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CHAPTER FIVE

The Nociceptin Receptor as an Emerging Molecular Target for Cocaine Addiction

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Abstract

Cocaine addiction is a global public health and socioeconomic issue that requires pharmacological and cognitive therapies. Currently there are no FDA-approved medications to treat cocaine addiction. However, in preclinical studies, interventions ranging from herbal medicine to deep-brain stimulation have shown promise for the therapy of cocaine addiction. Recent developments in molecular biology, pharmacology, and medicinal chemistry have enabled scientists to identify novel molecular targets along the pathways involved in drug addiction. In 1994, a receptor that showed a great deal of homology to the traditional opioid receptors was characterized. However, endogenous and exogenous opioids failed to bind to this receptor,

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which led scientists to name it opioid receptor-like receptor, now referred to as the nociceptin receptor. The endogenous ligand of NOPr was identified a year later and named orphanin FQ/nociceptin. Nociceptin and NOPr are widely distributed throughout the CNS and are involved in many physiological responses, such as food intake, nociceptive processing, neurotransmitter release, etc. Furthermore, exogenous nociceptin has been shown to regulate the activity of mesolimbic dopaminergic neurons, glutamate, and opioid systems, and the stress circuit. Importantly, exogenous nociceptin has been shown to reduce the rewarding and addictive actions of a number of drugs of abuse, such as psychostimulants, alcohol, and opioids. This paper reviews the existing literature on the role of endogenous nociceptin in the rewarding and addictive actions of cocaine. The effect of exogenous nociceptin on these processes is also reviewed. Furthermore, the effects of novel small-molecule NOPr ligands on these actions of cocaine are discussed. Overall, a review of the literature suggests that NOPr could be an emerging target for cocaine addiction pharmacotherapy.

1. INTRODUCTION

Addiction to cocaine and other addictive substances is a chronic and relapsing brain disorder brought about by neuronal adaptive changes along numerous brain circuits and is characterized by uncontrollable drug-taking and drug-seeking behaviors in spite of adverse consequences (such as loss of family, friendship, productivity, and most importantly risk of sudden death due to cocaine overdose) associated with continuation of such behaviors. Cocaine addiction is a major public health issue and places a tremendous burden on the person, relationships, productivity and society as a whole. Estimates show that about 1.2 million people consumed cocaine for the very first time in the United States in 2001.[1] Furthermore, in 2007, it was estimated that more than 2 million people over the age of 12 were current cocaine users and females were found to be more sensitive to the addictive actions of cocaine than males.[2] Estimates show that the lifetime prevalence of cocaine use in 2013 was 14.3% (http://www.drugabuse.gov/drugs-abuse/cocaine) in adults aged 12 and older. Despite these alarming estimates and negative consequences, there is no FDA-approved pharmacotherapy to treat cocaine addiction. Thus, further research is needed to characterize novel targets to develop new pharmacotherapy and effectively curb this chronic and relapsing brain disorder. Most drugs of abuse, such as cocaine, nicotine, opioids, and amphetamines increase dopamine levels in the nucleus accumbens albeit through different mechanisms. Cocaine enhances accumbal

dopamine levels by blocking the dopamine transporter. Therefore, the dopamine receptor and dopamine transporter have been the conventional targets for medication development for cocaine addiction. However, this strategy has failed to yield clinically useful cocaine dependence medications. Several other receptor systems that affect different phases of cocaine addiction are now being investigated. Among these, opioidergic, γ-amino butyric acid[3] -ergic,[4] endocannabinoid,[5] serotonergic, and cholinergic agonists have been investigated for their inhibition of cocaine reward. A growing body of evidence suggests that the nociceptin receptor[6] could be a potential target for novel medications to treat cocaine addiction. This review discusses the existing literature around this molecular target showing that NOPr agonists could potentially provide beneficial effects in curbing cocaine addiction.

2. ORPHANIN FQ/NOCICEPTIN/NOPr SYSTEM

In 1994, several laboratories[7–10] cloned a receptor that showed a great deal of homology to the classical opioid receptors, namely mu, delta, and kappa, in particular in the transmembrane domains, yet neither endogenous opioids nor exogenous opioid ligands (except a few) showed appreciable affinity toward this receptor. Therefore, this receptor was named the opioid receptor-like (ORL) receptor. Later on, the International Union of Pharmacology (IUPHAR) in agreement with the scientific community renamed it nociceptin/orphanin FQ receptor (NOR) and then nociceptin receptor (NOPr). In 1995, two laboratories independently identified a heptadecapeptide as the endogenous ligand of this receptor.[11,12] One group named this peptide nociceptin because intracerebroventricular administration of the peptide shortened hot-plate latency, indicative of pain in rodents;[11] while the other group called it orphanin FQ because the peptide was the endogenous ligand of an orphan receptor, and F and Q stand for the first (phenylalanine) and last (glutamine) amino acid of the peptide sequence.[12] Orphanin FQ/nociceptin (OFQ/N) is a heptadecapeptide that shows similarities to the endogenous opioid peptides and in particular to dynorphin 1–17.[11,13] Interestingly, the NOPr and classical opioid receptors also share common signaling mechanisms. Activation of the opioid receptors and the NOPr leads to inhibition of adenylyl cyclase,[11,12,14] decrease in calcium currents,[15,16] activation of potassium channels[17,18] and mitogen-activated protein kinase.[19–22]

Nociceptin and its receptor (NOPr) are widely distributed throughout the CNS[23,24] and have been implicated in many physiological responses ranging from modulation of pain to learning and memory, food intake, and drug reward (for review see Ref. [25]). Importantly, exogenously applied OFQ/N has been shown to reduce the activity of the mesolimbic dopaminergic neurons,[26–28] glutamatergic neurons,[29] opioidergic neurons,[30] and the stress circuit.[31–37] Interestingly, these neurons and circuits are involved in motivated behaviors, reward, learning and memory, anxiety and stress response, processes that play a major role in the development and maintenance of addictive behaviors. Therefore, the OFQ/N–NOPr system could be a potential target to develop small-molecule NOPr agonists to treat cocaine addiction because OFQ/N and other NOPr agonists have multiple effects that are opposite of cocaine's action at these molecular targets (for details see Section 3).

