Biology – Neurobiology

BIOLOGY – NEUROBIOLOGY

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ALCOHOL-DAMAGED BRAINS "RECRUIT" NEW BRAIN REGIONS TO PERFORM SIMPLE TASKS

- *Chronic alcoholism is known to damage the brain's cerebellum and frontal lobes.*
- *Researchers used brain imaging technology to watch abstinent alcoholics perform a simple motor task.*
- *Alcoholics performed the task, finger tapping, slower than non-alcoholics.*
- *Alcoholic brains also recruited other-than-normally activated regions of the brain to perform the task.*

Researchers know that many alcoholics continue to experience cognitive deficits even after long-term abstinence from alcohol. Results from a study in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* confirm that motor deficits also continue to plague abstinent alcoholics. By using functional magnetic resonance imaging (fMRI) to "watch" brain regions involved in a simple motor task – finger tapping – the study has found that the brain appears to compensate for alcohol-induced damage by "recruiting" other, unexpected brain regions.

"We know from neuropathological studies that the two parts of the brain that are most often damaged in chronic alcoholics are the cerebellum and the frontal lobes," said Peter R. Martin, professor of psychiatry and pharmacology, director of the Vanderbilt Addiction Center at the Vanderbilt University School of Medicine and corresponding author for the study. "Rapid self-paced motor activity such as finger tapping is a function of the motor cortex, the posterior part of the frontal lobe, which initiates a stimulus to the muscles of the hand, that is then coordinated by interplay between the cerebellum and the frontal lobes. In other words, I reasoned that there would probably be abnormalities in activation of these regions in alcoholics during finger tapping."

While undergoing MRI, two groups of participants performed repetitive, self-paced index finger-tapping exercises: eight (seven males, one female) alcohol-dependent patients after approximately two weeks of abstinence; and nine (seven females, two males) healthy volunteers or "controls." Participants alternated between using their dominant hands (DH) and non-dominant hands (NDH) to perform the index finger-tapping exercises. Researchers used fMRI analysis to compare DH and NDH performance in each subject group in order to examine whether the groups differed in the patterns of activation they exhibited in the cerebral cortex and cerebellum.

The detoxified alcohol-dependent patients performed the finger-tapping tasks significantly slower than the control group. However, contrary to expectations, the slower tapping was not accompanied by proportionately decreased fMRI brain activation in the cerebral cortex and cerebellum. Rather, the alcoholics had a significant increase of activation in the cortical brain region ipsilateral to (on the same side as) the active hand during DH tapping. In other words, the alcoholics had to use more of their brains to do less.

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"First, we found that alcoholics, generally speaking, tapped more inefficiently," said Martin. "Second, in order to generate a single tap, an alcoholic would activate a larger part of their brain than a normal person. So, the results seem to indicate that even though alcoholics, as they recover from drinking, can probably demonstrate relatively normal tapping, they have to use more of their brain to generate the taps."

"This study underlines the importance of considering the operation of brain circuitry involved even in an ostensibly simple task," said Edith Sullivan, associate professor of psychiatry at Stanford University School of Medicine. "Further, evidence for recruitment of brain regions that are not normally involved in a given task puts a person at risk for performance inefficiency for that particular task, other tasks that need to be done simultaneously, and more complex divided-attention tasks, such as driving."

Increased activity in the ipsilateral cortical region of the brain was highly unexpected, said Martin. "Normally, when I tap with my right hand," he said, "it's mostly my left motor cortex (part of the frontal lobes) that's firing, in conjunction with my right cerebellum. 'Ipsi' means same side, 'contra' means opposite side. So, we're talking about my contralateral cortex and my ipsilateral cerebellum. The significantly higher activity we found in the alcoholics was on the ipsilateral cortex, the side that we don't normally expect to be activated. This finding is compatible with the idea that different regions of the brain are being called into activity that would not normally be activated in order to meet the behavioral demands. Furthermore, this suggests that even though alcoholics at some level may seem to be performing normally, if you raised the level of complexity at which they are being asked to perform, they may exhaust their capacities ... there may be no more brain to bring in, to recruit, to compensate."

These findings lead to new questions, said Martin. "If we study patients as they progress with their abstinence, do these abnormalities get better? It may be that the brain gets better at compensating, but it doesn't normalize, it just learns how to bring in even more parts of the brain. You could say it learns to rewire itself. Another possibility could be that as the brain heals, less activation is required, and that's a real form of recovery. The answers rest with understanding not the tapping itself, but the mechanisms behind the tapping."

Article is based on the following published research:

Parks, M.H., Morgan, V.L., Pickens, D.R., Price, R.R., Dietrich, M.S., Nickel, M.K., Martin, P.R. (April 2003). Brain fMRI activation associated with self-paced finger tapping in chronic alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research*, *27*(4), 704-712.

How Alcohol Gives and Then Takes Away

- *Alcohol may be particularly damaging to key components of the "brain reward system."*
- *Alcohol sensitizes dopamine and serotonin neurons to toxic excessive excitation or "excitotoxicity."*
- *A brain growth hormone called BDNF can protect neurons against excitotoxicity.*
- *BDNF may have important implications for treating alcoholics going through withdrawal.*

Mental diseases, including addiction and alcohol dependence, may indeed be "all in your head." But not in the way you might think. Researchers have learned that alcohol may be particularly damaging to the brain's reward pathways, specifically dopamine and serotonin neurons. This damage – a sensitization of the neurons to a process called excessive excitation or "excitotoxicity" of the *N*-methyl-D-aspartate (NMDA) glutamate receptor – could be an important component in transitioning from experimentation to addiction. However, researchers may have also discovered that a brain growth hormone called Brain Derived Neurotrophic Factor (BDNF) may be able to protect neurons against this excitotoxicity.

"If dopamine and serotonin neurons are damaged," said Fulton T. Crews, director of the Center for Alcohol Studies at the University of North Carolina, "this would disrupt reward processes in ways that could contribute to addiction." Crews, lead author of a study recently published in the November edition of *Alcoholism: Clinical and Experimental Research (ACER)*, explained that his findings are related to what is called a "reward deficiency hypothesis" of addiction.

The "reward deficiency syndrome" links addictive, compulsive or impulsive disorders – such as alcoholism, substance abuse, smoking, compulsive overeating and obesity, Attention deficit disorder, Tourette's syndrome and pathological gambling – with a "chemical imbalance" in the brain. Researchers knew that pleasure, to various degrees, is a distinct neurological function that is linked to a complex reward and reinforcement system. In particular, dopamine appears to be a primary neurotransmitter of reward in the nucleus accumbens and hippocampus areas of the brain. Serotonin is believed to have an additive or synergistic effect on dopamine. Alcohol is known to initially lead to an increase in dopamine release, which supposedly enhances reward/pleasure. However, chronic and/or high levels of alcohol will eventually lead to a decrease in dopamine release. This disruption of intercellular interactions or "chemical imbalance" can result in negative feelings such as anxiety, anger or in a craving for a substance, such as alcohol, that can alleviate the negative feelings. Yet because chronic drinking releases a continuously reduced amount of dopamine, more and more alcohol is needed to feel "normal."

"Science has come to the realization that what alcohol may be doing," said Boris Tabakoff, chairman of the Department of Pharmacology at the University of Colorado School of Medicine, "is what I call 'downregulating' dopamine systems. This study shows that downregulation may actually be a result of neuronal damage. Alcohol leads to a sensitization to glutamate, the glutamate produces the damage, and the damage results in a lower function of the dopamine system."

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How Alcohol Gives and Then Takes Away

"This is important," added Tabakoff, "because it provides an explanation for why individuals may not be able to control their drinking because of biological factors. If the neurons are damaged, they can keep trying to use alcohol to attain some level of pleasure, but they'll never be able to do it."

