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Novel approaches for the treatment of psychostimulant and opioid abuse – focus on opioid receptor-based therapies

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Abstract

Introduction—Psychostimulant and opioid addiction are poorly treated. The majority of abstinent users relapse back to drug-taking within a year of abstinence, making ‘anti-relapse’ therapies the focus of much current research. There are two fundamental challenges to developing novel treatments for drug addiction. Firstly, there are 3 key stimuli that precipitate relapse back to drug-taking: stress, presentation of drug-conditioned cue, taking a small dose of drug. The most successful novel treatment would be effective against all 3 stimuli. Secondly, a large number of drug users are poly-drug users: taking more than one drug of abuse at a time. The ideal anti-addiction treatment would therefore be effective against all classes of drugs of abuse.

Areas Covered—In this review, the authors discuss the clinical need and animal models used to uncover potential novel treatments. There is a very broad range of potential treatment approaches and targets currently being examined as potential anti-relapse therapies. These broadly fit into 2 categories: ‘memory-based’ and ‘receptor-based’ and the authors discuss the key targets here within.

Expert opinion—Opioid receptors and ligands have been widely studied, and research into how different opioid subtypes affect behaviours related to addiction (reward, dysphoria, motivation) suggests that they are tractable targets as anti-relapse treatments. Regarding opioid ligands as novel ‘anti-relapse’ medications targets - research suggests that a ‘non-selective’ approach to targeting opioid receptors will be the most effective.

Keywords

Addiction; cocaine; morphine; heroin; buprenorphine; reinstatement; relapse

1. INTRODUCTION

The major challenge in treating drug addiction is to prevent relapse back to drug-taking. Although the first, often difficult, step in treating drug addiction is to achieve drug abstinence. This is achievable, yet, the majority of drug users relapse back to drug-taking

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after a period of abstinence. Even with current pharmacological and behavioural approaches to treatment, relapse rates are remarkably high, for both licit and illicit drug addiction. For example, longitudinal studies with heroin users have shown that 86% of users relapse back to drug-taking within 5 years after methadone-treated abstinence [1]. A similar study examining abstinence from cocaine, opioid and alcohol showed a median treatment career duration (that is, length of time between start of treatment for addiction and achieving >1 year of abstinence) of 9 years [2]. With nicotine addiction, the relapse rate figures are even higher; one study showing 97% of self-quitting smokers relapsed within 6 months [3]. These, and similar, studies have led to the widely-held view that addiction is a chronic relapsing disorder.

An excellent meta-analysis [4] exploring the efficacy of combined pharmacological and behavioural treatments for smoking cessation found the treatment approach to be highly effective; measuring abstinence at longest follow-up (generally at 12 months), the treatment was effective ($P<0.00001$ vs. control). However, this related to an abstinence rate of 15% in the treatment group vs 8% in the control group. So, although the treatment almost doubled the rate of abstinence, relapse (ie. failure of treatment) back to smoking was still 85%. There are numerous similar meta-analyses that demonstrate that although treatment approaches can be effective (although some aren't) still the overall success rate is low. Clinical studies in treatments for psychostimulant and opioid addictions are often confounded by high treatment drop-out rates or failure to attend follow-up sessions. This means that using data only from subjects who attended follow-up generally results in an over-estimation of abstinence at follow-up. Notwithstanding, relapse rates for psychostimulant and opioid addiction are of the order of 50–80% within 12 months post-treatment eg. [5–7]. The high degree of harms both to the subject and to society caused by substance abuse [8] support the need for novel effective treatments for addiction.

2. CURRENT THERAPIES

Despite the high prevalence of addiction to licit and illicit drugs, there are remarkably few licensed treatments for addiction. Current treatments generally rely on substitution or pharmacological blockade of the active ingredient. For example, methadone and nicotine replacement therapy are substitution therapies for opioid and nicotine addiction respectively. The drugs are delivered by routes of administration (eg. orally, transdermally) that deliver the drug more slowly than by injection or inhalation meaning that the reinforcing effects are attenuated [9] but avoiding the physical withdrawal symptoms associated with abrupt cessation of opioid or nicotine intake. Other approaches rely on blocking the pharmacological effects of the abused substance, eg. naloxone/naltrexone for opioids, naltrexone for alcohol, bupropion for nicotine (which is also a noradrenaline/dopamine reuptake inhibitor) [10]. Partial agonism shares both effects – substitution, and blockade of 'on-top' use – and is the basis for varenicline (a nicotinic receptor partial agonist) and buprenorphine (a mu-opioid receptor partial agonist), although buprenorphine has some unique pharmacological properties (see Section 5.4) that may mean it can be more than just a substitution therapeutic.

