in 1994 by another research group, also found sparse dopamine reuptake sites in nonviolent alcoholics, compared to nonalcoholics. That project, however, did not include alcoholics with a history of severe violence.

David Goldman, a psychiatrist at the National Institute on Alcohol Abuse and Alcoholism in Rockville, Md., doubts that such findings stem from wayward genes. "If confirmed, [the data] would indicate that alcohol exposure or other experience common to alcoholics is capable of inducing a long-lasting alteration of [dopamine] function," Goldman writes in a comment accompanying the new study.

Reduced dopamine transmission may contribute to cravings for alcohol, making it difficult for alcoholics to abstain from imbibing, Goldman says.

Tiihonen's group did not look at whether nonviolent alcoholics carry the A1 allele more often than violent alcoholics or nonalcoholics. But Goldman, whose research has found no link between alcoholism and the A1 allele, suspects it played no part in the Finnish findings.

The dopamine transporter (DAT1) gene, which helps to organize critical reuptake sites, may contribute more strongly to alcoholism, Goldman holds.

Ernest P. Noble, a psychiatrist at the University of California, Los Angeles, disagrees. Noble coauthored the first study to report a link between the A1 allele and severe alcoholism (SN: 9/21/91, p.190).

"The new data show that some alcoholics have greatly reduced dopamine function, as we argue," Noble holds. "Our findings indicate that there is an inherited form of alcoholism that includes the A1 allele and a reduced number of dopamine receptors in the brain."

Alcoholics bearing the A1 allele show marked drops in anxiety and alcohol craving after 3 to 6 weeks of treatment with a drug that boosts dopamine transmission through D2 receptors, Noble and his coworkers report in the April NATURE MEDICINE. The same drug yielded only mild improvement in alcoholics possessing another form of the D2 dopamine receptor gene.

Alcoholism researchers need to pin down the influence wielded by the A1 allele and other genes that affect dopamine's action, Noble contends.

— B. Bower

DNA repair enzyme: A structure revealed

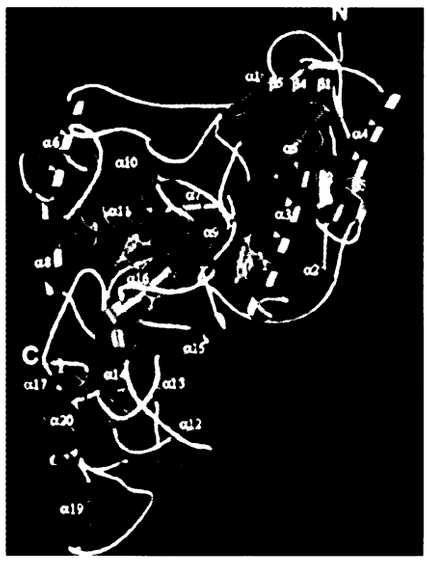
Like any complex machine, DNA has a tendency to break down—particularly under the onslaught of ultraviolet light.

Energetic UV rays from the sun create subtle glitches in the fragile genetic material present in every living cell. Left uncorrected, these glitches can eventually lead to biological disaster. Researchers have long known that intense or prolonged exposure of unprotected healthy cells to UV light and other forms of high-energy radiation can lead to cellular mutations and cancer.

Interestingly, nature has evolved at least one countermeasure to address this problem: the enzyme photolyase, which finds and corrects some of the damage to DNA caused by UV exposure. Present in many organisms—including bacteria, goldfish, rattlesnakes, and marsupials—photolyase meticulously snoops around fragile genes, detecting and fixing a specific type of UV-induced error. Unfortunately, people don't produce photolyase.

Hee-Won Park, a biochemist at the University of Texas Southwestern Medical Center in Dallas, and his colleagues have determined the structure of this intriguing enzyme, they report in the June 30 SCIENCE. By means of X-ray crystallography, the researchers have achieved a complete three-dimensional analysis of the enzyme's structure and binding site, using a form of photolyase culled from the bacterium *Escherichia coli*.

"This is a landmark in the field of DNA repair," says John E. Hearst, a chemist at the University of California, Berkeley. "Photolyase is a fundamentally important enzyme.



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The enzyme photolyase.