BJP British Journal of Pharmacology

DOI:10.1111/bph.13190
www.brjpharmacol.org

REVIEW

# The opioid receptors as targets for drug abuse medication

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Commissioning editors: Mike Curtis and Ken Takeda

**Received**
25 November 2014
**Revised**
24 April 2015
**Accepted**
10 May 2015

The endogenous opioid system is largely expressed in the brain, and both endogenous opioid peptides and receptors are present in areas associated with reward and motivation. It is well known that this endogenous system plays a key role in many aspects of addictive behaviours. The present review summarizes the modifications of the opioid system induced by chronic treatment with drugs of abuse reported in preclinical and clinical studies, as well as the action of opioid antagonists and agonists on the reinforcing effects of drugs of abuse, with therapeutic perspectives. We have focused on the effects of chronic psychostimulants, alcohol and nicotine exposure. Taken together, the changes in both opioid peptides and opioid receptors in different brain structures following acute or chronic exposure to these drugs of abuse clearly identify the opioid system as a potential target for the development of effective pharmacotherapy for the treatment of addiction and the prevention of relapse.

## Abbreviations

CPP, conditioned place preference; DOP receptor, δ-opioid receptor; KO, knockout; KOP receptor, κ-opioid receptor; Leu-enkephalin, leucine-enkephalin; Met-enkephalin, methionine-enkephalin; MOP receptor, μ-opioid receptor; NAc, nucleus accumbens; PDYN, prodynorphin; PENK, proenkephalin; PFC, prefrontal cortex; POMC, proopiomelanocortin; VTA, ventral tegmental area

## Tables of Links

| TARGETS |
|---|
| δ receptor (DOP receptor) |
| κ receptor (KOP receptor) |
| μ receptor (MOP receptor) |

| LIGANDS | | | |
|---|---|---|---|
| 5′-guanidinonaltrindol | CTOP | ICI-174,864 | Naloxone |
| β-endorphin | Dexamphetamine | JDTic | Naltrexone |
| Amphetamine | Diprenorphine | Leu-enkephalin | Naltrindole |
| Bremazocine | Dopamine | Met-enkephalin | Nicotine |
| Buprenorphine | Dynorphin | Methadone | Nor-BNI |
| Cocaine | Ethanol | Methylphenidate | Prodynorphin |
| CTAP | Glutamate | Nalmefene | U50,488 |
| | Glutamine | Naloxonazine | |

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 (Alexander *et al.*, 2013).

## Introduction

Addiction is a worldwide public health problem for which there are currently no satisfactory treatments. While the existing medications permit efficient detoxification, methods for curing this condition are not yet available. Whatever the drugs of abuse used, a very high percentage of patients relapse into drug use, even after a long period of abstinence. There is an urgent need for new therapeutic strategies that should be based on our new understanding of the neurobiological mechanisms of addiction.

Drug addiction vulnerability is affected by a combination of genetic, epigenetic and environmental factors coupled with drug-induced effects. Neurochemical alterations in the brain caused by addictive drugs have a cellular and molecular basis and, in the setting of repeated self-exposure, leading to addiction, these changes may be persistent. However, the understanding of the cellular and biochemical mechanisms underlying both compulsive drug-seeking behaviour and the very long persistence of addictive effects is still very limited.

The brain network mediating the rewarding properties of drugs and craving phenomena has been identified. The system has been shown to involve such structures as the nucleus accumbens (NAc), ventral tegmental area (VTA), prefrontal cortex (PFC) and limbic structures, in particular the so-called extended amygdala. The enhancement of dopamine secretion in the NAc is a common effect of drugs of abuse. This effect can result from both a direct action on dopaminergic neurons (e.g. cocaine and amphetamine) and an indirect effect by modifying the activity of certain populations of neurons such as GABAergic interneurons that interact with dopaminergic VTA neurons (e.g. ethanol, opioids). The last 60 years of research has provided extraordinary advances in our knowledge of the reward system. For a long time, research on reward mechanisms traditionally focused on brain dopamine. However, from all the results reported in the literature using dopamine agonists or antagonists, it clearly appears that while dopamine plays a key role in reward, it is not the only neurotransmitter involved.

Research on the endogenous opioid system has substantially contributed to our understanding of the molecular mechanisms of drug addiction. Opioid receptors and their endogenous peptide ligands are largely distributed through the CNS and peripheral tissues. The existence of opioid receptors in the brain was demonstrated for the first time in 1973 by three independent groups (Pert and Snyder, 1973; Simon *et al.*, 1973; Terenius, 1973), and it is only in the mid-1990s that the different opioid receptors were cloned: δ (DOP), μ (MOP) and κ (KOP) receptors (Evans *et al.*, 1992; Kieffer *et al.*, 1992; Chen *et al.*, 1993; Li *et al.*, 1993; Meng *et al.*, 1993; Thompson *et al.*, 1993; Yasuda *et al.*, 1993). Three precursors of endogenous peptides have also been cloned, proopiomelanocortin (POMC), proenkephalin (PENK) or prodynorphin (PDYN). These precursors generate several final active peptides: β-endorphin from POMC, methionine-enkephalin (Met-enkephalin) and leucine-enkephalin (Leu-enkephalin) from PENK, dynorphins and neo-endorphins from PDYN. These endogenous opioid ligands exhibit different affinities for each opioid receptor. β-Endorphin shows a higher affinity for MOP receptors, Met- and Leu-enkephalin bind to DOP receptors with an affinity 20-fold greater than that for MOP receptors, and dynorphins are the endogenous ligands for KOP receptors (for review, see Corbett *et al.*, 1993).

The different components of the endogenous opioid system are highly expressed in brain areas involved in reward and motivation (for review, see Mansour *et al.*, 1995). Thus, opioid peptides and receptors are present in the VTA, NAc, PFC, hypothalamus and extended amygdala (Mansour *et al.*, 1993; 1994a,b; 1995; Delfs *et al.*, 1994), and participate in the modulation of the reward circuits.