2.1 Effects of Exogenous OFQ/N on the Actions of Cocaine

The discovery of NOPr and its endogenous ligand, and the demonstration that OFQ/N exerts antiopioid effects in the brain, prompted Murphy and coworkers (1996) to assess the effect of this peptide on extracellular dopamine in the nucleus accumbens.[26] These authors found that intracerebroventricular administration of OFQ/N reduced accumbal dopamine in the microdialysate in anesthetized rats in a concentration-dependent manner,[26] suggesting that OFQ/N acts as a brake to regulate the function of the mesolimbic dopaminergic neurons. Subsequent studies demonstrated that local OFQ/N administration in the ventral tegmental area (VTA) reduced extracellular levels of dopamine in the nucleus accumbens (NAc),[27] suggesting that the VTA may be at least one of the sites where OFQ/N exerts its regulatory action on extracellular accumbal dopamine. Consistent with this notion, other investigators reported the presence of NOPr on dopaminergic neurons in the VTA.[38,39] Furthermore, exogenously administered OFQ/N was found to regulate the activity of dopaminergic neurons in the VTA.[40] The regulatory action of OFQ/N on extracellular dopamine in the NAc was later shown in freely moving mice.[41] These authors also showed the selectivity of OFQ/N's action in this regard, as OFQ/N failed to reduce the level of accumbal dopamine in mice lacking NOPr.[41] OFQ/N has also been shown to decrease synthesis of dopamine in synaptosomes obtained from rat NAc and striatum, as OFQ/N reduced phosphorylation of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines.[42] The action of OFQ/N on extracellular dopamine is reminiscent of the effect

of dynorphin, which is structurally similar to OFQ/N. However, unlike dynorphin and related κ-opioid receptor agonists, OFQ/N does not induce aversion in rats,[43] although Sakoori and Murphy have found a modest aversive response following OFQ/N administration in mice.[44] Nevertheless, it is not entirely clear why, even though the two peptides reduce extracellular accumbal dopamine, only dynorphin elicits aversion.[45,46] Thus, further research is needed in this area to delineate the underlying mechanism of this divergent effect of dynorphin and nociceptin on hedonic homeostasis.

While there is moderate to high density of NOPr expression in the mesolimbic areas, few studies have examined the effect of exogenous NOPr stimulation on cocaine-elevated extracellular dopamine in the NAc. Given that cocaine elevates extracellular dopamine by blocking the dopamine transporter and that this action of cocaine is impulse-dependent, OFQ/N might also reduce the ability of cocaine to elevate extracellular dopamine in the NAc. We tested this hypothesis first and showed that intracerebroventricular OFQ/N administration prior to systemic cocaine treatment reduced cocaine-elevated accumbal dopamine levels in anesthetized rats.[47] Recently, Vazquez-DeRose and coworkers demonstrated that this action of OFQ/N could also be mediated locally in the NAc, as they showed that retrodialysis of OFQ/N into the NAc shell abolished cocaine-elevated extracellular dopamine in the NAc.[48] Given that the ability of cocaine to elevate extracellular dopamine levels in the NAc plays an essential role in the motor stimulatory action of cocaine,[49] we tested whether OFQ/N could also reduce hyperlocomotion induced by cocaine. Our results revealed that intracerebroventricular administration of OFQ/N dose-dependently reduced cocaine-induced motor stimulation.[47] OFQ/N may exert its action, at least in part, in the VTA because local injection of OFQ/N in this brain region blunted cocaine-stimulated locomotor activity in rats.[50]

The effect of OFQ/N has also been studied on the rewarding actions of cocaine and other psychostimulants. In these studies, the conditioned place preference (CPP) paradigm has been used as an animal model of drug reward or drug-seeking behavior.[51] The first study reporting the effect of OFQ/N on the expression of CPP was by Kotlinska and coworkers, who showed that intracerebroventricular OFQ/N administration suppressed the expression of cocaine-induced CPP in rats.[52] This group also studied the effect of OFQ/N on the acquisition of amphetamine-induced CPP.[53] Rats treated with OFQ/N prior to each amphetamine injection during the acquisition phase of CPP were found to exhibit a significant reduction in amphetamine-induced CPP compared to their vehicle-treated controls. These authors also

showed that while OFQ/N did not affect the acute stereotypic effect of amphetamine, it was able to reduce the sensitized response that developed to this effect of amphetamine following its repeated administration, suggesting that OFQ/N affects the neuronal adaptive changes that develop following repeated drug administration.[53] In a similar experimental paradigm, using methamphetamine instead of amphetamine, Zhao and coworkers reported that OFQ/N reduced the rewarding action of methamphetamine in rats.[54] The effect of OFQ/N on the rewarding action of cocaine was also studied.[44] These authors demonstrated that intracerebroventricular administration of OFQ/N prior to cocaine administration on each conditioning day attenuated the CPP response, showing that OFQ reduced the rewarding action of cocaine.[44]

Repeated cocaine treatment causes neuronal adaptive changes along the mesolimbic dopaminergic and glutamatergic neurons (for a review see Ref. [55]). Along with these neuroadaptive alterations, the motor stimulatory, rewarding, and other behavioral effects of cocaine are enhanced, a phenomenon known as behavioral sensitization. Bebawy and coworkers showed that repeated cocaine treatment enhanced the rewarding action of cocaine and this conditioned rewarding effect of cocaine was reduced in mice treated with OFQ/N before each cocaine injection.[56]

