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Dynorphin and the Pathophysiology of Drug Addiction

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Abstract

Drug addiction is a chronic relapsing disease in which drug administration becomes the primary stimulus that drives behavior regardless of the adverse consequence that may ensue. As drug use becomes more compulsive, motivation for natural rewards that normally drive behavior decreases. The discontinuation of drug use is associated with somatic signs of withdrawal, dysphoria, anxiety and anhedonia. These consequences of drug use are thought to contribute to the maintenance of drug use and to the reinstatement of compulsive drug use that occurs during the early phase of abstinence. Even, however, after prolonged periods of abstinence, 80-90% of human addicts relapse to addiction suggesting that repeated drug use produces enduring changes in brain circuits that subserve incentive motivation and stimulus-response (habit) learning. A major goal of addiction research is the identification of the neural mechanisms by which drugs of abuse produce these effects. This article will review data showing that the dynorphin/ κ -opioid receptor system serves an essential function in opposing alterations in behavior and brain neurochemistry that occur as a consequence of repeated drug use and that aberrant activity of this system may not only contribute to the dysregulation of behavior that characterizes addiction but to individual differences in vulnerability to the pharmacological actions of cocaine and alcohol. We will provide evidence that the repeated administration of cocaine and alcohol up-regulates the dynorphin/ κ -opioid receptor system and that pharmacological treatments that target this system may prove effective in the treatment of drug addiction.

Keywords

dynorphin; kappa opioid receptor; glutamate; dopamine; drug and alcohol addiction

1. Introduction

Dynorphin A (1-17) (DYN), the endogenous ligand for the κ -opioid receptor (KOPr) is distributed throughout the brain and spinal cord. Although a role of DYN in the modulation of pain has long been recognized, increasing evidence indicates that the DYN/KOPr system may be an effective target for the treatment of drug addiction. The KOPr subtype is enriched in brain circuits that control mood and motivation. Its activation modulates the activity of dopaminergic and glutamatergic neurons located therein. KOPr and DYN are located in brain regions that subserve stimulus-response (habit) learning and that have been implicated in the compulsive drug-seeking behavior that characterize drug addiction. Cocaine and other drugs

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of abuse increase prodynorphin (PDYN) gene expression in these same brain regions. Studies using pharmacological and gene targeting techniques have provided evidence that dysregulation of DYN/KOPr systems may not only contribute to the anhedonia and depressive symptomology associated with drug dependence but to the drug-craving and drug-seeking that frequently occurs in the withdrawn addict. A link between this opioid system and individual differences in vulnerability to drug and alcohol addiction has also been suggested. This chapter will review the mechanisms by which DYN/KOPr systems modulate neurotransmission within several brain regions comprising the limbic cortical-striatopallidal circuit, and the relevance of these effects to alterations in behavior and brain chemistry that occur following the repeated use of cocaine and alcohol.

2. Physiology and Pharmacology of DYN/ KOPr Systems

DYN is the major posttranslational product of the PDYN gene and the presumed endogenous ligand for the KOPr (Chavkin et al., 1982; Corbett et al. 1982). Although DYN binds with highest affinity to KOPr, it binds with high affinity to μ - and δ - opioid receptors (MOPr; KOPr; Kosterlitz et al., 1989). Therefore, activation of multiple opioid receptor types may contribute to the effects of this peptide. Other posttranslational products of PDYN include the opioid peptide, DYN B, and biologically active cleavage products of DYN that lack the first amino acid essential for opioid receptor binding. The physiological and pathophysiological effects of these peptides will not be discussed.

To date, only one KOPr receptor type (KOPr-1: KOPr) has been cloned. Although pharmacological data indicate the existence of multiple KOPr receptor subtypes (KOPr-1, KOPr-2, KOPr-3) (Heyliger et al., 1999; Horan et al., 1993), a clear demonstration of KOPr heterogeneity has proved elusive. A recent study (Olianas et al., 2006) has shown that the prototypic KOPr-3 agonist, naloxonebenzoylhydrazine, is a partial agonist at the cloned μ - (MOPr), δ - (DOPr), and KOPr as well as an antagonist at opioid-like nociceptin receptors. Furthermore, the KOPr-2 subtype may, in fact, represent a DOPr and KOPr heterodimer whose localization is restricted to the spinal cord (Bhushan et al., 2004; Jordan and Devi, 1999).

A number of selective KOPr ligands have been synthesized. They include the arylacetamides, U69593 and U50488, as well as salvinorin A, a naturally occurring alkaloid found in the perennial herb *salvia divinorum* (Roth et al., 2002; Lahti et al., 1985; Von Voigtlander and Lewis, 1982). Selective KOPr-1 antagonists (e.g., nor-binaltorphimine; nor-BNI, 5'-guanidinonaltrindole, JDTC) are also available (Carroll et al., 2004; Jones and Portoghese, 2000; Portoghese et al., 1994). Regardless, however, of their structure, all currently available antagonists exert a long-lasting (= 3 week) blockade of KOPr (Metcalf and Coop, 2005).

A number of physiological functions have been ascribed to DYN/KOPr systems including antinociception, fluid homeostasis and modulation of the hypothalamic-pituitary axis (Bodnar and Klein, 2005). MOPr, DOPr and KOPr often subserve similar functions, with the notable exception that in contrast to MOPr or DOPr agonists, KOPr agonists are not self-administered (Tang and Collins, 1985). Rather, KOPr agonists function as negative reinforcers producing dysphoria in humans and aversive effects in experimental animals. (Mucha and Herz, 1985; Pfeiffer et al., 1985).

Place preference conditioning studies, which provide a measurement of the conditioned reinforcing effects of drugs in experimental animals, showed that the aversive effects of KOPr agonists are centrally mediated (Bals-Kubik et al., 1989). Conditioned place aversions are observed in response to the systemic administration of KOPr agonists as well as following their infusion into the ventral tegmental area (VTA), nucleus accumbens (NAc) or medial prefrontal cortex. These findings demonstrate that activation of KOPr in these regions is sufficient for the development of this effect (Bals-Kubik et al., 1993). Infusion of DA receptor antagonists

or the neurotoxin, 6-hydroxydopamine, into the NAc, but not the dorsal striatum, attenuates the conditioned response to systemically administered KOPr agonists suggesting that intact mesoaccumbal DA neurotransmission is necessary for the aversive effects of KOPr agonists (Shippenberg et al., 1993). Furthermore, the findings that KOPr agonists, in contrast to other drugs that produce rewarding effects, *decrease* mesoaccumbal DA neurotransmission suggest that a blunting of DA transmission underlies aversive and dysphoric effects of KOPr activation (Di Chiara and Imperato, 1988). Although the aversive effect of KOPr agonists are considered limiting factors in their therapeutic use, it is important to note that most studies have been conducted in drug naïve individuals. KOPr agonists fail to produce aversive effects in animals experiencing persistent pain (Shippenberg et al., 1988). Furthermore, the dose-response curve for the aversive effects of KOPr agonists is shifted to the right in individuals with a prior history of polysubstance abuse or those suffering from chronic pain (Pande et al., 1996; Walsh et al., 2001). Such findings are noteworthy in that they suggest that the effects of KOPr agonists and other psychoactive drugs may differ profoundly depending on the prior history of an individual.