The main goal of this review is to describe the current knowledge concerning the contribution of the endogenous opioid system to the addictive properties of the different drugs of abuse. Considering the substantial amount of data from animal studies implicating the endogenous opioid system in reward and addiction, combined with the results from human post-mortem brains or obtained by neuroimaging in addicts, several questions about their clinical relevance arise: to what extent is the endogenous opioid system a valuable target for developing new treatments for the management of addiction? How successful are pharmacotherapies targeting the opioid system for the treatment of addiction? What could be the future directions?

This review gives an overview of how the opioid system is regulated by different drugs of abuse, to achieve a better knowledge regarding the use of opioid ligands in addiction treatments. With this aim, a specific focus has been done on psychostimulants (i.e. cocaine, amphetamine, methylphenidate), alcohol and nicotine. Opioid and cannabinoid addictions have not been considered as opioid ligands are already largely used in clinic to treat opioid addiction. Moreover, although numerous preclinical evidences indicate interplay between opioid and cannabinoid systems, only few studies have investigated the potential therapeutic interest of opioid ligands in cannabis addiction.

## Cocaine

### *Modification of endogenous opioid system by psychostimulant treatment*

Acute and chronic administration of psychostimulants produce adaptive changes in opioid peptide content, gene expression and receptor densities in brain structures related to reward circuits. However, one of the major difficulties is the discrepancies in the results reported in the literature, which is not surprising as it is now well established that neuroadaptations depend on different factors, including drug administration pattern and withdrawal period (see Conclusion section).

The most reliable finding in terms of psychostimulant-induced regulation of opioid peptide gene expression is the increase in PDYN mRNA and peptide levels in the striatum, but only shortly after chronic treatment (30 min, 1 h or 3 h after the last injection of cocaine or methylphenidate; Smiley *et al.*, 1990; Steiner and Gerfen, 1993; Daunais and McGinty, 1995; Spangler *et al.*, 1996a; Torres and Horowitz, 1999; Brandon and Steiner, 2003; Fagergren *et al.*, 2003; Bailey *et al.*, 2005), which is abolished by a selective antagonist or deletion of $D_1$ receptors (Daunais and McGinty, 1996; Moratalla *et al.*, 1996). A return to control levels was observed

within 24 h (Smiley *et al.*, 1990), and in animals treated for 10 days with cocaine followed by a 10-day drug free period, a decrease of PDYN mRNA was reported (Svensson and Hurd, 1998). Regarding dynorphin peptide levels, while a single dose of cocaine did not affect the level of dynorphin, a repeated treatment (4 days) increased striatal content of dynorphin, which persisted for at least 4 days and returned to the basal level 12 days after the last injection (Sivam, 1989). Using a microdialysis approach, methamphetamine was also shown to elevate extracellular levels of dynorphin peptide in the striatum, suggesting an increase in peptide release (Bustamante *et al.*, 2002).

In other brain structures, preclinical studies provide conflicting data. For instance, repeated administration of cocaine or amphetamine (three injections per day for 5 days) was reported to induce a long-lasting increase in PDYN mRNA levels in the NAc (Turchan *et al.*, 1998), whereas other studies (three injections per day for 10 or 14 days) failed to detect cocaine-induced changes in PDYN gene expression in the same nucleus (Daunais and McGinty, 1995; Mathieu-Kia and Besson, 1998; Romualdi *et al.*, 2001).

Regarding changes in PENK mRNA following chronic cocaine treatment in rodents, the results are highly inconsistent whatever the brain structures studied and the specific pattern of drug administration, with increase (Branch *et al.*, 1992; Hurd *et al.*, 1992; Steiner and Gerfen, 1993; Przewlocka and Lason, 1995; Spangler *et al.*, 1996b; Mathieu-Kia and Besson, 1998; Svensson and Hurd, 1998; Crespo *et al.*, 2001; Zhang *et al.*, 2012), or no change (Hurd *et al.*, 1992; Daunais and McGinty, 1995; Mathieu-Kia and Besson, 1998; Alvarez Fischer *et al.*, 2001; Bailey *et al.*, 2005; Ziolkowska *et al.*, 2006). Taken together, the results of the studies reviewed here suggest that the magnitude and significance of the changes in PENK gene expression are complex and clearly depend upon the brain region (e.g. NAc, hypothalamus, central amygdala, frontal cortex, olfactory tubercle), the type of drug administration (self-administration, repeated injections) and also the duration of the withdrawal period. A *post-mortem* study in humans with a history of cocaine abuse, reported a decrease in PENK mRNA in the caudate putamen, with a reduction in enkephalin peptide levels (Hurd and Herkenham, 1993).

The involvement of β-endorphin in the acquisition of cocaine self-administration has also been reported, with a transient increase in extracellular levels of β-endorphin in the NAc during cocaine self-administration (Roth-Deri *et al.*, 2003; 2008). The rewarding action of acute cocaine was reduced in β-endorphin-deficient mice (Nguyen *et al.*, 2012). The release of β-endorphin in the NAc may function as a mechanism for lowering of cue-induced craving. However, this mechanism appears to be short-lived as 30 days after, cue exposure did not induce an increase in β-endorphin levels (Dikshtein *et al.*, 2013).

The influence of cocaine on MOP, DOP and KOP receptor immunoreactivity and binding remains controversial, and changes are dynamic and vary according to the stage of the addiction cycle and brain regions (Azaryan *et al.*, 1998; Bailey *et al.*, 2007; Gorelick *et al.*, 2008). In a *post-mortem* study, the density of KOP receptors in the NAc and other limbic brain regions was increased twofold in cocaine users as compared with control subjects (Staley *et al.*, 1997). In a preclinical study, a decrease in KOP receptor density has been reported in the NAc only after chronic cocaine treatment, whereas this decrease was observed in the striatum after both acute and chronic injections (Turchan *et al.*, 1998). This decrease in the striatum may reflect a compensatory down-regulation of KOP receptors in response to PDYN induction.

