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Selective Sensitization to the Psychosis-Inducing Effects of Cocaine: A Possible Marker for Addiction Relapse Vulnerability?

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Patients in inpatient rehabilitation for uncomplicated cocaine dependence were asked whether, compared with the time of their first regular use, they could now identify changes in the effects of similar doses of cocaine. We asked about a spectrum of cocaine effects "then" and "now" and whether the same amount of drug caused effects to occur to about the same degree, less intensely (tolerance), or more intensely (sensitization). Nearly half our sample developed predominantly paranoid psychoses in the context of cocaine use. Sensitization was consistently linked only to psychosis-related cocaine effects.

It has been proposed that mesolimbic dopaminergic sensitization might contribute to addiction severity. A preliminary followup of patients who were sensitized or nonsensitized to psychosis development suggests that rehospitalization for treatment of addiction may be more frequent in the sensitized group. **© 1997 American College of Neuropsychopharmacology [Neuropsychopharmacology 16:77–82, 1997]**

KEY WORDS: *Cocaine; Psychosis; Sensitization; Addiction; Relapse*

STUDY ONE: RATES OF OCCURRENCE OF VARIOUS COCAINE EFFECTS AND SENSITIZATION

"Sensitization" to CNS stimulants, a response pattern in which, after intermittent administration, indices of drug response become "augmented," is an extraordinarily robust finding in preclinical studies. Sensitization to the effects of cocaine, specifically, has been reviewed by Post et al. (1987).

In clinical studies sensitization to the psychosis-inducing effects of cocaine have been described by two groups. Satel et al. (1991) described transient, but frequently intense, paranoia in 68% (34/50) of the patients in inpatient rehabilitation for primary cocaine dependence. Three-fourths of the patients who became paranoid (26/34) said these experiences worsened over time, and about 60% (20/34) described a more rapid onset during use. Brady et al. (1991) studied 55 similar patients. Over half (29/55) reported episodes of cocaine psychosis. Of these three-fourths (21/29) also indicated that psychosis worsened over time, half (15/29) said that the psychosis occurred with less drug over time, and approximately half (14/29) also said they were now unable to use cocaine at all without becoming paranoid. The first part of this study attempted to (1) replicate these find-

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ings at our center; and (2) inquire about a spectrum of cocaine effects to see whether sensitization was linked to psychosis-inducing effects selectively or to other drug effects as well.

METHODS

Study Design

We interviewed fifty-seven patients in inpatient rehabilitation for uncomplicated (DSM-III-R) cocaine dependence. The interviews covered demographics, cocaine use history (duration since first use and first regular use and the amount used at those times and currently), the number of detoxifications and rehabilitations, exclusion criteria, and, particularly, changes in cocaine effects over time. The interviews emphasized the description of cocaine-related experiences. A questionnaire was used as an outline, but elaboration was specifically invited. The interviews lasted from half an hour to (in one case) over 2 hours.

Patients were asked whether, compared with the time of their first regular use, they could now identify changes in a spectrum of effects of apparently similar doses of cocaine. We used a clinical questionnaire to ask about:

1. *Euphoria* ("Compared to the first regular use the *same amount* of cocaine now makes me more high, less high, or has about the same effect?")
2. *Jitteriness* ("Compared to the first regular use the *same amount* of cocaine now makes me more jittery, less jittery, or has about the same effect"?)
3. *Increased sexual feelings* ("Some people find that cocaine increases their sexual feelings. Does this happen to you? If so, does the *same amount* of cocaine make it happen more, less, or about the same as when you began regular use?")
4. *Referentiality or unease* (*Referentiality*: "Some people feel that people are present, noticing or watching them, talking about them, or spying on them when they use cocaine. Does this happen to you? Did it happen with the first regular use? Does it happen with the *same amount* of cocaine now? If it does, does it take more, less, or about the same amount of cocaine for this to occur than the first time?" *Unease*: A feeling that "something bad may be going to happen" or "fearful feelings for no reason.")
5. *Delusions* ("Some people feel that they are in serious danger and believe frightening things that aren't true when they take cocaine, like the police are about to break in or other people are following them to kill them. Has this happened to you? Did it happen with first regular use? Does it happen with the *same amount* of cocaine now? Does it take more, less, or about the same amount of cocaine for this to occur as the first time?")
6. *Hallucinations* ("Some people hear voices when they take cocaine or have other hallucinations, such as seeing things that aren't there. Has this happened to you? Did it happen with first regular use? Does it happen with the *same amount* of cocaine now? If this has happened, does it take more, less, or about the same amount of cocaine to make it happen as when it first happened?")
7. *Seizures* ("Sometimes people have seizures after taking cocaine. Has this happened to you? More than once?