3. Neural Substrates of Drug and Alcohol Addiction

Drug addiction is a chronically relapsing disorder characterized by compulsion to seek and take drug(s) regardless of the adverse consequences that may ensue (American Psychiatric Association, 1994). Addicts typically exhibit decreased motivation for natural rewards (e.g., food, water, sex) that normally drive behavior. The abrupt cessation of drug use leads to the emergence of both affective (e.g., dysphoria, anxiety, anhedonia, somatic) and somatic withdrawal signs (Gawin, 1991; Koob and LeMoal, 1997; review: Koob, 2005). The contribution of VTA DA neurons projecting to the NAc to the rewarding effects of psychostimulants and other stimuli is well documented (Ranaldi et al., 1999; Wise, 1998). Similarly, several lines of evidence suggest an important role of this DA system in the transition from casual drug use to abuse (review: Wise, 2004). However, the application of a systems approach to the study of addiction has provided new insights as to the role of brain regions comprising the limbic cortical-striatopallidal circuit in mediating the dysregulation of behavior that characterizes addiction (review: Everitt and Wolf, 2002).

DA afferents arising from the VTA are key elements of the limbic cortical-striatopallidal circuit, a neural circuit that has been implicated in the control of mood, incentive motivation and habit (stimulus-response) learning (Schultz 2002; Graybiel, 2005). Brain regions comprising this circuit include the prefrontal cortex (medial, orbital and cingulate), VTA, substantia nigra, dorsal striatum and NAc (core and shell) as well as the hippocampus, amygdala and ventral pallidum (Everitt and Robbins, 2005; Heimer and Van Hoesen, 2006). Projections to the VTA arise from both the NAc and ventral pallidum and exhibit a mediolateral topography (Groenewegen et al., 1993; Zahm and Heimer, 1993). Projections from the NAc shell are restricted to the VTA whereas those from the core occupy the lateral part of the VTA and also extend through much of the substantia nigra pars compacta. VTA DA neurons project to the NAc and medial prefrontal cortex whereas DA neurons arising in the substantia nigra innervate the dorsal striatum (Graybiel 1990). Cross-talk between these regions is mediated in part, by glutamatergic neurons originating in the prefrontal cortex that project to the VTA, NAc and substantia nigra as well as by axons and axon collaterals of medium spiny neurons in the striatum and NAc (Kalivas et al. 2005).

Reciprocal connections between specific parts of the shell and core of the NAC have been documented (Haber et al., 2000; van Dongen et al., 2005). Anatomical studies suggest that output from the NAc shell can influence the function of ascending DA projections to the core which in turn modulate the activity of dorsal striatal neurons via projections to the substantia nigra. Within the striatum, excitatory inputs from cortical glutamatergic neurons and modulatory inputs from GABAergic and midbrain DA neurons converge onto dendritic spines

of medium spiny neurons (Yung and Bolam, 2000) which express GABA, DYN and other neuropeptides. Medium spiny neurons in both the striatum and NAc can be classified into two types. Both release GABA. However, one class contains DYN and predominately expresses the D1 DA receptor whereas the other contains enkephalin and the D2 class of DA receptors (Gerfen et al., 1990; Graybiel, 1990). DYN containing neurons project directly project to the substantia nigra and VTA to synapse on DA cells whereas the enkephalin pathway to DA cells is indirect.

DA neurotransmission in the NAc is essential for the processing of behaviorally relevant stimuli and the attribution of motivational valence to reward related events (Robinson and Berridge, 1993; Schultz, 1998; Schultz, 2002). Psychostimulants and other drugs of abuse increase extracellular DA levels in the NAc (DiChiara and Imperato, 1988). Both pharmacological and neurochemical studies have shown that this action underlies the rewarding effects of these agents and the initiation of drug abuse (Di Chiara et al., 2004; Wise, 1998; Wise, 2004). Cocaine produces this effect at the level of the DA nerve terminal by binding to and inhibiting the dopamine transporter (DAT), a transmembrane protein that re-uptakes DA released into the extracellular space (Ritz et al., 1987). In contrast, ethanol and opiates such as morphine stimulate the firing of mesoaccumbal DA neurons in the VTA (Brodie et al., 1999; Matthews and German, 1984).

Repeated cocaine use alters mesoaccumbal DA neurotransmission. However, the magnitude and type of effect observed can vary depending upon the dose and frequency of drug administration, duration of abstinence and sub-region examined. Several laboratories have shown that basal DA uptake is increased in the NAc core during the early phase of abstinence from repeated cocaine (Ng et al., 1991; Mateo et al., 2005; Thompson et al., 2000). By contrast, the ability of an acute injection of cocaine to inhibit DA uptake in either the shell or core, and hence, increase NAc DA levels is typically decreased at this time point (Kalivas and Duffy, 1993; Segal and Kuczenski, 1992). Decreased basal and drug-evoked DA neurotransmission is also observed in laboratory animals during the early phase of abstinence from alcohol and opiates (Diana et al., 1993, 1996; Spanagel et al., 1994; Weiss et al., 1996; Zapata et al., 2006). Decreased basal DA neurotransmission is thought to contribute to the “crash” that characterizes cocaine withdrawal, the anhedonic effects associated with opiate withdrawal, and to the affective component of alcohol withdrawal. With sustained abstinence, basal DA dynamics normalize and the ability of acute exposure to several drugs of abuse to increase NAc DA levels is enhanced (Kalivas and Duffy, 1993; Heidbreder et al., 1996). The time course of this enhancement parallels the progressive increase in the locomotor activating effects of cocaine that occurs as abstinence progresses (Kalivas and Duffy, 1993; Heidbreder et al., 1996) indicating an important role of the mesoaccumbal DA projection in mediating the long-term expression of sensitization to the psychomotor stimulant effects of cocaine. Although self-administration studies (Morgan et al., 2006) have shown that sensitization develops to the rewarding effects of cocaine, whether this effect is also associated with similar alterations in presynaptic DA transmission has not been examined.

Modulation of DA release in the prefrontal cortex as well as the NAc appears to be a critical mechanism by which cocaine and other drugs of abuse gain control over behavioral output (Kalivas and Volkow, 2005). In addition, emerging evidence indicates that the prefrontal cortex (PFC), a region critical for working memory, is a final common pathway by which exposure to stress, cues previously associated with the drug, or drug itself can trigger relapse (Breiter et al., 1997; Capriles et al., 2003; McFarland et al., 2004; Rebec and Sun, 2005). Studies of the medial PFC have shown that the repeated administration of cocaine is associated with alterations in basal and cocaine-evoked DA dynamics (Chefer et al., 2000; Meiergard et al., 1997; Williams and Steketee, 2005). During the early phase of cocaine abstinence, basal DA uptake is increased and depolarization-evoked DA release is reduced. Furthermore, the ability

of an acute cocaine challenge to increase DA overflow is reduced. Decreases in extracellular DA levels and D2 receptor function in the prefrontal cortex are postulated to lead to the compulsive drug-seeking and reduced drive for natural rewards that characterizes addiction (Kalivas et al., 2005).

The ventral pallidum regulates motivated behaviors (Mogenson and Yang, 1991) and it appears to be involved in cocaine-mediated effects. For example, intra-ventral pallidal injections of cocaine are sufficient to induce place conditioning (Gong et al., 1996). Furthermore, dopamine deafferentation of the pallidum attenuates the conditioned rewarding effect of systemically administered cocaine (Gong et al., 1997). Neurochemical data indicating the possible involvement of the mesopallidal projection in mediating cocaine as well as ethanol self-administration has also been demonstrated (Melendez et al., 2004; Smith et al., 2003).

