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Opioid–Dopamine Interactions: Implications for Substance Use Disorders and Their Treatment

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Two imaging reports in this volume highlight the importance of the interaction between the brain's opioid and dopamine (DA) systems in the reinforcing and addictive effects of substances of abuse. These studies use positron emission tomography (PET) to measure, in one instance (1), changes in DA induced by acute alcohol administration in healthy subjects (with [^{11}C] raclopride, a radioligand that binds to D2 and D3 receptors (D2R and D3R) and that is sensitive to competition with endogenous DA) and, in the other (2), μ opioid receptor (mOR) availability in cocaine abusers (with [^{11}C] carfentanil, an mOR specific radioligand).

All substances of abuse self-administered by humans that can result in addiction are believed to exert their reinforcing effects by increasing DA in the nucleus accumbens (NAc), which is achieved through different molecular targets by the various drug classes (3). For example, cocaine increases DA by blocking DA transporters, thus interfering with its removal from the synaptic space, whereas alcohol increases DA indirectly by affecting neurotransmitters that regulate DA cell-firing in the ventral tegmental area (opioids and γ -aminobutyric acid [GABA], among others). However, there is increasing evidence of the importance of endogenous opioids in the rewarding effects of substances of abuse (reviewed in Le Merrer *et al.* [4]). Moreover, opioid–DA interactions (as well as interactions with other neurotransmitters, including cannabinoids and GABA) in key reward regions of the brain (i.e., ventral tegmental area and NAc) are likely to ultimately modulate the rewarding and addictive properties of drugs (3). The relevance of these interactions has been documented by preclinical studies, including studies in knockout (KO) mice that have helped delineate the role of specific receptor subtypes (including DA and opioid receptors) in the reinforcing responses to substances of abuse. Table 1 summarizes results on how the rewarding effects of cocaine and alcohol are affected in the KO of receptors measured in the studies of Urban (D2R and D3R KO) and Ghitza (mOR KO).

Nonetheless, the relative contribution of one neurotransmitter over the other might differ for the various substances as a function of their pharmacological targets, which has served to guide the development/selection of medications in clinical trials of substance use disorders (SUD). For cocaine, which directly interacts with DA cells, many trials have focused on medications that enhance DA neurotransmission in an attempt to emulate the substitution therapy strategy used successfully in the treatment of heroin (i.e., methadone and buprenorphine) and nicotine (nicotine replacement therapy) addictions, although this strategy has proven unsuccessful in cocaine addiction so far. For alcohol, which indirectly increases DA by its effects on opioids (as well as GABA), successful clinical trials have been reported using the opiate receptor antagonist naltrexone in the treatment of alcoholism (reviewed in Pettinati *et al.* [5]).

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However, the articles by Urban *et al.* (1) and Ghitza *et al.* (2) point to the potential merit of medications that target the DA system in alcoholism and that of medications that target the opioid system in the treatment of cocaine addiction.

The study of Urban *et al.* documents that in humans (young non-alcohol-dependent individuals) acute alcohol administration increased DA in the striatum (as evidenced by a decrease in the specific binding of [¹¹C] raclopride due to competition with endogenous DA) that was most pronounced in the ventral striatum (location of the NAc). Alcohol-induced DA increases were greater for men than for women; and the magnitude of these DA increases was inversely correlated with the reported maximum alcohol consumption in a 24-hour period but only in males. This could be interpreted as indicating that the men, in whom alcohol produced the lower DA increases, would compensate by consuming larger doses of alcohol and suggests that alcohol's dopaminergic effects might contribute to the vulnerability for binge drinking. Such an interpretation is consistent with preclinical studies (in male rats) that showed that lower DA neurotransmission in NAc is associated with a genetic predisposition for alcohol preference (6). They are also consistent with clinical studies showing marked reductions in DA release in ventral striatum in alcoholic subjects when compared with healthy control subjects (reviewed in Volkow *et al.* [7]). Thus, the studies of Urban *et al.*, along with the preclinical and prior clinical studies, would suggest that medication strategies to enhance DA signaling could have potential benefit in alcohol use disorders (particularly in men). However, the merit of such a strategy cannot be properly assessed in light of the very few reported clinical trials of DA agonists for the treatment of alcoholism carried out to date. The results from Urban *et al.* also highlight the influence that gender has on the effects of alcohol, which could help explain gender differences in the prevalence rates of alcohol use disorders (men > women), in the trajectories from alcohol initiation into dependence (women progress faster than men), as well as differences in therapeutic responses (men tend to respond better than women) (reviewed in Pettinati *et al.* [5] and Zilberman *et al.* [8]). The mechanisms underlying the gender differences in acute and chronic responses to alcohol (as well as to other drugs) are likely to reflect gender differences in metabolism and bioavailability of drugs, the influence of gonadal hormones on the reward and emotion circuitries of the brain, and perhaps also sexual dimorphism in the organization and function of the human brain.