For each effect, we asked patients whether the same amount of drug caused the effect to occur to about the same degree, less intensely (tolerance), or more intensely (sensitization).

Because prior studies had indicated sensitization to the psychosis-inducing effects of cocaine (Brady et al. 1991; Satel et al. 1991) and because we wanted to focus on the psychosis-inducing and sensitizing effects of cocaine per se (not the interaction between cocaine and psychosis vulnerability factors), we attempted to exclude patients who had the potential for becoming psychotic for reasons other than cocaine exposure. We thus excluded patients who had ever had psychotic symptoms while "straight," who had had prior psychoses induced by drugs other than cocaine (PCP or hallucinogens), who showed evidence of schizotypy (Schulz et al, 1988; Satel and Edell, 1991) or who ever required psychiatric treatment, even for nonpsychotic conditions. Patients with clinically significant use of other drugs also were excluded (i.e., if chlordiazepoxide or methadone was ordered during detoxification). Because we were unsure about the psychosis- or sensitization-inducing effects of cocaethylene, we also excluded patients who usually drank (more than four drinks) during a cocaine binge. The sample, therefore, was by design *not* representative of all cocaine abusers.

Patients were classified as "paranoid" or "non-paranoid" based on their answer to the interview question about *delusions*. Patients who acknowledged having had delusions were categorized as showing transient cocaine-induced paranoia. Paranoid patients were classified as "sensitized" or "non-sensitized" based on whether or not their paranoia worsened over time and, particularly, whether or not it occurred after lower cumulative doses of cocaine during a binge.

RESULTS

Fifty-seven patients were interviewed (56 males, 1 female). Fifty-five smoked either freebase cocaine or crack. One was an intravenous user, and one currently used cocaine only intranasally, but had smoked extensively previously. Despite preliminary screening by a physician (BC), 17 of the 57 subjects failed to meet inclusion criteria and

Table 1. Number of Patients Excluded and Reason for Exclusion

Number Patients	Reason for Exclusion
5	Alcohol (5)
3	Inpatient treatment for nonpsychotic depression (3)
1	Schizotypy (1)
1	Inpatient psychiatric treatment (psychotic symptoms, possibly fabricated) (1)
1	PCP, mild delusions (1)
1	Alcohol; brief paranoia when "straight" (1)
1	Alcohol; inpatient treatment for depression (1)
1	Interview elicited craving; patient became upset (1)
1	Outpatient treatment for depression (1)
1	PTSD symptoms and psychosis requiring outpatient neuroleptic treatment developed 100 days after participation (1)
1	Major depression requiring inpatient treatment developed 60 days after participation (1)

were excluded from the research sample. Reasons for exclusion are shown in Table 1.

For the remaining 40 patients the average daily dose cost was $87.70, with a wide range ($20 per week to $1,000 in a single binge for two patients). The mean duration of regular use was 5.4 years. Seven patients used cocaine exclusively in binges, usually limited to (and consuming) pay checks. The amout of cocaine taken in these binges ranged from $150 to $200 over 4 to 5 hours to $1,000 over a night. An additional four patients reported such binges predominantly, but also less intensive use between binges.

Psychotic symptoms occurred in 19 patients (47.5%). Eighteen (45%) had paranoid delusions. Of these, five patients (12.5%) also had auditory hallucinations, and one (2.5%) had visual hallucinations. One (2.5%) patient had tactile and visual hallucinations, but no paranoid delusions.

The paranoid experiences were frequently accompanied by intense fear and influenced behavior. Five patients armed themselves (four with knives and one with a club). One "beat up" a girlfriend. Doors, windows, and locks were checked, often repeatedly. Lights were turned out. Drug paraphernalia were hidden or thrown away. One patient hung a blanket over his window; another played a radio to "conceal" the sound of his lighter. Patients hid in bathrooms or closets. One regularly retreated to a "special" room of his house equipped with "triple locks."