Although there is no such thing as a specific gene for alcoholism, there does seem to be a "genetic predisposition" to the development of alcoholism. Tabakoff spoke of one study in which 20 to 28 percent of individuals with at least one alcoholic parent went on to develop alcoholism themselves. Normally, among those who have no familial history of alcoholism, around eight to 10 percent develop alcoholism. In short, those with a family history of alcoholism seem to have a two to three time's greater chance of developing the disease. Although the exact role of biology in alcoholism has not yet been determined, research findings support both discovery as well as optimism.

"This is one of the first studies to show a relationship between excitotoxicity, which likely occurs during ethanol withdrawal, and NMDA receptors," said Richard A. Morrisett, associate professor of Pharmacology at the University of Texas at Austin. "But it is the first to show that BDNF can actually protect against this. The rescue or prevention of cell death is probably one of the most important aspects of this study."

"Clearly the future direction of this area of study is medication development and an understanding of protective factors," said Tabakoff. "If you have an individual who is drinking a lot but decides to stop, you need to treat that person with something more than moral support. The very process of withdrawal could damage the person's neurons." Tabakoff spoke of developing drugs that will protect the neurons, returning the individual's pleasure systems to normal while avoiding irrevocable damage.

Morrisett indicated there is a need for future studies that look at the effects of lower levels of alcohol on excitotoxicity. "The levels used in this study, 100 mM, are five times the legal levels of intoxication," he said. "I would like to see what occurs at 20mM, because that's more related to when we start to drink, when we may start to become dependent." When a person starts to drink and is experiencing the reinforcing aspects, he said, that's when "we're having a little engine misfire." At the point of full-blown alcoholism, he said, "we're addicted, we're dependent, we're drinking fifths of whiskey a day, the car is wrecked."

Article is based on the following published research:

Crews, F.T., Waage, H.G., Wilkie, M.B., & Lauder, J.M. (November 1999). Ethanol pretreatment enhances NMDA excitotoxicity in biogenic amino neurons: Protection by brain derived neurotrophic factor. *Alcoholism: Clinical and Experimental Research, 23*(11), 1834.

How Sensitive Is Your Brain to Alcohol-Induced Damage?

- *Alcohol's neurotoxic effects can cause brain injury.*
- *Alcohol-related brain injury may, in turn, place someone at greater risk of developing alcoholism.*
- *Exercising the brain's frontal cortex during treatment may help the recovery process.*
- *Thiamin supplements may also improve recovery of the brain and response to treatment.*

Symposium findings from the June 2000 Research Society on Alcoholism meeting in Denver suggest that alcohol-induced brain injury may be the medium for the progression of alcoholism. The summary, published in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)*, may change the way researchers think about the influence of alcohol-related brain injury on how people develop addictions, respond to treatment and ultimately recover.

"What these researchers are saying is that injury to the brain resulting from alcohol consumption is sum and parcel of the progression of the illness," said Peter R. Martin, professor of psychiatry and pharmacology and director of the Vanderbilt Addiction Center at the Vanderbilt University School of Medicine.

"It's a different perspective on how alcoholism may progress. In the past 20 years, the emphasis of research has been on what makes some people respond to alcohol, regardless of whether their brain is damaged. What they're saying here is that by drinking, you modify the brain, and the brain can be modified differentially in people. The neurotoxicity of alcohol 'feeds back' and determines, modulates or modifies the course of the alcoholism."

Symposium proceedings included four studies that addressed both preclinical (before the onset of the disease) and clinical (related to the symptoms and course of a disease) findings. According to Fulton T. Crews, director of the Center for Alcohol Studies at the University of North Carolina and one of the presenters, the symposium's common ground was the relation of alcohol-induced deficits in central nervous function to addiction and recovery.

"Data indicates that risk factors for alcoholism include heavy binge drinking, genetics and adolescent drinking," said Crews. "These may also be risk factors for increased brain damage." That's the bad news; that simply drinking alcohol can injure someone's brain, its neurotoxic effects depending on the individual's genetic makeup, age, metabolism and even gender. The good news is that because of the close 'working relationship' between alcohol and the brain, recovery seems possible with the right kind of treatment.

"Preclinical studies have suggested that brain damage is a component of the progression from casual drinking to addiction," said Crews. "We know that alcoholics have decreased brain size. Clinical studies have suggested that 'exercising the brain' likely improves brain regrowth as well as recovery from the addiction. Regrowth of the frontal cortex in particular could be

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How Sensitive Is Your Brain to Alcohol-Induced Damage?

essential for a successful recovery. Including certain activities in therapy – activities that require the use of the frontal cortex, the site of executive function, impulse inhibition and goal setting – have been shown to improve recovery and increase retention in the treatment program. Also, thiamin therapy seems to increase treatment effects, likely by restoring aspects of central nervous system function."

In short, therapies that exercise certain areas of the brain can improve its function. This can, in turn, help improve an individual's chances of recovery from alcoholism. The decrease in brain size that seems to accompany alcoholism appears to reverse during the recovery process. In addition, thiamin supplementation may help recovering alcoholics regain their capacity to remember.

"The main point to be made here for the reader is that drinking alcohol can cause brain injury," said Martin. "Maybe what determines why some people become alcoholics is not so much how they respond to the pharmacological actions of alcohol, but how sensitive their brain is to being damaged by alcohol, which modifies their brain, thereby modifying the pharmacological actions of alcohol."

Martin added that future research should be directed at recovery. "We need to remember that even when an alcoholic stops drinking, there have been changes in the brain. We need to spend more time trying to understand how the brain recovers after people stop drinking, because that's going to determine how well they ultimately do."

Article is based on the following published research:

Bowden, S.C., Crews, F.T., Bates, M.E., Fals-Stewart, W., & Ambrose, M.L. (February 2001). Neurotoxicity and neurocognitive impairments with alcohol and drug use disorders: Potential roles in addiction and recovery. *Alcoholism: Clinical and Experimental Research, 25*(2), 317-321.

THE BRAIN RISKS OF BINGE DRINKING

- *Neurodegeneration has been commonly thought to occur during alcohol withdrawal.*
- *A new study has confirmed that neuronal damage can occur during a binge pattern of drinking.*
- *Damage to the olfactory bulb, responsible for smell, occurred after just two days of binge drinking.*
- *Damage to other regions of the brain occurred after just four days of binge drinking.*

Scientists agree that alcohol is toxic and that chronic alcohol abuse can damage all organs – including the brain – to various degrees. There is less agreement, however, on whether or how much neurodegeneration is triggered by alcohol's toxicity during alcohol consumption or by the hyperexcitability caused by withdrawal from alcohol. A study in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* uses rodents to examine what effects just a few days of the equivalent of binge drinking can have on neuronal function.

"Most studies of alcohol-induced brain damage have looked at humans who have been alcoholic for decades or rats treated with alcohol for six to 18 months," said Fulton T. Crews, director of the Center for Alcohol Studies at the University of North Carolina and corresponding author for the study. "Our study shows significant damage in several regions of the brain after only four days, that it occurs during intoxication, and that the process is similar to a dark-cell degeneration that is primarily necrotic." Necrosis refers to the pathologic death of cells or a portion of tissue or organ due to irreversible damage.

Male Sprague-Dawley rats (n=120) were surgically implanted with intragastric catheters. Experimental rats (n= 80) were given alcohol at a rate equivalent to binge drinking, every eight hours for four consecutive days. Doses were based on their estimated blood alcohol levels. Control rats (n=40) were given an alcohol-free yet calorie-equivalent diet at the same rate. Several histological methods – such as amino cupric silver staining, fluoro-Jade B staining, hematoxylin and eosin staining, and transmission electron microscopy – were used to track the course, time points, and specific changes that occurred in conjunction with the alcohol intake. Some rats were sacrificed at two days, some at four days, and some after four days of alcohol and three days of withdrawal.

