Abusive Inheritance

Gene implicated in alcoholism may influence a wide array of drug abuse

By BRUCE BOWER

Of the approximately 100,000 genes that make up humanity's chemical blueprint, the D2 dopamine receptor gene currently attracts by far the most controversy. For more than two years, scientists have wrangled over whether a particular form of the D2 gene confers a susceptibility to severe alcoholism.

The latest twist in this debate goes beyond the bottle. A research team directed by neuroscientist George R. Uhl of Johns Hopkins University School of Medicine in Baltimore now reports that a second version of the D2 dopamine receptor gene – called B1 – appears more often among people who indulge heavily in several addictive drugs, including alcohol, cigarettes, marijuana, cocaine, heroin, tranquilizers, and amphetamines.

Many such drug abusers consume several types of substances, and few abstain from alcohol, Uhl's group notes.

This second form of the D2 gene shows a moderate, statistically significant association with heavy use of several drugs, the scientists report in the September ARCHIVES OF GENERAL PSYCHIATRY. Still, the absence of a robust link leaves considerable room for social and psychological influences on alcoholism, cigarette dependence, and other drug abuse, they hold (SN: 2/1/92, p.69). It also suggests that additional genes help create a proclivity for substance abuse, the investigators note.

Proponents of the D2 dopamine receptor gene as a prominent player in severe alcoholism welcome its implication in a broader spectrum of drug abuse, while critics see significant flaws in the new study. Both camps anxiously await the findings of federal researchers currently employing advanced molecular scanning techniques to search for specific chemical changes in the D2 gene that may distinguish alcoholics from nonalcoholics.

Uhl and his associates collected blood samples from 232 drug users who met the criteria for moderate or heavy use of several drugs – usually including alcohol and cigarettes – and from 56 controls who either used no drugs or on rare occasions consumed alcohol, cigarettes, or marijuana. The researchers isolated DNA from each blood sample, used special enzymes to cut the DNA into fragments, and placed the pieces into an electrically charged gel that sorted them into identifiable patterns. The investigators then used chemical probes to mark specific amino acid variations along two stretches of the D2 gene.

Heavy users of several drugs displayed a substantial excess of the B1 form of the D2 gene – which features a chemical modification near an "active" region responsible for producing and regulating proteins of dopamine receptors on brain cells. Dopamine serves as a chemical messenger and has important effects on pleasure-seeking behaviors.

One-third of the multiple-drug users displayed the B1 variant, compared with 14 percent of the controls, Uhl's group asserts. Further analysis indicates that alcoholics did not skew these results: One-third of the drug users who were not heavy alcohol drinkers possessed the B1 variant.

However, the extent of the association between the B1 variant and the abuse of multiple substances falls far short of that reported between the D2 gene and alcoholism by Kenneth Blum, a psychopharmacologist at the University of Texas Health Science Center at San Antonio, and Ernest P. Noble, a psychiatrist at the University of California, Los Angeles (SN: 9/21/91, p.190).

Noble views the new data on multiple-drug abuse as supportive of his theory that the dopamine receptor gene is one of several genes that predispose people to a broad spectrum of substance use and abuse. As further evidence for this notion, Noble cites an unpublished study conducted with Blum of two D2 gene variations – the same ones studied by Uhl's group – which showed an excess of both forms among cocaine abusers who abstain from other drugs.

A gene with close connections to the dopamine system probably orchestrates sensations of reward and drug dependence, Noble argues. He suspects that a particular form of the D2 dopamine receptor gene serves as a "gateway gene" that predisposes people to giving all sorts of drugs an initial try.

"There is no proposed mechanism to explain how [this] gene affects alcohol or drug use."

— Joel Gelernter

Researchers who previously challenged any connection between the D2 dopamine receptor gene and alcoholism also doubt the drug-use data presented by Uhl's group. Drug users in Uhl's sample, which consisted entirely of white adults, were not broken down into separate ethnic groups for genetic analysis, notes psychiatrist Joel Gelernter of the Department of Veterans Affairs Medical Center in West Haven, Conn. Several recent studies that take into account the ethnic backgrounds of participants show no link between the D2 gene and alcoholism, he says.

In fact, six studies reported in the past two years – including one directed by Gelernter (SN: 6/1/91, p.351) – fail to reveal any D2 gene link with alcoholism, whereas only the two studies conducted by Noble and Blum show a large excess of the D2 gene variant among alcoholics, Gelernter contends.

"There is no proposed mechanism to explain how a D2 dopamine receptor gene affects alcohol or drug use," Gelernter argues. Moreover, a molecular analysis of 36 variants of the D2 dopamine

receptor gene, including those studied by Uhl's group, uncovered no chemical differences thought to alter protein production, he maintains.

