Published in final edited form as:

Neurosci Lett. 2013 April 29; 0: 29–33. doi:10.1016/j.neulet.2013.02.037.

DBH gene as predictor of response in a cocaine vaccine clinical trial

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Abstract

We examined a pharmacogenetic association of the *dopamine β-hydroxylase (DBH)* gene with a response to an anti-cocaine vaccine that was tested in a recent clinical trial. This gene is associated with cocaine-induced paranoia, which has a slower onset than the euphoria from cocaine. The vaccine reduced euphoria by slowing the entry of cocaine into the brain, but it may not reduce aversive symptoms like paranoia. A 16-week Phase IIb randomized double-blind placebo-controlled trial of 114 cocaine and opioid dependent subjects who received five vaccinations over the first 12 weeks was examined. We genotyped 71 subjects for the rs1611115 (−1021C>T) variant of the *DBH* gene and compared vaccine to placebo subjects on cocaine-free urines. Using repeated measures analysis of variance, corrected for population structure, vaccine pharmacotherapy reduced cocaine positive urines significantly based on *DBH* genotype. Patients with the low DβH level genotype dropped from 77% to 51% on vaccine ($p = 0.0001$), while those with the normal DβH level genotype dropped from 83% to 72%. Placebo showed no effect on cocaine use overall or by genotype. This study indicates that a patient's *DBH* genotype could be used to identify a subset of individuals for whom vaccine treatment may be an effective pharmacotherapy for cocaine dependence.

Keywords

Gene; dopamine; polymorphism; cocaine; treatment; vaccine

1. Introduction

Cocaine dependence, which is common and has substantial social and economic impacts on those afflicted [31,41], has no FDA approved pharmacotherapy. However, a recent study of

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Conflict of interest

No conflict declared.

Trial Registration: Protocol ID: NIDA-15477-1

Clinical trials.gov ID: NCT00142857 <http://clinicaltrials.gov/ct/show/NCT00142857?order=2>

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a cocaine vaccine showed that about 40% of the actively vaccinated subjects attained sufficient antibody levels (over 40 ug/ml) to block most street doses of cocaine [16]. These 40% of subjects had significantly fewer cocaine urines than either the placebo patients or those with lower antibody levels [28]. Half of those with lower antibody levels had sufficiently high levels to block one to two doses of smoked cocaine [16]. This more modest blockade was considered sufficient to prevent relapse to repeated use and dependence after a single use of cocaine [10]. While most cocaine abusers might simply use more cocaine if they got no effect from their initial dose, some cocaine abusers develop aversive paranoid reactions to cocaine. This aversive response appears to be associated with a genetic polymorphism in the *dopamine β -hydroxylase* (*DBH*) gene, which leads to low dopamine β -hydroxylase (D β H) enzyme levels [7,19]. These low *DBH* allele carriers thereby may be not only blocked from getting significant euphoria from cocaine use, but also have greater sensitivity to cocaine's aversive properties. A possible interaction therefore might occur in which patients with low D β H would benefit even with low levels of antibody by preventing them from relapsing to repeated cocaine use due to additional aversive effects without euphoria. This type of pharmacotherapeutic interaction could allow patients with low antibody levels from the vaccine to reduce or eliminate the desire for more cocaine from the cocaine slip and, thereby, reinforce the weekly cognitive behavioral therapy (CBT) for relapse prevention [5,12].

We therefore hypothesized that the patients carrying the allele for a low D β H state (TT and CT genotypes) would benefit more from the vaccine plus CBT than those with the higher D β H (CC genotype) state who experience greater cocaine induced craving and desire for more cocaine and little cocaine paranoia.

2. Methods

2.1. Participants

Between October 2003 and April 2005 we enrolled and randomized 114 subjects who met DSM IV criteria [1] for cocaine and opioid dependence into an out-patient methadone maintenance treatment program in West Haven, Connecticut. The Addiction Severity Index (ASI) was completed on all subjects to assess baseline characteristics and to compare them across genotype and treatment groups [32]. We obtained genotyping results from 71 subjects for these analyses. Eligibility included men or women aged 18 to 55 who had urines positive for cocaine metabolites, and did not have a clinically unstable chronic disease. Enrolled women had to be non-child bearing or willing to use birth control. The institutional review boards of the VA Connecticut Healthcare System, Yale University School of Medicine, and the Baylor College of Medicine approved this study in which all subjects gave written informed consent.

