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NOP-related mechanisms in substance use disorders

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Abstract

Nociceptin/Orphanin FQ (N/OFQ) is a 17 amino acid peptide that was deorphanized in 1995 and has been widely studied since. The role of the N/OFQ system in drug abuse has attracted researchers' attention since its initial discovery. The first two scientific papers describing the effect of intracranial injection of N/OFQ appeared twenty years ago and reported efficacy of the peptide in attenuating alcohol intake whereas heroin self-admnistration was insensitive. Since then more than 100 scientific articles investigating the role of the N/OFQ and N/OFQ receptor (NOP) system in drug abuse have been published. The present article provides an historical overview of the advances in the field with focus on three major elements. First, the most robust data supportive of the efficacy of NOP agonists in treating drug abuse come from studies in the field of alcohol research, followed by psychostimulant and opioid research. In contrast, activation of NOP appears to facilitate nicotine consumption. Second, emerging data challenge the assumption that activation of NOP is the most appropriate strategy to attenuate consumption of substances of abuse. This assumption is based first on the observation that animals carrying an overexpression of NOP system components are more prone to consume substances of abuse, whereas NOP knockout rats are less motivated to self-administer heroin, alcohol and cocaine. Third, administration of NOP antagonists also reduces alcohol consumption. In addition, NOP blockade reduces nicotine self-admnistration. Hypothetical mechanisms explaining this apparent paradox are discussed. Finally, we focus on the possibility that co-activation of NOP and mu opioid (MOP) receptors is an alternative strategy, readily testable in the clinic, to reduce the consumption of psychostimulants, opiates and, possibly, alcohol.

Keywords

Nociceptin; Orphanin FQ; N/OFQ; NOP; Addiction; Relapse; Drug-Seeking

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1. Introduction

The 17 amino acid peptide Nociceptin/Orphanin FQ (N/OFQ) was discovered by screening brain extracts as the natural ligand for the orphan G protein-coupled receptor (GPCR) Opioid Receptor Like-1 (ORL1), now known as NOP (Meunier *et al.*, 1995; Reinscheid *et al.*, 1995). N/OFQ and its cognate receptor exhibit a high degree of sequence identity to dynorphin and kappa (KOP) opioid receptors, respectively. However, N/OFQ does not activate any of the classical mu (MOP), delta (DOP), and KOP opioid receptors. Based on structural similarities between N/OFQ and dynoprhin A a general consensus has been reached so that the N/OFQ-NOP system is now considered the fourth member of the opioid superfamily (Cox *et al.*, 2015; Toll *et al.*, 2016).

Since the very beginning, neuroanatomical studies in rodents revealed a high degree of distribution of N/OFQ and NOP receptors in major mesolimbic structures including the central amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and the ventral tegmental area (VTA). Moderate expression was also detected in the nucleus accumbens (Nac) and striatum. In addition, like all classical opioid peptides and receptors, the N/OFQ-NOP system is widely represented in cortical regions (Sim & Childers, 1997; Neal *et al.*, 1999; Letchworth *et al.*, 2000; Slowe *et al.*, 2001; Sim-Selley *et al.*, 2003; Gehlert *et al.*, 2006). More recent studies in dogs and humans replicated these findings confirming that the neuroanatomy of the system is highly conserved among species (Witta *et al.*, 2004; Kimura *et al.*, 2011; Lohith *et al.*, 2012; Witkin *et al.*, 2014; Narendran *et al.*, 2018). Due to the similarities between the N/OFQ and the other opioid systems one of the first scrutinzed areas of the system's neural function was that of pain and drug abuse. Indeed, the name nociceptin (Meunier *et al.*, 1995) was derived from observations of pro-nociceptive actions following supraspinal administration of the peptide. Subsequent studies have revealed that the modulation of pain pathways by N/OFQ is complex, with NOP receptors mediating analgesia in the spinal cord and hyperalgesia in the brain (see for review) (Darland *et al.*, 1998; Fioravanti & Vanderah, 2008; Lambert, 2008; Kiguchi *et al.*, 2016). In July 1998 and in January 1999 the first two studies linking the N/OFQ-NOP receptor system to drug abuse were published. In original work, Walker and colleagues showed that intracerebroventricular (ICV) microinjection of N/OFQ did not affect operant heroin self-administration in the rat (Walker *et al.*, 1998). In the other study, however, it was demonstrated that acute ICV administration of the peptide increased alcohol consumption in genetically selected alcohol preferring Marchigian Sardinian (msP) rats (Ciccocioppo *et al.*, 1999). However, repeated administration of N/OFQ markedly reduced alcohol drinking and prevented alcohol induced conditioned place preference (Ciccocioppo *et al.*, 1999). After these two earlier studies, several reports were published over the years with more than 100 articles currently listed in PubMed. The largest body of available data support the hypothesis that activation of NOP by its endogenous ligand or by highly selective synthetic small-molecule agonists attenuates drug abuse related behaviors (for review see also (Witkin *et al.*, 2014)). However, as in the case of pain, the pharmacology of the N/OFQ system appears more complex than originally thoughts and recent rapidly accumulating evidence points to the possibility that drug abuse related behaviors are inhibited by NOP antagonists rather than agonists (Post *et al.*, 2016; Rorick-Kehn *et al.*, 2016). Here, we will summarize the major findings generated over 20

years of research on N/OFQ and drug abuse, findings that were largely guided by the general hypothesis that activation of NOP attenuates the motivation for drugs of abuse. We then will review more recent data showing that attenuation of N/OFQ transmission has a protective role for the development of drug dependence and that NOP antagonism attenuates the consumption of substances including alcohol and nicotine. Finally, we will focus on a series of clinically available molecules such as buprenorphine and cebranopadol that activate both NOP and MOP receptors and that have shown promising features relevant for the treatment of drug abuse (Wnendt *et al.*, 1999; Bloms-Funke *et al.*, 2000; Huang *et al.*, 2001). To facilitate the analysis of the large number of papers published to date, the effects of NOP agonists, antagonists and mixed MOP/NOP compounds on different drugs of abuse will be described in separate paragraphs. Additional discussion on the role of N/OFQ-NOP system in drug abuse can be found in several recent reviews (Zaveri, 2011; Witkin *et al.*, 2014; Lutfy & Zaveri, 2016).

