# Genetics & Other Risk Factors

# GENETICS & OTHER RISK FACTORS

## Articles in the *Genetics & Other Risk Factors* Category

# A NEUROGENETIC APPROACH TO ALCOHOLISM

- *Researchers are integrating the fields of genetics and neurobiology to better understand the development of alcoholism.*
- *The neurotransmitter serotonin is a modulator or inhibitor of certain behaviors.*
- *Three behavior patterns are relevant to the development of alcoholism: disinhibition, negative mood states and a low response to alcohol.*
- *Pre-existing and alcohol-induced differences influence serotonergic neurotransmission.*

Scientists are moving beyond the knowledge that alcoholism is a disease. They are now integrating the previously disparate research fields of genetics and neurobiology to investigate how genetic influences may alter the function of neurotransmitters prior to and during the development of alcoholism. More specifically, a review in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the link between central serotonergic neurotransmission and three behavior patterns that are relevant for alcoholism: disinhibition (impulsive aggression), negative mood states (such as anxiety and depression) and a low response to alcohol.

"Several hypotheses have tried to explain the association between serotonergic dysfunction and alcoholism," noted Andreas Heinz, associate professor of addiction research at the University of Heidelberg and lead author of the paper. "Sometimes, these hypotheses seemed to be contradictory. For example, it was not easy to understand why serotonergic dysfunction should be associated with depression *and* aggression, or what the impact of disposition versus the consequences of long-term alcohol intake might have on the serotonergic system."

In this review, the neurochemical serotonin is the key player. Serotonin is an important modulator within the behavior inhibition system. The neurotransmitter is very likely influenced by genetics, early stress experiences, as well as alcohol itself. Serotonergic dysfunction has been linked to a number of psychiatric disorders, as well as the development and maintenance of excessive alcohol consumption and alcoholism. The authors believe that three behaviors or mechanisms in particular – disinhibition, negative mood states such as anxiety and depression, and a low response to alcohol – may explain the relationship between serotonin and alcoholism. They reviewed a number of primate and human studies to form an integrated perspective on serotonin and its role in the development of alcoholism.

David Goldman, chief of the Laboratory of Neurogenetics at the National Institute on Alcohol Abuse and Alcoholism, said that one of the key strengths of this approach to understanding alcoholism is its inclusive nature. "This article includes both the genetic influences, where there's a biological substrate or tendencies inherent to the person, and also the secondary changes that alcohol induces in the function of this neurotransmitter system."

Goldman noted that prior research had shown that people who are behaviorally disinhibited frequently have a lower turnover of serotonin. "But there has been inadequate attention paid to

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the common pathway of neurobiological changes that occur once a person becomes an alcoholic," he said. "There are many different reasons that a person might initially become an alcoholic. For example, they might drink because they are impulsive, because they are anxious, etc. ... but once they have begun, there is a common neurobiology experienced by all people who become addicted. These changes are induced in the brain regardless of what the pre-existing vulnerability was, and this review showed a common pattern of neurobiological change, at least as far as serotonin is concerned."

"Serotonin seems to play two roles," said Heinz. "One, an early deficit may result from genetic factors, as well as social stress, which can render subjects more tense, anxious and potentially aggressive. These subjects tend to drink more alcohol – most likely to calm down – and they have less negative effects from alcohol intake."

Having fewer negative effects from drinking alcohol means the same thing as having a low response to alcohol; these are people who can 'drink like a fish' without getting drunk. Sons of alcoholics, for example, are often low responders and most likely to develop alcoholism themselves. "Two," continued Heinz, "long-lasting alcohol intake may further disturb the serotonergic system and induce clinical depression, thus increasing the long-term relapse risk. A genetically defined subgroup of alcoholics may be specifically vulnerable to these effects."

Additional studies of human alcoholics have found that long-term alcohol intake seems to further disturb serotonergic neurotransmission. "A reduction in the serotonin transporter," said Heinz, "which recycles serotonin after it has been released from the nerve terminals, was correlated with clinical depression. This is, in turn, a predictor of an increased relapse risk when patients are followed for several years. In other words, the genetic constitution of the serotonin transporter may render some subjects more vulnerable to the neurotoxic effects of alcohol intake."

"We are beginning to understand what some of the clinical subgroups of alcoholism and psychiatric diseases are. These subgroups are going to have different vulnerabilities and also different treatment responses," noted Goldman.

"This review shows that social stress factors," said Heinz, "especially early social separation, have long-term effects on the brain and on neurotransmitter systems that affect social behavior and the response to alcohol. There are also negative long-term consequences of alcohol intake, such as a loss of serotonin transporters, that may affect mood states."

**Article is based on the following published research:**

Heinz, A., Mann, K., Weinberger, D.R., & Goldman, D. (April 2001). Serotonergic dysfunction, negative mood states, and the response to alcohol. *Alcoholism: Clinical and Experimental Research, 25*(4), 487-495.

# UNTANGLING THE MATRIX OF RISK FACTORS FOR ALCOHOLISM

- *A family history of alcoholism places a person at greater risk of developing alcohol problems.*
- *Children of alcoholics tend to exhibit other types of behavioral and emotional problems.*
- *The neurotransmitter serotonin is believed to regulate many behaviors and emotions.*
- *Genetic variation in the serotonin transporter gene may partially determine overall levels of serotonergic function.*

Children of alcoholics (COAs) have a high risk of developing alcoholism, simply by virtue of their family history of alcoholism. Many studies have found that COAs also tend to exhibit high levels of behavioral and emotional problems. In the July issue of *Alcoholism: Clinical and Experimental Research (ACER)*, researchers explore the biochemical basis of two aspects of behaviors of undercontrol. Their findings indicate that behavioral disinhibition (BD), such as impulsive aggression and negative affect (NA), such as depression and anxiety, may be genetically influenced through the regulation of a neurotransmitter called serotonin (5-HT).

"Serotonin's primary role appears to be that of an inhibitor," explained Geoffrey R. Twitchell, postdoctoral fellow at the UCLA Integrated Substance Abuse Programs and lead author of the study. "Dysfunction in 5-HT neurotransmission has been found in individuals who exhibit problems with behavioral and affective control. For example, 5-HT deficits have been observed in antisocial alcoholics who exhibit BD, such as aggressiveness and difficulty controlling alcohol consumption. The relationship between 5-HT dysfunction and impulsive aggression in non-alcoholic groups has also been reliably documented. In addition, many studies have found 5-HT dysfunction in individuals who exhibit increased NA, as indicated by depression and anxiety. Depressed and highly anxious individuals are often treated with 5-HT enhancing medications such as selective serotonergic reuptake inhibitors."

"Exactly how a serotonergic dysfunction relates to BD and NA is the realm of great speculation," commented Robert O. Pihl, professor of psychology and psychiatry at McGill University. "Because serotonergic dysfunction seems related to an exceedingly wide range of behaviors, a likely explanation is that of a regulatory role for many biochemical systems in the brain. A speculative analogy has serotonin acting much like the maestro of an orchestra, able to meld disparate sections in order to produce music rather than cacophonous noise. Thus, without appropriate modulation – which we assume is supplied by serotonin – individuals will overreact to emotional stimuli."

Knowing of the strong association between serotonergic dysfunction and behavioral disorders such as alcoholism, aggressiveness and depression, researchers wanted to further examine genetic variations in the serotonin transporter gene (5-HTTLPR). Genetic variation in 5-HTTLPR is related to efficiency in 5-HT reuptake, one aspect of 5-HT functioning. The long (LL) variation or genotype has been associated with an increased number and function of 5-HT transporters (the 5-HT structure that recycles synaptic 5-HT back into the pre-synaptic

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neuron) when compared to the short (SS) or the short/long (SL) genotypes. An increased functionality of the 5-HT transporter has the effect of reducing the amount of 5-HT available in the synapse. Decreased synaptic 5-HT has the effect of decreasing overall 5-HT functioning.

Some psychiatric genetic studies had previously documented a relationship between the SS variant of 5-HTTLPR and alcohol dependence, depression, anxiety and the personality trait neuroticism (which is also a marker of NA). Some studies of alcoholics, however, have found a relationship between the LL variant of 5-HTTLPR and low levels of response to alcohol, alcohol dependence and antisocial alcoholism. For the current study, researchers examined 47 families classified by the fathers' alcoholism subtype. (The data were taken from a larger, ongoing longitudinal family study on risks for developing alcoholism and other problems.) The authors found that the LL genotype of 5-HTTLPR was associated with both BD and NA in COAs. In addition, significantly more LL than SS/SL genotype children reported they had already consumed alcohol.