Neuroimaging of cocaine users using PET showed increased MOP receptor binding in several brain regions (e.g. frontal, lateral temporal, anterior cingulate cortex and amygdala) that correlated positively with cocaine craving and prevalence to relapse (Zubieta *et al.*, 1996; Gorelick *et al.*, 2005; Ghitza *et al.*, 2010). These results are in agreement with those reported in preclinical studies. Thus, acute binge cocaine administration increased MOP receptor mRNA levels in the frontal cortex, NAc and amygdala, but not in the striatum, thalamus, hippocampus and hypothalamus (Yuferov *et al.*, 1999). In addition a significant increase in the level of MOP receptor mRNA was detected in the NAc after 3 days of cocaine treatment with no modifications of DOP receptors in rats (Azaryan *et al.*, 1996). In another study, DOP receptor mRNA levels were elevated in the VTA of rats expressing amphetamine behavioural sensitization after short-term withdrawal (2 days; Magendzo and Bustos, 2003).

## *Action of opioid antagonists or agonists on reinforcing effects of psychostimulants*

MOP receptor antagonists were able to block the development of cocaine-induced behavioural sensitization, as well as the rewarding properties of cocaine, measured by the conditioned place preference (CPP) model. Given the evidence that MOP and dopamine receptors are co-localized within individual neurons of the striatum (Ambrose *et al.*, 2004), it is not surprising that the blockade of MOP receptors could have profound effects on behaviours mediated in part by the striatal dopamine system. Thus, μ preferential opioid antagonists, naloxone and naltrexone, and μ-selective antagonists (CTOP, CTAP, naloxonazine) were able to reduce cocaine-induced CPP in rodents (Rademacher and Steinpreis, 2002; Schroeder *et al.*, 2007). Moreover, MOP receptor antisense attenuated the expression of cocaine-induced behavioural sensitization and cocaine-induced CPP (Hummel *et al.*, 2006). In MOP receptor knockout (KO) mice, cocaine-induced CPP was maintained (Contarino *et al.*, 2002; Hall *et al.*, 2004; Nguyen *et al.*, 2012) or decreased (Hall *et al.*, 2004) depending on the dose and experimental conditions (number and duration of conditioning sessions). These data suggest that activation of MOP receptors by endogenous opioid peptides subsequent to cocaine administration plays an important role in the subjective rewarding effects of cocaine and the development of cocaine-induced CPP.

Systemic administration of naloxone or naltrexone was able to reduce cocaine self-administration in rats (Corrigall and Coen, 1991; Giuliano *et al.*, 2013), in good agreement with the results obtained in MOP receptor KO mice, where cocaine self-administration was reduced (Mathon *et al.*, 2005). Other studies have also shown that, following their microinfusion in the VTA, a selective μ-opioid receptor antagonists (CTOP) produced a small decrease in cocaine self-administration (Corrigall *et al.*, 1999), and a selective μ-agonist has been shown to enhance the reinforcing effects of the drug (Corrigall *et al.*, 1999). No effect was found following naltrexone microinjection in the caudate, amygdala,

NAc or medial PFC, while in the VTA, blockade of endogenous opioid receptors attenuated cocaine self-administration (Ramsey *et al.*, 1999).

Strikingly, high doses of methadone were able to block the acquisition and expression of cocaine-induced CPP, and to interfere with incubation of cocaine sensitization and associated alterations in gene expression (Leri *et al.*, 2012), while they did not alter self-administration (Leri *et al.*, 2009). There is also evidence that buprenorphine can reduce cocaine use in patients with a history of i.v. cocaine, inhibit cocaine self-administration in rats, reduce cocaine seeking during extinction in the self-administration model, and block cocaine-induced sensitization (Kosten *et al.*, 1991; Foltin and Fischman, 1996; Kuzmin *et al.*, 2000; Sorge *et al.*, 2005; Sorge and Stewart, 2006; Wee *et al.*, 2012). It remains puzzling that buprenorphine reduces cocaine seeking; one hypothesis could be that buprenorphine is able to increase basal levels of glutamate in the NAc, which could contribute to its moderating effects on cocaine-induced effects (Placenza *et al.*, 2008).

DOP receptors also seem to play an important role in the reinforcing effects of cocaine. Thus, naltrindole was able to significantly block cocaine-induced CPP, and inhibit cocaine self-administration (Menkens *et al.*, 1992; Suzuki *et al.*, 1994; Reid *et al.*, 1995). These data further support the role of processes associated with DOP receptors in the ability of cocaine to reinforce its own use. However, other studies have shown that naltrindole, at doses that did not modify the locomotor activity of animals (0.03–3.0 $mg \cdot kg^{-1}$), did not alter the number of cocaine infusions taken by the rats in the self-administration paradigm, while a higher dose of naltrindole (10 $mg \cdot kg^{-1}$), which markedly depressed locomotor activity, resulted in a low (16%) reduction of cocaine self-administration behaviour (de Vries *et al.*, 1995). In a more recent study, using brain microinjection, it has been demonstrated that naltrindole 5′-isothiocyanate decreased cocaine self-administration when injected into the NAc, but increased this behaviour when administered in the VTA (Ward and Roberts, 2007). Interestingly, administration of the δ-selective antagonist into the amygdala was without effect. This suggests that the modulation of cocaine rewarding effects by δ-opioid antagonists is brain region-dependent.

Several studies have investigated the role of κ-opioid ligands on the reinforcing effects of cocaine. Thus, it has been shown that κ-opioid agonists were able to reduce cocaine-induced CPP, cocaine self-administration and cocaine-induced decreases in intracerebral self-stimulation thresholds (Suzuki *et al.*, 1992; Glick *et al.*, 1995; Tomasiewicz *et al.*, 2008), suggesting that activation of KOP receptors reduces the reward-related effects of cocaine. Regarding cocaine-induced behavioural sensitization, the results are controversial. While it has been shown that a single injection of the KOP receptor agonists attenuated the expression of cocaine-induced behavioural sensitization in rats (Collins *et al.*, 2001; Morani *et al.*, 2012), it has also been reported that the κ-opioid antagonist nor-BNI blocked cocaine locomotor sensitization, but in a model of food restriction in rats (Allen *et al.*, 2013). The results obtained with the κ-antagonists remain highly controversial. While some authors suggest that these antagonists are able to reduce cocaine self-administration (Kuzmin *et al.*, 1998), others show that they produced either no effects or small effects that did not show consistent trends with doses (Corrigall *et al.*, 1999). Furthermore, blockade of KOP receptors attenuated the development of depressive-like behaviours induced by cocaine withdrawal in rats (Chartoff *et al.*, 2012).