Data indicating an involvement of dorsal striatal DA neurons in the pathogenesis of compulsive drug seeking, once, established, has more recently been obtained. Studies in which second order schedules of reinforcement have been used to distinguish drug-taking from drug-seeking indicate that DA input to this region is critical for cue-evoked drug-seeking in animals with an extended history of cocaine self-administration (Ito et al; 2002; Vanderschuren et al., 2005). These findings are particularly noteworthy in view of the distinct roles of the dorsomedial and dorsolateral striatum in mediating goal-directed and habit (stimulus-response) learning, respectively (Packard and Knowlton, 2002; Yin et al., 2005). Furthermore, as discussed below, cocaine-induced alterations in PDYN expression are most marked in these striatal sectors. When viewed in the context of the circuitry of the prefrontal cortico-striatal loop, these findings and others suggest that with repeated drug use, there is a transition from prefrontal cortical to striatal control over responding and from ventral to dorsal striatal subregions. As a consequence, drug use which was initially goal-directed becomes habitual and the motivational valence of other stimuli is reduced (Robbins and Everitt, 1999).

Glutamatergic systems are another important neuronal substrate of behaviors induced by drugs of abuse. During the early phase of abstinence, both stress- and drug-induced reinstatement of cocaine seeking are associated with an elevation of extracellular glutamate levels in the NAc core (McFarland et al., 2004). Inactivation of the dorsal PFC blocks stress-induced glutamate release within the Acb core and inhibits stress-induced reinstatement of drug-seeking. These findings, and those regarding pharmacological inactivation of the central extended amygdala, have led to the hypothesis that stress (e.g., footshock) activates limbic circuitry, which in turn activates a VTA dopamine projection to the PFC. Activation of a glutamatergic projection from the PFC to the NAc also appears necessary for cocaine-primed reinstatement of drug-seeking behavior (McFarland et al., 2003). Other studies have shown that blockade of glutamate transmission to the NAc core prevents drug-seeking behavior in response to cocaine associated cues (Di Ciano and Everitt, 2001; 2004). Like DA, glutamate levels in the NAc core are reduced during the early phase of cocaine abstinence (Baker et al., 2003; McFarland et al., 2003). It has been hypothesized that this reduction, and the resultant decrease in the activity of metabotropic glutamate autoreceptors, underlies the increase in extracellular glutamate levels that is associated with the reinstatement of compulsive drug-seeking (Kalivas et al., 2005). According to current theories, this increase may not only lead to a strengthening of drug-seeking behavior, making it more compulsive, but also decrease responding for non-drug stimuli.

Studies using a second order schedule of reinforcement in animals with an extensive history of cocaine-seeking and taking suggest that glutamate as well as DA transmission in the dorsal striatum is essential for drug seeking behavior elicited by cocaine-associated stimuli (Vanderschuren et al., 2005). Thus, intra-striatal infusion of a DA receptor antagonist or a selective AMPA/kainate receptor antagonist decreased cue-controlled cocaine seeking. These

findings highlight the importance of aberrant DA and glutamate neurotransmission in the addiction process. As discussed below, KOPr are present on DA and glutamate neurons in prefrontal cortico-striatal loop. Furthermore, ultrastructural studies have revealed multiple sites for presynaptic modulation of DA and glutamate by DYN/KOPr systems.

4. Localization of DYN and KOPr in the limbic cortical-striatopallidal system

DYN and KOPr are highly expressed in the prefrontal-cortico-striatal loop. PDYN expressing neurons are present throughout the neocortex with highest expression in the medial PFC and anterior cingulate (Alvarez-Bolado et al., 1990; Hurd, 1996). DYN content is low in comparison to other regions. However, immunoreactive cell bodies are found in layers II, III, V and VI. Neurons in layer V are presumed to be corticofugal fibers that innervate the NAc and other subcortical regions.

KOPr protein and mRNA are distributed in cortical laminae (Mansour et al., 1996; Schmidt et al., 1994; Wevers et al., 1995). In the medial prefrontal cortex, the majority of KOPr immunoreactive profiles are axon terminals, axons and axonal varicosities. A smaller proportion of immunoreactivity is observed on dendritic shafts and spines as well as glial processes (Svingos and Colago, 2002). KOPr terminals form both asymmetric and symmetric synapses with the former predominating. Co-localization of KOPr and NMDA receptor immunoreactivity is observed in dendrites, somata and glial processes as well as in axon terminals forming excitatory-type synapses. These findings are noteworthy in that they indicate an involvement of KOPr as well as glutamate receptors in the presynaptic regulation of prefrontal cortical excitatory amino acid transmission.

DYN immunoreactive axon terminals are found in the NAc core and shell (Van Bockstale et al., 1995). Clusters of immunoreactive fibers that form symmetric junctions with unlabeled somata and dendrites are found throughout rostrocaudal levels of the NAc shell and core (Van Bockstale et al., 1994). Immunoreactive soma and dendrites in this region receive input from DYN immunoreactive terminals, suggestive of an autoreceptor function, as well as from unlabeled axon terminals. Like DYN, KOPr exhibits a patch-like distribution in the NAc. Staining is predominately seen in the shell in small axons and axon terminals. Labeling of dendritic spines and dendrites is moderate (Meshul and McGinty, 2000; Svingos et al., 1999). KOPr is present in large axon terminals that contain DYN or that form excitatory-type synapses. This distribution is consistent with the role of KOPr in transducing the actions of DYN and in the presynaptic modulation of excitatory transmission (see below). KOPr is also observed in postsynaptic spines and apposing astrocytes. The latter finding is of particular note in view of the role of glia in the regulation of glutamate uptake. The majority of KOPr labeling, however is found in small axons and terminals having the morphological features of DA containing processes. This localization is consistent with neurochemical data (Spanagel et al., 1992; Chefer et al., 2005) indicating that KOPr in this region regulate the activity of mesoaccumbal DA neurons. Importantly, ultrastructural studies have not only confirmed the presence of KOPr in tyrosine hydroxylase positive neurons but have shown that this opioid receptor is apposed to DAT in both small axons and axon terminals (Svingos et al., 2001). Such findings are noteworthy in view of evidence that synthetic KOPr agonists regulate extracellular DA levels in this region by decreasing DA release and increase the activity of DAT in this region (Thompson et al., 2000). The NAc provides substantial DYN-containing inputs to the ventral pallidum, and both DYN and KOPr are highly expressed in this pallidal region (Zhou et al., 2003).

The dorsal striatum contains a dense plexus of DYN-labeled cell bodies. PDYN gene expression, however, varies between different striatal regions. Basal expression is greatest in the NAc and ventral striatal sectors. It is lowest in dorsal and dorsolateral sectors that receive

input predominantly from the sensorimotor cortex (Willuhn et al., 2003). The caudate-putamen shows a high density of KOPr immunoreactive fibers ventrally and immediately dorsal to the anterior commissure (Mansour et al., 1996). Staining in the remainder of the dorsal striatum is light and primarily restricted to medial portions.

DYN-like immunoreactivity is also seen in varicose processes that are distributed throughout the VTA and substantia nigra pars reticulata (Pickel and Sesack, 1993). DYN-containing terminals in both regions form synapses on or apposed to tyrosine hydroxylase-labeled dendrites suggesting that this peptide is positioned to modulate mesoaccumbal, mesocortical as well as nigral-striatal DA transmission. DYN terminals that form asymmetric synapses, although less prevalent, are apparent in the VTA and substantia nigra suggesting that DYN modulates excitatory neurotransmission in both these regions. Fiber terminal staining for KOPr is light in both the VTA and substantia nigra pars reticulata. However, some perikarya staining is observed in the lateral and dorsal aspects of the pars reticulata. Together, these findings suggest that the DYN/KOPr system is strategically located to modulate DA and glutamatergic transmission within the prefrontal cortico-striatal loop.

