Alcohol & Alcoholism, Vol. 31, Suppl. 1, pp. 17–25, 1996

ALCOHOL REINFORCEMENT AND NEUROPHARMACOLOGICAL THERAPEUTICS

MICHAEL J. LEWIS

Department of Psychology, Weiss Hall (265-66), Temple University, Philadelphia, PA 19122, USA

(*Received* 23 *August* 1995)

Abstract — The pleasant subjective effects produced by alcohol undoubtedly reinforce drinking behaviour. Alcohol positively reinforces or rewards drinking by producing a mild euphoria. Alcohol also has anxiolytic effects that negatively reinforce drinking. The reinforcing effects of alcohol are mediated by several neurochemical systems, with dopamine and serotonin playing major roles in reward and the γ-aminobutyric acid–benzodiazepine receptor system playing a major role in negative reinforcement. Research from our laboratory suggests that the behavioural effects of alcohol change when blood alcohol levels are changing and that these changes correspond to alterations of specific neurochemical systems. Behavioural activation and reward effects appear to occur as blood alcohol concentrations (BACs) increase. Depressive and aversive effects of alcohol occur during the period when BACs decrease. The observed correlation between behavioural and neuropharmacological changes and alcohol consumption suggest that alcohol produces a unique cascade over time that may provide clues to its long-sought specific mechanisms of action. In alcohol-dependent individuals, chronic exposure to alcohol may alter the function and communication between the liver, brain and other vital organ systems involved in hunger and the maintenance of nutrition. Under such conditions, the importance of alcohol in the diet may be enhanced such that hunger signals in the alcohol-dependent individual motivate the consumption of alcohol. Therefore, hunger for alcohol may provide an additional source of reinforcement. Endogenous opioid mechanisms may be important in this form of alcohol reinforcement

INTRODUCTION

Alcohol is undoubtedly consumed because it has pleasant subjective effects, which are produced by its basic actions on the central nervous system. These effects are the 'pharmacological' properties that reinforce alcohol-seeking and alcohol-drinking behaviour. Alcohol positively reinforces or rewards drinking by producing a mild euphoria. This is the 'buzz' or 'high' that youthful drinkers describe when they 'guzzle' a beer. It is also a major reason why social and moderate drinkers enjoy alcoholic beverages. Alcohol also reduces anxiety and the aversion associated with stressful life situations. This anxiolytic effect negatively reinforces alcohol consumption by allowing the drinker to remove or reduce the aversive physiological stimuli that are the well-known symptoms of anxiety. In addition to alcohol's basic effects, its consumption also may be secondarily reinforced by association with drinking during social situations which are themselves rewarding. This source of reinforcement may be particularly potent in some individuals. It is, however, a quite complex and relatively under-researched area that will not be discussed in this supplement.

BASIC NEUROBIOLOGICAL MECHANISMS OF ALCOHOL

Evidence of the rewarding effects of alcohol comes from basic research involving the following behavioural paradigms: oral self-administration (Samson *et al.*, 1988), conditioned place preference (Marglin *et al.*, 1988) and electrical brain stimulation reward (BSR) (Lewis and June, 1990). While less easily interpreted, an increase in locomotor activity has been considered a demonstration of the rewarding effects of alcohol (Lewis and June, 1990) as well as other drugs of abuse (Wise and Bozarth, 1987). Research in our laboratory has shown that alcohol produces reinforcement via oral self-administration (June *et al.*, 1994), enhancement of BSR (Lewis and Phelps, 1987; Lewis and June, 1990), and increased locomotor activity (Lewis and June, 1990).