Although cessation of psychostimulant abuse can cause profound psychological symptoms, there is no identified physical withdrawal syndrome, and there are currently no licensed treatments for psychostimulant addiction. The physical withdrawal symptoms caused by cessation of opioid intake are severe but relatively short-lasting (<1 week). However, even after the physical withdrawal syndrome has subsided the risk of relapse is still high (see section 1), and persists for months or years. Therefore, much research has been dedicated at designing and identifying novel 'anti-relapse' therapies.

3. ANIMAL MODELS OF RELAPSE

There are numerous animal models that are used to study various behavioural effects of drugs of abuse such as opioids and psychostimulants [11], but the two most widely-used animal models used to study novel anti-relapse medications are self-administration and conditioned place preference (CPP). Both have the advantage that they can model the different stages of drug-taking (acquisition, abstinence and reinstatement/relapse). Self-administration is a direct measure of drug-taking; rodents and non-human primates can be trained to self-administer a range of drugs abused by humans, including opioids and psychostimulants, whereby lever-pressing or nose-poking is linked to intravenous or intracerebroventricular administration of drug. This drug-taking can be paired with a conditioning stimulus (such as a light or auditory tone). To study reinstatement, animals undergo a period of 'extinction' whereby the lever or nose-poke is no longer linked to administration of drug. Then, most relevant to assessing novel anti-relapse therapies, self-administration can be reinstated. 'Reinstatement' is seen as an animal correlate of relapse back to drug-taking and can be precipitated by 3 main stimuli: stress, cue-conditioning, or a small dose of drug ('drug-priming'), stimuli which have also been implicated as risk factors for relapse in humans [12].

Conditioned place preference (CPP) is often used to assess the reward liability of a drug, but can also be used to model a form of drug-seeking behaviour. In CPP, the animal does not self-administer a drug of abuse at any stage but learns to associate a particular novel environment with experimenter-administered drug (eg. opioid, psychostimulant), and a different novel environment is associated with saline. After training, on a drug-free test day, the animal is free to explore the drug-paired and saline-paired environment. If the drug is rewarding, the animal will voluntarily spend more time in the drug-paired environment. After a period of extinction, when the animal is exposed to the drug-paired environment without pre-treatment with drug, CPP behaviour can be reinstated either with an acute stressful stimulus or with drug-priming. Cue-induced reinstatement cannot be modelled with CPP as the cue is intrinsic to the CPP test itself [13, 14]. Reinstatement to self-administration or CPP are both widely-used to assess the efficacy of novel anti-relapse medications by administering the candidate treatment immediately before the reinstatement stimulus (an acute stressful event, a drug-priming injection, or, in the case of self-administration, presentation of the drug-paired cue). Similar studies could also be performed whereby novel compounds could be tested on their ability to impair acquisition of both self-administration or CPP, but would generally be less relevant to reinstatement/relapse [14, 15]. For the purposes of this review, concentrating on novel treatments to inhibit relapse back to drug-taking in abstinent addicts, we have focussed, wherever possible, on studies

examining reinstatement to self-administration or CPP, rather than on acquisition or expression of those behaviours.

Although reinstatement to self-administration and CPP are widely used there are some issues surrounding the potential translational validity of current animal models. In particular, they generally fail to model two aspects of drug use seen in human addicts: the compulsive nature of drug intake, and continued drug use despite known negative consequences. This issue has led to the development of adapted self-administration paradigms in an attempt to better model these behaviours [16–18]. A further aspect of human relapse that is currently poorly modelled and poorly understood is the rapid transition from abstinence to compulsive drug use at the start of a relapse episode [19]. These differences between current animal models of addiction and human addiction may be related to chronic drug users having defective frontal cortex function, compared with ‘standard’ laboratory rodents [20]. As reinstatement to self-administration and CPP generally involves measuring drug-seeking behaviour rather than reinstatement to drug-taking itself, further development in the models is required to address this issue.