5. Modulation of dopamine and glutamate transmission by KOPr ligands

Microdialysis studies have shown that the systemic administration of selective KOPr agonists decreases DA overflow in the NAc (Chefer et al., 2005; Di Chiara and Imperato, 1988). The intra-NAc infusion of a selective KOPr agonist decreases DA levels in this region whereas intra-VTA infusion is without effect (Chefer et al., 2005; Margolis et al., 2006; Spanagel et al., 1992). Evidence that inhibition of mesoaccumbal DA transmission and the resulting decrease in D1 receptor activation underlies the aversive effects of KOPr agonists has been obtained (Shippenberg and Herz, 1988; Shippenberg et al., 1991; 1993). Data indicating an important role of the KOPr located in the NAc in mediating this effect has been obtained.

The reduction in DA levels produced by KOPr agonists has been attributed to inhibition of DA release. Consistent with this hypothesis, in vitro studies have shown that KOPr activation inhibits electrically-evoked [³H] DA release in the NAc (Heijna et al., 1993; Yokoo et al., 1992). More recent evidence indicates that KOPr regulate of DA uptake. Using the technique of rotating disk electrode voltammetry to measure the rate of DA clearance in minced tissue, Thompson et al. (2000) found that systemic administration of the selective KOPr agonist, U69593, produces a dose-related, nor-binaltorphimine reversible, increase in DA uptake. Increased DA uptake in the NAc is also observed in response to in vitro addition of KOPr agonists indicating a direct effect in this brain region (Shippenberg and Chefer, unpublished observation). These findings suggest that acute KOPr activation decreases mesoaccumbal DA neurotransmission by two distinct mechanisms; inhibition of release and stimulation of uptake. The demonstration that KOPr are co-localized with, and apposed to, DAT in NAc nerve terminals provides an anatomical basis for this latter effect (Svingos et al., 2001). It is noteworthy that the effects of acute KOPr activation on DA uptake and release are functionally opposite to those produced by cocaine and other drugs of abuse, which reduce uptake. Autoradiographic studies have shown that DAT transporter density and the maximal velocity of transport are reduced for at least three days following the cessation of repeated KOPr agonist administration. (Collins et al., 2001; Thompson et al., 2000) suggesting that in contrast to acute KOPr activation, down-regulation of DAT may occur a consequence of repeated exposure to KOPr agonists.

Pharmacological or gene targeting techniques that inactivate KOPr have shown that endogenous KOPr systems regulate the basal activity of mesoaccumbal DA neurons (Chefer et al., 2005; Spanagel et al., 1992). Infusion of nor-binaltorphimine into the NAc increases DA levels in this brain region whereas its infusion into the VTA is without effect. Extracellular

DA levels in the NAc are elevated in mice lacking the gene encoding KOPr suggesting the presence of a tonically active KOPr system that inhibits DA neurotransmission in this region.

Systemic administration of KOPr agonists decreases dialysate DA levels in the dorsal striatum (Di Chiara and Imperato, 1988). A similar effect is observed in response to the intra-striatal perfusion of U50488 or DYN (You et al., 1999; Zhang et al., 2004). By contrast, DA levels are increased in response to local perfusion of nor-binaltorphimine. These findings are analogous to those in the NAc and indicate tonic inhibition of striatal DA neurons by KOPr in this region. Studies by You et al. (1999) are also consistent with the existence of a tonically active KOPr system within the substantia nigra reticulata that inhibits DA neurotransmission in both the reticulata and striatum. Thus, endogenous KOPr systems regulate the activity of DA neurons projecting to both the ventral and dorsal striatum.

Using whole cell recordings in the rat, Margolis et al (2006) recently showed that the selective activation of KOPr in the VTA inhibits VTA DA neurons projecting to the medial prefrontal cortex. In that same study, dual-probe microdialysis revealed a marked decrease in medial prefrontal cortical DA levels in response to intra-VTA KOPr agonist perfusion. Consistent with electrophysiological studies, DA levels in the NAc were not affected. VTA perfusion of a selective KOPr antagonist blocked the agonist-induced decrease in prefrontal cortical DA levels. However, it did not modify basal DA levels suggesting the absence of a tonically active VTA DYN/KOPr system. These findings demonstrate that specific subsets of VTA neurons can be independently modulated by KOPr agonists. Furthermore, they show that in contrast to the ventral and dorsal striatum, endogenous KOPr systems in the VTA and prefrontal cortex do not regulate basal DA transmission.

As was discussed, DYN and KOPr are abundant in presynaptic terminals that form asymmetric, presumably glutamatergic, contacts in many regions where their modulation of DA neurotransmission has been demonstrated. However, relatively few studies have examined KOPr modulation of glutamate transmission. In-vitro studies using striatal synaptosomes have shown that KOPr agonists produce a nor-binaltorphimine-reversible decrease in 4-aminopyridine-stimulated glutamate release (Hill and Brotchie, 1995). Similar effects are observed in substantia nigra slices suggesting that KOPr agonists inhibit glutamate transmission in both input and output regions of the basal ganglia (Maneuf et al., 1995; Rawls et al., 1999). Studies in synaptosomes revealed no effect of KOPr activation on the calcium-independent increase in striatal glutamate efflux evoked by the excitatory amino acid transporter blocker, 1-trans-pyrrolidine-2,4-dicarboxylic acid (trans-PDC). However, vivo microdialysis studies (Rawls and McGinty, 1997; McGinty et al., 1999) demonstrated a marked reduction of trans-PDC-evoked glutamate overflow in response to a KOPr agonist. Importantly, the effects of trans-PDC observed in vivo were calcium-dependent. To account for the differential effects observed in vivo and in vitro, McGinty and colleagues (Rawls and McGinty, 1997; McGinty et al., 1999) attributed the calcium dependency to a reversal of the transporter and increased glutamate stimulation of postsynaptic receptors on medium spiny projection neurons. Glutamate receptor activation in vivo would trans-synaptically increase activity in the cortical-striatopallidal circuit. Elimination of the trans-synaptic circuitry, as occurs in synaptosomal preparations would, abolish the calcium-dependent component of trans-PDC evoked glutamate efflux. Taken together, these data are consistent with the hypothesis that basal ganglia circuitry mediates the calcium-dependent effects of KOPr in vivo. Furthermore, the KOPr-evoked inhibition of calcium-dependent glutamate overflow observed both in vitro and in vivo suggest that KOPr functions as an inhibitory presynaptic heteroreceptor on striatal glutamatergic terminals.

In vivo studies have failed to observe an effect of KOPr ligands on basal dialysate glutamate levels in either the striatum or substantia nigra reticulata (You et al., 1999). This failure may

indicate a selective influence of KOPr on stimulated as compared to basal release. However, only a small component of glutamate overflow that is sampled in microdialysis studies is tetrodotoxin-dependent suggesting that it is independent of neuronal activity. Furthermore, several studies suggest an important contribution of both glia and transporter-mediated processes to basal dialysate levels. Therefore, the lack of effect in dialysate studies may be due to methodological limitations arising from rapid, transport mediated uptake of neuronally released glutamate and the sampling of a non-neuronal (e.g., glial) pool.

Only two studies have examined KOPr modulation of NAc glutamate transmission (Hjelmstad and Fields, 2001; Yuan et al., 1992). Recordings from the NAc shell revealed a dose-related and nor-binaltorphimine- reversible inhibition of glutamatergic excitatory postsynaptic currents in response to the synthetic KOPr agonist, U69593. An increase in the paired-pulse ratio as well as a decrease in the frequency of spontaneous miniature events were seen suggesting a presynaptic site of action. KOPr activation reduces Ca^{++} and increases K^{+} conductances, in other regions either of which would reduce the probability of neurotransmitter release (Gross and MacDonald, 1987; Grudt and Williams, 1993). Inhibition of glutamatergic neuronal activity has been observed in the NAc core. However, this effect was not reversed by an opioid receptor antagonist, raising questions as to its opioid receptor mediation (Yuan et al., 1992). Although, in vivo release studies are lacking, these data provide functional evidence that KOPr activation inhibits glutamate release.