"This study shows significant damage in the olfactory bulb after just 2 days of heavy drinking," said Crews, "which is a short period of time relative to the decades of drinking that alcoholics do, and may be an important early process in the progression from experimentation with alcohol to addiction. In addition, the major current hypothesis regarding alcohol-induced brain damage suggests that damage occurs during withdrawal. All of these studies, however, were done in vitro (in an artificial environment). Our findings, which are in vivo (in the living body), indicate that alcohol-induced brain damage occurs during intoxication."

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THE BRAIN RISKS OF BINGE DRINKING

"In the rat," explained Michael A. Collins, professor of biochemistry at Loyola University Chicago, "which on one level is a 'walking nose,' the overall damage to the olfactory pathway is quite significant. The olfactory neurons in the bulb are some of the few neurons that are always turning over, dying and regenerating. One guess is that the repetitively elevated alcohol levels are pushing more of these neurons 'over the edge,' but apparently in a necrotic fashion."

Collins said that drinking patterns may specify the nature of neuropathology that occurs and the brain regions and neurons where it occurs. "The short-term binge pattern in these studies," he said, "which affords periodically high blood and brain alcohol levels, seems to damage the olfactory cortical regions quite selectively. In other models in which lower alcohol levels are sustained for several months – more akin to the primary type of alcohol abuse in countries like France and Spain – rodents show significant loss of brain neurons in regions evidently not affected in the brief binge-drinking model used here, for example, the cerebellum and the frontal cortex."

Collins added that even though chronic alcohol abuse damages all organs to greater or lesser degrees, most attention has been paid to liver damage, largely because it is easier for doctors to detect and measure, and can eventually lead to liver-failure death. However, he added, "a study of relatively young alcoholics published some time ago in the British journal *Lancet* showed that indicators of relatively permanent cognitive damage, measured by neuropsychological tests, actually showed up earlier than clinical signs of liver damage. Sadly, when the brain – the limbic cortex and dentate gyrus of the hippocampus, in this case – loses its excitable cells, for all practical purposes they are gone for good. In the day-to-day life of an alcoholic, this means a decreased ability to learn, to recall, to make decisions, and perhaps to sense and appreciate life in its fullest."

According to some estimates, said Collins, alcohol abuse in the United States is perhaps the third or fourth most common cause of brain damage, and may be even higher in other countries. "Given this," he said, "it is surprising that the mechanisms of brain neuronal degeneration due to a widely abused neurotoxicant are so understudied and therefore still somewhat obscure. Certainly this has implications for a college student contemplating a weekend of binge drinking. Seriously, though, it is possible that neuronal degeneration after a couple of days of heavy intoxication in the rat might translate to the human drinker who is not even a chronic alcohol abuser. There is no firm proof of this at present, and we would need brain imaging to determine whether acute short-term binge drinking in people could be permanently deleterious to olfactory or other neurons."

Article is based on the following published research:

Obernier, J.A., Bouldin, T.W., & Crews, F.T. (April 2002). Binge ethanol exposure in adult rats causes necrotic cell death. *Alcoholism: Clinical and Experimental Research, 26*(4).

ABSTINENCE MAY MAKE THE BRAIN GROW STRONGER

- *Chronic alcohol abuse leads to structural brain damage.*
- *The damage includes loss of gray matter in the cortex and loss of white matter throughout the brain.*
- *The greatest tissue loss occurs in the frontal lobe and cerebellum.*
- *Prolonged abstinence from alcohol appears to allow some reversal of structural brain damage.*

Substantial research has demonstrated that chronic alcohol abuse leads to structural brain damage, especially to white matter, and primarily in the frontal lobes and cerebellum. Researchers have wanted to know for quite some time to what extent these effects may be reversible with abstinence from alcohol. A study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* uses quantitative neuroimaging to reveal that prolonged abstinence may lead to partial reversal of structural brain damage, which suggests that brain function can improve with abstinence.

"We wanted to know if abstinence from alcohol reverses the kind of structural and metabolic abnormalities that have been demonstrated by previous studies," said Dieter J. Meyerhoff, associate professor of radiology at the University of California - San Francisco School of Medicine and lead author of the study. "We also wanted to know in what specific brain regions and tissue types (gray or white matter) damage would be reversed with prolonged abstinence."

Meyerhoff and his colleagues compared two groups. One group comprised alcoholics (with an average age of 46 years) who had already undergone treatment for their alcoholism and had been abstinent for an average of two years at the time of study. The second group comprised individuals who were heavy drinkers at the time of study and had never been treated for their drinking. The current drinkers were matched in drinking severity (average monthly alcohol use over lifetime and duration of alcohol use) to the prior drinking patterns of the abstinent alcoholics. A healthy control group was not included because the study's intent was to measure the effects of abstinence from chronic drinking on alcohol-induced injury. All participants underwent magnetic resonance imaging (MRI) and proton magnetic resonance (MR) spectroscopic imaging of the brain.

"These are non-invasive methods," explained Meyerhoff, "which allow taking a 'snapshot' of the structural and metabolic integrity of all parts of the brain. As opposed to computed tomography scans, MRI can distinguish between gray and white matter tissue, which is important when we want to talk about the functional significance of brain damage in alcoholism. In addition, we used a localization approach that allowed us to investigate structural and metabolic brain changes in relatively small, yet anatomically well-defined brain regions."

They found that the abstinent alcoholics had a greater volume of white matter in their frontal lobes than currently heavy drinkers did, but not in other parts of the brain. White matter

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ABSTINENCE MAY MAKE THE BRAIN GROW STRONGER

volume was greatest in those alcoholics who had been abstinent for the longest time. In addition, the amount of white matter lesions in the abstinent alcoholics was smaller than in the current drinkers in most of the brain regions investigated. Finally, the volume of gray matter in the abstinent alcoholics was greater in some but not all regions of the frontal lobes.

"These results suggest reversal of structural abnormalities in some brain regions of abstinent alcoholics," said Meyerhoff, "and persistent structural damage in other brain regions. We still need to learn, however, what this means for the individual's brain function."

"We know that alcohol abuse can cause extensive damage to the brain," said Edith Sullivan, associate professor of psychiatry at Stanford University Schoool of Medicine. "This can include volume deficits in cortical gray matter, which are neural cell bodies, as well as in white matter, which are the fibers that are extensions of the cell bodies and that connect cells. The regions most clearly affected are the frontal lobes. Additional brain structures affected are the corpus callosum (the large band of white matter fibers that connect the two cerebral hemispheres), the anterior aspect of the hippocampus and the mammillary bodies (brain structures that engage in consolidation of new memories) and the cerebellum (the 'little brain' that is critical to postural stability, motor timing and motor learning as well as certain components of cognitive functioning). The UCSF study suggests that the recovering alcoholic group, despite their older age, can experience a significant reversal of white matter abnormality with prolonged abstinence."

Sullivan said that future research needs to focus on longitudinal studies, using different modalities of brain imaging that follow alcoholics from early detoxification through periods of sobriety and relapse. She added that these studies need to take into account nutritional factors, withdrawal symptoms and functional outcomes in alcoholic men and women of all ages.

This is in fact what Meyerhoff and his colleagues have in the works: longitudinal studies of alcoholics who undergo treatment for their drinking problem. "These studies are ongoing and include structural and metabolic MR studies integrated with careful assessment of neuropsychological functioning. Both abstainers and relapsers are examined to assess postulated improvement with abstinence and postulated status quo or further deterioration with relapse." Although more data have yet to be collected and analyzed, said Meyerhoff, "it appears that even after many years of heavy drinking, the brain has the capacity to repair at least some of the structural damage that has occurred."

Article is based on the following published research:

O'Neill, J., Cardenas, V.A., & Meyerhoff, D.J. (November 2001). Effects of abstinence on the brain: Quantitative MRI and MR spectroscopic imaging in chronic alcohol abuse. *Alcoholism: Clinical and Experimental Research, 25*(11), 1673-1682.