The effect of exogenous OFQ/N on cocaine-induced locomotor sensitization has been studied.[50,56,57] The phenomenon of locomotor sensitization is referred to as an enduring increase in the motor-stimulatory action of cocaine that develops following its repeated intermittent treatment. Neuronal adaptive changes develop along the mesolimbic dopaminergic and corticolimbic glutamatergic neurons in animals sensitized to cocaine and other addictive drugs. Interestingly, similar alterations have been reported in human addicts and these changes are thought to mediate the motivational behavioral changes observed in drug addicts, such as craving and relapse. Therefore, the phenomenon of behavioral sensitization in rodents has been proposed to mimic some aspects of addiction in humans.[55,58–65] An earlier report failed to show any effect of OFQ/N on cocaine sensitization.[57] These authors used the same concentration of OFQ/N during the induction of sensitization (i.e., on days 1–3) and found that the inhibitory effect of OFQ/N on cocaine-induced motor stimulation was evident only on day 1 but not on days 2 and 3 of the cocaine-sensitizing regimen, raising the possibility that the lack of effect of OFQ/N might have been due to the development of tolerance. Interestingly, a rapid tolerance develops toward the motor suppressant effect of OFQ/N.[66]

However, using escalating doses of OFQ/N during the induction of sensitization, Lutfy *et al.*, demonstrated that intracerebroventricular as well as intra-VTA injection of OFQ/N blocked the development of locomotor sensitization in rats.[50] These results were replicated in C57BL/6 mice,[56] showing the generality of the inhibitory action of OFQ/N on this phenomenon. These authors also demonstrated that OFQ/N failed to alter cocaine-induced locomotor sensitization in mice lacking NOPr, showing that OFQ/N exerts its inhibitory action on cocaine sensitization via NOPr. An intriguing observation from these studies was that OFQ/N not only blocked the development of locomotor sensitization but also reversed the time course of an established sensitized response.[56] The reversal of cocaine sensitization suggests that OFQ/N may facilitate the process leading to extinction of the conditioned response. Interestingly, we recently discovered that extinction of cocaine-induced CPP was facilitated in mice treated with a novel small-molecule NOPr agonist (Lutfy and Zaveri, unpublished data), whereas the opposite was evident in mice lacking nociceptin as well as in wild-type mice treated with a NOPr antagonist, J-113397 (Marquez and Lutfy, unpublished data). Thus, the OFQ/N–NOPr system appears to alter behaviors induced by cocaine in mice, and may be a potential target to develop medications to treat cocaine addiction.

While OFQ/N clearly reduces the rewarding effects of psychostimulant drugs as measured in the place-conditioning paradigm, it does not appear to affect cocaine-seeking behavior after extinction in rats.[67] However, OFQ/N is able to attenuate stress-induced ethanol-seeking behavior. These results are in line with the previous observations that OFQ/N failed to affect heroin self-administration in rats at any dose, even though the higher doses (10 μg) caused suppression of spontaneous locomotor activity.[68] It is possible that the reinforcing properties of a drug, measured by the operant self-administration paradigm are different than the rewarding, hedonic effects of a drug, as measured in the place-conditioning paradigm, and that OFQ/N affects the rewarding effects but has no effect on the reinforcing properties of an abused drug. Alternatively, the OFQ/N–NOPr system may become overwhelmed following repeated drug administration in the operant conditioning paradigm, which involves more dosing with the drugs of abuse. Clearly, further studies using more aggressive OFQ/N treatment would be needed to understand these differences. Furthermore, studies with small-molecule NOPr agonists, which are expected to mimic NOPr activation by the neuropeptide OFQ/N, would be useful to determine the potential of NOPr agonism as a novel pharmacologic approach to treat the various aspects of substance abuse disorders.

2.2 Endogenous OFQ/N as a Brake to the Rewarding and Addictive Actions of Cocaine

While there is a clear indication that exogenous OFQ/N regulates the activity of the mesolimbic dopaminergic neurons, the role of the endogenous OFQ/N is not entirely clear although some research has been performed in this area. Koizumi *et al.* showed that while intracerebroventricular OFQ/N administration suppressed extracellular dopamine in the NAc, the NOPr antagonist peptide, [Nphe1, Arg14, Lys15] nociceptin-NH(2), known as UFP-101, failed to alter the levels of dopamine, suggesting that endogenous OFQ/N may not regulate the activity of mesolimbic dopaminergic neurons.[41] However, in a different report, these authors showed that basal level of dopamine was mildly higher (but not significant) in mice lacking NOPr compared to their wild-type controls.[69] These authors also showed that administration of Compound B (1-[(3R, 4R)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one), a small-molecule NOPr antagonist, increased extracellular dopamine in the NAc. However, this response was not affected by prior administration of OFQ/N. Also, the increase in dopamine induced by Compound B was not altered in mice lacking NOPr, suggesting that receptors other than NOPr may be involved in the action of Compound B. Thus, further research with selective NOP antagonists is needed to fully characterize whether endogenous OFQ/N regulates the activity of mesolimbic dopaminergic neurons.

