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Targeting Endogenous Mu- and Delta-Opioid Receptor Systems for the Treatment of Drug Addiction

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Abstract

Drug addiction is a chronic, relapsing disorder that is characterized by a compulsion to take drug regardless of the adverse consequences that may ensue. Although the involvement of mesoaccumbal dopamine neurons in the initiation of drug abuse is well-established, neuroadaptations within the limbic cortical- striatopallidal circuit that occur as a consequence of repeated drug use are thought to lead to the behavioral dysregulation that characterizes addiction. Opioid receptors and their endogenous ligands are enriched in brain regions comprising this system and are, thus, strategically located to modulate neurotransmission therein. This article will review data suggesting an important role of mu-opioid receptor (MOPr) and delta opioid receptor (DOPr) systems in mediating the rewarding effects of several classes of abused drugs and that aberrant activity of these opioid systems may not only contribute to the behavioral dysregulation that characterizes addiction but to individual differences in addiction vulnerability.

Keywords

Opioid receptors; drug self-administration; enkephalin; endorphin; cocaine; ethanol; morphine

1. INTRODUCTION

Drug addiction is a chronic, relapsing disorder characterized by compulsive drug-seeking and taking despite the negative consequences that may ensue [1]. Regardless of their pharmacological class, all drugs of abuse increases the activity of dopamine (DA) neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (Acb). This pathway, a component of the mesocorticolimbic system, is implicated in mediating the rewarding effects of natural reinforcers (e.g. food, water) and salience attribution. Both pharmacological and gene ablation studies indicate that stimulation of DA transmission in the Acb is critical for the rewarding effects of drugs and the initiation of drug abuse [2].

The repeated administration of opiates, psychostimulants and ethanol produces neuroadaptations in the mesocorticolimbic system and other brain regions comprising the limbic cortical- striatopallidal circuit. Increasing evidence suggests that alterations in neurotransmission within this circuit lead to the compulsive drug seeking that characterizes addiction [3, 4]. Withdrawal from chronic opiate use is associated with decreased DA transmission in the prefrontal cortex (PFC) and Acb. These adaptations contribute to the aversive effects of withdrawal and to continued drug use. The PFC, orbitofrontal cortex and

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anterior cingulate regulate emotional responses, cognitive processes and executive function. Dysregulation of the prefrontal cortical–Acb pathway is thought to underlie, at least in part, the diminished cognitive control and enhanced responsiveness to drug-associated stimuli that characterizes addiction [5]. The dorsomedial PFC and amygdala and interactions of these regions with the Acb core have been implicated in the reinstatement of compulsive drug seeking produced by exposure to stimuli that have previously signaled drug administration whereas the dorsomedial PFC, Acb core and the VTA are important for compulsive drug seeking produced by drug re-exposure [6, 7]

Opioid receptors and their endogenous ligands are enriched in the limbic cortical-striatopallidal circuit where they modulate the activity of DA, glutamate, and GABA neurons. They are, thus, strategically located to modulate the behavioral and neurochemical effects of various drugs of abuse. The repeated use of various drugs of abuse is associated with time-dependent and region-specific changes in opioid receptor function, and expression. Alterations in opioid peptide expression and release are also seen. Recent studies suggest that dysregulation of endogenous opioid systems may contribute to individual differences in vulnerability to acquire addiction and that targeting these systems may be effective in the treatment of cocaine, alcohol and opiate addiction.

This review will summarize our current knowledge regarding the pharmacology and physiology of mu- and delta-systems and the contribution of these systems to the addiction process. The role of the dynorphin/.kappa opioid receptor system in the pathogenesis of addiction was the subject of a recent review and will not be discussed here [8].

2. PHARMACOLOGY OF OPIOID RECEPTOR SYSTEMS

The existence of receptors for opiate drugs was first proposed by Beckett and Casy [9] based on the structure-activity relationships of a series of synthetic opiates in tests of antinociception. High-affinity, stereospecific binding sites for opiate drugs were subsequently documented in brain in 1973 [10, 11]. Three years later, Martin and colleagues [12] provided the first definitive evidence that opioid receptors did not form a homogeneous population. The proposed receptor forms were named the μ-opioid receptor (MOPr) for morphine and the κ-opioid receptor (KOPr) for cine. Pharmacological studies of opioid peptide effects in mouse vas deferens led to the discovery of a third opioid receptor named the δ receptor (DOPr) [13]. Each of these receptors has been cloned and the recombinant receptors exhibit binding and functional characteristics consistent with endogenous receptors.

Opioid Receptor Subtypes

Differences in the *in vivo* pharmacology of DOPr agonists led to the hypothesis of distinct DOPr1 and DOPr2 subtypes [14]. However, no DOPr variants have been characterized and knockout of the DOPr gene eliminates binding of these agonists. Therefore, pharmacological diversity of DOPr likely results from interactions with different proteins (e.g., formation of heterooligomers with other GPCRs) or differential posttranslational modifications. Based on their differing pharmacology, it has been proposed that [D-Pen^2, D-Pen ^{5}] enkephalin (DPDPE), D-Ala^2, D-Leu ^{5}] enkephalin (DADLE), [D-Ala^2, D-Leu ^{5}] enkephalyl-Cys (DALCE), 6 -guanidinonaltrindole (6'-GNTI) and 7-benzylidenenaltrexone (BNTX) are DOPr1 ligands whereas [D-Ser^2, Leu5] enkephalyl-Thr (DSLET), [D-Ala2] deltorphin II, naltrindole 5'-isothiocyanate (5'-NTI and naltriben bind to DOPr2 [15]. Increasing evidence indicates that the DOPr1 receptor is a DOPr and KOPr heterooligomer [16, 17]. At present, the physiological relevance of this heterodimer is unclear. However, the finding that 6'-GNTI, which activates DOPr-KOPr heterodimers but not homomers, produces analgesia

when administered in the spinal cord, but not in the brain, suggests that this heterodimer is functional in the spinal cord [18].

