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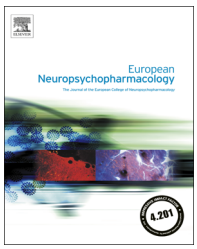

Pharmacogenetic randomized trial for cocaine abuse: Disulfiram and α_{1A}-adrenoceptor gene variation

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Abstract
Disulfiram is a cocaine addiction pharmacotherapy that inhibits dopamine β-hydroxylase (DβH) and reduces norepinephrine production. We examined whether a functional variant of the *ADRA1A* gene (Cys to Arg at codon 347 in exon 2, Cys347Arg) may enhance treatment response through decreased stimulation of this α_{1A}-adrenoceptor, since antagonists of this receptor show promise in reducing cocaine use. Sixty-nine cocaine and opioid co-dependent (DSM-IV) subjects were stabilized on methadone for two weeks and subsequently randomized into disulfiram (250 mg/day, $N=32$) and placebo groups ($N=37$) for 10 weeks. We genotyped the *ADRA1A* gene polymorphism (rs1048101) and evaluated its role for increasing cocaine free urines in those subjects treated with disulfiram using repeated measures analysis of variance, corrected for population structure. The 47 patients who carried at least one T allele of rs1048101 (TT or TC genotype) reduced their cocaine positive urines from 84% to 56% on disulfiram ($p=0.0001$), while the 22 patients with the major allele CC genotype showed no disulfiram effect. This study indicates that a patient's *ADRA1A* genotype could be used to identify a subset of individuals for which disulfiram and, perhaps, other α_1-adrenoceptor blockers may be an effective pharmacotherapy for cocaine dependence.
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1. Introduction

Cocaine dependence (CD) is widely recognized as a chronic medical illness for which there is currently no US Food and Drug Administration (FDA) approved pharmacotherapy (McLellan et al., 2000). CD frequently co-occurs with opioid dependence, particularly in methadone maintenance programs, and contributes to worsened psychosocial outcomes (Kosten et al., 1988). In this population, rates of cocaine use may range from 30% to 80% (Grella et al., 1997) and contribute to increases in HIV risk behaviors and/or transmission, continued illicit opioid use, increased number of hospitalizations for drug and alcohol problems, and increased

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emergency department utilization (Meandzija et al., 1994; Magura et al., 1998; Bovasso and Cacciola, 2003). Cocaine is also a common co-intoxicant in cases of fatal methadone overdose (Wolf et al., 2004). Various pharmacological approaches have been evaluated to reduce CD, but with only moderate success (Shorter and Kosten, 2011).

The psychostimulant properties of cocaine stem from its ability to inhibit reuptake at the dopamine, serotonin, and norepinephrine transporters, producing an increase in synaptic levels of these neurotransmitters (Rothman and Baumann, 2003). In persons abusing cocaine, evidence suggests that stimulation of the noradrenergic system contributes to reward and reinforcement from the drug. Dopamine transporter (DAT) knockout (KO) mice continue to self-administer cocaine, suggesting that blockage of DAT alone is not sufficient to account for the reinforcing effects of cocaine and that other neurotransmitter systems must contribute (Carboni et al., 1990). Additionally, norepinephrine transporter (NET) KO mice displays a reduced response to acute cocaine administration, when compared to wild-type controls, although behavioral sensitization to cocaine remained unchanged (Mead et al., 2002). A functional coupling of the noradrenergic system to the dopaminergic system may be mediated through the activation of α_{1A}-adrenoceptors, contributing to cocaine-induced increase in synaptic levels of norepinephrine (NE) and subsequent increase in firing of dopamine (DA) neurons in the ventral tegmental area and prefrontal cortex (Paladini and Williams, 2004). In addition to its role in the acute effects of cocaine, the noradrenergic system underlies the neurobiology for stress-induced reinstatement of drug seeking behavior. Preclinical evidence has demonstrated that pharmacologic blockade of this system attenuates reinstatement of cocaine-seeking behavior in rats (Leri et al., 2002). These findings suggest that decreasing noradrenergic stimulation of α_{1A}-adrenoceptors may represent an exciting potential pharmacotherapeutic target for treatment of CD.