The endogenous OFQ/N also plays a role in the rewarding and addictive actions of cocaine. Likewise, acute and chronic cocaine treatment each appears to modulate the level of endogenous OFQ/N. For instance, Romualdi and coworkers showed that the level of OFQ/N was reduced in the medial region of the caudate putamen as well as in the NAc shell and substantia nigra following chronic cocaine administration.[70] Furthermore, Lutfy *et al.* showed that the level of OFQ/N-immunoreactivity (OFQ/N-IR) was reduced in the midbrain area 1 h after a single cocaine (20 mg/kg) administration. Reductions were also seen in the striatum and prefrontal cortex but these changes were not significantly different from the saline-treated controls.[71] However, tissue content does not provide information about the release, metabolism, and/or synthesis of the peptide. Additionally, given that these changes were measured 1 h after cocaine administration, future studies using microdialysis in freely moving animals are needed to assess the dose–-response and time course effect of single and repeated cocaine administration on the release of endogenous OFQ/N. Interestingly, however, the level of OFQ/N-IR

was found to be increased in the hippocampus of rats that received repeated intermittent cocaine treatment and showed locomotor sensitization.[71] These results suggest that the endogenous OFQ/N may be involved in the acute and chronic actions of cocaine.

Consistent with these findings, Marquez and coworkers showed that the rewarding action of acute cocaine was enhanced in mice lacking NOPr compared to their wild-type littermates/controls.[72] In addition, cocaine-induced locomotor sensitization induced by repeated intermittent cocaine administration was enhanced in these mice compared to their wild-type controls.[73] This response appeared to be selective for the action of cocaine since locomotor sensitization induced by repeated amphetamine treatment was not altered in mice lacking NOPr.

2.3 Effect of Small-Molecule NOPr Agonists on Actions of Cocaine

Relatively little is known about the effect of small-molecule NOPr ligands on the rewarding and addictive effects of cocaine and other psychostimulants such as amphetamines. A number of laboratories have developed NOPr ligands that are relatively selective and have shown promise to reduce the rewarding action of morphine[74,75] and alcohol.[76,77] However, small-molecule NOPr agonists have not been extensively evaluated for their effects on cocaine-induced reward or other effects of cocaine. The few studies published with nonpeptide small-molecule NOPr agonists showed equivocal results regarding the effects of these compounds on cocaine-induced reward. Ro 65-6570, an NOPr agonist that belongs to the same class of NOPr agonists as Ro 64-6198[78] but has higher affinity at the μ-opioid receptor than Ro 64-6198, showed no effect on the expression of cocaine-induced place preference in rats[52] or on the acquisition of cocaine-induced place preference in rats,[79] although Ro 64-6198 itself was not investigated for these effects. It is possible that lower selectivity of this compound for NOPr versus the μ-opioid receptor (MOPr) may be responsible for the lack of any effect of this compound. Thus, a combination of a mu antagonist with such nonselective NOPr agonists may reduce the rewarding effect of cocaine more strongly than the nonselective compounds administered alone. The potential of such an approach is highlighted in a recent report by Cordery and coworkers, who used a combination of low doses of buprenorphine (which has higher affinity for MOPr than NOPr) and naltrexone, a nonselective opioid receptor antagonist, that elicited neither CPP nor aversion but completely blocked cocaine-primed reinstatement of an extinguished CPP in rats.[80]

Given the inhibitory effect of exogenous OFQ/N on cocaine-induced elevation of dopamine in the NAc and on the expression and acquisition of cocaine CPP, it is possible that selective small-molecule NOP agonists may decrease the rewarding effects of cocaine in these paradigms. Indeed, we found that AT-202, a selective NOP agonist which has a much higher affinity and selectivity for the NOPr over MOPr compared to buprenorphine, blocked drug- and stress-induced reinstatement of extinguished CPP in ICR mice.[81] However, AT-202 did not reduce the acquisition of cocaine CPP in these mice,[81] raising the possibility that following repeated administration of these drugs, for example, during the acquisition phase of CPP, as opposed to one time application of these compounds, that is, prior to reinstatement of CPP, the mu-mediated effect of these compounds may interfere with their NOPr-mediated actions, thereby leading to lack of a significant effect of these drugs on the development of cocaine CPP. Clearly, further studies with newer and more selective small-molecule NOPr agonists are warranted to establish the potential of NOPr agonism as an approach to treat cocaine (and possibly other psychostimulant) addiction.

3. MOLECULAR MECHANISMS OF COCAINE ADDICTION

Chronic cocaine use causes neuroadaptive changes along a number of brain circuits, leading to uncontrollable drug-taking and drug-seeking behaviors. However, there is no FDA-approved pharmacotherapy to treat cocaine addiction. The lack of approved treatment may be due to the fact that different neurochemicals contribute to different stages of cocaine addiction. The mesolimbic dopaminergic neurons and the corticolimbic glutamatergic neurons have been implicated in the initiation and maintenance of addictive behaviors to cocaine and other addictive drugs, respectively.[55,82–91] Furthermore, the endogenous opioid system has been implicated in cocaine addiction although the role of each opioid peptide and its receptor is distinct. For example, activation of the μ- and δ-opioid receptors is known to be proaddictive while stimulation of the κ-opioid receptor appears antiaddictive.[77,92–110] Recent evidence suggests that the dynorphin/κ-opioid receptor system may also mediate the negative-affective states associated with drug withdrawal.[93,111–117] Stress and anxiety have been reported to be among the leading causes of craving, relapse, and compulsive cocaine use and abuse.[114,118–128] Therefore, a drug that reduces anxiety and has antistress and antiopioid effects on the brain, decreases cocaine-mediated elevation of dopamine in the NAc, and

attenuates neuronal plasticity mediated by glutamate would have a broader spectrum of activity to reduce cocaine reward and reinforcement, and be a more effective pharmacotherapeutic agent to treat cocaine addiction. A growing body of literature suggests that OFQ/N possesses all of the previously mentioned characteristics (for review see Refs [5,35]) and the OFQ/N–NOPr system may be a potential target for medication development to treat cocaine addiction. The possible mechanism(s) through which OFQ/N could reduce the rewarding and addictive actions of cocaine have been discussed later in the chapter.