"This finding," said Twitchell, "supports the hypothesis that behavioral and emotional problems in COAs, which put them at increased risk for later development of alcoholism, may be genetically regulated in part by the 5-HT transporter. In other words, the 5-HTTLPR genotype may serve as a marker for vulnerability for COAs."

"The results of this study are fascinating," said Pihl. "Although we have learned to cautiously view genetic studies that attempt to explain behavior; this one makes sense. It suggests an overactive transporter gene could result in a deficiency of serotonergic synaptic functioning. This is another strong piece of evidence in this evolving story. "However," he added, "there remain gaps in our knowledge. We continue to be in a state much like what Newton described when he said 'we are finding interesting pebbles while the great ocean of truth lays undiscovered before us.'"

Twitchell hopes to move beyond those 'pebbles' one day. "Our group plans to follow these children over time with complete psychosocial assessments at three-year intervals into adulthood," he said. "Our finding of higher rates of alcohol consumption in LL genotype children as young as a mean age of 10.88 years is important because it suggests that this liability manifests early in one's life course. Those with a family history of alcoholism may want to be aware of their increased risk and monitor their alcohol use accordingly."

**Article is based on the following published research:**

Twitchell, G.R., Hanna, G.L., Cook, E.H., Stoltenberg, S.F., Fitzgerald, H.E., & Zucker, R.A. (July 2001). Serotonin transporter promoter polymorphism genotype is associated with behavioral disinhibition and negative affect in children of alcoholics. *Alcoholism: Clinical and Experimental Research, 25*(7), 953-960.

# USING BRAIN ACTIVITY TO IDENTIFY RISK FOR DISORDERS

- *A P300 event-related potential (ERP) is a brief electrical wave in a person's electroencephalogram (EEG).*
- *The P300 is a measure of the way the brain pays attention to and discriminates between potentially important and non-important stimuli.*
- *It is believed that people with anxiety disorders are more likely to use alcohol to self-medicate their anxiety than people without anxiety disorders.*
- *P300 amplitude may distinguish the anxious people who are vulnerable to becoming alcoholic.*

Individuals who wish to identify their risk for developing alcoholism can undergo a noninvasive measure of brain electrical activity called P300 event-related potential (ERP), one of the few brain measures associated with risk for alcoholism. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the variation in P300 amplitude in individuals with co-existing alcohol use and axiety disorders.

"We predicted," said Mary-Anne Enoch, a staff scientist in the Laboratory of Neurogenetics at the National Institute on Alcohol Abuse and Alcoholism and lead author of the study, "based on the results of previously published studies, that alcoholics would have low P300, anxiety disorder subjects would have high P300, but we could not predict which way alcoholics with anxiety disorders would go." Some of their findings were expected, while others were not.

"Even though our subjects had less severe forms of alcoholism and anxiety disorders, we nonetheless found that alcoholics had lower P300 amplitudes, and subjects with anxiety disorders had higher P300 amplitudes. When we looked at the subgroups, the results were much more dramatic. We found that it was the alcoholics with co-morbid anxiety disorders who had the lowest P300 amplitudes. Our study showed that the effects of alcoholism vulnerability on P300 amplitude wiped out or dominated the effect of anxiety vulnerability on P300 amplitude. It is often thought that people with anxiety disorders are more susceptible to alcoholism as they might tend to 'self-medicate'. However, our results suggest that P300 amplitude may distinguish which anxious individuals are vulnerable to becoming alcoholic."

"There are many different ways that someone can be at risk for developing alcoholism," concurred Cindy L. Ehlers, associate professor of neuropharmacology at The Scripps Research Institute, "and one of them is to have an anxiety disorder. Alcohol is an anxiolytic (or anti-anxiety) agent. People who have anxiety can get relief from drinking. In fact, this is referred to as 'relief drinking.' While it may seem confusing that the group with both alcoholism and anxiety disorders have the lowest P300 amplitudes, it's entirely plausible that someone with an anxiety disorder who does not develop alcoholism may have protective factors against the development of alcoholism that mediate their high risk. In other words, having a higher P300 may be a measure of a protective factor." Which, alternately, means that having the lowest P300 may indicate the most severe of risk factors. Either perspective both supports and extends P300 research that began in the early 1980s.

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An individual's electroencephalogram (EEG) – a recording of the continuous electrical activity going on in a person's brain – is like a distinctive fingerprint. Even when we're unaware of it, our brains are constantly on the alert for new stimuli or unusual changes in our immediate environment. If, for example, we are listening to the sound of rain and a clap of thunder interrupts, our brain will respond by producing a very brief electrical wave in our EEG. This is called an event-related potential (ERP). The maximum amplitude of the electrical wave occurs at around 300 millisecs after the onset of the stimulus, which is why it is called the P300 ERP.

There exist a number of ways to measure ERPs in the laboratory. A subject might be shown the same picture on a computer screen again and again, but occasionally, and randomly, a different picture will appear and the subject will produce a P300 ERP in response to the rare stimulus. Or, a subject might listen to a stream of low-pitched sounds, interrupted by a high-pitched sound, to which their brain will respond with a P300 ERP. The more unusual or rare the stimulus, the larger the amplitude of the P300.

The P300 is a measure of the way the brain pays attention to and discriminates between potentially important and non-important stimuli. An individual inherits some aspects of their P300. Alcoholism is also heritable. Some alcoholics react differently to stimuli than do non-alcoholics; the amplitude of their P300 response tends to be lower than that of non-alcoholics. Alcoholics with a strong family history of alcoholism tend to have the lowest P300 amplitudes of all. Even some non-drinking children of alcoholics have low P300 amplitudes. This suggests that a low P300 is not caused by drinking but is inherited. It also suggests that a person with a low P300 may be at risk of becoming an alcoholic.

"Anxious individuals tend to be less relaxed," said Enoch, "more alert and have heightened awareness. They are more likely to respond vigorously to changes in the environment. You could say that they are more 'jumpy'. They would therefore be expected to produce bigger P300 amplitude responses. Studies have also shown that people who have an anxiety disorder, but are not anxious at the time of testing, have high P300 amplitudes, suggesting that high P300 may be a risk factor for anxiety disorders."

"Alcoholism comes in many different forms," said Ehlers, "because different people have different risks. Someone who has conduct disorder and is at risk for alcoholism probably has a different set of genes coding for this vulnerability than someone who has anxiety disorder and is at risk for alcoholism, even though they both have alcoholism." She said that it is imperative to understand the different subgroups of alcoholism before discovering which genes are "coding" for particular disorders.

**Article is based on the following published research:**

Enoch, M., White, K.V., Harris, C.R., Rohrbaugh, J.W., & Goldman, D. (September 2001). Alcohol use disorders and anxiety disorders: Relation to the P300 ERP. *Alcoholism: Clinical and Experimental Research, 25*(9), 1293-1300.

# SEARCHING FOR BIOCHEMICAL MARKERS IN CHILDREN OF ALCOHOLICS

- *Genetic factors contribute up to 40 percent to the risk of developing alcoholism.*
- *Environmental factors likely contribute the remaining risk.*
- *Those at most risk are children of alcoholics (COAs), but not all COAs become alcoholics.*
- *Biochemical markers or "biomarkers" may help identify specific individuals at highest risk.*

Individuals with a family history of alcoholism are themselves at greater risk of developing alcoholism, yet some children of alcoholics (COAs) develop the disease while others don't, even within the same environment. A study published in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that a hormone called beta-endorphin (B-E) may help identify which individuals have the particular genetic combination that places them most at risk of becoming alcoholics.

"Alcoholism, rather than a weakness of will," said Janice C. Froehlich, professor of medicine at Indiana University School of Medicine and lead author of the study, "is a disease that has biological components to it. We know that alcoholism tends to run in families and that individuals with a family history of alcoholism are more likely to develop alcoholism themselves. However, not all children of alcoholics become alcoholic, in part, because not all family members will inherit a combination of genes that increases risk for alcoholism." The challenge is to be able to identify specific individuals in families with alcoholism who are at the greatest risk. One approach is to study the response of B-E to alcohol consumption.