2. The N/OFQ System and Alcohol Abuse

2.1 NOP agonism:

Together with nicotine, alcohol is the most commonly used drug of abuse in the world, with about 240 million people suffering from alcohol use disorder (Gowing *et al.*, 2015). Alcoholism follows a pattern similar to other abused drugs, characterized by binges of alcohol consumption consisting either of daily episodes or prolonged days of heavy drinking (Koob, 2013). Alcoholism, like other forms of substance abuse, can be conceptualized as a disorder that includes a progression from impulsivity (positive reinforcement) to compulsivity (negative reinforcement) where both genetic and environmental risk factors drive the progression to alcohol addiction (Goldman *et al.*, 2005; Koob, 2013; Costin & Miles, 2014; Spanagel *et al.*, 2014) (Spanagel, 2009).

The first study scrutinizing the role of the N/OFQ in alcohol abuse was published in 1999 (Ciccocioppo *et al.*, 1999). In that study it was shown that repeated ICV administration of N/OFQ attenuated voluntary two-bottle choice alcohol drinking (choice between 10% alcohol and water) in genetically selected alcohol preferring marchigian sardinian (msP) rats. Over the following years this initial finding was replicated using different experimental procedures and NOP selective agonists. For instance, it was demonstrated that activation of NOP by peptidic N/OFQ analogues as well as by small synthetic agonists, blunted the reinforcing and motivating effects of alcohol as measured in conditioned place preference (CPP) experiments in mice (Kuzmin *et al.*, 2003; Kuzmin *et al.*, 2007; Zaveri *et al.*, 2018b), and operant and home cage alcohol self-administration or relapse models in rats (Martin-Fardon *et al.*, 2000; Kuzmin *et al.*, 2007; Aziz *et al.*, 2016) (Ciccocioppo *et al.*, 2002c; Ciccocioppo *et al.*, 2003a; Economidou *et al.*, 2006; Economidou *et al.*, 2008). Most of the drinking studies were carried out in msP rats, but efficacy of these compounds in nonselected Wistar rats has also been documented (Kuzmin *et al.*, 2007; Aziz *et al.*, 2016). However, in studies in which msP and Wistar rats were tested in parallel, it was always found that suppression of alcohol drinking and relapse was more pronounced in the msP line (Economidou *et al.*, 2008; de Guglielmo *et al.*, 2015) (Martin-Fardon *et al.*, 2010). Compared to Wistar rats, the msP line exhibits overexpression of the corticotropin releasing

factor (CRF) system, likely driven by two single nucleotide polimorphysims at CRF1 receptor locus (Hansson *et al.*, 2006; Ayanwuyi *et al.*, 2013; Cippitelli *et al.*, 2015; Logrip *et al.*, 2018). As a consequence of this overexprssion, msP rats are more sensitive to stress, have a high anxiety-like phenotype, and show depression-like symptoms that are all improved by alcohol consumption (Ciccocioppo *et al.*, 2006; Ciccocioppo, 2013; Egervari *et al.*, 2018). In this rat line, two weeks of voluntary alcohol drinking reduced the overexpression of CRF1R receptors in various brain areas, which points to the possibility that these animals drink to self-medicate negative affect associated with their overactive stress system (Hansson *et al.*, 2007). Considering the possibility that activation of NOP receptors mediates a potent anxiolytic and anti-stress effect and that N/OFQ acts as a functional antagonist of the CRF1R system (Griebel *et al.*, 1999; Jenck *et al.*, 2000a; Jenck *et al.*, 2000b; Ciccocioppo *et al.*, 2001; Ciccocioppo *et al.*, 2002a; Ciccocioppo *et al.*, 2002b; Ciccocioppo *et al.*, 2003b; Ciccocioppo *et al.*, 2004a; Ciccocioppo *et al.*, 2014a), it is possible that in msP rats the effect on alcohol drinking produced by N/OFQ was due to its ability to alleviate the negative affective state (triggering excessive drinking) associated with heightened CRF1R transmission. Gene expression studies showed that msP rats are also characterized by an innate overexpression of the N/OFQ-NOP receptor system in several stress-regulatory brain regions, including the CeA. On one hand, this may represent a compensatory reorganization of N/OFQ neurotransmission to counteract the overactivity of the stress system (Economidou *et al.*, 2008). On the other hand, the overexpression of NOP receptors may contribute to confering higher sensitivity to NOP agonists that, when microinjected into the CeA, blocked both excessive alcohol intake and anxiety in this rat line (Economidou *et al.*, 2008; Aujla *et al.*, 2013). Wistar rats with a history of chronic alcohol exposure exhibit neuroadaptive changes of the N/OFQ-NOP and CRF1R systems resembling the innate dysregulation of these systems in msP rats. For instance, Wistar rats made dependent on alcohol through chronic intermittent ethanol vapor exposure showed increased anxiety, enhanced sensitivity to stress, overexpression of the CRF1R receptors in the CeA, and enhanced sensitivty to CRF1R antagonists (Gehlert *et al.*, 2007; Sommer *et al.*, 2008; Ciccocioppo *et al.*, 2009). Interestingly, administration of NOP agonists in alcohol dependent rats attenuated the expression of acute withdrawal signs (Economidou *et al.*, 2011). Moreover, following protracted abstinence, NOP activation reduced anxiety, excessive alcohol drinking, and stress-induced relapse triggered by the postdependent state (Martin-Fardon *et al.*, 2010; Economidou *et al.*, 2011; Aujla *et al.*, 2013; Ciccocioppo *et al.*, 2014a; de Guglielmo *et al.*, 2015). Additional evidence for alcohol-induced neuroadaptive changes of the N/OFQ-NOP receptor system comes from electrophysiological studies in CeA slice preparations This work showed that N/OFQ attenuated alcohol-evoked facilitation of $GABA_A$ neurotransmission, and that this effect was significantly more pronounced in msP and in alcohol dependent rats (Roberto & Siggins, 2006; Cruz *et al.*, 2012; Herman *et al.*, 2013). In addition, it was shown that, in the CeA, NOP receptor agonism diminished glutamatergic neurotransmission per se but at the same time occluded the inhibitory effect of alcohol on glutamate (Kallupi *et al.*, 2014). Altogether these findings suport two major conclusions: First, chronic exposure to high doses of alcohol (i.e., following passive alcohol intoxication) leads to neuroadaptive overexpression of the N/OFQ system in mesolimbic regions. Second, NOP agonism appears to be more efficacious in inhibiting alcohol-related behaviors when drinking is associated with high anxiety and enhanced stress sensitivity (i.e.