3.1 OFQ/N Alters the Positive Reinforcing Action of Cocaine

The primary mechanism of action of cocaine is to block the dopamine transporter[129–131] and elevate extracellular dopamine in the NAc.[132] The cocaine-elevated extracellular dopamine in the NAc is thought to mediate the motor stimulatory, rewarding, and motivational effects of cocaine. A number of studies using pharmacologic tools[130,131,133–135] or neurotoxins to cause lesion of the dopaminergic neurons[133,136–138] showed that dopamine plays an important role in the motor-stimulatory action of cocaine. The observation that mice lacking the dopamine transporter were hyperactive compared to their wild-type counterparts and that cocaine-induced hyperlocomotion was blunted in these mice, confirms that the site of action of cocaine to induce its motor-stimulatory action is the dopamine transporter. Interestingly, OFQ/N has been shown to decrease cocaine-elevated extracellular dopamine in the NAc and also reduce the motor-stimulatory action of cocaine.[47] Although a causal relationship has not been established between the two effects, they appeared to correlate with each other. The rise in extracellular dopamine in the NAc is also thought to mediate the acute pleasurable effects of cocaine as well as is proposed to be important in the initiation of cocaine addiction.[132] However, recent evidence suggests that dopamine may be involved in drug "wanting" than "liking."[139] Dopamine is also implicated in long-term potentiation (LTP) in the hippocampus and amygdala,[3,140–142] error prediction and aversion.[143–147] Nevertheless, dopamine-deficient mice exhibit a robust aversive response following administration of a κ-opioid receptor agonist,[148] raising concern about the importance of dopamine in the aversive effect of kappa agonists. Similarly, the role of dopamine in the rewarding and addictive actions of cocaine has been debated. For example, mice lacking the dopamine transporter and their wild-type controls exhibit a comparable cocaine-induced CPP, showing that cocaine retains its rewarding action in mice lacking the

dopamine transporter.[149] Similarly, cocaine was able to induce CPP in dopamine-deficient mice although the response was attenuated in dopamine-deficient mice compared to their wild-type controls. Nevertheless, cocaine CPP was blunted in wild-type mice treated with SCH-23390, a dopamine D1 receptor antagonist, suggesting that dopamine D1 receptor activation is necessary for the CPP response in wild-type mice.[150] Additionally, neither dopamine transporter knockout nor dopamine-deficient mice have been tested in the CPP paradigm following a single conditioning with cocaine, a measure of acute rewarding action of cocaine.[72,151] As an example, we have shown that the rewarding action of acute morphine was blunted in mice lacking the pituitary adenylyl cyclase activating polypeptide (PACAP) compared to their wild-type controls. However, following repeated conditioning, a comparable morphine-induced CPP was observed in mice of the two genotypes.[152] Thus, it is possible that dopamine is still important in the acute rewarding action of cocaine but the CPP paradigm used is unable to capture that. Clearly, in the orthodox CPP paradigm, where repeated conditioning is used, other mechanisms become engaged in the rewarding actions of cocaine, as we observed regarding the role of PACAP in morphine-induced CPP.[152] Indeed, Sora and coworkers used mice lacking not only the dopamine transporter but also the serotonin transporter and their wild-type controls and discovered that cocaine was no longer able to induce CPP in these mice, suggesting that in the absence of the dopamine transporter, the serotonin transporter compensates and, therefore, the absence of both transporters was necessary for the abolishment of the rewarding action of cocaine.[153] Thus, drugs that target both transporters, such as some of the currently used antidepressants with dual inhibitory action on dopamine and serotonin transporters may also be potential candidates to treat cocaine addiction.

The dopamine system has been implicated in the early phases of cocaine addiction, as shown in preclinical studies.[154–156] However, as stated earlier, targeting only the dopamine system has not been a fruitful approach to treat cocaine addiction since dopamine may be involved in the initiation phase of addiction. The OFQ/N–NOPr system, on the other hand, is an attractive target for medication development to treat cocaine addiction because OFQ/N has been shown to alter the activity of the mesolimbic dopaminergic neurons and the effect of addictive drugs on extracellular dopamine in the NAc[26,47,48,157] via a broader effect on multiple neurotransmitter systems involved in drug reward. As discussed later in the chapter, the beneficial effects of OFQ/N on cocaine reward do not appear to be solely due to its

ability to reduce extracellular dopamine in the NAc. OFQ/N has other actions that make it a unique peptide with the potential to reduce the rewarding and addictive actions of cocaine and other addictive drugs. Interestingly, OFQ/N has also been shown to alter the activity of serotonergic neurons.[33,158–163] Notably, OFQ/N may be devoid of any rewarding or aversive effects, as injection of OFQ/N into the lateral ventricles failed to induce CPP or aversion[43] although the same treatment reduced basal motor activity.[66] Thus, the OFQ/N–NOPr system may be a potentially better target to develop pharmacotherapy for cocaine addiction without inducing aversion. This also has a potential advantage for treatment of substance abuse in general, since OFQ/N has also been shown to reduce the rewarding action of other addictive drugs.[164–167] However, further research is needed to define the underlying mechanism of OFQ/N's action in reducing the rewarding action of cocaine and other addictive drugs. OFQ/N not only affects the dopamine and serotonin systems but also other mechanisms that could contribute to its antiaddictive properties. One such mechanism is the ability of OFQ/N to regulate the action of endogenous opioid peptides to exert its antirewarding actions (see below).