There are two further issues in designing a novel treatment to relapse to drug-taking. One is that there are 3 key stimuli that trigger relapse in humans (as well as in relevant animal models): stress, drug-priming and cue exposure. As such, it would be expected that the best novel treatment would be effective against all of those three stimuli. As each is thought to occur through separate, although potentially overlapping, neuronal pathways, this represents a considerable challenge [21–24]. The second issue is that poly-drug abuse in human addicts is extremely common, both when more than one illicit substance is used, as well as an illicit substance and nicotine and/or alcohol [25–27]. However, the vast majority of preclinical studies involve examining one substance at a time, and some candidate treatments do not appear to be effective against all classes of drugs of abuse. Consequently, the ideal novel drug treatment would be one that is effective against all relapse triggers, as well as being effective against relapse to all drugs of abuse.

4. NOVEL TARGETS FOR DRUG ADDICTION TREATMENT

4.1 ‘receptor-based’ approaches

The ideal novel treatment for drug addiction would be effective against all classes of drugs of abuse (opioids and psychostimulants, but also alcohol and nicotine). By considering the basic pharmacology of these drugs of abuse, at first glance, this would seem unlikely. The rewarding properties of all opioid drugs are via activation of mu-opioid receptors [28]. Mu-opioid receptors are expressed throughout the central nervous system, but the location where they elicit reward/euphoria is largely thought to be in the ventral tegmental area [29]. Here, they are located on GABAergic interneurons. As mu-opioid receptors, in common with all other opioid receptors, are inhibitory, Gi/o-coupled G-protein-coupled receptors, agonists at these receptors act to inhibit the GABAergic interneurons, in turn disinhibiting the output dopaminergic neurons, resulting in an increase in dopamine release at the targets of these neurons (principally the nucleus accumbens and prefrontal cortex). Psychostimulants have completely different pharmacology, acting at dopaminergic nerve terminals to inhibit reuptake of dopamine (in the case of both cocaine and amphetamine), as well as causing

direct release of dopamine from the terminals (in the case of amphetamine), most likely by reverse transport through the dopamine transporters [30]. Therefore, although the initial pharmacology of each class of abused drug is different, their neuronal actions converge at the level of dopamine release in the nucleus accumbens (and prefrontal cortex), an effect implicated as the source of the euphoric/rewarding effects of these drugs.

A plausible approach to treat drug addiction would therefore be to target dopamine receptors, to attempt to block the euphorogenic properties of all drugs of abuse, essentially at source. This approach has largely been ineffective, to date, and one of the reasons why highlights one of the particular challenges in treating drug addiction. Dopamine levels in the nucleus accumbens rise as a result of taking drugs of abuse, but also are elevated by endogenous (ie. 'natural') rewards such as food and sex; essential physiological drives [31]. Therefore, although dopamine D2 receptor antagonists have been shown to be effective in animal models of drug-taking and reward, this has not translated clinically [32–34]. By blocking the effects of dopamine released by drugs of abuse, the effects of dopamine released by endogenous rewards would also be blocked. Indeed, lower levels of D2 receptors in the nucleus accumbens has been identified as a risk factor for drug addiction, the hypothesis being that individuals (or animals) with lower levels of D2 receptors gain less endogenous reward and have heightened drive to gain reward exogenously, eg. via drugs of abuse [35]. A D2 receptor antagonist would be expected to have a similar (negative) effect. However, whereas D2 receptor antagonists are ineffective clinically, D3 receptor antagonists may still show some potential [36].