elicited by innate or environmentally evoked overexpression of the extrahypothalamic CRF system).

2.2. NOP Antagonism

As discussed above, a wealth of studies suggests that activation of NOP attenuates alcohol drinking and seeking (Table 1). However, evidence is emerging supporting the possibility that these effects can also be achieved with NOP antagonists (Table 1). For instance, in a study with LY2940094 (aka BTRX-246040), a selective and potent NOP antagonist recently developed by Eli Lilly(Toledo *et al.*, 2014), we found that this agent reduced alcohol consumption in two different lines of genetically selected alcohol preferring rats, including the msP line (Rorick-Kehn *et al.*, 2016). The same molecule, tested in a small clinical trial with 88 patients diagnosed with alcohol use disorder (AUD), showed efficacy in reducing the number of heavy drinking days which provided important proof-of-principle for the translational potential of NOP antagonism (Post *et al.*, 2016). Indirect evidence supporting the putative therapeutic potential of NOP antagonism comes from studies in genetically modified NOP knockout rats. Compared to wild-type controls, these engineered animals self-administer significantly smaller amounts of alcohol, cocaine and heroin, but show unimpaired motivation for saccharin, a natural reward (Kallupi *et al.*, 2017).

Why both NOP agonists and antagonists reduce the motivation for alcohol is still unclear. However, a critical analysis of historical data with NOP agonist may be of help to reconcile these apparently contrasting findings and to formulate new hypothesis on the role of the N/OFQ system in AUD. The first possibility to consider is that in pharmacologicl studies exogenous administration of non-physiological doses of NOP agonists may have depressed N/OFQ transmission through receptor desensitization. If so, NOP receptor agonism may have resulted in paradoxical antagonistic effects. It is known, in fact, that NOP receptors are subject to rapid desensitization, that may occur within minutes after administration of a high dose of an agonist or after chronic agonist treatment (Toll *et al.*, 2016). Most importantly, in a recent study that investigated the effect of chronic administration of the potent and selective NOP agonist MT-7716, it was shown that alcohol drinking was not affected acutely, progressively decreased during repeated drug administration and, compared with the control group, remained lower for several days after treatment discontinuation (Ciccocioppo *et al.*, 2014b). Indirectly, the NOP desensitization hypothesis is also supported by data demonstrating that compared to Wistar controls, high alcohol drinking msP rats have higher expression of N/OFQ and NOP receptor mRNA in numerous mesolimbic brain areas, including the CeA and NAc (Economidou *et al.*, 2008; Ciccocioppo *et al.*, 2014a). Moreover, in an earlier study in msP rats in which a low constant dose of N/OFQ was delivered ICV for 7 consecutive days by means of osmotic mini-pumps, a significant increase in alcohol intake was observed (Cifani *et al.*, 2006). At that time this finding was interperted as a consequence of the ability of N/OFQ to stimulate feeding and coloric intake. In msP rats increase in alcohol drinking following acute administration of Ro64–6198 was also observed; intake decreased after repeated dosing (Economidou *et al.*, 2006). In light of the NOP desensitization hypothesis, it is tempting to speculate that the increase in drinking following chronic N/OFQ was due to receptor stimulation under conditions in which the system did not undergo desensitization. Additional evidence supporting the possibility that NOP