Functional interactions between MOPr and DOPr were first observed by Vaught and Takemori [19], who reported potentiation of morphine-induced antinociception by a DOPr agonist. Subsequent studies indicate these functional interactions contribute to the development of morphine tolerance, dependence and sensitization [20–23]. Although MOPr and DOPr heterodimers have been reported in heterologous expression systems [24, 25], whether the *in vivo* synergy between MOPr and DOPr reflects a direct association between receptors, cell surface recruitment of intracellular DOPr or a circuit effect is unclear. Data regarding the effects of bivalent opioid ligands that contain MOPr agonist and DOPr antagonist pharmacophores have, however, provided initial evidence that MOPr and DOPr are not only physically associated *in vivo* but that their formation contributes to morphine tolerance and dependence [26]. Bivalent ligands separated by a 16 atom or longer spacer produced less dependence than either morphine or the monovalent MOPr pharmacophore. Furthermore, physical dependence and tolerance were suppressed with spacer lengths of 19 atoms or greater. These data suggest that a physical interaction between MOPr and DOPr modulates both tolerance and dependence. These bivalent ligands were also shown to lack conditioned reinforcing in place preference conditioning studies in mice suggesting a possible role of MOPr-DOPr complexes in the abuse liability of opiates [27].

Endogenous Opioid Peptides

Over 20 different endogenous opioid peptides, each of which exhibits differential affinity for the three opioid receptor types, have been identified [14, 15]. Except for nociception. orphanin FQ, all mammalian opioid peptides (except endomorphins) have an N-terminal enkephalin (ENK) sequence (Tyr-Gly-Gly-Phe-Met-Leu) and are derived from one of three precursors: proenkephalin (PENK), proopiomelancortin (POMC); prodynorphin (PDYN). Many contain a C-terminal extension which modulates receptor selectivity and susceptibility to proteases degradation. In the case of both PENK and PDYN, differential processing leads to multiple opioid peptides. The opioid peptides β-endorphin, methionine (met) ENK, leucine-ENK, and extended forms of met-ENK, including metorphamide and BAM-18, bind with high affinity to both MOPr and DOPr. Although DYN 1–17 and shorter truncated DYN peptides bind with high affinity to KOPr, they also bind to MOPr and DOPr. Thus, although opioid peptides may have higher affinity for one opioid receptor type, they typically bind to multiple opioid receptor types. Two putative endogenous opioid receptor ligands, endomorphin-1 and −2, that appear to produce their effects exclusively through the MOPr have been reported in brain [28]. However, no gene, precursor protein, or other mechanism for their endogenous synthesis has been identified. Selective ligands for each of the opioid receptor types have been synthesized (MOPr, DOPr: Table 1) and analysis of their effects has contributed greatly to our knowledge of the role of endogenous opioid receptor systems in addiction [29].

3. SUBSTRATES OF DRUG AND ALCOHOL ADDICTION

DA transmission within the Acb, a terminal projection area of VTA neurons, is essential for the attribution of motivational valence to reward related events [30, 31]. All drugs of abuse, regardless of their pharmacological class, increase extracellular DA levels in this region [32]. Both pharmacological and neurochemical studies have shown that this action underlies the rewarding effects of these agents [2, 33]. Cocaine increases extracellular DA concentrations by binding to and inhibiting dopamine transporters located at the nerve terminal. Amphetamines inhibit uptake and promote DA efflux whereas ethanol and opiates such as morphine increase DA release.

Drug addiction is a chronic, relapsing disorder characterized by compulsion to take drug despite the adverse consequences that may ensue [1]. Repeated drug use typically results in the development of tolerance to their pharmacological effects. Tolerance to the rewarding effects of drugs is one factor that may lead to the escalation of drug use that occurs in human addicts. The abrupt cessation of drug use generally leads to the emergence of affective (e.g., dysphoria, anxiety, anhedonia) and somatic withdrawal signs [34]. These consequences of drug use are implicated in the escalation and the reinstatement of drug use that occurs during the early phase of drug abstinence. The repeated intermittent administration of various drugs of abuse can also result in an enhancement of their behavioral effects. This phenomenon referred to as behavioral sensitization has been implicated in the reinstatement of compulsive drug use and the increased salience of cues that have signaled drug administration [35]. Increasing evidence, however, indicates that neuroadaptations within the limbic cortical–striatopallidal pathway that occur following repeated drug use underlie the more enduring changes in behavior that characterize addiction [3, 36, 37]. This circuit, which plays an important role in mood, incentive motivation and habit learning, consists of the prefrontal cortex (PFC: medial, orbital, and cingulate), VTA, substantia nigra (SN), dorsal striatum, core and shell divisions of the Acb, as well as the hippocampus, amygdala, and ventral pal-lidum [38–41].

Projections to the VTA arise from the Acb and ventral pallidum [42, 43]. Projections from the Acb shell are restricted to the VTA whereas those from the core extend through much of the SN pars compacta. VTA DA neurons project to the Acb and medial PFC. DA neurons originating in the SN innervate the dorsal striatum [44]. Cross-talk between these regions is provided by glutamatergic neurons originating in the PFC as well as by axons and axon collaterals of Acb and striatal medium spiny neurons [45]. There are also reciprocal connections between specific parts of the Acb shell and core [46]. Output from the shell can influence the function of DA projections to the core, which in turn affect the activity of dorsal striatal neurons *via* projections to the SN. In the striatum, cortical glutamatergic neurons and inputs from GABAergic and midbrain DA neurons converge onto dendritic spines of medium spiny neurons [47]. Medium spiny neurons in both the striatum and Acb release GABA. One class of medium spiny neurons contains ENK and the D2 class of DA receptors [48, 49]. The other class contains DYN and predominately expresses the D1 DA receptor. In contrast to DYN-containing neurons that project directly to the SN and VTA to synapse on DA cells, the ENK pathway is indirect.