Beyond dopamine receptors, numerous other receptors have been suggested as novel anti-addiction therapies. For example neurokinin (NK1), orexin (OX1), galanin (GalR1) and mGlu7 receptors. In brief, NK1 receptors have been implicated in both motivational behaviour and stress responses, and have shown good preclinical promise in reducing both stress-induced and drug-induced reinstatement. Interestingly, however, while NK1 antagonists/gene deletion have been shown to decrease stress-induced reinstatement to both opioids and psychostimulants, they have been shown to affect drug-induced reinstatement to opioids, but not to cocaine [37]. Orexin (OX1) receptors have shown promise in inhibiting both stress- and cue-induced reinstatement, though not drug-primed reinstatement, where its effects have been postulated as through effects on motivation and memory [38, 39]. Galanin receptor (GalR1) agonists have been shown to be effective against cocaine-primed reinstatement to cocaine self-administration [40], can attenuate morphine-induced reward [41] and also has modulatory effects on stress systems [42]. Positive allosteric modulators (PAMs) acting at mGlu7 receptors have been shown to inhibit both cue-induced and cocaine-primed reinstatement to cocaine self-administration [43].

Additionally, studies have investigated receptor systems involved in stress responses, for example, corticotropin-releasing factor (CRF) and noradrenaline. Both are involved in 'normal' stress responses, as well as being implicated in mediating stress-induced reinstatement of opioids and psychostimulants [44, 45]. In addition, acute administration of amphetamine-like psychostimulants induces release of noradrenaline, in addition to dopamine [46], and cocaine is a relatively non-selective monoamine reuptake inhibitor, inhibiting reuptake of noradrenaline and 5-HT as well as dopamine [47].

A further receptor system that has generated extensive research into novel anti-relapse therapies are the opioid receptors, covered in more depth in Section 5.

4.2 'memory-based' approaches

One psychological process that is being widely studied in terms of its contribution to addiction, as well as how candidate pharmacological agents can affect it, is memory. The burgeoning field of the role of memory in drug addiction has been excellently reviewed elsewhere (for example [48–50]). But, briefly, there must be a strong learning and memory component to addiction. Conditioned place preference and self-administration rely on the animal establishing memories based on environment and cue, linked with the positive rewarding effects of the drug of abuse, for experimenters to then measure drug-seeking behaviour or drug-taking, and the reinstatement of those behaviours. Equally, cue-induced relapse in human addicts, at least, must be essentially driven by memories established during drug-taking.

The key neuronal process underlying learning and memory is widely assumed to be synaptic plasticity (long-term potentiation and long-term depression). This means that one key advantage of studying the role of memory in drug addiction, and how it may be affected by candidate pharmacological treatments, is that behavioural and in vitro/ex vivo experiments can go hand-in-hand. A candidate compound can be examined in an animal model of reinstatement, along with electrophysiological or biochemical experiments examining neuronal markers of synaptic plasticity (see [51, 52]).

In terms of therapy, there are 2 overall approaches – one is to weaken existing memories by disrupting the process of reconsolidation, the other is to overlay a stronger inhibitory memory by enhancing 'extinction' of drug-related memories [48]. Both would require re-exposure therapy, with the aid of pharmacological agents. There has been considerable research investigating potential pharmacological agents that would either disrupt addiction-related memory reconsolidation (amnesic agents) or enhance their extinction (cognitive enhancers). As most memories are thought to be formed by strengthening or weakening of glutamatergic synapses (long-term potentiation (LTP) and long-term depression (LTD) respectively), one approach has been to affect glutamatergic transmission directly, for example with d-cycloserine which is a partial co-agonist at the NMDA receptors, and has been shown to enhance extinction of addiction-related memories to a range of drugs of abuse, both clinically and pre-clinically, including opioids and psychostimulants with some, albeit limited, efficacy [53, 54]. Other approaches that affect glutamatergic transmission directly include acamprosate which has been marketed as a therapy for the treatment of alcoholism for many years, despite the mode of action being poorly understood. It is now thought that acamprosate is an NMDA receptor modulator, and, as such, its clinical efficacy may be related to effects on drug-related memory. Preclinical studies have also demonstrated potential (limited) efficacy against cocaine, but not opioid, drug-seeking [55].

Beyond agents that directly affect ionotropic glutamatergic transmission, research has examined a wide range of other pharmacological targets that have been shown to affect addiction-related memory or addiction-related synaptic plasticity such as CB1 receptors [56] and metabotropic glutamate receptors [57, 58].