activation facilitates rather than decreases drinking comes from studies in Wistar rats exposed to chronic intoxicating concentrations of alcohol. These animals, in fact, show upregulation of the NOP receptor transcript in the CeA and BNST that is accociated with enhanced propensity to excessive drinking (Sommer *et al.*, 2008; Aujla *et al.*, 2013). At the mechanistic level, an intriguing hypothesis is that overexpression of the NOP system in msP and postdependent Wistar rats may have been induced by a 'physiological' attempt to counteract the pathological (genetically or environmentally determined) overactivity of the extrahypothalamic CRF system (Hansson *et al.*, 2006; Gehlert *et al.*; Sommer *et al.*, 2008; Ciccocioppo *et al.*, 2009; Aujla *et al.*, 2013; Ayanwuyi *et al.*, 2013; Cippitelli *et al.*, 2015). However, stimulation of NOP receptors in the mesolimbic circuitry may lead to a hypodopaminergic and hypohedonic state that can increase the motivation for drugs of abuse. It is known, in fact, that activation of NOP following intra-VTA administration of N/OFQ attenuates dopamine (DA) release in the NAc (Murphy & Maidment, 1999). Consistently, studies using NOP knockout mice showed that N/OFQ transmission facilitated chronic responses to alcohol and methamphetamine by suppressing the animals' basal hedonic state. Based on this finding, the authors concluded that the N/OFQ-NOP system may play a permissive role in the development of drug abuse (Sakoori & Murphy, 2008a).

3. The N/OFQ System and Opioid Abuse

The first study investigating the effect of N/OFQ manipulation on opioid abuse was published two decades ago (Walker *et al.*, 1998). Results were negative as ICV administration of N/OFQ did not reduce operant heroin self-administration in the rat. This finding was unexpected because pain studies showed that N/OFQ, despite being an opioid-like peptide, acted in the brain as a functional anti-opioid (Grisel *et al.*, 1996; Mogil *et al.*, 1996a; Mogil *et al.*, 1996b). In contrast to this earlier finding, later self-administration studies (Table 2) in rats and monkeys showed reductions in opioid intake following administration of Ro 64–6198 and SCH221510, two small synthetic NOP agonists (Ko *et al.*, 2009; Podlesnik *et al.*, 2011; Sukhtankar *et al.*, 2014). These effects were systematically blocked by pretreatment with the selective NOP anatgonist J-113397 (Podlesnik *et al.*, 2011; Sukhtankar *et al.*, 2014). The ability of NOP agonists to block opioid reward was further demonstrated in place conditioning experiments in which ICV administration of N/OFQ blocked the aquisition and the expression of morphine CPP (Murphy *et al.*, 1999; Ciccocioppo *et al.*, 2000; Sakoori & Murphy, 2004). In CPP experiments, opioid reward was also blocked following administration of the potent and selective NOP agonists Ro 64–6198, Ro 65–6570, and AT-312 (Shoblock *et al.*, 2005; Rutten *et al.*, 2010; Zaveri *et al.*, 2018a).

A key neurochemical correlate of these behavioral findings was identified in a microdialysis experiment showing that ICV administration of N/OFQ reduced morphine-induced dopamine (DA) release in the nucleus accumbens (NAcc) of conscious rats (Di Giannuario & Pieretti, 2000). Further support for this potential mechanism comes from immunohistochemistry experiments indicating that N/OFQ blocked the expression of c-fos, a marker of neuronal activation, induced by morphine in the shell of the NAc (Ciccocioppo *et al.*, 2000). In fact, rewarding stimuli, including morphine, potently increase c-fos expression in this area, reflecting activation of dopamine (DA) receptor-containing neurons (Barrot *et al.*, 1999).

Few studies investigated the hypothesis that N/OFQ contributes to the development of tolerance to the analgesic effect of opioids. This possibility was supported by an early study showing that repeated morphine injections increased the brain levels of this antiopioid peptide (Yuan *et al.*, 1999). Consistent with this hypothesis, it was also shown that treatment with selective NOP receptor antagonists prevented the development and expression of opioid tolerance (Scoto *et al.*, 2007; Scoto *et al.*, 2009). Moreover, NOP knockout mice showed a 50% reduction in tolerance to the analgesic effect of morphine (Ueda *et al.*, 1997). Based on these data, the possibility that N/OFQ may also influence the development of tolerance to other central effects of opiates (i.e., reward) cannot not be excluded. In this respect, it would be interesting to test the effect of NOP receptor antagonists for their potential in preventing the escalation of opioid self-administration.

Another behavioral outcome associated with drug addiction is locomotor sensitization, a phenomenon in which repeated intermittent administration of drugs of abuse leads to a progressive increase in locomotor activity (Robinson & Berridge, 1993). According to the incentive sensitization theory of addiction, this phenomenon may reflect an increase in drug "wanting" that occurs following repeated drug experiences (Robinson & Berridge, 1993). The effect of N/OFQ on morphine-induced sensitization has been studied, but results remained unclear. In fact, either no effect was reported following N/OFQ administration or, when Ro 64–6198 and Ro 65–6570 were tested, these agents reduced the expression of morphine-induced locomotor sensitization but these effects were impervious to blockade by the selective NOP antagonist [Nphe^1]N/OFQ(1–13)-NH_2 (Ciccocioppo *et al.*, 2000; Kotlinska *et al.*, 2005). Finally, as in the case of alcohol, activation of NOP has been shown to prevent the expression of somatic opiod withdrawal signs in morphine dependent rats (Kotlinska *et al.*, 2000).