Repeated drug use produces marked alterations in mesoaccumbal DA neurotransmission. Basal DA uptake is increased in the Acb core during the early phase of abstinence [49–51]. By contrast, the ability of cocaine to inhibit DA uptake in either the shell or core, and hence, increase DA levels is decreased [52]. These alterations in DA ‘set-point’ have been implicated in the “crash” that characterizes cocaine withdrawal. Similar changes in DA dynamics are observed in experimental animals during the early phase of abstinence from alcohol and opiates and are thought to contribute to the affective component of withdrawal [53–55]. As abstinence proceeds, basal DA dynamics normalize and the ability of drugs of abuse to increase Acb DA levels is enhanced [52, 56]. The time course of this enhancement parallels the sensitized behavioral response to drugs of abuse that occurs as abstinence progresses indicating an important role of the mesoaccumbal DA projection in mediating alterations in behavior that occur following prolonged abstinence. Importantly, however, whereas DA receptor blockade in the Acb core prevents the reinstatement of heroin self-administration, it does not affect cocaine seeking suggesting a differential involvement of DA in mediating the compulsive drug-seeking produced by these agents [57–59].

Dysregulation of glutamate transmission is implicated in the expression of behavioral sensitization to various drugs of abuse and cellular adaptations within the prefrontal-Acb

pathway are thought to contribute to the diminished cognitive control and hyper-responsiveness to drug-associated stimuli that characterize addiction [60]. Glutamatergic projections from the prefrontal cortex to the Acb core are necessary for the expression of cocaine- and heroin-seeking behavior [61–62]. Furthermore, human imaging studies have shown that the anterior cingulate cortex, the human homolog to the prelimbic cortex in rats [63], and the Acb are activated in response to cues associated with drug taking [64–67].

Finally, an involvement of dorsal striatal DA neurons in the pathogenesis of compulsive drug seeking has been suggested. Using second order schedules of reinforcement to distinguish drug-taking from drug-seeking, it has been shown that DA input to this region is critical for cue-evoked drug-seeking in animals with an extended history of cocaine self-administration [68]. These findings and those indicating distinct roles of the dorsomedial and dorsolateral striatum in goal-directed versus habit learning [69, 70] have led to the hypothesis that with repeated drug use, there is a transition from prefrontal cortical to striatal control over responding and from ventral to dorsal striatal sub-regions. As a consequence, drug use which was initially goal-directed becomes habitual and the motivational valence of other stimuli is reduced [71].

4. LOCALIZATION OF MOPR AND DOPR SYSTEMS IN THE LIMBIC-CORTICAL-STRIATOPALLIDAL PATHWAY

Opioid Receptors

MOPr and DOPr are enriched in brain regions comprising the limbic cortical–striatopallidal pathway, and, as such, are strategically located to modulate the effects of various drugs of abuse [72–75].

Dense MOPr binding is observed in the prefrontal and cingulate cortex. In the cingulate, the highest density of MOPr is found in Layer I, a major site of glutamatergic thalamocortical afferents. Using lesioning techniques, Vogt *et al.* have provided evidence that MOPr are both presynaptic and postsynaptic [76]. MOPr are expressed on cingulate afferent axons as well as by neurons that project primarily to the cortex and to a lesser extent to the caudate. MOPr immunoreactive cells are scattered predominantly in layers 2 and 3 of the frontal, parietal, temporal and occipital cortex. Some labeling is observed in layers 5 and 6 and may represent a subpopulation of cortical interneurons.

Modest DOPr staining is seen throughout layers II and V of the cingulate with intense labeling of pyramidal cells in the outer portion of layer V. Excitotoxic lesions that destroy anterior cingulate neurons significantly reduce DPDPE binding indicating that DOPr are expressed by cortical neurons [76]. The density of DOPr binding sites is high in layers II-III and V-VI of the cerebral cortex.

In the caudate-putamen, MOPr-like immunoreactivity is localized in densely-stained fiber patches and in the subcal-losal streak, a region of the caudate-putamen immediately medial to the corpus callosum. These striatal patches have a rostral-caudal gradient, with a larger number of patches seen in the rostral caudate-putamen. In addition to receptor patches, scattered fibers are seen in the matrix compartment. Prominent DOPr immunoreactivity is observed in the caudate putamen. Staining is more marked dorsolaterally than ventro medially and mainly consists of modestly labeled medium spiny neurons as well as a few large diameter neurons [73].

Both MOPr immunoreactive perikarya and fibers are observed in the Acb. The majority of immunostaining is localized in clusters of cells and fibers found predominantly in the shell compartment. Within this subregion, the highest density of receptor-like staining is seen in

fiber clusters along the ventral edge, the lateral border and the medial and dorsal septal pole region. Scattered among the clusters are numerous medium spiny neurons that are MOPr immunoreactive. DOPr labeling is observed primarily on axon terminals in the Acb shell where it is associated with discrete segments of the plasma membrane and membranes of small synaptic and large dense core vesicles [77]. Approximately 40 % of DOPr labeled profiles are either apposed to dopamine transporter immunoreactive terminals or contain the dopamine transporter. The majority of these appear to be axon terminals and small axons. Thus, DOPr is strategically positioned to directly modulate DA release, postsynaptic responses in spiny neurons that receive DA input and to control presynaptic release of other neurotransmitters in this region.

The large cells of the ventral pallidum show dense MOPr receptor-like immunoreactivity. These perikarya are terminated upon by a dense network of immunoreactive fibers. Dense staining is seen in the axons of the stria terminalis, a major neuronal pathway containing reciprocal projections between the amygdala and the bed nucleus of the stria terminalis. Medial and lateral subdivision of the bed nucleus of the stria terminalis also show a moderate to high density of MOPr receptor-like immunostaining. In contrast to MOPr, only moderate DOPr staining is observed in the stria terminalis.

