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Are Binge Drinkers More at Risk of Developing Brain Damage?

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HUNT, W. A. *Are binge drinkers more at risk of developing brain damage?* ALCOHOL 10(6) 559–561, 1993.—Alcoholism is often associated with brain damage and cognitive deficits. Because drinking patterns can include periods of alcohol consumption followed by abstinence, binge drinking may enhance the possibility of brain damage. Chronic administration of ethanol leads to upregulation of *N*-methyl-D-aspartate (NMDA) and calcium receptors and increased release of glucocorticoids. NMDA-mediated mechanisms and glucocorticoid actions on the hippocampus are associated with brain damage. Thus, ethanol withdrawal may make the brain more vulnerable to damage from these mechanisms, especially with binge drinking. Therapeutic adjuncts for treating ethanol withdrawal, including NMDA, calcium, and glucocorticoid antagonists, may eventually prove useful in preventing further brain damage in alcoholism.

Ethanol Binge drinking Repeated withdrawal Brain damage NMDA Calcium Glucocorticoids

MANY alcoholics exhibit brain damage and/or cognitive deficits. The factors that contribute to the susceptibility of brain damage are not well understood (22). Alcoholics encounter periodic interruptions of drinking (i.e., binge drinking) that can result in repeated withdrawal syndromes. Because of this pattern of drinking, a number of animal and some human studies have investigated the consequences of repeated ethanol withdrawal on brain damage and behavior.

Early studies on alcohol-induced brain damage in rodents suggest that damage after chronic ethanol administration does not occur during exposure but rather at some time after withdrawal (24,28,31). Functionally, considerable evidence from animals indicates that multiple exposures to ethanol result in a higher incidence of seizures during withdrawal than are found after continuous exposures of the same duration (5,7,9, 11,17,28). Such observations have led to the development of a kindling hypothesis to explain this phenomenon (3). "Kindling" refers to the result of intermittent low-intensity stimulations where subsequent intensities or frequencies of responses, such as seizures, increase. Support for the kindling hypothesis has also been found using human subjects, where a higher percentage of subjects with previous detoxifications exhibited seizures during withdrawal (8).

Repeated withdrawal syndromes have also been associated with increased cognitive deficits. Rodents subjected to several successive ethanol exposure and ethanol withdrawal periods exhibited impaired performance on a shuttlebox avoidance task (6,15). In humans, memory deficits have been correlated with the number of alcohol withdrawals, defined as a 24-h period of abstinence (16). Taken together, the studies reported suggest that binge drinking (each episode lasting days to weeks) may be one factor making one more susceptible to brain damage.

Two general lines of biological evidence suggest that binge drinkers may be more at risk of developing brain damage and cognitive dysfunction. One line of evidence is derived from the apparent role that *N*-methyl-D-aspartate (NMDA) receptors play in excitotoxicity and the actions of ethanol (12). Excitotoxicity related to brain damage involves an excessive NMDA-stimulated influx of calcium into neurons, followed by neurodegenerative processes and cell death.

Neurochemical and electrophysiological techniques have shown that acute ethanol exposure not only inhibits NMDA receptors (20,26), but also protects cultured cells from damage and death (10,27) and prevents calcium accumulation (20) induced by exposure to NMDA. On the other hand, chronic treatment with ethanol leads to an upregulation of NMDA receptors in several areas of the brain including the hippocampus (18), enhanced NMDA-mediated calcium influx (23), and increased NMDA-mediated neurotoxicity of cultured cerebral cortical neurons (12). In addition, calcium channels are upregulated after chronic ethanol administration (13). Thus, rather than being directly cytotoxic, ethanol is protective while it is present. However, after withdrawal from chronic ethanol administration, upregulated NMDA and calcium receptors, followed by increased calcium influx, may make the brain

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especially vulnerable to the cascade of events that can lead to cell damage and death.

The other line of evidence suggesting that binge drinkers are more at risk of brain damage is related to excessive glucocorticoid release during a withdrawal syndrome. Under such circumstances, a number of stressful events can occur, including seizures.

