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Review

Novel pharmacotherapeutic targets for the management of drug addiction

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Abstract

Despite individual variation in the liability to the abuse of psychoactive substances, there is substantial commonality shared by drugs of abuse. The knowledge of these common mechanisms together with the continued elucidation of the neurobiological underpinnings of withdrawal symptoms, drug intake, craving, relapse, and co-morbid psychiatric associations are critically important for the development of new therapeutic strategies. The present review will focus on recent advances in the development of innovative pharmacotherapeutic agents, which should promote higher efficacy (abstinence, prevention of relapse, long-term recovery) and patient compliance, as well as improved safety profiles.

Keywords: Alcohol; Cocaine; Drug addiction; Nicotine; Opiates; Pharmacotherapy

Contents

1. Introduction

The core feature of drug addiction, namely the compulsive use of drugs despite physical, psychological or social harm, has aspects of impulse control and compulsive disorders, which may lead to relapse or reinstatement of drug-seeking behaviours even

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after relatively long periods of abstinence. It is this late relapse that makes the therapeutic management of drug addiction a major challenge for current research and drug development.

Despite the societal burden of drug addiction and related psychiatric co-morbidities (Uhl and Grow, 2004), efficacious pharmacotherapeutic strategies are still lacking. For example, although nicotine replacement therapy in its two main formulations (the slow-acting transdermal nicotine patches, and the faster-acting formulations such as the nicotine gum, nicotine nasal spray, nicotine vapor inhaler, and the nicotine lozenge) has shown some efficacy in placebo-controlled clinical trials at both short-term (end of trial) and long-term (6–12 months) assessments, its overall efficacy rate remains rather disappointing. A similar statement can be made for the sustained-release formulation of the phenylaminoketone atypical antidepressant agent bupropion (Zyban®) (Ferry and Burchette, 1994) even though its use to prevent relapse to nicotine-seeking behaviour after the initial achievement of smoking cessation has been confirmed (Hays et al., 2001; Jorenby et al., 1999). Other approaches including the use of the non-competitive nicotinic receptor antagonist mecamylamine as an adjunct to transdermal nicotine patches (Rose et al., 1994, 1998), selective serotonin (5-HT) reuptake inhibitors such as fluoxetine (Prozac®) alone (Niaura et al., 2002) or in combination with nicotine replacement therapies (Blondal et al., 1999; Killen et al., 2000), the 5-HT_{1A} partial agonist Buspirone (Buspar®) (Schneider et al., 1996), the α_2-adrenoceptor agonist clonidine (Covey and Glassman, 1991; Gourlay and Benowitz, 1995; Hilleman et al., 1993), naltrexone alone or when given in combination with transdermal nicotine patches (Krishnan-Sarin et al., 2003), or the use of the nicotine-like alkaloid lobeline (Stead and Hughes, 2000) or silver acetate (McChargue et al., 2002) have all yielded either equivocal or negative results, or their potential benefits have not been reproduced in well-designed placebo-controlled studies.

In the alcohol dependence domain, efficacy of acamprosate and naltrexone has been assessed in several randomized, double-blind, placebo-controlled trials across a range of countries. Although these trials have led to divergent conclusions or interpretations, most studies showed consistent efficacy of acamprosate on the rate of abstinence, cumulative abstinence duration, time to first drink, and prevention of relapse (Carmen et al., 2004; Mason, 2003a,b). Despite a more problematic safety and tolerability profile that may hamper treatment compliance, naltrexone has also been reported to prevent relapse to heavy drinking (Carmen et al., 2004; Mason, 2003b).

There is currently no efficacious pharmacological strategy for the treatment of cocaine addiction despite many attempts using naltrexone (Somoza et al., 1998, but see Schmitz et al., 2001), risperidone and pergolide (Dackis and O'Brien, 2002; Silva de Lima et al., 2002), desipramine and carbamezapine (Campbell et al., 2003), amantadine (Shoptaw et al., 2002), methylphenidate (Grabowski et al., 1997), mazindol (Stine et al., 1995), nootropic agents such as piracetam and ginkgo bilboa (Kampman et al., 2003a), olanzapine (Kampman et al., 2003b), or either methadone or buprenorphine (Mello et al., 1993; Schottenfeld et al., 1997) (for recent comprehensive reviews, see Gorelick et al., 2004; Sofuoglu and Kosten, 2005). Finally, the only currently available long-term maintenance programs for the treatment of opiate dependence include methadone, levo-acethylmethadol (LAAM), and buprenorphine (Clark et al., 2002; Mattick et al., 2002a,b) or the use of α_2-adrenoceptor agonists such as clonidine or lofexidine (Gowing et al., 2002b; Howells et al., 2002) either alone or in combination with an opioid receptor antagonist such as naltrexone or naloxone (Gowing et al., 2002a).

Overall, this brief snapshot of medications that are currently available for the treatment of nicotine, alcohol, cocaine, and opiate addiction clearly demonstrates that there is significant room for improvement in both the efficacy (acute cessation, reduction in the number of cessation attempts, reduction in craving, prevention of relapse, long-term maintenance of abstinence, and compliance to treatment) and safety (improved side-effect profile) domains.

