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Review Article

Drug dependence: neuropharmacology and management

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Introduction

Drug dependency is a major scourge of contemporary society with wide ranging socio-economic implications. The term ''dependence'' is often used synonymously with ''addiction'' and reflects a state where there is a physical and/or psychological need for the presence of a pharmacological substance or some experiential entity (such as obsessional feeding or compulsive gambling) in order to maintain a sense of stability. A range of drugs are classically associated with abuse: cocaine, amphetamine, heroin and opioid analogues such as morphine, in addition to cannabis and the more socially accepted drugs, nicotine and alcohol. Benzodiazepines such as diazepam are also known to induce dependence.

Drug addiction can be defined as a chronic disorder that manifests as a psychological compulsion for the affected individual to maintain drug administration without being able to control or reduce intake. Drug dependence is an adaptive state. It presents as a set of intense physical symptoms when administration of the abused drug is suspended (Koob et al 1998). Physical aspects of dependence are expressed during drug withdrawal. In the case of opioids for example, the clinical symptoms include behavioural agitation, tremor, insomnia, nausea, sweating, diarrhoea and other autonomic signs. The overall state of physical dependence can be linked with certain neurochemical changes in the brain. Psychological dependence on the other hand, is characterized by a compulsion or drive to continue taking the drug. It invariably manifests as drug-craving or drug-seeking behaviour and is less readily identifiable through brain neurochemistry. Allied to these distinctive concepts of drug abuse are two other pharmacological phenomena, namely tolerance and sensitization. Tolerance may develop following repeated drug use, and describes the necessity to administer a drug in increasing doses in order to achieve the same effect. Sensitization can be considered the inverse of tolerance, whereby the perceived action of a drug becomes enhanced after repeated administration.

Against the background of a recent upsurge in the abuse of so-called ''hard'' drugs, we review some of the underlying mechanisms of opioid and stimulant drug dependence on a neuropharmacological basis. Furthermore, we examine the possibility that drugs modifying dopamine neurotransmission might influence central pathways, which may ultimately provide treatment targets or management strategies for patients who are drug dependent.

Models of drug dependence

Knowledge concerning the neural circuitry associated with drug dependence has been chiefly derived from animal studies. It was originally shown that rats would return to a particular environmental location if it was ''paired'' (associated) with a rewarding stimulus. This behaviour was termed conditioned place preference (CPP), the animals being considered to favour a particular place within their environment. Early studies employed electrical brain stimulation as the ''conditioning'' stimulus (Olds & Milner 1954). Later, the effect of drugs, food and sexual contact were investigated. The use of an electrical stimulus targeting certain brain regions identified areas closely associated

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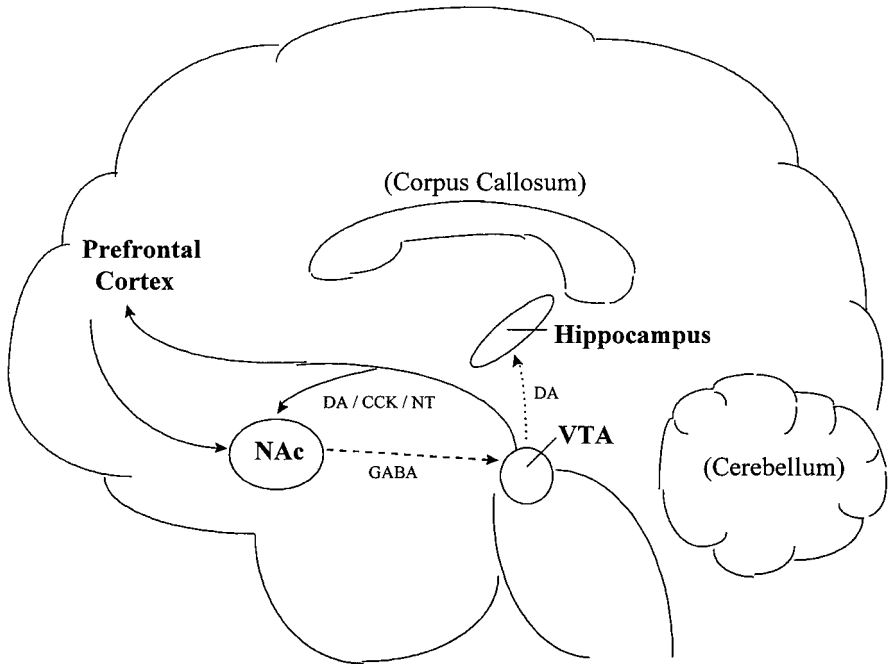

Figure 1 Brain regions implicated in drug dependence within the prefrontal cortex, hippocampus, ventral tegmental area (VTA) and nucleus accumbens (NAc) showing their neurotransmitter pathways: dopamine (DA), c-aminobutyric acid (GABA), cholecystokinin (CCK) and neurotensin (NT).

with reward. Hence, CPP was induced following electrical stimulation of the septal brain area (Olds & Milner 1954). This place preference activity has also been reported by a number of researchers in response to drugs such as opioids, amphetamine and cocaine, and it is often regarded as an indication of the rewarding potential of a compound (Mucha & Iversen 1984). Furthermore, place preference can be used to determine negative motivation resulting from the administration of an aversive drug (Stolerman 1992), and subsequently assess the ability of other compounds to attenuate these aversive properties or to evaluate withdrawal aversion from a dependence-inducing drug (Rafieian-Kopaei et al 1995).

Another technique involves drug self-administration, whereby agents are delivered either intravenously or stereotaxically targeted to a specific brain area via a self-operated lever. If the drug is rewarding, subjects continue to lever press, thereby increasing the frequency of drug delivery (Van Ree et al 1978). In this instance, lever pressing can be considered an emitted response. Any stimulus (such as a drug) that increases responding may be described as a positive reinforcer. Conversely, a compound or stimulus that reduces responding is a negative reinforcer. Self-administration can also be achieved via the oral route, with drug being presented in solution. The association between lever pressing and a learned response can also be used to examine negative motivational (or aversive) effects (see Stolerman 1992). Hence lever pressing can prevent the administration of a noxious compound, or alternatively, administration of an aversive stimulus can be used to reduce responding for a positive reinforcer.

A less direct method used to investigate reinforcing properties of compounds is drug discrimination. This technique exploits the ability of agents to elicit an internal (interoceptive) stimulus. Thus, drugs with comparable psychopharmacological profiles generate similar internal cues. It also allows opioids to be differentiated from both cocaine-like and non-reinforcing compounds (e.g. the peripherally acting opioid loperamide). Subjects are trained to turn in a specific direction at the junction of a T-maze or they are encouraged to press a particular lever in an operant conditioning chamber when given vehicle control. Concomitantly, they are conditioned to turn in the opposite direction (or press an alternate lever) when given drug. Once familiar with this task, substances can be administered to determine whether they generate drug-like or vehicle-like responses (e.g. Colpaert 1978).

Brain regions implicated in drug dependence

Certain regions of the brain that lie beneath the cerebral cortex are closely implicated in reinforcement, the term used to describe any tendency towards increased (positive) or decreased (negative) expression of a given behaviour. These anatomically well-defined brain regions form a major component of a complex neuronal circuit termed the mesocorticolimbic system (derived from: mesencephalon, midbrain, cerebral cortex and limbic system). It is constituted by areas that include the hippocampus, ventral tegmental area (VTA), nucleus accumbens (NAc) and the medial pre-frontal cortex (PFC) (Figure 1) (for review see Trujillo et al 1993). The roles played by these areas in the pharmacology of drug dependence are discussed below.

