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Opioids and addiction: Emerging pharmaceutical strategies for reducing reward and opponent processes

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Abstract

Conventional strategies for treating opioid abuse include cognitive/behavioral therapy, maintenance therapy and managed withdrawal. These strategies deal with the addictive state, but much effort has shifted toward developing preventative measures. One approach is to reduce the rewarding properties of abused drugs, which in the case of prescription pharmaceuticals such as opioid analgesics is clearly a worthwhile endeavor. First, we will review recent studies demonstrating that mice lacking various G-protein coupled receptors and their ligands show diminished opioid reward. These studies point to considerable interdependence among different neuromodulatory systems for establishing drug reward. Thus, we will highlight the potential for combining opioids with other receptor targets to maximize analgesia and minimize reward in order to prevent the establishment of euphoric memories and opponent processes driving addiction. A more complex issue is treating opioid addicts where many physiological shifts have developed to oppose the acute drug effects. These opponent processes occur both at the cellular level (e.g. adenylate cyclase supersensitivity) and behavioral level (e.g. dysphoria and hyperalgesia). Evidence will be presented showing that even weak opioid agonists can effectively induce the intracellular process of adenylate cyclase supersensitivity. Furthermore, opioid-induced hyperalgesia, a behavioral opponent process, may manifest differently depending on the pain stimulus, and may require a priming drug dose in some cases. Environmental stress interacts with these opponent processes and drives relapse and thus, is another variable that needs to be considered in the development of innovative pharmacotherapy options for opioid addicts.

Keywords: Morphine; Opiate; Withdrawal; Tolerance; Cyclic adenosine monophosphate (cAMP); Cannabinoid; Neurokinin; Cholecystokinin

1. Introduction

One of the powerful properties of opioid drugs, a property particularly associated with heroin, is the potential for creating addictive states. Following the decision to take the drug, the first step in the addiction process is activation of opioid receptors, which in turn modulates various signaling cascades that alter cellular function via ion channels and enzymes including kinases, phosphatases and adenylate cyclase [1]. Subsequent to receptor signaling, the downstream cellular pathways and circuitry leading to opioid reward and addiction remain somewhat obscure. It is generally considered that opioid drugs are rewarding because they inhibit tonic GABAergic suppression of the mesolimbic dopaminergic reward pathway [2] the end result being increased dopamine release in the nucleus accumbens (NAc). Indeed, as with most abused drugs, dialysis experiments clearly show opioid-induced dopamine release in the NAc [3]. Furthermore, administration of opioids results in synaptic plasticity in mesolimbic dopaminergic synapses as assessed structurally [4] and electrophysiologically [5]. Enhanced dopamine release in the NAc is probably not the entire story, however, and support for a separate mechanism for opioid reward comes from studies in rats showing maintained addictive behavior for heroin but not cocaine when the mesolimbic reward system is lesioned [6]. Furthermore, dopamine release in the NAc is increased as a result of both rewarding and aversive stimuli, questioning whether released dopamine is the 'reward signal per se' (reviewed by [3]). Current thought is that the mesolimbic dopaminergic system is utilized in focusing memory processes during salient events and evidence is strong that this pathway is involved in the development of reward-associated behaviors [7].

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There are many reasons for initially taking an opioid. Reasons can be clearly medicinal (e.g. for pain relief, diarrhea or coughing), to experience changes in mood or sensory perception or socially driven. The acute physiological effects of opioid agonists are predictable and include analgesia, respiratory depression, antitussive effects and constipation. The psychotropic effects are, however, quite variable across individuals. Some relay their initial experiences with opioids as distasteful and others as obsessively wonderful. The psychological or genetic basis for this variability is unknown. Given drug availability, the decision to continue taking the drug is extremely complex and may be related to the purpose for which the drug was taken, the route of administration, the nature of the drug-taking environment and susceptibility traits related to addiction [8].

Multiple targets exist for pharmacological intervention in opioid abusers. Opioid receptor antagonists are used for reversing overdose as well as for antagonist-induced rapid detoxification during managed withdrawal (reviewed by [9]). A separate strategy, usually following withdrawal and detoxification, is the treatment of addicts with pharmaceutical interventions primarily aimed at opioid maintenance therapy, usually with opioids such as methadone or buprenorphine. An important question is whether non-addictive, non-opioid drugs, can satisfactorily substitute for maintenance therapy in treating opponent processes and craving. Thus, treatment of addicts with non-opioid drugs represents another type of intervention and will be reviewed in this article. But first, we will discuss potential strategies for reducing the rewarding properties of prescribed drugs. Clearly the most effective approach would be to treat the primary disorders and syndromes arising from susceptibility genes or environmental risk factors for substance abuse, an intervention in its infancy and which is beyond the scope of this article.

2. Factors that influence opioid reward

There are many factors that could lead the casual user of opioids or a patient on opioid treatment to progress to addiction. The importance of the initial or continuing euphoric experience for triggering addiction is not simple to evaluate but decreasing the euphoric impact, whilst retaining clinical efficacy of opioids, should be a pharmaceutical goal.