3.2 OFQ/N as an Antiopioid Peptide in the Brain to Reduce Actions of Cocaine

The endogenous opioid system has long been known as a major regulator of the mesolimbic dopaminergic neuronal activity. In particular, beta-endorphin and enkephalins have been shown to increase the activity of the mesolimbic dopaminergic neurons and stimulate the release of dopamine in the NAc.[94,100] The endogenous opioid system has also been implicated in the rewarding and addictive actions of cocaine and other addictive drugs. For example, naloxone, a nonselective opioid receptor antagonist, has been shown to reduce the motor stimulatory and rewarding actions of cocaine.[101] Similar observations have been reported using selective μ-opioid receptor antagonists[168] and antisense oligonucleotides against the μ-opioid receptor,[103] suggesting that cocaine may exert some of its action via the endogenous opioid system. The observation that beta-endorphin induces reward[4] and that it has higher affinity for the mu compared to the δ- and κ-opioid receptors prompted us to hypothesize that cocaine may exert its effects via the release of beta-endorphin. Indeed, using microdialysis in freely moving rats, Olive and coworkers showed that the level of beta-endorphin increases following systemic administration of cocaine.[169] Later studies showed that the increase in the level of beta-endorphin is also observed in animals

engaged in cocaine self-administration[170–172] as well as in the incubation of cocaine-seeking behaviors.[173] Using the CPP paradigm as an animal model of reward,[51] we demonstrated that beta-endorphin may be involved in the rewarding action of acute cocaine, as mice lacking beta-endorphin exhibited blunted CPP compared to their wild-type littermates/controls.[151,174] Changes in the level of opioid peptides and their mRNA have also been reported following chronic cocaine treatment.[175–181] Given that OFQ/N is considered an antiopioid peptide in the brain[25,182] and that it regulates the activity of beta-endorphin-containing neurons in the hypothalamic arcuate nucleus,[30] which provide opioidergic inputs to the VTA and NAc,[183,184] we propose that OFQ/N may exert some of its inhibitory action on cocaine reward by blocking the action of beta-endorphin. Interestingly, we have observed that the rewarding action of acute cocaine was enhanced in mice lacking NOPr,[72] which is opposite of what is observed in mice lacking beta-endorphin, that is, reduced rewarding action of acute cocaine.[151] The two peptides (beta-endorphin and OFQ/N) exert opposite effects on the mesolimbic dopaminergic neurons causing, respectively, an increase[185] or decrease[26] in extracellular accumbal dopamine. Further investigation is needed to examine if OFQ/N exerts its action on cocaine reward via blocking the effect of endogenous opioid peptide(s), which may yield other potential targets and approaches to treat opioid and other forms of addiction.

3.3 OFQ/N as an Antistress Peptide in the Brain

Stress is known to increase the risk of drug use, abuse, and relapse (for review see Ref. [186]). Indeed, a positive correlation has been reported between negative-affective life events and drug abuse. For example, child abuse in the form of sexual or physical abuse has been linked to an earlier onset of substance use and abuse and other forms of mental illnesses.[187–190] In such individuals, a heightened responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis may be induced by chronic stress or drug use, resulting in a greater sensitivity of these individuals to the reinforcing properties of drugs of abuse, thereby contributing to compulsive drug use (for review see Refs [114,191]). The acquisition of cocaine self-administration has been facilitated by different forms of stress, such as isolation[192] or social defeat[123] (for reviews see Refs [114,120–122,191,193]).

The initial step in activation of the HPA axis is the release of corticotropin-releasing hormone (CRH) or corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus. Interestingly, CRH

is one of the major neuropeptides that play a prominent role in the development of addiction by inducing negative-affective states, such as anxiety and reward deficit via an action in the amygdala (for a review see Ref. [194]). Interestingly, OFQ/N has been shown to act as an antistress peptide and a physiologic CRF antagonist in the amygdala.[31,35,195] OFQ/N has been shown to reduce stress-mediated reinstatement of alcohol- (but not that of cocaine-) seeking behaviors.[67] Furthermore, AT-202, a small-molecule NOPr agonist has been shown to reduce stress-induced reinstatement of cocaine-induced CPP in mice.[81]

The negative reinforcing actions of cocaine also contribute to the maintenance of cocaine addiction. Indeed, the theory of the "dark side of addiction" suggests that occasional drug use leads to neuroadaptive changes along numerous neuronal circuits, in particular the mesolimbic dopaminergic neurons, the corticolimbic glutamatergic neurons, the stress and fear circuits involving CRH, dynorphin, and other peptides, leading to negative-affective states. For example, research in the past decade has shown that the level of CRH and dynorphin is altered following repeated cocaine administration, making the drug users experience negative-affective states in the absence of the drug, and forcing them to compulsively seek and take cocaine to reduce dysphoria, anxiety, and depression elicited by drug withdrawal. Thus, drugs that reduce these negative-affective states that develop following drug withdrawal may be useful to treat addiction to cocaine and other addictive drugs. It is important to note that OFQ/N has been shown to possess anti-CRF properties.[31,196,197] OFQ/N has also been shown to exert anxiolytic effects in a number of animal models of anxiety. For example, low concentration of OFQ/N as well as small-molecule NOPr agonists elicited anxiolytic effects in rats.[34,196–199] Consistent with these observations, mice lacking NOPr exhibit greater anxiety-like phenotype compared to their wild-type control in the elevated plus maze test.[200] Thus, activation of the OFQ/N–NOPr system has the potential to reduce negative-affective states following cocaine withdrawal and reduce craving, and this may be an additional mechanism through which small-molecule NOPr agonists may exert their beneficial effects on actions of cocaine and other addictive drugs. Interestingly, OFQ/N has been found to exert greater anxiolytic effects in animals with prior alcohol experience compared to their alcohol-naive controls.[201] However, in the same study, OFQ/N failed to reduce anxiety in alcohol-naive rats.[201] Thus, further studies are needed to determine if

OFQ/N would exert an anxiolytic effect in subjects with prior cocaine experience. This is particularly important because there are some reports showing that OFQ/N could be anxiogenic under certain experimental conditions.[196,197] Nevertheless, these studies highlight another potentially advantageous molecular mechanism and pharmacologic profile of NOPr agonists as drug addiction pharmacotherapy.

