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Butyrylcholinesterase Levels and Subjective Effects of Smoked Cocaine in Healthy Cocaine Users

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Abstract

Background—Butyrylcholinesterase (BChE) is beginning to attract attention as a possible target for cocaine abuse treatment because of its role in metabolizing cocaine.

Objective—The purpose of this analysis was to assess whether endogenous BChE levels are associated with the subjective effects of cocaine.

Methods—Data from 28 participants in five inpatient cocaine self-administration studies were included in the present analysis. Four minutes after each smoked cocaine dose, participants rated their drug-related effects from 0 to 100 using a computerized self-report Visual Analogue Scale (VAS). The main outcome measures were 9 change-in-VAS ratings between a baseline placebo dose and a 25-mg smoked cocaine dose.

Results—After controlling for age, sex, total years of cocaine use, total milligrams of cocaine administered before the 25-mg dose being analyzed, and baseline diastolic blood pressure, endogenous BChE was not significantly associated with any of the 9 change-in-VAS ratings.

Conclusion—Though BChE appears to be a possible target for cocaine abuse treatment, these data suggest that endogenous levels of BChE may not play a role in modifying the subjective effects of cocaine. Future larger studies of BChE with respect to the subjective effects produced by cocaine are needed to confirm or refute these findings.

Introduction

Cocaine abuse is a pervasive public health concern. As of 2012, there were 1.6 million cocaine users in the United States alone (1), and cocaine is one of the most reinforcing drugs of abuse (2). Yet, even with extensive research on cocaine over the years, there is no pharmacological treatment approved by the Food and Drug Administration.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Cocaine blocks the reuptake of dopamine by inhibiting the dopamine transporter (DAT), making traditional pharmacodynamic treatment approaches difficult (3). Synaptic dopamine is then free to continuously stimulate postsynaptic dopamine receptors (4, 5). Chronic cocaine use in humans may lead to alterations in DAT regulation in an effort to reestablish homeostasis. Continuous use has been shown to cause increased dopamine transport to the membrane and enhanced reuptake of dopamine over time (6). Therefore, the dynamic changes in the dopamine system make it a challenging target for cocaine treatment. In addition, altering the effects of a transport blocker without altering the dopaminergic system as a whole is difficult (7).

However, one molecule, butyrylcholinesterase (BChE), is beginning to be more actively studied as a possible target for treatment because of its role in cocaine metabolism (8, 9). (BChE, as used in this manuscript, is also known as pseudocholinesterase, nonspecific cholinesterase, and cholinesterase (10–13).) BChE catalyzes the hydrolysis of cocaine (14), and low BChE levels are associated with an increased risk of cocaine-induced medical complications (15–17). Therefore, if BChE can be engineered to break down cocaine at a faster rate, or if more BChE can be introduced to the system, cocaine may be unable to have prolonged or toxic effects on the individual.

Several studies have shown promising results along these lines. Some preclinical studies demonstrated that exogenously administered BChE degrades cocaine more quickly than natural BChE alone and prevents cocaine-induced toxicity (8, 12, 18, 19). BChE analogs also may be useful for treating cocaine toxicity (20, 21). Besides being indicated for cocaine overdose, increasing BChE levels may be useful in cocaine abuse treatment and relapse prevention (22, 23). BChE therapy is especially promising because it utilizes an enzyme that is already endogenous, and thus, well tolerated by humans. However, no studies thus far have examined what role BChE plays in modifying the positive subjective effects of cocaine in cocaine abusers. Because we measured endogenous BChE levels and their subjective responses to cocaine under the same experimental conditions, we were able to begin preliminary explorations on the topic.

The overall aim of this analysis was to assess whether endogenous BChE levels are associated with the subjective effects of cocaine. If endogenous BChE levels are directly related to how quickly cocaine is hydrolyzed in the body, then endogenous BChE should influence the magnitude of subjective effects that a participant experiences after using cocaine. We hypothesized that the association between endogenous BChE and the subjective effects of cocaine would be negative. Specifically, low endogenous BChE levels should be associated with greater positive subjective effects of cocaine since cocaine remains intact longer.