2.1. Drug pharmacokinetics

Even though drug abuse has been strongly associated with the efficacy or strength of the drug as a reinforcer, other factors influence the addiction liability of a drug. [10]. The mode of drug administration, whether intravenous (i.v.), nasal, transdermal, sub-lingual or oral, can significantly influence the euphoric experience, presumably as a result of varied pharmacokinetics. For example, when the partial agonist buprenorphine is administered sublingually, it does not appear very rewarding, yet when administered i.v., it is highly euphoric [11]. The route of administration can also influence the degree of opponent withdrawal responses [12], thus, further driving addiction.

The rate at which the drug is administered may also influence reinforcement efficacy. Marsch and co-workers administered i.v. morphine at different rates to human volunteers and found a reduced reinforcing effect with slower infusion [13]. Studies with cocaine have demonstrated that decreasing the infusion rate can decrease responding for the drug in monkeys [14,15]. The low potency, yet high efficacy of cocaine as a reinforcer has been attributed to cocaine's 1–4 min production of a 'high' after peripheral administration [16–19]. In contrast, other studies have shown that the rate of psychostimulant administration does not affect several measures of reinforcement (reviewed in [20]). Very recent data suggest that higher rates of drug administration may support addiction by more extensively activating mesocorticolimbic circuitry and inducing behavioral plasticity associated with drug wanting [20].

In addition to the rate of onset, the duration of action of a drug may also influence reinforcement efficacy. Volkow et al. [16] used positron emission tomography (PET) studies to show that the rate of clearance for the relatively more potent methylphenidate (Ritalin) was significantly slower than for cocaine and suggested that this could account for the much lesser abuse of methylphenidate than cocaine despite their otherwise similar pharmacologic properties. In contrast, Ko et al. [21] reported that the different durations of action of the opioid drugs fentanyl, alfentanil and remifentanil did not predict their reinforcing strength.

In sum, different pharmacokinetic parameters, including the route and rate of administration as well as the duration of action of abused drugs influence their rewarding value and contribute to their ability to induce neuroplasticity associated with addiction.

2.2. Drug receptor selectivities

Differential selectivity of opioids for the various opioid receptor subtypes can dramatically influence reward efficacy. Three distinct opioid receptors have been identified at the genetic level: the Mu receptor (MOP) through which agonists are rewarding, the delta receptor (DOP) through which agonists are neither rewarding nor aversive and the kappa receptor (KOP) through which agonists are aversive. Most prescription and abused opioid drugs are not entirely selective for any one of these receptors. Indeed, many have affinity for receptors other than classical opioid receptors such as a NMDA receptors (e.g. methadone [22]) and a receptor closely related to classical opioid receptors, the nociceptin receptor (NOP) (e.g. [23]). In Mu opioid receptor knockout mice, reward for morphine and many other opioid

drugs such as fentanyl and heroin is completely eliminated [24]. However, this is not true for all opioid drugs.

Buprenorphine, a non-selective mixed opioid agonist/antagonist is an excellent example of how complex opioid receptor pharmacology influences reward. Recent data in rodents demonstrates that unlike morphine this drug remains rewarding in the absence of Mu opioid receptors [25]. This retained reward is blocked by the non-selective opioid receptor antagonist naloxone, and further studies using more selective antagonists suggest that both the delta and kappa activity may contribute to its rewarding effects. However, in detoxified human heroin addicts, suboxone, a combination drug of naloxone/buprenorphine that is designed to reduce the rewarding effect of buprenorphine, remains reinforcing when injected i.v. although subjectively less so than buprenorphine alone [26]. The retention of the rewarding properties of the combination drug in humans may be explained by the incomplete blockade of Mu or delta opioid receptor activity. Indeed, the relative buprenorphine to naloxone concentration in the animal studies was significantly higher (1 mg/kg buprenorphine HCl to 1 mg/kg naloxone HCl) than used with suboxone (2 mg buprenorphine HCl/0.5 mg naloxone HCl). It should be recognized that the reinforcing/aversive effects of suboxone in opioid-dependent addicts will be vastly different given that naloxone will precipitate withdrawal in these individuals.

In addition to the fact that opioid drugs can differentially bind and activate or antagonize the three types of opioid receptors, there is the potential that these drugs are able to distinguish between various Mu receptor subtypes. Although there is only a single gene encoding Mu receptors, differential splicing and post-translational modifications of the receptor along with unique complexes of associated proteins with the receptors could lead to a vast array of receptor binding sites and potential for differential signaling (recently reviewed in [27,28]). It is thus possible that drugs selective for certain Mu opioid receptor complexes may emerge and corroborate the concept that some opioid drugs could elicit clinically useful effects such as analgesia while limiting undesirable effects such as reward, respiratory depression, and perhaps tolerance and dependence.

2.3. Endogenous opioids and reward

Given the euphoric and highly addictive nature of opioid drugs, two repeatedly asked questions are whether the endogenous opioid system plays a role in reward induced by other classes of abused drugs and whether the endogenous opioid system mediates behaviors that can become addictive such as eating, sex and attachment. Early studies that used opioid receptor antagonists implicated the endogenous opioid system in the rewarding properties of many different drugs and behaviors. Rewarding behaviors involving food, strenuous exercise, alcohol, nicotine, delta-9-tetrahydrocannabinol (Δ-9-THC; the main psychoactive compound in marijuana), could all be blocked or reduced by opioid receptor antagonists [29,30].