5. OPIOID RECEPTORS AS NOVEL TREATMENTS FOR DRUG ADDICTION

5.1 mu-opioid receptors

Mu-opioid receptor (MOPr) antagonists such as naltrexone have been examined as potential therapies for opioid addiction for many years. The mode of action is very basic pharmacology – by inhibiting the binding of mu-opioid agonists such as heroin, morphine and oxycodone to the MOPr, and thus inhibiting their effects ‘at source’. However, mu-opioid receptors are also involved in mediating or modulating the rewarding or addictive properties of other drugs of abuse. This is most well-characterised with regard to alcohol. The pharmacology of alcohol (ethanol) is very complex, with actions at numerous receptors, ion channels and signalling molecules. However, one mode of action is to increase release of endogenous opioid peptides such as endorphins. Consequently, mu-opioid receptor antagonists such as naltrexone and nalmefene have been shown to be somewhat effective in treating alcoholism [59], with some evidence that it is more effective in subjects with the A118G MOPr polymorphism; a polymorphism that affects receptor density, affinity of endorphins, and receptor signalling [60].

Further, MOPrs have been shown to mediate or modulate other rewarding or motivational behaviours. Many ‘natural’ rewarding stimuli such as palatable food-seeking, social behaviour and maternal reward have a MOPr-mediated component [61]. MOPrs also appear to play a role in mediating psychostimulant-induced behaviours. Until recently, there has been no systemically-active, selective MOPr antagonist (for example, while both naltrexone and naloxone are relatively selective for opioid receptors vs non-opioid receptors, they show only limited selectivity for MOPrs [62]), meaning that MOPr knockout mice, or irreversible antagonists such as beta-funaltrexamine need to be used. Although MOPr knockouts are vital experimental tools, they pose a problem in terms of studying the specific effects of MOPrs in reinstatement to drug-seeking behaviour, where the ideal experiment would be to perform CPP or self-administration training under normal conditions, and then inhibit MOPrs during the reinstatement phase only, as well as the possibility of compensatory changes that would affect the behaviour of the animal by a mechanism not directly related to the protein deletion. Consequently, there have been few studies specifically examining the role of MOPrs in drug-induced reinstatement. Using local intracerebral injections of the selective MOPr antagonist, CTAP, cocaine-induced reinstatement to self-administration was inhibited [63, 64]. Similar effects were seen in both cue-induced and drug-induced reinstatement to alcohol seeking [65]. More recently, the novel selective, systemically-active, MOPr antagonist GSK1521498 has been shown to inhibit cue-mediated cocaine (and heroin) seeking via self-administration in rats. In terms of self-administered drug intake itself however, the MOPr antagonist had no effect on cocaine self-administration, but increased heroin self-administration (presumably by the animals’ attempts to overcome competitive MOPr blockade by increasing doses of heroin) [66]. The precise mode of action of how MOPrs regulate psychostimulant addiction-related behaviour is unclear, although it has been suggested that MOPrs mediate incentive salience connected with drug-related cues, and so may act by affecting motivational memory [66]. Indeed, an elegant recent study using MOPr knockout animals has also shown that whereas the acquisition of cocaine self-administration was unaffected in MOPr knockout animals, cue-induced reinstatement was

inhibited [67]. This raises the possibility that MOPr antagonists may be effective anti-relapse therapies for all classes of drugs of abuse [68].

5.2 delta-opioid receptors

Numerous studies have examined the role of DOPr in animal models of addiction-related behaviour. Although initial studies suggested that activation of DOPr can contribute, albeit relatively weakly, to the euphoric/rewarding effects of a range of drugs of abuse including opioids and psychostimulants, it now seems more likely that it affects memory, specifically the ability to acquire cue-drug associations. The majority of studies to date have examined the effects of DOPr on the acquisition of self-administration or CPP to other drugs of abuse and, as cue-drug associations are intrinsic to the acquisition of these behaviours, agents that inhibit this type of associative memory would inhibit their acquisition [69–73]. Whilst this potential role of DOPr on associative memory may prove to be useful in designing novel anti-relapse therapies (see section 4.2), the precise effects of DOPr are unclear at present. Indeed, there have been few studies directly examining the role of DOPr in reinstatement to opioid or psychostimulant drug-seeking, and with conflicting results. Cocaine-induced reinstatement of cocaine-seeking via self-administration elicited by the enkephalinase inhibitor thiorphan was reduced by the DOPr antagonist naltrindole [63]. Infusion of beta-endorphin directly into the nucleus accumbens increased cue-induced cocaine-seeking, an effect that was inhibited by naltrindole [74], and cue-induced cocaine-seeking was attenuated in DOPr knockout animals [67].