Ventral tegmental area

The VTA represents an important group of dopaminergic neuronal cell bodies (designated A10 neurons) that form the basis of the ascending mesocorticolimbic dopamine system. Emanating from the VTA, neuronal fibres extend to the amygdala, hippocampus, NAc and PFC (Koob 1992). The effect of stimulating the VTA can be observed using the CPP and self-administration paradigms. Thus, micro-application of opioids into the VTA increases the occupancy time that subjects will spend in the drug-paired environment (Bals-Kubik et al 1993; Olmstead & Franklin 1997). Furthermore, self-administration of morphine to the VTA may be induced in a naloxone reversible manner (Bozarth & Wise 1981). Consequently, the VTA and its dopaminergic projections are thought to play a major role in the development of reinforcement and addiction.

Other studies have focused on the morphology of neurons constituting the dopaminergic projections from the VTA. Accordingly, it has been found that there is a 25% reduction in dopamine cell body size following chronic morphine exposure. Although the locus coeruleus is widely associated with withdrawal (Self & Nestler 1995), the involvement of other brain regions, including mesolimbic areas, has been proposed (Christie et al 1997), and these anatomical changes may underlie drug withdrawal (Sklair-Tavron et al 1996). In the presence of an opioid agonist, neurotransmission is artificially increased through inhibition of inhibitory pathways (Johnson & North 1992). On cessation of drug treatment, there is a subsequent decrease in neuronal activity, which may be compounded by the reduction in dopaminergic cell body size, leading to an inability to compensate for the drug withdrawal and which subsequently manifests as withdrawal symptoms.

Many molecular changes occur following the administration of drugs of abuse. It is beyond the scope of this review to detail these changes, some of which have been recently reviewed by Nestler (2001). However, the gradual onset of addiction suggests an aetiology involving changes in gene expression, as these would also be expected to occur over an extended period of time.

The cocaine and amphetamine regulated transcript (CART) gene is of particular interest, as it was found to be regulated in striatal tissue by cocaine and amphetamine administration (Douglass et al 1995). CART has been reported in neurons of both the VTA and NAc, and may be a peptide neurotransmitter (for review see Kuhar et al 2001). Interestingly, Kimmel et al (2000) have shown that intra-VTA injection of a CART peptide fragment (spanning residues 55–102) induces similar behavioural effects to stimulant administration, that is increased locomotor activity and promotion of CPP.

Nucleus accumbens

The NAc is located within the ventral midbrain area, and is composed of core (located dorso-laterally) and shell (located ventro-medially) regions. It is innervated by dopaminergic, opioidergic and GABAergic neurons and appears to play a pivotal role in drug reinforcement. The dopaminergic input originates mainly from the VTA. In addition to dopamine, peptidergic neurons from this region are thought to contain cholecystokinin (CCK) and neurotensin (NT), which may also have a role in reward mechanisms (Hokfelt et al 1980; Kalivas et al 1983). Other inputs originate from the hypothalamus and the limbic system, notably the amygdala (believed to be CCK-mediated) and limbic cortex. Dopamine receptors of D_1 and D_2 subtypes, as well as l, j and d opioid receptors (Mansour et al 1988), are associated with these neurons and are located throughout the NAc. The NAc also has efferent connections with the VTA, lateral hypothalamus and brain areas related to motor function, such as the ventral pallidum. It has been proposed that these motor outputs may be responsible for expression of emotion (Trujillo et al 1993) and this may well correlate with dependence.

Substances known to have reinforcing properties, such as opioids, cocaine, amphetamine, nicotine, ethanol and even food, all increase the level of extracellular dopamine in the NAc (Di Chiara 1998). Moreover, self-administration of morphine into the NAc has been reported (Olds 1982), and kainic acid lesions of this region (which would destroy the cell bodies of dopaminergic neurons) reduce the self-administration properties of both cocaine and heroin (Zito et al 1985). However, unlike the VTA, microinjection of opioid agonists into the NAc does not result in place preference conditioning (Bals-Kubik et al 1993; Olmstead & Franklin 1997).

Prefontal cortex

The PFC, like the NAc, is a terminal area for the A10 neuronal projection from the VTA, and has efferent connections not only into the NAc, but also subsequently back to the VTA. This correlates with the fact that increases in extracellular dopamine observed in the VTA and NAc following amphetamine and cocaine dosing are also observed in the PFC. However, drugs such as the tricyclic antidepressants, which are not generally regarded as addictive, also increase extracellular dopamine in the PFC (Tanda et al 1994, 1996). The majority of dopamine uptake from synapses occurs via the dopamine transporter (for review see Chen & Reith 2000), and there is also some evidence of dopamine uptake into noradrenergic terminals (Carboni et al 1990). Tricyclic antidepressants are thought to enhance synaptic dopamine levels by blocking these uptake mechanisms (Di Chiara 1998), and many of these agents display high affinities for the noradrenergic transporter in particular (Richelson & Pfenning 1984). Stronger evidence for a role of the PFC in reward is derived from the observation by Goeders & Smith (1983) that rodents will self-administer cocaine into this region, and this type of response has been reproduced with amphetamine in primates by Phillips & Rolls (1981). Furthermore, functional magnetic resonance imaging has demonstrated the PFC to be activated during cocaine-induced rush and craving in human volunteers (Breiter et al 1997).

Hippocampus

The hippocampus is heavily implicated in memory and learning, the acquisition of which is largely thought to be mediated through acetylcholine. Recent studies have shown that amphetamine, cocaine and morphine all stimulate the release of acetylcholine in the hippocampus. This effect is mediated by dopamine via D_1 and D_2 receptors, whereby stimulation reduces the inhibitory action of GABA interneurons, resulting in increased acetylcholine release. The role of the hippocampus in memory and learning suggests that this region may be responsible for the memory of the positive reinforcing effects of abused drugs (Imperato et al 1996).

Neuropharmacology of drug dependence

Central nervous system stimulants

The commonly abused central nervous system (CNS) stimulants include cocaine, amphetamine and the group of amphetamine derivatives known as ''designer'' drugs, an example of which is ecstasy. The substituted amphetamines such as ecstasy act mainly on the serotonin (5-HT) system (Liechti & Vollenweider 2000), whereas cocaine and amphetamine have their greatest effects on the dopamine system (Centonze et al 2002). Owing to similarities in their respective pharmacology, cocaine and amphetamine will be considered collectively for the purposes of this review. Classically, cocaine is regarded as a dopamine reuptake inhibitor, although it also potentiates both noradrenergic and serotonergic neurotransmission. The drug binds to membrane-bound transporter proteins responsible for the removal of dopamine, noradrenaline, and serotonin from synapses. The resulting inhibition of the uptake process increases synaptic availability of these neurotransmitters, potentiating their effects. It has been shown, however, that place preference to cocaine and another psychomotor stimulant, methylphenidate, occurs in mice lacking the dopamine or serotonin transporters. Although knockout animals cannot be expected to reflect the response of a wild-type subject (owing to adaptive processes), this does suggest an alternative site of action of cocaine in mediating reward (Sora et al 1998). Nevertheless, in animals lacking such reuptake transporters, any stress or drug-induced increase in synaptic neurotransmitter concentration would be potentiated by the absence of the transporter, perhaps resulting in rewarding effects through enhanced dopaminergic neurotransmission. Furthermore, extracellular dopamine concentration has been shown to be increased by antidepressants, which inhibit norepinephrine (noradrenaline) reuptake (Carboni et al 1990). The norepinephrine transporter is also inhibited by cocaine (Richelson & Pfenning 1984), and this action may also result in potentiation of dopaminergic transmission. Amphetamine shares these pharmacological properties with cocaine, but also stimulates the release of the transmitters from pre-synaptic neurons (Koob et al 1998).

