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Apathy predicts hedonic but not craving response to cocaine ☆

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Abstract

Cocaine-induced craving has been implicated in the maintenance of ongoing cocaine use and is presumed to be mediated by enhanced synaptic availability of monoamines, including dopamine. Apathy is a neuropsychiatric syndrome that is associated with hypodopaminergic functioning and is neurobiologically distinct from depression. Apathy has been observed to be prevalent during the initial phases of abstinence in cocaine-dependent individuals. In the current report, we sought to investigate the relationship between apathy, depression, and craving in response to an acute intravenous administration of cocaine. To this end, sixteen non-treatment seeking volunteers were evaluated. Following acute administration of cocaine (40 mg, IV), patients with low apathy scores exhibited increased craving, whereas patients with high apathy scores exhibited decreased craving. In addition, patients with high apathy scores exhibited increased ratings of the subjective measure of "High", suggesting that high apathy predicts a greater hedonic response in dependence. Self-reported ratings of depression did not account for the observed differences. The data reveal that cocaine-induced craving is not ubiquitous, and may not play a critical role in the maintenance of cocaine dependence. Overall, the findings suggest that apathy predicts hedonic but not craving response to cocaine.

Keywords: Cocaine; Apathy; High; Depression; Craving; Withdrawal

1. Introduction

On the basis of pre-clinical findings, researchers have sought to identify clinical syndromes that are mediated, at least partially, by dopamine (DA) tone, with the intent of developing pharmacological treatments for the amelioration of cocaine-induced craving. Cocaine-induced craving is characterized by increased desire for the drug after ingestion of a priming dose (Dudish-Poulsen and Hatsukami, 1997; Fischman et al., 1990; Jaffe et al., 1989; Preston et al., 1993). This phenomenon has been identified as a mechanism that potentially explains why, during abstinence, a single exposure to cocaine may precipitate escalating use and recidivism (lapse → relapse)(de Wit, 1996). Despite the assumption that cocaine-induced priming leads to relapse to dependence, little is known about the factors that mediate this phenomenon in humans. A variety of factors have been identified as potential mediators of drug-seeking behavior in pre-clinical models, including increased DA neurotransmission (Berridge and Robinson, 1998). These findings coincide with work in human laboratory models, in which self-reported drug craving is enhanced by compounds that increase DA activity (Reid et al., 1998), and is blocked by antagonists of the DA type-2 (D_2) receptor (Berger et al., 1996).

Research using imaging has shown that low levels of D_2 receptors are associated with increased ratings of "liking" following methylphenidate administration (Volkow et al., 1999a, 2002). Research in non-human primates has shown that increases in D_2 availability (induced by manipulations in the social hierarchy) were associated with reductions in the reinforcing effects of cocaine (Morgan et al., 2002). Similarly, autopsy studies have shown that drug dependence is associated with alterations in brain DA signaling generally (Mash et al., 2002; Staley et al., 1995; Worsley et al., 2000). Taken together, these data suggest that low levels of dopaminergic neurotransmission will be associated with enhancement of the effects produced by stimulant drugs.

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Of interest, mood has often been mentioned as a potential factor contributing to drug taking behavior. For example, in one report, the intensity of depressive symptoms was positively correlated with cocaine-induced craving following acute cocaine administration (measured using the Hamilton Depression Rating Scale, $r=0.81$)(Elman et al., 2002). Findings from other studies have not supported this hypothesis, however (Foltin and Fischman, 1997; Roache et al., 2000).

Given that depression is not consistently associated with cocaine-induced craving, it seems reasonable to consider other clinical syndromes that may be more closely linked. A candidate syndrome is apathy, which is similar to depression, but is considered to be neurobiologically distinct because it is more closely tied to dopaminergic functioning (Levy et al., 1998; Marin et al., 1994, 1995). Cardinal symptoms of apathy include amotivation, anhedonia and loss of interest. In the two studies that examined this phenomenon in cocaine-dependent individuals, preliminary findings showed that apathy is likely to be present during the initial phases of abstinence (Kalechstein et al., 2002; Newton et al., 2004).

Apathy is prominent in individuals diagnosed with frontal–subcortical disorders, such as Parkinson's and Alzheimer's diseases, in which reduced DA neurotransmission is a key feature (Cummings, 1993; Marin et al., 1994; Robert et al., 2002). Of importance, a number of published reports have demonstrated that administration of DA agonists resolves, at least to some degree, symptoms of apathy in individuals diagnosed with HIV-1 (Castellon et al., 1998), Parkinson's disease (Czernecki et al., 2002), and non-Alzheimer's frontal lobe dementia, cerebral infarction, intracranial hemorrhage, alcoholism, and traumatic brain injury (Marin et al., 1995). Furthermore, recent evidence demonstrated that apathy symptoms were relieved after treatment with bupropion (Corcoran et al., 2004) and that methylphenidate, which works by inhibiting DA reuptake, alleviated apathy in a patient with Parkinson's disease (Chatterjee and Fahn, 2002).