Medium spiny neurons which contain GABA, DYN and other opioid peptides provide substantial input to the ventral pallidum as do glutamatergic neurons arising in the medial prefrontal cortex and basolateral nucleus of the amygdala (Chrobak and Napier, 1993; Zaborsky et al., 1985; Zahm et al., 1985). DA projections from the VTA and substantia nigra are also well-documented (Klitnick et al., 1991; Napier and Potter, 1989). Although KOPr are expressed in the pallidum (Mitrovic and Napier, 1995; Zhou et al., 2003), neurochemical studies assessing the effects of KOPr ligands are lacking. However, electrophysiological studies in anesthetized animals have shown that local application of KOPr agonists attenuates the rate suppressant effects of VTA stimulation on pallidal neuronal firing (Mitrovic and Napier, 2002). Such findings suggest that KOPr activation can gate the influence of VTA DA transmission on limbic system outputs at the level of the ventral pallidum.

KOPr are observed in several layers of the neocortex and appear to be localized on neurons containing excitatory amino acids. Only limited data is available regarding modulation of cortical glutamate neurotransmission. In contrast to MOPr, KOPr activation does not alter basal glutamate efflux in cerebrocortical synaptosomes or slices (Nicol et al., 1996; Sbrenna et al., 1999). However, these authors noted a slight nor-binaltorphimine-reversible inhibition of K^{+} - efflux which suggests that KOPr may modulate activity-dependent glutamate release.

As has been discussed, enduring alterations in DA and glutamate transmission in the cortical-striatopallidal circuit have been implicated in the maintenance of compulsive drug use. The ability of KOPr to modulate DA and glutamate transmission in several regions comprising this circuit suggests that targeting of DYN/KOPr systems may be useful in the treatment of addiction. Evidence consistent with this hypothesis is summarized below.

6. Regulation of PDYN Gene Expression by DA and Drugs of Abuse

Manipulations that augment striatal DA transmission induce PDYN gene expression whereas depletion of striatal DA decreases DYN mRNA expression. Both effects have been attributed to the interaction of DA with D1 receptors located on DYN containing medium spiny neurons (Gerfen et al., 1991). Studies examining the signal transduction pathways mediating PDYN gene regulation have identified three cAMP response elements (CRE) within the PDYN

promoter. Studies in striatal cultures indicate that binding of CREB to these elements and subsequent phosphorylation underlies the D1-receptor mediated induction of PDYN (Cole et al., 1995).

Consistent with an ability to enhance presynaptic DA transmission, drugs of abuse increase striatal PDYN expression. This effect has been observed in post-mortem studies of human cocaine addicts and in experimental animals with a prior history of cocaine self-administration (Daunais et al., 1993; Hurd and Herkenham, 1993). Increases in striatal PDYN expression also observed in response to other psychostimulants, opiates, nicotine and ethanol (Brandon and Steiner, 2003; Di Benedetto et al., 2006; Mathieu-Kia and Besson, 1998). Since excitatory input from the cortex regulates DA neurotransmission, alterations in PDYN expression may occur, indirectly, as a consequence of altering glutamate transmission, or directly by affecting DA neurons. Disruption of cortical input or blockade of glutamate receptors attenuates stimulant-induced increases in PDYN expression, suggesting a role of corticostriatal afferents in this effect (Cenci and Bjorklund 1993; Wang. et al., 1994).

The induction of PDYN by cocaine in the striatum is sub-region specific. Using experimenter-administered injections of cocaine, Willuhn et al. (2003) showed robust increases in dorsal striatal aspects with weaker effects in medial and ventral aspects. As noted above, *basal* PDYN expression is greatest in ventral striatal areas and lowest in dorsal, dorsolateral and central areas indicating an inverse relationship between basal expression levels and levels induced by cocaine. Consistent with this hypothesis, cocaine-evoked c-fos expression is prominent in sub-regions with low levels of basal PDYN expression and less in those with high expression levels (Steiner and Gerfen, 1993). Studies in non-human primates have shown that PDYN upregulation is dependent on the dose and duration of cocaine self-administration (Fagergren et al., 2003). High dose administration initially leads to PDYN induction in the limbic related patch/striosome compartment. With continued drug use, induction was also seen in sensorimotor compartments.

These findings and those regarding the inhibitory effects of the KOPr agonists on DA and glutamate neurotransmission are consistent with the hypothesis that repeated exposure to cocaine upregulates DYN/KOPr systems. This increase may initially serve as a homeostatic response that opposes alteration in neurotransmission that occurs with drug use. However, following the discontinuation of drug use, the unopposed actions of this system would result in dysregulation of basal DA and glutamate transmission, thereby, contributing to aberrant activity within the prefrontal-cortico-striatal loop. Activation of KOPr in the Acb and mPFC has been implicated in the aversive and dysphoric effects of KOPr agonists (Bals-Kubik et al., 1993; Shippenberg et al., 1993). Increased KOPr tone in this region may, thus, contribute to the dysphoria and depression (see below) associated with the cessation of cocaine use. The sensorimotor striatum is associated with the expression of motor patterns and the mediation of habit learning (Packard and Knowlton, 2002). Therefore, the up-regulation of PDYN observed in these regions may also contribute to the perseverative drug-seeking behavior and decreased motivation for non-drug rewards that characterize addiction.

7. Behavioral Effects KOPr Agonists Relevant to Addiction

Experimental animals will work to obtain electrical stimulation of the lateral hypothalamus, an effect attributed to the activation of reward circuits in the brain (Olds and Forbes 1981). Acute administration of drugs of abuse decrease stimulation thresholds indicating that these agents activate the brain reward circuitry. Withdrawal from cocaine and other drugs of abuse is characterized by anhedonia, anxiety and depressive-like symptomology. Withdrawal from various drugs of abuse increases the threshold amount of stimulation required to sustain electrical self-stimulation in humans and experimental animals, a finding interpreted as

reflecting anhedonia (Barr et al., 2002; Markou et al., 1992; Wise and Munn, 1995). An increase in stimulation thresholds is observed in response to synthetic KOPr agonists and salvinorin A suggesting that KOPr activation produces depressant-like behavior in experimental animals (Carlezon et al., 2006; Todtenkopf et al., 2004). These agents also increase immobility in the forced swim test, an assay often used in the study of depression (Cryan et al., 2002). This effect is opposite to that seen with virtually all types of antidepressant treatments used in humans, including noradrenergic reuptake inhibitors and SSRIs (Porsolt et al., 1977; Mague et al., 2003) suggesting that KOPr agonists produce prodepressant-like effects. As is observed with both typical and atypical antidepressants, intracerebroventricular infusion of the KOPr antagonists, norBNI and 5'-guanidinonaltrindole dose-dependently decreases immobility in the forced swim test in rats (Mague et al., 2003) indicating a critical role of endogenous KOPr systems in the regulation of affect.

The affective consequences of cocaine withdrawal have been linked at least in part, to alterations in cAMP response element-binding protein (CREB), a transcription factor that is not only critical to the formation of long-term memory but that regulates PDYN gene transcription (Cole et al., 1995; Yin and Tully, 1996). Several laboratories have reported that cocaine and other psychostimulants activate CREB. Furthermore, this effect appears to increase with repeated drug use (review: Hyman et al., 2006). Using a viral vector approach, Nestler and colleagues (Newton et al., 2002) demonstrated that decreasing CREB activity in the NAc reduced PDYN gene expression and produced anti-depressant like effects in an animal model of learned helplessness. Reducing CREB activity in the NAc also produced non-binaltorphimine-reversible antidepressant-like action in the forced swim test indicating the generality of this effect (Pliakas et al., 2001).

