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REVIEW ARTICLE

Could a common biochemical mechanism underlie addictions?

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SUMMARY

The subject of 'drug addiction' is multifaceted and many aspects of it (even some of the definitions) are controversial. Collateral medical problems include the spread of HIV and hepatitis C virus secondary to i.v. drug abuse and effects on prenatal brain development (1). Progress in the understanding of the causes of addictions and its treatment has been impeded by the lack of a unifying biochemical theory. However, recent evidence suggests that some common mechanism might underlie addictions to otherwise apparently unrelated drugs. A major hypothesis has emerged suggesting that the neurotransmitter dopamine (DA) might play a central role in the molecular mechanisms of at least some addictions. If so, it would represent an important target for discovery of effective pharmacotherapy and revolutionize the pharmacist's role in treating addictions. This short overview outlines the status of the theory of a common biochemical mechanism of drug addiction.

IMPORTANCE OF THE QUESTION

Various pharmacological substances are abused. Although individual mechanisms of action are known for most of these substances, it is now recognized that many of them might directly or indirectly modulate the same biochemical process(es) within the brain which cause homeostatic dysregulation, alter the hedonic 'set-point' and activate the biochemical 'switch' that leads to chronic and detrimental drug abuse ('addiction'), craving and relapse (2–4). If a common biochemical mechanism exists, two positive outcomes might result: 'addicts' might be better treated as 'patients' and suitable pharmacotherapeutic treatment options might be discovered that would eliminate or ameliorate the condition (5, 6).

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DEFINITIONS

It is important first to define what constitutes drug 'addiction' and what does not. As described by the present Director of NIDA (National Institute on Drug Abuse, a division of the National Institutes of Health), drug addiction is ''… compulsive drug use without medical purpose and in the face of negative consequences'' (7). Continuity of use is not part of the definition, because 'binge' patterns of use should not be excluded. Likewise, physical or psychological dependence (i.e. dysphoric withdrawal symptoms upon cessation of use) are not included. Although one might suspect that avoidance of withdrawal symptoms might be sufficient motivation to continue drug use: (i) appropriate medication can manage even the florid symptoms of heroin withdrawal and (ii) many of the most addicting drugs, such as crack cocaine and methamphetamine, do not produce dramatic withdrawal symptoms (8). Perhaps less understood, is that the development of 'tolerance' is not part of the definition. The development of 'tolerance' (the requirement of more drug in order to maintain the same level of effect or, conversely, the progressive decrease in a drug's apparent potency with repetitive use) is a pharmacological property shared by many drugs, not only drugs of abuse. Although tolerance is a characteristic that often accompanies the abuse of some drugs, it does not by itself constitute a determination of 'addiction' or of an 'addict'. The contrary misconception is easily

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understandable, but just as easily dismissed when one considers the ever-increasing amounts of morphine that a patient with progressive cancer requires in order to relieve the ever-increasing level of pain. It would be incorrect to characterize such a patient as a 'drug addict'. Caffeine can be considered here as reference. Although use of the substance mirrors in many ways the use of 'drugs of abuse', the absence of obvious deleterious consequences for the individual or society highlights the importance of proper differentiation of scientific description of drug-use patterns and concomitant biochemical changes from the pattern of socially unacceptable and harmful pattern of behaviour that is commonly called 'addiction'. Although caffeine is the world's most widely consumed behaviourally active substance (9), its use is not restricted by regulatory agencies and it is not generally considered a drug of abuse. However, dependence and withdrawal occur and the associated behaviour serves as a background against which the criteria for how true drug 'addiction' is defined and regulatory issues are to be decided. It is important to note that not all psychoactive substances are abused.