Following cocaine administration, the dopamine concentration in the NAc is increased, and it is this capacity to modulate dopaminergic neurotransmission that is thought to account for the rewarding properties of drugs of abuse (Di Chiara & Imperato 1988b). Dopamine ligand binding studies have been used to examine changes in dopamine receptor density following repeated cocaine and amphetamine administration. Results have been conflicting, since both increases and decreases in receptor density have been reported depending on the treatment protocol, brain area and receptor subtype studied (Kleven et al 1990; Zeigler et al 1991; Unterwald et al 1994).

Studies of human cocaine abusers have attempted to identify the brain regions responsible for the ''rush'' and ''craving'' associated with the drug. Positron emission tomography scanning has been employed to demonstrate an increase in glucose metabolism in the PFC, amygdala and cerebellum when users are shown drug-related stimuli, at which time they also simultaneously express psychological craving for the drug (Grant et al 1996). Functional magnetic resonance imaging has also been used to examine cocaine-generated effects in human addicts. Results suggest that the VTA, basal forebrain and most of the PFC are associated with the rush, while the NAc, subcallosal cortex, amygdala and certain regions of the PFC are associated with craving (Breiter et al 1997).

Other workers have attempted to determine whether dopamine receptors are responsible for mediating the effects of stimulants, using agonist and antagonist tool drugs in place preference and self-administration studies. In this context, cocaine self-administration was shown to be unaffected by central application of the adrenoceptor antagonist, phentolamine (DeWit & Wise 1977), although a variety of dopamine antagonists such as chlorpromazine, haloperidol and sulpiride reduced cocaine reinforcement (Roberts & Vickers 1984). Dopamine receptor antagonists have also been shown to increase amphetamine self-administration, indicating a reduction in the reinforcing effects of this compound when dopamine transmission is impaired (Davis & Smith 1975). Additionally, it has been reported that cocaine self-administration increases under the influence of classical neuroleptics such as haloperidol and chlorpromazine, but is decreased by clozapine (an atypical neuroleptic believed to interact with D_4, a-adrenergic, muscarinic and 5-HT_2 receptors) (Roberts & Vickers 1984; Wilson et al 1998). In accord with this finding, it has also been demonstrated that another atypical neuroleptic, olanzapine, similarly reduced cocaine-mediated self-administration (Meil & Schechter 1997). Although the pharmacology of olanzapine is not fully understood, it exhibits some affinity for D_1, D_2, D_4, 5-HT and muscarinic receptors (Meltzer et al 1989; Van Tol et al 1991). An interaction with the serotonergic system may explain why food consumption was also reduced (a parameter not examined in earlier studies), and the fact that there were differences observed between typical and atypical neuroleptics with respect to cocaine self-administration. These differences on primary examination may appear paradoxical, but it is still thought that both classical and atypical neuroleptics may be of use in the treatment of addiction. Thus, any increase in self-administration of cocaine associated with classical neuroleptics suggests a reduction in the rewarding properties of

the stimulant, since animals must administer more of the drug to experience the same effect. Conversely, any reduction in self-administration caused by the atypical drugs may indicate an attenuation in the drive to self-administer cocaine.

CPP studies have been even less consistent than those using the self-administration paradigm. Classical neuroleptics such as haloperidol, pimozide and sulpiride were found to have no effect on either morphine or cocaine-induced place preference (Mackey & Van der Kooy 1985; Shippenberg & Herz 1988). However, these findings did not concur with the work of Leone & Di Chiara (1987), who noted that haloperidol blocked CPP induced by morphine. It is difficult to reconcile these conflicting data, although methodological issues, such as dose and route of administration, may account for some of the differences. A later study by Suzuki & Misawa (1995) used sertindole, an atypical neuroleptic with a pharmcological profile similar to that of clozapine. Sertindole was found to inhibit cocaine, morphine and methamphetamine-induced CPP. They attributed their observations to an action at $5HT_2$ receptors, since a similar type of result was observed by Meert & Clincke (1992), who employed ritanserin, a selective $5HT_2$ receptor antagonist, to block both morphine and dexamphetamine-induced CPP. Thus, it would appear that the propensity of a compound to affect CPP may be owing in part to its ability to interact with serotonergic pathways.

The complex and divergent findings of the above studies possibly stem from the breadth of mechanisms through which both drugs of dependence and currently available pharmacological tools mediate their effects. Cocaine itself inhibits the reuptake of noradrenaline and serotonin, as well as dopamine (Richelson & Pfenning 1984), and both the typical and atypical neuroleptics act on a variety of receptor subtypes, including those for dopamine and serotonin (Wilson et al 1998). The precise nature of the mechanism responsible for mediating the rewarding properties of drugs such as cocaine will only be determined with the aid of more selective agonists, many of which are now being developed and tested following cloning of the five dopamine receptor subtypes.

Opioids

Opioids exert their pharmacological effects via interactions with multiple receptor subtypes, (l , d and j), a theory first proposed in the 1950s and 1960s (Beckett & Casy 1954; Portoghese 1965). The endogenous peptide ligands corresponding to these receptors are endorphins (l), enkephalins (d) and dynorphins (j), respectively (for review see Dhawan et al 1996). All three receptor subtypes are found throughout the brain, with regions involved in mediating reward such as the NAc, PFC and hippocampus possessing significant populations, although the VTA has a relatively low density (Mansour et al 1988). An additional receptor described as opioid-receptor-like (ORL_1) has also been cloned (Bunzow et al 1994; Wang et al 1994), and was originally termed an orphan receptor since no endogenous ligand had been discovered at that time. The subsequent identification of the endogenous ligand, nociceptin (Meunier et al 1997) or orphanin FQ (Reinscheid et al 1995), further complicated the nomenclature of this receptor, although nociceptin is the favoured term for this ligand.

The three opioid receptor subtypes belong to the seven transmembrane domain, G protein coupled receptor superfamily (Uhl et al 1994). The effects of all three subtypes (which are largely inhibitory on cell firing) are mediated through coupling to $G_{i/o}$ proteins. Following agonist binding, the G proteins mediate changes in cAMP, protein kinase C, phospholipases and protein kinase A, which express the pharmacological actions of the drug. Unlike adrenergic receptors, which are associated with either the excitatory G_s protein or the inhibitory $G_{i/o}$ protein, there is evidence to suggest that a single opioid receptor may be coupled to both excitatory and inhibitory G proteins. In-vitro studies in dorsal root ganglion cells using selective modifiers of the function of each G protein (cholera and pertussis toxins) have revealed the possible role of the excitatory and inhibitory pathways in-vivo. The excitatory pathway has been hypothesized to have a role in the development of tolerance and dependence, while the inhibitory pathway appears to mediate analgesia (Crain & Shen 1998).

The discovery of selective ligands for different opioid receptors has led to an improved understanding of the role of each subtype in drug reinforcement. The l -selective agonists include etonitazine and fentanyl (Emmerson et al 1994). In animal models, the rewarding properties of l receptor agonists are illustrated by the development of CPP to fentanyl and etonitazine (Mucha & Herz 1985; Finlay et al 1988; Sala et al 1992) and the maintenance of self-administration by morphine and heroin (Ettenberg et al 1982). The opioid antagonist naloxone is aversive, and attenuates the rewarding properties of opioids and other compounds (Mucha et al 1982; Mucha & Iversen 1984; Trujillo et al 1991; Gerrits et al 1995). Similarly, the d receptor agonist, DPDPE, produces CPP activity, which is blocked by a l receptor antagonist. Morphine-induced place preference, however, is unaffected by d receptor antagonism, indicating that stimulation of either l or d receptors is sufficient to induce this effect (Shippenberg et al 1987).