MOPr staining is dense in the intercalated nuclei of the amygdala and the posteriomedial cortical amygdala. However, immunoreactive fibers are scarce in the lateral and basolateral nuclei. Immunoreactivity is also observed in the medial and basomedial nuclei of the amygdala, where immunoreactive fibers are detected. Rostral-caudal differences are seen in the medial nucleus of the amygdala, with denser staining observed caudally. In the central nucleus, immunoreactive fibers occur in both the lateral and medial subdivisions, with denser staining in the centromedial nucleus.

In both the SN pars compacta and pars reticulata, MOPr -like immunoreactivity is localized in fine varicosities and punctate fibers, suggestive of localization on terminals. Staining is denser in the pars compacta.. The rostral VTA has only light staining, with comparatively few immunoreactive fibers. More caudally, there is a high frequency of densely-labeled fibers but few immunoreactive perikarya. Staining is also seen in the interpeduncular nucleus, with dense fiber staining in the rostral, central and lateral subdivisions. Moderate to intense DOPr labeled cells are observed in the substantia nigra as well as in the VTA.

Opioid Peptides

The POMC system arises from neuronal perikarya in the arcuate region of the mediobasal hypothalamus and to a lesser extent from the nucleus tractus solitarius. Nerve fibers and terminals with β-END imunoreactivity are observed in heterogeneous brain regions, including the amygdala, VTA, Acb and other areas involved in reward processes [78]. Neurons containing PENK-derived peptides are found in areas reported to have high concentrations of opioid receptors such as the amygdaloid complex, Acb, globus pallidus, bed nucleus of the stria terminalis and VTA [79, 80]. High concentrations are also observed in the cingulate cortex. Interestingly ENK is expressed in both GABAergic and glutamatergic cells and appears to be primarily involved in modulating the presynaptic release of these neurotransmitters [79, 81].

5. OPIOID MODULATION OF THE LIMBIC CORTI-CAL-STRIATOPALLIDAL PATHWAY

Cortex

In vivo studies assessing the influence of MOPr and DOPr agonists on neurotransmitter release in cortical regions are limited. In contrast to other DA terminal regions, systemically administered MOPr agonists do not alter extracellular DA concentrations in the PFC [82]. However, acute administration of morphine has been shown to decrease glutamate overflow in the anterior cingulate [83]. Consistent with this finding acute MOPr activation attenuates excitatory neurotransmission in the anterior cingulate as well as the medial PFC [84, 85]. Decreased glutamatergic excitatory synaptic transmission in response to MOPr or DOPr agonists is also observed in rat neocortical neurons; an effect resulting from presynaptic inhibition of glutamate release [86].

VTA/Acb

The abuse liability of drugs has been linked to an enhancement of extracellular DA concentrations in the Acb. Consistent with the rewarding effects of MOPr agonists (see below), their acute administration increases extracellular Acb DA concentrations. Increased DA is observed in response to the systemic administration of MOPr agonists, and following intracerebroventricular (ICV) administration of β-END [32, 87, 88]. Increases are also observed in response to intra-VTA, but not intra-Acb, MOPr agonists, indicating a critical role of VTA opioid receptors in the DA releasing effects of MOPr agonists. The MOPr – evoked increase in DA has attributed to disinhibition of GABA neurons and an increase in the burst firing of DA neurons projecting to the Acb [89].

In contrast to MOPr agonists, systemic administration of a DOPr agonist does not reliably increase Acb DA concentrations [90]. These data are surprising in view of the DA-dependent effects of these agents in behavioral studies and findings that peptidergic DOPr agonists increase DA overflow following their ICV or intra-Acb perfusion [87, 91]. Whether the lack of effect of systemically administered agonists is due to the opposing effects of DOPr activation in other regions innervating the Acb or to DOPr subtype is unclear and warrants additional study.

Using receptor specific opioid receptor antagonists, the existence of a tonically active VTA MOPr system that stimulates DA release in the Acb has been obtained [92]. Thus, intra-VTA perfusion of a MOPr antagonist increases Acb DA overflow whereas blockade of either DOPr or KOPr in this region is without effect. These findings are noteworthy in that they suggest that the activity of VTA MOPr systems is necessary for the maintenance of basal mesoaccumbal DA transmission.

VTA glutamate synaptic input plays a key role in regulating DA cell excitability. However, relatively few studies have examined the role of MOPr and DOPr in modulating glutamate transmission in this region. Although an electrophysiological study in slices showed that acute MOPr activation inhibits glutamate EPSCs in DA cells in the VTA, neurochemical studies assessing glutamate release are lacking. Interestingly, recent microdialysis studies indicate a tonically active DOPr system in the VTA that inhibits basal glutamate in this region [93].

Dorsal Striatum

DOPr activation increases DA release and glutamate overflow in the dorsal striatum [94–96]. Decortication prevents the increase in both neurotransmitters and also decreases striatal DOPr binding sites. These findings are noteworthy in view of previous data showing that

DA release elicited by a DOPr agonist is unaltered by lesions that destroy striatal cell bodies [97] but it is prevented by NMDA receptor blockade [98]. Together, they indicate that DOPR activation increases glutamate release from corticostriatal terminals and this action triggers an increase in striatal DA release. DOPr antagonists do not alter basal glutamate or DA overflow indicating lack of a tonically active DOPr system that regulates the basal activity of DA and glutamatergic neurons projecting to this region [99].