The rewarding effects of alcohol have been

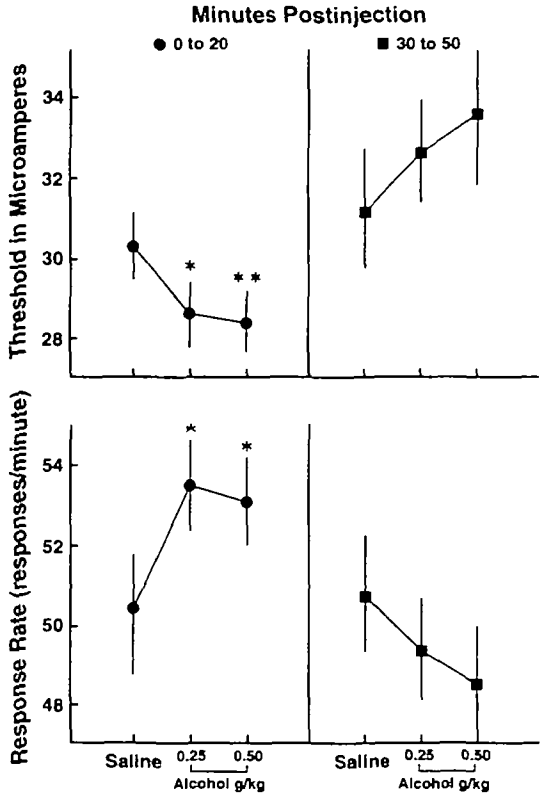

Fig. 1. Effects of two doses of alcohol on lateral hypothalamic brain stimulation reward threshold and response rate in rats measured at 0–20 and 30–50 min after intraperitoneal injection of alcohol. $^{*}P < 0.05$ versus saline-treated control group; $^{**}P < 0.01$ versus saline-treated control group. (Adapted with permission from Lewis and June, 1990.)

found to occur most clearly within a specific period after administration. Our research on BSR and the locomotor effects of alcohol strongly indicates that reward effects occur during the period immediately following administration of alcohol, when blood alcohol concentrations (BACs) are ascending. The threshold for BSR (measured by electrical current level) was found to be reduced and the response rate was found to be increased during the first 20 min after intraperitoneal injection of alcohol in rats (Fig. 1) (Lewis and June, 1990). Likewise, open-field locomotor activity was increased during the first 10 min after alcohol injection (Fig. 2) (Lewis and June, 1990). These effects were not observed during later periods of testing after alcohol injection, i.e. at 30–50 min with BSR (Fig. 1) and 30–40 min with locomotor activity (Fig. 2).

Figure 3 (Lewis and June, 1990) shows BAC after intraperitoneal injection of alcohol into three rats. BACs ascend during the first 10–25 min and then slowly descend. The intervals of enhanced BSR and locomotor activity correspond to intervals of increasing BAC. When BAC is decreasing, no enhancement of BSR is found and locomotor activity is depressed. Therefore, it is conceivable that drinking is rewarded initially by the mild euphoria that alcohol first produces and that the memory of this euphoria is an incentive for continued drinking. Moreover, continued drinking subsequently is rewarded by the return of the euphoria as BAC increases. Research with human subjects also confirms that alcohol has mild euphoric effects. Lukas and colleagues (Lukas *et al.*, 1986; Lukas and Mendelson, 1988) have shown that the strongest positive subjective effects of alcohol consumption occur when BAC is increasing.

A second action of alcohol that may reinforce drinking behaviour is the reduction of anxiety or stress. These effects are not found under all situations of alcohol consumption in studies involving human subjects. Experiments using animals and employing anticonflict tests (i.e. animals are presented with the possibility of engaging in a behaviour that has both pleasant and aversive consequences) are widely considered to be animal models of anxiety and also have shown various results. Several more recent experiments (Lister, 1988) using the plus- or X-maze seem to confirm previous research based on the modified Geller–Seifter passive-avoidance paradigm (Koob *et al.*, 1986), indicating that alcohol does increase conflict-suppressed behaviour in rats and mice. The reduction of anxiety or conflict then would negatively reinforce drinking by allowing the drinker to escape from the aversiveness of anxiety and stress.

BRAIN NEUROCHEMICAL MEDIATION OF ALCOHOL REINFORCEMENT

Neurobehavioural research indicates that the behavioural effects of alcohol are mediated by several specific neurochemical systems. Results from neuropharmacological studies of alcohol self-administration, locomotor activity and BSR