4. The N/OFQ System and Psychostimulant Abuse

The reinforcing properties of psychostimulants are linked to their ability to facilitate dopaminergic neurotransmission within the mesocorticolimbic circuit as a result of stimulating neurotransmitter release or blocking its reuptake (Di Chiara & Imperato, 1988; Nicolaysen & Justice, 1988; Wise & Rompre, 1989; Jones *et al.*, 1999). However, chronic exposure to these drugs leads to several neurobiological adaptations that occur at different stages of the addiction cycle and involve various transmitter systems (Nestler & Aghajanian, 1997; Nestler, 2001) (Koob *et al.*, 2004; Koob & Le Moal, 2008; Koob & Volkow, 2016).

Among these, the endogenous opioid system plays a primary role related to its modulation of the reinforcing effects of psychostimulants (Corrigal & Coen, 1991; Contet *et al.*, 2004; Le Merrer *et al.*, 2009)

The antiopioid nature of N/OFQ and its ability to reduce DA and glutamatergic transmission in mesolimbic regions have prompted the hypothesis that activation of NOP may counteract the effects of psychostimulants (Murphy & Maidment, 1999; Di Giannuario & Pieretti, 2000; Meis & Pape, 2001). Based on these considerations, several studies investigated the involvement of N/OFQ transmisssion in the acquisition of psychostimulant sensitization and place preference, with attention to the distinction between endogenous and exogenous

N/OFQ actions in influencing the incentive proprieties of cocaine and amphetamines (Table 3).

In particular, CPP studies showed that exogenous N/OFQ reduced the rewarding effects of cocaine and amphetamines (Kotlinska *et al.*, 2003; Sakoori & Murphy, 2004), and these findings were replicated with peripheral administration of brain penetrating synthetic agonists (Rutten *et al.*, 2010; Zaveri *et al.*, 2018a).

Consistent with these findings, it was shown in a microdialysis study that ICV administration of N/OFQ attenuated cocaine-induced increase in extracellular DA in the NAc (Lutfy *et al.*, 2001). In a similar study it was found that reverse dialysis of N/OFQ into the NAc shell significantly reduced cocaine-induced increase in extracellular DA levels in the same area and this effect of N/OFQ was prevented by administration of the selective NOP receptor antagonist SB-612111 (Vazquez-DeRose *et al.*, 2013)

On the other hand, administration of UFP-101, another selective NOP antagonist, did not significantly modify basal DA levels, suggesting a limited role of endogenous N/OFQ in modulating physiological DA transmission (Koizumi *et al.*, 2004; Calo *et al.*, 2005). However, UFP-101 was able to elicit modest CPP and enhanced methamphetamine-induced place preference (Sakoori & Murphy, 2008a). Moreover, mice lacking NOP exhibited enhanced cocaine CPP compared to their wild-type littermates (Marquez *et al.*, 2008b).

These findings, are consistent with the hypothesis that endogenous N/OFQ may contribute to producing an hypodopaminergic, hypoedonic state that, as suggested above (see the alcohol section), may contribute to enhancing the motivation for drugs of abuse.

A recent study reported that NOP receptor activation by the NOP agonist SR-8993 did not affect cocaine CPP, nor reinstatement elicited by cocaine priming or administration of the pharmacological stressor yohimbine (Sartor *et al.*, 2016).

Few studies explored the effects of N/OFQ manipulation on psychostimulant-induced locomotor sensitization. Evidence available to date shows that administration of the peptide blocks the development of cocaine and amphetamine-induced psychomotor sensitization (Lutfy *et al.*, 2002; Kotlinska *et al.*, 2003; Lutfy & Zaveri, 2016). This effect was not observed in NOP KO mice, further confirming that it is mediated by NOP activation(Bebawy *et al.*, 2010).

Very little is known about the effect of NOP modulation on psychostimulant self-administration. One early study showed that ICV administration of the peptide attenuated stress-induced reinstatement of extinguished lever pressing for alcohol but not for cocaine (Martin-Fardon *et al.*, 2000).

5. The N/OFQ System and Nicotine Abuse

Nicotine is the primary psychoactive component of tobacco and, like most drugs of abuse, acts upon the mesocorticolimbic reward system of the brain to initiate dependence (Pontieri *et al.*, 1996). So far, very few studies have investigated the significance of N/OFQ-NOP

neurotransmission in the regulation of nicotine-related behaviors (Table 3). In one of the first published studies it was demonstrated that mice lacking the NOP receptor show higher voluntary drinking of a low concentration of nicotine solution compared to wild-type mice (Sakoori & Murphy, 2009). NOP KO mice show increased hippocampal acetylcholine release, providing additional evidence of the modulatory role of N/OFQ on acetylcholine transmission (Uezu *et al.*, 2005).

More recently Cippitelli and colleagues investigated the role of the NOP system in a model of nicotine and alcohol co-administration. The NOP receptor agonist AT-202 increased nicotine self-administration in nicotine post-dependent and non-dependent rats. Conversely, the specific NOP antagonist SB-612111 reduced nicotine self-administration in both groups of animals, suggesting that NOP receptor antagonists rather than agonists may show potential as treatments for nicotine dependence (Cippitelli *et al.*, 2016).

Additional studies will be necessary before drawing conclusions about the therapeutic potential of NOP antagonists in nicotine addiction. However, considering that NOP antagonists are efficacious in attenuating alcohol drinking and that alcohol and nicotine are among the most frequently co-abused drugs, it will be a priority to evaluate the therapeutic potential of this approach in future studies.

6. The N/OFQ System: Coactivation of NOP and MOP receptors

Growing evidence suggests that compounds that co-activate MOP and NOP opioid receptors (Table 4) have potential for the treatment of drug abuse (Ciccocioppo *et al.*, 2007; Toll *et al.*, 2009; Toll, 2013; Kallupi *et al.*, 2018).