B-E is a hormone that is manufactured within the endogenous opioid system of the brain. It produces euphoria and acts like the body's own morphine, said Froehlich. Endorphin levels increase, for example, during childbirth, trauma and running (known as the "runner's high"). Endorphin levels also increase in response to alcohol drinking, and this hormone may contribute to feelings of well-being produced by alcohol.

"Prior work has shown that the beta-endorphin response to alcohol is greater and more prolonged in people with a family history of alcoholism," said Froehlich. "This suggests that the beta-endorphin response to alcohol may possibly predict, in a high-risk family, which people will abuse alcohol and which people won't. But before a hormone can be used as a biomarker of genetic risk for alcoholism, it must be demonstrated that the hormonal response can be inherited. Our study demonstrated that the beta-endorphin response to alcohol is heritable."

"This is the first report of the heritability of a hormonal response to alcohol," said Froehlich. "When taken together with several other lines of evidence, the study suggests that the beta-endorphin response to alcohol may be a new biomarker that can be used to identify specific individuals who are at high genetic risk for developing alcoholism."

Behavioral geneticists have used several approaches to study the influence of genetic and environmental factors on behaviors such as alcoholism, including adoption, twin, and

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# SEARCHING FOR BIOCHEMICAL MARKERS IN CHILDREN OF ALCOHOLICS

genetic-marker studies. Adoption analysis is one of the more direct approaches. In the popular twin-studies approach, monozygotic or identical twins are compared with dizygotic or fraternal twins, both groups having been raised in the same environment. Identical twins share all of their genes whereas fraternal twins, like ordinary siblings, share approximately 50 percent of their genes. The genetic-marker approach seeks to identify those specific genes – out of the 50,000 to 100,000 genes that comprise the "human genome" or human genetic material – that may influence a person's likelihood of developing alcoholism.

Using the twin-study approach, Froehlich's paper adds to a growing body of research seeking to isolate a set of responses to alcohol that may be used as biomarkers to identify individuals who are at elevated genetic risk for developing alcoholism. One use of biomarkers is preventative. Researchers now believe there are at least two types of alcoholism, one of which is more affected by genetic factors than the other. Biomarkers could provide the basis for screening tests to allow early identification of those individuals who would benefit from early prevention. Biomarkers may also reveal information about the neurochemistry of alcoholism that can lead to the design of drugs to treat the disease.

Gary S. Wand, professor of medicine and psychiatry at Johns Hopkins University School of Medicine, believes Froehlich's study makes at least two important contributions to the field. The first is finding that the B-E response to alcohol has a strong hereditary component; the second is further demonstrating the involvement of the endogenous opioid system in alcoholism. Wand himself studies the effects of opioid antagonists in the brains of nonalcoholic COAs.

"This is a novel, important study," said Wand. "The findings highly suggest that people may be born with differences in their brain opioid function that lead them to this susceptibility. For more than a decade now, evidence has demonstrated that part of the biological vulnerability to alcoholism involves alcohol's ability to activate opioid pathways within the brain."

The next step will be to look at the predictive nature of the B-E response to alcohol, explained Froehlich. B-E will be examined in people in high-risk families before they become alcoholics, and they will then be watched over time to determine whether a larger B-E response to alcohol is highly correlated with the development of alcoholism. Wand believes that future studies will also need to investigate if opioid levels in the brain can be altered to reduce the chances of developing alcoholism.

**Article is based on the following published research:**

Froehlich, J.C., Zinc, R.W., Li, T-K., & Christian, J.C. (March 2000). Analysis of heritability of hormonal responses to alcohol in twins: Beta-endorphin as a potential biomarker of genetic risk for alcoholism. *Alcoholism: Clinical and Experimental Research, 24*(3), 265-277.

# THE EYES HAVE IT: SEEKING EXPRESSIONS OF THE GENETIC RISK FOR DEVELOPING ALCOHOLISM

- *Prior research indicates that the brain's response to alcohol is related to a genetic risk for alcoholism.*
- *New research examines high-velocity eye movements, called saccades, in individuals with and without a family history of alcoholism.*
- *Those with a family history of alcoholism have slightly but consistently slower saccadic eye movement than those without a history, yet appear to "adapt" more quickly to continued alcohol exposure.*

Genetic factors play a key role in the development of alcoholism. A family history of alcoholism does not, however, guarantee that individual offspring will develop the disease. In an effort to discover identifying "markers" of those at risk for alcoholism, researchers in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* evaluate the influence of a family history of alcoholism on the response of saccadic eye movements to alcohol.

Saccades are high-velocity eye movements made from one point to another, as in reading. Their main function is to bring the image of a target from the visual periphery onto the fovea centralis (center of the retina), where vision is most acute. The saccadic control system is sensitive to alcohol, and saccadic parameters provide reliable measures of alcohol's effects in a dose-dependent manner.

"The premise of our research is that the brain's response to alcohol is related to a genetically influenced risk for alcoholism," said Sean O'Connor, professor of psychiatry at Indiana University School of Medicine and corresponding author for the study. "We used a familial history of alcoholism as a proxy for genetic influence, since specific genes cannot yet be identified. Saccadic eye movements fulfilled all the criteria for a good measure of the brain's response to alcohol: they are known to be genetically influenced; they are a very reliable measure of brain function as most people will execute these movements in the same way day after day; they are quite sensitive to alcohol; and a lot is known about the systems of neurons that control the movements." O'Connor explained that associating response of saccades to alcohol with the genetic risk for alcoholism is the first step in seeking specific genes increasing that risk.

Researchers evaluated saccadic performance in 54 adults (27 males, 27 females) with a family history of alcoholism, and 49 adults (24 males, 25 females) without a family history of alcoholism. Participants were given alcohol and a placebo in a counter-balanced order. The alcohol was administered intravenously in order to achieve a breath alcohol concentration of 60 mg% in 20 minutes and to maintain it for 160 minutes. Saccadic eye movement was tested before each session (called baseline), and twice during the maintained level of intoxication.

The two groups showed significant overall differences in operational characteristics of the saccadic control system, both at baseline and when the brain was exposed to alcohol. Subjects with a family history of alcoholism were slightly, but consistently, slower than subjects without

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a history throughout the sessions, and appeared to "recover" baseline measures despite prolonged and constant exposure to alcohol.

"A key finding of our study is that the adaptive response of saccades to alcohol is associated with a family-history status known to be associated with a genetic influence on the risk for alcoholism," said O'Connor. In other words, brain function among those with a family history of alcoholism returned towards "normal" despite continued exposure to alcohol.

"We are still trying to learn what is actually inherited that affects the risk of alcoholism," said David Crabb, professor of medicine, biochemistry and molecular biology at Indiana University School of Medicine. "In other words, is the inherited risk related to brain control functions; to the inability to control drinking; or to the euphoria of drinking? We need to know this in order to devise therapies that address the actions of alcohol on the brain." He called the study's identification of brain functions (the control of eye movement at a subconscious level) that are both influenced by genetic factors (the family history of alcoholism) and show responses to alcohol "an incremental yet important step toward understanding genetic influences on alcohol's effects on the brain."

Crabb said these findings may one day have practical applications, such as developing a battery of easy-to-use measures of risk. "We could test children of alcoholics," he said. "Perhaps combining the results of the eye movement tests in young people with other measures would predict their risk of alcoholism or other alcohol problems. If we could accurately tell people if they are at a higher or lower risk of alcoholism based on their test results, this could influence some people to reduce their drinking."

O'Connor said it's important for the field of alcohol research to continue to examine the question, "What does alcohol have to do with an increased risk for alcoholism?" His own research plans include quantifying the degree to which genes influence responses to alcohol, examining how other brain functions respond to alcohol, and expanding those studies to include experimental control of how quickly alcohol reaches and leaves the brain.

**Article is based on the following published research:**

Blekher, T., Ramchandani, V.A., Flury, L., Foroud, T., Kareken, D., Yee, R., Li, T.K., O'Connor, S. (October 2002). Saccadic eye movements are associated with a family history of alcoholism at baseline and after exposure to alcohol. *Alcoholism: Clinical and Experimental Research, 26*(10), 1568-1573.