On the basis of these findings, we hypothesized that baseline apathy would be positively correlated with cocaine-induced craving. We additionally hypothesized that depressive symptoms would not be associated with cocaine-induced craving, and that the association between apathy and depression would be modest.

2. Methods

2.1. Participants

Sixteen non-treatment seeking cocaine-dependent males ($N=13$) and females ($N=3$) were recruited from the community through advertisements in local newspapers. Potential participants were excluded for a history of stroke or epilepsy, dependence on drugs other than cocaine and nicotine, or a diagnosis of a thought or mood disorder, assessed using the SCID (Spitzer et al., 1995). Pregnant females were excluded. Laboratory tests, including complete blood count, electrolytes, and electrocardiogram, were within pre-determined limits. Because HIV infection can alter cognition and mood, subjects were excluded for testing HIV seropositive (one potential volunteer was excluded for this reason).

All participants met DSM-IV criteria for cocaine dependence, reported using at least 0.5 g of cocaine or crack per week for the six months prior to the study, and produced a positive urine benzoylecgonine test within two weeks of entering the study. All participants primarily smoked crack cocaine. Urine drug toxicology screens were collected every several days and whenever participants left the inpatient unit to ensure abstinence from self-administered cocaine or other non-study drugs.

The mean age of the sample was 38.7 years (range 25 to 48) and the mean education level was 12.6 years (range 10 to 16). The racial makeup of the group was 11 African-Americans, 3 Caucasians, 1 Latino, and 1 Native American. After complete description of the study to the subjects, written informed consent was obtained. Participants were reimbursed for participation. Subjects included in this analysis were participating in studies evaluating the safety of a cocaine challenge during the administration of potential medication treatments for cocaine dependence. The assessments described here were performed before initiation of any medication treatment.

2.2. Study procedures

On the day of admission, study participants were administered a battery of surveys, including the Addiction Severity Index (McLellan et al., 1992). Daily after admission, subjects were administered the apathy subscale of the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), and the Beck Depression Inventory (Beck et al., 1968). The NPI was chosen as it has been shown to have strong biological correlates. Specifically, changes in prefrontal and anterior temporal blood flow were highly correlated with NPI apathy scores using single photon emission tomography (Cummings, 1993). The validity and reliability of the NPI is established and it is accepted as a measure of neuropsychiatric symptoms (Cummings, 1993). It contains a structured clinical interview, which is scored through informant knowledge of the participant, focusing on observable symptoms and behaviors. If any of these symptoms are present, they are rated on a 4-point frequency scale and a 5-point severity scale. The product of the frequency and severity scales within each domain produces a total domain score. In this study, only the apathy subscale was completed. This consisted of a 7-item scale for which participants answered Yes or No to the items.

Four days after admission, participants received cocaine (20 mg, IV) at 1 mg/s as a safety screen. On the following day, participants were administered a higher dose of cocaine (40 mg, IV). Cardiovascular parameters were monitored to ensure the safety of the participants, and at baseline, 3, 6, 10, 20, 30, and 40 min after cocaine administration, participants provided verbal ratings on a 0 to 10 point scale for a variety of subjective effects, including "Crave". For this adjective, we instructed subjects to rate how intensely they craved cocaine at that moment. Zero reflected minimal craving, and 10 reflected maximal craving. For "High", verbal ratings on a 0 to 10 point scale were given by subjects on the basis of the intensity of the

"High" produced by cocaine at that moment. Zero reflected minimal High, and 10 reflected maximal High.

2.3. Assurances

All procedures in the experimental protocol were approved by the UCLA Institutional Review Board for the use of human subjects in research, and all procedures were in compliance with the Declaration of Helsinki for human subjects.

2.4. Data analysis

The sample was divided into two groups based on apathy ratings on the day of the 40 mg cocaine administration, using a median split. Seven subjects reported minimal apathy (3 or less on the NPI apathy subscale) whereas 9 subjects reported moderate apathy (4 or higher). ANOVAS were used to compare Craving or High in the low apathy group versus craving in the high apathy group at each time-point following cocaine administration. Associations among apathy, depression, Craving and High were also examined, using simple linear regression correlations. Because apathy ratings were not normally distributed, non-parametric correlation coefficients were used (Spearman's rho). Significance was set at $p<0.05$.