The Director of NIDA also argues that recent biological research findings lead to the conclusion that drug 'addiction' is different from drug 'abuse'. Specifically, that ''Drug use and drug addiction do not reside together along a continuum, say, drug use, drug abuse, a whole lot of drug abuse, and then addiction …. Addiction is a qualitatively different state because the addicted brain is, in fact, different in its neurobiology from the non-addicted brain'' (7). What might at first seem an extreme position, the view that addiction is a ''brain disease'' (8), indeed a ''chronic, relapsing disorder'' set in a context of environmental, historical and physiological factors that affect the way in which drug use interacts with the brain (7, 8), might help explain why relapses are common and, more importantly, ''Elucidation of the biology underlying the metaphorical switch is key to the development of more effective treatments, particularly anti-addiction medications'' (8).

BACKGROUND (HISTORY)

The use of mood or 'mind-altering' drugs has prevailed for thousands of years (10). Ethanol (11) has been used for at least 8000 years, explainable in part because it was a safe alternative to contaminated drinking water. The custom of chewing coca leaves has been practised for over 1200 years. Cannabis (marijuana) use has existed in Asia for thousands of years and was used by the ancient Greeks (12). Similar historical use (often associated with religious ceremonies) applies to opium, mescaline (peyote), tobacco and a host of other centrally active substances.

The transition from ceremonial, recreational or even transient experimental drug use to 'drug addiction' is where the difficulty arises for the individual and for society. Reports of dependence in non-addicts following a single dose (13) or therapeutic use (14) of morphine are quite rare. Individuals show marked differences (vulnerability) in each aspect of drug abuse: initiation, maintenance, psychological and physical dependence, craving and propensity to relapse. Each might be influenced by genetic predisposition. However, the genetics of addictions are complex (15). Perhaps the most clearly established genetic influence is in a particularly virulent form of alcoholism (16). Genetic predisposition implies a biochemical basis.

POSSIBLE CONNECTIONS TO DOPAMINE

Through extensive investigation, the biochemistry of abused drugs is becoming more clear. Although abused drugs alter multiple brain pathways, they also appear to share some common effects. A prevailing view is that the primary brain circuits relevant to drug addiction (equated to activation of neurochemical reward pathways) involve dopaminergic pathways, such as the mesolimbic dopamine system (17–19). The mesolimbic dopamine system extends from dopamine (DA)-containing cell bodies within the ventral tegmental area (VTA) in brainstem to the nucleus accumbens (NuAcc) (part of the basal ganglia), prefrontal cortex and dorsal striatum and reciprocal projections. The hypothesis is that many abused substances (except perhaps the benzodiazepines) enhance dopamine release in either the nucleus accumbens, the prefrontal cortex or both (20). For example, amphetamine, cocaine, ethanol and nicotine all increase the intracellular levels of dopamine in the NuAcc and lesions of mesolimbic DA neurones attenuate

nicotine self-administration in rats (21–24). Areas that receive projections from the nucleus accumbens, such as the globus pallidus and amygdala, are also believed to be important. In addition, other monoaminergic nuclei, such as those in the locus coeruleus (norepinephrine-containing cell bodies) and raphe (5-HT containing cell bodies) are also believed to be important (17, 25). Furthermore, chronic use of drugs leads to the disruption of normal homeostatic levels of neurotransmitters, and abrupt withdrawal unmasks the compensatory adjustments, which may explain some of the dysphoric aspects of withdrawal syndromes (26).