### *Therapeutic perspectives*

Effective medications to treat cocaine dependence have not been identified. Numerous studies have pointed out a role for endogenous opioid systems in behavioural effects induced by cocaine (see also for recent reviews, Yoo *et al.*, 2012; Charbogne *et al.*, 2014). Overall, these findings suggest that endogenous opioid transmission facilitates cocaine-influenced behaviour and that MOP and KOP receptors may represent specific target sites for therapeutic or behavioural intervention related to cocaine addiction. Mixed κ- and μ-ligands have been developed, with either agonist or antagonist properties, which are able to decrease cocaine self-administration in rats (Archer *et al.*, 1996; Glick *et al.*, 1998; Neumeyer *et al.*, 2001). The use of buprenorphine in preclinical studies consistently induced a reduction in cocaine self-administration (Mello *et al.*, 1989; Carroll and Lac, 1992). In the clinic, the efficacy of buprenorphine in reducing cocaine use among opiate-dependent subjects has been demonstrated (Mendelson *et al.*, 1992; Strain *et al.*, 1994; Foltin and Fischman, 1996; Kouri *et al.*, 1996; Montoya *et al.*, 2004), but with differences in subject characteristics (e.g. differences in cocaine use or in comorbid psychiatric disorders) or differences in study methods that may affect treatment outcome. Buprenorphine together with naltrexone is being investigated as a potential combination treatment in response to the need to expand treatment options for cocaine dependence (Mooney *et al.*, 2013). Interestingly, similar results to those obtained with buprenorphine were obtained with methadone (Strain *et al.*, 1994; Foltin and Fischman, 1996).

The effects of naltrexone on the subjective and physiological effects of amphetamine were also investigated, using dexamphetamine as a model substance in patients diagnosed with amphetamine dependence (Jayaram-Lindstrom *et al.*, 2008). This study was performed on a small homogeneous population of male amphetamine-dependent patients, and needs to be extended. However, the results clearly demonstrated that naltrexone attenuated the subjective effects and the craving for dexamphetamine.

## Alcohol

### *Modification of endogenous opioid system by alcohol treatment*

Many data have demonstrated a change in the opioid system (peptides and receptors) upon acute or chronic ethanol treatment. Similar to cocaine, the most consistent effect of alcohol on opioid peptides is an increase in dynorphin in reward-related brain structures. Indeed, the dynorphin level (mRNA or protein) was increased in the NAc (Przewlocka *et al.*, 1994; Lindholm *et al.*, 2000) and amygdala (D'Addario *et al.*, 2013b), a stress-related brain area, following chronic ethanol exposure. This increase, especially after a protracted withdrawal would contribute to the negative effects of ethanol

withdrawal (Gillett *et al.*, 2013). Recent data suggested that dynorphin up-regulation by alcohol could be caused by epigenetic modifications (D'Addario *et al.*, 2013a). Data are scarce concerning the influence of ethanol on opioid peptides in humans but they seemed to match with those obtained in animals. Thus, in *post-mortem* human brains of alcoholics, PDYN mRNA was increased in the dorsolateral PFC (Bazov *et al.*, 2013).

The results with enkephalins are more controversial, as an increase, decrease or no change have been observed whatever the duration of ethanol exposure (acute or chronic), type of administration (contingent or non-contingent), the withdrawal period or the brain structure considered (Schulz *et al.*, 1980; Seizinger *et al.*, 1983; Przewlocka *et al.*, 1997; Lindholm *et al.*, 2000; Marinelli *et al.*, 2005; Mendez and Morales-Mulia, 2006; Jarjour *et al.*, 2009). For instance, following an acute injection of ethanol, the Met-enkephalin level was increased in the NAc (Seizinger *et al.*, 1983; Marinelli *et al.*, 2005; Mendez *et al.*, 2010) but not in the VTA (Jarjour *et al.*, 2009). In humans, no change in PENK mRNA was detected in any brain structures tested (dorsolateral PFC, orbitofrontal cortex and hippocampus; Bazov *et al.*, 2013). This result supports a minor role of enkephalins in ethanol addiction as evidenced by the ability of enkephalin KO mice to still prefer ethanol in a two-bottle choice (Koenig and Olive, 2002) and self-administration paradigms (Hayward *et al.*, 2004).

There are few data on the effects of ethanol exposure on β-endorphin in reward-related brain structures. However, most of the data demonstrates that acute ethanol promotes an increase in β-endorphin, and chronic ethanol had mixed effects (increase, decrease or no changes). Using microdialysis, Gianoulakis and co-workers found an increase in β-endorphin after an acute injection of ethanol in the central amygdala and VTA (Lam *et al.*, 2008; Jarjour *et al.*, 2009) that could involve corticotropin-releasing hormone receptors (Lam and Gianoulakis, 2011). In rats continuously exposed in a one-bottle access situation to ethanol, no variation in β-endorphin was measured in the NAc or VTA (Leriche and Mendez, 2010). However, in a protocol of voluntary alcohol ingestion using the two-bottle choice paradigm, POMC mRNA was increased in the NAc Shell (Zhou *et al.*, 2013). In humans the β-endorphin neuropeptide level was augmented in blood during ethanol intoxication (Barret *et al.*, 1987; Aguirre *et al.*, 1995b), whereas it was diminished during withdrawal (Aguirre *et al.*, 1990; 1995a) contributing to anxiety (Kiefer *et al.*, 2002).

