

REVIEW OF NEUROTRANSMITTERS AND THEIR ROLE IN ALCOHOLISM TREATMENT

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Abstract — Studies on the genetic basis of addiction indicate that the tendency to develop alcoholism is inherited. In addition, alcoholism appears to be associated with a specific neurochemical disorder. Research has focused on the mesolimbic system, which is associated with the ability to feel pleasure (i.e. hypothalamic control centres are related to daily survival activities, and the medial forebrain bundle is involved in the positive reinforcement of addictive drugs). Current findings support the hypothesis that a neurochemical deficiency causes alcohol-dependent individuals to drink. Thus, pharmacotherapy may play an important part in treating those who are not helped by psychosocial therapy alone. Future therapies may include agents that block, enhance, or normalize neurotransmitter function as well as genetically engineered agents that could target a specific cause of alcoholism.

INTRODUCTION

The search for methods to treat alcohol dependence has begun to focus on the role of neurotransmitters and neurochemical pathways involved in addiction. Current neuroscientific findings indicate that drugs, even genetically engineered substances, may prove to be effective treatments in the future. A major problem in medicine has been the lack of understanding about: (a) how alcohol acts in the brain; (b) the nature of the disease of alcoholism; and (c) the role that research can play in helping medicine deal with political and ethical problems associated with combatting alcohol dependence. Basic neurochemical research is now regarded as an ally in understanding the causes of alcoholism and expanding the treatments for this disease.

It is important to recognize the difference between alcohol dependence and alcohol misuse or abuse (Erickson, 1992). Dependence is characterized by loss of control over consumption and an apparent inability to modify drinking habits despite adverse consequences. Abuse or misuse refers to use by choice; the use may be illegal, unsafe, at inappropriate times or places, or harmful to self or others. The contemporary literature suggests that addiction (dependence) is characterized by a harmful pattern of chronic, compulsive, drug-taking behaviour. The primary symptom is impaired control over drug use

(Rinaldi *et al.*, 1988; Morse and Flavin, 1992). Impaired control may have genetic or neurochemical causes. Recent neurochemical studies on alcohol lend additional support to hypotheses about the brain dysfunctions that probably exist in persons with alcoholism — dysfunctions associated with 'impaired control over consumption' or the 'inability to stop drinking' (Erickson *et al.*, 1990).

Biomedical diagnostic tests that differentiate between alcohol dependence and abuse are not available, although carbohydrate-deficient transferrin (CDT) may be a possible marker (see Lesch and Walter, 1996 in this supplement).

GENETIC AND NEUROCHEMICAL CAUSES OF ADDICTION

Genetic studies

During the past 15–20 years, genetic studies (i.e. family, twin, and adoption studies) have provided substantial evidence of a powerful genetic component in the development of alcoholism (Goodwin *et al.*, 1973; Cloninger *et al.*, 1985; Cadoret *et al.*, 1986; George and Goldberg, 1989; Comings *et al.*, 1991; Pickens *et al.*, 1991). Research does not suggest that alcoholism is a genetic disease; rather, the tendency to become alcoholic is inherited. Although many believe that alcoholic behaviour could be passed from one generation to the next, adoption studies indicate

that children reared in non-alcoholic families still have the tendency to become alcoholic if a biological parent was alcohol dependent (Goodwin *et al.*, 1973; Cadoret *et al.*, 1986). Environmental, psychological, and sociological components may be necessary to trigger the disease in some people who have a genetic tendency.

In addition, there may be a genetic factor that protects against alcoholism. US government statistics indicate that there are at least three men for every woman with alcoholism (Grant *et al.*, 1994). Perhaps future research should focus on protective factors that may be found in women. In addition, P₃ event-related potential studies have identified an electrical abnormality in those with alcoholism and their children (Begleiter *et al.*, 1984; Pfefferbaum *et al.*, 1991). Because nerve cells communicate chemically, this is probably an electrochemical abnormality. Thus, there may be neurochemical differences in the brains of children of those with alcoholism compared with children of those without alcoholism.

Neurochemistry of the mesolimbic system

Much neuroscientific research on addiction has focused on the mesolimbic system, the portion of the brain involved in the ability to experience pleasure. At the cellular level, the effects of almost every addictive drug as well as drugs used to treat addiction will eventually be explained by their actions in the presynaptic and postsynaptic areas of the cells in the mesolimbic system. For example, cocaine blocks the dopamine reuptake system (the so-called dopamine transporter) and the accumulation of dopamine in the synapses leads to the stimulation associated with cocaine use (Wise and Rompre, 1989).