Method

Study Procedures and Measures

Data from 28 participants in five inpatient cocaine self-administration studies conducted between 2003 and 2010 at the Substance Use Research Center, Columbia University/New York State Psychiatric Institute, were included in the present analysis (24–28). The studies

ranged in duration from 12 to 105 days. All studies were approved by the New York State Psychiatric Institute's Institutional Review Board. All participants provided written informed consent.

All studies required participants to be non-treatment seeking, between 21–50 years of age and not dependent on any drugs besides cocaine, tobacco, and caffeine. The primary route of cocaine use was smoking for all participants. Exclusion criteria included a history of Axis I psychiatric disorders, any significant medical conditions that would make participation unsafe, clinically low plasma BChE levels (less than 350 Units/Liter), and insufficient cocaine use (less than an average of \$50/week). We had both safety and scientific reasons for excluding individuals with clinically low BChE levels. We had concerns that the participants with extremely low BCE levels would not be able to adequately metabolize the doses of cocaine that we were testing, and we wanted to avoid potential cocaine-induced cardiotoxicity in those participants.

Plasma BChE levels were measured approximately two weeks prior to the first laboratory session of each study and analyzed by Quest Diagnostics (New York, NY); the reference range for plasma BChE levels by Quest Diagnostics was 350 to 934 Units/Liter. Samples were collected following the standardized procedures used by Quest Diagnostics. One full lavender-top (EDTA – Ethylenediaminetetraacetic acid) tube of whole blood was drawn and spun within 1 hour to separate plasma from red blood cells. The plasma was then poured into a plastic aliquot tube and refrigerated until shipping. Quest Diagnostics picked up the samples each weekday and transported the samples in a refrigerated manner using cold packs.

Quest Diagnostics' analysis of cholinesterase (the company's terminology for BChE) level is based on the Roche Diagnostics Cholinesterase Method by Ellman et al. (29). The reagents/working solutions included a phosphate buffer (pH 7.2), dithiobisnitrobenzoic acid, and acetylthiocholine iodide. The calibrator machine is a Calibrator for Automated Systems (Cat. No. 10759350 360), which is used with 0.9% NaCl. Calibration includes traceability and two-point frequency. The lower detection limit is 25 Units/Liter. Repeatability coefficient of variation (CV) values were: 0.9% (human serum pool), 0.6% (Precitrol N-Control), and 0.7% (Precitrol A-Control). Intermediate precision CV values were: 0.8% (human serum pool), 1.4% (Precitrol N-Control), and 1.0% (Precitrol A-Control). For method comparison, 97 samples were measured. The Passing/Bablok (30) equation was: $y = 0.998x + 15.9$, with SD (m95) = 123.4; the linear regression equation was: $y = 0.997x + 21.7$, with $r = 0.998$ and $Sy.x = 51.6$.

If a study involved medication administration, only data from the placebo medication condition were used in this analysis. In the studies, participants were allowed to self-administer repeated doses of smoked cocaine (0, 6, 12, 25, and/or 50 mg per dose) on multiple occasions. Maximum possible exposure to cocaine in each study ranged from 486 mg/week to 1598 mg/week. The data in this analysis only included the first administration of 25 mg cocaine within a session compared with baseline placebo administration in the same session. From our past experience with dose-response relationships of smoked cocaine in the laboratory (31–35), we only analyzed the intermediate strength 25-mg dose to avoid floor

and ceiling effects associated with subjective responses to smaller (6 and 12 mg) and greater (50 mg) doses. In addition, we did not have enough power to look at the 6, 12, or 50 mg doses in this analysis, as these doses varied among studies. The participant was blind-folded during each dose administration, so that they would not be able to see how much cocaine they were receiving.

Four minutes after each smoked cocaine dose, participants completed a subjective effects questionnaire using a 100-mm Visual Analogue Scale (VAS). Participants were told to respond based on how they were feeling at that moment. The following 9 items were used for this analysis: “I am craving cocaine,” “I feel high,” “I feel stimulated,” “I feel a good drug effect,” “I feel a bad drug effect,” (“bad” means a negative effect) “The dose was of high quality,” “The dose was potent,” “I liked the choice,” and “For the dose I would pay...”.