Studies into the roles of DOPr in reinstatement models are complicated by 2 factors. First, the postulation that there are two subtypes of DOPr (DOPr1 and DOPr2). Despite there being only one DOPr gene, potentially the subtypes can arise from heterodimerisation, or by cell-type specific splice variants or accessory signalling proteins [75]. Indeed, various pharmacological tools have shown some selectivity at one or other of the subtypes. Second, in naïve animals, DOPr activation is anxiolytic (knockout of DOPr is anxiogenic), thus, positive effects of DOPr agonists in animal models may be due to their anxiolytic effects rather than by an ‘anti-addiction’ effect, per se, a process perhaps most salient when studying alcohol-related effects because of the anxiogenic effects of alcohol withdrawal. DOPr have been extensively studied in models of alcohol addiction, where DOPr antagonists have generally been shown to be effective in both cue- and stress-induced reinstatement to alcohol drinking [76, 77], although selective DOPr1 agonists have also been shown to reduce alcohol consumption [78], suggesting perhaps that DOPr1 and DOPr2 may have opposite actions.

5.3 kappa-opioid receptors

As mentioned in section 3, there are 3 main triggers to drug relapse/reinstatement: drug-priming, cue exposure and stress. Whereas MOPr can mediate the initial rewarding/euphoric effects of opioids (and alcohol), and affect motivational, cue-related memory to a range of drugs of abuse, and DOPr appear to play a role in cue-related associative memories, kappa-opioid receptors (KOPr) play a well-defined role in stress-induced reinstatement to psychostimulants.

KOPr antagonists block stress-induced potentiation of cocaine CPP and self-administration [79–82]. Similarly, KOPr agonists can reinstate cocaine self-administration [83] and amphetamine self-administration [84], effects attributed to be due to KOPr agonists mimicking the effects of acute stressful stimuli [85, 86]. Significantly, KOPr antagonists can inhibit stress-primed but not drug-primed reinstatement to cocaine CPP and self-administration [80, 87, 88]. Fewer studies have been performed with reinstatement to opioid-seeking behaviour, but KOPr antagonists have recently been shown to inhibit stress (food deprivation)-induced reinstatement to morphine self-administration [89], and prevent escalation of heroin self-administration [90]. Similar effects have been demonstrated with nicotine CPP and self-administration [91, 92].

Further, KOPr antagonists have been shown to exhibit anxiolytic-like and antidepressant-like effects in various behavioural paradigms (for a recent review see [93]), with KOPr agonists exhibiting dysphoria [82]. This is likely to contribute to the more complicated picture of KOPr effects on alcohol seeking and drinking where KOPr antagonists have been shown to selectively attenuate alcohol-dependent self-administration while leaving non-dependent alcohol self-administration intact [94], consistent with earlier findings of a decrease in alcohol self-administration in KOP receptor knockout mice [95]. More recently, KOPr antagonists have been shown to decrease cue-induced reinstatement of alcohol drinking with no effect on stress-induced reinstatement, an effect attributed to KOPr antagonists reducing alcohol-induced withdrawal anxiety [96, 97].

Overall, there is robust evidence that KOPr antagonists are effective at inhibiting stress-induced, but not drug-prime-induced, reinstatement to psychostimulant drug-seeking behaviour. Similar research into reinstatement to opioid-seeking behaviour is limited but consistent with findings in psychostimulants.