The study of Ghitza *et al.* builds on their prior findings in cocaine abusers, in whom they showed increased mOR availability in limbic brain regions, which was interpreted to reflect a decrease in the concentration of endogenous opioids (because the binding of [¹¹C] carfentanil to the mOR is sensitive to competition with endogenous opioids) (9). In the new study, they show that the elevated mOR availability in brain regions associated with the enhanced incentive motivation value of the drug in addiction (i.e., frontal [middle and medial gyri], anterior cingulate, middle temporal, and insula) predicted treatment outcome in cocaine abusers in an outpatient treatment setting. The higher the mOR the shorter the abstinence and the greater the cocaine use during treatment, and its predictive power was greater than that of clinical variables. In light of their prior findings and those from preclinical studies reporting alterations of the endogenous opioid system with chronic cocaine exposure (reviewed in Leri *et al.* [10]), these results consolidate the importance of neuroadaptations in mOR-mediated neurotransmission in cocaine addiction. Moreover, the predictive value of regional mOR changes with respect to clinical outcomes suggests that this might be a neurobiological indicator of addiction severity. The current findings also have therapeutic implications, because they help us understand and evaluate the role that medications that target the opioid system might have in the treatment of cocaine addiction. In fact, the mOR agonists methadone and buprenorphine decrease cocaine self-administration in laboratory animals (10), and in clinical studies, buprenorphine has been shown to reduce cocaine use in dually dependent cocaine/heroin abusers (reviewed in

McCann [11]). However, in the case of buprenorphine, its κ antagonist properties as well as its agonist effects at the orphanin receptor are likely to contribute to its therapeutic effects in decreasing cocaine use. Positive results have also been reported with the nonselective opiate receptor antagonist (naltrexone) in preclinical studies showing decreased cocaine administration and reduced cue-induced relapse to cocaine-seeking (12), although clinical studies have been inconclusive (reviewed in Pettinati *et al.* [5]). For dually addicted subjects (alcohol/cocaine) the results have been mixed, with some studies failing to see improved outcomes with naltrexone (50 and 100 mg/day) and some showing benefit with a higher dose of naltrexone (150 mg); in one of these the benefits were only observed in men (reviewed in Pettinati *et al.* [5]).

Finally, both studies bring to light the significant intersubject variability with respect to the parameters studied, both in nondependent control subjects (alcohol-induced DA increases in ventral striatum varied for nondisplaceable binding potential from 0% to 25%) and in cocaine abusers (mOR availability in right middle frontal gyrus varied from .17 to .80). The extent of this variability is likely to reflect differences between individuals in the brain's DA and opioid systems that are likely to contribute to the diversity in the behavioral responses to drugs, to the vulnerability for SUD, and to the response to SUD treatments. Future studies that investigate the factors (genetic/epigenetic, environmental) underlying the variability in the ability of specific drugs to increase DA in NAc and on the nature of the neuroadaptations that ensue with chronic drug exposures (in the opioid as well in other relevant neurotransmitter systems) will also be of value in helping to develop personalized therapeutic interventions for SUD.

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Table 1
Results for KO for Receptors Evaluated by PET Studies in Rewarding Responses to Cocaine and Alcohol

	Cocaine	Alcohol
D2R KO	CPP slight decrease SA increased ^a	CPP abolished SA decreased
D3R KO	CPP increased ^b SA not tested	CPP not affected SA not affected
mOR KO	CPP inconsistent results SA decreased	CPP decreased SA decreased

Results for knockout mice (KO) for the receptors evaluated by positron emission tomography (PET) studies of Urban *et al.* (D2 [D2R] and D3 [D3R] receptors) and Ghitza *et al.* (μ opioid receptor [mOR]) in the rewarding responses to cocaine and alcohol as assessed by conditioned place preference (CPP) and drug self-administration (SA). Reviewed in Le Merrer *et al.* (4), Le Foll *et al.* (13), and Sora *et al.* (14).

^a D2R limit the rates of high-dose cocaine SA.

^b One study reported no changes in CPP.