Hypothalamic control centres. Any consideration of the sites of action of alcohol and other addictive drugs should begin with the hypothalamus. Hypothalamic control centres (those controlling water-drinking, feeding, sexual activity, pleasure and satiety) govern survival on a daily basis (see Lewis, 1996 in this supplement). Research has established these control centres as sites of action for drugs that cause clinical problems for which treatment is sought. I speculate that such hypothalamic control centres cause eating or sexual disorders if those specific control centres are abnormal. Since all hypothalamic centres are located close together, disruption of

one centre may be related to a broad neurochemical disorder that affects other control centres, leading to co-morbid conditions such as alcoholism and eating disorders.

Medial forebrain bundle (MFB). The MFB is primarily responsible for the positive reinforcement associated with drugs of addiction (Gold and Miller, 1992). It is popularly known as the 'pleasure pathway' because electrical or chemical stimulation of the MFB leads to intense feelings of pleasure in animals and humans. The MFB has four functional parts: the lateral hypothalamus, the ventral tegmental area (VTA), the nucleus accumbens (ACC), and the frontal cortex (Wise, 1987; Koob and Bloom, 1988; Koob, 1992; Samson and Harris, 1992).

Opiates primarily affect the VTA; stimulants, such as cocaine, primarily affect the ACC (for review, see Wise and Bozarth, 1987). Thus, drugs of opposite pharmacological categories appear to affect the pleasure pathway to produce euphoria or a sense of well-being.

Gold and Miller (1992) reviewed the pathways from the VTA to the ACC that rely on dopamine transmission. The output pathways from the ACC rely on enkephalin (Fig. 1). Another pathway from the locus coeruleus (LC) involves norepinephrine (noradrenaline, NE) regulation and may explain how certain sedative-hypnotic drugs affect MFB function. Input pathways based on the inhibitory neurotransmitter γ -aminobutyric acid (GABA) modulate the activity of nerve cells in the VTA and the LC (Kalivas *et al.*, 1990). Other pathways involving enkephalin and serotonin affect the VTA. The cortical tegmental pathway also affects the VTA. Thus, the VTA has a number of inputs from different pathways that rely on different neurotransmitters.

Sites of drug-induced euphoria. Neuroscientists are beginning to unlock the mysteries of the MFB pleasure pathway and the related input pathways that can be affected by drug action (Table 1). Microdialysis probes have been used to demonstrate that amphetamines, cocaine, opiates, ketamine, nicotine, tetrahydrocannabinol (THC, the active ingredient in marijuana), and phencyclidine (PCP) all exert their primary effects by increasing the amount of dopamine released in the nucleus accumbens (Manley *et al.*, 1992). The VTA is probably the site of action for opiates and alcohol as well. Although alcohol has no receptor site, it

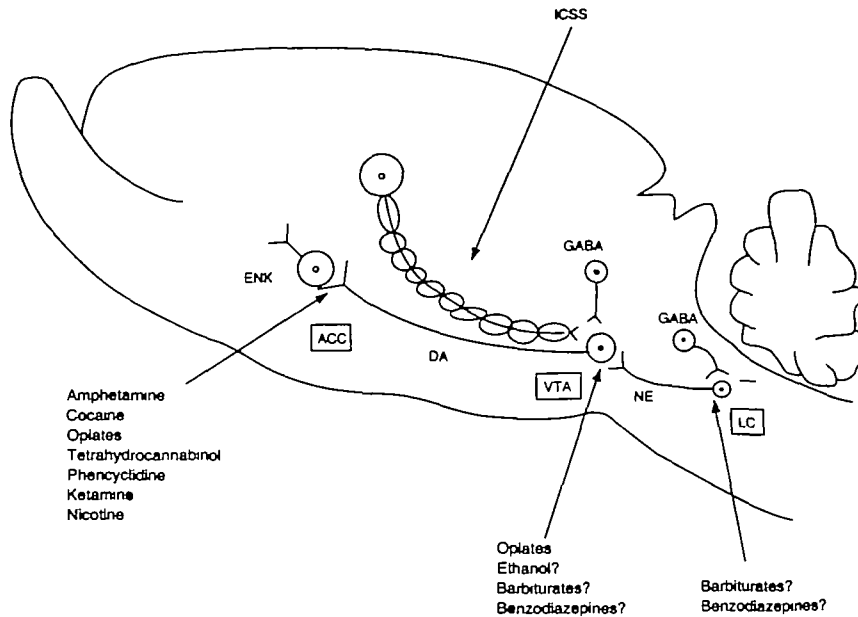


Fig. 1. Diagram of the brain-reward circuitry of the mammalian (laboratory rat) brain.

