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Dopamine D_3 Receptor Function and Cocaine Exposure

Dopamine D_3 receptors have been implicated as potential pharmacotherapeutic targets for cocaine addiction because of their restricted localization to limbic brain regions and involvement in the behavioral effects of cocaine (Heidbreder and Newman, 2010). The rationale for developing D_3 receptor-selective treatment candidates has been strengthened by evidence suggesting a history of cocaine use dynamically impacts D_3 receptor expression and activity.

The recent development of high-affinity D_3 receptor-selective compounds and the validation of agonist-elicited yawning as a D_3-specific unconditioned behavior (Collins *et al*, 2007) have provided an experimental framework for the examination of the relationship between cocaine exposure and D_3 receptor function. One strategy for drug development is the use of partial agonists—compounds with less functional activity than full agonists *in vitro*. However, a limitation of this approach has been an inability to identify agonist actions of partial agonists *in vivo*. We recently reported that the partial agonist CJB090 and D_3 receptor-selective compound PG619 elicited yawns similar to that of the D_3 agonist quinpirole in monkeys with an extensive history of cocaine self-administration, while displaying no agonist-like activity in drug-naïve controls (Blaylock *et al*, 2011). This finding suggests that D_3 receptors may be functionally sensitized in response to chronic cocaine, thus differentially affecting the *in vivo* profile of low-efficacy D_3 compounds. Although CJB090 and PG619 appeared to function as full agonists when measuring an unconditioned behavior (yawning), neither drug elicited reinstatement of cocaine seeking in these same monkeys, whereas quinpirole did. These findings suggest that D_3 receptors contribute differentially to the multitude of behavioral effects associated with cocaine use.

Several key findings have suggested that cocaine-induced alterations to D_3 receptors may persist and become more pronounced even after withdrawal from cocaine exposure. Using the behavioral sensitization paradigm, Collins *et al* (2011) reported progressive enhancements in agonist-elicited yawning in rats exposed to non-contingent cocaine injections for a 7-day period. These increases continued over the 42-day study and were associated with higher D_3 receptor binding as determined with *in vitro* receptor autoradiography. Interestingly, exposure to cocaine *in utero* has also been shown to influence D_3 receptor activity well into adulthood, as monkeys gestationally exposed to large amounts of cocaine displayed greater responses to quinpirole-elicited yawning than control monkeys up to 13 years after their prenatal cocaine exposure (Hamilton *et al*, 2010). Collectively, these findings suggest that cocaine exposure has long-lasting impacts on D_3 receptor activity and expression.

As it relates to cocaine self-administration, we recently began studies using a food–drug choice self-administration paradigm and found that PG619 treatment reduced cocaine self-administration, which was enhanced with continued PG619 administration. Although there have not been clinical trials reported with partial D_3 receptor agonists, D_3 receptor antagonists are currently being examined in phase I and II clinical trials for treatment of addiction-related disorders, including tobacco dependence and obesity (NIDA, 2000). The evidence described above strongly demonstrates a relationship between cocaine exposure and D_3 receptor alterations, and encourage clinical investigation of D_3 partial agonists and antagonists for cocaine addiction treatments.

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Brandi L Blaylock[1] and Michael A Nader[1,2]

[1]Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC, USA; [2]Department of Radiology, Wake Forest University School of Medicine, Winston-Salem, NC, USA

E-mail: mnader@wakehealth.edu

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Chronic *N*-acetylcysteine after cocaine self-administration produces enduring reductions in drug-seeking

A key feature of successful pharmacological treatment of psychostimulant addiction is the prevention of relapse following abstinence. During abstinence from cocaine, basal corticostriatal glutamate is dysregulated and reversal of this deficit has become a target for potential addiction pharmacotherapy. The glutamate prodrug, *N*-acetylcysteine (NAC), drives the cystine-glutamate antiporter and restores basal glutamate levels after cocaine self-administration, thus normalizing compromised corticostriatal function (Moussawi *et al*, 2011). NAC does not alter the reinforcing mechanisms associated with cocaine, but prevents drug-seeking by a reduction or reversal of the neuroplasticity required for reinstatement to cocaine-seeking (Amen *et al*, 2011; Madayag *et al*, 2007; Moussawi *et al*, 2011). For example, repeated NAC prevented cocaine-induced changes in cystine transport, basal glutamate levels, and cocaine-evoked glutamate release in the nucleus accumbens (Madayag *et al*, 2007). Further, chronic NAC restored synaptic strength as determined by both presynaptic glutamate release and postsynaptic potentiation in prefrontal projections to the nucleus accumbens (Moussawi *et al*, 2011).

These neurobiological normalizations parallel behavioral measures of decreased cocaine-seeking well into extended periods of abstinence. Following cocaine self-administration, chronic NAC (100 mg/kg) administered before daily extinction trials and during abstinence reduced cocaine-primed reinstatement, and a combination of cocaine + cue-induced reinstatement (Moussawi *et al*, 2011; Reichel *et al*, 2011). NAC not only showed efficacy when biologically available during testing, but also produced persistent decreases in cocaine-seeking 2 weeks later, when neither cocaine nor NAC was biologically present. These lasting reductions in cocaine-seeking after discontinuation of pharmacotherapy constitute a critical achievement for potential clinical efficacy of an antirelapse medication.

Although it is difficult to extrapolate preclinical findings to cocaine-dependent patients, the use of NAC has recently crossed the translational bridge from preclinical animal models of addiction to clinical trials. To date, NAC has shown promising results in subjects with cocaine, heroin, and tobacco addiction. An initial pilot open-label study demonstrated that NAC was well tolerated at doses of 1200, 2400, and 3600 mg/day. Of the subjects that finished the study, most terminated or reduced cocaine use during the treatment (Mardikian *et al*, 2007). NAC also decreased desire for cocaine in a cue-reactivity procedure as measured by psychophysical and subjective data in response to slides depicting cocaine and cocaine use (LaRowe *et al*, 2007). Additionally, recent data indicate that repeated administration (4 days) of NAC (1200–2400 mg/day) to cocaine-dependent participants reduced craving following an experimenter-delivered IV injection of cocaine (Amen *et al*, 2011).

Although there are no approved medications for cocaine or other psychostimulant addictions, converging lines of research fully support the clinical utility of NAC for treatment of cocaine addiction. First, behavioral pharmacology studies demonstrate that NAC persistently decreases both conditioned cue-induced and drug-primed reinstatement to cocaine seeking. Second, clinical findings report reduced cocaine craving in humans. And third, the neurobiological mechanisms by which NAC exerts its lasting effects on glutamate function have been identified. Further characterization of these mechanisms in appropriate animal models and clinical laboratories will lead to improved medications for the treatment of multiple forms of addiction.

Carmela M Reichel[1] and Ronald E See[1]
[1]Department of Neurosciences, Medical University of South Carolina, Charleston, SC, USA
E-mail: seere@musc.edu

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Methamphetamine-Induced Oxidation of Proteins and Alterations in Protein Processing

Methamphetamine (METH) is a CNS stimulant with high potential for abuse.