Decreased DA neurotransmission has been implicated in some forms of depression (review: Willner et al., 2005). Therefore, aberrant increases in DYN neurotransmission may, by dampening mesoaccumbal DA neurotransmission, not only contribute to the pathogenesis of depression, but to the affective consequence of drug withdrawal. Furthermore, other conditions (e.g. stress) that activate the DYN system, could by inducing a depressant-like state, enhance the rewarding effects of cocaine and other drugs of abuse.

8. Cocaine-Antagonist-Like Effects of KOPr agonists

The studies discussed above provide suggestive evidence that KOPr antagonists may be effective in attenuating alterations in behavior that occur during withdrawal from cocaine. A wealth of studies indicates that KOPr agonists can, when administered concurrently with cocaine, prevent cocaine-induced alterations in behavior and brain chemistry.

Acute pretreatment with KOPr agonists decreases the psychomotor stimulant and conditioned rewarding effects of cocaine in rats (Crawford et al., 1995). Acute KOPr agonist pretreatment is also effective in decreasing the rate of intravenous cocaine self-administration in rodents (Glick et al. 1995, Kuzmin et al. 1997; Schenk et al. 1999). In the non-human primate, continuous infusion of a KOPr agonist produced only slight reductions in the rate of cocaine self-administration (Mello and Negus, 1998; Negus et al., 1997). Furthermore, using a concurrent schedule of food and cocaine self-administration procedure in rhesus monkeys, Negus (2004) showed that continuous infusion of a KOPr agonist increased the rewarding effects of cocaine relative to that of food. The differing effects in rats versus non-human primates are noteworthy and may reflect species differences. Indeed, the distribution and trafficking of KOPr differs in primates and rats (Li-Chen, 2004; Peckys and Landwehrmeyer, 1999). Alternatively, they may reflect differences in the rate-dependency of the self-administration procedure employed. Importantly, however, in those studies where a slight decrease or increase in cocaine self-administration was seen, KOPr agonists were infused

continuously during multiple self-administration sessions. KOPr desensitize rapidly upon continued agonist exposure and prolonged agonist exposure induces marked alterations in the activity of endogenous DYN/KOPr systems (Liu-Chen, 2004; Romualdi et al., 1991). In this regard, it is important to note that KOPr agonists inhibit the locomotor activating effects of cocaine when administered acutely or when administered in an intermittent schedule, for several days prior to acute cocaine administration. This latter finding suggests that tolerance may not develop to KOPr agonists following their repeated, intermittent administration (Heidbreder et al., 1993) and that the pattern of KOPr agonist administration may be a critical factor determining the interaction of KOPr agonists with cocaine.

Evidence indicating an involvement of DYN/KOPr systems in attenuating the rewarding effects of cocaine has also been obtained. Using a conditioned place preference paradigm, Carlezon et al., (1998) showed that overexpression of CREB in the NAc decreases the rewarding effects of cocaine and makes low doses of the drug aversive. Conversely, overexpression of a dominant-negative mutant CREB produced a nor-binaltorphimine reversible increase in the rewarding effects of cocaine. These findings are consistent with the hypothesis that increased transcription of DYN and the resulting increase in KOPr serves an important function in the conditioning of cocaine reward.

In seeming contrast to these findings, a recent study showed that synthetic KOPr agonists can potentiate or suppress cocaine-evoked place preference conditioning depending upon the pretreatment interval employed (McLaughlin et al., 2005). Importantly, KOPr agonists produce conditioned place aversions, effects attributed to a decrease in NAc DA neurotransmission. A potentiated response to cocaine was only apparent at a time point when KOPr agonists produce maximal inhibition of NAc DA levels. Therefore, this response most likely reflects the ability of cocaine to increase DA levels, thereby, reversing the negative affective state produced by acute KOPr activation.

Stress increases DYN levels (Przewlocki et al., 1987). In view of the link between stress and vulnerability to addiction, attention has focused on contribution of KOPr systems to stress-induced alterations in the rewarding effects of cocaine. McLaughlin and colleagues (2003) showed that the conditioned reinforcing effects of cocaine are enhanced following repeated exposure to forced swim stress. This increase was prevented by nor-binaltorphimine and absent in mice lacking the KOPr gene leading the authors to conclude that an increase in the activity of the DYN/KOPr system enhances the rewarding effects of cocaine. These findings are in apparent contrast to previous work showing that prior induction of DYN *attenuates* the rewarding effects of cocaine (Carlezon et al., 1998) and that KOPr agonists *reduce* the rewarding effects of intracranial self-stimulation (Todtenkopf et al., 2004). As discussed above, however, KOPr agonists produce dysphoria and conditioned aversive effects in cocaine-naïve subjects. Therefore, the enhancement of place conditioning most likely reflects the ability of cocaine to suppress the aversive effects produced by acute KOPr activation.

The repeated administration of cocaine is associated with the development of behavioral sensitization. An involvement of sensitization in both the maintenance and reinstatement of compulsive drug-seeking behavior has been suggested (De Vries et al., 1998; Robinson and Berridge, 1993; 2001). The repeated co-administration of KOPr agonists with cocaine attenuates the development and long-term expression of cocaine-induced locomotor sensitization (Heidbreder et al., 1995). It also prevents the development of sensitization to the conditioned reinforcing effects of this psychostimulant (Shippenberg et al., 1996). Other studies have shown that co-administration of KOPr agonists with cocaine prevents changes in basal DA dynamics that occur in the NAc during early stages of abstinence (Chefer et al., 2000; Heidbreder and Shippenberg, 1995; Thompson et al., 2000). KOPr treatment also prevents the augmentation of cocaine-induced DA levels that occurs in this region during

protracted abstinence (Shippenberg et al., 2003). These effects most likely result from KOPr agonist regulation of basal DA uptake and release in the NAc. Cocaine antagonist-like effects of KOPr agonists are observed in the medial prefrontal cortex (Chefer et al., 2000). Alterations in basal DA uptake and release that occur in response to repeated cocaine administration are abolished by KOPr agonists, as is the blunted DA response to a challenge dose of cocaine that occurs during the early phase of abstinence. In contrast to the NAc, KOPr activation does not regulate basal DA uptake in the prefrontal cortex suggesting that distinct substrates may mediate the cocaine-antagonist-like effects of KOPr agonists in these regions.

Data regarding the influence of KOPr agonists on the reinstatement of cocaine-seeking is limited. Schenk and colleagues (1999, 2000) showed that acute KOPr agonist treatment attenuates the reinstatement of cocaine-seeking behavior produced by experimenter-administered cocaine. In contrast, systemic administration of the KOPr antagonist, nor-binaltorphimine did not affect reinstatement suggesting that endogenous KOPr systems do not play a role in the inhibition of this behavior. Only one study has examined the influence of KOPr ligands on stress-induced reinstatement of cocaine seeking. Using a novel KOPr antagonist, Beardsley et al. (2005) showed a reduction in foot-shock evoked reinstatement of cocaine-seeking. However, analogous to the findings of Schenk et al. (1999; 2000), KOPr antagonist treatment was ineffective in blocking the reinstatement of lever pressing produced by experimenter-administered cocaine and even produced a slight increase in responding.