2.2. Study Design and Medications and Counseling

The study design details of this randomized, placebo controlled clinical trial are provided in the original publication [28]. For the current analysis, we examined weeks one through 16 in order to extend past the 12 weeks needed to complete the full vaccination series. Differential efficacy between the placebo and active vaccine was expected to begin after week 8, when most vaccine responders should have significant IgG anti-cocaine levels [22,27].

Methadone maintenance therapy was initiated two weeks prior to the first vaccination and doses stabilized at 60 mg daily. The vaccine is succinylcocaine covalently linked to cholera B (SNC-rCTB) and adsorbed onto aluminum hydroxide adjuvant. Subjects were randomized to receive either five vaccinations of 360 micrograms of active (SNC-rCTB) or placebo as 0.5 ml intramuscular deltoid injections at 0, 2, 4, 8, and 12 weeks. All subjects participated in individual, weekly 30–45 minute cognitive behavioral relapse prevention

therapy (CBT) sessions conducted by trained substance abuse counselors [5,6]. Urine toxicology results were reviewed with the subjects during these counseling sessions.

2.3. Outcome measures and laboratory tests

Supervised urine samples were obtained thrice weekly and tested for the presence of the cocaine metabolite benzoylecgonine using an Olympus AU 640 Emit system (Olympus America Inc., Melville, NY) with a cut-off concentration of 300 ng/ml. We obtained saliva samples for the isolation of DNA for genotyping.

Serum anti-cocaine IgG was measured by an Enzyme-Linked ImmunoSorbent Assay (ELISA). The antigenic target was cocaine conjugated to bovine serum albumin (BSA). Human IgG bound to this antigen was detected with horseradish peroxidase conjugated second antibody and appropriate substrate [22]. Nonspecific antibody binding to the carrier alone was subtracted. Each ELISA plate included wells with serially diluted polyclonal human IgG to provide an internal standard. Specificity and reproducibility was validated using serial dilutions of a humanized monoclonal antibody to cocaine, 2E2, from Dr. Andrew Norman at the University of Cincinnati [36]. No data was collected on measures of paranoia.

2.4. Genotyping

DNA was purified as previously described [21]. Briefly, DNA was isolated using the Gentra Puregene Buccal Cell Kit (Qiagen, Valencia, CA) following the manufacturer's recommendations from pelleted buccal cells that were obtained by centrifugation of 10 ml Scope mouthwash that was used to rinse the subject's mouth for 60 seconds.

Genotypes were determined using 5'-fluorogenic exonuclease assays (TaqMan®, Applied Biosystems, Foster City, CA). The *DBH* rs1611115 (−1021C/T) variant was genotyped using the TaqMan® primer-probe set Assay ID C_2535786_10 (Applied Biosystems). PCR amplifications were performed using Platinum® quantitative PCR SuperMix-UDG (Invitrogen, Carlsbad, CA) on a GeneAmp® PCR system 9700 per manufacturer's recommendations. The amplification products were analyzed using an Applied Biosystems Prism® 7900 sequence detection system and SDS 2.2 software (Applied Biosystems). All genotype analyses were performed by an individual unaware of the clinical status of the subjects. Sex was determined using an SRY rs11575897 (C_32310143_10, Applied Biosystems) TaqMan® assay incorporating the TaqMan® Exogenous Internal Positive Control (4308323, Applied Biosystems). Ten ancestry informative markers were evaluated using the TaqMan® primer-probe sets (rs722869, C_7566096_20; rs1858465, C_11417706_10; rs1876482, C_11640969_10; rs1344870, C_8767848_10; rs1363448, C_3169933_1_1; rs952718, C_8844929_10; rs2352476, C_26357333_20; rs714857, custom order; rs1823718, C_12080106_10; rs735612, C_2043758_10, Applied Biosystems). The TaqMan® assays were performed in duplicate. DNA was not available for all patients so the *DBH* genotype was obtained only for 71 patients.

2.5. Statistical Analysis

The two treatment groups were compared for baseline differences in cocaine use history and demographics using χ^2 or t-test as appropriate. As previously described [21], a repeated measures analysis of variance using the number of cocaine positive urines over the total number of visits (six) for each two-week period was used to compare vaccine to placebo over time and to determine if the effect of vaccine is modulated by genotype using R version 2.9.1 [38]. The explanatory variables were condition (whether a patient was taking vaccine or placebo) and genotype group (0 = TT/CT, 1 = CC). A repeated measures ANOVA was performed using the data on all individuals who had complete urine data ($N = 66$) and

unbalanced repeated measures ANOVA for all individuals ($N = 71$). Similar results were obtained from each analysis.