5.4 opioid receptor-based combination therapy

There is growing evidence, presented above, that a combination of MOPr antagonism and KOPr antagonism may be an effective anti-relapse therapy, with the precise role of DOPr, at least in opioid and psychostimulant addiction, as yet unclear. However, the challenge has been how best to derive a pharmacological treatment to achieve MOPr and KOPr antagonism. One idea is to combine buprenorphine (a high affinity MOPr partial agonist, KOPr antagonist [98]) with naltrexone (a pan-opioid antagonist with some selectivity for MOPr [99]). Unusually, proof of concept for this approach derives from clinical, rather than preclinical trials, with two clinical trials using a combination of buprenorphine and naltrexone demonstrating significant reduction of both heroin and cocaine use [100–102]. Currently, buprenorphine is licensed as an opioid substitution therapy, but is in itself rewarding via activation of the mu-opioid receptor [103]. Combination of buprenorphine with sufficient naltrexone can block buprenorphine's mu-opioid receptor agonism [104, 105] thus increasing regulatory acceptability, and feasibility of its use in psychostimulant addicts. Naltrexone is itself licensed as an abstinence-promoter but treatment success is hindered by low compliance. Naltrexone provides no reinforcement or pleasure, but, as a mu-opioid receptor antagonist, is likely to block rewards caused by release of endogenous opioid peptides [106, 107]. Indeed, in laboratory animals, naltrexone alone has been shown to be

aversive at high doses [108, 109]. Another component of the pharmacology of a buprenorphine/naltrexone combination is to act as a partial agonist at the NOP receptor. Selective NOP agonists are neither rewarding nor aversive [110] and, although the mechanism is poorly understood, they have been shown in rodents to oppose the effects of cocaine and morphine [111–3], inhibiting drug-primed reinstatement of morphine CPP [114], although having no effect on stress-primed reinstatement of cocaine self-administration [115].

This has led to the idea that a combination of buprenorphine and naltrexone (at the correct ratio) could be non-aversive and non-rewarding. This approach has led to some success in preclinical trials in rats. Buprenorphine+naltrexone inhibited ‘compulsive’ extended access cocaine self-administration without inducing physical dependence [116]. And, buprenorphine+naltrexone was non-aversive and non-rewarding, but inhibited drug-primed reinstatement to both cocaine and morphine CPP [117]. Based on the known effects of KOPr antagonists (section 5.3) this combination is likely to also be effective at inhibiting stress-induced reinstatement, although this is yet to be tested. Further, based on the known effects of MOPr antagonists (section 5.1) it is possible it may also have some effects against cue-induced reinstatement.

Clinical trials are ongoing with a buprenorphine and naltrexone combination [118] to test its effectiveness against cocaine use. A further combination product (ALKS 5461; a combination of buprenorphine plus the MOPr antagonist ALKS 33) is being developed by Alkermes and reports suggest efficacy against major depressive disorder. Indeed ALKS 5461 has recently been granted Fast Track status by the FDA and is entering Phase 3 clinical trials. It is important to note that suboxone (a combination of buprenorphine and naloxone) is currently used clinically but for very different reasons to that outlined above. The naloxone component of suboxone is present solely to deter diversion and reduce abuse by intravenous injection. Suboxone is administered sublingually: buprenorphine has good sublingual bioavailability, naloxone does not. If taken intravenously the effect of naloxone will predominate.

Although the buprenorphine + MOPr antagonist approach is in clinical trials this may pose a problem in terms of user compliance and in terms of pharmacokinetics and the challenge inherent in simultaneously titrating plasma levels of two distinct molecules. Consequently, approaches have been taken to synthesize novel single compounds that mimic the combination of buprenorphine and naltrexone (high affinity, but very low efficacy, at MOPrs, KOPr antagonism) [119].

6. CONCLUSIONS

There are many novel targets for the treatment of opioid and psychostimulant abuse that are currently in preclinical studies, with a small number advancing to clinical trials. The aetiology of addiction is undoubtedly complex, incorporating numerous brain regions and neurotransmitter systems. Indeed, reinstatement studies in rodents, although a relatively reductionist approach to studying human drug addiction, have shown that different triggers can induce reinstatement, each incorporating different neurochemical processes. It now

seems likely that real progress may come from treatment approaches that affect numerous neurotransmitters/receptors rather than a 'single target' approach.

