

THE ROLE OF NEUROTRANSMITTERS IN ALCOHOL DEPENDENCE: ANIMAL RESEARCH

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Abstract — Animal studies have demonstrated that alcohol changes neurotransmitter concentrations in the brain. These changes in levels of dopamine, serotonin, γ -aminobutyric acid (GABA), endogenous opioid peptides, and noradrenaline are associated with activation of reward centres in the brain. It is this property of alcohol that is believed to be responsible for the reinforcing effect of alcohol consumption in rats. One class of neurotransmitters, the endogenous opioid peptides, are believed to play an important role in alcohol reinforcement. This view is supported by the reduced preference for alcohol consumption found in rats given an opiate agonist. The widely distributed inhibitory neurotransmitter GABA is also believed to play a fundamental role in mediating the effects of alcohol. A better understanding of the mechanisms that support alcohol dependence in animals offers hope for the development of pharmacological interventions to block these mechanisms, an approach that is now being explored in humans.

INTRODUCTION

Animal studies have shown that acute and chronic alcohol consumption can affect neurotransmitter concentrations in the brain, especially those of dopamine, noradrenaline, serotonin, endogenous opioid peptides, and γ -aminobutyric acid (GABA) (Tabakoff, 1977; Littleton, 1978; Imperato and Di Chiara, 1986; Gewiss *et al.*, 1991). Studies have also shown that alcohol activates reward centres in the central nervous system that stimulate the desire for drinking. However, there are no known receptors for alcohol in the brain (Reid and Hunter, 1984). Therefore, alcohol must react in some way with receptors for known neurotransmitters, especially those that act upon central neural systems involved in positive reinforcement (Reid and Hunter, 1984). It appears that dopamine, serotonin, endogenous opioids and GABA are the neurotransmitters most associated with activation of alcohol reward centres in the central nervous systems of rats (Fibiger, 1978; Wise and Bozarth, 1982; Khatib *et al.*, 1988; Benjamin *et al.*, 1991; Froehlich *et al.*, 1991; Yoshimoto *et al.*, 1992).

NEUROTRANSMITTER CHANGES IN THE BRAIN AFTER ACUTE AND CHRONIC ALCOHOL CONSUMPTION

Table 1 summarizes the central neurotransmitter changes affected by chronic alcohol con-

sumption and by alcohol withdrawal. Acute alcohol consumption enhances the release of serotonin [5-hydroxytryptamine (5-HT)], GABA and taurine, and results in increases in chloride flux and decreases in neuronal excitability in rats (Tabakoff and Hoffman, 1992; Yoshimoto *et al.*, 1992; Dahchour *et al.*, 1994). However, chronic alcohol consumption decreases serotonin release and increases concentrations of endogenous opioid peptides, while increasing the number of glutamate binding sites in synaptosomal membranes (Carmichael and Israel, 1975; Michaelis *et al.*, 1978). In addition, the numbers of muscarinic cholinergic receptors and β -noradrenergic receptors, neuronal calcium entry, and neuronal excitability are also increased in the brain after chronic alcohol consumption (Karoum *et al.*, 1976; Tabakoff, 1977).

ALCOHOL REWARD SYSTEMS IN THE BRAIN

Animals will repeat a behaviour that elicits a reward, and Koob (1992) and Yoshimoto *et al.* (1992) have reported that alcohol activates neurophysiological reward pathways in animals. It has been suggested that the neurotransmitter dopamine plays a key role in the neurophysiological changes that occur after alcohol consumption (Koob, 1992). In the rat, systemic administration of alcohol increases extracellular concentrations of dopamine in the nucleus accumbens region of

Table 1. Neurotransmitter changes in the brain after acute and chronic alcohol consumption and alcohol withdrawal

Acute consumption	Chronic consumption	Withdrawal
↓ AChE	↑ AChE muscarinic receptors	Cholinergic antagonist (motor impairment)
↓ NA	↑ β -NA receptors	β -Blockers
↑ 5-HT	↓ 5-HT	Pro-serotonergic drugs (reuptake-blocking antidepressants)
↓ Opiates	↑ Opiates (sensitive to enkephalins)	Opiate antagonist (naloxone)
↑ Inhibitory amino acids (GABA, taurine)	↑ Excitatory amino acids (glutamate aspartate)	GABA _A agonist, GABA _B antagonist, NMDA antagonist
↑ Cl ⁻ flux	↑ Ca ²⁺ entry	Ca ²⁺ channel blockers (inhibition of Ca ²⁺ channels)
↓ Neuronal excitability	↑ Neuronal excitability	

↑ = increase; ↓ = decrease; AChE = acetylcholinesterase; NA = noradrenergic; Ca²⁺ = calcium; Cl⁻ = chloride ion; NMDA = *N*-methyl-D-aspartate; 5-HT = serotonin.

the brain (Imperato and Di Chiara, 1986), and it appears that dopamine must be released into the nucleus accumbens before the rewarding properties of alcohol can be activated (Wise and Bozarth, 1982). For example, dopamine receptor antagonists reduce lever pressing for alcohol and alcohol drinking in non-deprived rats (Pfeffer and Samson, 1985, 1986, 1988).