Responses mediated by j opioid receptors tend to be functionally opposite to those of l . Thus, j agonists are aversive in the place conditioning paradigm (Shippenberg & Herz 1991; Bals-Kubik et al 1993), inhibit the rewarding effects of morphine (Bolanos et al 1996), antagonize l effects on mesolimbic dopamine levels, and induce dysphoria rather than euphoria (Pan et al 1997; Pan 1998). These differences in functional pharmacology occur even though these two receptors are coupled to the same G protein system, and despite their similar distributions throughout the CNS (Mansour et al 1995). The basis for this diversity appears to be the nature of the neurons on which the receptors are situated in any given brain region. Hence, both receptors inhibit neuronal firing, but l receptors may inhibit inhibitory GABAergic neurons resulting in excitation or disinhibition (Johnson & North 1992), while j receptors cause direct inhibition (Pan 1998).

Agonist binding at ORL_1 receptors leads to activation of potassium and inhibition of calcium conductance, and inhibition of cAMP formation, similar to that evoked by other opioid receptors (Meunier 1997). These effects appear to be mediated through inhibitory $G_{i/o}$ proteins (see Calo et al 2000). In place conditioning experiments, nociceptin produces neither place preference nor aversion (Devine et al 1996), although it does attenuate morphine-induced CPP (Murphy et al 1999) and this may be through inhibition of opioid-induced dopamine release in the mesolimbic system (Pieretti & Di Giannuario 1999). Since the action of ORL_1 receptors appears to be linked to the same second messenger systems as the other opioid receptors, it seems likely that its l opposing action (like that of the j receptor) may be attributable to differential receptor location. In addition to its effects on nociception and reward, nociceptin has anxiolytic and appetite-stimulating properties, as well as producing a range of effects on peripheral tissues (Calo et al 2000).

The reinforcing effects of opioid drugs are thought to be dependent on increased dopaminergic transmission as well as through direct interactions at opioid receptors. Hence, biochemical dopaminergic lesions induced by 6-hydroxydopamine and microinjections of dopamine antagonists into the NAc disclosed the consequences of disrupting dopaminergic transmission on opiate reinforcement. Both of these pharmacological manoeuvres reduce CPP behaviour associated with morphine dosing (Shippenberg et al 1993). Moreover, selective agonists at opiate receptors have different effects on dopamine release in the NAc, and drugs such as morphine, methadone and fentanyl, which are mainly l preferring, stimulate dopamine release and metabolism, whereas j agonists such as U50,488 and bremazocine reduce it (Di Chiara & Imperato 1988a).

Clinical management of drug dependence

Pharmacological modification of reward pathways

The use of substances to promote abstinence in the management of drug addiction has so far been largely unsuccessful, alcohol dependence being a classic example that is difficult to treat. Some progress has been made in identifying the kind of pharmacological approach that might prove more appropriate in the clinic. Potentiation of c-aminobutyric acid (GABA) function appears to reduce administration of abused drugs. Thus, following acute doses of baclofen (a $GABA_B$ agonist), animals exhibit a reduced tendency to self-administer cocaine (Roberts & Andrews 1997), while responding for food remains unaffected, indicating some behavioural selectivity in the decreased response for cocaine. Another drug thought to act by potentiating GABA transmission is acamprosate. Although its actual mechanism of action remains unclear, this compound significantly reduces ethanol intake in animal models, and this effect is blocked by bicuculline (a $GABA_A$ antagonist). Importantly, acamprosate had no influence on food or fluid intake (Wilde & Wagstaff 1997).

The efficacy of neuroleptic drugs (D_1 and D_2 antagonists) in attenuating cocaine reinforcement has been investigated in both animal and human studies. Gawin et al (1989) used intramuscular depot injections of flupenthixol to treat crack cocaine users in an outpatient setting. The aim of the study was to exploit the pharmcological interaction between cocaine and neuroleptics, and it was concluded that the depot was well tolerated, and appeared to reduce craving and cocaine consumption.

Current treatment approaches

The aims of management strategies when treating patients who misuse drugs are as follows (Department of Health/Welsh Office 1999):

- to help the patient to maintain as healthy a life as possible, until they can achieve a drug-free life;
- to reduce illicit drug use and the chance of future relapse;
- to reduce the need for criminal activity to finance drug misuse;
- to stabilize the patient where appropriate on a substitute drug to alleviate withdrawal symptoms;
- to improve overall personal, social and family functioning.

There are three approaches to fulfilling these aims: rapid withdrawal/detoxification, longer-term dose reduction regimens, and long-term maintenance therapy. The first two strategies attempt to achieve a drug-free state, while the third is designed to improve the health of the individual and to reduce any inclination towards criminal activity.

Rapid detoxification may be appropriate for patients who, with general support and symptomatic relief of withdrawal symptoms, can achieve a drug-free state. The patient must be highly motivated, and the best results may be achieved when the patient is willing to change their lifestyle and environment. Medication to alleviate withdrawal symptoms can be prescribed; for opioids, this may include a substitute for example methadone, buprenorphine or dihydrocodeine (Department of Health/Welsh Office 1999). Both methadone mixture ($1\ mg\ mL^{-1}$) and buprenorphine sublingual 8-mg tablets (equiv. 30 mg methadone) are now licensed for this use in the UK (Bellingham 2001). Codeine-based drugs are unlicensed, but are used by some practitioners towards the end of detoxification. Although associated with certain side-effects, drugs such as lofexidine and clonidine can be used to treat withdrawal symptoms (Guthrie 1990); lofexidine is licensed for this particular use, whereas clonidine is not. Loperamide, metoclopramide and NSAIDs may be useful in treating diarrhoea, nausea, muscular pains and headache, which may be associated with abstinence (Department of Health/Welsh Office 1999), while naltrexone may be effective in reducing the risk of relapse to opioid use (Wills 1994). To assist stimulant detoxification, psychiatric counselling and support has a major impact. Psychiatric disorders should be treated symptomatically, and antidepressants may be useful in treating any concomitant major depression. Dexamphetamine sulfate has been prescribed for amphetamine misuse, although its effectiveness is unclear as a substitution tactic (Mattick & Darke 1995).

Longer-term dose reduction regimens for opioid withdrawal invariably rely on oral methadone as a substitute for the drug of abuse, whereby after a stabilization period,

the methadone dose is reduced over a period of 4 to 6 months. As with the rapid detoxification method, this approach is most effective when the patient is motivated and willing to make lifestyle changes. This longer-term reduction approach can also be used to treat benzodiazepine misuse. The patient is initially transferred to diazepam, which has a relatively long half-life (and so can be given once a day), and the dose reduced as appropriate.

Maintenance prescribing is used where other treatment options have failed, with the intention of reducing injecting behaviour, illicit opioid use and criminal activity. Methadone mixture is most widely used and studies from the United States suggest that large doses may be appropriate to prevent the concomitant use of illicit street drugs (D'Aunno & Vaughn 1992). Other possible compounds include buprenorphine, which is licensed, and levo-a-acetylmethadol or LAAM, which is not licensed in the UK (Wills 1994).

Possible novel management strategies

The recent introduction of two new drugs to the market has raised the possibility of a non-opioid treatment strategy for opioid dependence. Acamprosate (mentioned briefly above in relation to ethanol addiction), and bupropion (or Zyban) have both been granted UK product licences for the treatment of ethanol and nicotine addiction, respectively. In addition to its role in maintaining abstinence in ethanol addiction, the ability of acamprosate to attenuate the aversive nature of opioid withdrawal has been studied using place conditioning. The conditioned place aversion associated with naloxone precipitated morphine withdrawal has been shown to be inhibited by acamprosate (Kratzer & Schmidt 1998). The underlying mechanism responsible for this effect remains unclear, although acamprosate is not self-administered (Grant & Woolverton 1989), thus substitution for the opioid is unlikely, while an interaction with NMDA receptors has been suggested (Kratzer & Schmidt 1998).