Amygdala

The central nucleus of the amygdala plays an important role in stimulus-reward learning. Using whole-cell voltage-clamp recordings, Zhu and Pan [100] have shown that MOPr, but not DOPr, are present on presynaptic glutamatergic terminals in central amygdala and their activation reduces the probability of glutamate release. MOPr are also expressed postsynaptically on central amygdala neurons and their activation inhibits neuronal activity [101]. Since efferent projections from this region are predominantly GABAergic [102], their activation would inhibit neurons in the projection targets and, presumably, reduce stimulus-reward learning. Synthetic DOPr agonists or endogenously released opioid peptides in the central amygdala, by inhibiting glutamate release, may facilitate stimulus-reward learning. The basolateral amygdala provides extensive input to the central amygdala. A recent study has shown that presynaptic MOPr primarily attenuates GABAergic synaptic inputs to central amygdala projecting neurons in the basolateral amygdala [103].

Ventral Pallidum

The ventral pallidum provides a major output for limbic and basal ganglia. It receives GABA and neuropeptide input from the Acb, glutamatergic input from the medial PFC and basolateral nucleus of the amygdala [104] as well as DA input from the SN and VTA [105]. Systemically administered MOPr agonists hyperpolarize ventral pallidal neurons *in vitro* and suppress spontaneous firing *in vivo*. A similar effect is observed in response to iontophoresis of a DOPr agonist [106]. Studies examining the role of ventral pallidal MOPr in modulating pallidal responses to afferent stimulation have provided evidence that MOPr activation enhances the "signal-to-noise" relationship of VP responses to activation of glutamatergic inputs from the PFC and amygdala. By contrast, the same activation attenuates slow excitatory responses to substance P and GABA-induced inhibition that result from Acb activation [107]. These results suggest that a consequence of opioid transmission in the VP is to attenuate the influence of midbrain DA and Acb GABA input while potentiating the efficacy of cortical and amygdaloid glutamate input. These actions may diminish the influence of reward (VTA, Acb) on cognition (PFC) and affect (amygdala) which in turn may contribute to drug craving that occurs even in the absence of reward.

EFFECTS OF MOPR AND DOPR LIGANDS

The rewarding effects of morphine and other MOPr agonists are well documented. These agents are self-administered by humans and experimental animals and produce conditioned rewarding effects. Conditioned reward is also produced by the ICV administration of β-END and DOPr agonists indicating that activation of either MOPr or DOPr produces rewarding effects [108]. Microinjection studies indicate a critical role of mesoaccumbal opioid receptors in mediating these effects. Met ENK or a metabolically stable analog is self-administered into both the Acb and VTA and MOPr agonists produce conditioned place preferences when infused into the VTA but not other regions [109–111]. DOPr agonists or an enkephalinase inhibitor produces conditioned place preferences when injected into the VTA or Acb of rats [112, 113]. Manipulations that decrease mesoaccumbal DA transmission attenuate the conditioned response to MOPr agonists suggesting a critical role of DA neurons projecting to the Acb in mediating these effects [108].

Endogenous opioid systems appear necessary for 'hedonic homeostasis' (e.g., regulation of basal affective state). Systemic administration of the opioid receptor antagonists, naloxone and naltrexone, produce dysphoria in humans [114] and conditioned aversive effects in animals [115]. Several lines of evidence suggest the specific involvement of MOPr opioid systems. Thus, conditioned place aversions are produced by MOPr but not DOPr antagonists [116–118]. Furthermore, naloxone is not aversive in MOPr knock out mice [119]. Interestingly naloxone failed to induce aversive effects in PENK knockout mice but retained this ability in **[**β-END deficient animals indicating a critical role of ENK in hedonic homeostasis [120].

Infusion of MOPr antagonists into the VTA, Acb and ventral pallidum, but not other regions, is sufficient to produce conditioned aversive effects. Together, these data indicate an important role of MOPr in these regions in the maintenance of hedonic homeostasis and the incentive motivational effects of MOPr agonists [121, 122].

Both genetic and pharmacological studies indicate a role of DOPr in the regulation of anxiety and depression [123–125]. DOPr knockout mice display increases in anxiety and depressive-like behaviors in animal models. Anxiogenic effects of naltrindole have been reported whereas a DOPr agonist reduces anxiety [124]. These findings are noteworthy since withdrawal from various drugs of abuse is associated with anxiety and depression and, as will become apparent, repeated use of opiates, ethanol and psychostimulants leads to marked alterations in the DOPr/ENK systems.

7. MODULATION OF MOPR AND DOPR SYSTEMS BY DRUGS OF ABUSE

Opiates

Opioid Gene Expression/Peptide Release—Chronic morphine administration down-regulates hypothalamic POMC, the precursor of β-END [126]. In contrast, chronic opioid receptor antagonist administration increases POMC expression consistent with auto-regulation of the POMC system by endogenous opiate peptide(s).

To date, studies of opiate regulation of PENK gene expression have focused on the Acb and dorsal striatum. PENK expression is unaltered following acute morphine administration. Most studies have reported no alteration in PENK expression in response to morphine treatment regimens that produce physical dependence. However, PENK mRNA is reduced in the Acb for at least 3 days following repeated, injections of moderate doses of morphine that produce behavioral sensitization [127]. Decreased PENK expression is also observed in the caudate, putamen, as well as the core and shell regions of the Acb of human heroin users [128]. Interpretation of changes in gene expression is difficult in the absence of measures of release. However, the results obtained in experimental animals and humans indicate that repeated opiate use is associated with persistent changes in the activity of ENK neurons.

