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N-Acetylcysteine reduces cocaine-cue attentional bias and differentially alters cocaine self-administration based on dosing order

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ABSTRACT

Background: Disrupted glutamate homeostasis is thought to contribute to cocaine-use disorder, in particular, by enhancing the incentive salience of cocaine stimuli. *n*-Acetylcysteine might be useful in cocaine-use disorder by normalizing glutamate function. In prior studies, *n*-acetylcysteine blocked the reinstatement of cocaine seeking in laboratory animals and reduced the salience of cocaine stimuli and delayed relapse in humans.
Methods: The present study determined the ability of maintenance on *n*-acetylcysteine (0 or 2400 mg/day, counterbalanced) to reduce the incentive salience of cocaine stimuli, as measured by an attentional bias task, and attenuate intranasal cocaine self-administration (0, 30, and 60 mg). Fourteen individuals (N = 14) who met criteria for cocaine abuse or dependence completed this within-subjects, double-blind, crossover-design study.
Results: Cocaine-cue attentional bias was greatest following administration of 0 mg cocaine during placebo maintenance, and was attenuated by *n*-acetylcysteine. Cocaine maintained responding during placebo and *n*-acetylcysteine maintenance, but the reinforcing effects of cocaine were significantly attenuated across both maintenance conditions in participants maintained on *n*-acetylcysteine first compared to participants maintained on placebo first.
Conclusions: These results collectively suggest that a reduction in the incentive salience of cocaine-related stimuli during *n*-acetylcysteine maintenance may be accompanied by reductions in cocaine self-administration. These results are in agreement with, and link, prior preclinical and clinical trial results suggesting that *n*-acetylcysteine might be useful for preventing cocaine relapse by attenuating the incentive salience of cocaine cues.

1. Introduction

Glutamate, the principal excitatory neurotransmitter in the central nervous system, is strongly implicated in the development and maintenance of cocaine-use disorder (D'Souza, 2015; Kalivas et al., 2009). Disrupted glutamate homeostasis following repeated cocaine use is thought to enhance the incentive salience of cocaine stimuli (Kalivas, 2009). Incentive salience refers to the attention-grabbing effect of cues that have become associated with rewards that may then motivate behavioral responses to obtain and consume the primary reward (Berridge and Robinson, 2016; Robinson and Berridge, 2000). Alterations in glutamate function have been linked to changes in incentive salience hypothesized to underlie compulsive patterns of drug use. Preclinical studies indicate that repeated cocaine exposure increases the salience of cocaine relative to non-drug reinforcers. This change in reinforcer salience corresponds with reductions in glutamate levels during abstinence (Baker et al., 2003; Bowers et al., 2004; Choi et al., 2011; Kalivas and Volkow, 2011; McFarland et al., 2003; Pierce et al., 1996). These studies also indicate that cue- or cocaine-induced increases in glutamate during abstinence ameliorate this deficit, thereby promoting the cyclic pattern of drug use, abstinence, and relapse that characterizes cocaine-use disorder.

n-Acetylcysteine is a cysteine prodrug used to treat chronic-obstructive pulmonary disease (COPD) and acetaminophen overdose (Repine et al., 1997; Smilkstein et al., 1988). Recent evidence suggests that *n*-acetylcysteine may have promise as a medication for cocaine-use

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disorder (Berk et al., 2013; McClure et al., 2014). Preclinical studies have demonstrated that repeated cocaine administration disrupts glutamate signaling, and that *n*-acetylcysteine treatment increases the expression and function of the cysteine-glutamate exchanger and the glial glutamate transporter-1, restoring glutamate homeostasis (Baker et al., 2003; Madayag et al., 2007; Moran et al., 2005; Moussawi et al., 2009). Restoration of glutamate homeostasis with *n*-acetylcysteine might directly attenuate the reinforcing effects of cocaine. Preclinical studies have shown that *n*-acetylcysteine selectively reduced cocaine-maintained responding compared to responding maintained by non-drug reinforcers and prevented the escalation of cocaine intake during extended access self-administration sessions (Baker et al., 2003; Knackstedt et al., 2010; Ward et al., 2011; but see Amen et al., 2011; Ducret et al., 2016; Murray et al., 2012). Whether *n*-acetylcysteine maintenance decreases the reinforcing effects of cocaine in human drug self-administration procedures has not been determined.

Although preclinical findings suggest that *n*-acetylcysteine might reduce cocaine use by directly attenuating the reinforcing effects of cocaine, normalization of glutamate function might also decrease cocaine use by reducing the salience of cocaine-related stimuli. In clinical studies, repeated *n*-acetylcysteine treatment attenuated self-reported desire for cocaine and time spent viewing cocaine-related images in cocaine users (Amen et al., 2011; LaRowe et al., 2007). This reduction in craving and the salience of cocaine cues might promote continued abstinence. A secondary analysis of an 8-week, double-blind trial revealed that 2400 mg/day *n*-acetylcysteine delayed relapse in treatment-seeking cocaine users who had achieved abstinence prior to the outset of the trial (LaRowe et al., 2013). Although the primary analysis did not detect a significant effect of *n*-acetylcysteine treatment on cocaine-use outcomes, these secondary results suggest that *n*-acetylcysteine may have utility in the treatment of cocaine-use disorder. Despite the importance of these clinical findings, they do not provide direct insight into the mechanisms responsible for *n*-acetylcysteine's effects on cocaine use. *n*-Acetylcysteine might reduce cocaine use in humans by altering the incentive salience of cocaine cues, directly attenuating the reinforcing effects of cocaine as suggested by preclinical studies, or some combination of the two.