2. Where should drug discovery start from?

Drug discovery in the addiction area may benefit from recent advances in behavioural pharmacology and neurochemistry, neuroimaging, synapse-specific plasticity, transcriptomics, and proteomics.

First, behavioural neurochemistry studies confirmed that one of the characteristics shared by drugs of abuse is to produce a significant increase in the activity of mesolimbic dopamine neurons originating in the ventral tegmental area and projecting toward limbic forebrain regions including the nucleus accumbens. Although numerous studies have correlated dopamine release in the nucleus accumbens with the hedonic or aversive value of rewarding stimuli, more recent views support the idea that the mesolimbic dopamine system plays a rheostatic role in the learning of the motivational significance (better-than-expected vs. worse-than-expected) of a stimulus rather than in the mediation of the hedonic/aversive value of the stimulus per se (e.g., Salamone et al., 2005; Wise, 2004). In order to apply this hypothesis to drug addiction, one must thus assume that any response to the drug that occurs during the period of raised extracellular dopamine may have the potential of acquiring incentive salience and contribute to enhanced attentional processing of drug-related cues. A corollary hypothesis is that this attentional bias toward drug-related cues elicits drug craving and contributes to compulsive drug use and relapse to drug seeking behaviour. In this respect, recent studies investigating the link between abnormal information processing in the mesocorticolimbic system and changes in responding for delayed or intermittent reinforcement are valuable (e.g., Cardinal et al., 2004; Wakabayashi et al., 2004).

Second, significant progress has been made in the understanding of the neurocircuitry underlying reinstatement of drug seeking behaviour (for a recent review, see Weiss, 2005). For example, dopamine neurotransmission in the nucleus accumbens is involved in cue-controlled drug-seeking behaviour (Di Ciano et al., 1998; Ito et al., 2000; Wyvell and Berridge, 2000). In addition, different sub-territories of the amygdala seem to play an important role in drug-enhanced stimulus-reward associations (Harmer and Phillips, 1999;

Ledford et al., 2003) and stress-triggered relapse to cocaine-seeking behaviour (Erb et al., 2001; Leri et al., 2002). Finally, the anterior cingulate cortex appears to serve as a common link in the neural circuitry (Heidbreder and Groenewegen, 2003) underlying reinstatement of drug-seeking behaviours. These preclinical findings can also be translated into human brain imaging findings showing that (1) drug-related cues produce increased activity in the mesolimbic system (e.g., Due et al., 2002); (2) drug craving and attentional processes seem to involve similar neural circuits (Childress et al., 1999; Grant et al., 1996; Tamminga, 1999); (3) chronic drug use hampers frontal cortex function (Volkow and Fowler, 2000); (4) deficits in frontal cortex function may contribute to impaired impulse control, as well as lack of judgement and risk assessment (Bechara et al., 1994), and (5) the personality trait of novelty seeking, of which impulsiveness is one component, is linked to increased extracellular levels of dopamine in the nucleus accumbens (Boileau et al., 2003) and addictive propensity (Cloninger et al., 1988).

Third, research in synapse-specific plasticity suggests that exposure to either drugs of abuse or stress can elicit long-term potentiation at excitatory synapses in the mesolimbic dopamine system, in the ventral tegmental area in particular (Saal et al., 2003; Wolf et al., 2004). This long-term potentiation mechanism may be even more effective if one considers that several drugs of abuse also block long-term depression at synapses in the ventral tegmental area (Jones et al., 2000; Thomas et al., 2000; for a comprehensive review, see Jones and Bonci, 2005). Changes in synaptic plasticity are further supported by recent findings showing that drugs of abuse produce persistent changes in dendritic spine density and number of branched spines in the rat nucleus accumbens and prefrontal cortex (Robinson and Kolb, 1997, 2004).

Fourth, despite the current lack of sensitivity to detect low abundance genes and splice variants, the use of DNA microarrays or gene chips for the study of brain tissues from preclinical addiction models or human post-mortem studies revealed alterations in a number of myelin-related genes, energy metabolism genes, oligodendrocyte function genes, cytoskeleton-associated genes, and genes implicated in neuronal plasticity (Rhodes and Crabbe, 2005). Importantly, several studies also showed that a series of genes are only transiently expressed and return to baseline expression levels shortly after exposure to the drug. The question of whether or not genes transiently altered by drugs of abuse (Berke et al., 1998; Simpson et al., 1995) might trigger persistent changes in synaptic structure via changes in the expression of other genes (McClung and Nestler, 2003), which in turn would be responsible for specific behavioural phenotypes will be one of the main challenges of future research. Future studies combining parallel transcriptomics screen with proteomics investigations should offer unprecedented opportunities to track down key genes associated with drug addiction (Williams et al., 2004).