Studies in our laboratory have shown the serotonin selective reuptake inhibitors (SSRIs), fluvoxamine and paroxetine, to have some effect on naloxone precipitated withdrawal aversion. Acute administration of fluvoxamine and chronic treatment with paroxetine reduced the conditioned place aversion seen after naloxone administration to opioid-dependent subjects (Rafieian-Kopaei et al 1995). This effect may be owing to an interaction with dopaminergic neurotransmission, which is also implicated in the rewarding properties of SSRIs (Subhan et al 2000). Bupropion is a non-tricyclic antidepressant, which has been marketed successfully as an aid in smoking cessation. In common with most other antidepressants, it is an inhibitor of monoamine reuptake, although its efficacy is quite low, with inhibitor constants (K_i values) for noradrenaline and serotonin approximately 160-times higher than amitriptyline. However, its inhibition of the dopamine transporter is more comparable with SSRIs (Bolden-Watson & Richelson 1993), and drug discrimination studies have demonstrated that dopamine reuptake inhibitors will substitute for bupropion (Terry & Katz 1997). This suggests that inhibition of dopamine reuptake is a likely anti-addictive mechanism of bupropion, which may render it useful in managing a range of drug dependencies.

As mentioned previously, neuroleptics such as clozapine and olanzapine appear to counteract reward, and may constitute novel treatment options for cocaine dependence. Unfortunately, these compounds are associated with troublesome motor side-effects through inhibition of D_2 receptor function. The cloning of multiple dopamine receptors has, however, facilitated the development of selective dopamine agonists and antagonists. Recently, it has been reported that the D_3 partial agonist, BP 897, attenuates cocaine seeking behaviour, perhaps through an interaction in the NAc (Pilla et al 1999), since this is an area rich in D_3 receptors (Levesque et al 1992). Other studies have also suggested a role for the D_3 receptor in drug addiction (Caine & Koob 1993; Staley & Marsh 1996), and the use of selective ligands at this receptor may represent a useful approach in the management of dependence to stimulant drugs.

The aldehyde dehydrogenase inhibitor, disulfiram, is clinically approved for the supervised management of alcohol dependence. Recent studies suggest that it reduces cocaine intake among opioid addicts undergoing methadone maintenance therapy, possibly via inhibition of dopamine b-hydroxylase (Carroll et al 2000; George et al 2000; Petrakis et al 2000). Inhibition of this metabolizing enzyme would tend to reduce the conversion of dopamine into norepinephrine, leading to a generalized increase in dopamine levels at the expense of norepinephrine. Consequently, the positive reinforcing properties of cocaine as a catecholamine reuptake inhibitor might be dulled (Petrakis et al 2000). There is some evidence to suggest that the indole alkaloid, ibogaine, also reduces the abuse of opioids and alcohol, in addition to nicotine. The underlying mechanism is poorly understood, although ibogaine does appear to modulate dopaminergic neurotransmission, possibly through interactions with j opioid and NMDA receptors, or the serotonergic system (Sershen et al 1997). Animal studies have reported a reduction in opioid withdrawal symptoms and decreased cocaine self-administration, although these effects are species dependent (for review see Sershen et al 1997). Clinical evidence for the efficacy of ibogaine in treating addiction is currently limited. There are reports that opioid users abstain from their habit after ibogaine treatment and, furthermore, that morphine and cocaine craving is attenuated (Sheppard 1994; Kovera et al 1998).

One of the more innovative approaches to the management of drug addictive states is immunization. Abused drugs, such as cocaine, are generally small molecules that do not tend to induce antibody production when taken alone. They therefore need to be conjugated with a much larger molecule (hapten) in order to be recognized by the immune system. In the case of cocaine, keyhole-limpet hemocyanin (KLH) is most often used as the hapten. Immunization with cocaine–KLH conjugate generates antibodies that bind to administered cocaine rendering it so large as to be unable to penetrate the brain in quantities capable of eliciting central effects. This has been demon-

strated using both self-administration (Carrera et al 2000) and drug discrimination paradigms (Johnson & Ettinger 2000). However, excessive intake of cocaine may conceivably saturate the antibodies, leaving unbound drug free to access the brain in amounts sufficient to generate positive reinforcement (Johnson & Ettinger 2000; Kantak et al 2000). The immunization approach has also been utilized for nicotine addiction, although similar doubts concerning antibody saturation have been raised (e.g. Hieda et al 1999). Furthermore, although these studies go to great lengths to establish the specificity of the antibodies generated, this becomes a problem in dealing with opioid-based addictive states, where one compound may be more easily substituted for another. It also gives cause for concern regarding other abused drugs, whereby addicts will simply swap to other, possibly totally synthetic, compounds (''designer drugs'').

Endogenous butyrylcholinesterase (BchE) is responsible for hydrolyzing peripherally circulating cocaine into two inactive metabolites: ecgonine methylester and benzoic acid. The activity of this enzyme can be dramatically enhanced by direct administration, the effectiveness of a single injection of BchE lasting for several days (Gorelick 1997). This alone has been explored as a possible therapeutic avenue, but another immunization approach is based on the generation of catalytic antibodies (Landry et al 1993), founded on the known action of BchE. Catalytic antibodies are designed to bind and breakdown cocaine before penetration of the blood–brain barrier (Landry et al 1993). Both direct BchE administration and catalytic antibody treatment are vulnerable to saturation, but may have potential as antidotes for extreme cocaine intake. However, both of these methods depend on modifying the pharmacokinetic profile of the abused drug, rather than manipulating CNS function. Thus, they should be less susceptible to side-effects, except those that might be predicted from any compound capable of affecting the immune system (namely allergenic activity).

Summary

This overview has attempted to highlight the brain regions associated with reward, and the pathways and neurotransmitters responsible for communication between these regions. Work conducted in this field has shown that stimulants and opioids, despite interactions with different receptor types and different neurotransmitter reuptake transporters, appear to share a common action on brain reward pathways. Their effects on these pathways (the distinct brain regions making up the mesocorticolimbic dopaminergic system) are predominantly mediated through changes in dopamine neurotransmission, and compounds aimed at selectively modulating these effects may form the basis of drugs to treat addiction. Other transmitters such as GABA, acetylcholine and serotonin inevitably have a role to play in reward, although at present the exact nature of their effects remains unclear. Diverging from manipulating the CNS directly as a management strategy for dependence, it might be possible to exploit the immune system to prevent administered psychostimulants penetrating the brain, but antibody saturation and specificity are problematic.