Only three studies haves assessed opiate-evoked changes in ENK release. Using *in vivo* microdialysis in conjunction with place preference conditioning, Nieto *et al.* [129] showed that extracellular concentrations of Met-ENK increase in the Acb following placement of rats in an environment previously paired with doses of morphine that produce conditioned rewarding effects. Although, the unconditioned effects of acute morphine administration were not assessed, these data provide suggestive evidence that ENK release may contribute to the expression of the conditioned rewarding effects of MOPr agonists and/or reward expectation. The ventral pallidum receives dense ENK innervation from the Acb [130] and is implicated in reward related behavior. ENK release in the pallidum is enhanced in response to systemic administration of morphine or its direct perfusion into this region [131, 132]. Such findings demonstrate that acute MOPr activation increases ENK transmission

and that activation of pallidal MOPr is sufficient for this effect. Interestingly, analysis of the association between *PENK* polymorphisms and heroin abuse in human addicts revealed that heroin abuse was significantly associated with *PENK* polymorphic 3' UTR dinucleotide repeats [128]. Of individuals homozygous for the 79-bp allele, ca. 79.4% were heroin abusers. Such findings, together with those in experimental animals suggest a link between opiate addiction and the ENK system.

Opioid Receptors—A significant association between heroin abuse and an A118G single nucleotide polymorphism of the MOPr gene has been observed in European Caucasians [133]. Postmortem analysis revealed that ca. 90% of 118G allelic carriers were heroin users. Whereas down-regulation of PENK was evident in all heroin users, the effects were greater in 118G subjects and were most prominent in the Acb shell. In contrast to the pooled heroin population, levels of a PENK-derived peptide were significantly reduced in heroin abusers carrying the 118G allele. Evidence that the A118G SNP directly influences the expression of MOR, at both the mRNA and protein levels has been obtained [134]. In view of the postulated role of both the Acb and PENK-derived peptides systems in reward processing, these findings may suggest that there is greater dysregulation of reward processing in individuals with this allele and that this dysregulation contributes to enhanced opiate abuse vulnerability.

Psychostimulants

Opioid Peptide Gene Expression/ Release—Repeated binge presentation of cocaine increases hypothalamic POMC expression [135]. This increase, however, is transient and only observed after the first injections of cocaine. DA reduces POMC mRNA levels in primary cell cultures of rat hypothalamus [136]. Thus, the transient reduction in POMC mRNA levels after acute 'binge' cocaine administration is likely due to cocaine-evoked increases in DA and the development of rapid tolerance to this effect.

Acute administration of amphetamine or cocaine increases extracellular β-END concentrations in the Acb [137]. Cocaine self-administration also produces a DA-dependent increase in β-END overflow as does placement of rats in the self-administration chamber even though no drug is forthcoming [138]. Therefore, release of β-END in the Acb may be one neuronal event that contributes the incentive motivational effects produced by cocaine and exposure to drug-associated cues. Consistent with this hypothesis, the conditioned rewarding effects of cocaine are reduced in mice lacking β-END [139].

Most studies have reported no effect of repeated cocaine administration on PENK expression [140, 141]. When however, the duration of cocaine self-administration is increased and an extinction period is interposed between cocaine administration sessions, region-dependent alterations in PENK mRNA levels are observed. PENK mRNA concentrations are elevated in the Acb and striatum of self-administering animals and remains elevated for at least 10 days following the extinction of cocaine administration [142]. In contrast, PENK mRNA concentrations in the amygdala are reduced in animals with a history of contingent but not non-contingent drug administration. The central amygdala receives dense DA input from the VTA. In view of brain-imaging studies suggesting a role for the amygdala in cocaine craving [143] the observed changes in this region may be linked to drug craving and relapse to addiction.

Opiate Receptor—Repeated injection of cocaine [144, 145] increases MOPr density in terminal fields of the nigrostriatal and mesocorticolimbic neurons. Binding density is also increased in the cingulate cortex, basolateral amygdala and caudate putamen [144]. Using positron emission tomography, upregulation of MOPr binding potential (indicative of

decreased endogenous ligand or increased receptor density) has been found in several subregions of the frontal cortex of cocaine-dependent individuals during 1–4 weeks of abstinence. Importantly upregulation is positively correlated with craving intensity [146].

Data regarding the influence of repeated psychostimulant administration on DOPr are conflicting and may be due to the existence of DOPr subtypes. Although repeated cocaine administration does not affect DOPr1 agonist binding, binge cocaine administration decreases the density of DOPr1/2 antagonist binding sites [147]. Such findings provide suggestive evidence that DOPr1 is down-regulated by cocaine. Consistent with this hypothesis, functional DOPr down-regulation has recently been reported [148].

Alcohol

Opioid Peptide Gene Expression / Release—Daily voluntary ethanol consumption increases hypothalamic β-END and POMC mRNA content in C57BL/6 mice [149]. In contrast, POMC expression is initially decreased following a seven week daily cycle of ethanol consumption and withdrawal [150]. However, following prolonged withdrawal, POMC expression is increased. β-END produces rewarding effects in various animal models. Therefore, decreased basal POMC activity (and release) may lead to increased consumption of ethanol in an attempt to normalize opioid activity. Consistent with this hypothesis, mice expressing low basal levels of this peptide (50% of normal) drink more ethanol than wild-types [151].

Microdialysis studies have shown that acute ethanol administration increases β-END overflow in the Acb and amygdala [152, 153]. In view of the rewarding effects of β-END, an increase in its release may serve to enhance further bouts of ethanol consumption. Increased β-END in the central amygdala may facilitate ethanol reinforcement *via* MOPr-mediated modulation of GABAergic and glutamatergic activity [103]. In this regard it should be noted that opioid and as well as GABA-A receptors in this region regulate operant responding for ethanol [154, 155]. Whether peptide release is decreased during ethanol withdrawal and this deficit contributes to the reinstatement of compulsive ethanol seeking behavior is unknown.