Population structure was determined as previously described [17,21,24,37]. All analyses were corrected for any possible confounding effects by including the proportion of each subject from the founder populations as well as gender as covariates in the model. P -values were similar to those obtained when we did not correct for these covariates. Analyses were performed with the total group, then within the two genotype subgroups.

3. Results

3.1 Baseline characteristics and retention by medication and DBH

We obtained genotypes for *DBH* on only 71 of the 114 patients enrolled in this clinical trial. The 71 patients had been randomized: 34 to the vaccine and 37 to placebo. The patients included 37 with the CC, 29 with the CT, and five with the TT genotypes. The 71 patients were mostly Caucasian males with a mean age of 36 years, who abused cocaine for a mean of 13 years, and spent a mean of \$429 on cocaine in the month before entering the study. The Addiction Severity Index showed few problems, except in the drug abuse area. As shown in Table 1, we found no significant baseline differences among the four treatment by genotype groups in any clinical characteristics ($p > 0.05$). Ninety-three percent of the subjects completed the 16-week study and these subjects also showed no baseline differences.

3.2 Cocaine Treatment Outcomes and DBH

There were only two patients with a TT genotype treated with placebo and three patients with a TT genotype treated with vaccine in our cohort. To maintain statistical power, we grouped our patients into two genotype groups based on their *DBH* genotypes: those homozygous for the major C allele (i.e., patients with a CC genotype) and those who were carriers of the minor T allele (i.e., patients with either a CT or a TT genotypes). The cocaine positive urine rates changed significantly across the 16-week clinical trial ($F = 5.7$; $df = 8,532$; $p < 0.02$) and differed in the vaccine group for patients in the CT/TT versus CC group ($F = 20.0$; $df = 1,270$; $p < 0.00001$), but not for those in the placebo group ($F = 0.55$; $df = 1,262$; $p > 0.05$). Only the vaccine group and not the placebo group showed a change over time ($F = 5.7$; $df = 8,270$; $p < 0.02$) (Figure 1).

The rate of cocaine positive urines for the patients in the vaccine group was 77% for those with the CT/TT genotypes and 83% for those with the CC genotype during the two baseline weeks. Positive urine cocaine rates in these groups decreased to 51% and 72%, respectively, in the last four-week period. In contrast, cocaine positive urine rates for placebo patients did not decrease significantly during the 16-week trial, going from 66% to 50% for the CT/TT group and 67% to 59% for the CC group. If we included only the 66 patients who completed the study, vaccine treatment remained effective only in the CT/TT group ($F = 14.3$; $df = 1,240$; $p < 0.0002$).

4. Discussion

We found that the dopamine β -hydroxylase (*DBH*) polymorphism (*DBH*-1021C/T) that is associated with low $D\beta H$ levels also was associated with greater improvement in cocaine positive urines in the vaccine-treated group. Cocaine urine rates on the vaccine dropped from 77% to 51% for those patients carrying the low activity *DBHT* allele and from 83% to 72% for the normal CC *DBH* genotype group (35% versus 10% drop from baseline). The placebo group showed no significant difference between the genotype groups.

This genetic polymorphism may have functional significance. Some of the differences in plasma levels of D β H among individuals have been found to be associated with this C-1021T (-1021C>T) variant (rs1611115) [7,8,35,40,47,48,50]. The variant C-1021T is positioned ~1000 nucleotides upstream from the initiation codon of the *DBH* gene. The T allele appears to decrease transcription thereby decreasing plasma levels of D β H, accounting for up to 50% of the overall variation in enzyme levels [3,20,50,51]. Individuals that are homozygous for the T allele have the lowest levels of plasma D β H activity. The cerebrospinal fluid level of the dopamine metabolite homovanillic acid (HVA), an indirect measure of DA concentration in the brain, is correlated with the *DBH*-1021T genotype [18].