References

Bals-Kubik, R., Ableitner, A., Herz, A., Shippenberg, T. S. (1993) Neuroanatomical sites mediating the motivational effects of opioids mapped by the conditioned place preference paradigm in rats. *J. Pharmacol. Exp. Ther.* **264**: 489–495

Beckett, A. H., Casy, A. F. (1954) Synthetic analgesics: stereochemical considerations. *J. Pharm. Pharmacol.* **6**: 986–1001

Bellingham, C. (2001) Recent developments in treating opiate misuse. *Pharm. J.* **266**: 541

Bolanos, C. A., Garmsen, G. M., Clair, M. A., McDougall, S. A. (1996) Effects of the j -opioid receptor agonist U-50,488 on morphine-induced place preference conditioning in the developing rat. *Eur. J. Pharmacol.* **317**: 1–8

Bolden-Watson, C., Richelson, E. (1993) Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci.* **52**: 1023–1029

Bozarth, M. A., Wise, R. A. (1981) Intracranial self-administration of morphine into the ventral tegmental area in rats. *Life Sci.* **28**: 551–555

Breiter, H. C., Gollub, R. L., Weisskoff, R. M., Kennedy, D. N., Makris, N., Berke, J. D., Goodman, J. M., Kantor, H. L., Gastfriend, D. R., Riorden, J. P., Thomas Matthew, R., Rosen, B. R., Hyman, S. E. (1997) Acute effects of cocaine on human brain activity and emotion. *Neuron* **19**: 591–611

Bunzow, J. R., Saez, C., Mortrud, M., Bouvier, C., Williams, J. T., Low, M., Grandy, D. K. (1994) Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a mu, delta or kappa receptor type. *FEBS Lett.* **347**: 284–288

Caine, S. B., Koob, G. F. (1993) Modulation of cocaine self-administration in the rat through D_3 dopamine receptors. *Science* **260**: 1814–1816

Calo, G., Guerrini, R., Rizzi, A., Salvadori, S., Regoli, D. (2000) Pharmacology of nociceptin and its receptor: a novel therapeutic target. *Br. J. Pharmacol.* **129**: 1261–1283

Carboni, E., Tanda, G. L., Frau, R., Di Chiara, G. (1990) Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: evidence that dopamine is taken up in vivo by noradrenergic terminals. *J. Neurochem.* **55**: 1067–1070

Carrera, M. R. A., Ashley, J. A., Zhou, B., Wirsching, P., Koob, G. F., Janda, K. D. (2000) Cocaine vaccines: antibody protection against relapse in a rat model. *Proc. Natl Acad. Sci. USA* **97**: 6202–6206

Carroll, K. M., Nich, C., Ball, S. A., McCance, E., Frankforter, T. L., Rounsaville, B. J. (2000) One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. *Addiction* **95**: 1335–1349

Centonze, D., Picconi, B., Baunez, C., Borrelli, E., Pisani, A., Bernardi, G., Calabresi, P. (2002) Cocaine and amphetamine depress striatal GABAergic synaptic transmission through D2 dopamine receptors. *Neuropsychopharmacology* **26**: 164–175

Chen, N., Reith, M. E. A. (2000) Structure and function of the dopamine transporter. *Eur. J. Pharmacol.* **405**: 329–339

Christie, M. J., Williams, J. T., Osborne, P. B., Bellchambers, C. E. (1997) Where is the locus in opioid withdrawal? *Trends Pharmacol. Sci.* **18**: 134–140

Colpaert, F. C. (1978) Discriminative stimulus properties of narcotic analgesic drugs. *Pharmacol. Biochem. Behav.* **9**: 863–887

Crain, S. M., Shen, K.-F. (1998) Modulation of opioid tolerance and dependence by G_s-coupled, GM1 ganglioside-regulated opioid receptor functions. *Trends Pharmacol. Sci.* **19**: 358–365

D'Aunno, T., Vaughn, T. E. (1992) Variations in methadone treatment practices: results from a national study. *JAMA* **267**: 253–258

Davis, W. M., Smith, S. G. (1975) Effect of haloperidol on (+)-amphetamine self-administration. *J. Pharm. Pharmacol.* **27**: 540–542

Department of Health/Welsh Office (1999) *Drug misuse and dependence: guidelines on clinical management.* London, HMSO

Devine, D. P., Reinscheid, R. K., Monsma, F. J. J. R., Civelli, O., Akil, H. (1996) The novel neuropeptide orphanin FQ fails to produce conditioned place preference or aversion. *Brain Res.* **727**: 225–229

DeWit, H., Wise, R. A. (1977) Blockade of cocaine reinforcement in rats with the dopamine blocker pimozide, but not with the noradrenergic blockers phentolamine and phenoxybenzamine. *Can. J. Psychol.* **31**: 195–203

Dhawan, B. N., Cesselin, F., Raghubir, R., Reisine, T., Bradley, P. B., Portoghese, P. S., Hamon, M. (1996) International Union of Pharmacology. XII. Classification of opioid receptors. *Pharmacol. Rev.* **48**: 567–592

Di Chiara, G. (1998) A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. *Psychopharmacology* **12**: 54–67

Di Chiara, G., Imerato, A. (1988a) Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. *J. Pharmacol. Exp. Ther.* **244**: 1067–1080

Di Chiara, G., Imperato, A. (1988b) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc. Natl Acad. Sci. USA* **85**: 5274–5278

Douglass, J., McKinzie, A., Couceyro, P. (1995) PCR differential display identifies a rat brain mRNA that is transcriptionally regulated by cocaine and amphetamine. *J. Neurosci.* **15**: 2471–2481

Emmerson, P. J., Liu, M. R., Woods, J. H., Medzihradsky, F. (1994) Binding affinity and selectivity of opioids at mu, delta and kappa receptors in monkey brain membrane. *J. Pharmacol. Exp. Ther.* **271**: 1630–1637

Ettenberg, A., Pettit, H. O., Bloom, F. E., Koob, G. F. (1982) Heroin and cocaine self-administration in rats: mediation by separate neuronal systems. *Psychopharmacology* **78**: 204–209

Finlay, J. M., Jakubovic, A., Phillips, A. G., Fibiger, H. C. (1988) Fentanyl-induced conditional place preference: lack of associated neurochemical events. *Psychopharmacology* **96**: 534–540

Gawin, F. H., Allen, D., Humblestone, B. (1989) Outpatient treatment of "crack" cocaine smoking with flupenthixol decanoate. *Arch. Gen. Psychiatry* **46**: 322–325

George, T. P., Chawarski, M. C., Pakes, J., Carroll, K. M., Kosten, T. R., Schottenfeld, R. S. (2000) Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. *Biol. Psychiatry* **47**: 1080–1086

Gerrits, M. A. F. M., Patkina, N., Zvartau, E. E., van Ree, J. M. (1995) Opioid blockade attenuates acquisition and expression of cocaine-induced place preference conditioning in rats. *Psychopharmacology* **119**: 92–98

Goeders, N. E., Smith, J. E. (1983) Cortical dopaminergic involvement in cocaine reinforcement. *Science* **221**: 773–775

Gorelick, D. A. (1997) Enhancing cocaine metabolism with butyrylcholinesterase as a treatment strategy. *Drug Alcohol Depend.* **48**: 159–165

Grant, K. A., Woolverton, D. (1989) Reinforcing and discriminative stimulus effects of calcium-acetyl homotaurinate in animals. *Pharmacol. Biochem. Behav.* **32**: 607–611

Grant, S., London, E. D., Newlin, D. B., Villemagne, V. L., Liu, X., Contoreggi, C., Phillips, R. L., Kimes, A. S., Margolin, A. (1996) Activation of memory circuits during cue-elicited cocaine craving. *Proc. Natl Acad. Sci. USA* **93**: 12040–12045

Guthrie, S. K. (1990) Pharmacologic interventions for the treatment of opioid dependence and withdrawal. *Ann. Pharmacother.* **24**: 721–734

Hieda, Y., Keyler, D. E., Van DeVoort, J. T., Niedbala, R. S., Raphael, D. E., Ross, C. A., Pentel, P. R. (1999) Immunization of rats reduces nicotine distribution to brain. *Psychopharmacology (Berl)* **143**: 150–157

Hokfelt, T., Rehfeld, J., Skirboll, L., Ivemark, B., Goldstein, M., Markey, K. (1980) Evidence for the coexistence of dopamine and CCK in mesolimbic neurones. *Nature* **285**: 476–477