Acute injection of moderate doses of ethanol induces a rapid elevation of PENK expression in the Acb that persists for several hours (156, 157]. Increased PENK expression is also observed in the caudate-putamen, central, mPFC and amygdala, as well as several hypothalamic nuclei [157]. In contrast, PENK expression in the VTA is transiently decreased. The elevation of gene expression may be a consequence of increased release of endogenous ligand since striatal tissue levels of Met ENK as well as overflow of this peptide in the Acb are increased following doses of ethanol comparable with those used in gene expression studies. Given the behavioral data discussed below, these findings indicate that region specific alterations in the synthesis and release of ENK may not only represent a key event in ethanol reinforcement but contribute to certain behavioral consequence of repeated alcohol use.

Opioid Receptors—Data regarding the effects of acute ethanol administration on MOPr density are contradictory. Upregulation in the Acb shell and basolateral amygdala has been reported after acute injection of a moderate dose (2.0 g/kg) of ethanol [158]. However, reduced VTA MOPr levels and an increase in the PFC have also been described [159]. Using a chronic ethanol regimen that result in physical dependence, Turchan *et al.* [147] have shown decreased MOPr density in the Acb within 3 hrs after cessation of ethanol exposure an effect that persists for 96 hrs thereafter. Decreased MOPr immunoreactivity is also observed in the Acb, cortex, and striatum [160]. In contrast to MOPr, chronic ethanol

administration does not alter DOPr ligand binding or immunoreactivity in the Acb or other limbic regions [147, 158, 160].

Various laboratories have examined the role of MOPr polymorphisms in human alcoholics with both positive and negative results having been reported. Few studies have examined DOPr polymorphisms in relation to alcoholism. However, examination of two coding variants of the DOPr, G80T and T921C, in alcohol-dependent Taiwanese Hans and heroin- and alcohol-dependent Caucasians found no evidence for an association [161, 162].

8. INFLUENCE OF MOPR AND DOPR LIGANDS ON THE BEHAVIORAL EFFECTS OF DRUGS OF ABUSE OPIATES

Not surprisingly, MOPr antagonists attenuate morphine and heroin self-administration. Microinjections studies suggest an involvement of MOPr in the caudal but not rostral Acb in this effect [163].

Increasing evidence suggests an important role of DOPr in mediating the rewarding effects of MOPr agonists. Tonic inhibition of DOPr2 by a long-lasting antagonist attenuates the reinforcing effects of heroin without influencing its anti-nociceptive effects [164]. The dose-effect curve was shifted to the right and downward, consistent with a noncompetitive mechanism of action. The differential effect of DOPr2 antagonists on self-administration and antinociception is noteworthy in that it indicates that it may be possible to develop agents that are effective analgesics with low abuse liability. A recent study has shown that that morphine place conditioning is attenuated in DOPr knock out mice or in wildtype mice pretreated with the DOPr1/2 antagonist, naltrindole [23]. Such findings suggest an important role of DOPr in the conditioned reinforcing effects of morphine. DOPr1/2 or DOPr1 blockade also attenuates sensitization to the conditioned rewarding effects of morphine suggesting that DOPr recruitment contributes to the enhanced conditioned responses to morphine that develop as a consequence of its repeated, intermittent administration [165].

An involvement of DOPr in the development of morphine dependence has also been demonstrated. DOPr 1/2 antagonism prevents the expression of the affective component of withdrawal in rats [166]. Furthermore, DOPr1 or DOPr2 antagonists suppress somatic signs of withdrawal [167]. Suppression of antinociceptive tolerance has also been demonstrated [22]. As discussed earlier, the mechanisms underlying the *in vivo* synergy of MOPr and DOPr are unknown. The efficacy of DOPr antagonists in preventing the behavioral effects of repeated MOPr agonist administration may result from the formation of MOPr-DOPr heterodimers or recruitment of DOPr from vesicles to the plasma membrane. Regardless of the mechanism, these data suggest that the development of mixed MOPr agonist-DOPr antagonist drugs may result in potent analgesics with reduced potential for tolerance and which lack abuse liability.

Psychostimulants

Infusion of naltrexone into the VTA but not into the Acb, medial PFC, caudate, or amygdala attenuates intravenous cocaine self-administration in the rat suggesting VTA opioid receptors modulate the reinforcing efficacy of cocaine [168]. Repeated administration of naltrexone has also been shown to produce a progressive attenuation of the reinstatement of cocaine-seeking produced by a priming injection of cocaine [169]. These data suggest that opioid receptor blockade may be effective in the treatment of stimulant addiction. Consistent with this hypothesis, naltrexone administration significantly attenuated the subjective effects produced by dexam-phetamine in dependent patients and blocks craving for this drug [170]. Furthermore, a recent placebo controlled trial showed reduced risk of relapse in naltrexone-treated individuals [171].

Preclinical studies suggest that MOPr blockade may be critical for the naltrexone psychostimulant interaction. Infusion of a MOPr antagonist into either the Acb or ventral pallidum did not alter the rewarding effects of cocaine as assessed using a fixed ratio-1 schedule of reinforcement. However, MOPr blockade in these regions attenuated responding maintained on a progressive ratio schedule [172]. Furthermore, infusion of a selective MOPr antagonist into the ventral pallidum prevented the reinstatement of cocaine-self administration whereas MOPr activation reinstated this behavior [173].

MOPr antagonists modulate the conditioned rewarding effects of cocaine. MOPr antagonist infusion into the Acb core or rostral VTA, but not the caudal VTA, striatum or medial Acb shell, attenuates the development of cocaine-induced place preference. In contrast, antagonist infusion into the Acb shell but not the core attenuates the expression of the conditioned response [174].

Literature concerning the involvement of DOPr in the reinforcing effects of cocaine is equivocal. Although one study reported that a DOPr1/2 antagonist or a DOPr2 antagonist, attenuate place conditioning produced by cocaine and amphetamine [175]. others have reported no effect [13, 109]. Similarly naltrindole has been reported to have no effect, to attenuate cocaine self-administration without affecting other behaviors or to produce non-selective reductions in cocaine self-administration [176–178]. These results suggest that DOPr antagonists are unlikely to be useful as a treatment for cocaine addiction.

