

Alexander GM, Rogan SC, Abbas AI, Armbruster BN, Pei Y, Allen JA *et al* (2009). Remote control of neuronal activity in transgenic mice expressing evolved G protein-coupled receptors. *Neuron* **63**: 27–39.

Armbruster BN, Li X, Pausch MH, Herlitze S, Roth BL (2007). Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand. *Proc Natl Acad Sci USA* **104**: 5163–5168.

Ferguson SM, Eskenazi D, Ishikawa M, Wanat MJ, Phillips PE, Dong Y *et al* (2011). Transient neuronal inhibition reveals opposing roles of indirect and direct pathways in sensitization. *Nat Neurosci* **14**: 22–24.

Guettier JM, Gautam D, Scarselli M, Ruiz de Azua I, Li JH, Rosemond E *et al* (2009). A chemical-genetic approach to study G protein regulation of beta cell function *in vivo*. *Proc Natl Acad Sci USA* **106**: 19197–19202.

Rogan SC, Roth BL (2011). Remote control of neuronal signaling. *Pharmacol Rev* **63**: 291–315.

Neuropsychopharmacology Reviews (2012) **37**, 296–297; doi:10.1038/npp.2011.179

Dopamine D₃ Receptor Function and Cocaine Exposure

Dopamine D₃ 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 D₃ receptor-selective treatment candidates has been strengthened by evidence suggesting a history of cocaine use dynamically impacts D₃ receptor expression and activity.

The recent development of high-affinity D₃ receptor-selective compounds and the validation of agonist-elicited yawning as a D₃-specific unconditioned behavior (Collins *et al*, 2007) have provided an experimental framework for the examination of the relationship between cocaine exposure and D₃ 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 D₃ receptor-selective compound PG619 elicited yawns similar to that of the D₃ 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 D₃ receptors may be functionally sensitized in response to chronic cocaine, thus differentially affecting the *in vivo* profile of low-efficacy D₃ 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 D₃ receptors contribute differentially to the multitude of behavioral effects associated with cocaine use.

Several key findings have suggested that cocaine-induced alterations to D₃ 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 D₃ receptor binding as determined with *in vitro* receptor autoradiography. Interestingly, exposure to cocaine *in utero* has also been shown to influence D₃ 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 D₃ 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 en-

hanced with continued PG619 administration. Although there have not been clinical trials reported with partial D₃ receptor agonists, D₃ 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 D₃ receptor alterations, and encourage clinical investigation of D₃ partial agonists and antagonists for cocaine addiction treatments.

ACKNOWLEDGEMENTS

These studies were supported by the NIDA grant DA 12460.

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DISCLOSURE

The authors declare no conflict of interest.

Blaylock BL, Gould RW, Banala A, Grundt P, Luedtke RR, Newman AH *et al* (2011). Influence of cocaine history on the behavioral effects of dopamine D₃ receptor-selective compounds in monkeys. *Neuropsychopharmacology* **36**: 1104–1113.

Collins GT, Newman AH, Grundt P, Rice KC, Husbands SM, Chauvignac C *et al* (2007). Yawning and hypothermia in rats: effects of dopamine D₃ and D₂ agonists and antagonists. *Psychopharmacology* **193**: 159–170.

Collins GT, Truong YN, Levant B, Chen J, Wang S, Woods JH (2011). Behavioral sensitization to cocaine in rats: evidence for temporal differences in dopamine D₃ and D₂ receptor sensitivity. *Psychopharmacology* **215**: 609–620.

Hamilton LR, Czoty PW, Gage HD, Nader MA (2010). Characterization of the dopamine receptor system in adult rhesus monkeys exposed to cocaine throughout gestation. *Psychopharmacology* **210**: 481–488.

Heidbreder CA, Newman AH (2010). Current perspectives on selective dopamine D₃ receptor antagonists as pharmacotherapeutics for addictions and related disorders. *Ann NY Acad Sci* **1187**: 4–34.

National Institute on Drug Abuse; Massachusetts General Hospital (2000). Effectiveness of GSK598809, a selective D₃ antagonist, added to cognitive behavioral therapy and nicotine replacement therapy for smoking cessation and prevention of very early relapse to smoking. In: ClinicalTrials.gov (Internet). National Library of Medicine (US): Bethesda (MD). (cited 2011 Jul 17).

Available from: <http://clinicaltrials.gov/ct2/show/NCT01188967>. NLM Identifier: NCT01188967.

Neuropsychopharmacology Reviews (2012) **37**, 297–298; doi:10.1038/npp.2011.170

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 pre-synaptic glutamate release and post-synaptic 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.

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DISCLOSURE

The authors declare no conflict of interest.

- Amen SL, Piacentine LB, Ahmad ME, Li S-J, Mantsch JR, Risinger RC *et al* (2011). Repeated N-acetylcysteine reduces cocaine seeking in rodents and craving in cocaine-dependent humans. *Neuropsychopharmacology* **36**: 871–878.
- LaRowe SD, Myrick H, Hedden S, Mardikian P, Saladin M, McRae A *et al* (2007). Is cocaine desire reduced by N-acetylcysteine? *Am J Psychiatry* **164**: 1115–1117.
- Madayag A, Lobner D, Kau KS, Mantsch JR, Abdulhameed O, Hearing M *et al* (2007). Repeated N-acetylcysteine administration alters plasticity-dependent effects of cocaine. *J Neurosci* **27**: 13968–13976.
- Mardikian PN, LaRowe SD, Hedden S, Kalivas PW, Malcolm RJ (2007). An open-label trial of N-acetylcysteine for the treatment of cocaine dependence: a pilot study. *Prog Neuropsychopharmacol Biol Psychiatry* **31**: 389–394.
- Moussawi K, Zhou W, Shen H, Reichel CM, See RE, Carr DB *et al* (2011). Reversing cocaine-induced synaptic potentiation provides enduring protection from relapse. *Proc Natl Acad Sci U S A* **108**: 385–390.
- Reichel CM, Moussawi K, Do PH, Kalivas PW, See RE (2011). Chronic N-acetylcysteine during abstinence or extinction following cocaine self-administration produces enduring reductions in drug-seeking. *J Pharmacol Exp Ther* **337**: 487–493.

Neuropsychopharmacology Reviews (2012) **37**, 298; doi:10.1038/npp.2011.164

Methamphetamine-Induced Oxidation of Proteins and Alterations in Protein Processing

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