3.4 OFQ/N Alters Glutamate-Mediated Neuronal Plasticity

Earlier studies showed that glutamate neurotransmission is involved in behavioral changes observed following repeated cocaine administration. For example, Karler *et al.* showed that MK-801 (dizocilpine), which blocks the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors, reduced cocaine sensitization.[202] Neurotransmission at the excitatory synapses through the release of glutamate is now implicated in a number of neuropsychiatric disorders, including drug addiction.[85,203,204] In particular, neuronal plastic changes have been shown to occur in the NAc core following cocaine withdrawal. For example, calcium permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor accumulates in the NAc, and mediates the intensified cue-induced craving following withdrawal from long-access cocaine self-administration.[205] Additionally, glutamate may mediate the effect of neutral environmental stimuli that gain saliency once they are associated with drug administration and can serve as cues in the absence of the drug to elicit craving. Indeed, previous studies have shown that relapse to drug-seeking behavior occurs following exposure to drug-related cues and the motivation to self-administer drugs of abuse increases over the course of abstinence.[206–211] One of the major problems in the pharmacotherapy of drug addiction is the high frequency of relapse.[212,213] However, if the drug is unavailable (cue but no drug) during this critical period, these repeated cue-no-drug associations could lead to a decrease in the strength of the conditioned response or consolidation of new memory, thereby resulting in extinction of the conditioned response.

Research has shown that the level of basal glutamate is reduced in the NAc following repeated cocaine administration, raising the possibility that the activity of glutamate transporters is altered following cocaine treatment.[214] Indeed, the expression of glutamate transporter 1 is decreased in animals that underwent withdrawal, leading to increased glutamatergic neurotransmission in this brain region.[215] Therefore, drugs that reduce glutamatergic neurotransmission in this brain region may have potential to reduce

cue-induced cocaine-seeking behaviors. Interestingly, Li and Markou have recently proposed that a viable approach to reduce glutamatergic neurotransmission is via activation of the metabotropic glutamate 7 receptors (mGluR7), which are located presynaptically.[216] These authors showed that systemic or local administration of an allosteric modulator of mGluR7, AMN082, into the NAc reduced cocaine self-administration and cue-induced cocaine-seeking behaviors.[216] Administration of an mGluR1 receptor allosteric modulator is another useful approach since this treatment has been shown to reduce the accumulation of calcium permeable AMPA receptors in the NAc that occur following cocaine withdrawal.[217,218] These studies show that a drug that can reduce glutamate release or reverse neuronal adaptive changes induced by repeated cocaine administration may have potential to reduce cocaine-seeking behaviors. Interestingly, OFQ/N has been shown to reduce potassium-evoked glutamate release in cortical slices.[29] OFQ/N has also been shown to reverse cocaine-induced behavioral sensitization.[56] The glutamate system has been implicated in mnemonic processes and OFQ/N exerts inhibitory effects on learning and memory and these mnemonic effects of OFQ/N may involve the NMDA receptor.[219–223] Thus, this may be another mechanism through which OFQ/N and related NOPr agonists reduce the rewarding and addictive actions of cocaine and other addictive drugs (see later in the chapter). However, studies are needed to assess whether OFQ/N can affect changes in glutamate neurotransmission in the NAc that occur in response to cocaine treatment and withdrawal.

3.5 Mnemonic Effects of OFQ/N and Cocaine Addiction

The transition from occasional drug use to compulsive drug intake or abuse involves instrumental and classical conditioning processes (for reviews see Refs [63,82,91,224,225]). Thus, when administration of cocaine or another drug of abuse is repeatedly associated with a distinct environment, the context serves as a cue and this cue-drug association can elicit positive subjective feelings even in the absence of the drug. Once this conditioned response is acquired and consolidated, it can last for months and even years, due to its persistent nature.[226] The reason for this may be that compulsive drug taking can further lead to overlearning and "automatic" compulsive behavior (for reviews see Refs [91,224,226]). Importantly, subsequent exposure to the same surroundings, even in the absence of drugs, brings up old memories in abstinent addicts, thereby leading to drug-seeking behaviors and relapse.[63,224,225,227,228]

A growing body of evidence suggests that OFQ/N and other NOPr agonists impair learning and memory. The first electrophysiologic study by Yu and coworkers showed that bath application of OFQ/N reduced LTP in the CA1 region of the hippocampus.[229] Subsequently, these authors demonstrated a similar inhibitory effect of OFQ/N in the dentate gyrus.[223] Behavioral studies also demonstrated that local injection of OFQ/N in the CA3 region of the hippocampus caused memory impairment in the water maze test.[230,231] This effect of OFQ/N was mediated via NOPr because it was blocked by UFP-101, a NOPr antagonist.[230] Exogenous OFQ/N has also been shown to reduce learning and memory in the passive avoidance and contextual fear tests.[219,232–234] The inhibitory effect of OFQ/N on mnemonic processes has been replicated using small-molecule NOPr agonists, as Ro64-6198 reduced contextual but not cued fear learning in C57BL/6N mice.[219] Considering that behavioral sensitization and place preference each involves conditioned learning, that is, association between subjective effects of addictive drugs and contextual cues, that LTP and other forms of neuronal plasticity, such as long-term depression (LTD), are the basis of memory formation, and that OFQ/N reduces LTP[223,229] and impairs spatial and other forms of memory,[231,235,236] it is possible that OFQ/N may selectively reduce the learning and remembrance of reward-related behaviors because OFQ/N failed to reduce naloxone-induced conditioned place aversion.[44] However, as stated earlier, OFQ/N has been shown to regulate potassium-evoked glutamate release in cortical slices,[29] suggesting that OFQ/N may exert its effects on the rewarding and addictive actions of cocaine via more than regulation of learning and memory in the hippocampus. Further studies are definitely needed to assess the impact of OFQ/N, locally injected into the hippocampal regions compared to its administration in the lateral ventricles, on the rewarding and addictive effects of cocaine.