Chronic ethanol exposure might lead to different effects on opioid receptors with opposite results on DOP and MOP receptors. In rats with free access to an ethanol-containing liquid diet, immunohistochemistry analysis revealed a decrease in MOP receptors in NAc, cortex and hippocampus whereas DOP receptors were decreased in the hippocampus (Saland *et al.*, 2005). Interestingly, after acute exposure using an intra-gastric injection, the number of MOP receptors in the striatum was not modified (Mendez *et al.*, 2003; Leriche and Mendez, 2010). With regard to the KOP receptors, a recent study found a transient increase (only observed 30 min after the last injection, but no later) of its coding mRNA in the amygdala after a 5 day treatment of intra-gastric administration of ethanol (D'Addario *et al.*, 2013b).

Using [$^{11}$C]-diprenorphine (a non-selective opioid receptor ligand), Williams and co-workers found an increase in opioid receptor availability in the early abstinence period of ethanol-dependent patients and a positive correlation between [$^{11}$C]-diprenorphine volume distribution and craving (Williams *et al.*, 2009). The same correlation was found with MOP receptors using a selective ligand, [$^{11}$C]-carfentanil. Indeed, an increase in MOP receptors was found in detoxified patients and correlated with the severity of alcohol craving (Heinz *et al.*, 2005). Apparent opposite results were found by Bencherif and co-workers, where a lower MOP receptor binding potential in some sub-regions of the cortex was associated with a higher craving in alcohol-dependent subjects (Bencherif *et al.*, 2004). This discrepancy might be explained by the different structures analyzed as Heinz and collaborators observed these changes in the ventral striatum, a structure not tested in Bencherif's study.

## *Action of opioid antagonists or agonists on reinforcing effects of alcohol*

Numerous papers have been published on the role of opioid receptors in ethanol intake and reinforcing effects. Using naloxone, it was shown that the blockade of opioid receptors reduced ethanol intake and preference in Sprague-Dawley rats (Reid and Hunter, 1984; Barson *et al.*, 2009) or in rats selectively bred for high ethanol preference (Froehlich *et al.*, 1990).

The three opioid receptors were individually tested for their role in ethanol addiction. In MOP receptor KO mice, no operant self-administration of ethanol was observed and the two-bottle choice test even revealed an aversion for alcohol (Roberts *et al.*, 2000). Microinjection of CTAP revealed that the NAc and ventral pallidum are important regions for these MOP receptor-mediated effects on ethanol consumption (Perry and McNally, 2013a,b). The VTA is also important as a knockdown of MOP receptors in this region with small hairpin-RNA reduced ethanol intake in the two-bottle choice paradigm in mice (Lasek *et al.*, 2007). However, results for the involvement of the DOP receptor are less consistent. DOP receptor KO mice showed a preference for ethanol measured in the two-bottle choice paradigm and have an increased ethanol intake in this same test only after operant ethanol administration (Roberts *et al.*, 2001). In contrast, other authors found that ICI-174,864 and naltrindole, two DOP-selective antagonists, reduce ethanol intake in the two-bottle choice test in rats selectively bred for ethanol preference (Krishnan-Sarin *et al.*, 1995), whereas other authors did not observe such results in regular (not ethanol preferring) rats (Stromberg *et al.*, 1998) or rhesus monkeys (Williams and Woods, 1998). KOP receptor agonists such as U50,488H (Lindholm *et al.*, 2001) or bremazocine (Nestby *et al.*, 1999) decreased ethanol intake in the two-bottle choice paradigm. U50,488H has also been found to block acquisition of ethanol in CPP (Logrip *et al.*, 2009). According to these data, nor-BNI had no effects on ethanol intake (Holter *et al.*, 2000) or operant self-administration (Doyon *et al.*, 2006) in naive animals. However, in certain conditions, the role of KOP receptors in ethanol addiction switches. Indeed, in a rat strain, selectively bred for alcohol preference, or in ethanol-dependent animals, KOP antagonists reduce operant self-administration (Walker and Koob, 2008; Kissler *et al.*, 2014;

Rorick-Kehn *et al.*, 2014). Taken together, these findings indicate that whereas KOP receptor activation reduces ethanol reinforcement in non-dependent animals probably via an aversive effect, the κ-opioid system may participate in ethanol seeking in dependent subjects (Wee and Koob, 2010).

### *Therapeutic perspectives*

Preclinical data strongly suggest that blocking opioid receptors might be helpful in reducing some characteristics of ethanol addiction. Naltrexone, a preferential MOP receptor antagonist that is able to bind to other opioid receptors at higher concentrations (Raynor *et al.*, 1994; Wang *et al.*, 2007), was the first drug acting on opioid receptors approved for the treatment of ethanol dependence and the second drug specific for the treatment of this condition 40 years after disulfiram. Naltrexone has been shown to reduce ethanol intake in the two-bottle choice paradigm (Stromberg *et al.*, 1998; Parkes and Sinclair, 2000) and inhibit operant self-administration of alcohol in rodents (Bienkowski *et al.*, 1999; Walker and Koob, 2008). Naltrexone is rapidly absorbed when taken orally and is converted into several metabolites including 6β-naltrexol, the main metabolite, which has been shown to reduce ethanol drinking in rodents (Stromberg *et al.*, 2002). Using [$^{11}$C]-carfentanil, a PET study demonstrated that 50 mg of naltrexone (corresponding to the daily dose) block 90% of brain MOP receptors after 48 h (Lee *et al.*, 1988) explaining its long-term action. Studies have also shown that oral administration of naltrexone for a few weeks reduces craving (Chick *et al.*, 2000) and prevents relapse (Morris *et al.*, 2001). However, its efficacy fades over time as demonstrated by studies investigating long-term treatment (Balldin *et al.*, 2003; Krystal *et al*, 2001). Interestingly, some factors that contribute to a naltrexone-positive response have been identified, such as the MOP receptor single-nucleotide polymorphism A118G (Oslin *et al.*, 2003; Anton *et al.*, 2008) and adherence to treatment (Chick *et al.*, 2000; Krystal *et al*, 2001). This could explain the differences in the ratio between responding versus non-responding patients among clinical studies. To avoid a lack of adherence to treatment, an injectable extended-release formula of naltrexone has been developed and has been shown to be effective at blocking MOP receptors in rats for 1 month (Bartus *et al.*, 2003). It seems to be well-tolerated and promoted reductions in heavy drinking among treatment-seeking alcohol-dependent patients during 6 months of therapy (Garbutt *et al.*, 2005). More interestingly, it improved their quality of life, specifically in numerous domains such as mental health and social functioning (Pettinati *et al.*, 2009).