# ON THE CUTTING EDGE OF BRAIN GENE ANALYSIS

- *Alcohol targets the central nervous system to produce its effects.*
- *Researchers have for the first time used a new technique called gene array technology to analyze brain gene expression in human alcoholism.*
- *Chronic alcohol abuse can change the molecular programming and circuitry of the frontal cortex.*
- *Thousands of gene products may now be analyzed simultaneously to ascertain the effects of complex diseases such as alcoholism.*

Alcohol's primary target is the central nervous system, where it influences neurotransmission to produce intoxication. Chronic alcohol abuse produces tolerance, dependence and neurotoxicity. Although changes in brain gene expression are believed responsible for these effects, research that appears in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* is the first to use an exciting new technique called gene array technology to study gene expression in human alcoholism.

"A critical question in addiction," said R. Adron Harris, director of the Waggoner Center for Alcohol and Addiction Research at the University of Texas at Austin and lead author of the study, "is how the reprogramming of the brain leads to long-lasting, severe, life-threatening dependence. This study provides insight regarding the molecular neurocircuitry of the frontal cortex that is altered in alcoholism. A key point here is that we study the superior frontal cortex. This is also called the 'executive cortex' because it is critical for judgement and decision making, tasks that are corrupted in addiction. Just as a computer virus can change the programming of specific functions, our data show that chronic alcohol abuse can change the molecular programming and circuitry of the frontal cortex."

All of our cells have exactly the same deoxyribonucleic acid (DNA), which means they all have the same genes. The reason that different cells can appear and work so differently with the same genes (giving us, for example, unique eyes, skin, hair, etc.) is that only some genes are used or "turned on" in each cell. This is called gene expression. The sequence of events is for DNA or genes to make ribonucleic acid (RNA), also called a "message," which is then used to make proteins. These proteins determine the appearance and function of each cell and, in turn, the proteins' existence depends on gene expression. Thus, gene expression is a normal function of all cells and is well regulated to avoid mistakes.

"Drugs can change gene expression and thereby disturb normal functions of the cell and tissue," explained Harris. "Alcohol can change gene expression in the brain and this is believed to be responsible for many of the hallmarks of addiction, such as tolerance, physical dependence, and craving as well as the consequences of chronic alcoholism, such as neurotoxicity (brain damage). The problem has been to find which genes are 'incorrectly' turned on or off in the brains of human alcoholics. This is because there are about 50,000 genes and any of these may

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# ON THE CUTTING EDGE OF BRAIN GENE ANALYSIS

be important. Previously, it was impossible to analyze more than a handful of these genes. Gene array technology has now changed that."

"Gene expression measurements that use arrays can simultaneously detect expression of thousands of gene products," said Boris Tabakoff, chair of the Department of Pharmacology at the University of Colorado School of Medicine. "This is a novel and fruitful approach for understanding patterns of changes produced by various disease processes."

A gene array is a small glass microscope slide that has thousands of different DNA samples attached to the glass. Knowing that DNA makes RNA, and wanting to know which genes have been turned on to make RNA, researchers measured the level of thousands of RNAs in the brain. RNA samples were extracted from post-mortem samples of superior frontal cortex of 10 alcoholics and 10 non-alcoholics, and measured by two different types of microarrays (the Affymetrix and Genome systems). Using two microarrays – a more complicated, challenging and expensive venture than just one – provided more complete gene coverage and enhanced the reliability and replication of the findings.

"The key," said Harris, "is that RNA can be converted to a complimentary DNA called cDNA with a fluorescent or colored tag that will very selectively bind to or partner with its corresponding DNA. We can put a drop of this brain cDNA on the gene array and each spot of DNA that shows a colored tag will indicate that it is a gene that is turned on in the brain. Thus, each DNA element on the array has a color that reflects how much the gene is turned on in the alcoholic relative to the control."

In this study, more than 4,000 genes in brain tissue were analyzed simultaneously. Of these, 163 (or roughly 4%) were found to differ by 40 percent or more between the alcoholics and non-alcoholics. The genes that seemed to change were those related to the generation of white matter in brain, and it was thought by the authors that the results may indicate that alcohol has a particularly damaging (or down regulating) effect on the generation of this white matter (which is called myelin). Myelin forms an insulation between information-carrying cells of the brain, and loss of white matter may result in cognitive deficiencies. These findings provide evidence for an extensive reprogramming of brain gene expression due to alcoholism.

Harris said, "This study is a beginning to unraveling the undesirable changes in the brain produced by chronic exposure to alcohol. Such studies will eventually result in new and better treatments for alcoholism and other addictions."

**Article is based on the following published research:**

Lewohl, J.M., Wang, L., Miles, M.F., Zhang, L., Dodd, P.R., & Harris, R.A. (December 2000). Gene expression in human alcoholism: Microarray analysis of frontal cortex. *Alcoholism: Clinical and Experimental Research, 24*(12), 1873-1882.

# GENETIC CONTRIBUTIONS TO ALCOHOL SENSITIVITY

- *Sensitivity to alcohol's "incoordinating" effects seems to predict the later development of alcoholism.*
- *Individuals who seem resistant, or less sensitive, to alcohol's effects may drink more.*
- *Genetic differences contribute to alcohol sensitivity.*
- *Scientists have established an important link among genetics, a neurochemical messenger called adenosine 3':5'-cyclic monophosphate, and alcoholism.*

Understanding a disease such as alcoholism, like many other diseases, involves years of research dedicated to "teasing out" its multiple and interactive components. Scientists now know that alcoholism is influenced by both environmental and genetic factors. A study in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* looks closely at how genetic differences in the intracellular signaling capacity of a neurochemical messenger called adenosine 3':5'-cyclic monophosphate (cAMP) may relate to alcohol sensitivity and the later development of alcoholism.

"There are different theories as to the cause of alcoholism," said Shelli Kirstein, a graduate student in pharmacology, and Boris Tabakoff, chair of the Department of Pharmacology at the University of Colorado School of Medicine. Tabakoff is the senior author and Kirstein is the co-author of the paper. "One possibility involves differences in sensitivity. Less sensitive individuals may drink more because they do not receive the same cues of impending intoxication as individuals with a high sensitivity. Another possibility is that some individuals have the capacity to develop greater or more rapid tolerance and hence can drink more. Both low sensitivity and alcohol tolerance can lead an individual to drink more and become dependent on alcohol. It is not known how these two pre-existing conditions are related genetically and if being genetically programmed in one direction or the other is sufficient by itself to cause an individual to become alcoholic."

Alcohol can affect several different neurotransmitter receptors, causing them to couple to or activate intracellular signaling systems, such as adenylyl cyclases, which produces cAMP as a messenger. Signaling pathways can set the tone for alcohol's effects by either inhibiting (turning off) or potentiating (turning on) certain pathways. This study used different strains of specifically bred mice to examine what role cAMP signaling might play in setting the tone for alcohol sensitivity and tolerance. Sensitivity was measured as the ability to balance on a dowel following alcohol injections. This procedure mimics the "incoordinating" or disharmonizing effects that alcohol can have for some individuals. Tolerance was measured as the difference between sensitivity after the initial dose of alcohol and sensitivity after a subsequent dosing with alcohol.

"One key finding," said Tabakoff, "is that there is a genetic correlation between cAMP signaling in the cerebellum and initial sensitivity on the dowel test for ataxia." Ataxia is the inability to coordinate voluntary bodily movements. For example, a staggering drunk would appear ataxic.

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# GENETIC CONTRIBUTIONS TO ALCOHOL SENSITIVITY

"Also, there is a lack of correlation between initial sensitivity and tolerance, and there is a lack of genetic correlation between tolerance and cAMP signaling in the cerebellum or any brain region tested. Results from testing different strains of mice under similar environmental conditions reflect a genetic influence on the behavioral or biochemical phenotype investigated. Simply stated," he added, "this means that a common gene or genes influence both initial sensitivity and cAMP signaling. Next, we would like to try to identify those genes."

"The cAMP signaling system is much like the traffic controller at a large airport," explained Richard Deitrich, professor of pharmacology at the University of Colorado School of Medicine. "It controls which systems are turned on or off in a given situation. That is, which planes or systems are allowed to take off or land, and which planes or systems are put into a holding pattern or not allowed to function. Alcohol, by its ability to affect these systems, is analogous to a malfunctioning radar system. Airport operations are slowed by a marginally malfunctioning system, or a low dose of alcohol, or completely disrupted by an acutely malfunctioning radar system, or a large dose of alcohol. In such cases, the airport has to be shut down, or the individual loses fundamental brain functions. In this study, the dose of alcohol was low and so the function of the animals was only partially disrupted. That is, they could still stagger around and were not unconscious."