The opiates, morphine and codeine, and related opioids such as heroin, produce their effects by mimicking the endogenous substances β-endorphin and Leu- and Met-enkephalin. Opioids activate 7-transmembrane G protein-coupled receptors, termed μ, δ and κ (27). The μ-opioid receptor appears to be the most closely associated with drug dependence, which has been linked to the DA system (28–30). Cocaine, derived from 'coca' (from the Aymara word 'khoka' meaning 'the tree') (31), produces multiple pharmacologic effects. It has a local anaesthetic action and is a vasoconstrictor (as a consequence of inhibition of neuronal reuptake of norepinephrine). The primary mechanism of action believed to be related to its misuse is the inhibition of the dopamine transporter, which is responsible for the reuptake of dopamine into the presynaptic nerve terminal (28, 32). Inhibition of the dopamine transporter (DA-T) increases the synaptic concentrations of dopamine, enabling more activation of DA receptors. This mechanism is supported by experiments on genetically altered mice which have been produced without the DA-T (33). These mice mimic the behavioural actions of cocaine without receiving the stimulant, and show no further changes in behaviour after cocaine administration (32, 33). Amphetamines block monoamine neuronal reuptake and enhance their release (34). Although amphetamines and cocaine raise synaptic concentrations of the three monoamine neurotransmitters norepinephrine (NE), DA and 5-HT, selective antagonists for only DA block the rewarding effects (35, 36). Ethanol has more diffuse and less specific actions than many of the other abused substances. GABA, opioid, N-methyl-D-aspartate (NMDA) and glycine receptors all appear to be affected directly or indirectly by ethanol (37). The sedation associated with ethanol can be attributed to enhanced GABA function (GABA is an inhibitory amino acid neurotransmitter). Some of the intoxicating effects of ethanol might be related to the inhibition of the effects of glutamate (the major excitatory amino acid in the brain) at its NMDA receptors (38), consistent with the association of NMDA receptors with alcohol withdrawal syndrome after chronic use has been discontinued (39). Opioid receptors have been implicated with ethanol abuse because the opioid antagonist drug naltrexone reduces the craving for alcohol and is used to treat alcoholism (28). Barbiturates enhance GABA function by increasing the duration of GABA-gated Cl^- influx. Δ^9-THC (Δ^9-tetrahydrocannabinol), the major active constituent of *Cannabis sativa*, acts at receptors (40) for endogenous cannabinoid (41). Two cannabinoid receptor subtypes (CB1 and CB2) (42), have been cloned and characterized. The CB1 subtype predominates in the brain (43). The neural basis of the mechanism(s) of action of abused inhalants (e.g. volatile alkyl nitrites such as amyl nitrite, nitrous oxide and volatile solvents, fuels and anaesthetics) is not well understood. It is possible that some of the effects involve smooth muscle relaxation (vasodilation), opioid systems, DA pathways or multiple other biochemical systems (44). The xanthines such as caffeine, theophylline and theobromine have multiple biochemical actions. It is presently believed that the chief mechanism of action of caffeine in humans is related to the blockade of G protein-linked adenosine receptors, particularly the adenosine A_1 and A_{2A} receptors (45). At high doses caffeine also blocks $GABA_A$ receptors, inhibits phosphodiesterases and increases intracellular calcium levels (9). The predominant action of nicotine is as an agonist at a subclass of acetylcholine receptors (nAChRs) located throughout the brain, with links to DA systems (46, 47).

A COMMON PATHWAY?

Many neurotransmitter systems are altered during chronic drug (ab)use. Dopamine appears to have a central role, particularly in the early stages of initiation of compulsive drug use (32, 48), as discussed below. Noradrenergic neurone activity is decreased in certain brain regions by opioids. The compensatory process produces a hyperadrenergic

state, which might explain some adrenergic-like symptoms during withdrawal and the amelioration of some of these symptoms by drugs such as clonidine, which inhibit the release of NE from the presynaptic nerve terminal (25). Interactions between the DA and NE systems can occur in the nucleus accumbens and prefrontal cortex, neuroanatomic areas thought to be important in drug abuse (49). Changes in 5-HT systems are believed to be involved in the changes in appetite, in the impulsivity, and in the craving following abstinence (25). Alterations in the nicotinic cholinergic receptor system follow chronic nicotine use (50). In addition, chronic use of drugs alters the levels of endogenous neuropeptides. In some instances the endorphins and enkephalins are activated, possibly explaining the therapeutic benefit of using the opioid antagonist naltrexone in the treatment of alcohol dependence (51). Chronic drug use also leads to cell molecular adaptations, such as at the level of second messenger transduction systems and protein transcription (12). Most important to the present review, though, is the hypothesis that many drugs of abuse share some common biochemical pathway(s).