3. Results

The participants in the high versus low apathy groups did not differ significantly with regard to age, gender, or average years of cocaine use. The data revealed that acute cocaine administration increased craving in participants with low apathy scores to a greater extent than those with high apathy scores (Fig. 1). Higher levels of apathy were associated with lower levels of cocaine-induced craving at 3, 6 and 10 min, but this was significant only at 3 min following cocaine administration ($\rho=-0.51$, $p<0.05$). The noteworthy nature of these responses for each individual (from 0–6 min) is highlighted in Fig. 2. Visual analog ratings of depression did not change following cocaine administration and were similar in the low apathy (3.87±3.4) and high apathy groups (3.87±2.9) (Table 1). Correlations between depression (measured using BDI) on the day of drug administration and both cocaine-induced Craving and High were not significant at any time-point following cocaine administration. In contrast to the findings with Craving, cocaine administration increased High in participants with *high* apathy scores to a greater extent than those with low apathy scores (Fig. 3). Higher levels of apathy were correlated with higher levels of cocaine-induced High at 3, 6 and 10 min, but this approached significance only at 3 min following cocaine administration ($\rho=0.50$, $p<0.06$).

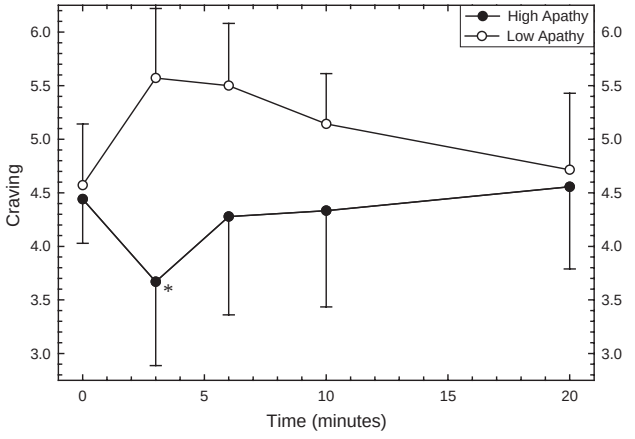

Fig. 1. Mean (±S.E.M.) craving for cocaine at baseline ($T=0$), and 3, 6, 10 and 20 min and following acute cocaine (40 mg, IV) administration.

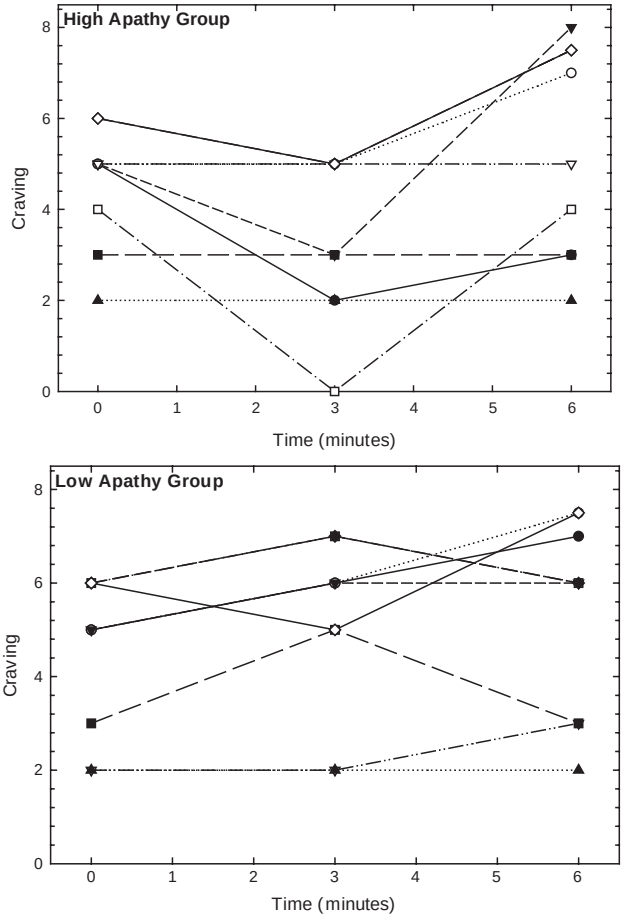

Fig. 2. Craving scores for individual subjects in High Apathy (top) and Low Apathy (bottom) groups at baseline ($T=0$), and 3 and 6 min and following acute cocaine administration.

