Cocaine Addicts Prone to Cocaine-Induced Psychosis Have Lower Body Mass Index Than Cocaine Addicts Resistant to Cocaine-Induced Psychosis — Implications for the Cocaine Model of Psychosis Proneness

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Abstract: Background: The specific pathogenesis of increased vulnerability to cocaine-induced paranoia/psychosis is unknown. Weight loss has been long observed in patients abusing stimulants (including cocaine and the amphetamines). In the current study, we compared Body Mass Index (calculated as weight in kilograms divided by the square of height in meters) in Cocaine-Induced Psychosis cases, referred to as "Cocaine-Induced Psychosis-prone" (n=40) and non-Cocaine-Induced Psychosis cases, referred to as "Cocaine-Induced Psychosis-resistant" (n=29) consecutively admitted to a research substance abuse unit to determine whether Body Mass Index is associated with Cocaine-Induced Psychosis. Height and weight were measured and Body Mass Index calculated by a licensed nutritionist using a standardized protocol. Cocaine-induced psychosis and cocaine use patterns were assessed using the Cocaine Experience Questionnaire. Results: Body Mass Index in the Cocaine-Induced Psychosis-prone patients was significantly lower than in the Cocaine-Induced Psychosis-resistant patients (i.e., 23.1 kg/m² ± 2.5 vs. 25.4 kg/m² ± 3.5 (P=.003), respectively). Percentage of Ideal Body Weight also differed significantly between the two groups. Conclusions: The data suggest that lower Body Mass Index may be associated with increasing proneness to developing psychotic symptoms in the context of crack cocaine use or that higher Body Mass Index might be associated with some protection against Cocaine-Induced Psychosis in the context of similar use patterns. In the Discussion the authors speculate as to why Cocaine-Induced Psychosis is more commonly observed in the patient population with lower Body Mass Index and lower percentage of Ideal Body Weight. They evoke possible involvement of cocaine's influence on the anorexigenic cytokine Tumor Necrosis Factor, Cocaine-and-Amphetamine-Regulated Transcript, or suppression of the appetite stimulating Neuropeptide Y, or cocaine-induced deficits in nicotinic cholinergic neural-transmission, all of which have not only been linked to weight and appetite, but also to idiopathic psychosis. It could be speculated that one or more of these systems might be differentially affected by cocaine addiction in the psychosis prone Cocaine-Induced Psychosis group vs. the psychosis resistant non-Cocaine-Induced Psychosis group. Further exploration of these possible associations seem warranted. Such findings would have implications for the cocaine model of psychosis proneness and perhaps for the stimulant model of psychoses in general.

Introduction

Regular crack cocaine use is associated with a paranoid psychosis (cocaine-induced paranoia/psychosis, or CIP) in up to 80% of crack addicts (1) and is thought by many to be at least a partial drug-induced model of schizophrenia. However, some (2) have argued that the model is limited, because of qualitative differences in the subjective phenomena described by the patients with schizophrenia and those with CIP (3, 4, 5). In spite of the limitation of the model, Harris and Batki (3) reported that although the patients they studied with stimulant psychoses all had a predominance of positive symptoms from the Positive and Negative Syndrome Scale (PANSS) (6), “some subjects had substantial Negative Scale scores (26%), bizarre delusions (95%), and Schneiderian hallucinations (63%), mimicking a broad range of schizophrenic symptoms” (3, p. 28).

Some factors that might increase the vulnerability of a cocaine user to develop psychotic symptoms have been studied. These include investigations of
psychological psychosis proneness scales (5) and sensory gating studies (7, 8). Further, deficits in sensory gating and attention have been reported in schizophrenia (9) and their seemingly unaffected relatives, and in those cocaine addicts prone to CIP (7, 8).

The specific pathogenesis of increased vulnerability to CIP remains unknown. Weight loss has been long observed in patients abusing stimulants (such as cocaine) (10); low BMI has recently been associated with the neurological disorder of essential tremor (ET)(11). Thus, weight loss may be associated with impaired CNS functioning. In the current study, we compared body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) and percentage of ideal body weight in CIP-prone patients and CIP-resistant patients admitted to an inpatient substance abuse research unit to determine whether body leanness was associated with vulnerability to CIP.

Additionally, prior reports have suggested that body weight gain (BWG) might be an important correlate of antipsychotic medication response (e.g. there have been prior reports of increased BWG associated with better antipsychotic response) (e.g. 12-15).

Methods

Subjects: 69 "otherwise healthy" (60 male, 9 female) crack cocaine dependent subjects (ages 23-49) consecutively admitted to a locked inpatient substance abuse research and treatment unit were studied. Subjects remained on the locked ward throughout the study period except for their radiological evaluations, during which they were under supervision at all times.