Nalmefene, a naltrexone analogue, has been approved by regulatory agencies in the treatment of alcohol dependence. Nalmefene differs from naltrexone by the presence of a methylene group instead of the ketone at the 6-position, which increases affinity towards opioid receptors (Emmerson *et al.*, 1994), and half-life (10 h; Dixon *et al.*, 1987). In a preclinical study, nalmefene reduced operant self-administration of ethanol in rats (June *et al.*, 1998). With the exception of one study (Anton *et al.*, 2004), clinical trials have demonstrated the efficacy of nalmefene in treating ethanol dependence (Mason *et al.*, 1999; Karhuvaara *et al.*, 2007; Gual *et al.*, 2013; Mann *et al.*, 2013), with a reduced relapse rate to heavy drinking when this treatment was combined with cognitive behavioural therapy (Mason *et al.*, 1999). Recently, a new opioid receptor antagonist has been released, LY2196044 (WO 2004/026305) and presents promising results in increasing the abstinence period in ethanol-dependent, treatment-seeking patients (Wong *et al.*, 2014).

## Nicotine

### *Modification of endogenous opioid system by nicotine treatment*

As with cocaine and alcohol exposures, tobacco smoking induces functional alterations in the endogenous opioid system. Because nicotine is considered as the main active component responsible for the addictive properties of tobacco, numerous studies have focused on the effects of chronic nicotine administration on the endogenous opioid system in various regions of the brain (for review, see Berrendero *et al.*, 2010; Drews and Zimmer, 2010; Hadjiconstantinou and Neff, 2011). Chronic exposure to nicotine alters the release of endogenous opioid peptides in the brain and those alterations are specific to the nature of the endogenous opioid peptide being investigated. In addition, these modifications are persistent, dynamic and time-specific [e.g. it depends when the measure is done during nicotine treatment, or when the measure is performed after nicotine withdrawal (early vs. late)].

With regard to the effects on dynorphin synthesis and release induced by chronic nicotine administration, a decrease in dynorphin content was observed in the mice striatum from 30 min to 72 h after the last nicotine injection (Isola *et al.*, 2008). A compensatory mechanism involving opioid synthesis is also implemented, in which PDYN mRNA was increased in the same reward-related brain structure from 8 h to 96 h after the last injection. However, no change was observed in the biosynthesis and release of dynorphin in rat striatum (Hollt and Horn, 1992; Mathieu *et al.*, 1996; Mathieu-Kia and Besson, 1998), indicating the importance of nicotine dose, treatment schedule and species for the observed changes.

The effects of chronic nicotine treatment on Met-enkephalin and PENK have been extensively investigated by many research groups. PENK mRNA was decreased in the striatum of mice 2 h following nicotine cessation followed by a rebound increase lasting for over 72 h (Houdi *et al.*, 1998). Similarly, following 14 days of chronic nicotine treatment, Met-enkephalin levels were decreased in the rat striatum after 1 h of nicotine cessation (Wewers *et al.*, 1999). PENK mRNA was increased in striatum and NAc 24 h after the last injection of a chronic nicotine treatment in rats (Mathieu *et al.*, 1996) and mice (Dhatt *et al.*, 1995) but not 2 h after nicotine cessation in rats (Mathieu-Kia and Besson, 1998). From 4 to over 72 h after nicotine cessation, Met-enkephalin levels and PENK mRNA were increased in the NAc (Isola *et al.*, 2002). Overall, these findings highlight a biphasic change in the levels of Met-enkephalin and PENK mRNA in striatum, with a decrease during early withdrawal and an increase during a more protracted withdrawal period. This biphasic response may reflect alterations in the synthesis and metabolism of Met-enkephalin.

Chronic nicotine treatment was shown to have a biphasic effect on the hypothalamic β-endorphin level in mice (Rosecrans *et al.*, 1985). Chronic nicotine exposure induced first a decrease in hypothalamic β-endorphin levels 24 h after the last injection (Gudehithlu *et al.*, 2012). Within 7 days, the β-endorphin levels returned to the baseline and even increased above the baseline after 14 days of nicotine withdrawal. In contrast, another study reported a long-lasting inhibition of POMC gene expression in the mediobasohypothalamus (Rasmussen, 1998). It seems that chronic nicotine diminishes the synthesis of β-endorphin in the limbic areas (e.g. striatum, hippocampus, hypothalamus, PFC) that might contribute to aversive states associated with nicotine withdrawal (Berrendero *et al.*, 2010; Drews and Zimmer, 2010; Hadjiconstantinou and Neff, 2011; Gudehithlu *et al.*, 2012). However, the situation is far less clear with the nicotine-induced release of β-endorphin if we consider the clinical studies. In current smokers, their levels of peripheral plasma β-endorphin have been found to be increased (Backon, 1989; del Arbol *et al.*, 2000; Gilbert *et al.*, 1992; Pomerleau *et al.*, 1983; Seyler *et al.*, 1986). This apparent discrepancy between animal and human findings may result from the lack of a direct relationship between peripheral and central β-endorphin levels (Berrendero *et al.*, 2010).

Several studies have investigated the effects of chronic nicotine treatment on the densities, affinities and functional activities of MOP, DOP and KOP receptors. It has been shown that a 14 day treatment with nicotine induces an up-regulation of MOP receptors in rat striatum (Wewers *et al.*, 1999). Chronic nicotine administration decreased the density of MOP receptors in the striatum and NAc in C57BL/6 mice (Galeote *et al.*, 2006) but not in NMRI mice (Vihavainen *et al.*, 2008). However, both the affinity and the functional activity of MOP receptors were unchanged by the chronic treatment in these two strains (Galeote *et al.*, 2006; Vihavainen *et al.*, 2008). Finally, an uncoupling and desensitization of KOP and DOP receptors in the striatum and NAc were observed during nicotine withdrawal, whereas the densities of these receptors were unaltered (McCarthy *et al.*, 2010; 2011).