The diagram shows sites at which various abusable substances may act to enhance brain reward and thus to induce drug-using behaviour and possibly drug craving. Intracranial self-stimulation has identified a descending, myelinated, moderately fast-conducting component of the brain-reward circuitry impacting the ventral tegmental area (VTA). Other components include noradrenergic fibres (NE), which originate in the locus coeruleus (LC) and synapse into the general vicinity of the ventral mesencephalic dopamine (DA) cell fields, and enkephalin (ENK). γ -Aminobutyric acid (GABA) includes the GABAergic inhibitory fibre systems synapsing on both the NE in the LC and the ventral mesencephalic DA cell fields. ACC indicates nucleus accumbens. (From Gold and Miller, 1992, with permission.)

Table 1. Sites of drug action in the medial forebrain bundle

Nucleus accumbens	Ventral tegmental area
Amphetamines	Opiates (primary site)
Cocaine	Alcohol?
Opiates (secondary site)	*Barbiturates?
Ketamine	*Benzodiazepines?
Nicotine	Nicotine?
Tetrahydrocannabinol (THC)	
Phencyclidine (PCP)	

* = locus coeruleus?

has also been shown to act in the ACC and seems to act throughout the brain. Barbiturates and benzodiazepines may affect the VTA or the LC (Wise, 1987).

The MFB comprises more than one pathway (Fig. 2), and a number of pathways may be involved in the action of a particular drug. This

leads to speculation about which pathways may cause the impaired control that characterizes drug addiction.

Loss of control

Euphoria, craving, or need. According to the 'incentive sensitization' theory of addiction, drug dependence is associated with sensitization of a brain pathway to the positively reinforcing, dopamine-mediated effects of a drug (Robinson and Berridge, 1993). Repeated use of addictive drugs produces neuroadaptations in dopamine transmission that make the individual increasingly sensitized to drugs and drug-associated stimuli. According to this theory, a 'like' pathway could be related to the euphoria and the development of tolerance that drugs produce with chronic use. Another pathway, which Robinson and Berridge call the 'want' pathway, could mediate the craving