"Our results suggest those areas of the brain important for balance and coordination can be genetically programmed for sensitivity to alcohol's incoordinating effects," said both Tabakoff and Kirstein. "While the genes that influence this sensitivity are by no means the only genes that may predispose someone to alcoholism, they may influence sensitivity to certain effects of alcohol. This could make it easier to identify individuals at risk for alcoholism, as well as serve as an easily measured characteristic that contributes to the risk but does not explain the entire disorder."

"This study is very relevant to understanding the underlying differences between those individuals who drink and do not become alcoholic, and those who drink and do become alcoholic," said Deitrich. "The research shows that a combination of behavior, pharmacology, neurochemistry and genetics can be a powerful tool in investigating the basic mechanisms by which alcohol brings about its effects. Only by understanding these basic mechanisms can we design rational measures for the prevention or treatment of human alcoholism."

**Article is based on the following published research:**

Kirstein, S.L., & Tabakoff, B. (June 2001). Genetic correlations between initial sensitivity to ethanol and brain cAMP signaling in inbred and selectively bred mice. *Alcoholism: Clinical and Experimental Research, 25*(6), 791-799.

# INVESTIGATING A "PROTECTIVE GENE" AGAINST ALCOHOLISM

- *Alcohol dehydrogenase (ADH) is one of two important alcohol metabolizing enzymes.*
- *The ADH2*3 allele is a variant form of the gene that codes for the ADH enzyme.*
- *ADH2*3 has been documented only in people of African descent and certain Native American tribes.*
- *The ADH2*3 allele may be associated with a lowered risk for developing alcoholism.*

Many alcohol researchers believe that a person's genetic predisposition interacts with their environment to produce his or her overall risk for alcoholism. In addition, ethnic differences in rates of alcohol use and abuse have been linked to differences in the genes that code for certain enzymes that break down alcohol. Two enzymes in particular – alcohol dehydrogenase (ADH) and mitochondrial aldehyde dehydrogenase (ALDH) – are highly involved in alcohol metabolism. The ADH2*3 allele (a variation of the gene) has been documented to occur only in persons of African descent and certain Native American tribes. A study in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* investigates if an association exists between the presence of ADH2*3 alleles in young African American adults and a family history of alcohol dependence.

"We know that alcoholism is hereditary," said Cindy L. Ehlers, associate professor of neuropharmacology at The Scripps Research Institute and lead author of the study. "But we only have very limited information on what is inherited, and almost no information on what genes might be involved except in the case of alcohol metabolizing enzymes."

Differences in alcohol metabolizing enzymes, and the genes that encode them, are the best understood factors that influence drinking behavior and the risk of alcoholism. Alcohol is metabolized principally in the liver by two enzymes that act sequentially. ADH converts alcohol to acetaldehyde, and aldehyde dehydrogenase (ALDH) subsequently converts acetaldehyde to acetate. Acetate is then metabolized by tissues outside of the liver. Individuals with a mutation in the gene that encodes for ALDH2 (predominantly of Far East Asian descent) instead accumulate acetaldehyde in the blood and tissues after drinking. These individuals experience a more intense response to drinking alcohol, notably facial flushing, headaches, palpitations, dizziness and nausea. Understandably, few individuals in the world who possess two defective ALDH2 alleles (thereby intensifying their response to alcohol) have developed alcoholism.

"The present study extends previous research to the ADH2*3 allele," said Ehlers. "This gene codes for a form of the ADH enzyme which may provide more efficient or more rapid alcohol metabolism. In the past, it has been shown that African American women with this gene are less likely to have children with birth defects due to alcohol use during pregnancy. In fact, our results demonstrate that the ADH2*3 allele is associated with a negative family history of alcoholism. These findings suggest that, in this sample of young African American adults, the ADH2*3 allele may be associated with a lowered risk for the development of alcoholism."

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# INVESTIGATING A "PROTECTIVE GENE" AGAINST ALCOHOLISM

A positive family history of alcoholism is one of the most consistent and powerful predictors of a person's risk for developing the disorder. For example, individuals with a positive family history of alcoholism (usually a father) have a four to five times greater risk for developing alcoholism.

"Having a biological relative such as a father or brother who is alcoholic increases the chances of an individual developing the disease. However, as with all genetic diseases, not all offspring or relatives get the risk genes, and all individuals live in different environments that affect risk," explained David W. Crabb, professor of medicine, biochemistry and molecular biology, and chair of the Department of Medicine at Indiana University Medical Center.

It is this interaction between a genetic predisposition for alcoholism and environmental variables that continues to intrigue researchers. Most believe that it is a 50/50 interaction. "The variables that we believe are most important psychosocially," said Ehlers, "are religion, family intactness, being employed and positive peer influences. These are called protective factors. Their opposite – that is, no religion, divorce, an absent parent or poor family ties, unemployment and negative peer influence – are considered risk factors. These factors, like genes, can differ somewhat between ethnic groups. For instance, acculturation stress is said to influence drinking in Hispanic second-generation adolescents. Among African Americans, religion is one key variable. However, studies have shown that it is not so much practicing a religion, but rather, attending religious services that is important. And this is particularly important in supporting alcohol abstinence."

Although Crabb calls this study "long awaited," he would like to see future studies compare the presence of the high-activity ADH2*3 allele between African American alcoholics and nonalcoholics. "We would predict that the frequency of ADH2*3 will be lower in the alcoholics than in the nonalcoholics," he said. "Similar findings have been obtained with individuals with another high-activity ADH allele, ADH2*2, that is found in Asians and Jews."

"All in all," said Ehlers, "I think this finding definitely strengthens the case for the genetics of alcoholism. It also further delineates the importance of ethnic and cultural differences when looking at risk and protective factors for alcoholism."

**Article is based on the following published research:**

Ehlers, C.L., Gilder, D.A., Harris, L., & Carr, L. (December 2001). Association of the ADH2*3 allele with a negative family history of alcoholism in African American young adults. *Alcoholism: Clinical and Experimental Research, 25*(12), 1773-1777.

# BRIDGING THE GAP BETWEEN GENETICS AND MOTIVATIONS TO DRINK ALCOHOL

- *Genetic variation appears to influence drinking to relieve social anxiety and improve mood.*
- *People's alcohol expectations are known to influence their likelihood of developing alcohol problems.*
- *New research has found that a person's genetic makeup may influence their motivation to drink, leading to behaviors that increase the risk for alcoholism.*
- *Particularly important motivations involve drinking to relieve social anxiety and improve mood.*

Alcohol researchers already know that people who expect positive results from drinking – a better mood or social ease – are more likely than other drinkers to develop alcohol problems. Conversely, those who have negative expectations – queasiness, dizziness or fatigue – are less likely to develop alcohol problems. A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that a person's genetic makeup may influence their motivation to drink, which can, in turn, enhance behaviors that increase the risk for alcoholism.

"We were interested in learning if beliefs about alcohol provided a partial explanation for how risk for alcoholism is transmitted across generations," said Carol A. Prescott, associate professor of psychiatry and psychology at the Virginia Institute for Psychiatric and Behavioral Genetis Virginia Commonwealth University and first author of the study. "This transmission could be either environmental, in that young adults model the drinking behavior and motivations of their parents, or through genetic mechanisms, meaning there are physiological reasons alcohol is perceived as more pleasurable by some people and this is transmitted from alcoholic parents to their offspring via genes."

"Although there is much consensus that alcohol abuse and dependence are caused, in part, by genetic factors, there is less certainty concerning what is inherited and how that genetic vulnerability is manifested," added Kenneth J. Sher, curators' professor of psychological sciences at the University of Missouri and the Midwest Alcoholism Research Center. "Drinking motives represent a possible genetic mediator of alcoholism risk in multiple ways. For example, if genetic variability predisposes someone to experience greater neuropharmacological reward from alcohol, it could lead to stronger motives to drink for positive reinforcement. Furthermore, genetic vulnerability to depression or anxiety could serve as the foundation for drinking to alleviate negative mood states. Thus, the study attempts to answer the question of how genetic risk might be related to the various reasons individuals report for why they drink."

Prescott and her colleagues examined data gathered from 2,529 female and 3,709 male adult twins participating in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders. "The data from twin pairs are used to estimate the degree to which individual differences can be attributed to differences among people in their genetic, family environmental and individual-specific environmental causes," explained Prescott.