Disulfiram (Antabuse, Antabus), which acts on multiple enzymes through copper chelation, inhibits dopamine β-hydroxylase (DβH), the enzyme responsible for transformation of DA to NE (Gaval-Cruz and Weinshenker, 2009). Disulfiram has shown initial promise in treating CD among opioid-dependent patients (George et al., 2000; Petrakis et al., 2000; Carroll et al., 2004; Schroeder et al., 2010) as well as CD in the context of abuse of other substances (i.e., alcohol) (Carroll et al., 1998). Inhibition of DβH decreases brain NE levels, leading to a subsequent reduction in stimulation of α_{1A}-adrenoceptors. In a series of recent studies, our group found that pharmacologic antagonism of α_{1A}-adrenoceptors with prazosin reduced cocaine-induced reinstatement of cocaine-seeking in rats (Zhang and Kosten, 2005; Zhang and Kosten, 2007), and doxazosin reduced cocaine use in humans (Shorter et al., 2013).

The strong genetic basis of CD, estimated at up to 72% (Goldman et al., 2005) encourages a molecular genetics approach to understanding disulfiram's mechanism of action in the treatment of this illness. In a previous study, our group showed that a *DBH* genetic polymorphism associated with relatively low DβH levels (rs1611115), (CT/TT) identified CD patients who do not reduce their cocaine use in response to treatment with disulfiram, perhaps reflecting the relatively small reduction in NE levels observed in this group and the subsequently small reduction in noradrenergic stimulation (Kosten et al., 2013). As part of this larger pharmacogenetics study, and in order to further identify clinical subpopulations in which the efficacy of disulfiram may be improved, in this present study we examined selected CD patients based upon *ADRA1A* genotype. The gene *ADRA1A* that codes for the α_{1A}-adrenoceptor has a functional polymorphism rs1048101 in exon 2 coding for the substitution of an arginine (ARG) for a cytosine (CYS) at codon 347 of the C-terminus (Lei et al., 2005), that may alter the activity of this receptor and impact cognition. More specifically, this polymorphism may impact activation of α_{1A}-adrenoceptors reported to influence critical functions for prevention of relapse in CD including vigilance, impulsivity, and working memory (Puumalu et al., 1997; Arnstein et al., 1999).

The first aim of this study is to determine whether CD patients who were carriers of the T allele (TT/TC) which codes for the Cys347 form of the α_{1A}-adrenoceptor have a different response to disulfiram than patients who are homozygous (CC) for the Arg347 form of the receptor. We hypothesize that individuals who are T allele carriers (Cys form) will respond preferentially to disulfiram, displaying a greater reduction in cocaine use when compared to individuals who are Arg347Arg homozygous. If one of these genotype groups is associated with a preferential response to disulfiram, a second aim is to examine the impact of this "preferred" *ADRA1A* genotype in the context of DBH activity. We hypothesize that patients with a genotype pattern consisting of those carrying the preferred *ADRA1A* allele (i.e., the Cys form) with the *DBH*-1021C/T CC genotype that is associated with normal DβH levels will have a better response to disulfiram, in contrast to a poorer response to the medication in the group of patients with lower DβH levels (CT/TT) or the *ADRA1A* Arg347Arg CC genotype.

2. Experimental procedures

2.1. Patients

From 2005 to 2006 at Yale University ($N=40$) and then from 2006 to 2008 at the Baylor College of Medicine ($N=53$), 93 patients entered into a clinical trial to evaluate disulfiram for cocaine dependence. At the time of screening, patients underwent physical examination and psychiatric evaluation as well as assessment of laboratory values. During intake, each participant was interviewed using the Mini International Neuropsychiatric Interview (MINI (English Version 5.0.0., 1 July 2006); Sheehan et al., 1998) and completed the Addiction Severity Index (ASI-Lite; McLellan et al., 1992). Initially, patients entered a two-week screening period during which they were stabilization on methadone maintenance. Patients were selected based on thrice weekly urine toxicology being positive for both opiates and cocaine metabolites during this screening and were retained if they had at least one cocaine positive urine samples leading to 11 patients being excluded. Eight additional patients dropped out during the screening period (i.e., lost to follow-up). Five additional patients were excluded from the remaining 74 cocaine and opioid dependent patients due to lack of genotypic data (Kosten et al., 2013). All patients met DSM-IV criteria for opioid and cocaine dependence. Other exclusions included a current diagnosis of other drug or alcohol dependence (other than tobacco), current major medical illness that was not stabilized on medications, a history of major psychiatric disorder (psychosis, schizophrenia, bipolar), current suicidality, and an