Table 2 shows the percentage of patients who reported sensitization, tolerance, no change, or "never experienced" for the various cocaine effects. Eighty-five percent of the sample (34/40) experienced Referentiality or Unease. Of these, 65% reported sensitization (22/34) to these effects. Forty-five percent of patients (18/40) became frankly Delusional. Of these, 61% (11/18) also reported sensitization over time.

There was little sensitization of cocaine effects unrelated to paranoia. Euphoria was experienced by all 40 subjects, but their most frequent assessment (24/40; 60%) was that this did not change over time. Only 5 (12.5%) reported sensitization, and 11 (27.5%) indicated that euphoria decreased over time. Whether the latter patients experienced true pharmacological tolerance to cocaine-induced euphoria or whether the euphoria was increasingly admixed with paranoia-related feelings is uncertain (see Discussion).

Jitteriness was noted by 35/40 (87.5%) of our patients. Of these, over half (19/35) indicated that jitteriness increased over time. Whether this response should be interpreted as pharmacological sensitization or, alternatively, an increasing admixture of paranoia-related feelings also is questionable (see Discussion).

Increased libido occurred in over three fourths of the patients (31/40). Among these, the most common report was that this effect did not change over time (17/31; 55%). For those who did note changes in this effect, equal numbers reported sensitization and tolerance (7/31; 23%). Over half of the patients who developed increased libido (16/31) were impotent at these times.

Hallucinations were infrequent in our sample and occurred in only seven patients (17.5%). Five (classified as "no change") indicated that their hallucinations occurred only occasionally after unusually intense or prolonged

Table 2. Number and Percentage of Patients Reporting Various Changes in Cocaine Effects (n = 40)

Cocaine Effect	Sensitization	Tolerance	No Change	Never Experienced
Referentiality/Unease	22 (55%)	4 (10%)	8 (20%)	6 (15%)
Delusions	11 (27.5%)	3 (7.5%)	4 (10%)	22 (55%)
Euphoria	5 (12.5%)	11 (27.5%)	24 (60%)	0 (0%)
Jitteriness	19 (47.5%)	6 (15%)	10 (25%)	5 (12.5%)
Increased libido	7 (17.5%)	7 (17.5%)	17 (42.5%)	9 (22.5%)
Hallucinations	1 (2.5%)	1 (2.5%)	5 (12.5%)	33 (82.5%)
Seizures	0 (0%)	0 (0%)	0 (0%)	40 (100%)

binges. Three of these five heard voices, one saw two people in his apartment and armed himself with a knife, and one (the only female in the sample) felt and at times saw "bugs" on her skin, particularly in areas with body hair (head, axillae, and pubis). In one patient, the voices and footsteps "went away." The seventh patient reported sensitization of "scratching sounds" on the wall of his apartment.

Seizures did not occur in our sample. Many patients knew seizures could occur after cocaine use. One, who frequented "crack houses," had witnessed a seizure, and another had a girlfriend who had seized while taking cocaine.

Clinical variables and measures of cocaine use for nonparanoid and paranoid patients are presented in Table 3 [detoxification and rehabilitation data were available for 85% (34/40) of the sample]. The results show that the two groups do not differ significantly in age, duration of cocaine use, amount of cocaine used, or number of detoxifications or inpatient rehabilitations.

Paranoid patients were classified as "sensitized" or "nonsensitized" depending on whether or not the paranoia occurred after lower doses of cocaine or, if the dose was difficult to estimate, whether paranoia worsened over time. Clinical variables and measures of cocaine use for sensitized and nonsensitized patients are shown in Table 4. Sensitized and nonsensitized patients do not differ in the number of detoxifications, inpatient rehabilitations, age, duration since earliest cocaine use, or amount used at the time of first regular cocaine use. However, sensitized subjects do show a significantly longer regular cocaine use. At the same time, nonsensitized subjects show a significantly greater dose escalation (cost now minus cost of first regular use) over time.

DISCUSSION

Table 5 shows the present data in the context of the two similar previous studies. The rates of occurrence of psychosis and of sensitization to the psychosis-inducing effects of cocaine appear comparable. One discrepancy in the prior two studies concerned the occurrence of hallucinations. Brady et al. (1991) found these to occur in nearly all psychotic patients, whereas Satel et al. (1991) did not encounter hallucinations but did note that "frequently actual stimuli (sounds and flashes of light) were misinterpreted as evidence that menacing individuals were immediately outside the room or window, preparing to enter." In our sample, hallucinations were reported, but occurred infrequently (auditory in 5/40 patients; visual in 1, and tactile and occasionally visual in 1). As described in the Satel et al. (1991) study, our patients' psychoses were predominately paranoid, brief (lasting several hours), and of quite severe intensity. Insight into the drug-induced basis of the paranoid experiences was lost, but was regained as the psychosis waned. As also noted by Satel et al. (1991), bizarre delusions were not seen.