"If a connection exists between this gene and drug abuse, it needs to be demonstrated by finding specific mutations that occur more often among abusers," Gelernter contends.

Such a study is under way at the National Institute of Mental Health (NIMH) in Bethesda, Md. Researchers take individual DNA samples, amplify the D2 dopamine receptor gene, make copies of it, and pinpoint chemical mutations using a recently developed molecular scanning procedure.

The project now includes more than 100 DNA samples from alcoholics and healthy controls. Gelernter, Blum, and Noble have contributed DNA from their own experiments to the NIMH study.

A preliminary analysis failed to identify any mutations that distinguish the D2 dopamine receptor genes of alcoholics from those of controls, says NIMH psychiatrist Pablo Gejman, who heads the study. Mutations refer to random changes in specific chemical building blocks along a gene. Studies such as Uhl's target mutations along a small portion of the D2 dopamine receptor gene, whereas the NIMH researchers can identify chemical changes along the entire gene.

"This is a very hot topic," Gejman says. "My personal feeling is that it's improbable we'll find an important D2 gene mutation in alcoholics. The genetic locus for a predisposition to alcoholism may lie elsewhere."

Wherever that predisposition site lies, the genetics of alcoholism continues to tantalize researchers. In the Oct. 14 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, a research team led by psychiatrist Kenneth S. Kendler of the Medical College of Virginia in Richmond asserts that genes account for about half of a woman's tendency toward alcoholism, a figure comparable to that previously reported for men.

The researchers base their conclusion on a study of 1,030 pairs of identical and fraternal twins, each pair consisting of two women. Alcoholism occurred far more often among both identical twins than among both fraternal twins, the researchers report.

Kendler says he suspects the D2 dopamine receptor gene may indeed play a role in male alcoholism, although the way in which it contributes to uncontrolled alcohol consumption remains a matter of speculation. Alcoholism-related genes among women remain even more mysterious, he notes. □

Biomedicine

Carol Ezzell reports from Anaheim, Calif., at the annual meeting of the Society for Neuroscience

For a good memory, dream on

You've been asleep for about an hour, and you're having a really great dream about piloting the space shuttle. There's just one problem: The control panel keeps making a ringing sound, and you can't find the right button to shut it off. Slowly, as you emerge from layers of sweet slumber, you realize that the ringing isn't occurring in your dream – it's the phone on your bedside table.

Beware, you may have just lost some of your memory.

A new study suggests that rapid eye movement (REM) sleep – the sleep stage during which you dream – plays an important role in consolidating the day's events into memory.

Avi Karni of the Weizmann Institute of Science in Rehovot, Israel, and his colleagues have found that people don't remember a learned task as well if they are awakened each time they enter REM sleep. In contrast, waking someone during non-REM sleep – which constitutes roughly three-fourths of sleeping time – has no effect on their ability to remember the task, the researchers determined.

Karni – now on a fellowship at the National Institute of Mental Health in Bethesda, Md. – and his colleagues trained four volunteers to recognize patterns of horizontal and diagonal lines portrayed on a computer screen a few hours before the subjects went to bed. The researchers found that the volunteers could perform the task faster the next morning if they'd had a good night's sleep.

However, when Karni's group awakened the subjects each time they entered REM sleep, they did no better on the pattern-recognition task the next day than they had the night before. Conversely, the morning after they were awakened during non-REM sleep, they did just as well as when they had slept undisturbed, the Israeli researchers discovered.

Karni and his colleagues conclude that REM sleep, and perhaps dreaming itself, cements memories in the brain. Next, they plan to study whether some psychoactive drugs that are known to disrupt REM sleep may also impair memory.

A peppery preventive for pain

Capsaicin, the chemical that puts the zing in chili peppers, can block a person's ability to feel pain without producing numbness, according to a new study. The finding suggests that physicians may one day slather capsaicin-like compounds on the skin of burn patients or smear it into the incisions of individuals undergoing surgery.

Richard A. Meyer of Johns Hopkins University School of Medicine in Baltimore and his colleagues injected a capsaicin analog under the skin of one inner forearm of each of eight volunteers. The volunteers received a control injection of an inactive substance in the other inner forearm.

The volunteers reported reduced pain in the capsaicin-treated forearm immediately after receiving a burn on each arm equivalent to touching a hot stove. Moreover, on the day after the burns, the subjects said the treated arm was much less sensitive to touch and heat than the control arm.

Meyer says capsaicin works by killing small-diameter nerve fibers, the ones responsible for pain. However, it has no effect on large-diameter nerve fibers, he says, and so does not totally numb a treated area. Capsaicin has also proved beneficial in treating cluster headaches (SN: 7/13/91, p.20).

Meyer and his colleagues are working with Procter & Gamble scientists to develop drugs based on capsaicin analogs.