Molecules with mixed MOP/NOP agonist properties were first investigated with the aim to develop successful analgesics with reduced tendency to evoke tolerance and low abuse liability compared to classical MOP agonists (Khroyan *et al.*, 2011b; Toll, 2013; Ding *et al.*, 2016). These compounds, in addition to analgesic activity, preserve most of the classical MOP agonist effects including relaxation, feeling of pleasure and respiratory depression but at lower intensity compared to heroin, morphine, methadone and other traditional opioid agonists (Lambert *et al.*, 2015; Calo & Lambert, 2018; Gunther *et al.*, 2018; Ruzza *et al.*, 2018).

The potential of MOP/NOP agonists or partial agonists in drug abuse treatment was initially suggested by studies with buprenorphine. This drug is classically viewed as a partial agonist at MOP and antagonist at DOP and KOP receptors (Huang *et al.*, 2001). However, more recent studies demonstrated that it also acts as a low affinity partial agonist at NOP (Wnendt *et al.*, 1999; Bloms-Funke *et al.*, 2000; Huang *et al.*, 2001). Most importantly, activation of NOP by buprenorphine appears to have distinct pharmacological consequences (Lutfy *et al.*, 2003; Marquez *et al.*, 2008a; Khroyan *et al.*, 2009). For instance, activation of NOP contributes to attenuating the analgesic effects of high doses of buprenorphine (Lutfy *et al.*, 2003; Marquez *et al.*, 2008a; Khroyan *et al.*, 2009). Moreover, in a study with alcohol preferrig msP rats, buprenorphine produced a bidirectional effect on alcohol drinking. Low doses increased alcohol consumption while high doses reduced it. Buprenorphine-induced

increases of alcohol drinking were blocked by naltrexone, suggesting that this effect was mediated by MOP receptors. On the other hand, reductions of alcohol intake were selectively blocked by the NOP agonist UFP-101 but not by naloxone (Ciccocioppo *et al.*, 2007). These findings demonstrate that inhibition of drinking by buprenorphine was specifically mediated by NOP receptors, for which the drug has low affinity, and this observations may also explain why anti-alcohol effects occurred at high buprenorphine doses. Interestingly, in an earlier clinical study in heroin addicts abusing alcohol, it was shown that high buprenorphine doses were also able to reduce alcohol consumption in this population (Kakko *et al.*, 2003). In another clinical study conducted in heroin addicted patiens co-abusing cocaine it was also shown that high doses of buprenorphine reduced the consumption of the psychostimulant. Interestingly, this effect was evident only at highest doses of buprenorphine and appeared to be independent from reductions in heroin use. This clinical study replicated evidence from a number of preclinical investigations that systematically demonstrated the efficacy of buprenorphine in attenuating cocaine self-administration in rats and monkeys and humans (Lukas *et al.*, 1995; Montoya *et al.*, 2004; Sorge *et al.*, 2005; Sorge & Stewart, 2006; Kallupi *et al.*, 2018). In some circumstances, the "therapeutic" effect of buprenorphine on cocaine intake was attenuated by administration of naltrexone (Mello *et al.*, 1993; Wee *et al.*, 2012). However, in a more recent investigation, administration of naltrexone was not sufficient to prevent buprenorphine-induced inhibition of cocaine self-administration in rats (Kallupi *et al.*, 2018). In this latter study that attempted to more precisely characterize the mechanism of action of buprenorphine on cocaine self-administration, buprenorphine's effects were tested against naltrexone, the selective NOP antagonist SB-612111, or a combination of both drugs. The results showed that buprenorphine-induced reduction of cocaine self-administration was prevented only if NOP and MOP receptors were simultaneously blocked by coadministration of the two antagonists (Kallupi *et al.*, 2018). Based on this finding the authors concluded that reduction of cocaine self-administration by buprenorphine requires actions at both MOP and NOP receptors and is only achieved at high drug doses due to its low affinitity for NOP. Support for the co-activation hypothesis came from a study with AT-034 and AT-201, two new molecules specifically designed to activate MOP and NOP, with much weaker affinity for DOP and KOP that, like buprenorphine, reduce operant cocaine self-administration (Zaveri *et al.*, 2013; Journigan *et al.*, 2014). Notheworthy, NOP binding affinity and efficacy of these 3 molecuIs are different, which opens questions on the intimate mechanism responsible for their effect on cocaine.

An interesting development was the recent discovery of cebranopadol, a panopioid agonist that activates MOP and NOP receptors with similar potency and efficacy, and with slighly lower affinity, also DOP and KOP (Linz *et al.*, 2014; Schunk *et al.*, 2014; Lambert *et al.*, 2015). Recently, two independent studies demonstrated that cebranopadol is efficacious in attenuating the motivation for cocaine in drug self-administration studies while leaving unaffected (or slighly increased) the consumption of natural rewars (de Guglielmo *et al.*, 2017; Shen *et al.*, 2017). Most importantly, in one of these studies replicating earlier findings with buprenorphine, the authors demonstrated that the effect of cebranopadol was blocked by co-administration of naltrexone and SB-612111, but not when these two antagonists were given separately (Shen *et al.*, 2017).