Withdrawal from various drugs of abuse is associated with anxiety and depressive-like states. These effects are thought to contribute to the reinstatement of compulsive drug use. As discussed previously, the density and function of DOPr is decreased in brain regions that subserve incentive motivation and decreased DOPr function produces anxietylike behavior in the rat. A recent study in rats has shown that systemic administration of the DOPr agonist, SNC-80, reverses the anxiety behavior produced by withdrawal from repeated cocaine administration. Furthermore, this treatment attenuates depressive-like behavior observed in the forced swim test [124]. These findings suggest that targeting DOPr may be effective in preventing relapse during the early phase of abstinence from psychostimulants.

Ethanol

Numerous laboratories have provided evidence that ethanol reinforcement and high alcohol drinking is mediated, at least in part, by a neurobiological mechanism involving ethanol-induced activation of the endogenous opioid system [179–181]. This activation may in turn enhance the hedonic value and the reinforcing properties of ethanol.

The systemic administration of non-selective opioid receptor antagonists decreases both operant self-administration of ethanol and voluntary ethanol consumption [179–183]. Based on these studies and the efficacy of opioid receptor antagonists in attenuating the reinstatement of alcohol seeking in animal models, naltrexone is now an approved drug for the treatment of alcoholism. Microinjections studies suggest an important role of mesoaccumbal and amygdala opioid receptors in mediating the interaction of opioid receptor antagonists with ethanol. Infusion of opioid receptor antagonists at the level of either the Acb or VTA attenuate voluntary ethanol drinking or bar pressing for ethanol but not for water [184, 185]. In addition, microinjection of an opioid receptor antagonist at the level of the central amygdala decreases operant ethanol self-administration [184].

Naltrexone reduces the efficacy of stimuli previously paired with ethanol administration to reinstate extinguished responding for ethanol in rodents and has been shown to reduce the urge to drink elicited by alcohol cues in human alcoholics [186, 187]. Studies in rodents have shown that the MOPr antagonist, naloxonazine, inhibits cue-evoked ethanol-seeking

indicating that MOPr blockade is sufficient for this effect [188]. Evidence that selective MOPr blockade suppresses ethanol self-administration in both alcohol-prefering and Wistar rats has also been obtained [189].

The role of DOPr in ethanol self-administration and reinstatement of ethanol seeking behavior remain unclear. The DOPr2, antagonist, naltriben, has been shown to decrease ethanol drinking in both free choice and operant self-administration paradigms [190, 191]. Decreases in ethanol consumption after administration of the DOPr1/2 antagonist, naltrindole, have been reported [183, 189]. However, other studies found no effect of this compound on ethanol self-administration [192, 193]. Naltrindole was also shown to attenuate ethanol seeking evoked by cues previously associated with its administration but this effect was associated with some behavioral suppression [188]. Importantly, in this and several other studies reporting positive effects of DOPr antagonists, the doses of antagonists tested were those shown to interact with MOPr and other neurotransmitter receptors [194–196]. Therefore, the data should be interpreted cautiously.

SUMMARY AND CONCLUSIONS

An increasing body of evidence suggests an involvement of MOPr and DOPr systems in drug addiction. Ethanol, cocaine, and D-amphetamine increase extracellular concentrations of β-END in the Acb. Extracellular concentrations of ENK are increased in response to the acute administration of morphine or ethanol. Behavioral studies suggest that region specific increases in the activity of these opioid peptide systems, enhances the rewarding effects of several drugs of abuse, thereby, increasing motivation to take drug.

The repeated administration of opiates, psychostimulants and ethanol produces marked, time-related alterations in opioid peptide gene expression and opioid receptor function. Accumulating data suggest that these neuroadaptations contribute to compulsive drug seeking and relapse to addiction. Animal models have shown that naltrexone or naloxone attenuates the reinstatement of compulsive drug seeking behavior produced by morphine, cocaine, and ethanol in rodent models. Furthermore, naltrexone attenuates craving in alcoholics and in amphetamine dependent individuals. Data regarding the effects of opioid receptor antagonists on drug self-administration suggest that targeting endogenous opioid peptides systems may be effective in the treatment of drug and alcohol addiction. However, additional studies are still necessary to identify the opioid receptor subtypes mediating these effects.

Importantly, the last decade has brought new insights as to the potential contribution of DOPr to MOPr function, and, to drug addiction. Pharmacological data not only suggest the existence of MOPr-DOPr heteroligomers *in vivo* but that their formation contributes to the development of opiate tolerance and dependence. The efficacy of DOPr2 antagonists in attenuating both sensitization to the conditioned rewarding effects of morphine and the expression of opiate dependence suggest that DOPr recruitment following the continued use of morphine may be another neuroadaptation that underlies the hedonic dysregulation that characterizes addiction. These findings and the documented functional interactions of MOPr and DOPr may not only offer new targets for the treatment of opiate and psychostimulant addiction, but provide an effective strategy for the development of opiate analgesics with reduced side effects.

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Table 1

Ligands for MOPr and DOPr

Receptor	Endogenous Peptides	Agonists	Selective Antagonist
MOPr	Endomorphins β-endorphin β-neoendorphin	*Selective:* DAMGO PL 017 *Synthetic Agonists* Morphine, fentanyl, sufentanyl	CTAP Naloxonazine β-funaltrexamine
DOPr	Leu-enkephalin Met-enkephalin Deltorphin Deltorphin I Deltorphin II	*DOPr1:* DPDPE, DADLE, DALCE *DOPr2:* [D-Ala^2]-deltorphin II DSLET SNC 80 TAN-67	*DOPr1*: BNTX *DOPr2:* Naltriben DOPr1/2: Naltrindole TIPPΨ ICI 174864 DALCE (irreversible) –