These studies are complex to interpret for a few reasons. First, the alkaloid opioid antagonists that have been principally used are naloxone and naltrexone, which are not selective for a single receptor type. Second, and perhaps more importantly, is that many opioid receptor antagonists are aversive in drug-naïve animals, suggesting that opioid receptor inactivation can by itself drive opponent behaviors. These issues have been addressed with the use of ligand and receptor knockout mice and, in some cases, have revealed surprising results and new avenues for pharmacotherapeutic treatments for addiction [31]). However, the use of knockout mice has its own caveats, such as the lack of generality due to the presence, absence or degree of inbred strain-specific traits, the interaction of background strain with the absence of the gene, and the potential for compensatory changes during development. Clearly, complementary results from the use of both antagonist and knockout strategies provide the most compelling evidence for receptor-dependent motivational behaviors.

Deletion of the Mu opioid receptor, but not the delta or kappa opioid receptors, results in a dramatic motivational phenotype in mice. In addition to the loss of rewarding properties of many opioid drugs (as described above), Mu opioid receptor knockout mice no longer find other drugs of abuse rewarding such as alcohol, THC or nicotine [31]. The implication, as depicted in Fig. 1, is that many addictive drugs that do not directly activate Mu opioid receptors, rely on an intact endogenous opioid system in order to exhibit rewarding properties. Thus, these drugs may induce release (or rely on tonic release) of endogenous opioid peptides, dynorphins, enkephalins, and/or endorphins, which in turn, activate Mu opioid receptors. The use of proenkephalin, prodynorphin and pro-opiomelanocortin knockout mice will unequivocally indicate which endogenous opioids are responsible for the rewarding effects of nicotine, alcohol

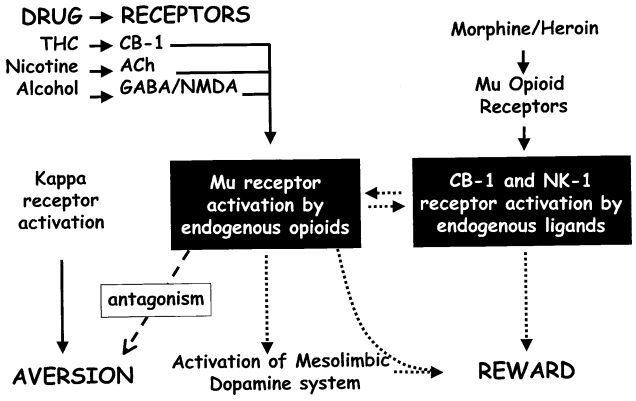

Fig. 1. Interdependence of drug reward on different neuromodulatory systems. Dotted lines represent potential alternative routes to reward. The dashed line indicates Mu opioid receptor antagonist-induced aversion. Black boxes indicate potential pharmaceutical receptor targets where antagonists are predicted to reduce drug reward.

and THC. In the case of nicotine conditioned place preference, both the Mu receptor and the proenkephalin knockout mice share the same phenotype, suggesting that nicotine reward requires opioid peptides derived from proenkephalin which, in turn, activate Mu opioid receptors [32].

The effect of deleting the Mu opioid receptor with regard to ethologically relevant motivational behaviors has been less clear. Mu receptor knockout mice appear to drink, eat, reproduce, and care for their young, similar to normal mice. Some behaviors, however, such as the attachment of pups to their mother are severely impaired [33]. Wild-type but not Mu receptor knockout pups vocalize with ultrasonic distress calls on separation from the mother and also discriminate the mother's nest from that of another female's. Interestingly, the lack of attachment behavior exhibited by the Mu receptor knockout mice does not generalize to loss of other behaviors associated with maternal care. The pups retain their drive to nurse, their preference for a female odor-impregnated nest over a clean nest, and an intense aversion of a male odor-impregnated nest. Clearly many motivational behaviors are retained in Mu receptor knockout animals, although one could question whether they are rewarding.

2.4. Opioids and aversion

The non-selective opioids antagonists naloxone and naltrexone are highly aversive in rodents as measured by conditioned place aversion. In this behavioral assay, animals injected with opioid receptor antagonists in a specific environment subsequently avoid this environment in the absence of drug. This suggests that tonic activation of endogenous opioid receptors contributes to hedonic homeostasis in mice. A series of studies using opioid receptor knockout animals has demonstrated that Mu opioid receptors, but not kappa or delta receptors, mediate this antagonist-induced aversion [34]. Furthermore, this aversion is eliminated in proenkephalin knockout mice yet is completely retained in proopiomelanocortin knockout mice, suggesting that in order for naloxone to produce aversion, it must disrupt opioid peptides derived from proenkephalin activating Mu opioid receptors [35]. It should be mentioned that although non-selective opioid antagonists are highly aversive in rodent models, the data on humans are much less clear since naltrexone is tolerated well by most drug-naïve subjects [36].