COGNITIVE NEUROSCIENCE TAKES ON ALCOHOL

- *Alcohol is known to impair an individual's ability to control his/her behavior.*
- *Impaired behavioral control is known to be a factor in accidents, antisocial acts and binge drinking.*
- *Psychologists are jointly investigating the effects of alcohol on brain activity that is associated with behavioral control.*
- *Findings show that specific cognitive processes, certain individual characteristics, and some environmental conditions can all influence alcohol's effects on behavioral control.*

A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines how alcohol – through its effects on underlying cognitive processes – may effect someone's self-control in different ways.

"Drinkers can sometimes display foolish, inappropriate or harmful behavior that they would not exhibit when sober," said Muriel Vogel-Sprott, professor of psychology at the University of Waterloo and first author of the paper. "This is commonly attributed to the effects of alcohol, for example, explaining away the behavior by saying 'I couldn't stop myself' or 'I didn't mean it.'" Vogel-Sprott's paper was based on research presented at a symposium during the June 2000 Research Society on Alcoholism meeting in Denver. Researchers tested the effects of a moderate dose of alcohol (approximately two or three beers) on social drinkers' performance of a task. The objective was to assess specific cognitive processes that govern behavior.

"Some of the presentations showed that alcohol could diminish cognitive control of response inhibition," said Vogel-Sprott, "and that vulnerability to this disinhibition varied among individuals. In addition, there are some personal attributes – such as impulsivity, symptoms of attention deficit disorder, and the capacity to keep in mind the relevant information needed to guide behavior – that are related to poorer inhibition under alcohol. Yet other research used event-related functional magnetic resonance imaging (MRIs or brain scans) to identify those brain areas and networks that are activated when cognitive inhibitory tasks are performed. This work showed that both successful and unsuccessful inhibition of behavior is distinguishable by different brain activity and, furthermore, these effects are altered by alcohol."

Vogel-Sprott's own research examined intentional control of behavior, assessing the degree to which conscious (intentional) and unconscious (automatic) cognitive processes influence performance. She found that a moderate dose of alcohol selectively diminished intentional control when social drinkers' behavior had no environmental consequence. However, when performance under alcohol had some 'payoff' (for example, money or verbal approval), intentional control was well retained.

"Was the behavior due to alcohol," mused Vogel-Sprott, "or was it intentional? This question is controversial, particularly in the courts, where the intentionality of an alcohol-related offence can affect the sentence. The research presented in this symposium indicates that the answer is

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COGNITIVE NEUROSCIENCE TAKES ON ALCOHOL

complex. On one hand, it appears that alcohol can impair cognitive processes controlling inhibition and intentional behavior. But, on the other hand, the intensity of impairment may also depend upon the characteristics of the drinker and the consequences of behavior in the drinking situation."

Mark Fillmore, assistant professor of psychology at the University of Kentucky, was another of the presenters during the symposium. His research examined how a drug such as alcohol can disturb a person's ability to control behavior. His findings showed that alcohol-induced impairment of inhibitory control appears to have some commonalities with Attention Deficit Hyperactivity Disorder (ADHD).

"It seems that alcohol reduces the ability to stop some actions," he said. "This is important because we all have to sometimes stop what we are doing to reflect and plan more appropriate actions. Impulsiveness can lead to a host of problems in school, work and with peer relations. My work discovered that low to moderate doses of alcohol impair the ability to stop actions much in the same way that individuals with ADHD have difficulty stopping inappropriate actions, such as throwing a punch. The effects of alcohol are short-lived, lasting only about an hour or so. But these observations suggest that alcohol can produce a temporary mental state in some individuals that resembles impulsiveness, and perhaps, ADHD-like symptoms."

Fillmore's work also found that stimulant drugs can block the impairing effects of alcohol so that the ability to stop actions while under the influence of alcohol is improved. This is similar to findings that stimulant drugs (such as Ritalin) can increase the ability to stop behaviors in individuals with ADHD.

"The fact that both ADHD and acute doses of alcohol can impair the ability to withhold inappropriate behavior," he said, "raises the possibility that people with ADHD might suffer greater impairment from alcohol. The major challenge for alcohol researchers has been to figure out why some people develop problems, while others do not. The ability to identify a pre-existing trait (such as ADHD) among some individuals that contributes to alcohol problems is a very important development."

The varied yet interconnected research presented at the symposium demonstrates how scientists using research tools from cognitive science and neuropsychology are working together to study how alcohol impairs behavioral control. "We didn't find an easy answer," said Vogel-Sprott, "but we have a better 'big picture' understanding of how alcohol impairs behavior."

Article is based on the following published research:

Nicolas, J.M., Fernandez-Sola, J., Fatjo, F., Casamitjana, R., Bataller, R., Sacanella, Tobias, E., Badia, E., & Estruch, R. (January 2001). Increased circulating leptin levels in chronic alcoholism. *Alcoholism: Clinical and Experimental Research, 25*(1), 83-88.

JUST A SPOONFUL OF THIAMIN?

- *Two neurological disorders are linked through thiamin deficiency.*
- *One disorder can be treated with thiamin supplements; the other may be incurable.*
- *Heavy drinkers, anorexics and senior citizens are considered at risk.*
- *Up to 10 percent of alcoholics in the U.S. may be affected.*
- *Australian cases decreasing, but thiamin may yet be added to beer.*

Something as simple as thiamin (vitamin B1) may help, or hinder, your brain's capacity to function and perhaps even survive. Alcoholics, anorexics and senior citizens may be especially vulnerable, according to recent studies of two neurological disorders called Wernicke's Encephalopathy (WE) and Korsakoff's Syndrome (KS). The two studies, published in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)*, jointly found that mammillary bodies in the brain may shrink as cognition and memory decrease.

"These findings are significant because they point toward the importance of nutritional factors in the condition of the brain," said Edith Sullivan, associate professor of psychiatry at Stanford University School of Medicine and lead author of one of the studies. Sullivan based her study on *in vivo*, or living patients.

WE is a potentially fatal disorder caused by thiamin deficiency. WE usually occurs in people who have been drinking heavily and not eating, but can also occur after persistent vomiting or during hunger strikes. Recent studies have shown that young women suffering from anorexia nervosa may also develop WE due to severe nutritional deficiencies. Of increasing concern is the potentially large number of senior citizens who may be apathetic about the quality of their diet, may not be eating enough, or may forget to eat altogether. Heavy drinkers are those known to be most affected by WE.

"Brain damage as a result of alcohol consumption is probably the second most common cause of dementia in the United States, behind Alzheimer's Disease," said Dr. Peter Martin of the Vanderbilt University School of Medicine. Heavy drinkers often eat improperly. Furthermore, alcohol impedes the digestive tract's normal absorption of those few nutrients that may be consumed. Nerve, muscle and brain tissue are extremely sensitive to low levels of vitamins, nutrients and minerals, and can begin to deteriorate when deprived. Body stores of thiamin can be depleted within about three weeks.

WE is characterized by double vision, mental confusion, muscle weakness and unsteady gait. Unlike other disease states caused by alcohol, WE may reverse through rapid treatment with thiamin. If left untreated, however, the person can go into a coma and die. In some cases, even if treated, they can develop permanent memory damage in the form of KS.

KS is often associated with a previous episode of WE, but is distinguished by amnesia. KS is often recognized when the confusion associated with WE clears following thiamin treatment.

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JUST A SPOONFUL OF THIAMIN?

Although KS may sometimes respond to thiamin treatment, it is often permanent. Researchers agree that the nutritional deficiencies caused by heavy drinking can lead to WE, and if not treated, eventually KS.