Together these findings suggest that (1) enhanced dopamine neurotransmission in the nucleus accumbens may amplify the attentional processing of drug-related cues; (2) drug-related cues and craving are associated with increased activity in brain regions such as the amygdala, anterior cingulate, dorsolateral prefrontal, and orbitofrontal cortices, which are involved in attention, emotional processing, goal-directed behaviour, associative learning, decision making, and response suppression; (3) drug-induced synaptic plasticity in the mesolimbic dopamine system may play an important role in learning of addictive behaviours by modifying the fine tuning of dopaminergic cell firing, and (4) exposure to drugs of abuse results in long-lasting neuroadaptive responses, which may involve changes in gene expression.

3. Toward the development of new pharmacotherapeutic strategies for the management of drug addiction

In the previous Section, we have shown that repeated exposure to drugs of abuse produces long-term molecular and neurochemical changes, which may explain the core features of addiction, the compulsive seeking and taking of the drug and the drug-, cue-, or stress-dependent risk of relapse. A growing number of new molecular and cellular targets of addictive drugs have been identified. Furthermore, rapid advances are being made in relating those targets to specific behavioural phenotypes in animal models of addiction. In this Section, we will briefly review some of the most promising strategies that target different neurotransmitter systems with the hope of developing new molecules with increased clinical efficacy and safety.

3.1. Dopamine-based strategies

The role of dopamine in the attentional processing of drug-related cues together with drug-induced increase in dopamine in the mesolimbic system as a key factor for the expression of drug-seeking behaviour clearly point toward the potential use of dopamine receptor antagonists as candidate medications to reduce drug seeking and craving. However, non-selective dopamine receptor antagonists such as haloperidol and tiapride, which have been shown to increase abstinence and/or attenuate measures of drug-and cue-induced craving in humans (Modell et al., 1993; Shaw et al., 1994), have also the potential to induce long-term neurological side effects and are not suitable as anti-craving medications.

A growing body of evidence shows that dopamine D3 receptors are significantly involved in the control of drug-seeking behaviour without altering motor and natural reward functions. There are four main arguments in support of a key role of the dopamine D3 receptor in drug addiction. First, although inter-species differences have been reported in the distribution of the dopamine D3 receptor, its density in the rat and human brain is highest in limbic regions such as the ventral striatum and amygdala, which seem to play a key role in behaviours controlled by the presentation of drug-associated cues. Second, post-mortem studies report an up-regulation of dopamine D3 receptors in the nucleus accumbens of cocaine overdose fatalities. Third, dopamine D3 mRNA and receptors are increased in cocaine cue-conditioned hyperlocomotion, and termination of a cocaine self-administration regimen increases dopamine D3 binding over time in the ventral striatum.

Furthermore, nicotine-induced conditioned locomotion and nicotine behavioural sensitisation are both associated with a significant increase in D3 receptor binding and mRNA levels in the shell sub-region of the nucleus accumbens. Sub-chronic administration of morphine also produces a significant increase in D3 receptor mRNA in the caudate-putamen and ventral midbrain. Fourth, selective blockade of dopamine D3 receptors by SB-277011A (trans-*N*-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2yl)ethyl]cyclo-hexyl]-4-quinolininecarbo-xamide), a highly potent and highly selective dopamine D3 receptor antagonist, is efficacious in models of cocaine-, nicotine-, alcohol-, and heroin-seeking behaviours in the rat (for comprehensive reviews in support of these four arguments, see Heidbreder et al., 2004, 2005; Joyce and Millan, 2005; Newman et al., 2005).

A series of studies also demonstrated the efficacy of the partial dopamine D3 receptor agonist BP4.897 (*N*-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-2-naphthamide) in animal models of cocaine (for a review of preclinical evidence, see Heidbreder et al., 2005). However, the selectivity profile of BP4.897 over dopamine D2 receptors and other receptors has been called into question and BP4.897 alone may produce conditioned place aversion (Gyertyán and Gál, 2003, but see Aujla and Beninger, 2005) and may have anxiolytic properties (Rogoz et al., 2003). BP4.897 is in Phase II trials in schizophrenia, Parkinson's disease and the prevention of relapse in cocaine, alcohol and nicotine addiction.

One alternative approach is to develop selective dopamine D1 receptor agonists and antagonists. For example, ecopipam (SCH-39166; ((−)-*trans*-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5H-benzo[d]naptho-(2,1-b)azepine)) attenuates cocaine-induced effects in several preclinical paradigms (McCance-Katz et al., 2001). However, two out of three inpatient studies demonstrated that ecopipam failed to alter the behavioural and subjective effects of cocaine (Haney et al., 2001; Nann-Vernotica et al., 2001). Despite these findings, Addex Pharmaceuticals is currently planning to initiate a US Phase II trial with ADX 10061 (CEE-03-310, formerly NNC-01-0687; (+)-5-(2,3-dihydrobenzofuran-7-yl)-3-methyl-8-nitro-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-ol), a benzazepine dopamine D1 receptor antagonist, for use in smoking cessation. A US Phase II trial with CEE-03-310 was previously conducted at Yale University to improve alcohol craving in problem drinkers. CEE-03-310 also showed potential in cocaine dependence (for a review, see Eder, 2002). Adrogolide hydrochloride (DAS-431, ABT-431; (-)-trans 9,10-acetoxy-2-propyl-4,5,5a,6,7,11-b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride) is a dopamine D1 receptor agonist (Shiosaki et al., 1996) currently under development by DrugAbuse Sciences as a treatment for cocaine dependence. In Phase II clinical trials in cocaine-dependent patients, the intravenous administration of adrogolide hydrochloride decreased the subjective effects of cocaine, reduced cocaine craving and was well tolerated (for reviews, see Giardina and Williams, 2001; Gorelick et al., 2004).