Not only the exogenous but also endogenous OFQ/N regulates mnemonic processes, as mice lacking NOPr exhibit enhanced memory.[221,233,235,236] Additionally, these mice have also been reported to show heightened cocaine-induced CPP[72] and behavioral sensitization,[73] raising the possibility that the amplified response observed in NOPr knockout mice was due to enhanced memory in these mice. However, morphine-induced CPP[72] and amphetamine-induced locomotor sensitization[73] were comparable between mice lacking NOPr and their wild-type littermates/controls. Thus, further studies are needed to delineate the exact mechanisms of regulatory action of endogenous OFQ/N on process of memory, as related to drug reward.

3.6 The OFQ/N–NOPr System and Gene Expression

A number of studies have shown that epigenetic mechanisms play an important role in the development and maintenance of addictive behaviors. It has been well documented that the effect of addictive drugs, contextual cues, and other environmental stimuli are translated through gene expression/repression and involve chromatin remodeling.[237] Chromatin is made of DNA tightly wrapped around by a protein called histone. Different forms of histone proteins exist, such as H2A, H2B, H3, and H4. Chemical modifications of the N-terminus of histones make the DNA sequence accessible or inaccessible for translation. Acetylation of histones is shown to increase gene expression.[238] On the other hand, deacetylation or methylation (but not in all cases) of histone proteins leads to tight wrapping of DNA around the histone protein and unavailability of the DNA sequence for translation.[239]

An overwhelming body of evidence suggests that drugs of abuse increase or decrease plasticity at different synapses and induce structural and behavioral changes through epigenetic mechanisms in different brain areas (for reviews see Refs [237,240]). Chronic cocaine treatment, for example, has been shown to increase histone (H3) acetylation of cyclin-dependent kinase 5 (CDK5) and brain-derived neurotrophic factor (BDNF) at their promoters.[241] Interestingly, inhibitors of histone deacetylase 5 (HDAC5), an enzyme responsible for deacetylation of histone proteins has been shown to enhance the rewarding action of cocaine,[241] suggesting that HDAC5-derived genes are involved in the rewarding actions of cocaine. Indeed, cocaine has been shown to alter the activity of HDAC5 in the NAc. Additionally, overexpression of HDAC5 in the NAc has been shown to reduce the rewarding action of cocaine.[242] HDAC has also been implicated in the reinstatement process, as an HDAC inhibitor has been shown to reduce reinstatement of cocaine-induced CPP.[243] However, the role of HDAC5 in cocaine self-administration is not yet clear (for a review see Ref. [240]).

While there is a great deal of interest in epigenetic mechanisms, a survey of the literature revealed only a single report, which studied the effect of cocaine on gene expression at the promoter regions of OFQ/N and NOPr.[6] The authors of this study showed that continuous subcutaneous cocaine infusion reduced pOFQ/N gene expression in the NAc and lateral, but not medial, caudate. Concomitantly, they showed increased NOPr gene expression in the NAc and reduced expression in the lateral,

but not medial, caudate. These changes were associated with methylation of tyrosine 4 and 27 of H3 protein.[6] However, further studies are needed to delineate the effect of cocaine on expression of genes encoding for OFQ/N and NOPr, because the previously mentioned study utilized subcutaneous cocaine infusion, which does not mimic cocaine regimens of cocaine addicts. In addition, further studies are needed to understand the role of endogenous OFQ/N on gene expression induced by cocaine treatment. Similarly, the effect of exogenous OFQ/N on cocaine-induced gene expression needs to be studied. OFQ/N reduces the level of phosphorylated CREB (pCREB, cAMP response element-binding protein), a transcriptional factor involved in gene expression. We propose that OFQ/N may possibly alter chromatin remodeling via reducing the level of pCREB. Interestingly, mice lacking the CREB-binding protein showed reduced cocaine-induced locomotor activity and attenuated locomotor sensitization.[244] Given that OFQ/N not only blocked the development of behavioral sensitization but also reversed its time course, we hypothesize that exogenous OFQ/N would also reverse chromatin remodeling induced by repeated cocaine treatment. Future studies are thus needed to enhance our understanding of the role of endogenous OFQ/N and the effect of exogenous OFQ/N on changes in chromatin remodeling induced by cocaine treatment.

4. CONCLUSIONS

Molecular targets of cocaine addiction involve a number of neurotransmitter and neuropeptide systems and therefore it is difficult, if not impossible, to treat this chronic and relapsing brain disorder. Drugs that affect more than one of these molecular targets and neurotransmitter systems may be useful to reduce the rewarding and addictive actions of cocaine. OFQ/N has been shown to possess antistress, anxiolytic, and antiopioid effects as well as to reduce the activity of dopaminergic and glutamatergic neurons. Thus, the OFQ/N–NOPr system is a promising target to develop medications to treat cocaine addiction. The development of nonpeptide small-molecule NOPr agonists and investigation of their efficacies on the various aspects of cocaine addiction will provide further validation of this approach for cocaine addiction treatment. Indeed, this approach has been proven useful for other drug addictions, as small-molecule NOPr agonists have been shown to reduce the rewarding action of morphine and alcohol

(Lutfy and Zaveri, unpublished data). We therefore expect that small-molecule NOPr agonists would also attenuate the rewarding and possibly addictive effects of cocaine.

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