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# BRIDGING THE GAP BETWEEN GENETICS AND MOTIVATIONS TO DRINK ALCOHOL

The researchers used four scales to measure individual differences in drinking motives: drinking to manage mood states, to relieve social anxiety, in social situations and to improve mental functioning. They also determined lifetime alcohol abuse and/or dependence among the study participants through use of a structured interview that used criteria from the *Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV)*.

"The findings contribute to our understanding of how genetic risk results in alcoholism," said Prescott. "It has long been known that alcoholism runs in families. Twin and adoption studies in the past 20 years have shown that this familiality is in large part due to genetic factors shared by family members. But we don't know very much about how differences among people in their DNA sequences result in differences in risk for drinking problems. This study provides evidence that one way in which genetic factors lead to alcoholism is that genetic factors influence drinking motives, in particular, drinking to alleviate social anxiety. Although motives are still a long way from DNA, they are one step closer to the biology than the clinical disorder of alcoholism."

Prescott noted that there are several ways in which genetic factors may intersect with social drinking. "There is an overlap of the genetic factors which influence risk for alcoholism and those which influence drinking to relieve social anxiety," she said. "Also, alcohol works on the brain in a way quite similar to anti-anxiety drugs, and there are genetic influences on how these drugs affect brain receptors. In addition, personality characteristics such as the need for social stimulation and 'risk taking' are in part inherited. People with these personality traits may be more likely to seek social activities which involve drinking and this in turn increases their risk for alcoholism."

"It's important to note that our results don't prove that motives are causal, only that they are consistent with a causal explanation," said Prescott. "Nonetheless, these findings have important implications for intervention. These results, in combination with others, suggest that drinking motives may have a causal influence on alcoholism. If so, this provides an important point of intervention among individuals at high risk. Motives can be measured prior to the development of drinking problems, and at-risk individuals can be taught strategies for reducing their social anxiety other than using alcohol."

**Article is based on the following published research:**

Prescott, C.A., Cross, R.J., Kuhn, J.W., Horn, J.L., Kendler, K.S. (January 2004). Is risk for alcoholism mediated by individual differences in drinking motivations? *Alcoholism: Clinical and Experimental Research, 28*(1), 29-40.

# WHEN ALCOHOL AND NICOTINE INTERACT

- *A blood alcohol concentration (BAC) indicates both a level of intoxication and severity of toxicity.*
- *Nicotine can significantly reduce the peak BAC among newborn rodents.*
- *People who drink and smoke at the same time may consume more alcohol to achieve a desired level of intoxication.*
- *The more alcohol consumed to attain 'intoxication' in the presence of nicotine, the greater the build up of toxic agents in the system.*

Mixing alcohol with other drugs – over-the-counter, prescription, legal or illegal – is a recipe for damage. The concurrent use of aspirin and alcohol, for example, leads to more severe effects on fetal brain development than the use of alcohol alone. Heartburn medications such as Tagamet® and Zantac® slow the activity of a stomach enzyme that is responsible for breaking down alcohol, thereby leaving organ systems exposed to alcohol's toxic effects for an extended period of time. Alcohol and cocaine together exert more cardiovascular toxicity than either drug alone; they also produce a compound called cocaethylene, similar to cocaine but more lethal. Now, a study in the July issue of *Alcoholism: Clinical and Experimental Research (ACER)* confirms the damaging interaction of alcohol and nicotine.

"Blood alcohol concentration is an important determinant for level of intoxication and severity of toxicity," explained Wei-Jung A. Chen, assistant professor of anatomy and neurobiology at Texas A&M University System Health Science Center and lead author of the study. "Our results confirm that blood alcohol concentration can be significantly reduced in the presence of nicotine." In a prior study, Chen and his colleagues found that high doses of nicotine lowered blood alcohol concentrations (BACs) among neonatal rats. In this study, they found that even low nicotine doses have an effect on BACs. In either case, the results indicate that people who drink and smoke at the same time will have to drink more if they want to feel any kind of intoxicating effect.

"In the alcohol field, we know that alcohol abusers generally 'drink to effect,'" said Susan E. Maier, research assistant professor in the department of human anatomy, College of Medicine at the Texas A&M University System Health Science Center. "This means they drink until they feel an expected level of intoxication from alcohol. It is also known that smokers drink more alcohol than non-smokers, and that people who misuse alcohol are more likely to smoke than those who do not misuse alcohol. The findings from this study suggest a possible reason why this may occur. If nicotine lowers the BAC, more alcohol needs to be consumed in order to achieve that alcohol intoxicating effect. The consumption of sufficiently more alcohol to reach that 'high' may lead to adverse effects on organ systems other than the brain, such as the liver and the heart."

The first step in the metabolism of alcohol is its conversion to acetaldehyde, which belongs to a class of compounds called aldehydes (such as formaldehyde, a disinfectant and preservative).

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# WHEN ALCOHOL AND NICOTINE INTERACT

Acetaldehyde is a highly reactive and toxic chemical that can damage the cells of any living thing. Although nicotine reduces a person's BAC, possibly leading them to drink more, nicotine does not affect the levels of agents such as acetaldehyde. The level of acetaldehyde would likely continue to build up in the system and have an adverse effect on the brain, liver and heart.

"My research primarily concerns the effects of substance abuse on the developing brain," said Chen, "so most of my studies use newborn rat pups. This is the developmental stage that most closely represents the brain-growth equivalent of the human fetus during the third trimester. However, we have results from adult rats showing the same effects of nicotine on reducing the BAC." Although Chen was hesitant to equate the nicotine doses used in the rodent study to human use because of the confounding effects of a number of variables (metabolism, smoking habits, smoking preferences, etc.), he did comment on what would have been considered a medium nicotine dose in the study. "There is limited information in the literature," he said, "to suggest that 1.5 mg/kg/day administered to rats may be equivalent to a human smoking one pack of cigarettes in a day."

"The best discoveries in science," said Maier, "are those that come from serendipitous findings, and I believe that the results described in this study fall into that category. What we once thought was coincidence – that smokers drink more alcohol – has suddenly gained a plausible explanation from the results of this study. Despite a plethora of studies examining the effects of each drug alone on various parameters, it is not until the interactive effects of both drugs are examined, that exciting and important findings such as these reveal themselves."

**Article is based on the following published research:**

Chen, W-J.A., Parnell, S.E., & West, J.R. (July 2001). Nicotine decreases blood alcohol concentration in neonatal rats. *Alcoholism: Clinical and Experimental Research, 25*(7), 1072-1077.

# EXPLORING THE GENETIC COMMONALITY OF ALCOHOL AND TOBACCO ABUSE

- *Alcohol and tobacco abuse often go together.*
- *Rodents selectively bred for high, low and control sensitivity to alcohol were tested for their sensitivity to nicotine.*
- *Rodents with high sensitivity to alcohol were also more sensitive to nicotine-induced locomotor activity depression than rodents with low sensitivity to alcohol.*
- *This suggests that common genes modulate, at least in part, the actions of alcohol and nicotine.*

Addiction researchers are both familiar with and intrigued by the strong connection between smoking and drinking. Recent human studies have suggested that one or more genes may play a critical role in increasing vulnerability to alcohol and tobacco addiction. A study in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* uncovers new evidence which supports the theory that common genetic factors influence sensitivity to both alcohol and nicotine.

"Numerous studies in the last several decades have confirmed that drinking and smoking are positively correlated," said Christopher M. de Fiebre, assistant professor of pharmacology and neuroscience at the University of North Texas Health Science Center at Fort Worth and corresponding author for the study. "Nowhere is this association seen as clearly as in alcoholic populations. While the percentage of smokers in the general American population has decreased over the last several decades, the rate of smoking among alcoholics has remained at approximately 90 percent, a rate well above that seen in nonalcoholic populations. We knew that whether an individual develops alcoholism or becomes dependent on tobacco is mediated by both genetic and environmental factors. We hypothesized that common genetic factors were involved in modulating sensitivity to alcohol and nicotine and this, in turn, influenced the development of the co-abuse of these two agents."

Male and female rats selectively bred for high (HAS), low (LAS) and control (CAS) sensitivity to alcohol were tested for nicotine sensitivity using several different measures. The HAS rodents were found to be more sensitive to one measure in particular – nicotine-induced locomotor activity depression – than the LAS rodents. Researchers also measured plasma and brain levels of nicotine and its primary metabolite, cotinine, as well as the binding of three nicotinic ligands in eight brain regions. Since no differences in plasma or brain nicotine levels were seen between the HAS and LAS rodents, the authors speculate that the HAS/LAS differences arise because of differences in the sensitivity of the central nervous system (CNS) to nicotine.