Data Analysis

We conducted all analyses using IBM SPSS Statistics version 22 (Armonk, NY). We initially conducted descriptive analyses on all variables. We used z-scores to assess continuous variables for extreme values (> 3.29 or < -3.29); any extreme values were adjusted to the next highest value. Due to the exploratory nature of the analyses, we considered p-values < 0.05 as significant. The main outcome measures were the 9 change-in-VAS ratings between a baseline placebo dose and a 25-mg smoked cocaine dose in the same session.

Using the correlation function in SPSS, we examined the correlation of BChE level and the 9 change-in-VAS ratings. We conducted both uncontrolled and controlled analyses. Since there is some evidence that sex can affect BChE levels (36–38), we controlled for sex. We controlled for age and total years of cocaine use, as some studies have shown an association between the subjective effects of cocaine and age or total years of cocaine use (39–43). We controlled for baseline diastolic blood pressure, as this variable was associated with some of the VAS ratings. Finally, we controlled for the total milligrams of cocaine administered before the 25-mg dose being analyzed, in order to remove any subjective effects associated with previous doses of cocaine administered.

We also conducted a linear regression in SPSS, where we examined the prediction of the 9 change-in-VAS ratings by BChE level. In block 1, we included age, sex, total years of cocaine use, total milligrams of cocaine administered before the 25-mg dose being analyzed, and baseline diastolic blood pressure as predictors. In block 2, we included the BChE level as a predictor. We report the *b*-values, standard errors, and significance of BChE as a predictor while the effects of all other predictors were held constant.

Results

Table 1 contains the demographic and clinical features of the sample. Most participants were high school-educated African-American men with a mean age of 40.9. On average, participants currently used \$451 of cocaine per week and had used for 20.9 years. Participants also used alcohol for 20.6 years, marijuana for 21.7 years and cigarettes for 13.2

years. Figure 1 graphically displays the individual BChE results. Table 2 contains the mean absolute and change-in-VAS ratings.

Table 3 presents the correlation and regression analyses for the 9 change-in-VAS ratings. After controlling for age, sex, total years of cocaine use, total milligrams of cocaine administered before the 25-mg dose being analyzed, and baseline diastolic blood pressure, endogenous BChE was not significantly associated with any of the 9 change-in-VAS ratings.

Discussion

We assessed whether endogenous BChE levels are associated with the subjective effects of cocaine from 28 participants in five inpatient cocaine self-administration studies. We found that endogenous BChE levels were not associated with the subjective effects produced by cocaine.

Our negative results may be due to a few reasons. First, we were only able to analyze the 25-mg dose, since we did not have enough power to analyze other doses. Second, initial evidence in preclinical studies may not translate to studies in human populations. Third, we studied endogenous BChE, which may be different from exogenously administered BChE. Finally, focusing on BChE alone may not be sufficient to impact a complex disorder such as cocaine abuse.

This analysis has several strengths. First, we were able to combine data from 5 different cocaine self-administration studies. While 28 participants may seem small for a clinical trial, this sample size is comparable to other human abuse liability studies. Second, we were able to use change scores as an outcome measure to adjust for any individual differences in VAS ratings. Finally, we were able to analyze 9 different VAS ratings, which included both positive and negative subjective effects.

This analysis also has a few limitations. First, the studies were not originally designed to address the aim of this post-hoc analysis. Second, the sample mainly consisted of African-American men, and the lack of diversity in our sample may have influenced the results. Third, since all participants were not seeking treatment for their drug use and had no comorbid substance dependence or psychiatric disorders, these results may not be generalizable to clinical populations, such as in a community-based addiction treatment program. Finally, individuals with clinically low BChE levels were excluded from participation. It would be of interest to study in a controlled setting the effects of cocaine in individuals with low BChE levels who currently use cocaine to better assess how BChE levels may affect the response to cocaine.

Conclusion

Though BChE appears to be a possible target for cocaine abuse treatment, these data suggest that endogenous levels of BChE may not play a role in modifying the subjective effects of cocaine. Future larger studies of BChE with respect to the subjective effects produced by cocaine are needed to confirm or refute these findings.

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Figure 1.
Graph of Individual Plasma Butyrylcholinesterase Results.

Table 1

Demographic and Clinical Features.