NEUROCHEMICAL REWARD PATHWAY

Positive reinforcing effects are important for the establishment of a habit or pattern of continued drug use that might lead to drug-seeking behaviour (52). An anatomical pathway in the brain that is involved with reward or reinforcement of specific behaviours was described in 1954 by Olds and Milner (53). They found that rats would return to places where they received electrical stimulation in some brain regions, but not all. Whether or not stimulation of such regions leads to 'pleasure' is still debated. Nevertheless, activation of these neuronal pathways, either electrically or chemically, is unequivocally reinforcing and can maintain established behaviours, suggesting the concept of an anatomical reward pathway (54). As reviewed by Wise (49, 55), the mesolimbic dopamine system, including its projections to the nucleus accumbens, and local GABAergic afferents, has been most clearly associated with the habit-forming aspects of drugs of abuse. The evidence includes: (i) lesions in the NuAcc attenuate the rewarding effects of cocaine (56, 57) and amphetamine (58), (ii) rats learn to lever-press for microinjection into the NuAcc of amphetamine (59, 60), dopamine (61) and selective DA reuptake inhibitors (62), (iii) nACh receptors on DA cells are important for nicotine reward (24), and (iv) DA is elevated in the NuAcc by opioids, nicotine, ethanol and cannabis (20, 21, 63, 64). According to the extension of these findings to drug abuse, activation of reward pathways reinforces drug-seeking behaviour, possibly to a greater extent in individuals with an enhanced sensitivity or responsiveness to activation of the critical brain regions.

ANTI-REWARD SYSTEMS

Equally important to the overall problem are the factors that promote continued drug use, 'binge' patterns of use and relapse. In the case of maintenance, avoidance of negative reinforcement (in the form of dysphoric affective and physical withdrawal symptoms) plays an important, if not predominant (65), role. As reviewed by Kreek and Koob (66), chronic drug use alters a host of neurotransmitter (including DA) and other biochemical systems. Recent work has also suggested that protracted abstinence can change the 'set point' for hedonic processing or relieving physical or mental discomfort (67). A prolonged reward dysregulation occurs for all major drugs of abuse (67). Chronic drug use also results in the recruitment of systems, perhaps involving dynorphin, neuropeptide FF or orphanin FQ, which counteract the changes induced by the abused drugs (66). Hence, cessation of drug-taking results in physical and affective motivational impetus for reinstatement (relapse). Drug-seeking and drug-craving often persist despite long periods of abstinence, the consequence of long-term neuroadaptations in brain reward or anti-reward systems (68).

FINAL COMMON PATHWAY?

The basic research and clinical implications of a possible final common pathway involving dopamine has resulted in several excellent reviews in the scientific (18, 69, 70) and lay (19) press. It has also been a framework upon which other 'dependencies' such as on caffeine, chocolate, sugar, or even gambling or sex have been reevaluated (19). Recent

research has further narrowed the focus to the dopamine transporter (DA-T) or the brain vesicular monoamine transporter (VMAT2). The VMAT2 is a proton-dependent mechanism by which vesicles accumulate monoamines (including DA and 5-HT) from the cytoplasm. The DA-T is the protein-based mechanism by which the dopamine that is released into the synapse is reabsorbed into the presynaptic nerve terminal, terminating its action (Fig. 1). Several drugs associated with addiction affect VMAT2 or DA-T. In addition, transgenic mice that overexpress the DA-T have an enhanced place-preference for locations in which cocaine was previously experienced (71). In order to separate the role of DA transporters from other aspects of dopamine control mechanisms, molecular biological techniques have been applied to create mice that selectively lack VMAT2 or DA-T. Such mice are called 'knockouts' (KO), because VMAT2 or DA-T has been selectively knocked out, leaving other aspects of DA processing intact (Fig. 1B). These knock-outs offer a unique opportunity to study the importance of VMAT2 (72, 73) and DA-T (33, 71, 74, 75) to drug 'addiction'. They allow the comparison of total (homozygous, −/−) and partial (heterozygous, +/−) knockouts to normal ('wild type', +/+) mice. The application of this technique to drug dependence research has recently been reviewed (76, 77).