Consensus Structured Clinical Interview for DSM-III-R (SCID) (16) ratings (see Figure 1) were completed on all study subjects and the diagnosis of cocaine dependence confirmed. All patients with personal histories of idiopathic psychotic disturbance (e.g., schizophrenia, bipolar disorder, paranoic disorder) or any history of other psychotic

Figure 1. Process for identifying and dividing out CIP from non-CIP cocaine users. CIP subjects with history of psychotic symptoms outside of period of cocaine high were excluded per CIP criteria of Satel et al. and Satel and Edell (1, 5)

CIP = Cocaine-induced psychosis; SCID = Structured Clinical Interview for DSM-III-R; CEQ= Cocaine Experience Questionnaire.
disorder outside of a period of cocaine/other past stimulant intoxication were excluded from the study. Patients with substance use dependence disorders other than cocaine dependence were also excluded from the study, based on consensus SCID findings and other clinical evidence of use of other substances besides cocaine. Medical, laboratory, and other diagnostic examinations revealed no comorbid medical disorders in the study patients, if significant neurological or medical conditions were found, the subjects were excluded from the study. Chest X-rays and CT scans of the head were all WNL in the included study subjects.

Consensus rating interviews using the Cocaine Experience Questionnaire (CEQ) (1, 5) were performed on all study subjects by trained raters who were “blind” to the hypothesis outlined above regarding a possible relationship between CIP and lower body weight. The CEQ was used to determine: a) current and past patterns of cocaine use; b) which subjects experienced cocaine-induced paranoia (CIP/psychosis) during periods of cocaine intoxication; and c) the severity of cocaine-induced paranoid/psychotic symptoms. At the time of admission to the unit, the urine toxicology screens were positive for cocaine. However, at the time all of the clinical assessments were performed (including the SCID, CEQ, nutritional assessments and measures of body weight and height), urine toxicology screens were negative. All patients provided written informed consent for this approved study.

From the time of admission to the unit to the time of nutritional assessment by a licensed nutritionist, the subjects were on no medications. Anthropomorphic body weight assessments including Body Mass Index (BMI) and Percent (%) Ideal Body Weight (IBW) were completed within one week of admission to the substance abuse research unit (voluntary locked inpatient unit) by the nutritionist. From the time of admission to the unit, all subjects were provided three meals daily (all with double portion size) and provided snacks ad libitum. Weights and anthropomorphic body evaluations were completed using a standard computer program to calculate BMI and % IBW (all subjects were measured on the same scale [Scaletronix, Wheaton, IL] and attached height ruler). The nutritionist was blind to subject group and hypothesis outlined above.

## Results

Examination of the SCID and CEQ demographic data and cocaine patterns of use data revealed no statistically significant differences between the CIP-prone and CIP-resistant groups (see Table 1). However, as can be seen in Table 2, CIP-prone subjects were significantly leaner than CIP-resistant subjects (as measured both by Body Mass Index [BMI] and Percentage of Ideal Body Weight [%IBW]), even when covaried for years of use.

Table 1. Mean Age and Patterns of Crack Cocaine Use in the CIP (n=40; 4 women) vs. Non-CIP Subjects (n=29; 5 women)

<table>
<thead>
<tr>
<th></th>
<th>CIP (n=40)</th>
<th>NonCIP (n=29)</th>
<th>t-value (df)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of study subjects (SD)</td>
<td>31.3 (6.4)</td>
<td>33.9 (5.9)</td>
<td>1.8 (67)</td>
<td>.08</td>
</tr>
<tr>
<td>Mean # yrs of regular cocaine use (SD)</td>
<td>7.2 (4.9)</td>
<td>6.3 (4.2)</td>
<td>-.78 (62)</td>
<td>.44</td>
</tr>
<tr>
<td>Mean # grams of use (SD)</td>
<td>3.5 (2.5)</td>
<td>5.6 (9.4)</td>
<td>1.3 (62)</td>
<td>.21</td>
</tr>
<tr>
<td>Mean duration of binges/wk (hrs) (SD)</td>
<td>26.2 (23.8)</td>
<td>34.1 (32)</td>
<td>1.1 (60)</td>
<td>.27</td>
</tr>
<tr>
<td>Mean # binges/wk (SD)</td>
<td>2.4 (2.1)</td>
<td>2.3 (2.1)</td>
<td>-.15 (61)</td>
<td>.88</td>
</tr>
<tr>
<td>Mean # total hours spent binging/wk (SD)</td>
<td>46.3 (47)</td>
<td>41.8 (33.8)</td>
<td>-.41 (60)</td>
<td>.68</td>
</tr>
<tr>
<td># days since time of last use to time of admission (SD)</td>
<td>3.8 (2.7)</td>
<td>3.8 (2.8)</td>
<td>-.06 (43)</td>
<td>.95</td>
</tr>
<tr>
<td># days from admission to time of nutritional assessment (SD)</td>
<td>4.7 (4.2)</td>
<td>3.7 (3.7)</td>
<td>-.78 (38)</td>
<td>.44</td>
</tr>
</tbody>
</table>
### Table 2. Mean Body Mass Index (BMI) and % Ideal Body Weight (IBW) in the CIP vs. Non-CIP Subjects