Cebranopadol is currently under clinical development for chronic pain (Linz *et al.*, 2014; Schunk *et al.*, 2014; Lambert *et al.*, 2015; Christoph *et al.*, 2017; Scholz *et al.*, 2018). At pharmacological effective doses it exibits low tendency to produce respiratory depression and produces no impairment of motor coordination (Dahan *et al.*, 2017; Gunther *et al.*, 2018). Moreover, cebranopadol appears to have lower abuse potential compared to classical opioid agonists (Shen *et al.*, 2017; Tzschentke *et al.*, 2017; Ruzza *et al.*, 2018; Gohler *et al.*, 2019).

Based on these findings it is tempting to hypothesize that coactivation of MOP and NOP receptors may represent a novel highly promising strategy to treat drug abuse. The advanced stage of development of cebranopadol allows for rapid translation of these preclinical findings into clinical trials in addicted patients. Moreover, there are other molecules under development that selectively activate NOP and MOP without affecting other opid receptors that are promising candidates for development in the field of drug abuse (Ding *et al.*, 2016; Ding *et al.*, 2018)

7. Conclusions

Two decades of research on N/OFQ and drug abuse provided significant evidence supporting the therapeutic potential of NOP agonists in the treatment of drug abuse. The most robust evidence has been generated in the field of alcoholism, followed by the psychostimulant and opioid fields. Very little is known about the role of N/OFQ in nicotine abuse. However contrary to what was observed with other substances of abuse, activation of NOP appers to have a permissive role for nicotine reward as it increases nicotine consumption. New studies with selective NOP antagonists that have ~~beeen~~ recently become available are revealing more complicated scenarios. For instance, it was shown that, similar to NOP agonism, NOP receptor blockade reduced alcohol drinking and seeking in laborabory animals and in humans. To reconcile these contrasting findings, we proposed here the hypothesis that high basal N/OFQ-NOP transmission is responsible for inducing an hypohedonic state that can ultimatly motivate drug consumption. This is why animals with innate (msP rats) or alcohol induced (postdependent Wistar rats) overexpression of NOP show higher motivation for alcohol. Whereas rats with genetic deltion of NOP self-administer less alcohol cocaine and heroin (Table 5). Derived from these observation we then proposed that the effect of NOP agonists on behavior motivated by alcohol and on other substances of abuse may depend upon rapid desensitization of the N/OFQ-NOP system following agonist administration. This hypothesis is supported by at least three main elements: First NOP receptors are subject to rapid desensitization following exogenous administration of NOP agonists. Second, in few studies acute administration of N/OFQ increased rather than decreased alcohol drinking. Third, the effect of NOP agonists increases during chronic drug administration and is maintained for several days after the treatment is stopped.

A final consideration concerns mixed MOP/NOP agonists. Buprenorphine is the propotype of this class of molecules, but recently other compounds with higher potency and efficacy for NOP have been synthesized. Cebranopadol is an example of this new class of molecules, but it binds to all four opioid receptors. However, other recently developed compounds, like BU08070, BU08028, AT-121 and SR16435 activate only MOP and NOP receptors (Khroyan

et al., 2007; Khroyan *et al.*, 2011a; Ding *et al.*, 2016; Ding *et al.*, 2018). Considering the efficacy of buoprenorphine and cebranopadol on alcohol, cocaine and opioid self-administration it is tempting to hypothesize that combinations of MOP/NOP agonists may provide an additional strategy to treat drug abuse.

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Table 1:

Compounds targeting the N/OFQ-NOP receptor system, relative developmental stage and effects on alcohol abuse.

Agonist	Chemical entity	Effects	Dev. Phase	Ref.
N/OFQ	Peptidic	↓ Alcohol intake ↑ Alcohol intake ↓ Alcohol Self-Administration ↓ Somatic withdrawal signs ↓ Stress-Induced Reinstatement ↓ Cues-Induced Reinstatement ↓ Alcohol-Induced CPP ↓ Alcohol intake	Preclinic	(Ciccocioppo *et al.*, 1999; Economidou *et al.*, 2006) (Cifani *et al.*, 2006) (Ciccocioppo *et al.*, 2004b; Economidou *et al.*, 2008) (Economidou *et al.*, 2011) (Martin-Fardon *et al.*, 2000) (Ciccocioppo *et al.*, 2004b) (Kuzmin *et al.*, 2003) (Ciccocioppo *et al.*, 2014b)
MT-7716	small molecule	↓ Somatic withdrawal signs ↓ Stress-Induced Reinstatement ↓ Cues-Induced Reinstatement		(Ciccocioppo *et al.*, 2014b; de Guglielmo *et al.*, 2015) (Ciccocioppo *et al.*, 2014b; de Guglielmo *et al.*, 2015) (Ciccocioppo *et al.*, 2014b)
SR-8993	small molecule	↓ Alcohol intake; Alcohol Self-Administration; Progressive Ratio; Stress- and Cues- Induced Reinstatement		(Aziz *et al.*, 2016)
AT-312	small molecule	↓ Alcohol-Induced CPP		(Zaveri *et al.*, 2018b)
Ro 64–6198	small molecule	↓ Alcohol Self-Administration ↑ Alcohol intake		(Kuzmin *et al.*, 2007) (Economidou *et al.*, 2006)
UFP-112	peptidic	↓ Alcohol intake		(Economidou *et al.*, 2006)
UFP-102	peptidic	↓ Alcohol intake		(Economidou *et al.*, 2006)
OS-462	peptidic	↓ Alcohol intake		(Economidou *et al.*, 2006)
UFP-101	peptidic	↓ Alcohol Self-Administration	Preclinic	(Ciccocioppo *et al.*, 2007)
LY2940094	small molecule	↓ Alcohol Intake; Alcohol Self-Administration; Progressive Ratio; Stress-Induced Reinstatement		(Rorick-Kehn *et al.*, 2016)
LY2817412	small molecule	↓ Alcohol Self-Administration		(Kallupi *et al.*, 2017)
J-113397	small molecule	↑ Alcohol intake		(Miranda-Morales *et al.*, 2013)
SB-612111	small molecule	↓ Alcohol Self-Administration		(Cippitelli *et al.*, 2016; Kallupi *et al.*, 2017)
Nphe	peptidic	— Alcohol intake		(Ciccocioppo *et al.*, 2002c)
LY2940094	small molecule	↓ Alcohol intake	Clinical	(Post *et al.*, 2016)