Conditioned place aversion in mice is also observed with kappa receptor agonists [37], suggesting that like the Mu receptor, tonic activation of the kappa receptor system may also contribute to hedonic homeostasis, but in a reciprocal manner. A number of opioid drugs are kappa agonists, which could modulate the rewarding effects of Mu agonist activity. The identification of the active hallucinogenic compound Salvinorin A from the mint plant, *salvia divinorum*, as a potent kappa agonist [38] may contribute to the understanding of the psychological nature of kappa receptor-induced aversion in humans and perhaps, kappa receptor-mediated analgesia, since it is used recreationally and for ceremonial purposes. One possibility is that kappa analgesia is mediated through kappa-induced aversion and hallucinations, with the end result being analgesia via stress and/or diversion of attention.

2.5. System interdependence for opioid-mediated reward

Thus far, the impression is that the endogenous opioid system is the critical mediator of a number of rewarding activities. However, the situation is considerably more complex. On examination of the cannabinoid-1 (CB-1) receptor knockout mice, it is clear that, like Mu receptor knockout mice, they have lost their ability to show reward for opioids. Thus, in mice there is reciprocal dependence between opioid and cannabinoid systems for the rewarding effects of the two drug classes (Fig. 1). Given the likely premise that endogenous opioids mediate the rewarding effects of other drugs of abuse and behaviors, a logical hypothesis is that both the CB-1 and the endogenous opioid systems are required to be intact for the rewarding effects of alcohol, nicotine and some natural rewards. The importance of the opioid system in alcohol reward has been recognized for many years [39], but recent data indicate the importance of CB-1 receptors in both alcohol and nicotine reward [40–45]. Interestingly, opioid reward also depends on substance P [46] and neurokinin 1 (NK-1) receptors [47], an effect that has been localized in the amygdala [48] (Table 1). Again, the reverse is true: reward produced by substance P is blocked by the opioid antagonist naloxone [49]. To our knowledge, the contributions of NK-1 receptors to cannabinoid, nicotine, and alcohol reward have not been addressed. In sum, it is possible that genetic or pharmacologic disruption of the neurokinin or cannabinoid systems will mimic the Mu receptor knockout mice with respect to other drugs of abuse and some natural rewards. Indeed, like Mu opioid receptors, disruption of NK-1 inhibits neonatal vocalizations [50] indicating the likelihood that this system is involved in other opioid-related behaviors.

3. Opponent processes: cellular and behavioral

After prolonged administration of opioids, tolerance to many of the acute effects ensues and upon cessation of use, opposite responses can emerge. These include hyperalgesia, restlessness, dysphoria, diarrhea, increased heartbeat, and anxiety. These opponent processes in many cases counteract the acute effects of opioids and can contribute to tolerance and underlie physical dependence [51]. Hyperalgesia, an increased sensitivity to pain, is a particular problem for opioid addicts in opioid maintenance programs (reviewed by [52]). Furthermore, mood disturbances during abstinence represent another opponent process [53]. Koob and Le Moal [54] incorporated the contribution of opponent processes to

Table 1
Pharmacotherapeutic potentials for preventing drug reward based on knockout data and pharmacological studies in rodents

Pharmacotherapy	Aversive	THC reward	Alcohol reward	Nicotine reward	Opioid reward	Mu-opioid analgesia
Mu-opioid ant.	Yes [94,95]	Reduces [96]	Reduces [97]	Reduces ko [32]	Blocks [98]	Blocks [99,100]
κ-opioid ant.	No [101]	Unmasks ko [102]	Enhances [103] Reduces ko [104]	?	No effect [105]	No effect ko [106]
NK-1 ant.	No [87]	Reduces?	Reduces?	Reduces?	Reduces ko [47]	No effect/ Reduces [107]
CB-1 ant.	No [88]	Blocks [108,109]	Reduces [41,110, 111]	Reduces [42] (ko)	Reduces [87,112, 113]	No effect [109]
CRF-1 ant.	No [114]	?	Reduces [115]	?	?	?
CCK-2 ant	No [116]	?	No effect [117]	?	Enhances [116]	Enhances
Alpha2 ag	Yes/No	?	Reduces [118]	?	Reduces [119]	Enhances

Ant., antagonist; Ag., agonist. Question marks designate unknown actions. 'Reward' refers to studies using either conditioned place preference or self-administration paradigms. We acknowledge that conditioned place preference could be revealing other processes as well such as learning and memory or state dependency, or avoidance of withdrawal which may become conditioned, and thus, interpretations should be made with caution. Citations refer to knockout and antagonist studies. ko, only knockout references were available.

addiction by hypothesizing that chronic administration leads to a shift in hedonic setpoint so that addicts continue using to overcome this persistent dysphoric shift in mood and physiology so that they can feel 'normal.' Addicts will take increasing amounts of drug to overcome the new hedonic setpoint so that they feel 'high.' The result is a vicious cycle leading to a constantly changing hedonic setpoint and escalation of drug use. Rodent studies indicate that, like the rewarding state, the opponent aversive state requires the extended amygdala [55]. The hypothalamic–pituitary-axis is recruited during spontaneous withdrawal and antagonist-precipitated withdrawal and contributes to the aversive state via the release of corticotropin releasing factor (CRF) in the amygdala [56]. Also, noreprinephrine release in the extended amygdala during protracted withdrawal has been proposed to contribute to the dysphoric state that is relieved by reinstatement of drug use [57].