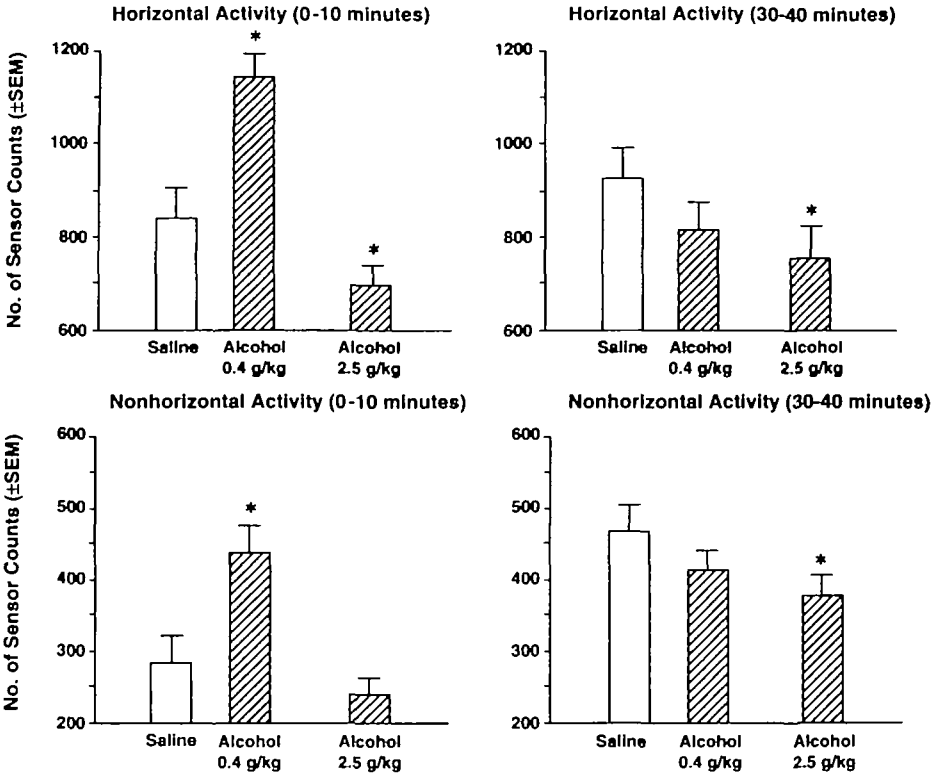

Fig. 2. Horizontal (primarily ambulation) and non-horizontal (i.e. rearing up in the air) open-field locomotor activity of rats with low levels of locomotor activity measured at 0–10 and 30–40 minutes after intraperitoneal injection of alcohol. *$P < 0.05$ versus saline-treated control group (Adapted with permission from Lewis and June, 1990.)

suggest a complex mediation of these behaviours, with prominent but differential roles being played by dopamine (DA) and serotonin (5-HT) mechanisms in the brain. Like other drugs of abuse, low doses of alcohol increase extracellular DA concentrations in the nucleus accumbens (Imperato and Di Chiara, 1986), although this increased concentration is less than that produced by cocaine (Di Chiara and Imperato, 1988). In addition, collaborative research (Lewis *et al.*, 1990) using 2-deoxyglucose autoradiography shows that alcohol increases functional brain activity in regions that are rich in DA, most notably the olfactory tubercle and the nucleus accumbens. The increase in both DA concentration and functional brain activity in areas of the ventral striatum occurs during the first 20 min after alcohol administration, which corresponds with the period during which BAC is increasing. These effects also correspond to the period when

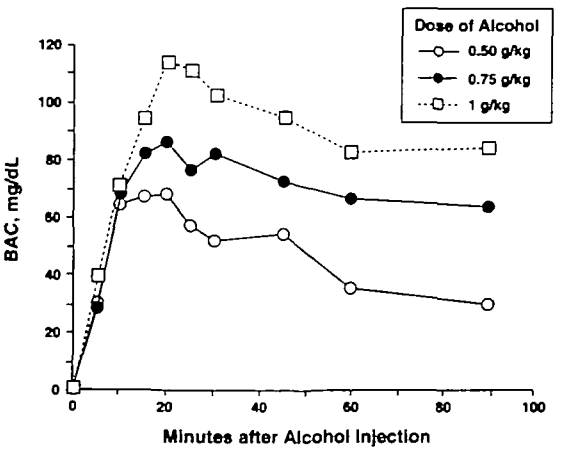

Fig. 3. Blood alcohol concentration (BAC) curve of three rats given 0.50, 0.75 and 1.0 g/kg of alcohol intraperitoneally. (Adapted with permission from Lewis and June, 1990.)

alcohol enhances locomotor activity and BSR as discussed earlier.