"The authors' speculation is actually a very logical conclusion," said Allan C. Collins, professor of pharmacology and behavioral genetics at the University of Colorado. "Many years of research done by many laboratories have demonstrated that mice, rats and humans may differ in behavioral reactions to a drug for two primary reasons: differences in drug pharmacokinetics,

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# EXPLORING THE GENETIC COMMONALITY OF ALCOHOL AND TOBACCO ABUSE

or differences in brain or CNS sensitivity." The pharmacokinetics of a drug refers to the way it moves through the body, including its absorption into the circulation, its distribution to different parts of the body, its metabolism, and eventual elimination. "The authors measured the pharmacokinetic parameters via plasma and brain levels and found no difference," continued Collins. "This leaves brain or CNS differences in sensitivity as the most likely explanation."

"The key finding of this study is that there appears to be a commonality in the genes which modulate the actions of both nicotine and alcohol," said de Fiebre. "Some, but not all, of the genes which modulate sensitivity to alcohol are probably the same as some, but not all, of the genes which modulate sensitivity to nicotine. Although we do not currently know which genes are responsible for modulating the actions of these two drugs ... we hypothesize that the overlap in genes controlling sensitivity to these two drugs may in part explain why smokers drink and drinkers smoke."

"Which genes may be responsible for modulating the actions of alcohol and nicotine? The answer to this question remains largely unknown," said Collins. "However, these findings add to the data which argues that common genes influence some of the behavioral actions of two of the most frequently abused drugs. It may be that studies that include both alcohol and nicotine may yield answers to questions that have remained unresolved for many years when the two drugs have been studied individually. Interestingly, Joe Medium and Sally Average have known for years that alcoholics are smokers. Yet this common knowledge has been, by and large, ignored by the scientific community. This paper will not change life as Joe and Sally know it, but it may help them to understand that there are biological or genetically determined reasons that contribute to individual differences in vulnerability to both alcohol and tobacco abuse."

**Article is based on the following published research:**

De Fiebre, N.C., Dawson, Jr., R., deFiebre, C.M. (June 2002). The selectively bred high alcohol sensitivity (HAS) and low alcohol sensitivity (LAS) rats differ in sensitivity to nicotine. *Alcoholism: Clinical and Experimental Research*, *26*(6), 765-772.

# ABNORMALITIES IN STRESS HORMONE RESPONSE AMONG ALCOHOLICS

- *The reward and stress systems of the brain are closely interconnected.*
- *The euphoria caused by normal drinking is associated with the release of stress hormones.*
- *Alcoholism, in contrast, may be associated with a dysfunctional stress response.*
- *Some alcoholics may drink to relieve the prolonged elevation of the stress hormone cortisol.*

The brain's reward and stress systems are closely interconnected, both anatomically and functionally. For example, the euphoric response to alcohol that most people experience is related to the release of stress hormones, whereas a dysfunctional stress response may be associated with alcoholism. A study in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* has made two important findings related to this association. One, some recovering alcoholics with a lengthy abstinence may have a chronically subdued stress system. Two, their systems are hypersensitive to a neurotransmitter called serotonin, which is a key player in the body's stress response. The implication is that some alcoholics will respond differently than non-alcoholics to stressful situations that involve the brain's serotonin system.

Serotonin is an important neurotransmitter that influences most functions, including general motor activity, learning and memory, reproduction, the stress response, sleep and food intake. Disturbances in serotonergic activity have been linked with numerous behavioral disorders, including alcoholism, drug abuse and depression. Fenfluramine is a drug formerly used to treat appetite disorders by increasing serotonin activity in the brain. In this study, fenfluramine was given to recovering alcoholics in order to cause an acute increase of serotonin activity. This, in turn, is believed to cause increased activity in the limbic-hypothalamic-pituitary-adrenal (LHPA) axis – an interconnected system of brain structures and hormone-producing organs that becomes especially active when an individual is stressed – leading to the secretion of a steroid called cortisol from the adrenal glands.

"Our major finding," said Robert M. Anthenelli, associate professor of psychiatry in the College of Medicine at the University of Cincinnati, director of substance dependence programs at the Cincinnati Veterans Affairs Medical Center and lead author of the study, "was that alcoholics who'd been abstinent for an average of more than four months had a two-fold greater cortisol response compared with non-alcoholics following administration of fenfluramine. This result was surprising because all other published studies of alcoholics with shorter lengths of abstinence found they had a blunted or unchanged stress response following serotonergic stimulation. We also found that the stress hormone response in recovering alcoholics did not return to baseline levels as quickly as it did in age- and race-matched non-alcoholic comparison subjects. In other words, it appears that some of our recovering alcoholic subjects had difficulty turning off the fenfluramine-induced stress response."

When an individual either perceives (psychological stress) or is faced with an actual threat (physical stress), the brain sets into action a cascade of signals intended to help respond to the threat. The end product of that cascade is the release of the stress hormone, cortisol, which

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# ABNORMALITIES IN STRESS HORMONE RESPONSE AMONG ALCOHOLICS

produces numerous effects throughout the body and brain. These effects include mobilizing more glucose for the body to use as energy to respond to the threat, raising blood pressure and suppressing the immune system. The stress response also triggers the sympathetic nervous system to increase heart rate and dilate the pupils (known as the fight-or-flight response). After mobilizing resources to meet the challenge, a reversed order of the process returns the body to a level of homeostasis (or non-stressed levels). Although stress response is important for survival, chronic stress or alterations in this response may contribute to various diseases.

"When stressors are short-lived," explained Stephen Woods, professor of psychiatry and neuroscience at the University of Cincinnati, "the LHPA axis is very effective at ensuring that the body functions optimally until the situation changes for the better. When stress is more chronic, continued stimulation of the LHPA axis can have detrimental effects throughout the body." This study, he said, clearly showed that abstinent alcoholics stimulated with fenfluramine (mimicking a stress-related increase of serotonin) had high blood cortisol levels for a significantly longer period of time than other individuals.

"While the Anthenelli report does not speculate on what some of the specific consequences of this might be," said Woods, "it is reasonable to speculate that there are physical consequences. Whether this change in the LHPA axis response to a serotonin challenge is related to brain damage, or alteration resulting from former consumption of large amounts of alcohol, is not known. An interesting clue, however, is the authors' recognition that the elevated cortisol response is reminiscent of what has been observed in individuals who have never before experienced alcohol, but who are considered high risk for developing alcoholism. One possibility, therefore, is that the prolonged elevation of cortisol following fenfluramine is characteristic of certain alcoholism-prone individuals and can be observed either before they ever drink or after a prolonged period of abstinence."

"Based upon these findings," said Woods, "one could go out on a limb and speculate that one reason some individuals have a tendency to imbibe more and more when exposed to alcohol, and eventually become alcoholic, is that a 'defect' in their LHPA response to serotonin is 'corrected' by alcohol. Remember that a prolonged cortisol response has undesirable consequences in the brain or throughout the body. Individuals who have such a prolonged response might find that it is remedied in the presence of alcohol. If this were the case, alcohol would provide a greater degree of reward value for them than for individuals who do not have the same 'defect.'"

**Article is based on the following published research:**

Anthenelli, R.M., Maxwell, R.A., Geracioti Jr., T.D., & Hauger, R. (May 2001). Stress hormone dysregulation at rest and after serotonergic stimulation among alcohol-dependent men with extended abstinence and controls. *Alcoholism: Clinical and Experimental Research, 25*(5), 692-703.

# TASTE TESTING MAY HELP IDENTIFY ALCOHOLISM RISK

- *Individuals with a family history of alcoholism are considered at-risk for developing the disorder.*
- *Not all family members, however, will develop alcoholism.*
- *Scientists are searching for "markers" to help pinpoint which individuals are most at risk.*
- *Taste perception of sour and salty solutions may be one such marker.*

Individuals with a family history of alcoholism are known to be at greater risk of developing the disorder than those without such a family history. In order to pinpoint these individuals, researchers are searching for "markers" of alcoholism risk. Both animal and some human studies have shown an association between sweet preference and excessive alcohol intake. A study in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* extends this research, finding that individuals with a positive paternal history (PHP) of alcoholism rate salty solutions as less pleasurable and sour solutions as more intense and less pleasurable than individuals with a negative paternal history (PHN) of alcoholism.