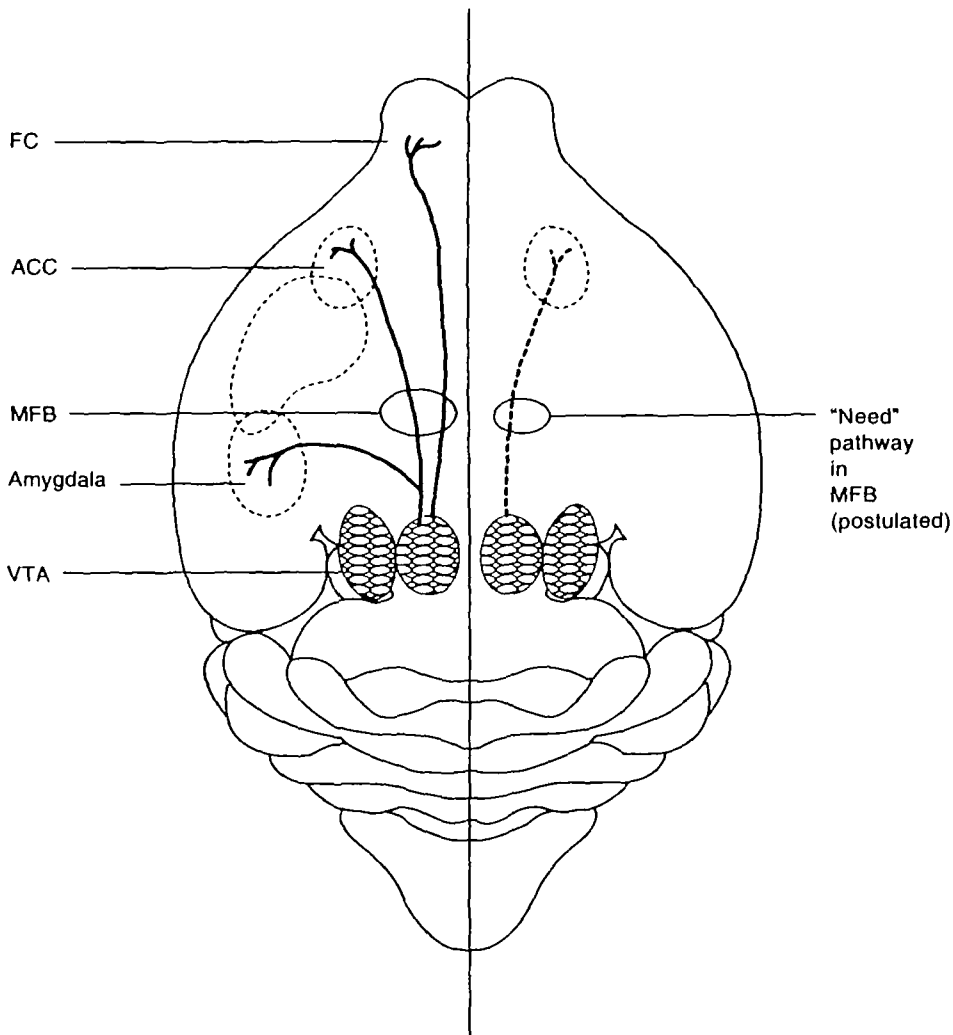


Fig. 2. The medial forebrain bundles (MFB).

Left illustrates two known pathways that could carry drug effects such as 'like' and 'want'. Right illustrates postulated pathway involved in 'need' for a drug in a dependent individual. All pathways would exist on both sides of the brain in two bundles. FC, frontal cortex; ACC, nucleus accumbens; VTA, ventral tegmental area.

effect of the drug that becomes more accentuated with chronic drug use. It is proposed that the progressive increase in drug 'wanting' that characterizes drug-seeking behaviour is not accompanied by an increase in the pleasure derived from drugs.

The existence of a 'need' pathway in the MFB is suggested by recovering alcoholics who report that instinctual 'need' is the essence of alcoholism. Such individuals consistently report 'I need the

drug.' Their response is beyond craving; they *need* the drug much as they need to breathe (Erickson, 1995).

In considering the possibility of a need pathway, it is important to remember that the pleasure pathway runs through the hypothalamus, which regulates survival behaviour. A dysfunction in the proposed need pathway of the MFB may produce the 'impaired control' component of addiction. In searching for a possible neurochemical disorder

of the MFB, scientists are now focusing on four neurotransmitters: dopamine, serotonin, endorphins, and GABA (National Institute on Alcohol Abuse and Alcoholism, 1993). Based on extensive published biomedical research, it appears that alcohol-dependent individuals may have dysfunctions involving dopamine in the ACC, endorphins or serotonin in the VTA or ACC, or GABA in the VTA. I speculate that there may be different neurotransmitter deficiencies associated with each subtype of alcoholism and each addictive drug. Multiple deficiencies may exist in the more severe forms of alcoholism, in patients with multiple dependencies, or in dually diagnosed patients.

A working hypothesis

In trying to understand the neurochemistry of addiction, a working hypothesis may be that alcohol-dependent individuals lack normal concentrations of one or more neurotransmitters in the MFB and, perhaps, in areas yet to be identified. Such individuals drink to feel 'normal' (i.e. to elevate their neurotransmitter levels to normal). When they stop drinking, they must find treatment(s) that normalize(s) brain neurotransmitter levels.

CURRENT THERAPY AND INVESTIGATIONAL STRATEGIES

Can present therapy change brain chemistry in patients successfully treated for alcohol dependence? Current treatment is effective in some of these patients (Litten and Allen, 1991). Alcoholics Anonymous (AA) has demonstrated efficacy for only a small percentage of alcohol-dependent patients (5–15% of these patients in the United States) (Erickson and O'Neill, 1995). This suggests that pharmacotherapy may be necessary in treating individuals who are not helped by present 12-step or other psychosocial therapies.

On another front, a large consortium of geneticists in the USA is seeking to identify the genes that cause alcoholism (National Institute on Alcohol Abuse and Alcoholism, 1993). These abnormal genes presumably lead to deficient neurotransmitter levels or a functional disruption of the neurotransmitters. There is also evidence for chemical deficiencies in Parkinson's disease and diabetes. Therefore, it is logical to propose

that alcoholism could be a disease caused by deficiency of one or more of the neurotransmitters discussed previously. This working hypothesis is reasonable, based on existing knowledge, and is testable.