Recent studies show that when low doses of alcohol are combined with cocaine, a DA agonist, BSR performance is enhanced (Lewis and June, 1994). This research suggests that DA may be a common neurochemical mechanism involved in the reward produced by both drugs. Current research on the role of DA in drug reward has begun to focus on specific DA receptors. Some research has suggested a role for the D_2 receptor in the rewarding effects of alcohol (McBride *et al.*, 1990).

5-HT also appears to play a major role in alcohol's reinforcing effects. 5-HT reuptake inhibitors, which enhance its neurotransmission, appear to decrease alcohol consumption (for reviews, see McBride *et al.*, 1989). The role of 5-HT in alcohol reinforcement is probably quite complex, because there are diverse types and subtypes of 5-HT receptors. It appears that several of the known 5-HT receptors produce inhibitory behavioural actions. Enhancement of these receptors (e.g. use of 5-HT reuptake inhibitors) generally decreases alcohol consumption.

Among the 5-HT receptors, the 5-HT_3 receptors are quite different in that they are generally excitatory. The 5-HT_3 receptors, which belong to the family of ligand-gated ion channels, appear linked to alcohol's rewarding actions in the brain. Selective antagonists for these receptors block alcohol-induced increases in DA concentration in the nucleus accumbens, even when the alcohol is locally administered (Carboni *et al.*, 1989; Wozniak *et al.*, 1990). This suggests that 5-HT_3 receptors are important to alcohol-induced increases in the DA concentration in the nucleus accumbens and that these receptors are found in this region of the brain. Whether alcohol's effects on the DA system in the ventral striatum are also produced via 5-HT_3 receptors remains to be determined.

Currently, there is considerable interest in the role of endogenous opioid neuropeptide systems in the effects of alcohol, which include the craving for and rewarding effects of alcohol. The opioid antagonist naloxone reduces alcohol consumption (Reid and Hunter, 1984; Froehlich *et al.*, 1990; Weiss *et al.*, 1990). Although the effects of opioid agonists, such as morphine, have been variable, there is evidence that low doses of morphine increase alcohol consumption (Reid and Hunter, 1984). Research on the role of opioid mechanisms in alcohol's effects on locomotor activity and BSR have not been investigated. Recent controlled clinical studies suggest that the long-acting opioid antagonist naltrexone may be effective in the treatment of persons with alcoholism (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992). (See the section on Alcohol Reinforcement in the Alcohol-Dependent Individual for further discussion.)

Research on the γ-aminobutyric acid–benzodiazepine (GABA) receptor system suggests a prominent role of this complex system in mediating the locomotor depressant and anxiolytic effects of alcohol. The GABA receptor is a complex ligand-gated chloride channel with multiple binding sites for compounds that modulate the influx of chloride ions. The binding of benzodiazepine agonists, antagonists, and inverse agonists modulates GABA activity at its receptor. Considerable interest has been focused on this receptor complex since it was discovered that the benzodiazepine receptor inverse agonist Ro15-4513 can reverse and antagonize alcohol's intoxicating, locomotor and anticonflict effects (Suzdak *et al.*, 1986). More recent research shows that alcohol potentiates GABA-induced increases in chloride influx at $GABA_A$ receptors in discrete regions of the brain such as cerebellar Purkinje's cells (Lin *et al.*, 1991). These cells may play a key role in alcohol's locomotor effects. Recent research has focused on the specificity of the $GABA_A$ receptor subunits in determining which brain areas are most sensitive to alcohol. Receptors with the alpha-6 subunit appear to be important in mediating Ro15-4513's antagonism of alcohol's effects (Morrow *et al.*, 1991).

Other research (Lovinger *et al.*, 1989; Tsai *et al.*, 1995) suggests the role of the excitatory neurotransmitter glutamate, and specifically, the *N*-methyl-D-aspartate (NMDA) receptors, in the behavioural effects of alcohol. These include the loss of memory and motor coordination as a consequence of intoxication. Although the roles of NMDA and other glutamate receptor systems are undoubtedly important, they do not appear to play a major role in alcohol reinforcement.