Table 2:

Compounds targeting the N/OFQ-NOP receptor system, relative developmental stage and effects on opioids abuse.

Agonist	Chemical entity	Effects	Dev. phase	Ref.
N/OFQ	peptidic	↓ Morphine-Induced CPP — Heroin Self-Administration ↓ Morphine induced somatic withdrawal signs	Preclinic	(Ciccocioppo *et al.*, 1999; Murphy *et al.*, 1999;Ciccocioppo *et al.*, 2000; Sakoori & Murphy, 2004; Economidou *et al.*, 2006; Sakoori & Murphy, 2008b) (Walker *et al.*, 1998) (Kotlinska *et al.*, 2000)
SR-8993	small molecule	↓ Morphine-Induced CPP		(Zaveri *et al.*, 2018a)
Ro 64–6198	small molecule	↓ Morphine-Induced Reinstatement		(Shoblock *et al.*, 2005)
Ro 65–6570	small molecule	↓ Oxycodone-Induced CPP ↓ Tilidine-Induced CPP ↓ Morphine-Induced CPP ↓ Heroin-Induced CPP		(Rutten *et al.* 2010)

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Table 3:

Compounds targeting the N/OFQ- system, relative developmental stage and effects on psychostimulants and on nicotine abuse.

Agonist	Chemical entity	Effects	Dev. phase	Ref.
N/OFQ	peptidic	↓ Cocaine-Induced CPP ↓ Methamphetamine-Induced CPP — Stress-Induced Cocaine Reinstatement — Cocaine-Induced CPP — Reinstatement induced by stress or cocaine ↓ Cocaine-Induced CPP ↓ Morphine induced somatic withdrawal signs ↓ Cocaine-Induced locomotor sensitization ↓ Amphetamine-Induced locomotor sensitization	Preclinic	(Kotlinska *et al.*, 2002; Sakoori & Murphy, 2004) (Kotlinska *et al.*, 2003; Zhao *et al.*, 2003) (Martin-Fardon *et al.*, 2000) (Sartor *et al.*, 2016) (Kotlinska *et al.*, 2000) (Lutfy *et al.*, 2002) (Kotlinska *et al.*, 2003)
AT-202	small molecule	— Cocaine Self-Administration ↑ Nicotine Self-Administration		(Kallupi *et al.*, 2018) (Cippitelli *et al.*, 2016)
AT-312	small molecule	↓ Morphine-Induced CPP ↓ Cocaine-Induced CPP		(Zaveri *et al.*, 2018a)
Ro 65–6570	small molecule	↓ Cocaine-Induced CPP		(Rutten *et al.* 2010)
Ro 64–6198	small molecule	↓ Morphine-Induced CPP		(Shoblock *et al.*, 2005)

Table 4:

Mixed MOP/NOP receptors compounds, relative developmental stage and effects on substance abuse.

Agonist	Chemical entity	Effects	Dev. phase	Ref.
Buprenorphine	small molecule	↓ Alcohol intake through NOP receptors (High doses) ↑ Alcohol intake through MOP receptors (Low doses) ↓ Cocaine Self-Administration ↓ Heroin Seeking during extinction ↓ Cocaine Seeking during extinction ↓ Heroin-Induced Reinstatement ↓ Cocaine-Induced Reinstatement ↓ Cocaine intake — Heroin intake	Preclinic	(Ciccocioppo *et al.*, 2007) (Lukas *et al.*, 1995; Kallupi *et al.*, 2018) (Sorge *et al.*, 2005) (Sorge & Stewart, 2006)
Cebranopadol	small molecule	↓ Escalation of Cocaine Self-Administration ↓ Conditioned Reinstatement of Cocaine-seeking behavior ↓ Cocaine Self-Administration		(de Guglielmo *et al.*, 2017) (Shen *et al.*, 2017)
AT-034	small molecule	↓ Cocaine Self-Administration		(Kallupi *et al.*, 2018)
AT-201	small molecule	↓ Cocaine Self-Administration		(Kallupi *et al.*, 2018)

Table 5:

Genetic deletion of NOP receptor in rat and mice and related effects on drug abuse-related behaviors.

NOP (−/−)	Effects	Ref.
Rat	↓ Cocaine Self-Administration ↓ Progressive Ratio for Cocaine ↓ Heroin Self-Administration — Cocaine-Induced CPP ↓ Alcohol Self-Administration	(Kallupi *et al.*, 2017)
Mouse	↓ Cocaine-Induced locomotor sensitization ↓ Amphetamine-Induced locomotor sensitization ↑ Cocaine-Induced CPP ↑ Nicotine intake	(Marquez *et al.*, 2013) (Marquez *et al.*, 2008b) (Sakoori & Murphy, 2009)