IMPLICATIONS FOR FUTURE TREATMENT OF ALCOHOLISM

These findings suggest the following four types of future therapies. The first two are already available:

- (1) Non-specific 'craving blockers' that would affect the function of serotonin, dopamine, and/or the endorphins (Naranjo *et al.*, 1990; Litten and Allen, 1991; Volpicelli *et al.*, 1992; O'Malley *et al.*, 1992).
- (2) Non-specific neurotransmitter 'restoratives' would return functioning of the neurotransmitter systems to normal. These would include acupuncture (Bullock *et al.*, 1989), alpha-theta brain wave biofeedback training (Peniston and Kulkosky, 1989), and cranial electrotherapy stimulation (Schmitt *et al.*, 1986).
- (3) I speculate that highly specific neurotransmitter 'normalizers' could correct abnormalities in cells and normalize neurotransmitter function. Treatment of these cells might be accomplished through localized intracerebral injection, defect-seeking chemicals, or laser therapy to target over-producing cells. However, neurochemical research in humans must first identify specific abnormal nerve cells in the MFB or elsewhere.
- (4) Based on ongoing genetics research, genetically engineered 'cures' could be targeted to specific facets of alcohol addiction.

CONCLUSIONS

Evidence points to a specific neurochemical disorder as the primary cause of the complex array of physical, emotional, and behavioural symptoms known as drug dependence (addiction). Identification of this 'neurological gateway' is only the beginning of an exciting future, which will involve many areas of research to find the causes of and better treatments for various addictions such as alcoholism.