In addition to dopamine D1 and D3 receptor agonists and antagonists, dopamine reuptake inhibitors with slow onset of action and long duration of action to minimize their potential abuse liability have also been proposed for the treatment of cocaine addiction. For example, vanorexine (GBR 12909; 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-3(phenylpropyl)-piperazine) is a noncompetitive inhibitor of the dopamine transporter that acts either as a cocaine antagonist or as a stimulant that substitutes for the effects of cocaine itself (Preti, 2000). Phase I clinical trials with vanorexine for the treatment of cocaine abuse are currently ongoing. ATI-61X (Cobrex) is also under development by Recovery Pharmaceuticals to replace the reinforcing signal of cocaine and to act as a cognitive enhancer to overwrite the memories driving drug-seeking behaviour. Finally, NRP-104 is a pro-drug of amphetamine, under development by New River Pharmaceuticals for the treatment of attention deficit hyperactivity disorder. Approval for the treatment of cocaine dependence has been granted by the Food and Drug Administration. New River has been in discussions with the National Institute on Drug Abuse to develop a protocol for studying the use of NRP-104 as a treatment for cocaine dependence.

3.2. Serotonin-based strategies

The ventral tegmental area and nucleus accumbens both receive serotonergic afferents from the raphe nuclei and one may assume that serotonergic agents can indirectly modulate mesolimbic dopamine function (Walsh and Cunningham, 1997). One may also hypothesize that reductions in synaptic levels of dopamine, serotonin, and/or norepinephrine may contribute to withdrawal-induced depression, drug craving, and relapse. Thus, pharmacotherapies that enhance synaptic levels of monoamines may reduce the reinforcing efficacy of drugs of abuse and alleviate drug withdrawal, dysphoria, and craving. For example, the acute co-administration of fluoxetine or paroxetine, two selective serotonin reuptake inhibitors, and 4-(2′-methoxy-phenyl)-1-[2′-(*n*-(2″-pyridinyl)-*p*-iodobenzamido]-ethyl-piperazine (*p*-MPPI), a 5-HT_{1A} receptor antagonist, alleviates the diminished interest in brain stimulation reward observed during withdrawal from either nicotine or amphetamine in rats (Harrison et al., 2001; Markou et al., 2005). These findings suggest that co-administration of a selective antagonist at 5-HT_{1A} receptors and a selective serotonin reuptake inhibitor may be a useful approach to prevent relapse to drug seeking behaviour.

An alternative approach consists of developing compounds with substrate activity at both the serotonin and dopamine transporters. One of these compounds, PAL-287 (1-napthyl-2-aminopropane), was recently identified as a non-amphetamine dual dopamine/serotonin releasing agent (Rothman et al., 2005). Finally, selective ligands at serotonin receptor subtypes might offer some therapeutic potential. For example, the 5-HT_{2C} receptor agonist Ro 60-0175 ((*S*)-2-(6-chloro-5-fluoroindol-1-yl)-1-methylethylamine) fumarate) reduces responding for cocaine and nicotine self-administration, oral ethanol consumption in rats, and is effective in a model of drug reinstatement (Higgins and Fletcher, 2003). Recent findings also suggest that the concomitant blockade of α_{1b}-adrenoceptor and 5-HT_{2A} receptors mediates the locomotor response, ventral striatum dopamine release, as well as the development and expression of behavioural sensitisation to morphine (Auclair et al., 2004).

3.3. GABA-based strategies

The increase in synaptic levels of gamma-amino butyric acid (GABA) is thought to reduce psychostimulant-induced increases in dopamine levels in the nucleus accumbens, thereby reducing their reinforcing properties (Dewey et al., 1997; Gerasimov et al., 2001). This hypothesis is also supported by studies showing that gabapentin (Neurontin®), which is currently marketed for the treatment of refractory partial seizures, significantly reduces the amount and frequency of cocaine craving in cocaine-dependent patients (Raby and Coomaraswamy, 2004, but see Berger et al., 2005; Hart et al., 2004), and can be used as an add-on medication to a standard detoxification regime in heroin addicts undergoing outpatient opiate withdrawal treatment (Martinez-Raga et al., 2004). Similarly, Tiagabine (Gabitril®), a selective blocker of the presynaptic GABA reuptake transporter type 1 (GAT1) currently used as an add-on anticonvulsant, was recently reported to reduce the severity of alcohol withdrawal symptoms in the mouse (Nguyen et al., 2005), to increase the number of cocaine-free urine samples, to decrease self-reported cocaine use in Man (Gonzalez et al., 2003; Winhusen et al., 2005, but see Lile et al., 2004), and to reduce nicotine craving and improve cognitive performance in abstinent smokers (Sofuoglu et al., 2005).