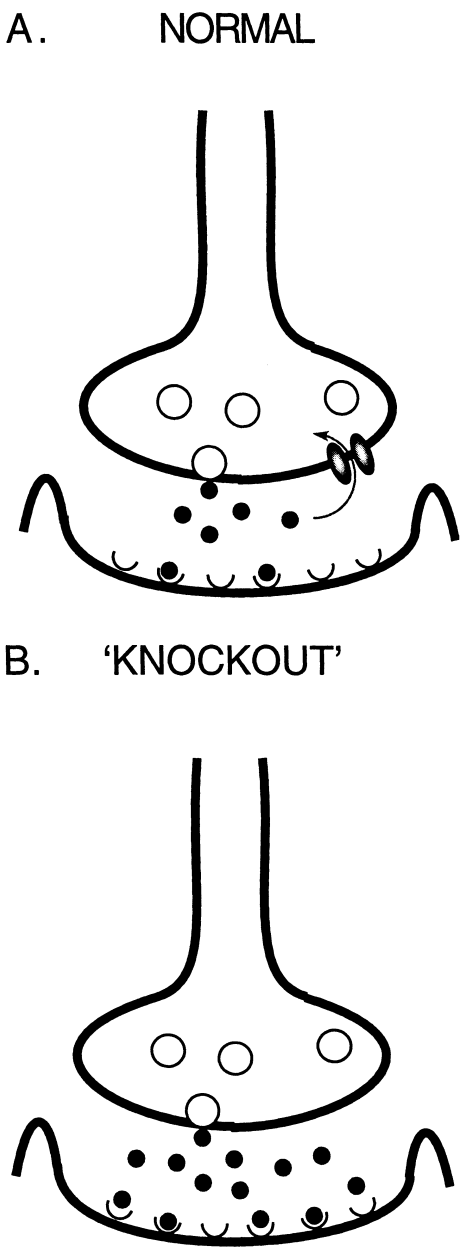

Fig. 1. The dopamine transporter (DA-T) provides a reuptake mechanism (arrow) by which DA (solid circles), released from vesicles (open circles) into the synaptic cleft, is reabsorbed into the presynaptic nerve terminal (A). In DA-T 'knockout' animals (B), the DA within synapses builds to higher concentrations and exerts a greater effect on the postsynaptic DA receptors.

KNOCKOUT MICE

In the first of such studies (Table 1) (33), mice made deficient in the DA-T were tested. In such mice, amphetamine does not increase extracellular DA (75). The wild-type (DA-$T^{+/+}$) and heterozygous knockout (DA-$T^{+/-}$) mice responded to amphetamine or cocaine with the usual increase in locomotor activity. However, neither amphetamine nor cocaine increased the locomotor activity of the homozygous knockouts (DA-$T^{-/-}$). Thus, there was a possibility that the DA-$T^{-/-}$ mice might also be unresponsive to the rewarding effects of amphetamine or cocaine. When this was tested in follow-up studies, DA-$T^{+/-}$ and DA-$T^{-/-}$ mice established a conditioned place-preference (preference for the place where drug was received) for cocaine or methylphenidate (71) and DA-$T^{-/-}$ mice still self-administered cocaine (74). Hence, to some extent the importance of the DA-T in addiction has come into question. However, it should be pointed out that cocaine might operate at several substrates in addition to the DA transporter and that an increase in extracellular DA might not be necessary and sufficient to maintain self-administration. Furthermore, possible compensatory adaptations in the