The neurochemical data discussed above suggest that alcohol produces many effects on key neurotransmitter systems in the brain. It is difficult to discern any specificity in this broad spectrum

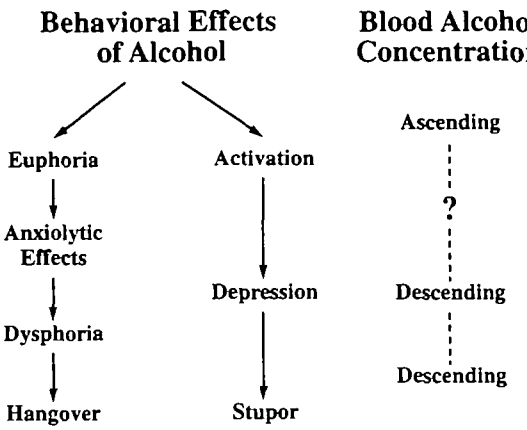

Fig. 4. The relationship between behavioural effects of alcohol and blood alcohol concentration (BAC).

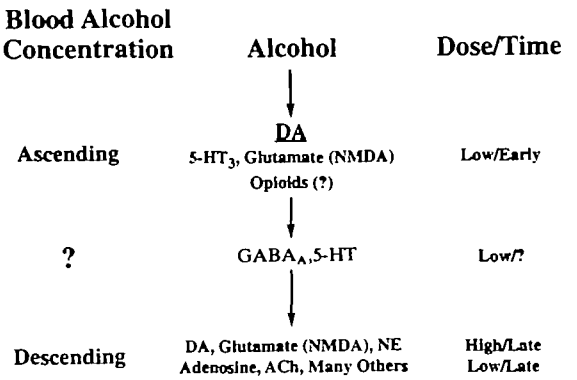

Fig. 5. The relationship between the neurochemical and behavioural cascades. NE = noradrenaline, ACh = acetylcholine. High and Low = doses of alcohol. Early = effects during the first 20 min. Late = effects after 20 min.

of effects. However, when the various behavioural effects produced by consumption of even very small quantities of alcohol are considered, such diverse neurochemical effects seem less bewildering. Stimulation, euphoria, anxiolytic effects, depression, dysphoria, and intoxication all may be experienced in a drinking session depending on the quantity and concentration of alcohol consumed as well as the period of consumption.

Our research (Lewis and June, 1990; Lewis *et al.*, 1990) suggests that the behavioural effects of alcohol change during the period when BACs rise and fall (Fig. 4) and that these changes correspond to alterations of specific neurochemicals. The behavioural activation and reward effects appear to occur when BACs are increasing; the depressive and aversive effects of alcohol appear to occur when BACs are decreasing. Temporal changes in 2-deoxyglucose metabolic activity, microdialysis-measured neurotransmitter concentrations and neuropharmacological responses suggest that a neurochemical cascade corresponds to a behavioural cascade over time (Fig. 5). Further research on the correspondence of the neurochemical changes with the variation in behavioural effects of alcohol may provide clues to its long-sought specific mechanisms of action.

ALCOHOL REINFORCEMENT IN THE ALCOHOL-DEPENDENT INDIVIDUAL

The mechanisms discussed above mediate the reinforcing effects of alcohol in those who drink socially, abuse alcohol without being alcohol-dependent, or are alcohol-dependent. Among alcohol-dependent individuals, however, drinking may have an additional motivational component. Long-term exposure of the brain, liver, and other vital organ systems to alcohol appears to be another possible mechanism for the reinforcement of drinking. Such exposure may change the essential functioning of the brain and vital peripheral organ systems. The deterioration of these organ systems is known to occur in patients with long-term alcohol dependence. Before the development of severe pathology, such as alcohol-related hepatitis, cirrhosis and encephalopathy, there may be major functional changes in the brain, liver and pancreas, as well as communication between these organs that may produce a disruption of the vital signals about the nutritional status of the individual. Under such circumstances, the importance of alcohol in the diet may be enhanced.