Exact numbers of those afflicted are difficult to find but Martin speculated that at least 10 percent of alcoholics have some degree of the two syndromes. Even though most alcoholics do not have the characteristics of an "extreme stage of brain damage" such as Wernicke's or Korsakoff's, "70 percent of alcoholics have some sort of brain damage," he said. "At one point I calculated that there were about 10 million people in the U.S. who may have some sign of brain damage related to alcohol," he said.

In Australia, the two disorders are often referred to jointly as Wernicke-Korsakoff Syndrome (WKS), according to Clive Harper, professor of neuropathology at the University of Sydney and Royal Prince Alfred Hospital and lead author of the second study. During the 1980s, Australia had the ignoble distinction of having the highest recorded rates of WE in the world, mostly among the alcoholic population, as well as large numbers of people needing long-term care because of KS. Harper estimated the former at 500 cases per year, the latter at 2,000 per year.

The problem was considered so acute that in 1991, the Australian government mandated that bread flour be enriched with thiamin. This same requirement has been mandatory for a number of years in the United Kingdom, Canada and Denmark. In the U.S., most bread flour is enriched, but enrichment is not mandatory. Since the 1991 enrichment of bread flour in Australia, WKS rates have significantly decreased but remain higher than those in most other Western countries – enough to prompt discussion of thiamin supplementation of alcoholic beverages, primarily beer (the preferred beverage of many WE patients).

Harper said that "WE diagnosis is probably missed about 80 percent of the time worldwide. About one in every hundred people who have a coroner's autopsy are found to have WE, even though it is very easy to treat, because the diagnosis can easily be missed." People suffering from WE or KS or WKS, whatever name you prefer, he said, clearly make up "a big hidden group throughout the world that needs further study."

Article is based on the following published research:

Sheedy, D., Lara, A., Garrick, T., & Harper, C. (October 1999). Size of mamillary bodies in health and disease: Useful measurements in neuroradiological diagnosis of Wernicke's encephalopathy. *Alcoholism: Clinical and Experimental Research, 23*(12), 1624.

Sullivan, E.V., Lane, B., Deshmukh, A., Rosenbloom, M.J., Desmond, J.E., Lim, K.O., & Pfefferbaum, A. (October 1999). In vivo mammillary body volume deficits in amnesic and nonamnesic alcoholics. *Alcoholism: Clinical and Experimental Research, 23*(12), 1629.

ALCOHOL AND THIAMIN DEFICIENCY TOGETHER: A DANGEROUS COMBINATION?

- *Heavy alcohol use is associated with thiamin (Vitamin B1) deficiency.*
- *Alcohol and thiamin deficiency together may have a more damaging impact on the brain.*
- *Learning and reference memory appear to be the most sensitive to their synergistic effects.*
- *The role of thiamin supplementation is examined.*

Researchers and clinicians know that chronic abuse of alcohol may lead to a deficiency in thiamin (also known as Vitamin B1). This deficiency can wreak havoc on the brain, causing a wide spectrum of deficits in cognition, behavior and motor coordination. What researchers now suspect, as noted in a recent study in *Alcoholism: Clinical and Experimental Research (ACER)*, is that chronic alcohol consumption and thiamin deficiency combined may have a synergistic and even more devastating effect on the brain and mental capacities.

"We were looking for an interaction between ethanol and thiamin deficiency," explained Philip Langlais, professor of psychology at San Diego State University, professor of neurosciences at the University of California - San Diego, and lead author of the study. "We wanted to see if you took thiamin deficiency and combined it with chronic alcohol intake, would you then create a situation that would produce a more severe impairment of cognition and memory than you would with either thiamin deficiency alone, or exposure to chronic alcohol ingestion alone."

Using rat subjects, they did indeed find a synergistic effect, sometimes. Learning (for example, figuring out the rules of chess) and reference memory (remembering and consistently applying the rules) appeared the most sensitive to the damaging, synergistic effects of alcohol and thiamin deficiency. Short-term working memory (incorporating the rules of chess into game strategies), on the other hand, was most affected by alcohol alone. Neurological symptoms were most associated with thiamin deficiency.

Alcohol impedes the digestive tract from absorbing needed nutrients. Nerve, muscle and brain tissue are exquisitely sensitive to low levels of vitamins, nutrients and minerals such as thiamin, magnesium, potassium and phosphorus. When nutrients disappear, tissues slowly deteriorate.

Thiamin deficiency contributes to two clinical conditions along the alcoholic's path toward dementia. The first 'phase' is called Wernicke's Encephalopathy (WE), in which people become extremely confused, develop abnormal eye movements, experience muscle weakness, and demonstrate gait disturbances. The second phase is called Wernicke-Korsakoff Syndrome (WKS). It is associated with a more severe amnesia and significant cognitive and reasoning impairments. The first two conditions may respond to, and possibly be reversed by, thiamin treatment. The final and – for all practical purposes, untreatable – phase is dementia.

"This study significantly adds to the database in at least one respect," said David V. Gauvin, psychopharmacologist and drug science specialist at the Drug Enforcement Administration.

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ALCOHOL AND THIAMIN DEFICIENCY TOGETHER: A DANGEROUS COMBINATION?

"It shows that there are unique interactions between alcohol and thiamin deficiency. We don't see that one plus one equals two; rather, one plus one equals three." Gauvin said that he would add a third component to the damaging equation: thiamin supplementation.

"This unique synergism is not just about alcohol and thiamin deficiency," he said, "it's also about thiamin supplementation, and the whole issue of mega-dosing." Gauvin mentioned a study in which he participated where researchers found that thiamin injections made the recipients even more sensitive to the effects of alcohol. He is concerned that the standard practice of giving alcoholics thiamin injections, in order to counteract the progression to symptoms of WE and WKS, may be more detrimental than helpful.

"When you have a surplus of thiamin," he explained, "you have the capacity to induce magnesium deficiencies, which have been linked to a number of alcohol's negative effects." He conjectured that thiamin-induced magnesium deficiency could be the root cause of a new sensitization to alcohol's effects.

Another way of counteracting thiamin deficiency – most often linked to poor nutrition among alcoholics, anorexics and senior citizens – is food supplementation. Both Langlais and Gauvin noted the Australia example (see *Just a Spoonful of Thiamin?* article).

"When we gave our animals regular food that contained thiamin, they did not develop sensitization to alcohol," said Gauvin. "The body can naturally absorb and process low-graded doses of thiamin in the gut and the liver. It's the whopping injections that are problematic. Gauvin is less comfortable with the proposition of supplementing alcohol with thiamin. "If you supplement alcohol with mega-doses of Vitamin B, what you may actually be doing is inducing magnesium deficiencies."

Conversely, Langlais believes that we nonetheless need to "re-examine the issue of fortifying alcoholic beverages and perhaps other foods. We also need to seriously think about educating alcoholics with respect to their diet and nutrition."

Gauvin had one final caution. "What does this say about vitamin supplementation? We have such a benign feeling about vitamins, that we can mega-dose all we want to. Yet there is a physiological result from the overuse or abuse of vitamins. The bowel and the whole digestive system have been developed in such a way to allow for a very unique interaction between food and our needs. Yet bigger is not better, more is not better."

Article is based on the following published research:

Ciccia, R.M., & Langlais, P.J. (May 2000). An examination of the synergistic interaction of ethanol and thiamin deficiency in the development of neurological signs and long-term cognitive and memory impairments. *Alcoholism: Clinical and Experimental Research, 24*(5), 622-634.

CHRONIC DRINKING INCREASES CORTISOL DURING INTOXICATION AND WITHDRAWAL

- *Cortisol, a "stress hormone," plays an important role in the regulation of emotion, cognition, reward, immune functioning and energy utilization.*
- *New research has found that long-term chronic drinking produces an increase in cortisol both during intoxication and withdrawal.*
- *Cortisol appears to increase significantly during the progression from chronic intoxication to withdrawal.*
- *Health implications may include sleep disruption, cognitive deficits, diabetes and mood disturbances.*

Cortisol, known as a "stress hormone," plays an important role in the regulation of emotion, cognition, reward, immune functioning and energy utilization. A study published in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that long-term chronic drinking produces an increase in cortisol both during intoxication and withdrawal.