3.1. Adenylate cyclase supersensitivity

Mechanisms of opioid tolerance from studies at the cellular level were thought to include changes in surface receptor number and decreased coupling of opioid receptors to their inhibitory G-proteins. In addition, a striking cellular opponent process that occurs following chronic opioid treatment that was first reported by Marshall Nirenberg and colleagues in the 1970s is cAMP 'overshoot' or adenylate cyclase 'supersensitivity.' Acutely, opioid receptor agonists inhibit adenylate cyclase and thus, decrease cAMP levels. After chronic administration, however, a compensatory increase in adenylate cyclase activity is observed, leading to a dramatic increase in both basal and stimulated cAMP levels [58]. Surprisingly, the molecular mechanisms mediating supersensitivity remain largely unknown but have been associated with upregulation and increased phosphorylation of various isoforms of adenylate cyclase and a shift from inhibitory to excitatory G-protein-mediated signaling [59]).

The functional link between cAMP overshoot and opioid tolerance and dependence remains obscure. Following chronic morphine treatment in vivo, adenylate cyclase supersensitivity has been observed in different brain areas e.g. the nucleus accumbens and amygdala; [60] but mostly in the locus coeruleus [61], an area rich in Mu opioid receptors that was traditionally thought to be involved in the expression of physical withdrawal symptoms during opioid dependence [62]. However, subsequent lesioning data questions the importance of the locus coeruleus in opioid dependence [63]. Nevertheless, other events indicating the importance of elevated cAMP levels in opioid dependence include a protein kinase A-dependent increase in the activity of the transcription factor cyclic AMP response element binding protein (CREB) in the locus coeruleus and an increase in CRE-mediated transcription in the locus coeruleus as well as the extended amygdala [64]. These observations, in conjunction with studies demonstrating the importance of CREB activity during opioid withdrawal, indicate that increased cAMP levels play a role in opioid dependence [65,66]. Recent direct evidence indicates that another brainstem structure, the nucleus raphe magnus, demonstrates upregulation of the cAMP pathway and enhanced cAMP-dependent glutamate transmission that contributes to pain sensitization after chronic morphine [67]. A potential mechanism for the cAMP-dependent increase in glutamate release may involve a cAMP/PKA-dependent downregulation of glutamate transporters [68].

We have tested the modulation of cAMP levels in a cell line expressing Mu receptors by the peptide full agonist DAMGO, the strong partial agonist morphine, as well as two weak partial agonists RTI-1c and RTI-1d (*cis*-isomers of ohmefentanyl). These isomers are very interesting because they do not induce any analgesia but animals show place preference for these drugs [69–71]. Additionally, RTI-1c but not RTI-1d induces dependence as measured by naloxone-precipitated jumping [72]. We found that RTI-1c and RTI-1d produce approximately a 20% acute reduction from control cAMP levels, whilst both DAMGO and morphine produce a 70–80% reduction in cAMP levels (Fig. 2). This confirms the weak partial agonist activity of these ohmefentanyl isomers

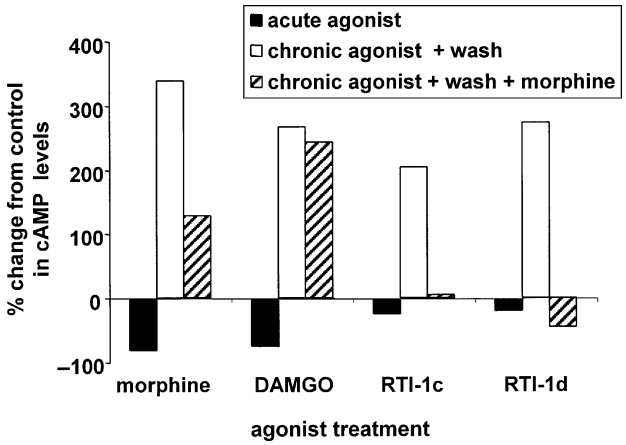

Fig. 2. Acute adenylate cyclase inhibition and adenylate cyclase supersensitivity after chronic treatment with full and partial agonists. HEK-293 cells transfected with Mu receptors [158] were treated for 15 min with agonist (acute; black bars) or 18 h (chronic) and forskolin-stimulated cAMP levels were measured. For chronic treatment, drugs were washed three times with PBS prior to the addition of forskolin without morphine (white bars) or with morphine (striped bars). Data are presented as percent change from control levels of cAMP.

at the Mu opioid receptor. Chronic treatment with all of the agonists led to a 2–3.5-fold increase in forskolin-stimulated cAMP levels, indicating that even weak partial agonists can produce sizeable cAMP overshoot (Fig. 2). Thus, RTI-1d induces sizeable overshoot but no physical dependence [72], raising the question of whether the presence of adenylate cyclase supersensitivity in and of itself always accompanies dependence.