THE ROLE OF THE ENDOGENOUS OPIOID PEPTIDES IN ALCOHOL REINFORCEMENT

The endogenous opioid peptides found in the central nervous system of humans and other mammals are divided into three families: the enkephalins, the endorphins, and the dynorphins. Each family of peptides is derived from a distinct precursor polypeptide, e.g. met-enkephalin from proenkephalin, β -endorphin from pro-opiomelanocortin, and dynorphin from prodynorphin (Khachaturian *et al.*, 1985; Jaffe and Martin, 1993).

Several studies have suggested that the endogenous opioid peptides play an important role in alcohol reinforcement (Reid and Hunter, 1984; Linseman, 1989; Froehlich *et al.*, 1991). In addition, animal studies have demonstrated that alcohol consumption can be significantly reduced in rats by the administration of naloxone or naltrexone, which are opioid antagonists (Reid and Hunter, 1984; Froehlich *et al.*, 1991). It has also been reported that alcohol reduces the number of

opioid peptides and increases the number of opioid receptors in the central nervous system. Therefore, opiate receptors become hypersensitive, presumably because more sites are externalized at the nerve terminals; this interpretation is consistent with the increased number of brain opiate receptors observed after chronic ethanol treatment (Seizinger *et al.*, 1983).

In a study of alcohol-dependent rats, De Witte *et al.* (1990) found that rats treated with naloxone (an opiate antagonist) and bezitramide (an opiate agonist) showed a decreased preference for alcohol. Wood and Rao (1991) have reported that morphine, a non-specific opiate agonist, stimulates the release of dopamine in the limbic system. In addition, other studies have shown that the endogenous opioid peptides modulate the turnover of serotonin and the release of dopamine in the nucleus accumbens of the rat (Spanagel *et al.*, 1990; Robert *et al.*, 1991).

Benjamin *et al.* (1993) infused a 5% alcohol solution into the brains of male rats via dialysis probes. Dialysate samples were collected before and after the alcohol infusions so that alcohol-induced changes in dopamine levels could be quantified. Intraperitoneal injections of naltrexone (cumulative dosing, 0.25, 0.5 and 1.0 mg/kg i.p.) were then administered to the rats, and additional dialysate samples were collected. The rats also received intraperitoneal injections (1.0 mg/kg) of apomorphine, a dopamine-receptor agonist, to ensure that dopamine level changes that occurred in response to the administration of

alcohol and naltrexone were of neuronal origin.

Results showed that the alcohol infusions resulted in statistically significant increases ($P < 0.05$) in dopamine levels in the nucleus accumbens, but that administration of naltrexone effectively reversed alcohol-induced increases in dopamine and its metabolite, homovanillic acid. These findings support the hypothesis that endogenous opioids play a role in the neurophysiological changes that occur after alcohol reinforcement that induce alcohol consumption.

THE ROLE OF GABA IN ALCOHOL DEPENDENCE

GABA is the most widely distributed inhibitory neurotransmitter in the central nervous system (Koob, 1992). At the molecular level, GABA increases chloride ion flux in synaptic neurosomal preparations. This increase in ion flux is potentiated by alcohol, as well as by benzodiazepines and barbiturates (Suzdak *et al.*, 1986a).

Evidence from neurochemical, behavioural and radioligand binding studies suggests that GABA plays a fundamental role in mediating the effects of alcohol and alcohol-drinking behaviour (Volicer and Biagioni, 1982; Gewiss *et al.*, 1991). It has been reported that GABA is involved in regulating the inhibition of presynaptic and postsynaptic neuronal activity (Gewiss *et al.*, 1991). In addition, it has been suggested that the excitatory effects produced by small doses of alcohol are caused by inhibition of the GABA system, and that the sedative effects produced by large doses of alcohol are caused by activation of this system (Smith, 1977).

Alcohol, benzodiazepines and barbiturates have sedative and hypnotic actions that include euphoria, disinhibition, anxiety reduction, sedation, and hypnosis (Koob, 1992). The ability of alcohol to stimulate GABA receptor-mediated Cl^- transport may explain several of these actions and may provide a mechanism for the common psychopharmacological effects of alcohol, benzodiazepines and barbiturates (Suzdak *et al.*, 1986b). The anxiolytic property of sedatives and hypnotics may be a major component of their reinforcing actions (Koob, 1992).

In conclusion, animal studies have shown that dopamine, endogenous opioid peptides and GABA are involved in the neurophysiological

mechanisms that stimulate alcohol consumption and reward. Such studies also provide a model for changes that occur in the human brain before and after alcohol consumption. Ultimately, animal research will lead to new and better treatments for patients with alcohol dependence.

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