The irreversible inhibitor of GABA transaminase, γ-vinyl GABA (GVG, Vigabatrin®), which is currently used for the treatment of epilepsy and infantile spasms, is also a potential pharmacotherapy to treat drug addiction and craving. Double-blind, placebo-controlled trials will be required to confirm the outcome of two recent open-label studies supporting the efficacy of vigabatrin in reducing cocaine craving (Brodie et al., 2003, 2005).

Topiramate (Topamax®) appears to be more effective than placebo with regard to all self-reported drinking and craving outcomes (Johnson et al., 2003). These studies also revealed that patients who received topiramate, compared with placebo, were significantly less likely to have positive serum cotinine levels, and that drinking reductions were accompanied by smoking decreases in the topiramate group, but not the placebo group. Further studies are now warranted to assess whether or not topiramate may be useful to treat both nicotine and alcohol dependencies (Johnson, 2004). Encouraging efficacy signs have also been reported for the use of topiramate to treat cocaine dependence in a 13-week, double-blind, placebo-controlled pilot trial (Kampman et al., 2004).

Several preclinical and clinical studies have evaluated the potential of γ-amino butyric acid-B ($GABA_B$) receptor subtype agonists such as baclofen (beta-(4-chlorophenyl)-γ-amino-butyric acid) as a pharmacotherapy for substance abuse (for reviews, see Brebner et al., 2002; Cousins et al., 2002). In clinical populations, baclofen has also been shown to reduce cocaine, as well as alcohol craving and intake (Addolorato et al., 2003; Shoptaw et al., 2003). The recent identification of positive allosteric modulators of the $GABA_B$ receptor such as CGP7930 (2,6-Di-*tert*-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol) and GS39783 (N,N'-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine), which interact synergistically with GABA to enhance its effects, might also represent a potentially new development in the use of GABAergic drugs to treat drug dependence (Urwyler et al., 2003). Both CGP7930 and GS39783 are effective at decreasing the reward-facilitating effects of cocaine (Slattery et al., 2005; Smith et al., 2004). Furthermore, the $GABA_B$ receptor agonist CGP445323 (amino-2[*S*]-hydroxypropyl)-methylphosphinic acid) selectively decreases nicotine self-administration compared to food-maintained responding (Paterson et al., 2004, 2005), prevents cue-induced reinstatement of nicotine-seeking behaviour (Paterson et al., 2005), and reduces cocaine-induced enhancement in brain stimulation reward (Dobrovitsky et al., 2002). These effects are similar to those reported previously for baclofen, thus supporting the potential use of $GABA_B$ receptor agonists or positive allosteric modulators as pharmacotherapies for drug addiction.

3.4. Glutamate-based strategies

Extracellular levels of glutamate in the nucleus accumbens are under the control of a non-synaptic cystine–glutamate transporter that exchanges extracellular cystine for intracellular glutamate (Lu et al., 2004). Withdrawal from cocaine produces a decrease in extracellular levels of glutamate in the nucleus accumbens and is associated with a reduced affinity of the cystine–glutamate transporter for cystine (Baker et al., 2003). Importantly, the systemic administration of cysteine pro-drugs (*N*-acetylcysteine and (−)-2-oxothiazolidine-4-carboxylic acid) restores extracellular levels of glutamate and blocks reinstatement of cocaine seeking (Baker et al., 2003). Furthermore, glutamate derived from the cystine–glutamate exchange system stimulates extrasynaptic group II metabotropic glutamate autoreceptors, which are known to regulate synaptic glutamate release (Dietrich et al., 2002). Together, these findings suggest that targeting extrasynaptic glutamate transmission by using cysteine pro-drugs or compounds acting on metabotropic glutamate (mGlu) receptors might have a selective effect on reinstatement of drug seeking behaviour. In fact, functional down-regulation of $mGlu_2$ and $mGlu_3$ receptors could be associated with the increased release of glutamate in response to a cocaine challenge injection or a cocaine-paired cue during cocaine withdrawal (Xi et al., 2002). This hypothesis is strengthened by the finding that the mixed $mGlu_2$ and $mGlu_3$ receptor agonist LY-379268 ((−)-2-oxa-4-aminobicylco hexane-4,6-dicarboxylic acid) blocks the expression of amphetamine sensitisation (Kim et al., 2005; Kim and Vezina, 2002), and prevents conditioned reinstatement of cocaine-or heroin-seeking behaviour (Baptista et al., 2004; Bossert et al., 2004). LY-379268 is the 2-oxabicyclo-(3.1.0)-hexane analogue of Eglumegad (LY-354740) that is currently being developed by Eli Lilly for both anxiety and to aid smoking cessation.