"It has not been known whether the body adapts to the stress of drinking following daily heavy drinking in the non-laboratory setting, or whether cortisol levels continue to be elevated even after several weeks or months of drinking," said Bryon Adinoff, distinguished professor in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas, medical director of the Substance Abuse Team at the Veterans Affairs North Texas Health Care System in Dallas, and first author of the study. "In this study, we show that even persons drinking for several months continue to show elevated levels of cortisol. In addition, levels of cortisol increase even further when the drinking stops. This increase occurs even before alcohol is gone from the body. The daily, heavy drinker may therefore have levels of cortisol two to three times the normal amount throughout the day and night."

Cortisol is the primary glucocorticoid in humans. Glucocorticoids are produced by the adrenal glands, two thumb-size organs that lie behind both kidneys. When a body's stress-response system is activated by stressors, usually unpredictable or fear- and/or anxiety-causing in nature, cortisol is increased. Stress-induced cortisol can focus alertness and attention, increase blood pressure, and suppress 'less necessary' bodily functions such as wound repair, bone growth, digestion and reproduction.

"Alcohol can increase cortisol through a variety of mechanisms," said Adinoff. "Alcohol directly affects many brain chemicals that signal the adrenal glands to produce and secrete cortisol. High levels of intoxication may be interpreted as general 'stress,' which could stimulate cortisol release. Finally, after drinking a lot of alcohol for a long time, the sudden stopping of drinking can produce a stressful 'withdrawal' state, which can also increase cortisol production."

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CHRONIC DRINKING INCREASES CORTISOL DURING INTOXICATION AND WITHDRAWAL

For this study, researchers examined salivary cortisol levels and breath alcohol concentrations in two groups of males: 73 alcohol-dependent patients presenting themselves for treatment in an intoxicated, withdrawal, or post-withdrawal state; and 22 abstinent alcohol-dependent patients already enrolled in a residential treatment program.

"The usual method of obtaining cortisol levels is by obtaining a blood sample," said Adinoff. "However, it is much easier for both the patient and researcher to obtain a sample of saliva rather than a blood sample ... and less painful for the patient."

Salivary cortisol is also a better measure of active cortisol. When cortisol is in the blood, it is in two forms, "bound" and "unbound." Bound cortisol is not active because it is attached to a protein. Only the unbound, or free, cortisol is physiologically active. Most of the cortisol in blood is bound. Conversely, all of the cortisol in saliva is unbound, free or active. Therefore, saliva measures of cortisol give a better picture of how much active cortisol is in the body.

Study authors found that cortisol concentrations in alcohol-dependent individuals increase during both intoxication and withdrawal, compared to abstinence. Of the 73 alcohol-dependent patients presenting themselves for treatment, 38 were intoxicated. These 38 individuals, as well as 30 non-intoxicated individuals going through acute alcohol withdrawal, had significantly increased salivary cortisol concentrations when compared to abstinent individuals. Furthermore, cortisol concentrations increased during the progression from intoxication to withdrawal.

"Up until now, it is has not been known whether cortisol remains elevated in chronic drinkers not in a laboratory setting," said Adinoff. "The confirmation that cortisol does, indeed, remain elevated throughout the drinking cycle suggests that it may be important to decrease cortisol levels during both chronic drinking and withdrawal. This suggestion is tentative, however, as it has not yet been shown that it is cortisol itself that is responsible for the medical and psychiatric problems associated with heavy drinking. Future studies should explore the relationship between elevated levels of cortisol during intoxication and withdrawal and the medical and psychiatric consequences of drinking, which may include sleep disruption, cognitive deficits, diabetes and mood disturbances."

Article is based on the following published research:

Adinoff, B., Ruether, K., Krebaum, S., Iranmanesh, A., Williams, M.J. (September 2003). Increased salivary cortisol concentrations during chronic alcohol intoxication in a naturalistic clinical sample of men. *Alcoholism: Clinical and Experimental Research, 27*(9), 1420-1428.

REPEATED ALCOHOL DETOXIFICATIONS CAN IMPAIR COGNITIVE FUNCTION

- *Patients undergoing alcohol detoxification are more likely to have seizures if they have had previous episodes of detoxification.*
- *New research confirms that repeated detoxifications can also impair cognitive function through damage to the frontal lobes.*
- *Patients with mild to moderate alcoholism who have had two or more withdrawals performed worse on maze, vigilance and delay tasks.*

Researchers and clinicians know that patients undergoing alcohol detoxification are more likely to experience seizures if they have undergone previous episodes of detoxification. Prior research has also indicated that multiple withdrawals may lead to changes in brain functioning. A study in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* confirms previous findings of neurocognitive changes in alcoholics, extends those findings to individuals with mild to moderate alcoholism, and demonstrates a relationship of those changes to multiple withdrawals.

"Results from this study support previous findings of impaired frontal-lobe function in alcoholics," said Theodora Duka, associate professor at the University of Sussex and first author of the study. "Our study adds to that by showing that such impairments can be found also in non-severe alcoholics. But its major contribution to the field is that the number of detoxifications that patients experience contributes significantly to these impairments."

"Some clinicians tend to ignore the issue of multiple withdrawals, whereas other clinicians feel they're important, having come to realize that patients who have had multiple withdrawals are much more likely to have more severe withdrawal subsequently, and probably not respond as well to medication to block the withdrawal symptoms," said Robert Malcolm, professor of psychiatry, family medicine and pediatrics, and clinical investigator at the Center for Drug and Alcohol Programs, Medical University of South Carolina. "This study squarely points out the relevance of multiple withdrawals by demonstrating some alterations in neurocognitive functioning in this group of people."

Study authors examined 85 volunteers divided into two groups: 42 abstinent alcoholics (24 males, 18 females) in inpatient treatment, and 43 social drinkers (23 males, 20 females) recruited from a university setting. The patient population was further divided into two populations based on information about prior, medically supervised detoxifications: patients with fewer than two experiences (n=36) and patients with two or more experiences (n=6). All of the subjects were asked to complete four types of tasks designed to measure executive function, which is responsible for supervising the production and execution of responses based on demands from the environment. The four tasks included a maze, which measured the ability to follow goals; a color-naming task; a vigilance task, which measured the ability to pay attention and disinhibit a pre-potent response; and a delay task, which measured the ability to wait before a response in order to receive a reward.

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REPEATED ALCOHOL DETOXIFICATIONS CAN IMPAIR COGNITIVE FUNCTION

Results indicate that repeated withdrawals from alcohol are associated with increased impairment of cognitive function, specifically, frontal-lobe damage. "The frontal lobes are extremely important for inhibiting behaviors," said Malcolm, "and are also important for tasks that require attention." The results showed that patients with two or more previous, medically supervised detoxifications performed worse than patients with less than two or no withdrawal experiences in the maze, vigilance and delay tasks.

"Compared to social drinkers," said Duka, "the alcoholics were impaired in all the tasks except for the color-naming task. The age that patients started drinking, and the amount of alcohol they used to drink up to the last six months before treatment appeared also to play a role. Only measures of the delay task, the ability to wait before a response in order to receive a reward, appeared to depend solely on the number of detoxifications."

These findings pertain to "mild to moderate alcoholics, not severe alcoholics. These were generally functioning people who, if they were seen in a clinician's office, would not appear to be cognitively impaired, but yet they are," added Malcolm.

"Another interesting finding of Dr. Duka's is an association between multiple withdrawals and higher levels of nicotine or cigarette smoking," said Malcolm, "which I think is a fascinating phenomenon and needs to be followed up on."