4. Discussion

The current study demonstrated that cocaine-induced craving is negatively associated with baseline apathy ratings,

Table 1
Results of *T*-tests comparing high and low apathy groups on cocaine-induced craving and depression

	Low apathy, $n=7$	High Apathy, $n=9$	t (14)	$p \leq$
	Mean rating 1.1±1.4	Mean rating 6.0±2.1		
Change in craving	1.0 (0.58)	−0.78 (0.68)	2.1	0.05
Depression	3.87 (3.4)	3.87 (2.9)	–	NS

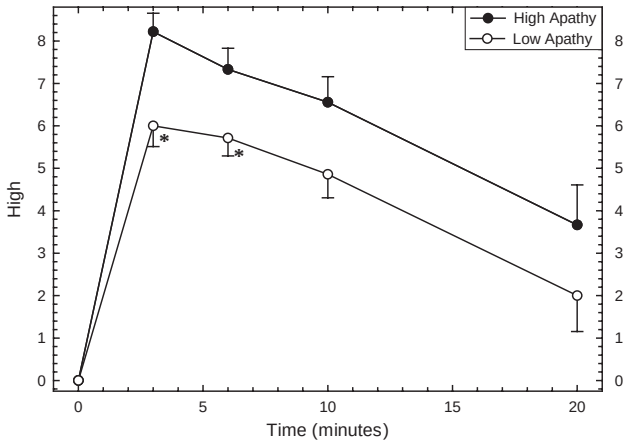

Fig. 3. Mean (±S.E.M.) scores for High at baseline ($T=0$), and 3, 6, 10 and 20 min and following acute cocaine (40 mg, IV) administration.

and the subjective measure of High is positively associated with baseline apathy ratings. The reported effects were not due to depression since these values were similar among high versus low apathy groups. The observed drug effects were of very short duration. Cocaine-induced changes in craving were significant only at 3 min after cocaine administration, and changes in High were significant at 3 and 6 min. The brief duration of both of these effects limits the clinical implications of the finding to the time period immediately following drug use, such as during a binge. Cocaine addicted patients are not a homogenous group and differ from one another in responses to laboratory measures of craving, apathy and high. This variability may reflect premorbid characteristics and/or differential exposure to cocaine or other drugs.

Apathy is characterized by anhedonia, decreased initiative, and decreased spontaneous activity (Levy et al., 1998; Marin, 1990, 1996). In the neurological literature, apathy is generally considered the result of diminished function in subcortical regions. Examples of this include apathy in Parkinson's disease, Alzheimer's disease, and stroke. From our perspective, apathy in the context of cocaine dependence could be the result of premorbid impairments in DA system functioning or the consequence of long-term exposure to stimulant drugs. It is unlikely that apathy, in and of itself, is a manifestation of cocaine withdrawal as apathy persists after other symptoms (e.g., depression) have resolved.

These data support the interpretation of apathy as reflective of a relative impairment of dopaminergic functioning. Compared to non-drug-using volunteers, addicts showed increased DA release (measured using raclopride displacement) following methylphenidate administration in the thalamus, and this was associated with increased cocaine craving. Similarly, greater DA release was associated with greater increases in self-reported High (Volkow et al., 1999b). The expected converse of this profile is a reduction in DA release in the striatum, which was associated with reduced ratings of High (Volkow et al., 1997). Our finding that lower levels of apathy were associated with increased ratings of craving coincides with expected lower levels of DA in brain, though are incongruent with anticipated ratings of High given this profile. A central measure of brain DA was not obtained in our patients, therefore this matter cannot be resolved fully with the available data.

Apathy has received little attention in the drug abuse literature, which is surprising since an early study showed that 50 out of 75 cocaine-dependent participants reported apathy after the initiation of abstinence (Brower et al., 1988). It may be that the prevalence of apathy has been under-reported in cocaine-dependent populations because apathy is not typically viewed as a clinically distinct syndrome. For example, apathy is characterized as a symptom of depression in the DSM-IV TR and the HRSD. This characterization might not be warranted given that apathy appears to be neurobiologically distinct from depression (Levy et al., 1998) and that the syndrome is treatable with DA specific compounds, but not necessarily conventional antidepressants (Marin et al., 1995). This is bolstered by our own data (this report) showing no correlation between depression and apathy.

There are important limitations to the current report; in particular, the sample size ($N=16$) was small. Craving was assessed using a simple visual analogue scale, which, though standard, may not reflect all aspects of craving. Further, with isolated exceptions, craving per se has not been shown to predict subsequent stimulant use, either in the laboratory (Dudish-Poulsen and Hatsukami, 1997; Foltin and Haney, 2000) or in the clinic (Weiss et al., 1995).

Overall, this study extends ongoing research with respect to the use of apathy as a predictor of important outcome measures, including cocaine-induced craving. While this study examined craving following a single dose of cocaine, it remains to be seen how apathy and syndromes affecting dopaminergic functioning will also mediate craving over longer time periods or in other settings.

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