In addition to $mGlu_2$ and $mGlu_3$ receptors, increased interest in the role of $mGlu_5$ receptors in drug addiction came from studies showing that mice with targeted deletion of the $mGlu_5$ receptor fail to self-administer cocaine and do not respond to the acute locomotor activating effects of cocaine (Chiamulera et al.,

2001). These findings were corroborated by the observation that the $mGlu_5$ receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks the behavioural effects of cocaine, nicotine, and alcohol (Backstrom et al., 2004; Kenny and Markou, 2004; Kenny et al., 2005; Paterson and Markou, 2005; Rasmussen et al., 2005; Schroeder et al., 2005; Tessari et al., 2004). Furthermore, both MPEP and 3-[(2-methyl-1,3-thiazol-4-yl) ethyl]pyridine (MTEP) reduce naloxone-precipitated somatic signs of morphine withdrawal (Kenny and Markou, 2004; Rasmussen et al., 2005).

Extensive preclinical literature and preliminary clinical observations also suggest that *N*-methyl-D-aspartate (NMDA) receptor antagonists are potential candidates to treat withdrawal syndromes from opioids, alcohol and other sedatives (Krystal et al., 2003; Nagy et al., 2004). Merz is currently developing Neramexane (MRZ 2/579: 1-amino-1,3,3,5,5-pentamethyl–cyclohexane hydrochloride), a low-affinity non-competitive NMDA receptor antagonist with rapid blocking/unblocking kinetics and strong voltage dependence. Neramexane is currently in a placebo-controlled US Phase II trial for alcohol dependence. Preliminary results from clinical studies also suggest that memantine hydrochloride (Ebixa®, Namenda®, Axura®), a non-competitive NMDA receptor antagonist, may decrease morphine intake in addicts.

3.5. Acetylcholine-based strategies

3.5.1. Neuronal nicotinic cholinergic receptors

Studies on nicotinic cholinergic receptors have led to the identification of two major heteromeric isotypes in the mesostriatal dopamine system: $\alpha_4\beta_2$ and $\alpha_4\alpha_6\beta_2$ nicotinic receptors. Strong evidence suggests that β_2 nicotinic receptors play a prominent role in the effects of nicotine on dopamine neurons, including dopamine release in the nucleus accumbens and nicotine self-administration (Hogg and Bertrand, 2004; Maskos et al., 2005). The partial agonist at $\alpha_4\beta_2$ nicotinic receptors, varenicline (CP 526555; 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine), is being developed by Pfizer as a potential aid to smoking cessation and is currently being evaluated in a US phase III trial. Sanofi-Aventis is also assessing the efficacy of SSR 591813 ((5aS,8S,10aR)-5a,6,9,10-tetrahydro-7H,11H-8,10a-methanopyrido[2′,3′:5,6]pyrano[2,3-d]azepine), another selective partial agonist at $\alpha_4\beta_2$ nicotinic receptors, in Phase IIa trials in Europe. In addition, the University of Florida (USA) is investigating nicotine analogues that act as partial agonists at the $\alpha_4\beta_2$ nicotinic receptor, as potential agents to aid smoking cessation.

3.5.2. Neuronal muscarinic cholinergic receptors

Muscarinic cholinergic receptors have also been implicated in mechanisms of drug dependence. Cholinergic neurons in the laterodorsal tegmental nucleus of the pons are a main source of the excitatory cholinergic input to dopamine-containing neurons in the ventral tegmental area, and electrical stimulation of the laterodorsal tegmental nucleus can evoke a rapid increase in dopamine release in the nucleus accumbens (Miller and Blaha, 2005). This effect is absent in muscarinic M_5 receptor-deficient mice or in wildtype mice receiving either systemic scopolamine or scopolamine microinfusion directly into the ventral tegmental area (Forster et al., 2002). Furthermore, the rewarding effects of morphine and cocaine were significantly reduced in muscarinic M_5 receptor-deficient mice (Basile et al., 2002; Fink-Jensen et al., 2003). Thus, selective antagonism at M_5 receptors might represent a novel target for the treatment of drug addiction.

3.6. Opiate-based strategies

Most advanced strategies focusing on the opioid system involve different formulations of the opioid receptor antagonists naltrexone and nalmefene. For example, DrugAbuse Sciences is developing naltrexone depot (Naltrel®), a microencapsulated formulation of naltrexone, using its Lactiz sustained-release technology, for the treatment of alcohol and opiate addiction. Naltrexone depot is administered by monthly intramuscular injections to overcome compliance problems with the tablet formulation of naltrexone, which must be taken daily. Encouraging results have been recently reported in a 12-week US double-blind, placebo-controlled, multicentre Phase III trial in 300 DSM-IV alcohol-dependent patients. Another Phase III trial to assess naltrexone depot in alcohol and opiate addiction is currently ongoing.