Alcohol is the only drug of abuse that has any nutritional value. It provides calories (~80 calories per ounce) that are inconsequential in the non-dependent drinker. During the long-term, high-level exposure to alcohol found in alcohol-dependent individuals, the calories, and perhaps other physiological effects of alcohol, may become increasingly significant to the individual's sense of well-being. Specific regions of the brain (e.g. hypothalamus) work in concert with key information emanating from the liver, pancreas, and upper gastrointestinal tract to control food intake

and maintain nutritional balance. Because of the functional changes (mainly deterioration) in all of these systems, especially in the brain and the liver, alcohol may shift from a low- to a high-priority food substance. Hence, alcohol-dependent individuals may develop a nutritional 'need' for alcohol that further reinforces alcohol consumption.

The need and motivation that alcohol produces then would establish the conditions under which alcohol might function as a negative reinforcer (i.e. permit the drinker to escape from the 'hunger' for alcohol). This negative reinforcement situation is quite different from that produced by the presence of physical dependence. Although the role of physical dependence in motivating continued drinking in the alcohol-dependent individual has been doubted by many researchers and clinicians, the relief from alcohol withdrawal symptoms produced by drinking would be an additional form of negative reinforcement.

While the merit of this hypothesis awaits more direct support, there are a number of promising findings that suggest that alcohol intake may be controlled by mechanisms similar to those that mediate food intake and maintain nutritional balance. First, there are a number of similarities between alcoholism and obesity, which is the most common eating disorder. Both involve problems of controlling intake. Obese individuals consume excess amounts of calories, usually in the form of highly palatable fat- and carbohydrate-rich foods. Moreover, the normal physiological signals that elicit eating and later produce satiety are not effective. Likewise, drinking among alcohol-dependent individuals is uncontrolled and the calories derived from alcohol may eventually make up as much as 50% of their total caloric intake (Lieber, 1990). Recovering alcohol-dependent individuals frequently crave highly palatable foods (e.g. sweets), particularly during periods when the craving for alcohol is highest.

The physiological decline experienced by alcohol-dependent individuals suggests the development of major nutrient deficiencies and alterations in body metabolism (Fig. 6). During the period when severe liver damage becomes apparent, there are a number of deficits in various organ systems, including decreased blood flow through the liver, decreased gastric motility in the small intestine, pancreatic insufficiency and hyperglycaemia, and impaired transport of key nutrients (glucose, amino acids, thiamine, electrolytes, vitamin B_{12} and calcium) (Lieber, 1988, 1990). The liver becomes fatty and distended and, with heavy long-term drinking, it eventually becomes inflamed and fibrous and subsequently develops alcohol-related hepatitis and cirrhosis (Lieber, 1988, 1990). This functional decline alters the critical communication between the liver and the brain concerning nutritional status. Under these conditions, the nutrient deficiency produces a chronic state of need in which a ready source of calories becomes the highest in demand.

Early Functioning	Later Functioning
Brain-liver healthy and normal communication	**Brain-liver reduced functioning**
Monitor nutrient intake (eg, glucose levels)	Monitoring and communication altered (?)
Preference for essential nutrients *high*	**Preference for essential nutrients *low***
Preference for alcohol *low*	**Preference for alcohol *high***

Fig. 6. Brain–liver mechanism in hunger.

Foods such as sweets and fats are preferred by obese individuals and those with diabetes under such deficit conditions; however, alcohol may become the preferred 'food' in the alcohol-dependent individual, because it produces immediate signals that nutrients are being provided. The basis of these signals may come from the following sources: (1) an immediate release of insulin that makes circulating nutrients available to cells; (2) positive feedback to the brain that key nutrients are being provided through the increased availability of calories; (3) alcohol directly stimulating neurons, which convey the status of glucose and other nutrients to the brain; and (4) the fact that alcohol supplies some calories. These messages and perhaps others may cause alcohol-dependent individuals to sense falsely that alcohol is meeting their nutritional needs. This might be seen after periods of brief abstinence, such as sleeping. Many alcohol-dependent individuals awaken 'needing a drink'. The consumption of alcohol

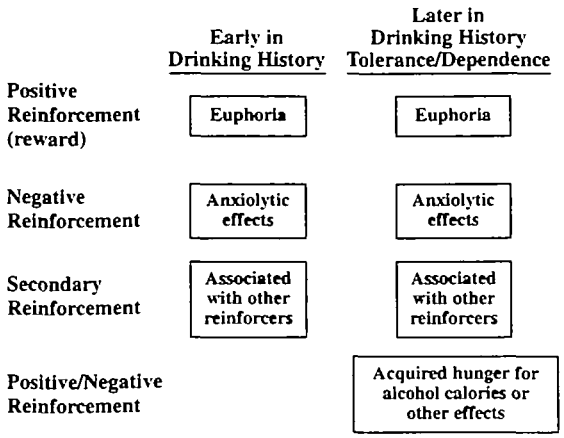

Fig. 7. Alcohol reinforcement with long-term drinking.