In humans, using [$^{11}$C]-carfentanil a down-regulation of MOP receptors in the thalamus, ventral basal ganglia and amygdala has been reported after smoking nicotine cigarettes (Scott *et al.*, 2007; Weerts *et al.*, 2014). In addition, a basal reduction in MOP receptor availability in different brain structures (caudate, cingulate, globus pallidus, insula, putamen, thalamus and ventral striatum) has been reported to be negatively correlated to severity of nicotine dependence (Weerts *et al.*, 2014).

## *Action of opioid antagonists and agonists on reinforcing effects of nicotine*

Pharmacological and genetic approaches in preclinical studies have provided evidence for the involvement of the endogenous opioid system in nicotine-rewarding effects (for review, see Berrendero *et al.*, 2010; Maldonado, 2010; Charbogne *et al.*, 2014). The MOP receptor is particularly involved in nicotine-rewarding effects and nicotine withdrawal. Thus, administration of the glycyl-glutamine, a MOP receptor antagonist, inhibited the acquisition and the expression of nicotine-induced CPP and attenuated withdrawal signs in rats (Goktalay *et al.*, 2006). The preferential MOP antagonist naloxone abolished nicotine-induced CPP (Zarrindast *et al.*, 2003; Walters *et al.*, 2005), attenuated nicotine-induced conditioned place aversion in mice (Zarrindast *et al.*, 2003) and decreased nicotine self-administration in rats (Ismayilova and Shoaib, 2010; but see also, Corrigall and Coen, 1991). Activation of MOP receptors is required for the reinforcement of nicotine in rats, as shown by the reduction of nicotine self-administration in rats pretreated with the selective MOP receptor antagonist naloxonazine (Liu and Jernigan, 2011). In addition, naltrexone, another preferential MOP antagonist, was able to attenuate nicotine cue-maintained responding during extinction and cue-induced reinstatement of nicotine-seeking behaviour after extinction in a self-administration test, suggesting that MOP antagonists would be good candidates for the prevention of smoking relapse triggered by exposure to environmental smoking cues (Liu *et al.*, 2009).

Studies using genetically modified mice have confirmed the crucial role of MOP receptors in the rewarding effects of nicotine. Indeed, nicotine-induced CPP was attenuated in mice lacking MOP receptors, PENK or β-endorphin (Berrendero *et al.*, 2002; 2005; Trigo *et al.*, 2009). These findings strongly suggest that activation of MOP receptors by endogenous enkephalins and β-endorphins are required to obtain the reinforcing effects of nicotine (Berrendero *et al.*, 2010).

A KO study suggested that DOP/PENK signalling also contributed to the reinforcing effects of nicotine (Berrendero *et al.*, 2012). In this study, DOP receptor KO mice did not express a nicotine-induced CPP and displayed a lower percentage of acquisition of i.v. nicotine self-administration. This result has been confirmed by a decrease in the rate of acquisition in wild type mice pretreated with the DOP receptor antagonist naltrindole. However, other pharmacological studies failed to reveal an effect of naltrindole on nicotine self-administration in rats (Ismayilova and Shoaib, 2010; Liu and Jernigan, 2011).

KOP receptor agonist and antagonist studies are difficult to interpret and how KOP receptor activity influences nicotine reinforcement needs to be investigated further. For example, the KOP agonist U50,488 has revealed a dual role of the endogenous κ-opioid system on nicotine self-administration with a decrease in nicotine intake at the high dose of agonist and a trend for an increase with a lower dose in rats (Ismayilova and Shoaib, 2010), suggesting that κ-agonists bind with lower affinity to other receptors, activation of which produces opposing effects to those resulting from the activation of a higher affinity binding site. Nevertheless, using 5′-guanidinonaltrindole, a selective KOP antagonist, Liu and Jernigan reported a lack of involvement of KOP receptor activation by dynorphin on nicotine self-administration (Liu and Jernigan, 2011). In addition, the selective KOP antagonist JDTic failed to block the expression of nicotine reward in the CPP paradigm (Jackson *et al.*, 2010), supporting a role for the KOP/dynorphin system in mediating dysphoric aspects during withdrawal rather than the reinforcing properties of nicotine. This contribution of dynorphin to aversive effects of nicotine has been supported by a recent study in PDYN KO mice, showing a decrease in self-administration of a low dose of nicotine (Galeote *et al.*, 2009).

### *Therapeutic perspectives*

The high prevalence of smoking among heroin addicts (Mello *et al.*, 1980) and methadone- or buprenorphine-maintained patients (Chait and Griffiths, 1984; Mello *et al.*, 1985; Mutschler *et al.*, 2002; Zirakzadeh *et al.*, 2013) highlights interactions between the opioid and nicotine systems that may lead to an increase in the reinforcing effects of smoking. Because of the critical role of MOP receptors in the reinforcing effects of nicotine, one of the therapeutic strategies available is to attenuate the rewarding effects of cigarette smoking by opioid antagonists. Thus, numerous clinical trials have been performed to evaluate the effect of preferential μ-opioid antagonists, naloxone and naltrexone, on smoking cessation (see David *et al.*, 2013 for review). However, it seems that there were no or weak overall effects of naloxone alone or in association with nicotine replacement therapy on long-term smoking abstinence (Karras and Kane, 1980; Nemeth-Coslett and Griffiths, 1986; Gorelick *et al.*, 1988). Because naloxone displays a short duration of action, a lot of recent studies focused on naltrexone, an opioid antagonist with longer acting effects, but the same inconclusive results have been obtained (Covey *et al.*, 1999; Wong *et al.*, 1999; Ahmadi *et al.*, 2003; Krishnan-Sarin *et al.*, 2003; O'Malley *et al.*, 2006; Toll *et al.*, 2010; David *et al.*, 2013). Moreover, evaluation of naltrexone effects in preventing nicotine relapse and craving did not result in a clear picture (Wewers *et al.*, 1998; Hutchison *et al.*, 1999; Krishnan-Sarin *et al.*, 2003; Rohsenow *et al.*, 2007). Compared with placebo, significant trends towards a cessation at the end of naltrexone treatments were recorded among patients; however, these positive effects did not seem long lasting, differences between both groups were attenuated at 6 months (Covey *et al.*, 1999). Interestingly, naltrexone in combination with nicotine replacement therapy resulted in an increase in abstinence rates (Krishnan-Sarin *et al.*, 2003) and prevented weight gain following smoking cessation (Krishnan-Sarin *et al.*, 2003; O'Malley *et al.*, 2006).