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REFERENCES

- Begleiter, H., Porjesz, B., Bihari, B. and Kissin, B. (1984) Event-related brain potentials in boys at risk for alcoholism. *Science* **225**, 1493–1496.
- Bullock, M. L., Culliton, P. D. and Olander, R. T. (1989) Controlled trial of acupuncture for severe recidivist alcoholism. *Lancet* **i**, 1435–1439.
- Cadore, R. J., Troughton, E., O'Gorman, T. W. and Heywood, E. (1986) An adoption study of genetic and environmental factors in drug abuse. *Archives of General Psychiatry* **43**, 1131–1136.
- Cloninger, C. R., Bohman, M., Sigvardsson, S. and von Knorring, A.-L. (1985) Psychopathology in adopted-out children of alcoholics: the Stockholm adoption study. In *Recent Developments in Alcoholism*, Galanter, M. ed., pp. 37–51. Plenum Press, New York.
- Comings, D. E., Comings, B. G., Muhleman, D., Dietz, G., Shahbahrani, B., Tast, D., Knell, E., Kocsis, P., Baumgarten, R., Kovacs, B. W., Levy, D. L., Smith, M., Borison, R. L., Evans, D. D., Klein, D. N., MacMurray, J., Tosk, J. M., Sverd, J., Gysin, R. and Flanagan, S. D. (1991) The dopamine D₂ receptor locus as a modifying gene in neuropsychiatric disorders. *Journal of the American Medical Association* **266**, 1793–1800.
- Erickson, C. K. (1992) A pharmacologist's opinion — alcoholism: the disease debate needs to stop. *Alcohol and Alcoholism* **27**, 325–328.
- Erickson, C. K. (1995) Voice of the victims. *Alcoholism: Clinical and Experimental Research* **19**, 1209–1210.
- Erickson, C. K. and O'Neill, J. T. (1995) *It Is Time*. National Council on Alcoholism and Drug Dependence Amethyst 3 (summer), pp. 1–2. National Council on Alcoholism and Drug Dependence, New York.
- Erickson, C. K., Javors, M. A. and Morgan, W. W. (1990) Drug dependence: defining the issues. In *Addiction Potential of Abused Drugs and Drug Classes*, Stimmel, B. ed., pp. 1–7. Haworth Press, New York.
- George, F. R. and Goldberg, S. R. (1989) Genetic approaches to the analysis of addiction processes. *Trends in Pharmacological Sciences* **10**, 78–83.
- Gold, M. S. and Miller, N. S. (1992) Seeking drugs/alcohol and avoiding withdrawal: the neuroanatomy of drive states and withdrawal. *Psychiatric Annals* **22**, 430–435.
- Goodwin, D. W., Schulsinger, F., Hermansen, L., Guze, S. B. and Winokur, G. (1973) Alcohol problems in adoptees raised apart from alcoholic biological parents. *Archives of General Psychiatry* **28**, 238–243.
- Grant, B. F., Harford, T. C., Dawson, D. A., Chou, P., Dufour, M. and Pickering, R. (1994) Prevalence of DSM-IV alcohol abuse and dependence: United States, 1994. *Alcohol Health and Research World* **18**, 243–248.
- Kalivas, P. W., Duffy, P. and Eberhardt, H. (1990) Modulation of A10 dopamine neurons by γ -aminobutyric acid agonists. *Journal of Pharmacology and Experimental Therapeutics* **253**, 858–866.
- Koob, G. F. (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends in Pharmacological Sciences* **13**, 177–193.
- Koob, G. F. and Bloom, F. E. (1988) Cellular and molecular mechanisms of drug dependence. *Science* **242**, 715–723.
- Lesch, O. M. and Walter, H. (1996) New 'state' markers for the detection of alcoholism. *Alcohol and Alcoholism* **31** (Suppl. 1), 59–62.
- Lewis, M. J. (1996) Alcohol reinforcement and neuropharmacologic therapeutics. *Alcohol and Alcoholism* **31** (Suppl. 1), 17–25.
- Litten, R. Z. and Allen, J. P. (1991) Pharmacotherapies for alcoholism: promising agents and clinical issues. *Alcoholism: Clinical and Experimental Research* **15**, 620–633.
- Manley, L. D., Kuczenski, R., Segal, D. S., Young, S. J. and Groves, P. M. (1992) Effects of frequency and pattern of medial forebrain bundle stimulation on caudate dialysate dopamine and serotonin. *Journal of Neurochemistry* **58**, 1491–1498.
- Morse, R. M. and Flavin, D. (1992) The definition of alcoholism. *Journal of the American Medical Association* **268**, 1012–1014.
- Naranjo, C. A., Kadlec, K. E., Sanhueza, P., Woodley-Remus, D. and Sellers, E. M. (1990) Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. *Clinical Pharmacology and Therapeutics* **47**, 490–498.
- National Institute on Alcohol Abuse and Alcoholism (1993) *Eighth Special Report to the U.S. Congress on Alcohol and Health*. US Department of Health and Human Services, Rockville, MD, USA.
- O'Malley, S. S., Jaffe, A. J., Chang, G., Schottenfeld, R. S., Meyer, R. E. and Rounsaville, B. (1992) Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Archives of General Psychiatry* **49**, 881–887.
- Peniston, E. G. and Kulkosky, P. J. (1989) α - θ -Brain-wave training and β -endorphin levels in alcoholics. *Alcoholism: Clinical and Experimental Research* **13**, 271–279.
- Pfefferbaum, A., Ford, J. M., White, P. M. and Mathalon, D. (1991) Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. *Alcoholism: Clinical and Experimental Research* **15**, 839–850.
- Pickens, R. W., Svikis, D. S., McGue, M., Lykken, D. T., Heston, L. L. and Clayton, P. J. (1991) Heterogeneity in the inheritance of alcoholism: a study of male and female twins. *Archives of General Psychiatry* **48**, 19–28.
- Rinaldi, R. C., Steindler, E. M., Wilford, B. B. and Goodwin, D. (1988) Clarification and standardization of substance abuse terminology. *Journal of the American Medical Association* **259**, 555–557.
- Robinson, T. E. and Berridge, K. C. (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research Reviews* **18**, 247–291.
- Samson, H. H. and Harris, R. A. (1992) Neurobiology of alcohol abuse. *Trends in Pharmacological Sciences* **13**, 206–211.
- Schmitt, R., Capo, T. and Boyd, E. (1986) Cranial electrotherapy stimulation as a treatment for anxiety in chemically dependent persons. *Alcoholism: Clinical and Experimental Research* **10**, 158–160.

- Volpicelli, J. R., Alterman, A. I., Hayashida, M. and O'Brien, C. P. (1992) Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* **49**, 876–880.
- Wise, R. A. (1987) The role of reward pathways in the development of drug dependence. *Pharmacology and Therapeutics* **35**, 227–263.
- Wise, R. A. and Bozarth, M. A. (1987) A psychomotor stimulant theory of addiction. *Psychological Review* **94**, 469–492.
- Wise, R. A. and Rompre, P.-P. (1989) Brain dopamine and reward. *Annual Review of Psychology* **40**, 191–225.

