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 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.

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DISCLOSURE
The authors declare no conflict of interest.

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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.

Moreover, studies of human METH abusers reveal evidence of neurotoxicity as indicated by long-term decreases in the neuronal marker, n-acetylaspartate (Ernst *et al*, 2000), and in animals, long-term decreases in markers of dopamine (DA) and 5-HT terminals, including decreases in DA and 5HT transporters and content, VMAT2, and tyrosine and tryptophan hydroxylases. Despite these findings, it is unclear if these changes are indicative of actual neuronal damage, although recent evidence indicates that oxidative stress, hyperglutamatergic activity and microglial activation have important roles.

Emerging findings support the contention that METH produces excitotoxicity and oxidative damage. Calcium influx through ionotropic glutamate receptors and the activation of calcium-dependent proteases cause the breakdown of the structural membrane component, spectrin, in an AMPA receptor-dependent manner (Staszewski and Yamamoto, 2006). Although, METH increases free radicals (Giovanni *et al*, 1995), only recently has there been evidence of actual oxidative damage after METH. Eyerman and Yamamoto (2007) showed that decreases in VMAT2 after METH were likely due to the nitrosylation of VMAT2 as early as 1 h after METH. Furthermore, the nitrosylation and the long-term reduction in VMAT2 and DA transporter protein were attenuated by inhibition of neuronal nitric oxide synthase (nNOS). This indicates that METH causes a rapid glutamate and nNOS-dependent oxidation of VMAT2 that precedes the long-term reductions in DA and 5HT content, thereby linking glutamate and oxidative damage to long-term decreases in markers of monoamine terminals.

Recent evidence shows that METH can affect protein degradation through oxidative damage. Impairment of the ubiquitin–proteasome system (UPS) can result in neurodegeneration such as that observed in Parkinson's disease. Most recently, Moszczynska and Yamamoto (2011) showed that METH causes an oxidative modification to parkin, one of the E3 ubiquitin–protein ligases, which add polyubiquitin chains to proteins destined for degradation. Parkin protein was decreased at 1 to 24 h after METH administration through the conjugation of parkin with 4-hydroxy-2-nonenal, a lipid peroxidation product. Moreover, METH also decreased the activity of the 26S proteasome. Both the oxidative conjugation of parkin protein and the decreased activity of the 26S proteasome were attenuated by pretreatment with antioxidant, vitamin E. Other evidence indicates that METH can oxidatively modify pyruvate kinase isoform M2, a mediator of cellular energetics and proliferation of neural progenitor cells (Venkatesan *et al*, 2011), thereby producing decrements in cell metabolism and turnover.

Recently, our preliminary data indicate that α-synuclein levels increased by 200% in the striatum and hippocampus of the rat after METH. α-synuclein is a presynaptic protein that is overexpressed in some neurodegenerative conditions. Its accumulation and the eventual degeneration of the dopaminergic neuron have been associated with parkin, although α-synuclein is not traditionally considered a substrate of parkin and E3 ligase activity. This suggests that there could be a different E3 protein ligase that is oxidatively modified by METH. Further studies are warranted that examine how METH can affect the UPS and its subsequent effects on protein accumulation and degradation.

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DISCLOSURE

The authors declare that except for income received from their primary employer, no financial support of compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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Neuropsychopharmacology Reviews (2012) **37**, 298–299; doi:10.1038/npp.2011.173

Placental Source for 5-HT that Tunes Fetal Brain Development

Deciphering the influences of fetal programming on adult mental disorders causality depends on the identification of specific molecular pathways involved in their etiology. New insights will provide the means for reducing developmentally based disorder risk, and new therapeutic targets for treatments in adulthood. For example, our recent discovery of maternal–placental–fetal interactions that may influence brain development leads to new hypotheses regarding the mechanisms by which fetal programming of adult mental disorders may occur. A tryptophan (the precursor of serotonin—5-HT) metabolic pathway in the placenta (Bonnin *et al*, 2011) reflects the potential importance of extra-embryonically derived 5-HT in modulating developmental processes such as brain circuit wiring, thus affecting long-term brain function. This concept is consistent with classic genetic (5-HT1A knockout) and pharmacological (SSRI exposure) studies showing that disruption of 5-HT