Imperato, A., Obinu, M. C., Casu, M. A., Mascia, M. S., Carta, G., Gessa, G. L. (1996) Chronic morphine increases hippocampal acetylcholine release: possible relevance in drug dependence. *Eur. J. Pharmacol.* **302**: 21–26

Johnson, M. W., Ettinger, R. H. (2000) Active cocaine immunization attenuates the discriminative properties of cocaine. *Exp. Clin. Psychopharmacol.* **8**: 163–167

Johnson, S. W., North, R. A. (1992) Opioids excite dopamine neurons by hyperpolarisation of local interneurons. *J. Neurosci.* **12**: 483–488

Kalivas, P. W., Burgess, S. K., Nemeroff, C. B., Prange, A. J. (1983) Behavioural and neurochemical effects of neurotensin microinjection into the ventral tegmental area of the rat. *Neuroscience* **8**: 495–505

Kantak, K. N., Collins, S. L., Lipman, E. G., Bond, J., Giovanoni, K., Fox, B. S. (2000) Evaluation of anti-cocaine antibodies and a cocaine vaccine in a rat self-administration model. *Psychopharmacology* **148**: 251–262

Kimmel, H. L., Gong, W., DallVechia, S., Hunter, R. G., Kuhar, M. J. (2000) Intra-ventral tegmental area injection of rat cocaine and amphetamine-regulated transcript peptide 55-102 induces locomotor activity and promotes conditioned place preference. *J. Pharmacol. Exp. Ther.* **294**: 784–792

Kleven, M. S., Perry, B. D., Woolverton, W. L., Seiden, L. S. (1990) Effects of repeated injections of cocaine on D_1 and D_2 dopamine receptors in rat brain. *Brain Res.* **532**: 265–270

Koob, G. F. (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol. Sci.* **13**: 177–184

Koob, G. F., Sanna, P. P., Bloom, F. E. (1998) Neuroscience of addiction. *Neuron* **21**: 467–476

Kovera, C. A., Kovera, M. B., Singleton, E. G., Ervin, F. R., Williams, I. C., Mash, D. C. (1998) Decreased drug craving during inpatient detoxification with ibogaine. *NIDA Res. Monogr.* **179**: 294

Kratzer, U., Schmidt, W. J. (1998) The anti-craving drug acamprosate inhibits the conditioned place aversion induced by naloxone-precipitated morphine withdrawal in rats. *Neurosci. Lett.* **252**: 53–56

Kuhar, M. J., Joyce, A., Dominguez, G. (2001) Genes in drug abuse. *Drug Alcohol Depend.* **62**: 157–162

Landry, D. W., Zhao, K., Yang, G. X. Q., Glickman, M., Georgiadis, T. M. (1993) Antibody-catalyzed degradation of cocaine. *Science* **259**: 1899–1901

Leone, P., Di Chiara, G. (1987) Blockade of D-1 receptors by SCH23390 antagonises morphine-induced place preference conditioning. *Eur. J. Pharmacol.* **135**: 251–254

Levesque, D., Diaz, J., Pilon, C., Martres, M.-P., Giros, B., Souil, E., Schott, D., Morgat, J.-L., Schwartz, J.-C., Sokoloff, P. (1992) Identification, characterization and localization of the dopamine D_3 receptor in rat brain using 7-[^{3}H]-hydroxy-N,N di-n-propyl-2-aminotetralin. *Proc. Natl Acad. Sci. USA* **89**: 8155–8159

Liechti, M. E., Vollenweider, F. X. (2000) The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. *J. Psychopharmacol.* **14**: 269–274

Mackey, W. B., Van der Kooy, D. (1985) Neuroleptics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning. *Pharmacol. Biochem. Behav.* **15**: 159–160

Mansour, A., Khachaturian, H., Lewis, M. E., Akil, H., Watson, S. J. (1988) Anatomy of CNS opioid receptors. *Trends Neurosci.* **11**: 308–314

Mansour, A., Fox, C. A., Akil, H., Watson, S. J. (1995) Opioid-receptor mRNA expression in the rat CNS: anatomical and functional implications. *Trends Neurosci.* **18**: 22–29

Mattick, R. P., Darke, S. (1995) Drug replacement treatments: is amphetamine substitution a horse of a different colour? *Drug Alcohol Rev.* **14**: 388–394

Meert, T., Clincke, G. (1992) Evidence for a possible role of the 5-HT_2 antagonist ritanserin in drug abuse. *Ann. N. Y. Acad. Sci.* **654**: 483–486

Meil, W. M., Schechter, M. D. (1997) Olanzapine attenuates the reinforcing effects of cocaine. *Eur. J. Pharmacol.* **340**: 17–26

Meltzer, H. Y., Matusaubara, S., Lee, J. C. (1989) Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin$_2$ pKi values. *J. Pharmacol. Exp. Ther.* **251**: 238–246

Meunier, J. C., Mollereau, C., Toll, L., Suaudeau, C., Moisand, C., Alvinerie, P., Butour, J. L., Guillemot, J. C., Ferrara, P., Monserrat, B., Mazarguil, H., Vassart, G., Meunier, J. C. (1997) Nociceptin/orphanin FQ and the opioid receptor-like ORL1 receptor. *Eur. J. Pharmacol.* **340**: 1–15

Mucha, R. F., Herz, A. (1985) Motivational properties of j and l opioid receptor agonists studied with taste and place preference conditioning procedure. *Psychopharmacology* **86**: 274–280

Mucha, R. F., Iversen, S. D. (1984) Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: a procedural examination. *Psychopharmacology* **82**: 241–247

Mucha, R. F., Van Der Kooy, D., O'Shaughnessy, M., Bucenieks, P. (1982) Drug reinforcement studied by the use of place conditioning in rat. *Brain Res.* **243**: 91–105

Murphy, N. P., Lee, Y., Maidment, N. T. (1999) Orphanin FQ/nociceptin blocks acquisition of morphine place preference. *Brain Res.* **832**: 168–170

Nestler, E. J. (2001) Molecular basis of long term plasticity underlying addiction. *Nat. Rev. Neurosci.* **2**: 119–128

Olds, J., Milner, P. M. (1954) Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol.* **47**: 419–427

Olds, M. E. (1982) Reinforcing effects of morphine in the nucleus accumbens. *Brain Res.* **237**: 429–440

Olmstead, M. C., Franklin, K. B. J. (1997) The development of a conditioned place preference to morphine: effects of microinjections into various CNS sites. *Behav. Neurosci.* **111**: 1324–1334

Pan, Z. Z. (1998) l -Opposing actions of the j -opioid receptor. *Trends Pharmacol. Sci.* **19**: 94–98

Pan, Z. Z., Tershner, S. A., Fields, H. L. (1997) Cellular mechanism for anti-analgesic action of agonists of the j -opioid receptor. *Nature* **389**: 382–385

Petrakis, I. L., Carroll, K. M., Nich, C., Gordon, L. T., McCance-Katz, E. F., Frankforter, T., Rounsaville, B. J. (2000) Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction* **95**: 219–228

Phillips, A. G., Rolls, E. T. (1981) Intracerebral self-administration of amphetamine by rhesus monkeys. *Neurosci. Lett.* **24**: 81–86

Pieretti, S., Di Giannuario, A. (1999) Orphanin FQ effects on morphine-induced dopamine release in the accumbens of rats. *Regul. Pept.* **80**: 126

Pilla, M., Perachon, S., Sautel, F., Garrido, F., Mann, A., Wermuth, C. G., Schwartz, J.-C., Everitt, B., Sokoloff, P. (1999) Selective inhibition of cocaine-seeking behaviour by a partial dopamine D receptor agonist. *Nature* **400**: 371–375