Increasing evidence indicates that excessive glucocorticoid release induced by stress or a number of neurological insults, including excitotoxins, ischemia, and seizures, can damage neurons in the hippocampus (29,36,37). Increased glucocorticoids directly affect hippocampal neurons through Type II (glucocorticoid), but not Type I (mineralocorticoid), corticosteroid receptors (30), and the damage can be blocked by a Type II antagonist or adrenalectomy (38). In addition, damage may involve an inhibition of glucose transport by glucocorticoids into hippocampal cells (21). Such an action would block energy-dependent processes. Supplementation with carbohydrates reduces the damage (35).

Finally, the neurotoxicity of glucocorticoids appears to involve excessive activation of the NMDA receptor. This effect may arise as a result of inhibition of glutamate uptake, an energy-dependent process, by hippocampal glial cells (43) and the subsequent accumulation of glutamate in the synapse (39). In further support, NMDA receptor inhibition blocks glucocorticoid-induced brain damage (2). Consequently, ethanol-mediated glucocorticoid release might exacerbate the actions of ethanol on the NMDA receptor.

Several lines of research support the hypothesis that ethanol exposure and withdrawal could increase the release of glucocorticoids to enhance the possibility of hippocampal damage. First of all, both acute and chronic ethanol administration is associated with an increased release of glucocorticoids in both experimental animals and humans (14,32,42). The chronic effect of ethanol on blood glucocorticoids may also be influenced by stressful withdrawal states. Although the rise in blood glucocorticoid concentrations after acute ethanol administration is reversible with the elimination of ethanol (19), the effect can last several days after withdrawal from chronic administration (1,4,42). Consequently, the damaging effects of ethanol could be prolonged through the actions of glucocorticoids and may be related to stress associated with ethanol withdrawal, especially when seizures are present.

Only one study addressed whether long-term ethanol administration affects glucocorticoid receptors (33). Ethanol administration for 20–24 weeks did not affect binding to either Type I or Type II receptors. However, with this regimen of ethanol exposure no differences in blood corticosterone concentrations were found, even though hippocampal damage was present and the animals were not apparently physically dependent (44). Thus, hippocampal damage can occur in the absence of withdrawal seizures, elevated glucocorticoids, and alterations in glucocorticoid receptors.

Manipulating corticosteroid levels has been reported to alter seizure susceptibility during ethanol withdrawal (40,41). Adrenalectomy decreases the incidence of withdrawal seizures, whereas glucocorticoid replacement enhances seizures. In addition, withdrawal seizure-prone mice have more severe convulsions after both acute and chronic ethanol administration when treated with a glucocorticoid but have less severe convulsions after inhibition of glucocorticoid synthesis (34). Withdrawal seizure-resistant mice are unaffected by these treatments after ethanol administration. Thus, increased glucocorticoid release might contribute to ethanol withdrawal-induced seizures.

With the NMDA and glucocorticoid mechanisms in mind, how might binge drinking increase the vulnerability to ethanol-induced brain damage? One danger to binge drinkers may arise as a result of several factors, including the wide range of ethanol concentrations found in the brain with each binge and the number and frequency of binges. Essentially, with an increasing number and frequency of binges, the brain could have a greater exposure to the potentially harmful effects of upregulated NMDA and calcium receptors and glucocorticoid exposure.

Another danger of brain damage to binge drinkers may result from multiple ethanol withdrawal syndromes, especially those not properly treated, and stress-induced responses to them. Several studies indicate successive bouts of high ethanol intake and abstinence lead to increasingly more severe withdrawal syndromes (5,7,9,17,28). Consequently, repeated, elevated glucocorticoid concentrations after ethanol withdrawal might further damage the brain through repeated increases in NMDA-mediated calcium influx.

In summary, upregulated NMDA and calcium receptors and elevated glucocorticoid levels represent two mechanisms by which binge drinkers may be at enhanced risk of developing brain damage. Furthermore, these mechanisms may be interactive, whereby glucocorticoids could intensify responses of already overactive NMDA mechanisms.

In light of these findings, antagonists of NMDA, calcium, and/or Type II glucocorticoid receptors may be potentially useful therapeutic adjuncts in the treatment of ethanol withdrawal. Evidence has been reported that NMDA and calcium antagonists can suppress ethanol withdrawal seizures (18,25). It is possible, therefore, that these agents may also serve to protect the brain from damage resulting from multiple withdrawal syndromes and overactive NMDA receptors and concomitant calcium influx. Further research will be needed to verify this possibility.

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