Table 1. Knockout mice

Ref.	Knockout	Results
Giros *et al*., 1996 (33)	DA-T[1]	'Indifferent' to the locomotor-stimulating effects of cocaine
Caron, 1997 (73)	VMAT2[2]	Supersensitive to the locomotor-stimulating effects of apomorphine (a dopamine agonist), amphetamine, cocaine and ethanol
Takahshi *et al*., 1997 (72)	VMAT2$^{(+/-)}$	Enhanced amphetamine locomotor-stimulation; diminished amphetamine place preference, no change in cocaine place-preference
Jones *et al*., 1998 (75)	DA-T	No increase in extracellular DA by amphetamine
Sora *et al*., 1998 (71)	DA-T	Retain cocaine- and methylphenidate conditioned place-preference
	5-HT-T[3]	Display an enhanced cocaine- and methylphenidiate conditioned place-preference
Rocha *et al*., 1998 (74)	DA-T	Self-administer cocaine
Drago *et al*., 1998 (78)	D_1-DAR[4]	Retain cocaine-conditioned place preference
	D_2-DAR[5]	Absence of opiate rewarding effects

[1] Dopamine transporter
[2] Vesicular monoamine transporter 2
[3] 5-hydroxytryptamine (serotonin) transporter
[4] Dopamine D_1 receptor
[5] Dopamine D_2 receptor

KO mice might have obscured the importance of the transporter under normal conditions. A prominent role for VMAT2 was suggested by the report (72) that VMAT2$^{+/-}$ mice display diminished conditioned place-preference to amphetamine compared to wild-type mice. In related work, the contribution of each of the subtypes of the DA receptor to addiction is being examined (78, 79).

NOT DOPAMINE?

In a rather surprising development, the very basis of DA involvement in addictions has recently come into question. It was reported recently (80) that rats in which stimulating electrode placement elicited DA release in the NuAcc learned to press a lever in order to receive an intracranial electrical stimulation (ICS), but the DA release was consistently observed only when the stimulus was applied to an untrained animal and not during ICS. The authors conclude that DA might be ''… a neural substrate for novelty or reward expectation rather than reward itself.'' They cite research in support of this position which shows that DA neurones in the substantia nigra of monkeys increase their firing rate when an appetitive reward is delivered in an unpredictable way, but not if a conditioned stimulus (tone) precedes the reward. In the latter case, the rate increases not to the reward, but rather to the tone (81).

OTHER SITES

The μ opioid receptor or other sites have also been targeted as a possible common mechanism for addiction. For example, in μ opioid receptor KO mice, not only is morphine-induced place-preference virtually absent, but cocaine-induced place-preference is significantly reduced (82). These data suggest an important role for μ opioid receptors in the rewarding aspects of not only opioids, but also of psychostimulants. Other targets include transcription factors (83). Chronic exposure to drugs of addiction desensitizes induction of the *fos* and *jun* genes and results in a slow, but steady accumulation of FRAs (Fos-related antigens). These isoforms of ΔFosB (a truncated splice variant of the *fosB* gene) have long half lives, build-up within the brain, and might work as molecular switches or triggers for drug addiction (83).

ONE PHARMACOTHERAPY?

A common mechanism of addiction might lead to more successful pharmacotherapy. Optimism has

been heightened by the recent approval by the FDA of naloxone HCl (REVIA), an opioid antagonist, for the treatment of alcohol dependence. In addition to blocking the effects of opioids, naltrexone reduces alcohol craving and relapse (84), particularly when used as part of a comprehensive programme that includes other treatment modalities (85–89). Selective μ and δ opioid receptor antagonists also decrease alcohol consumption in operant conditioning models (90).

OVERVIEW

Recent research has raised the possibility of a common biochemical mechanism of addiction to drugs, other chemical substances, or behaviours. The first candidate involved the neurotransmitter dopamine and its pathways. Specific targets included dopamine's receptors and the DA-T and VMAT2 transporters. Serotonin was also implicated early (91–93), with specific targets analogous to those of DA. Recent studies cast some doubt on whether DA or 5-HT exclusively play critical roles. Based on findings, such as those cited above, that cocaine-induced place-preference is significantly reduced in μ opioid receptor knockouts (82), the μ opioid receptor is another candidate for a final common pathway for addictions. The excitement, and hope, of a common biochemical mechanism is that a common pharmacotherapy might be developed. The apparent clinical effectiveness of opioid antagonists as adjunct therapy in drug abuse treatment paradigms lends credence to this view.

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