Portoghese, P. S. (1965) A new concept on the mode of interaction of narcotic analgesics with receptors. *J. Med. Chem.* **8**: 609–616

Rafieian-Kopaei, M., Gray, A. M., Spencer, P. S. J., Sewell, R. D. E. (1995) Contrasting actions of acute or chronic paroxetine and fluvoxamine on morphine withdrawal-induced place conditioning. *Eur. J. Pharmacol.* **275**: 185–189

Reinscheid, R. K., Nothacker, H. P., Bourson, A., Ardati, A., Henningsen, R. A., Bunzow, J. R., Grandy, D. K., Langen, H., Monsma, F. J. J. R., Civelli, O. (1995) Orphanin FQ: a neuropeptide that activates an opioid like G protein-coupled receptor. *Science* **270**: 792–794

Richelson, E., Pfenning, M. (1984) Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes: most antidepressants selectively block norepinephrine uptake. *Eur. J. Pharmacol.* **104**: 277–286

Roberts, D. C. S., Andrews, M. M. (1997) Baclofen suppression of cocaine self-administration: demonstration using a discrete trials procedure. *Psychopharmacology* **131**: 271–277

Roberts, D. C. S., Vickers, G. (1984) Atypical neuroleptics increase self-administration of cocaine: an evaluation of a behavioural screen for antipsychotic activity. *Psychopharmacology* **82**: 135–139

Sala, M., Braida, D., Calcaterra, P., Leone, M. P., Gori, E. (1992) Dose-dependent conditioned place preference produced by etonitazene and morphine. *Eur. J. Pharmacol.* **217**: 37–41

Self, D. W., Nestler, E. J. (1995) Molecular mechanism of drug reinforcement and addiction. *Annu. Rev. Neurosci.* **18**: 463–495

Sershen, H., Hashim, A., Lajtha, A. (1997) Ibogaine and cocaine abuse: pharmacological interactions at dopamine and serotonin receptors. *Brain Res. Bull.* **42**: 161–168

Sheppard, S. G. (1994) A preliminary investigation of ibogaine: case reports and recommendations for further study. *J. Subst. Abuse Treat.* **11**: 379–385

Shippenberg, T. S., Herz, A. (1988) Motivational effects of opioids: influence of D-1 versus D-2 receptor antagonists. *Eur. J. Pharmacol.* **151**: 233–242

Shippenberg, T. S., Herz, A. (1991) Influence of chronic lithium treatment upon the motivational effects of opioids: alteration in the effects of mu- but not kappa-opioid receptor ligands. *J. Pharmacol. Exp. Ther.* **256**: 1101–1106

Shippenberg, T. S., Bals-Kubik, R., Herz, A. (1987) Motivational properties of opioids: evidence that an activation of receptors mediates reinforcement processes. *Brain Res.* **436**: 234–239

Shippenberg, T. S., Bals-Kubik, R., Herz, A. (1993) Examination of the neurochemical substrates mediating the motivational effects of opioids: role of the mesolimbic dopamine system and D-1 vs. D-2 dopamine receptors. *J. Pharmacol. Exp. Ther.* **265**: 53–59

Sklair-Tavron, L., Shi, W.-X., Lane, S. B., Harris, H. W., Bunney, B. S., Nestler, E. J. (1996) Chronic morphine induces visible changes in the morphology of mesolimbic dopamine neurons. *Proc. Natl Acad. Sci. USA* **93**: 11202–11207

Sora, I., Wichems, C., Takahahsi, N., Li, X.-F., Zeng, Z., Revay, R., Lesch, K.-P., Murphy, D. L., Uhl, G. R. (1998) Cocaine reward models: conditioned place preference can be established in dopamine- and in serotonin-transporter knockout mice. *Proc. Natl Acad. Sci. USA* **95**: 7699–7704

Staley, J. K., Marsh, D. C. (1996) Adaptive increase in D_3 dopamine receptors in the brain reward circuits of human cocaine fatalities. *J. Neurosci.* **16**: 6100–6106

Stolerman, I. (1992) Drugs of abuse: behavioural principles, methods and terms. *Trends Pharmacol. Sci.* **13**: 170–176

Subhan, F., Deslandes, P. N., Pache, D. M., Sewell, R. D. E. (2000) Do antidepressants affect motivation in conditioned place preference? *Eur. J. Pharmacol.* **408**: 257–264

Suzuki, T., Misawa, M. (1995) Sertindole antagonizes morphine-, cocaine-, and methamphetamine-induced place preference in rat. *Life Sci.* **57**: 1277–1284

Tanda, G., Carboni, E., Frau, R., Di Chiara, G. (1994) Increase of extracellular dopamine in the prefrontal cortex: a trait of drugs with antidepressant potential? *Psychopharmacology* **115**: 285–288

Tanda, G., Bassareo, V., Di Chiara, G. (1996) Mianserin markedly and selectively increases extracellular dopamine in the prefrontal cortex as compared to the nucleus accumbens of the rat. *Psychopharmacology (Berl)* **123**: 127–130

Terry, P., Katz, J. L. (1997) Dopaminergic mediation of the discriminative stimulus effects of bupropion in rats. *Psychopharmacology* **134**: 201–212

Trujillo, K. A., Belluzzi, J. D., Stein, L. (1991) Naloxone blockade of amphetamine place preference conditioning. *Psychopharmacology* **104**: 265–274

Trujillo, K. A., Herman, J. P., Schafer, M. K.-H., Mansour, A., Meador-Woodruff, J. H., Watson, S. J., Akil, H. (1993) Drug reward and brain circuitry: recent advances and future directions. In: Korenman, S. G., Barchas, J. D. (eds) *Biological basis of substance abuse*. New York, Oxford University Press, pp 119–142

Uhl, G. R., Childers, S., Pasternak, G. (1994) An opiate-receptor gene family reunion. *Trends Neurosci.* **17**: 89–93

Unterwald, E. M., Ho, A., Rubenfeld, J. M., Kreek, M. J. (1994) Time course of the development of behavioral sensitization and dopamine receptor up-regulation during binge cocaine administration. *J. Pharmacol. Exp. Ther.* **270**: 1387–1396

Van Ree, J. M., Slangen, J. L., De Wied, D. (1978) Intravenous self-administration of drugs in rats. *J. Pharmacol. Exp. Ther.* **204**: 547–557

Van Tol, H. H. M., Bunzow, J. R., Guan, H. C., Sunahara, R. K., Seeman, P., Niznick, H. B., Civelli, O. (1991) Cloning of a gene for the human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature* **350**: 610–614

Wang, J. B., Johnson, P. S., Imai, Y., Persico, A. M., Ozenberger, B. A., Eppler, C. M., Uhl, G. R. (1994) cDNA cloning of an orphan opiate receptor gene family member and its splice variant. *FEBS Lett.* **348**: 75–79

Wilde, M. I., Wagstaff, A. J. (1997) Acamprosate: a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs* **53**: 1038–1053

Wills, S. (1994) Drugs and substance misuse: opioids. *Pharm. J.* **252**: 157–160

Wilson, J. M., Sanyal, S., Van Tol, H. H. M. (1998) Dopamine D_2 and D_4 receptor ligands: relation to antipsychotic action. *Eur. J. Pharmacol.* **351**: 273–286

Zeigler, S., Lipton, J., Toga, A., Ellison, G. (1991) Continuous cocaine administration produces persisting changes in brain neurochemistry and behavior. *Brain Res.* **552**: 27–35

Zito, K. A., Vickers, G., Roberts, D. C. S. (1985) Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens. *Pharmacol. Biochem. Behav.* **23**: 1029–1036