		Mean (S.D.) or % <i>n</i> = 28 ^a
Demographic Features	Age	40.9 (3.0)
	Male	67.9%
	Female	32.1%
	Caucasian	10.7%
	African-American	85.7%
	Mixed race	3.6%
	Hispanic	7.1%
	Employed	32.1%
	Single marital status	92.9%
	Years of education	12.8 (1.8)
Clinical Features	\$ of cocaine used/week	451.3 (393.9) [<i>n</i> = 25]
	Total years of cocaine use	20.9 (4.9)
	# of standard alcohol drinks used/day	3.5 (2.5) [<i>n</i> = 14]
	Total years of alcohol use	20.6 (8.8) [<i>n</i> = 8]
	\$ of marijuana used/week	19.3 (14.2) [<i>n</i> = 13]
	Total years of marijuana use	21.7 (7.5) [<i>n</i> = 14]
	# of cigarettes smoked/day	10.6 (6.4) [<i>n</i> = 20]
	Total years of cigarette use	13.2 (8.5) [<i>n</i> = 5]
	Plasma Butyrylcholinesterase level (Units/Liter)	738.8 (174.7)
	Body Mass Index (kg/m ²)	27.0 (4.2)
	Beck Depression Inventory total score	6.7 (8.9)
	Baseline systolic blood pressure	120.0 (14.4)
	Baseline diastolic blood pressure	73.6 (10.5)
	Total milligrams of cocaine administered before the 25-mg dose being analyzed	473.5 (400.3) [<i>n</i> = 17]

^aSample sizes in some cells vary due to missing data points.

Table 2

Visual Analogue Scale Ratings.

		Mean (S.D.) n = 28
VAS Ratings after 25-mg Cocaine Dose	Cocaine Craving	45.1 (27.8)
	High	36.3 (26.3)
	Stimulated	36.9 (28.2)
	Good Drug Effect	34.1 (27.3)
	Bad Drug Effect	4.7 (13.0)
	High Quality	36.5 (29.0)
	Potent	32.9 (29.7)
	Liked Choice	34.6 (28.6)
	Would Pay (\$)	5.8 (6.0)
Change-in-VAS Ratings after 25-mg Cocaine Dose from Baseline	Cocaine Craving	18.4 (42.9)
	High	33.4 (26.2)
	Stimulated	34.5 (27.2)
	Good Drug Effect	31.1 (26.9)
	Bad Drug Effect	2.0 (16.0)
	High Quality	35.4 (28.7)
	Potent	7.5 (29.0)
	Liked Choice	34.0 (28.7)
	Would Pay (\$)	5.3 (6.1)

Table 3

Correlation and Regression Analyses of Butyrylcholinesterase Levels and VAS Ratings.

	Uncontrolled correlation coefficient and significance	Controlled correlation coefficient ^a and significance	Linear regression ^a b-values, standard error and significance
Change-in-VAS Ratings after 25-mg Cocaine Dose from Baseline	Cocaine Craving	$r = 0.082, p = 0.679$	$B = 0.22, SE = 0.117, p = 0.087$
	High	$r = 0.145, p = 0.46$	$B = -0.24, SE = 0.055, p = 0.671$
	Stimulated	$r = 0.116, p = 0.558$	$B = -0.005, SE = 0.05, p = 0.927$
	Good Drug Effect	$r = 0.083, p = 0.675$	$B = -0.052, SE = 0.057, p = 0.382$
	Bad Drug Effect	$r = -0.171, p = 0.385$	$B = -0.049, SE = 0.03, p = 0.133$
	High Quality	$r = 0.221, p = 0.259$	$B = 0.05, SE = 0.057, p = 0.4$
	Potent	$r = -0.311, p = 0.107$	$B = -0.003, SE = 0.072, p = 0.97$
	Liked Choice	$r = 0.025, p = 0.898$	$B = -0.008, SE = 0.06, p = 0.9$
	Would Pay (\$)	$r = 0.101, p = 0.609$	$B = 0.013, SE = 0.015, p = 0.389$

^a All analyses controlled for age, sex, total years of cocaine use, total milligrams of cocaine administered before the 25-mg dose being analyzed, and baseline diastolic blood pressure.