<table>
<thead>
<tr>
<th></th>
<th>CIP</th>
<th>NonCIP</th>
<th>t-value (df)</th>
<th>p-value</th>
<th>F-value (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (SD)</td>
<td>23.1 (2.5)</td>
<td>25.4 (3.5)</td>
<td>3.14 (67)</td>
<td>.003</td>
<td>11.4 (1,68)</td>
<td>.001</td>
</tr>
<tr>
<td>%IBW (SD)</td>
<td>98.1 (8.9)</td>
<td>106.1 (12.2)</td>
<td>3.14 (67)</td>
<td>.003</td>
<td>10.9 (1,68)</td>
<td>.002</td>
</tr>
</tbody>
</table>

### Discussion

The above results, although preliminary, seem to support the notion that patients addicted to crack cocaine who are leaner (with lower BMI and percent ideal body weights) are in a group more likely to endorse CIP on the CEQ. Hence, lower BMI may be a “vulnerability factor” to psychosis in the context of regular crack cocaine use. And as low BMI has recently been associated with the neurological disorder of essential tremor (ET) (11), CIP perhaps can now be added to the neuropsychiatric conditions associated with lower BMI (or seen slightly differently higher BMI might be somehow “protective” against similar patterns of cocaine use).

Possible connections to further understanding why CIP is more commonly observed in the patient population with lower BMI and %IBW might involve cocaine’s influence on the anorexigenic cytokine Tumor Necrosis Factor (TNF) and its related Cocaine- and Amphetamine-Regulated Transcript (CART), cocaine-suppression of the appetite stimulating Neuropeptide Y, or cocaine-induced deficits in nicotinic cholinergic neural-transmission. It could be speculated that one or more of these systems might be differentially affected in the psychosis prone CIP group vs. the psychosis resistant non-CIP group. These possible links to the study findings are more fully outlined below.

### Cocaine and Tumor Necrosis Factor (TNF)

Studies have shown that exposure to cocaine can trigger the proinflammatory pathways, including induction of expression of the inflammatory genes in immune competent human brain microvascular endothelial cells (HBMEC) (17). For instance, treatment with cocaine induced a dose-dependent expression of the Tumor Necrosis Factor-alpha (TNF-alpha) gene; TNF is a cytokine involved in the physiological and metabolic abnormalities found in cachectic states (18), and has also been reported to possibly play a role in idiopathic psychosis (19, 20). It has been said that TNF may have a key role in the control of body mass in normal weight-controlled situations and that abnormalities in either its production (during cachexia) or action (during obesity) are responsible for the lack of control of body weight (21). TNF is also thought to play a role in the weight gain induced by the atypical antipsychotic agents (22).

### Cocaine and Cocaine-and-Amphetamine-Regulated Transcript (CART)

TNF is also associated with “CART” (Cocaine-and-Amphetamine-Regulated Transcript), a novel member of the tumor necrosis factor receptor-associated protein family (23). Elevated levels of CART are associated with reduced food intake and increased energy expenditure.

Interestingly, while Cocaine /Amphetamine Related Transcript (CART) is an established anorectic agent, there is also a growing animal literature demonstrating that CART administration is associated with increased arousal/anxiety and perhaps even psychosis (e.g., CART induces stereotypies in rodents and impairment of auditory sensory inhibition in the [PPI]-Prepulse Inhibition Paradigm) (24-26).

### Cocaine and Nicotinic Cholinergic Neural-transmission

Another possible link to a further understanding of why CIP is more commonly observed in the patient population with lower BMI and %IBW involves cocaine’s influence on nicotinic cholinergic neural-transmission, as there is a growing literature on the role of such neural-transmission in central body weight regulation (27) as well as its role in idiopathic psychosis (28). In fact, Adler et al. (8) suggest diminished nicotinic cholinergic neural-transmission as
the mechanism of physiological aberration found in cocaine addicts prone to CIP vs. those who are not; and the reason for their showing deficits of auditory sensory inhibition (7), the latter a putative marker of “psychosis proneness.” Such nicotinic deficits have also been described in schizophrenia (28).

Cocaine and Neuropeptide Y

Studies have shown that exposure to cocaine can result in decreases in the appetite stimulating Neuropeptide Y (29). Hence, it is possible that the cocaine appetite-suppressing effects via Neuropeptide Y suppression might be more robust in the CIP subjects. There is a growing literature implicating Neuropeptide Y in psychosis (30) as well.

Future Directions

Further exploration of possible associations between weight, appetite and psychosis in the context of crack cocaine addiction seem warranted (31). An elucidation of these associations might contribute to a better understanding of the neuropathophysiology of psychosis and, perhaps, better treatments (31). Czobor et al. (12) note: “The possibility of an association between weight gain and favorable clinical response to neuroleptic treatment was raised in the early [psychopharmacology] literature.” A perhaps related neuropathophysiological question raised by this current paper is: Does higher BMI confer some central “protection” against CIP in persons who are becoming addicted to crack cocaine? The possible relevance of this association, if it exists, to enhancement of the therapeutic response to antipsychotic medications for patients who experience body weight gain remains to be elucidated.

Acknowledgements

This work was supported by a grant from the Department of Veterans Affairs to S.I.D. and Inter-Agency Agreement No. RA-ND-90-10 between the National Institute on Drug Abuse and the Department of Veterans Affairs Medical Center, Washington, D.C. (S.I.D., principal investigator).

References