## Conclusion

In the past decades, many advances in our understanding of the underlying biology of addiction have opened the doors to the development of novel pharmacotherapies. As reported in this review, both endogenous opioid peptides and receptors play a key role in many aspects of addictive behaviours. It clearly appears that drugs of abuse modify the activity of the endogenous opioid system, and produce adaptive changes that play important roles in the development/maintenance of addiction. Moreover, the modifications of endogenous opioid systems induced by drugs of abuse are dynamic processes and vary according to the stage of the addiction cycle. These dynamic changes should be taken into consideration, and may explain why clinical trials, using pharmacotherapies to treat addiction, report modest efficacy, or describe efficient results only on a sub-population of patients (Potenza *et al.*, 2011; Volkow and Skolnick, 2012).

This review shows that opioid ligands may be very useful, whatever the drug of abuse used, as the endogenous opioid system is a common neurobiological substrate for certain components of addictive processes induced by the different drugs of abuse. Nevertheless, it clearly appears throughout the review that the data in the literature are not consistent. Regarding the regulation of endogenous opioid system by psychostimulants, alcohol or nicotine, numerous protocols have been used (treatment duration, withdrawal period, pattern of administration, strains of animals . . .) that may explain the divergence, as it is now well established that neuroadaptations depend on different factors. The time after drug of abuse administration appears to be a determining factor for detecting increased gene expression. Moreover, numerous brain structures are heterogeneous (e.g. cortex, striatum, amygdala, NAc), and discrete changes within the larger structures may be missed, or different results may be observed in subregions. Some technical approaches do not allow us to discriminate between these subregions (e.g. Western blot), and/or the precise areas of analyses in most papers are not described, pointing out the limitations of the methods that may explain the differences in the results reported. Similarly, several discrepancies are reported in the literature regarding the action of opioid ligands on the reinforcing effects of psychostimulants, alcohol and nicotine. Several animal models are used to investigate different components of drug addiction, with different protocols. Animal models of substance abuse include both non-contingent (experimenter-administered) and contingent (self-administered) drug administration. A simple animal model to study the rewarding effect of drugs, CPP uses a classical Pavlovian conditioning procedure to pair an unconditioned stimulus (e.g. cocaine) with a designated area and measure the preference for the stimulus-paired area compared with the unpaired area. An increase in preference for the stimulus-paired area serves as a measure of its Pavlovian rewarding effects (e.g. Bardo and Bevins, 2000; Tzschentke, 2007). Another model, behavioural sensitization, is defined as a progressive enhancement of drug-induced responses that develops during repeated drug treatment and then persists even after weeks of withdrawal. It can be produced by exposure to either contingent or non-contingent drugs of abuse. The induction of sensitization involves brain structures common to those known to play a role in reward processes, and it is considered to be a good marker of neurochemical changes that underlie addiction (e.g. (Vanderschuren and Kalivas, 2000). The third model largely used in preclinical studies is the self-administration paradigm that refers to training rodents in an operant chamber to press a lever or poke their nose in a hole in order to receive an i.v. infusion of drug (e.g. Ahmed, 2012). Self-administration procedures can differ in many ways, including whether training to respond for food precedes drug self-administration, the dose of drug available, the number of responses required to obtain the drug, and the daily duration of drug access. Clinical studies using opioid ligands also report some discrepancies. However, they are generally conducted on a small or on a heterogeneous population of patients. In addition, the end points defined in the clinical trials to measure the effects of a treatment and how this treatment may improve health status are often different, which makes it difficult to compare results across studies. Whatever the reasons behind the variable results, overall, the potential of opioid ligands as a pharmaceutical treatment for psychostimulants, alcohol and nicotine is promising and merits further investigation.

Another therapeutic approach that could be helpful in the future is the enkephalin-degrading enzyme inhibitors, as it has been suggested that such inhibitors could represent effective treatments for addiction (Roques and Noble, 1996; Noble and Roques, 2003). These inhibitors could be used alone or in association with positive allosteric modulators (Burford *et al.*, 2013; 2014; 2015), which have the specific advantage of only modulating the activity of the receptor when the orthosteric site binds an endogenous agonist, thus maintaining spatial and temporal control of receptor signalling *in vivo*. These allosteric modulators have little or no detectable functional activity when bound to the receptor in the absence of an orthosteric agonist, but can potentiate the activity of bound orthosteric agonist, seen as an increase in apparent potency and/or efficacy of the orthosteric agonist.

However, in order for an effective treatment to prevent the relapses in addicted patients, pharmacotherapies must be associated with structured psychosocial therapies to enhance strategies to prevent relapse and encourage compliance with treatment. Moreover, a consideration of any genetic variants of opioid receptors is important when determining treatment options for different individuals, and possibly crucial in determining which patients are likely to respond to opioid ligand treatment (Oslin *et al.*, 2006; Sturgess *et al.*, 2011; Thorsell, 2013; Garbutt *et al.*, 2014). Benefits of such an approach, in addition to increasing treatment response and health, may increase the cost-effectiveness of a treatment, as well as decreasing the risk of exposing individuals to medication that is ineffective.

## Author contributions

F. N., L. M. and N. M. managed the literature searches, and contributed to write the first draft of the manuscript. F. N. organized the first draft and prepared the final version of the manuscript. All the authors contributed to and have approved the final manuscript.

## Conflict of interest

The authors declare they have no conflict of interest.

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