Duka said her findings have implications not only for individuals who have experienced multiple withdrawals from alcohol, but also the clinician who treats them. "These individuals might be more difficult to treat," she said. "When they are being helped to detoxify from alcohol, they may need extra support to prevent them from relapsing. It might even be sensible to wait a while before starting detox, if it helps to get the post-detox support organized."

"The truth of the matter," said Malcolm, "is that researchers really know very little about the effects of multiple withdrawals on cognitive function. This paper points out the relevance of clinicians asking patients about past withdrawals, the number of them, and how severe they were. Hopefully, it may influence clinicians to do further cognitive testing in order to get a sense of their patients' capabilities for rehabilitation and present and future functioning. In other words, these findings represent a clue that some patients who have had multiple withdrawals might be impaired and might have trouble with their work and in their personal lives because of their impaired thinking processes."

Article is based on the following published research:

Duka, T., Townshend, J.M., Collier, K., Stephens, D.N. (October 2003). Impairment in cognitive functions after multiple detoxifications in alcoholic inpatients. *Alcoholism: Clinical and Experimental Research, 27*(10), 1563-1573.

BLOCKING SELECTED NEUROTRANSMITTER ACTIVITY MAY DECREASE ALCOHOL CONSUMPTION

- *Neuropeptide Y (NPY) is a neurotransmitter that is integral to neurobiological functions such as anxiety, pain, memory and feeding behaviors.*
- *Researchers have found that a compound which blocks NPY activity decreases both the onset as well as the repetition of alcohol consumption.*
- *These findings have important implications for the treatment of both alcohol abuse and dependence.*

Peptides are a class of neurotransmitters, chemicals used by brain cells to communicate with each other. Neuropeptide Y (NPY) is the most abundant and widely distributed peptide, and is involved in a variety of neurobiological functions including anxiety, pain, memory and feeding behavior. Although previous animal research has implicated NPY systems in alcohol abuse and alcoholism, findings published in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* are the first to show that a compound that blocks NPY activity may be useful for alcohol treatment.

"NPY is the most potent stimulant of feeding behavior known," explained Clyde W. Hodge, associate professor in the departments of psychiatry and pharmacology at the University of North Carolina at Chapel Hill and corresponding author for the study. "For example, the primary brain region involved in control of eating is the hypothalamus. Animal studies have shown that repeated treatment of the hypothalamus with NPY produces dietary obesity in otherwise normal rats. We suspect that alcohol may usurp brain systems that evolved to perform other functions, such as eating, because these neural systems evolved long before humans discovered alcoholic beverages. Alcohol and drug abuse, therefore, can be considered disorders of consumption."

"Since NPY is a signal molecule, it produces its effects via several NPY receptors in the brain, such as the NPY-Y5 receptors," added Subhash C. Pandey, associate professor and director of Neuroscience Alcoholism Research in the Department of Psychiatry at the University of Illinois at Chicago. "This research suggests that alcohol-preferring mice may have higher levels of NPY-Y5 receptors in the brain. Other research suggests that these mice have lower NPY levels in the brain area involved in reward of alcohol drinking. It is also possible that both lower NPY levels and higher NPY-Y5 receptors in the brain may be associated with the excessive alcohol drinking behaviors of these mice."

This study uses alcohol-preferring mice called C57BL/6 to examine the effects of the NPY-Y5 receptor antagonist L-152,804 on the onset and maintenance of alcohol self-administration. "Most of the known compounds that target NPY receptors do not cross the blood-brain barrier," said Hodge. "L-152,804, however, is a novel compound that was recently shown to both cross the blood-brain barrier and block NPY-Y5 receptors."

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BLOCKING SELECTED NEUROTRANSMITTER ACTIVITY MAY DECREASE ALCOHOL CONSUMPTION

Researchers housed 59 male C57BL/6 mice in standard Plexiglass cages (four per cage) with food and water always available. Mice were trained to self-administer either alcohol (10% v/v) or water during 16-hour sessions. After four months, the mice were injected systemically with L-152,804 (0, 10, 30 or 60 mg/kg) prior to the sessions.

Results indicate that not only does L-152,804 delay the onset of alcohol self-administration, which is considered an index of relapse potential, but it also seems to reduce the reinforcing or rewarding effects of alcohol.

"The process by which drug self-administration behavior becomes repetitive is called positive reinforcement," said Hodge. "It reflects the tendency of all animals, human and non-human, to repeat responses that produce a desired outcome. In general, this process functions to sustain behavior that is essential to the individual or species, such as eating, drinking or reproduction. In this particular case, L-152,804 appeared to block the reinforcing effects of alcohol. When taken together, these results suggest that L-152,804 might reduce the motivation to start drinking as well as decrease the amount of alcohol consumed. Thus, L-152,804 might make relapse less likely and possibly dampen its consequences.

Both Hodge and Pandey said these results have clear implications for the medical management of alcohol abuse and alcoholism. "If these studies are replicable and consistently produce findings that alcohol preference and dependence are associated with increased NPY-Y5 receptors in the brain," said Pandey, "then blocking these receptors with L-152, 804 may be useful in treating alcoholism. Furthermore, since this receptor antagonist is able to delay the onset of alcohol-drinking behaviors in alcohol-preferring mice, it also has potential in preventing relapse to alcohol abuse."

"Approved medications for alcoholism such as Naltrexone," added Hodge, "may help prevent relapse but do not decrease drinking by chronic alcoholics who are actively drinking. L-152,804 has the potential to both prevent relapse and decrease active drinking. When you also consider the fact that L-152,804 can be administered orally, we believe that medications that block NPY actions at its receptors have great potential for the medical management of alcoholism."

Article is based on the following published research:

Schroeder, J.P., Iller, K.A., Hodge, C.W. (December 2003). Neuropeptide-Y Y5 receptors modulate the onset and maintenance of operant ethanol self-administration. *Alcoholism: Clinical and Experimental Research, 27*(12), 1912-1921.

PROBING THE ROLE OF THE DELTA OPIOID RECEPTOR IN ALCOHOL CONSUMPTION

- *The body's endogenous opioid system has three classes of opioid receptors: mu, delta and kappa.*
- *Previous research showed that mice lacking the mu opioid receptor do not drink alcohol.*
- *A new study shows that mice lacking the delta opioid receptor drink more alcohol.*
- *The delta opioid receptor may also play a mediating role between stress and alcohol consumption.*

The body's endogenous opioid system has traditionally been linked with peptides such as enkephalins and endorphins, which influence the brain's reward pathway to act as the body's natural response to pain. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that the endogenous opioid system may also be important for the reinforcing properties of alcohol. Researchers discovered that "knocking out" the delta opioid receptor led to an increased state of anxiety as well as an increase in drinking.

"There are three classes of opioid receptor currently recognized," said Amanda Roberts, assistant professor of neuropharmacology at The Scripps Research Institute and lead author of the study. "They are the mu, delta and kappa receptors. We had previously shown that mice lacking the mu opioid receptor do not drink alcohol under several different experimental conditions." For the current study, Roberts and her colleagues used mice produced by coauthor Brigitte L. Kieffer in France that had been genetically modified by having their delta receptor "knocked out."

"After becoming familiar with alcohol, mice lacking the delta receptor consumed more alcohol than their genetically intact counterparts (wild type mice) did," said Roberts, "suggesting that a decrease in delta receptor activity is associated with an increase in alcohol drinking behavior. This is a surprising finding as it suggests that, at least under certain conditions, the mu and delta receptors may act in an opposing manner to regulate alcohol consumption."

In addition to the endogenous opioid system's influence on the brain's reward pathway, it also plays an important role in the body's stress response. Alcohol researchers believe that stress and anxiety are important components of alcohol consumption. In fact, stress reduction is one of the most commonly reported psychosocial benefits of drinking alcohol. Another finding of Roberts' study supports a potential link among the endogenous opioid system, stress and alcohol consumption. The delta receptor knockout (KO) mice in this experiment exhibited increased anxiety prior to drinking and, in fact, seemed to use alcohol for its anxiolytic or calming effects.