Paranoid and nonparanoid patients showed similar clinical profiles. In the study by Satel et al. (1991), statistically significant differences in cocaine use between paranoid and nonparanoid patients were not found. However, Brady et al. (1991) found greater lifetime use and heavier use in the past year in psychotic patients.

Some differences between sensitized and nonsensitized paranoid patients, however, emerged in our sample. Sensitized patients showed longer regular cocaine use and also less dose escalation over time, suggesting that psychotic experiences may have somewhat limited use. Similarly, Brady et al. (1991) noted that "many psychosis-positive subjects reported decreasing their cocaine use as a result of increasing paranoia." In contrast, Satel et al. (1991) explicitly noted the absence of such an effect. "In all but three of the [34] paranoid patients, cocaine use was sustained at the before-paranoia level for at least 12 months after the onset of paranoia."

Table 3. Clinical Variables: Nonparanoid versus Paranoid Patients

Variable	Nonparanoid (n = 22 Mean ± SD)			Paranoid (n = 18 Mean ± SD)		
Age	37.7	±	6.4	39.6	±	8.0
Duration since first use (yrs)	11.9	±	6.5	11.9	±	8.2
Duration regular use	5.7	±	5.2	5.0	±	4.0
Cost first regular use ($/day)	49.8	±	38.2	50.1	±	40.8
Cost now ($/day)	96.6	±	108.2	77.4	±	46.9
Dose escalation[a]	34.4	±	83.4	27.4	±	52.7
Detoxifications[b]	0.9	±	1.2	1.7	±	1.2
Rehabilitations[b]	0.8	±	1.0	0.8	±	0.8

[a] Dose escalation: Cost now minus cost of first regular use.
[b] Data available for 34 subjects only.

Table 4. Clinical Variables: Nonsensitized vs. Sensitized Paranoid Patients

Variable	Non-sensitized (n = 7 Mean ± SD)			Sensitized (n = 11 Mean ± SD)		
Age	42.7	±	9.8	37.6	±	6.3
Duration since first use (yrs)	9.5	±	9.9	13.4	±	7.0
Duration regular use[a]	2.3	±	1.6	6.7	±	4.2
Cost first regular use ($/day)	43.3	±	44.3	53.9	±	40.4
Cost now ($/day)	100.1	±	64.8	63.0	±	25.1
Dose escalation[b,c]	61.0	±	34.3	9.1	±	52.9
Detoxifications[d]	1.2	±	0.8	2.0	±	1.4
Rehabilitations[d]	0.7	±	0.5	0.9	±	0.9

[a] Sensitized versus nonsensitized (F = 6.91; df = 1, 16; p = .02)
[b] Dose escalation: Cost now minus cost of first regular use.
[c] Sensitized versus nonsensitized (F = 4.63; df = 1, 16; p = .05)
[d] Data available for 16 patients only.

Table 5. Rates of Occurrence of Cocaine Psychosis and of Sensitization of Psychotic Effects in Three Studies

Study	Psychotics (%)	% of Psychotic Patients Who Showed Sensitization to Psychotic Effects (%)	Patients Showing Psychosis and Sensitization (%)
Satel et al. 1991		76.5, worsened symptoms	52
	68	58.8, lower dose	40
Brady et al. 1991		72.4, worsened symptoms	38.2
	53	52, lower dose	27.3
Present data			
Referentiality/unease	85	65, lower dose	55
Delusions	45	61, lower dose or worsened symptoms	27.5

Referentiality or Unease covaried closely with and appeared to be a precursor to paranoid delusions. Of the 11 patients who noted sensitization to delusions, nine noted concomitant sensitization to Referentiality or Unease, and another experienced Referentiality or Unease prior to delusions, but scored it as unchanged over time. Only one patient reported delusions in the absence of Referentiality or Unease. This relationship is strikingly similar to observations by Ellinwood (1967, 1972) regarding amphetamine psychosis, in which he noted that a "ubiquitous feeling of being watched" became a precursor to paranoid delusions.