7. EXPERT OPINION

The major unmet need in the treatment of opioid and psychostimulant addiction is in reducing rate of relapse back to drug-taking. This provides a series of challenges. Firstly, there are 3 primary triggers that precipitate relapse: stress, drug-priming and cue exposure. These have distinct, although potentially overlapping, neuronal mechanisms making it difficult to design a drug treatment regimen that would be effective against all 3 triggers. Secondly, many drug users are poly-drug users meaning that they take more than one illicit or licit drug of abuse at the same time. Consequently, if an individual is both an opioid and psychostimulant user, designing a novel anti-opioid relapse treatment, for example, may only be effective against relapse in that individual to opioids, not to psychostimulants. The 'holy grail' of novel anti-addiction therapies would therefore be effective against all classes of drugs of abuse, but also effective against all triggers to relapse. Although this clearly presents a challenge there are numerous approaches currently being taken.

One overall approach is to target the memories encoded during drug-taking, that then get reactivated on presentation of relapse triggers. If these unwanted memories can be weakened during abstinence, or if a stronger inhibitory memory can be overlaid upon the unwanted memory, this approach could be successful. Although this approach has shown some clinical benefit in inhibiting other unwanted cue-conditioned memories such as those inherent in post-traumatic stress disorders [120–122] there are limited clinical studies in the addiction field [123]. It is likely that what is required is a better understanding of the molecular mechanisms involved in addiction-related memories, which could then lead to the development of pharmacological agents that are effective specifically against addiction memories, rather than globally active amnesic or cognitive-enhancing agents. Even so, there is still the suggestion that the mechanisms underlying opioid addiction memories and psychostimulant addiction memories may be different [124, 125].

An alternative approach is to target opioid receptors. Although the evidence for the specific role of DOPr in opioid and psychostimulant addiction is unclear at present, there is growing evidence that MOPr and KOPr antagonists may be effective anti-relapse agents, and, potentially, against all 3 triggers to relapse. Much work still needs to be done to optimise this treatment approach, but work to date has generally focussed on a combination of buprenorphine with a MOPr antagonist (often naltrexone). Buprenorphine has an interesting and unusual pharmacology that lends itself to this approach. It is a high affinity KOPr antagonist, as well as a high affinity, low efficacy, MOPr agonist. Generally speaking, agonists at MOPr have lower affinity than antagonists, in part because of the 'GTP shift' in agonist binding. However, buprenorphine exhibits minimal GTP shift and has very high affinity (while retaining partial agonist activity) [126, 127], meaning that it is more likely to inhibit subsequent binding of either endogenous or exogenous opioids, and also increasing the likelihood of success of combining buprenorphine with antagonists to 'titrate' the amount of buprenorphine-induced MOPr activation – resulting in sufficient MOPr activation not to be aversive, but insufficient MOPr activation to be rewarding. However, the problems

inherent in co-administration of 2 compounds, both in terms of the pharmacokinetic challenge of balancing effective concentrations of two compounds, and that one of the compounds (buprenorphine) is itself rewarding, remain.

Although taking a ‘single target’ approach to drug discovery is necessary in terms of preclinical validation of potential novel targets, evidence to date, and our current understanding of the psychological and neurochemical complexities underlying human addiction suggest that this approach will be suboptimal as a clinical treatment approach. Simultaneously targeting numerous neurochemical/receptor systems may lead to advances in the treatment of opioid and psychostimulant abuse.

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ARTICLE HIGHLIGHTS

- The major unmet need in the treatment of psychostimulant and opioid addiction is prevention of relapse back to drug-taking after a period of abstinence.
- The neuronal bases of addiction are complex, and relapse can be triggered by different stimuli involving distinct, but overlapping, neuronal pathways.
- Numerous pharmacological targets are being examined as potential anti-relapse treatments that can be broadly separated into ‘memory-based’ and ‘receptor-based’ approaches.
- The most successful novel treatment approach is likely to be one that is effective against each relapse stimulus, and against all classes of drugs of abuse.
- Opioid receptors provide a tractable, fairly well-understood, target.
- Current research suggests a ‘non-selective’ approach to targeting opioid receptors would be the most effective.