Taken together, the majority of findings indicate that selective KOPr agonists antagonize both the behavioral and neurochemical effects of cocaine. Antagonist-like effects are observed in response to acute or repeated, intermittent KOPr agonist administration and when cocaine is administered acutely or repeatedly. To what extent the effects of acute KOPr agonist pretreatment reflect a pharmacological interaction with cocaine or are due to the aversive effects of the agonists, themselves, remains unclear. There is also evidence to suggest that an increase in the activity of KOPr systems may, in fact, contribute to stress-induced reinstatement of compulsive drug use. Therefore, the question arises as to whether KOPr agonists or antagonists would be effective in the treatment of cocaine addiction. We propose that KOPr agonists may be clinically efficacious when taken during the time of cocaine administration, whereas KORr antagonists would be more useful in blunting the negative affects that occur during initial abstinence from drug-taking.

During the early phase of abstinence, the dynorphin/KOPr system is upregulated and mesoaccumbal DA neurotransmission is decreased. Administration of a KOPr antagonist should, by normalizing DA neurotransmission, attenuate the negative affective consequence of withdrawal, thereby preventing relapse during this period. It may, also, prevent stress-induced reinstatement of drug-use. As abstinence progresses, the activity of the DYN/KOPr system normalizes and may even decrease (Svensson and Hurd, 1998) and an augmented behavioral response to cocaine is seen. Therefore, the use of KOPr antagonists at this early stage of the addiction cycle could, in fact, promote drug-seeking. KOPr agonists prevent the development and long-term expression of behavioral sensitization when co-administered with cocaine or when agonist treatment is initiated some days after the commencement of cocaine administration (Shippenberg et al., 1996). As sensitization processes may contribute to the reinstatement of compulsive drug use during protracted withdrawal, the administration of KOPr agonists prior to the cessation of drug use may prove effective in limiting behavioral and neurochemical adaptations that are observed during abstinence. Studies assessing the effects of KOPr ligands administered during various stages of the addiction/withdrawal cycle are needed to verify these possibilities.

9. Role of endogenous DYN/KOPr Systems In Mediating Vulnerability to Cocaine

It has been suggested that repeated drug-use increases the activity of DYN/KOPr systems and that this increase is a homeostatic mechanism that opposes alterations in behavior and brain function that occur as a consequence of drug use. (Shippenberg et al., 1996; Shippenberg et al., 2001). Until recently, a direct test of this hypothesis was lacking. Studies, however, by Chefer et al. (2005) revealed that constitutive deletion of KOPr is associated with an enhancement of basal DA release and uptake in the NAc as well as a decrease in the induction of immediate early gene expression by cocaine. The ability of an acute injection of cocaine to stimulate locomotor activity was enhanced in knock out mice and the magnitude of this effect was equal to that of wild-type mice that had received a behavioral sensitizing cocaine treatment regimen. Furthermore, although repeated cocaine administration to wild-type mice produced behavioral sensitization, knock-out mice exhibited no additional enhancement of behavior. These data indicate that, in the absence of KOPr, animals are in a "sensitized state" such that repeated cocaine administration is ineffective in further enhancing behavior. Pharmacological inactivation of KOPr also resulted in an augmented behavioral and DA response to cocaine, suggesting that hypofunction of the DYN/KOPr system results in increased vulnerability to the acute behavioral and neurochemical effects of this psychostimulant. Analogous to the knockout mice, nor-binaltorphimine pretreated animals exhibited profound changes in basal DA dynamics. These findings are consistent with those regarding the cocaine-antagonist like effects of KOPr agonists and indicate that the set-point of endogenous KOPr systems may be a critical factor influencing the propensity of an individual to acquire, maintain and reinstate compulsive cocaine use. Recent genetic studies in human subjects provide additional support for this conclusion. Genotyping of cocaine-dependent and control individuals revealed that the variable nucleotide tandem repeat polymorphism in the 5' promoter region of the prodynorphin gene is associated with cocaine dependence (Chen et al., 2002; Dahl et al., 2005). Taken together, these findings suggest that KOPr systems may be novel therapeutic targets for the treatment of cocaine and psychostimulant addiction, a concept that also may be applicable to the addiction liability of other psychoactive drugs.

10. Role of KOPr Systems in mediating the effects of Ethanol

Evidence from both human and animals studies support the involvement of endogenous opioid systems in the effects of alcohol (Herz, 1997; Oswald and Wand, 2004). The opioid antagonist naltrexone is approved by the FDA for the treatment of alcoholism and reduces relapse to alcohol drinking in abstinent alcoholics (see O'Brien, 2005 for review). Recent studies have indicated an important role of the MOPr in alcohol drinking behavior (Hyytia, 1993; Roberts et al., 2000). However, information regarding the contribution of other opioid receptor systems to this behavior is limited.

Several laboratories have examined whether propensity to self-administer ethanol is associated with differences in basal expression of DYN or KOPr. Levels of KOPr and DYN differ in strains of mice exhibiting high (C57BL/6j) and low (DBA/2j) ethanol preference. C57BL/6j mice have lower levels of DYN B immunoreactivity in the prefrontal cortex, hippocampus and striatum relative to DBA/2j mice (Ploj et al., 2000). PDYN and KOPr levels in the NAc are also lower in the preferring C57BL/6j strain (Jamensky and Gianoulakis, 1997; Ploj et al., 1997). Higher levels of different DYN-derived peptides in the NAc of ANA rats when compared with the AA rats were described in experiments using radioimmunoassay on homogenized samples (Nylander et al., 1994). Although these data prompted the hypothesis that enhanced activity of the DYN/KOPr system decreases vulnerability to alcohol abuse, the findings in AA and ANA rats were not replicated using in situ hybridization (Marinelli et al., 2000). Other studies revealed no difference in either basal DYN or KOPr levels in the NAc of

rats selectively bred for alcohol preference or alcohol aversion (Fadda et al., 1999). In contrast to the mice strains examined, the rat strains tested were bred for differences in alcohol sensitivity. Therefore, it is likely that the alterations observed in the mouse are not specific for an ethanol trait. Analytical methods that permit quantification of basal DYN release are lacking. Since, quantification of PDYN expression and tissue levels of peptides provide only limited information as to changes in release, fundamental questions remain as to any link between the activity of KOPr systems and vulnerability to ethanol addiction.

Several laboratories have shown that repeated ethanol exposure increases PDYN mRNA expression in both the ventral and dorsal striatum (Gulya, 1993; Przewlocka et al., 1997). An increase in DYN B peptide immunoreactivity has been reported in the NAc of rats after repeated ethanol administration (Lindholm et al., 2000). In contrast, decreases in KOPr mRNA expression have been reported in both the NAc and VTA (Rosin et al., 1999), suggesting an adaptive post-synaptic compensation to increased concentrations of endogenous ligand. In most of the above studies, changes in DYN and KOPr were apparent for an extended period of time after withdrawal. Changes in expression were observed 1-2 days as well as 21 days following the cessation of chronic ethanol treatment (Lindholm et al., 2000). The persistence of these changes contrasts with those produced by repeated cocaine administration and demonstrates that response of the DYN/KOPr system to these drugs of abuse differ.

Ethanol withdrawal is associated with increased neuronal excitability and, in severe cases, seizures. Studies in experimental animals have suggested an involvement of DYN in the pathogenesis of epilepsy (Simonato and Romualdi, 1997; Solbrig et al., 2006). KOPr agonists exert protective effects in various seizure models. Furthermore, polymorphisms in PDYN are associated with increased vulnerability to temporal lobe epilepsy, status epilepticus and secondary generalized seizures (Gambardella et al., 2003; Stogmann et al., 2002). It has been hypothesized that dysregulation of DYN/KOPr systems may also contribute to withdrawal-induced seizures. In accord with this hypothesis mice selectively bred for increased alcohol seizure susceptibility have a lower level of KOPr binding sites than mice bred for low withdrawal seizure susceptibility (Beadles-Bohling, 2005).