A once-a-month sustained-release formulation of naltrexone has been developed by Alkermes using its Medisorb formulation system for the treatment of alcohol and opiate addiction. Using the Medisorb technology, naltrexone is encapsulated in microspheres made of a biodegradable polymer, which dissolve slowly and release the drug at a controlled rate following intramuscular injection. Medisorb Naltrexone (Vivitrex®) is in a randomized, double-blind, placebo-controlled Phase III trial in 624 alcohol-dependent patients across 24 centres in the US, to study the efficacy and safety of repeated intramuscular doses over 28 days. A New Drug Application has been submitted to the Food and Drug Administration for marketing approval of Vivitrex. If approved, Vivitrex would be the first medication available for the treatment of alcohol dependence in a formulation that is administered once-monthly by injection. Another extended release (3 month or more) implant formulation of naltrexone, VP-004, is under development by Valera for the treatment of opioid dependence, and is currently in Phase II clinical trials.

BioTie Therapies is developing a tablet formulation of nalmefene® for the treatment of alcohol addiction. Encouraging results have been reported in two multicentre, placebo-controlled Phase III trials in Finland and in the United Kingdom. As announced in November 2004, Somaxon licensed the North American rights to develop, manufacture and commercialize oral nalmefene from BioTie Therapies as a potential treatment for impulse control disorders. Oral nalmefene has completed a US Phase II study for the treatment of patients diagnosed with pathological gambling. Somaxon intends to initiate Phase III trials for this indication during 2005. In addition, Somaxon intends to initiate a proof-of-principle study this year for the use of oral nalmefene to decrease nicotine dependence.

ProNeura (Titan Pharmaceuticals) is developing Probuphine®, a subcutaneous delivery formulation of buprenorphine, using its ProNeura drug delivery system, for the treatment of opiate addiction over a 6-month period. An Australian pilot Phase I trial is underway in 18 heroin-dependent subjects to evaluate safety, pharmacokinetics and maintained therapeutic benefit.

3.7. Targeting endocannabinoid systems

The isolation of the major psychoactive component of the hemp plant, Δ^9-tetrahydrocannabinol, the cloning of the central CB_1 cannabinoid receptor, and the characterization of the selective CB_1 receptor inverse agonist, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-1-piperidinyl-1H-pyrazole-3-carboxamide (SR141716, Rimonabant) significantly boosted research on the interaction between cannabinoids and brain reward function (Barth and Rinaldi-Carmona, 1999). A growing body of evidence has shown that Δ^9-tetrahydrocannabinol acts on brain reward systems in a manner similar to non-cannabinoid addictive drugs (Gardner, 2005; Gardner and Lowinson, 1991; Gardner et al., 1998). This fact may partly explain the efficacy of SR141716 in blocking the reinforcing properties of heroin, morphine, ethanol, cocaine, and nicotine (for a review, see Le Foll and Goldberg, 2005). These findings suggest that activation of the endogenous cannabinoid system may participate in the motivational and dopamine-releasing effects of several drugs of abuse. Rimonabant is under development by Sanofi-Aventis and is currently in Phase III trials in the US, Europe, Australia, and Canada for obesity, smoking cessation and alcohol addiction. Sanofi-Aventis is also developing another selective CB_1 receptor antagonist, SR-147778 (5-(4-Bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-(1-piperidinyl)-1H-pyrazole-3-carboxamide) (Rinaldi-Carmona et al., 2004). The compound is in Phase I trials for smoking cessation, obesity and alcohol dependence.

Vernalis is also developing selective cannabinoid CB_1 receptor antagonists/inverse agonists for the treatment of obesity and smoking cessation. Finally, researchers at Pfizer have recently reported a series of pyrazolo[1,5-a] pyrimidine derivatives that act as cannabinoid CB_1 receptor antagonists. These compounds are expected to be useful for the treatment of obesity, bulimia, attention deficit disorders, dementia, alcoholism, and tobacco abuse, among other disorders.

3.8. Strategies targeting the hypothalamic–pituitary–adrenal axis

Several drugs of abuse, including psychomotor stimulants (cocaine, amphetamine, and nicotine), depressants (morphine and alcohol), and hallucinogens can affect the activity of the hypothalamic–pituitary–adrenal axis (Sarnyai et al., 2001). In addition, the drug withdrawal syndrome resembles physiological and behavioural changes associated with responses to stressors linked to activation of the brain corticotropin-releasing factor (Weiss et al., 2001). Furthermore, exposure to stressors is associated with increased drug-taking behaviour and relapse to drug seeking behaviour in both humans and laboratory animals (Stewart, 2003). These findings, together with data on the effect of CRF_1 receptor antagonists on cocaine self-administration, drug withdrawal from several drug classes, and stress-induced relapse to heroin, cocaine, and alcohol seeking in rats (Nie et al., 2004; Shaham et al., 1998) provide a rationale for the use of CRF_1 receptor antagonists in the treatment of compulsive drug use in humans.