Following chronic agonist treatment, we found that despite the sizeable overshoot produced by all drugs, the acute efficacy of the agonist predicted the ability of a low concentration of morphine (10 nanomolar) to reverse supersensitivity. Specially, following chronic high efficacy agonist treatment (DAMGO and morphine), a submaximal concentration of morphine (10 nM) had little effect on reversing supersensitivity. In contrast, following chronic low efficacy treatment (RTI-1c and RTI-1d), morphine lowered cAMP levels to approximately control levels. Thus, while both high and low efficacy agonists produce sizable overshoot, it appears that chronic high efficacy treatment produces much more effective resistance to reversibility of this cellular adaptation than chronic low efficacy treatment. We propose that the resistance to reversibility of overshoot may be more related to the establishment of behavioral opponent processes than simply overshoot per se.

3.2. System adaptations and hyperalgesia

It is now evident that Mu receptor adaptations (e.g. downregulation and desensitization) do not fully encompass the adaptations associated with tolerance. For instance, chronic opioid treatment in mice produces complete tolerance to morphine-induced Mitogen-Activated Protein (MAP) kinase activation in cortical cells [73]. This activation in the cortex is NMDA receptor-dependent, is mediated by the Mu receptor (unpublished knockout data), and occurs in cells adjacent to those expressing Mu receptors. In a similar model, chronic opioid treatment results in undetectable changes in the signaling capability of cortical Mu receptors, as measured by Mu agonist stimulated GTPγS binding [74]. These observations indicate that plasticity occurs in cells other than those of primary opioid modulation, which may contribute to opponent processes. It also highlights the limitations of focusing solely on adaptations in cells containing Mu opioid receptors (e.g. adenylate cyclase supersensitivity) and perhaps, the need to focus on circuitry adaptations to fully explain mechanisms of analgesic tolerance and dependence.

Following chronic opioid treatment, hyperalgesia often develops which is, in part, mediated by anti-analgesia systems. Opioid-induced hyperalgesia can require NMDA receptor activation [75], spinal dynorphin, cholecystokinin-2 (CCK-2) and, calcitonin gene-related peptide [76]. We have found that the detection of spontaneous hyperalgesia following a chronic morphine regimen in male C57BL/6J mice depends on the type of pain assay employed. In the tail withdrawal assay, spontaneous hyperalgesia is present the next day after the last morphine injection as indicated by a significantly lower baseline latency in morphine-tolerant mice (Fig. 3A). In the hot plate assay, we found that spontaneous hyperalgesia did not develop after the same morphine regimen, yet can eventually be observed after a subsequent morphine challenge. Chronically treated mice have similar baseline hot plate latencies but at 150 min post-morphine, display delayed hyperalgesia (Fig. 3B), as previously shown [73,77]. In contrast, control mice still exhibit significant acute morphine analgesia at this time point. Thus, using two pain assays, different types of opioid-induced hyperalgesia can be observed; one that occurs spontaneously and one that appears to require a morphine challenge. An obvious clinical implication is that opioids may not always be the optimal choice for treating pain [78] because they may eventually aggravate existing symptoms and create additional pain. Furthermore, opponent processes could manifest differently depending on the type or physical location of the noxious stimulus.

3.2.1. Conditioned opponent processes

Opponent processes do not solely occur as autonomic physiological responses, but may also be expressed as learned responses. The opponent processes become conditioned through associative learning mechanisms linking the environment with the drug effects. For example, analgesic tolerance can become conditioned to the environment in which the opioid is administered and is accompanied by conditioned hyperalgesia [79], a phenomenon that, like opioid-induced hyperalgesia (see Fig. 3B), also depends on the type of pain assay [80]. Conditioned opioid tolerance has been shown to depend on anti-analgesic