Finally, the possible role of emerging early paranoid symptoms (e.g., referentiality/unease) in modifying responses about Euphoria and Jitteriness should be noted. Of the 11 patients who noted declines in euphoria, 9 noted concomitant increases in Referentiality or Unease. Satel et al. (1991) also commented that "an inverse relationship was noted between cocaine high and paranoia." Similarly, of the 19 patients in our sample who experienced increased jitteriness over time, 15 also noted a concomitant increase in Referentiality or Unease. In our questioning, we tried to draw a distinction between physical jitteriness and anxiety or vague fearfulness, but we cannot be certain whether our patients actually grasped this distinction.

STUDY TWO: POSSIBLE RELATIONSHIP BETWEEN PSYCHOSIS SENSITIZATION AND RELAPSE VULNERABILITY

Often, cocaine addiction is severe enough to lead to the loss of all funds and property, jobs, friends, and family. A recently hypothesized substrate for this complusive behavior (Robinson and Berridge 1993) is sensitization of a dopaminergic brain system mediating appetitiveness, incentive, and salience to drug-related cues and thoughts. As the authors point out, the autonomous, dysregulated operation of such a system could help "make sense" of the many irrationalities of addictive behavior and its continuation despite the recognition of declining pleasure and of the massive negative consequences.

As dopaminergic mechanisms are known to be important substrates of stimulant psychosis (Angrist et al. 1974) we reasoned that patients who had developed sensitization to the psychosis-inducing effects of cocaine would also be likely to display a sensitization of the appetitive "incentive salience" system proposed in Robinson and Berridge's (1993) concept. Accordingly, we hypothesized a worse treatment outcome on followup in patients who reported psychosis sensitization than in those who did not. This hypothesis was tested in a retrospective analysis of hospital charts of subjects in our research sample. As our treatment outcome measure, we examined the number of rehospitalizations for cocaine detoxification and/or rehabilitation occurring after a subject's participation in Study One. We hypothesized that sensitized paranoid patients would show a greater number of rehospitalizations than nonsensitized and nonparanoid patients.

METHODS

Hospital charts were sought for all subjects interviewed at least 6 months prior to the time of the chart review. Thirty-seven of the 40 patients were eligible for inclusion. Their interview dates ranged from September 1991 to July 1995. For these, 32 charts were actually obtained. This group included 18 of the 22 Study One patients without paranoia; 5 of the 7 Study One patients who showed paranoia without sensitization; and 9 of the 11 Study One patients who showed sensitized paranoia. For each patient, we tallied the number of inpatient cocaine detoxifications occurring after a subject's participation in Study One.

RESULTS

The average number of rehospitalizations (mean ± SD) was 0.28 ± 0.46 for nonparanoids (N = 18), 0 for nonsensitized paranoids (N = 5), and 0.78 ± 1.09 for sensitized paranoids (N = 9). We hypothesized that sensitized patients

would show a higher rate of relapse than other patients. This hypothesis was tested by an analysis of variance (ANOVA) with group (nonparanoid vs. nonsensitized vs. sensitized) as the between-subjects factor. This indicated a trend toward group differences ($F = 2.57$; df = 2,29, p = .09). For heuristic purposes, an analysis of simple group effects was performed. This indicated a possible difference between nonsensitized and sensitized paranoid patients ($F = 4.28$, df = 1,29, $p = .05$), as well as a trend toward a difference between nonparanoid and sensitized patients ($F = 3.30$, df = 1,29; $p = .08$). In general, the analysis indicates a trend toward a larger number of rehospitalizations among sensitized paranoid patients. (The data for nonparanoids vs. nonsensitized patients: $F = 0.67$, df = 1,29, $p = .42$).

DISCUSSION

Given the small number of patients, these results must be considered very preliminary. The retrospective nature of the rehospitalization data also is a drawback that makes these findings very tentative. Clearly, failure to be rehospitalized could mean either successful abstinence or relapse without treatment. Nonetheless, the results tentatively support the hypothesized relation between sensitization and relapse suggested by the Robinson and Berridge (1993) concept.

If confirmed, these findings may help to identify patients at particular risk for relapse. More important, they imply that medications that block the expression of sensitization in animals may prove helpful in the treatment of cocaine addiction.

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