There are many factors that may cause an individual to progress from a social drinker to an alcoholic. In addition to environmental influences, there is growing evidence that genetic and environmental factors interact to influence alcohol consumption. Dr. Todd E. Thiele, a post-doctoral fellow at the Bowles Center for Alcohol Studies, has focused much of his research on a protein called neuropeptide Y (NPY), which is distributed throughout the nervous system and is believed to modulate neurons involved in feeding behavior, anxiety, and depression. As in an article in Nature in 1998, he published his findings on the role of NPY in voluntary alcohol drinking behavior. Compared to their wild-type littermates, the knockout mice consume more alcohol and the transgene mice consume less. In addition, knockout mice show less intoxication than wild-type mice following alcohol administration, and transgenic mice show more. These results provide a basis for greater exploration of the mechanisms by which NPY influences drinking, norepinephrine on the NPY receptors that are responsible for this effect. Again using knockout and transgenic mice, Thiele has found that the NPY Y1-Y2 receptor appears to mediate voluntary consumption of alcohol, and that the Y2 receptor may be involved with regulating alcohol’s intoxicating effects.

A second line of research focuses on an intracellular second messenger, cAMP-dependent protein kinase (PKA). Many neurotransmitters, including NPY and dopamine, transduce their signal through cAMP via PKA activation. Early research indicates that alcohol influences PKA function. With PKA knockout mice, Thiele showed that PKA signaling also modulates voluntary alcohol drinking and some of its intoxicating effects. Together, these research premises prompt us to ask how one step closer to mapping out the genetic patterns associated with alcoholism.

Like many aspects of life, the alcoholism of Edgar Allan Poe, the legendary American writer and father of the detective story, his best-known step closer to mapping out the genetic patterns associated with alcoholism. As an article in Nature in 1998, he published his findings on the role of NPY in voluntary alcohol drinking behavior. Compared to their wild-type littermates, the knockout mice consume more alcohol and the transgene mice consume less. In addition, knockout mice show less intoxication than wild-type mice following alcohol administration, and transgenic mice show more. These results provide a basis for greater exploration of the mechanisms by which NPY influences drinking, norepinephrine on the NPY receptors that are responsible for this effect. Again using knockout and transgenic mice, Thiele has found that the NPY Y1-Y2 receptor appears to mediate voluntary consumption of alcohol, and that the Y2 receptor may be involved with regulating alcohol’s intoxicating effects.

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Todd E. Thiele, Ph.D.

This document is supported by donations to the Bowles Center for Alcohol Studies.
rats in withdrawal from a diet of chronic alcohol voiced live into their phones as many as twice as often as control rats not undergoing withdrawal. After a year of experiments, Knapp and his colleague subsequently found that certain drugs such as the corticosteroid releasing factor antagonist CQR1000, the benzodiazepine receptor antagonist flumazenil, and the NMDA receptor antagonist MK801 mitigated withdrawal-associated anxiety in these rats. The severity of this withdrawal anxiety was not affected by the type I benzodiazepine receptor agonist diazepam, the NMDA receptor antagonist (GABA) or the cholinergic neurotransmitter nicotine. Brain Res 810:115–131.

Knapp was concerned that these experiments, involving a single, prolonged episode of exposure to alcohol, are not representative of the experience of the typical alcoholic. Most alcoholics, he noted, undergo periods of alcohol bingeing separated by periods of abstinence, and they experience repeated episodes of alcohol withdrawal. Would the severity of anxiety associated with alcohol withdrawal and its vulnerability to pharmacologic treatment differ in an animal that had undergone one withdrawal episode compared with an animal that was undergoing multiple withdrawal episodes? To answer this question, Knapp and collaborator David Overstreet turned their attention to the effects of repeated bouts of alcohol consumption on the animal withdrawal symptom of anxiety. They found that rats exposed to three 1-day regimens of alcohol-containing diet with 2 days of withdrawal between each regimen (equivalent to 3 days of moderately heavy drinking separated by periods of abstinence) showed significantly higher levels of behavioral tests than did rats exposed to diet only, or to 2 days of withdrawal exposed to ethanol continuously over 15 days with no

Alcohol withdrawal is a clinical syndrome that can affect people accustomed to regular alcohol intake when drinking is decreased or stopped completely. Alcohol has the most severe physical withdrawal symptoms of any drug of abuse, but some individuals may experience anxiety, tremors, and other symptoms of withdrawal. These symptoms can last for days or weeks, and may lead to relapse and continued alcohol use. Understanding the processes that underlie withdrawal-induced anxiety and its vulnerability to pharmacologic intervention is important in developing effective treatment strategies for alcohol dependence.

The literature on alcohol withdrawal-induced anxiety is extensive, and studies have shown that many factors contribute to the severity and duration of withdrawal-induced anxiety. The severity of withdrawal-induced anxiety is influenced by both genetic and environmental factors, as well as by the individual’s history of alcohol use. For example, individuals who have a history of chronic alcohol use tend to experience more severe withdrawal symptoms than those who use alcohol intermittently. Additionally, the severity of withdrawal-induced anxiety is influenced by the rate of alcohol consumption and the length of abstinence before withdrawal.

Understanding the processes that underlie withdrawal-induced anxiety and its vulnerability to pharmacologic treatment is important in developing effective treatment strategies for alcohol dependence. Our research is funded by the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). For more information about our research, please visit our website at www.med.unc.edu/alcohol.