makes them feel 'normal'. Thus, alcohol-dependent individuals experience a hunger for alcohol, and alcohol would reinforce drinking behaviour in the same way that, under normal conditions, food reinforces behaviour that leads to eating. This reinforcement would not negate the reward of euphoria or the negative reinforcement of anxiety reduction discussed earlier; however, these consequences become secondary to the basic hunger for alcohol in the alcohol-dependent individual (Fig. 7).

The neurochemical mediation of food intake parallels that of alcohol reinforcement. Although there appear to be multiple systems involved in both food intake (Halmi, 1995) and alcohol reinforcement, the role of the endogenous opioid system is important, especially in pathological situations. The opioid agonists (the enkephalins, β-endorphin, and morphine) increase food and alcohol consumption (Reid and Hunter, 1984). In addition, the opioid antagonist naloxone reduces food intake in non-obese subjects (Margules, 1978) and, to a greater extent, in obese subjects (Margules *et al.*, 1978). Naloxone also reduces alcohol consumption and reinforcement (e.g. Reid and Hunter, 1984; Marfaing-Jallat *et al.*, 1983; Froehlich *et al.*, 1990). Recent research indicates that delta- and kappa-opioid receptors may play key roles in alcohol reinforcement and food intake, respectively. For example, the kappa-opioid agonist dynorphin is a more potent stimulant of food intake than are mu-opioid agonists (Morley *et al.*, 1986). Delta-opioid receptors may be crucial to the reinforcing actions of alcohol (Froehlich *et al.*, 1991). More research on these systems and their interaction with other important neurochemical systems (e.g. DA, 5-HT and noradrenaline) is necessary to delineate their roles in the complex mediation of food intake and alcohol reinforcement in both dependent and non-dependent individuals.

CONCLUSIONS AND COMMENTS

Alcohol produces both reward and negative reinforcement by its production of mild euphoria and reduction of anxiety, respectively. These basic effects reinforce drinking behaviour in both alcohol-dependent and social drinkers, and tend to produce alcohol abuse. These effects are mediated in the brain by a neurochemical cascade that involves several neurochemical systems. The neurochemical cascade mediates the reinforcing effects of alcohol, as well as its depressant and aversive actions. DA release in the ventral striatum appears to be important in the reward produced by alcohol; 5-HT release appears to antagonize it. $GABA_B$ mechanisms also appear to play a major role in the anxiolytic effects of alcohol. Endogenous opioid mechanisms may interact with these systems in the reinforcing actions of alcohol.

The reinforcement that alcohol produces in alcohol-dependent individuals, however, may involve an additional more compelling source of reinforcement that is produced when alcohol-dependent individuals develop a hunger for alcohol. This hunger may be produced by long-term exposure to alcohol that changes the function of the brain and vital peripheral organ systems. Under conditions of long-term exposure to alcohol, the dynamics of nutritional requirements change as vital organ systems deteriorate. It is hypothesized that the role of alcohol as a nutrient and as an indicator of nutritional status becomes more important during this process of change. The alcohol-dependent individual, therefore, develops a need to consume alcohol to restore a sense of homeostatic balance and comes to prefer it over other nutrients. This sense of basic nutritional need reinforces alcohol consumption and eventually becomes more important to the alcohol-dependent individual than the euphoric and

anxiolytic properties of alcohol. Endogenous opioids may play the most important role in the mediation of these effects.

In conclusion, the research discussed in this paper suggests that the behavioural effects produced by alcohol are mediated by multiple neurochemical systems and that some of these effects provide the basis for reinforcing alcohol consumption. Pharmacotherapeutic agents that are designed to modify the neurochemical basis of the various types of reinforcement may prove to be valuable adjuncts in the treatment of alcohol abuse and alcoholism.

Acknowledgements — This work was supported in part by grants AA0623 and RR08016 and by funding from Temple University

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