Changes in the salience of cocaine-related stimuli during *n*-acetylcysteine treatment may be determined in a human laboratory setting by measuring the ability of drug-related stimuli to capture and hold attention versus non-drug-related stimuli (i.e., attentional bias; see Field and Cox, 2008 for review). Attentional bias is thought to arise from classical conditioning processes by which drug-related stimuli acquire incentive-motivational properties following repeated pairings with drug rewards (Field and Cox, 2008; Robinson and Berridge, 1993) and/or may reflect the current motivational state of the individual (Klinger and Cox, 2011). Attentional bias is commonly inferred using reaction-time based measures such as the visual-probe task (Field et al., 2014). Individuals typically respond faster to probes that follow motivationally salient images compared to neutral images (Mogg and Bradley, 1998). For example, subjects with cocaine-use disorder display a robust attentional bias to cocaine cues relative to controls and individuals who abuse other classes of drugs (Leeman et al., 2014). Although the results of previous clinical studies described above suggest that *n*-acetylcysteine decreases time spent viewing cocaine images and self-reported cocaine craving, the impact of *n*-acetylcysteine maintenance on cocaine-cue attentional bias is unknown, as is the impact of acute cocaine administration on cocaine-cue attentional bias.

The present study addressed two gaps in the literature on the potential utility of *n*-acetylcysteine to treat cocaine-use disorder. First, this study assessed the impact of *n*-acetylcysteine maintenance on the incentive salience of cocaine cues by measuring the allocation of attention to cocaine-related and neutral stimuli following acute cocaine administration using a visual-probe task. Second, human drug self-administration procedures were used to determine the effects of *n*-acetylcysteine maintenance on the reinforcing effects of intranasal cocaine. It was hypothesized that *n*-acetylcysteine maintenance would reduce cocaine-cue attentional bias and decrease cocaine self-administration. Because the effects of *n*-acetylcysteine on the subject-rated and physiological effects of cocaine are also unknown, the current study evaluated the impact of *n*-acetylcysteine, alone and in combination with cocaine, on these measures.

2. Methods

2.1. Participants

Fourteen (N = 14) non-treatment-seeking cocaine users between the ages of 30–52 participated in this within-subject, double-blind, placebo-controlled, crossover-design study. Participants met diagnostic criteria for cocaine abuse or dependence according to a computerized version of the structured clinical interview for the DSM-IV (American Psychiatric Association, 2000), reported recent cocaine use verified by a benzoylecgonine-positive urine specimen during screening, and were required to be daily cigarette smokers to be eligible for participation. Participants had experience with alcohol and a variety of other drugs but did not meet diagnostic criteria for abuse or dependence for any of these substances, except alcohol. Two participants met diagnostic criteria for alcohol dependence and two met diagnostic criteria for alcohol abuse (see Table 1). These individuals were not excluded from participation because they were not physiologically dependent on alcohol and agreed to discontinue their alcohol use during participation. Other information on screening procedures and inclusion/exclusion criteria are provided in the Online Supplement. Participants were generally in good health with no contraindications to cocaine or *n*-acetylcysteine. The Institutional Review Board at the University of Kentucky Medical Center approved the informed consent document and study procedures. All procedures were carried out in accordance with the guidelines established in the Declaration of Helsinki. Participants provided their written informed consent prior to enrollment and were compensated $1360 USD upon successful completion of the study. The overall number of choices for money in the Drug Choice Procedure (see Section 2.4.2) was added to the total compensation above (up to $9 USD). Demographic information is shown in Table 1.

2.2. General procedures

Participants enrolled as inpatients at the University of Kentucky Chandler Medical Center Clinical Services Core (CSC) for 17 days. Participants completed one practice and six experimental sessions (see Supplementary Fig. 1). During the consent process, participants were informed that they would receive oral *n*-acetylcysteine, intranasal cocaine, and placebo (orally and intranasally) alone or in combination. Beyond this general information, participants (as well as medical and research staff) were blind to the type or dose of drug administered in any given experimental session. Participants were told that the purpose of the study was to learn more about how drugs affect mood, physiology, and behavior. Otherwise, participants received no instruction of what they were supposed to do or what outcomes might be expected.

Prior to their admission to the CSC, participants were required to provide an expired breath sample that was negative for the presence of alcohol using a hand-held breathalyzer (Intoximeters, Saint Louis, MO, U.S.A.) and pass a field sobriety test. They were also required to provide a urine specimen that was screened for recent use of commonly abused drugs (see Online Supplement for further detail). Urine drug screens were required to be negative for all substances other than cocaine and cannabis [and negative for pregnancy in female participants] prior to admission. Following admission to the CSC, participants were allowed to acclimate to the unit for 24 h. During this acclimation period, participants were medically monitored, including observation for signs and symptoms of drug and/or alcohol withdrawal. Withdrawal was not detected in any participant during this time, or at any point during the