"This suggests that the delta receptor," said Roberts, "while perhaps being important in directly modulating the activity of the brain's reward pathway, also may be a key player in mediating the link between stress and alcohol consumption."

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PROBING THE ROLE OF THE DELTA OPIOID RECEPTOR IN ALCOHOL CONSUMPTION

According to Tamara Phillips, professor of behavioral neuroscience at Oregon Health & Science University and the Portland VA Medical Center, the study's findings also have ramifications for those alcoholism treatment strategies that utilize opiate antagonists. Opiates are drugs derived from opium – like heroin and morphine – that act like chemicals the brain produces naturally, called endogenous (from within) opioids, which stimulate pleasurable feelings and suppress pain. Medications known as opiate antagonists bind with the brain's receptors for endogenous opioids, thus blocking the desired effects of heroin and similar drugs while having no effect themselves. Although alcohol is not an opiate-like substance, opiate antagonists like Naltrexone seem to block some of alcohol's rewarding effects.

"Drugs of abuse like alcohol," explained Phillips, "appear to activate some of the same brain neurochemical pathways as those activated by natural rewards such as food, water, sweets and sex. A key neurochemical is dopamine. Dopamine pathways play a well-documented role in alcohol reward and reinforcement. Opioids are known to moderate the activity of dopamine pathways, and it is possible that alcohol addiction is partly associated with alterations in opiate receptor-mediated processes. Animal and human studies documenting reductions in alcohol consumption by treatment with Naltrexone, an opiate receptor antagonist drug, ultimately led to its clinical utilization for the treatment of alcoholism." Phillips added that although Naltrexone is widely used in conjunction with clinical counseling, its success has been limited.

"Because this drug influences all three of the known opioid receptor subtypes: mu, delta and kappa," she said, "a worthwhile endeavor is to examine the specific roles that each of the opiate receptor subtypes might play in alcohol addiction. Naltrexone has a greater tendency to interact with mu than with delta and kappa opiate receptors. It is possible that its success in alcoholism treatment is associated with its relative affinities for these receptor subtypes, and that a better treatment agent could be developed. This study, for example, shows the importance of the delta receptor in influencing voluntary alcohol consumption."

Roberts and her colleagues plan to continue with their examination of the endogenous opioid system. They will more closely examine the brain regions and pathways responsible for the role of the mu and delta opioid receptors in alcohol's rewarding effects, as well as what role(s) the endogenous opioid system may play in addiction and relapse.

Article is based on the following published research:

Roberts, A.J, Gold, L.H., Polis, I., McDonald, J.S., Filliol, D., Kieffer, B.L., & Koob, G.F. (September 2001). Increased ethanol self-administration in 8-opioid receptor knockout mice. *Alcoholism: Clinical and Experimental Research, 25*(9), 1249-1256.

BEHAVIORAL SENSITIZATION: A NEW PERSPECTIVE ON ALCOHOLISM

- *Alcoholics may drink because they get a "bigger bang" each time they drink.*
- *This phenomenon is known as "behavioral sensitization."*
- *Behavioral sensitization is the opposite of tolerance; it is even known as "reverse tolerance."*
- *A neurochemical called MK-801 may block alcohol's sensitizing effects.*

One of the ways by which people are believed to develop alcoholism is called "behavioral sensitization" to the effects of alcohol. This is another way of saying that each time someone drinks, they may find the alcohol more rewarding. In a recent study published in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)*, researchers explained how they may have found a way to "block" the increasingly rewarding effects of alcohol.

"What we've tried to show in this study," said Rosana Camarini, the study's lead author who is conducting post-doctoral research in neurology at the University of California–San Francisco, "is that it may be possible to block behavioral sensitization to alcohol by using NMDA receptor antagonists. The specific one we studied is called MK-801."

Alcohol's effects on the glutamate system are of particular interest to researchers. Glutamate acts as one of the brain's endogenous (made within the body) excitatory systems. A subtype of glutamate receptors, the n-methyl-d-aspartate (NMDA) receptor, is highly sensitive to low doses of alcohol. Evidence indicates that alcohol may interact directly with the NMDA receptor complex. Indeed, NMDA receptors may be involved in sensitization to, tolerance of, and physical dependence on a variety of drugs, including opiates, nicotine, antidepressants and alcohol. NMDA receptor antagonists – in this case, MK-801 – appear to be able to "block" some of the pleasing effects of alcohol.

"This study provides evidence," said Clyde Hodge, assistant professor of neurology at the University of California in San Francisco, "that MK-801 blocks one of the addictive properties of alcohol, its sensitizing effects. From a perspective of therapeutics, it means that NMDA receptors could be a valid target for treatment."

To those familiar with the concept of tolerance, the phenomenon known as behavioral sensitization is intuitively confusing. Yet many aspects of the processes that underlie the transition from initial drinking to uncontrolled drinking remain unknown and under research. For example, studies of amphetamine and cocaine have shown that with repeated and intermittent administration both behavioral and neurochemical responses are progressively enhanced. This phenomenon, behavioral sensitization, contrasts with the well-known observation that repeated, frequent or continuous drug administration can lead to many diminished responses (tolerance). Indeed, behavioral sensitization is also called "reverse tolerance." Despite the potential confusion, behavioral sensitization may help explain how substances of abuse can become addicting.

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BEHAVIORAL SENSITIZATION: A NEW PERSPECTIVE ON ALCOHOLISM

"We believe that people may drink more and more because of the pleasurable and euphoric effects of alcohol," said Camarini, "and these effects increase with time. In fact, there are theories that, after time, once this phenomenon is very well established in a person, it may actually change the responses in their gene expression. That is why behavioral sensitization is difficult to reverse."

Researchers studied the effects of alcohol by measuring locomotor activity. They measured the distance that laboratory animals traveled following alcohol ingestion. Given independently, MK-801 stimulated locomotor activity, as did alcohol. When given together, however, the two substances diminished locomotor activity. This is how researchers determined that MK-801 might block the development of behavioral sensitization to alcohol as measured by locomotor activity.

"The results are not entirely anomalous," said Hodge. "But it is a curious finding that a drug that increases locomotor behavior, and acts like alcohol, would block the locomotor-activating effect of alcohol." Hodge said that a similar case of this phenomenon is the use of Ritalin for treating hyperactivity in children. "Ritalin is a stimulant," he said. "Yet it is a general finding that stimulants will decrease behavior occurring at high rates."

Both Camarini and Hodge admit that it's difficult to distinguish when, in the continuum of addiction development, sensitization and tolerance may develop and/or co-exist. Hodge speculated that sensitization might occur early on in an individual's exposure to a drug like alcohol, but noted that several ethical and practical considerations would impede testing that theory. A more procurable group would be alcoholics at risk of relapse.

"Sensitization may occur in relation to recent cessation of drinking," said Hodge. "An alcoholic who has been alcohol-free for some time may start drinking again. MK-801 could be useful, in this case, to diminish the effects of drinking."

Camarini and Hodge affirm the need for further research in this area, both to explore how something that acts like alcohol can block alcohol's effects, and also how this finding can be turned into a drug that can help alcoholics.

"We don't know if MK-801 can be used in the future as a prevention tool or as a reversal of alcoholism," said Camarini, "but we do know that it makes alcohol less appealing to someone when they drink it."

Article is based on the following published research:

Camarini, R., Frussa-Filho, R., Goldnadel-Monteiro, M., & Calis, H.M. (March 2000). MK-801 blocks the development of behavioral sensitization to ethanol. *Alcoholism: Clinical and Experimental Research, 24*(3), 285-290.