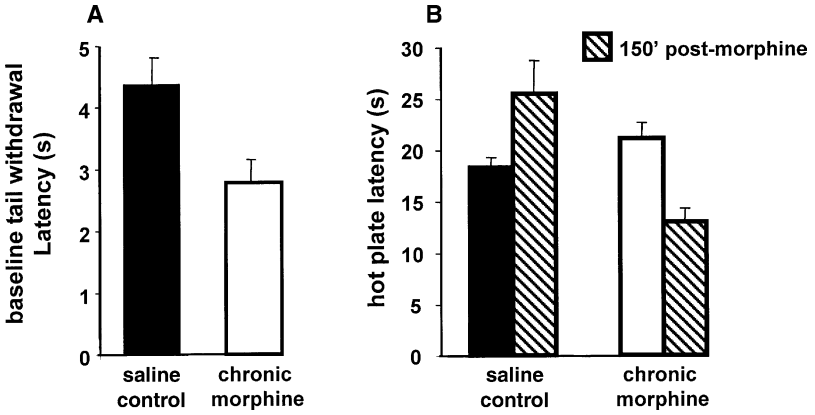

Fig. 3. (A) Spontaneous hyperalgesia revealed in the tail withdrawal test after chronic morphine. Male C57BL/6J mice ($N=7$–8) were treated for 6 days with saline (s.c., black bar) or escalating doses of morphine (10–40 mg/kg, s.c. white bar). On day 7, the 48.0 °C tail withdrawal assay was used to record baseline latencies. Student's *t*-test indicated a significantly lower baseline latency in mice chronically treated with morphine ($t=2.86$; $P=0.01$). (B) Morphine-induced hyperalgesia revealed in the hot plate test. C57BL/6J mice were treated for 6 days with saline or escalating doses of morphine (10–40 mg/kg, s.c.). On day 7, mice were tested for baseline latency and administered a challenge dose of morphine (10 mg/kg, s.c.) and tested for analgesia every 30 min for 150 min. Repeated measures ANOVA indicated a main effect of treatment ($F1,50=4.90$; $P<0.05$), and an interaction of treatment with time ($F1,50=19.36$; $P<0.0001$). Subsequent one-way ANOVA ($F3,100=7.05$; $P<0.05$) followed by post-hoc comparison revealed that control mice still exhibited analgesia at 150 min ($P<0.05$) whereas mice chronically treated with morphine exhibited hyperalgesia ($P<0.05$). No differences in baseline latencies were observed ($P>0.05$), indicating the requirement of a subsequent morphine challenge for the induction of hyperalgesia.

mechanisms and requires CCK-2 receptor activation in the amygdala [81]. Thus, it appears that in some cases, conditioned opponent processes engage similar mechanisms as the unconditioned processes. A clinical example of conditioned opponent processes is that of heroin addicts who experience conditioned withdrawal responses and craving when re-exposed to cues and environmental contexts that were previously associated with drug use [82,83]. A likely substrate for opioid-induced conditioned withdrawal and craving is the extended amygdala [57,84], the same set of brain structures activated during naloxone-precipitated withdrawal [57,85]. In short, drug memories can engage opponent processes in response to environmental contexts and cues by utilizing the same brain areas and mechanisms as unconditioned opponent processes (e.g. antagonist-precipitated withdrawal) and thereby contribute to opioid addiction.

4. Emerging pharmaceutical strategies

Given the above findings, a number of treatment strategies for reducing reward value of different abused drugs emerge. Opioid receptor antagonists are currently approved for the treatment of alcohol abuse [8] and there is clear potential for the use of opioid antagonists in reducing nicotine, alcohol and cannabinoid reward. However, given the dependence of these drugs of abuse on the endogenous opioid system for reward, it is likely that opioid receptor antagonists may, in fact, trigger either physical or motivational aspects of withdrawal and may explain some of the adverse effects and non-compliance of antagonists in alcoholics reported in some studies [86]. As discussed above, opioid reward also requires intact cannabinoid and neurokinin-1 systems. Unlike opioid receptor antagonists, antagonists for these receptors are not aversive [87,88] and intriguingly, NK-1 antagonists also decrease the expression of physical signs of morphine withdrawal [89–92], suggesting that this system can be used in both prevention and treatment of addicted state. However, CB-1 antagonists enhance opioid withdrawal, [93] highlighting at least one limitation of disrupting the cannabinoid system in treating opioid addiction as well as the recognition that different pharmaceutical strategies will be required for prevention versus treatment measures in addiction (Tables 1 and 2).

4.1. Preventing addiction and the development of opponent processes in pain patients: analgesia without reward? Chronic prescription use without dependence?

Perhaps the most exciting aspect about NK-1 and CB-1 receptor antagonists from a therapeutic perspective is the potential that these agents may block the rewarding, but not the analgesic properties of opioid drugs. The observation that mice lacking NK-1 receptors [107] or CB-1 receptors [108] show relatively intact morphine analgesia, yet no morphine reward, suggests that modulation of these systems may prove clinically useful. This could have major implications for addiction prevention in relieving pain in opioid-naïve patients. Interestingly, these same pharmacotherapies may also block the development of opponent processes and thus, could reduce the motivation to continue taking the drug in order to alleviate the aversive physiological and psychological effects of withdrawal. For instance, mice lacking NK-1 receptors show reduced naloxone-precipitated withdrawal following chronic

Table 2
Pharmacotherapeutic potentials for the reducing the development and expression of opponent processes, craving and relapse in opioid addicts

Pharmacotherapy	Development of opponent processes	Expression of opponent processes	Craving/relapse/stress-induced relapse
Mu-Opioid antagonist	Reduces	Enhances	Enhances/Reduces
κ-opioid antagonist	Enhances [132]	Enhances [133,134] no effect [135] Reduce ko [106]	Reduces [136]
NK-1 antagonist	Reduces ko [46,47]	Reduces [89–92]	?
CB-1 antagonist	Reduces [87,120]	Enhances [93]	Reduces [137,138]
CRF-1 antagonist	Reduces [114]	Reduces [114,139]	Reduces [139]
CCK-2 antagonist	Reduces [140,141]/no effect [142]/ Enhances ko [143]	Reduces [76,144] Enhances ko [143]	?
Alpha-2 agonist	Reduces [124,145–147]	Reduces [124]	Reduces [125,126,147]

Both unconditioned and conditioned opponent processes are included in the references. Craving/relapse refers primarily to studies looking at reinstatement models. '?' indicates that we were unable to find studies related to this question. "Ko" refers to knockout studies.

morphine administration and genetic or pharmacological disruption of CB-1 receptors attenuates the development of opioid withdrawal [46,87,120] (Table 2). Exciting progress has been made in the development of CB-1 receptor antagonists targeting obesity [121] and NK-1 receptor antagonists for anxiety and depression [122], indicating their clinical potential for psychiatric conditions such as addiction.