"Administering taste tests to offspring of alcoholics, those who have not yet developed alcoholism, is a way to examine taste perception without the possible interference of taste alterations that might occur in heavy drinkers," said Henry R. Kranzler, professor of psychiatry at the University of Connecticut Health Center and corresponding author for the study. "As research in this area has moved from evaluating alcoholics to assessing offspring of alcoholics, new studies have also expanded the investigation of taste perception to include salty, sour and bitter tastes."

"Taste preference is an innate reaction that may be detected within minutes after birth," added Alexei B. Kampov-Polevoy, assistant professor of psychiatry at Mt. Sinai School of Medicine. "The most consistent finding that links taste preference and alcohol consumption [has been in animals] such as rats, mice and monkeys, that are prone to [both] excessive consumption of alcohol – in quantities sufficient for the development of physical dependence – and sweet solutions, sometimes quadrupling their normal daily fluid intake." To date, however, not all studies of alcohol and sweet preference have yielded consistent findings.

For this study, researchers recruited 112 non-alcoholic participants (62 females, 50 males) between the ages of 18 and 40 from other studies of alcoholism risk and through advertisements. Family history interviews were used to identify psychiatric disorders and alcohol dependence among first-degree family members. Of the 112, 45 were considered PHP (32 females, 13 males), 67 were PHN. All participants were given a series of salty and sour solutions in varying concentrations, and asked to rate each for intensity and pleasantness.

"PHP individuals rated the salty solutions as less pleasurable than PHN subjects," said Kranzler. "They also experienced the sour stimulus as more intense and less pleasurable than PHN subjects. These findings extend previous research by demonstrating the phenomenon of different

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# TASTE TESTING MAY HELP IDENTIFY ALCOHOLISM RISK

taste characteristics among a larger and more diverse sample, and also support preliminary results from a study in Poland. We interpret these findings as evidence of unique taste perception among individuals with a paternal history of alcoholism compared to those without such a history."

"We evaluated a group of nonalcoholic offspring of alcoholic fathers," Kranzler said. "Participants were screened to exclude those who had ever experienced any alcohol, drug, and psychiatric disorders. In light of that, there are two possible explanations for our findings. First, these results could indicate that PHP individuals who are protected from alcoholism possess unique taste characteristics which contribute to this protection, that is, decreased pleasantness of salt and increased perception of intensity of sour. Alternatively, certain groups of individuals with a paternal history of alcoholism may inherit genetic alterations in taste characteristics that put them at increased risk for alcoholism. The implication of the latter explanation, altered taste characteristics, has yet to be fully explored in relation to alcoholism risk."

Taste characteristics may interact with other factors in the development of alcoholism, said Kranzler. "Sweet-taste sensitivity has been linked to impulsiveness and other related behavioral factors associated with alcoholism," he said, "but salty and sour taste differences are not as easily linked to such markers. We know that a decreased sensitivity to the intoxicating effects of alcohol appears to put one at risk of developing alcoholism. Perhaps salty and sour taste characteristics exert indirect independent effects that may be more important in the acquisition of drinking behavior, while decreased sensitivity to alcohol's intoxicating effects may influence the maintenance of drinking behavior."

Kampov-Polevoy's research has also uncovered a connection between taste characteristics and other factors, finding that combining a sweet preference test and a personality profile can predict alcoholic versus nonalcoholic status with "fair" sensitivity and "good" specificity. "These data indicate that the sweet preference itself may not be sufficient for prediction of alcoholism in humans," said Kampov-Polevoy. "However, if combined with some personality traits, it has a better predictive value regarding alcoholism," he said.

**Article is based on the following published research:**

Sandstrom, K.A., Rajan, T.M., Feinn, R., Kranzler, H.R. (June 2003). Salty and sour taste characteristics and risk of alcoholism. *Alcoholism: Clinical and Experimental Research*, *27*(6), 955-962.

# A SWEET TOOTH MAY BE A "MARKER" FOR THE GENETIC RISK FOR DEVELOPING ALCOHOLISM

- *Prior research has found an association between a liking for sweets and alcohol intake.*
- *New research indicates that a liking for sweets precedes alcoholism.*
- *A liking for sweets among individuals with a family history of alcoholism may serve as a "marker" for the genetic risk for developing alcoholism.*

Although both animal and human research has found an association between a liking for sweets and alcohol intake, it has been unclear if a liking for sweets among humans was caused by years of drinking or was linked to a genetic predisposition for alcoholism. Findings published in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* indicate that a liking for sweets precedes alcoholism and may in fact serve as a "marker" for the genetic risk for developing alcoholism.

"Previous research has established that in mammals such as mice, rats and monkeys, the preference for and consumption of sweet fluids are strongly correlated with voluntary alcohol intake," said Alexei B. Kampov-Polevoy, assistant professor of psychiatry at Mt. Sinai School of Medicine and first author of the study. "It is thus possible to measure the amount of sweet solution that an animal drinks per day and accurately predict how much alcohol it will drink if given a chance."

Kampov's prior research also showed that alcoholic patients prefer stronger sweet solutions than do non-alcoholics. "However," said Kampov, "it was not clear whether the increase in sweet preference was caused by a long history of drinking or if a higher sweet preference existed before the onset of alcoholism and somehow reflects predisposition for this disease. Our present manuscript is focused on resolving this issue."

Researchers recruited 163 social drinkers from a university setting, dividing them into two groups: 81 (27 males, 54 females) had a paternal history of alcoholism; 82 (38 males, 44 females) did not. Each study participant rated a series of sucrose solutions for intensity of sweetness and palatability.

"Because humans consume their food based on both biological and environmental factors," said Kampov, "we study the hedonic or pleasurable response to various concentrations of the sugar solutions. This trait is much less controlled by environmental factors. People may regulate the amount of sweet foods they consume, but they usually have less concern about their hedonic reaction to various sweet tastes. Thus, this test better reflects the biological reaction to sweet taste."

Individuals with a paternal history of alcoholism were two and a half times more likely to like sweets than those who did not have a paternal history of alcoholism. "This finding indicates that sweet-liking precedes alcoholism," said David Overstreet, associate professor of psychiatry with the Bowles Center for Alcohol Studies at the University of North Carolina at

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Chapel Hill. "This suggests that the association previously reported is unlikely to be due to differential histories of alcohol exposure. This finding adds further weight to the hypothesis for the association between the liking for sweets and the genetic risk for alcoholism. However, it does not provide definitive proof."

The present study produced some unexpected results as well: individuals with a paternal history of alcoholism disliked the tastes of the two weakest sucrose concentrations, while individuals without a paternal history of alcoholism rated the tastes as neutral.

"This finding may provide a mechanistic explanation of the association between sweet preference and risk for alcoholism," explained Kampov. "Pleasurable reactions to both alcohol and sweet substances are regulated by the same mechanism, namely, the brain's opioid system. Activation of this system results in increased consumption of both alcohol and sweets, while blockade of this system causes the opposite effect. The latter is used in medicine when opioid antagonists such as Naltrexone are prescribed to alcoholics to reduce their drinking. We believe that children of alcoholics have a genetic abnormality of the brain opioid system, which leads to an increased sensitivity to the rewarding effects of alcohol. The same abnormality of the brain opioid system may also lead to a preference for stronger sweet solutions."

"These studies imply that a person whose relatives are alcoholics may be at greater risk for developing alcoholism if he or she likes sweets," said Overstreet. "By demonstrating that a liking for sweets is dependent on the family history of alcoholism in young individuals, this paper has provided one further step in developing 'sweet-liking' as a marker for alcoholism."

Overstreet suggested that future research be long-term in nature. "The current study could follow these individuals for a period of five or 10 years and repeat the assessments," he said. "If the liking of sweets is predictive of the later development of alcoholism, then sweet-likers with a positive family history of alcoholism will exhibit more ... problems related to alcohol drinking. Another area that could be explored is conducting the sweet test in even younger individuals. It is not uncommon for children of alcoholics to have started heavy drinking during their teenage years. Being able to advise and counsel individuals at risk before alcohol abuse has started may help prevent its onset and/or progression."

**Article is based on the following published research:**

Kampov-Polevoy, A.B., Garbutt, J.C., Khalitov, E. (November 2003). Family history of alcoholism and response to sweets. *Alcoholism: Clinical and Experimental Research, 27*(11), 1743-1750.