Despite evidence of increased activation of DYN/KOPr systems after chronic alcohol experience, there is little consensus as to the role of this opioid system in modulating alcohol consumption. Several studies have investigated the effects of manipulating the DYN/KOPr system in alcohol drinking paradigms in rodents and conflicting results have been obtained. Using a two-bottle free choice paradigm with restricted access to ethanol, acute KOPr agonist treatment decreased ethanol consumption in Lewis rats with no significant effect on water consumption (Lindholm 2001). Interpretation of these findings, however, is complicated by the aversive effects of KOPr agonists since a reduction in consumption may reflect a pharmacological interaction of KOPr agonists with ethanol or malaise. The effect of chronic infusion of the KOPr agonist, CI-977, on the alcohol deprivation effect has been examined. The alcohol deprivation effect, which is observed in humans and experimental animals, refers to the transient increase in ethanol consumption and preference that occurs after a period of imposed ethanol abstinence. In contrast to the results described above, chronic KOPr agonist treatment increased both ethanol intake and preference (Holter et al., 2000). Whether the different results of these studies reflect acute versus chronic KOPr exposure, differences in the rat strain employed or the duration of prior ethanol exposure is unclear. Interestingly, acute CI-977 administration decreased the deprivation effect on ethanol when an operant paradigm was employed. However, total lever pressing also decreased suggesting a non-specific effect (Holter et al., 2000).

Data regarding the influence of KOPr blockade upon ethanol consumption is also conflicting. Work in non-human primates found no alteration in consumption following nor-

binaltorphimine administration (Williams and Woods, 1998). Similarly, this antagonist did not alter the alcohol deprivation effect in rats when either home cage drinking or operant responding was assessed (Holter et al., 2000). Using a higher dose of nor-binaltorphimine and different rat strain, Mitchell et al. (2005) reported a significant increase in ethanol consumption in animals with a history of stable ethanol self-administration. This increase was not associated with a change in water consumption or weight gain suggesting it reflects an enhancement of ethanol-evoked reward. This finding, however, contrasts with those in KOPr knock out mice, in which lack of the gene encoding KOPr decreased ethanol drinking (Kovacs et al., 2005). KOPr knock out mice exhibited lower saccharin preference and higher quinine preference suggesting a more global effect of gene deletion on taste preference. Thus, the effects of manipulating the DYN/KOPr appear to be highly variable. Variations may reflect differences in the drinking paradigm employed or the time post agonist/antagonist administration. Since KOPr antagonists exert a long-lasting blockade of KOPr, the duration of blockade may also influence the results obtained.

Ethanol is consumed because of its reinforcing effects. An extensive body of literature indicates that enhanced DA release in the NAc is a common mechanism mediating the incentive motivational effects of most drugs of abuse. Acute ethanol administration evokes DA release in the NAc of rats and mice (Yoshimoto et al., 1992). A recent study reported that pharmacological blockade or genetic deletion of KOPr resulted in an enhanced NAc DA response to acute ethanol administration (Zapata and Shippenberg, 2006). This finding indicates that endogenous activation of KOPr would normally function to oppose ethanol evoked activation of the mesolimbic DA system, thereby, dampening acute the reinforcing effects of acute ethanol dministration. In support of this notion, pharmacological blockade of KOPr in rats enhances the conditioned rewarding effects of ethanol (Matsuzawa et al., 1999).

The influence of KOPr blockade on ethanol self-administration and dialysate levels of DA in the NAc has been examined (Doyan et al., 2006). Microdialysis revealed a transient elevation in dopamine concentration within 5 min of ethanol access in control rats. Rats that had received nor-binaltorphimine did not exhibit this response, but showed a latent increase in DA levels at the end of the access period. No effect of nor-binaltorphimine on DA levels was observed in rats self-administering 10% sucrose. The altered DA response during ethanol drinking suggests that KOPr systems may inhibit ethanol-evoked increases in DA release, an effect that is unmasked following antagonist treatment. Despite, however, these neurochemical changes, nor-binaltorphimine did not alter operant responding or ethanol intake, suggesting that the KOPr is not involved in ethanol-reinforced behavior under the conditions studied.

A very recent study (Walker and Koob, 2007) has shown that the effects of nor-binaltorphimine on ethanol self-administration vary depending upon whether an animal is naïve or physically dependant. Using an operant procedure, rats were first trained to self-administer ethanol using a sweetened fading procedure. Dependence was then induced by exposure to ethanol vapor (14 h/day) for one month. Self administration test sessions were then interposed between the vapor exposures and conducted at a time period that produced acute withdrawal. Intracerebroventricular infusion of nor-binaltorphimine immediately prior to self-administratration sessions decreased operant responding for ethanol only in dependent animals. These findings are consistent with the hypthesis that an increase in the activity of endogenous KOPr systems contributes to the reinforcing effects of ethanol that occur during withdrawal. It should, however be noted, that nor-binaltorphimine exerts MOPr– mediated actions for several hours after its administration (Broadbear et al., 1994;.). Since nor-binaltorphimine was administered immediately prior to sessions, some questions exist as to the opioid receptor type mediating the reduction in self-administration.

In summary, evidence derived from animal studies suggests that ethanol, like cocaine increases the activity of the DYN/KOPr system. It is also apparent that increases in the activity of this system oppose alterations in DA transmission that occur in the NAc in response to both the acute and repeated administration of these drugs of abuse. However, in contrast to cocaine, the role of KOPr in modulating other effects of ethanol remains unclear.

A recent study in which the association of KOPr and PDYN gene polymorphisms to the risk for alcoholism was examined in human subjects revealed that 7 consecutive single nucleotide polymorphisms in intron 2 of the KOPr were significantly associated with alcoholism (Xuei et al., 2005). Haplotype analyses further confirmed this association. Given these findings, a systematic evaluation of the effects of KOPr ligands in animal models of alcohol dependence appears warranted.

Conclusions and Therapeutic Perspectives

Until recently, the development of effective therapies for the treatment of addiction has had as its primary focus the prevention or suppression of acute drug effects. However, recognition of the enduring alteration in brain function that occurs as a consequence of repeated drug use has highlighted the potential importance of drug-induced neuroadaptations in maintaining compulsive drug seeking behavior. Dysregulation of the DYN/KOPr system is one consequence of repeated drug use. Data from experimental animals have provided cellular, neurochemical and behavioral evidence that a decrease in the activity of the KOPr system may lead to enhanced vulnerability to the acute effects of cocaine. Although variable results have been obtained in the case of ethanol, there is sufficient evidence to suggest that pharmacological treatments that target the DYN/KOPr systems may be effective in the treatment of drug and alcohol addiction.

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Abbreviations

KOPr	κ-opioid receptor
DYN	dynorphin A 1-17
PDYN	prodynorphin
MOPr	μ-opioid receptor
DOPr	δ-opioid receptor
DA	dopamine
NAc	nucleus accumbens
VTa	ventral tegmental area

PFC prefrontal cortex

Fig.1.

Simplified schematic representation of the basal ganglia-thalamo-cortical neuronal circuitry illustrating neurotransmitter interactions between limbic and sensory-motor regions of the brain. Abbreviations: AMG – amygdala, DSTR dorsal striatum, GPe – external globus pallidus, NAc – nucleus accumbens, PFC – prefrontal cortex, SN substantia nigra, STN – subthalamic nucleus, THAL – thalamus, VTA – ventral tegmental area. Black symbols represent excitatory glutamatergic pathways. Dark shaded symbols represent dopaminergic pathways. Light shaded symbols represent GABAergic pathways. Small trapezoids represent localization of KOPr.