The predicted outcome of reducing reward and the physiological adaptations from repeated use in naïve patients is likely to be straightforward - blocking euphoria and the development of opponent processes while retaining analgesia should eliminate drug seeking behaviors. However, if the reward value of the drug is reduced in the addict, drug-taking behavior is less predictable. In some animal models, reducing the drug reward makes the animals work harder to receive the drug. Thus, human addicts may simply take more of a drug or drug combination that only partially blocks opioid reward (with danger of overdose) or seek out additional sources. In short, simply decreasing reward value in addicts may be insufficient and potentially harmful.

4.2. Treating established opponent processes in addicts

A potentially more effective strategy for the treatment of addicts is to target the expression of opponent processes with the goal of normalizing physiological and motivational states (Table 2). Clonidine, an alpha-2 noradrenergic receptor agonist that binds to presynaptic autoreceptors and reduces noradrenaline release, is a historic example of pharmacotherapy in opioid dependence [123]. In addition to reducing some opioid withdrawal symptoms [124], it also prevents stress-induced heroin and cocaine seeking behaviors [125,126], indicating its potential for treating craving and relapse. However, side effects such as sedation and hypotension occur with this drug. More recently, lofexidine, an analog of clonidine, has been used because it exerts fewer side effects [9]. Nevertheless, because of the limited success with the noradrenergic system in treating opioid dependence, other strategies for treating established opponent processes are indicated. For instance, disruption of NK-1 can attenuate the expression of withdrawal [89–92]. In addition, Cholecystokinin-2 (CCK-2) receptor antagonists have been shown to attenuate physical and motivational withdrawal symptoms [127], including opioid-induced hyperalgesia [76] and offer another potential treatment option. CCK-2 receptors also contribute to nicotine and alcohol withdrawal, [128–130] as well as cocaine craving [131], suggesting the potential of modulating this system in treating opponent processes in polysubstance abusers (which comprises most addicts).

An additional system to consider in treating at least some established opponent processes is the kappa opioid system. Chronic morphine treatment is associated with an up-regulation of prodynorphin transcripts [148] and dynorphin levels [149]. A kappa receptor knockout study highlights the potential for kappa antagonists as effective drugs in the treatment of opioid dependence given that these mice show attenuated naloxone-precipitated withdrawal symptoms [106]. However, as is the case with all knockout studies, it is impossible to distinguish if receptor disruption attenuates the development or expression of opponent processes. Furthermore, chronic Mu opioid treatment induces a spinal dynorphin-dependent hyperalgesia [150]. Studies indicating the recruitment of the kappa system in mediating opponent processes are in contrast to previous studies indicating that kappa receptor antagonists such as nor-BNI exacerbate withdrawal symptoms in morphine-dependent animals [133]. However, these results could be explained by non-selectivity of nor-BNI in vivo. Thus, the development of highly selective kappa antagonists may be useful in treating opioid dependence [151].

4.3. Preventing relapse

Finally, stress is an important factor to consider in treating drug addicts. Exaggerated responsiveness to stress is often present in former drug abusers, which has been linked to chronic relapse [152]. Thus, drugs that normalize stress responsiveness following drug abstinence may be effective pharmacotherapies for treating addiction. For example, a CRF-1 receptor antagonist blocks

the development of conditioned place aversion to opioid withdrawal [114] and stress-induced relapse to heroin and cocaine seeking [153], suggesting that these drugs may alleviate the dysphoric state in addicts during withdrawal and in stressful situations. Although CRF-1 receptors do not contribute to cocaine reward [154], disruption of CRF-1 decreases alchohol consumption [115], thus, suggesting that these drugs might be useful in preventative strategies for opioid addiction in pain treatment as well. Additionally, CCK-2 receptor antagonists may show promise in modulating stress responsiveness in opioid addicts since they prevent stress-induced reactivation of cocaine conditioned place preference [155]. Last, the kappa opioid receptor system is a potential avenue in treating stress-induced relapse as it is activated in response to stress (e.g. [156,157]), and when activated, can produce aversion. Rothman and colleagues have proposed that upregulation of dynorphin produces an imbalance in abstinent Mu opioid-dependent individuals and dysphoric mood states, which can result in the desire to take Mu opioid agonists to normalize mood [136]. Thus, in addition to the potential for treating opioid withdrawal symptoms, highly selective kappa receptor antagonists [151] may also prove useful for preventing stress-induced relapse to opioids as it has recently been demonstrated in rodents [136,151].

4.4. Summary

Characterization of G-protein coupled receptors at the molecular level has provided the critical tools to develop animal models that, in conjunction with antagonist studies, clearly identify pharmacotherapeutic targets for substance abuse. Interdependence of different neuromodulator systems in mediating reward and adaptive opponent processes to different drugs of abuse has become apparent and offers an array of treatment options. Possible preventative strategies have been provided as well as separate strategies for treating opponent processes and craving in opioid addicts. Predicting clinical success in humans from pre-clinical findings is uncertain, but success made in other clinical fields with the same pharmacologic tools has provided promise in treating addictive disorders.

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