Glucocorticoid hormones have also been shown to facilitate the acquisition, stable maintenance, and relapse to cocaine self-administration (Deroche et al., 1997). It has been hypothesized that the glucocorticoid receptor is implicated in these effects. For example, mice with inactivation of the glucocorticoid receptor in the central nervous system show a flattened cocaine self-administration dose–response curve and do not seem to develop behavioural sensitisation to cocaine (Deroche-Gamonet et al., 2003). In addition, the glucocorticoid receptor antagonist, mifepristone, reduces the reinforcing efficacy of cocaine and the behavioural sensitisation to amphetamine (Deroche-Gamonet et al., 2003). These findings suggest that the development of selective glucocorticoid receptor antagonists may be useful for the treatment of psychostimulant addiction.

3.9. Immunopharmacotherapeutic strategies

The rationale behind the use of immunopharmacological strategies for the treatment of drug addiction is to elicit the production of antibodies, which will bind drugs of abuse and alter their pharmacokinetic properties in a manner that is therapeutically helpful. On the basis of preclinical work, vaccines for cocaine and nicotine are now in Phase I and Phase II clinical trials because they may offer long-term protection with minimal treatment compliance (Kantak, 2003; Haney and Kosten, 2004). Xenova is developing TA-CD® as an injectable therapeutic vaccine for cocaine addiction. The vaccine consists of a cocaine derivative linked to recombinant cholera toxin B and adsorbed onto aluminium hydroxide gel adjuvant in saline. It is in a randomized, placebo-controlled Phase IIb trial in 132 methadone-dependent cocaine addicts to assess efficacy and to determine appropriate endpoints for a Phase III trial.

The nicotine abuse vaccine began human testing in early 2002 by Nabi Biopharmaceuticals under the trade name NicVAX®. NicVAX® is a nicotine conjugate vaccine, conjugated to a carrier protein, recombinant exoprotein A (Heading, 2003). Nabi Biopharmaceuticals recently announced positive Phase II clinical results for NicVAX®. The complete data set from this study is expected to be released sometime in 2005. CYT002-NicQb® is another nicotine vaccine under development by Cytos Biotechnology for the treatment of smoking addiction (Maurer et al., 2005). The vaccine uses antigens delivered in a repetitive configuration such as viruses or virus-like particles that can directly activate B cells and are, therefore, in contrast with soluble and monomeric antigens, highly immunogenic. Cytos has just completed full enrolment

for a one-year, randomized, double-blind, placebo-controlled phase II trial in three centres in Switzerland. The first results of the study are expected in the second quarter of 2005. Xenova is also developing TA-NIC®, an intramuscular vaccine for nicotine abuse. The vaccine comprises nicotine conjugated to a carrier protein and an adjuvant. Xenova has reported results from a dose-escalating, randomized, double-blind, placebo-controlled phase I trial of TA-NIC®. Xenova expects to begin Phase II trials for TA-NIC® in 2005 with interim Phase II results expected in 2006.

InfleXion Therapeutics has received a business development grant from the National Institute on Drug Abuse to conduct clinical trials for the first antibody treatment for addiction to phencyclidine. The company's technology has potential to be extended from phencyclidine treatment to other drugs, such as methamphetamine.

Together, these findings suggest that key success criteria for the vaccine approach can be defined around issues of immunogenicity, immunospecificity, immunotolerance, as well as clinical safety and efficacy. Potential issues such as the lack of protection against a structurally dissimilar molecule that produces the same effects as the drug, the individual variability in antibody formation, and the potential lack of motivation to take booster vaccinations must still be addressed. Furthermore, vaccination is not likely to be a stand-alone monotherapy, as it is not expected to show efficacy against drug craving and withdrawal. Thus, vaccination may complement the actions of existing medications or prove useful in combination with them.

4. Conclusions

The drug abuse epidemic targets large segments of the World population. Recent surveys estimate that there are about 200 million users of illegal drugs worldwide, which represent 3.4% of the world population. Alcohol dependence impacts 32 million adults in the top seven markets, whereas about 1.2 billion smokers are estimated worldwide, comprising approximately one-third of the global population aged 15 or older. The World Health Organization estimates that the worldwide number of smokers will continue to increase to 1.6 billion by 2025. Among other neuropsychiatric diseases, alcohol and drug abuse per se costs the American economy an estimated overall $544.11 billion per year in lost productivity, health care expenditures, crime, and other conditions (Uhl and Grow, 2004). In the present review we have shown that most drugs of abuse share common neural, molecular, and neurochemical substrates to produce acute reward and long-term neuroadaptations, which ultimately lead to addiction. The growing understanding of the mechanisms responsible for persistent changes in these common pathways is critical for the development of new pharmacotherapies for the treatment of drug addiction. New molecular and cellular targets of addictive drugs have been identified, and rapid advances are being made in relating those targets to specific behavioural phenotypes in animal models of addiction. Although the proof of efficacy of pharmacotherapeutic agents is to be derived from clinical trials, only sustained efforts in drug addiction research will ultimately lead to new strategies that will promote long-lasting drug abstinence and long-term recovery, ensure satisfactory patient compliance, and have a good safety profile.

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