Our results are consistent with the finding that the low *DBH* genotype is associated with more paranoia when using cocaine. A survey found that three times more low D β H cocaine abusers endorsed paranoia than no paranoia with cocaine use, while the normal D β H abusers endorsed a relatively low rate of paranoia from cocaine [7]. A human laboratory study found approximately about three fold greater amounts of paranoia when using cocaine among the low *DBH* versus normal *DBH* subjects [19]. Our hypothesis is that when the vaccine blocks the euphoria of cocaine, using cocaine with low D β H leads to paranoia. This paranoia is less likely with high or normal D β H levels. The mechanisms may be twofold. First, the slow entry of cocaine into the brain will produce paranoia and other aversive properties of cocaine, but not euphoria, and the vaccine has the pharmacokinetic action of slowing cocaine entry into the brain [34]. Second, when cocaine enters the brain and blocks reuptake of norepinephrine into the releasing neurons, these neurons attempt to make more norepinephrine. When low D β H limits the conversion of dopamine to norepinephrine, the neuron instead starts to release dopamine in the cortex [4,46]. This release of dopamine into the frontal cortex can produce paranoia [9].

The connection between low D β H and paranoia has been further supported through work with disulfiram, which produces paranoia in some cocaine abusers when they are given cocaine in a laboratory setting [2,15,29,30]. Studies in rats also support disulfiram affecting cocaine induced behaviors [14]. Decreasing D β H through disulfiram treatments or via genetic manipulation enhances anxiety-like behavioral effects [42,43] and the aversive nature of cocaine [42]. Interestingly, like the vaccine, disulfiram raises blood levels of cocaine, which may contribute to the paranoia [30]. The *DBH* genotype effect appears to be in the opposite direction for treatment with disulfiram than with the vaccine, since the normal *DBH* genotype is associated with the better therapeutic response to disulfiram and with a worse response for the vaccine. Perhaps, this could be due to the vaccine raising blood levels of cocaine through retention on the antibody, while disulfiram inhibits cocaine's metabolism.

In summary, cocaine addiction has a strong genetic basis, with the vulnerability to develop an addiction estimated to be as high as 72% [13]. Therefore, the pharmacotherapy of this relapsing brain disease may be better treated using a molecular genetics approach [25,44,45,49]. Tailoring pharmacological treatment to a person's genetic background can enhance therapeutic response [23], increase compliance [33], and decrease drug toxicity [11,26,39]. This study showed an enhanced therapeutic response based on an interaction between a blocking agent that alters the kinetics of cocaine uptake and a patient's genetic background, taking advantage of a genetic risk factor for enhanced and more frequent paranoia from cocaine use.

Acknowledgments

Supported by: NIH/NIDA 5 P50 DA018197-05 (TK), the Veterans Health Administration, and the Toomim Family Fund. None of the funding agencies had a role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. We thank Mark Harding and Wen Huang for technical assistance.

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HIGHLIGHTS

- Cocaine vaccine pharmacotherapy reduced cocaine-free urines of cocaine dependent addicts.
- Cocaine vaccine was effective in patients with low activity dopamine β -hydroxylase genotypes.
- Mechanism may involve greater cocaine induced paranoia in patients with low activity D β H.

Fig. 1. Percentage of cocaine positive urine toxicology screens for two-week time blocks across the 16-week trial for the vaccine treated patients by the two *DBH* genotype groups: CC (solid line) and CT/TT (dashed line). Standard error bars are shown at each time point.

Table 1Demographic and clinical characteristics by treatment and *DBH* genotype

Characteristic	Placebo		Vaccine	
	CT/TT	CC	CT/TT	CC
N	18	19	16	18
% Male	60	74	50	72
% Caucasian	89	79	100	83
Age years (s.d.)	35 (10)	39 (9)	34 (9)	35 (10)
Cocaine \$ last 30 days	324 (477)	305 (410)	393 (389)	482 (447)
Cocaine years	13 (8)	16 (9)	12 (9)	13 (8)
Addiction Severity Index ($\times 10$) (sd)				
Medical	3 (12)	5 (21)	8 (24)	3 (10)
Employment	11 (24)	27 (37)	14 (30)	7 (20)
Alcohol abuse	2 (10)	4 (19)	0 (0)	0 (0)
Drug abuse	90 (0)	88 (51)	89 (25)	87 (121)
Legal	12 (24)	2 (10)	0 (0)	0 (0)
Family	13 (27)	2 (9)	0 (0)	6 (21)
Psychological	0 (0)	0 (0)	0 (0)	0 (0)