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A Qualitative and Quantitative Review of Cocaine-Induced Craving: The Phenomenon of Priming

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Abstract

Drug-induced craving is thought to play an important role in relapse occasioned by a “slip”, or an isolated use of a previously abused drug after a period of abstinence. Clinical experience suggests that acute exposure to cocaine elicits craving (hereafter referred to as “priming”); however, this has received surprisingly little attention in the clinical literature.

Aims—The intentions of this review are to provide a qualitative review of the literature as well as a more stringent quantitative review of the existence and presence of cocaine-induced priming effects.

Methods—In order to determine whether priming effects occur following cocaine administration, we conducted qualitative and quantitative reviews of studies in which participants received cocaine under experimentally controlled conditions in the laboratory.

Results—The results of the qualitative review were equivocal, while the quantitative review revealed that cocaine administration was associated with a significant increase in craving for cocaine, and the effect size of this relationship was large.

Conclusion—A review of the individual studies revealed marked variability, suggesting that priming effects did not occur consistently and that there may be factors that mediate or moderate the intensity of the priming effects induced by cocaine. The implications of these findings are discussed.

Keywords

cocaine; priming; craving; reinstatement; relapse

Introduction

Several preclinical studies have shown that experimenter administered cocaine reinstated extinguished responding for animals trained to self-administer cocaine (de Wit & Stewart, 1981;Schenk & Partridge, 1999;Weissenborn, Yackey, Koob, & Weiss, 1995). It was found in the preceding studies that after receiving a “priming” dose of cocaine, rats increased cocaine self-administration, an occurrence known as “reinstatement”. Following this “priming” dose, the incident of reinstatement is a common and consistent happening across the preclinical literature.

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In 1989, Jaffe and colleagues (Jaffe, Cascella, Kumor, & Sherer, 1989) reported that experimental administration of cocaine in humans was associated with increased "wanting" and "craving" for cocaine. The issue of increased "wanting" or "craving" following cocaine administration, which has also been characterized as "priming" (de Wit, 1996), has been the subject of follow-up investigations. Unlike the preclinical literature, the findings of these clinical investigations were mixed; whereas a subset of studies replicated the results reported by Jaffe and colleagues (Fischman, Foltin, Nestadt, & Pearlson, 1990;Jaffe et al., 1989;Kosten et al., 1992;Nann-Vernotica, Donny, Bigelow, & Walsh, 2001;Sofuoglu, Brown, Babb, Pentel, & Hatsukami, 2000a,b;Walsh, Haberny, & Bigelow, 2000;Ward, Haney, Fischman, & Foltin, 1997a,1997b;Ward, Haney, Fischman, & Foltin, 1998), others did not (De La Garza, Newton, & Kalechstein, 2005;Foltin & Haney, 2000;Foltin et al., 2003;Romach et al., 1999;Sofuoglu, Pentel, Bliss, Goldman, & Hatsukami, 1999). To our knowledge, the clinical phenomenon of priming has not been addressed by a formal literature review. Because "priming" may be an important factor in relapse to dependence (de Wit, 1996), it seems essential to confirm that the association between cocaine administration and subsequent craving for the drug.

To address this, we conducted a qualitative review and a quantitative meta-analytic review of studies in which participants received cocaine under experimentally-controlled conditions. The qualitative review is intended to give an overview of previous studies that have reported cocaine-induced craving, regardless of whether actual statistics were provided. The quantitative review provides a statistical analysis, thus providing a more concrete answer to the debate. The meta-analytic approach provides a number of advantages over qualitative reviews. A primary advantage is this approach is that it provides the capacity to combine the results of studies utilizing different methodologies and statistical models in order to calculate a single effect size that quantifies the magnitude of the association between two variables, substantially increasing statistical power (Rosenthal, 1991). However, one limitation of the meta-analytic approach is that the review includes only those publications that include sufficient data to convert the statistical findings into effect sizes. As a result, studies that may be otherwise informative are generally excluded. To assure adequate coverage of all possibilities, the current report includes both a qualitative analysis and a quantitative meta-analytic review.

Methods

Qualitative Review

Pub-Med searches of studies published from 1966 through November 2006 were used to identify studies in which cocaine was administered in the laboratory and changes in self-reported craving or desire for cocaine were recorded. Keywords included "cocaine", "administration", "and "human" (as well as "cocaine craving") with follow-up searches using the reference sections of the initial studies. The initial search identified 2,801 reports.

Studies were included in the qualitative review if cocaine was administered in the laboratory, craving was assessed, and there was an interpretable report of craving. The results may have been reported as statistics, or as a figure or table showing whether the priming effect was observed following cocaine administration. Based on these criteria, 38 studies were considered appropriate for inclusion in the qualitative review.

Quantitative Review

Studies were included in the quantitative, meta-analytic review if the sample was greater than or equal to four study participants (to enhance stability of the findings), if cocaine was administered via the intravenous (IV) or smoked routes, if there was a single dose of cocaine administered, and if cocaine was the only stimulant administered. Studies utilizing oral and

nasal routes of administration were excluded from the quantitative review because cocaine taken by these routes is absorbed more slowly and this may alter the subjective effects produced (Kouri, Lundahl, Borden, McNeil, & Lukas, 2002). In addition, it has been found that the smoked and IV routes of administration have similar pharmacodynamic characteristics as well as similar times to reach the brain (Jeffcoat, 1989). Studies that did not provide the necessary statistics (e.g. means and standard deviations and/or standard errors) were not included in the quantitative review; however, these articles were still included in the qualitative review. Moreover, studies that did not use standard terms for assessing cocaine-induced craving, such as "crave", "craving", "desire", "want," were excluded. Based on these more stringent selection criteria, 12 studies were included in the quantitative review. Please see Table 1 for list of studies included in the quantitative review (designated with a # symbol next to the author line). Data were coded by both ADK and JJM to ensure accurate calculation during the analysis.

Meta-analytic methods

Effect Size—In order to determine the magnitude of the differences between the means of comparison groups, effect size estimates were calculated using standard techniques (Rosenthal, 1991). Estimates of the magnitude of the association between cocaine administration and change in craving were operationally defined as Pearson's *r* and Cohen's *d*

Combined Probabilities—To compute combined probabilities for the various subgroups of studies, we employed the method described by Rosenthal (Rosenthal, 1991). Specifically, we derived the meta-analytic Z (Z_{ma}) by converting the Pearson's *r* for each correlation to a *Z* score, summing the *Z* scores for each subgroup of investigations, and dividing this sum by the square root of the number of studies included for each subgroup. The p-value associated with the Z_{ma} indicates the level of statistical significance for associations between drug administration and self-reported craving.

Fail-safe N—If Z_{ma} was significant, we computed the Fail-safe N (N_{fs}) to determine the number of studies with null findings that would be needed to invalidate the conclusion that a significant association existed between cocaine administration and craving (Rosenthal, 1991). N_{fs} was obtained by summing the *Z* scores for the particular subgroup, dividing this sum by the *Z* score associated with a particular probability value, squaring this new number, and finally, subtracting the number of studies in that subgroup. A larger N_{fs} indicates a more reliable association between cocaine administration and craving.

Estimating the magnitude of the effect size—According to previously published methods (Pedhazur & Schmelkin, 1991), Cohen constructed the most frequently used guidelines for the estimation of the magnitude of effect size using Cohen's *d* (Cohen, 1988). For the latter, Cohen proposed that a difference between means of .2 of a standard deviation be characterized as small, .5 as medium, and .8 as large. Another measure of estimating the magnitude of effect size is Pearson's *r*. A measure of .1 is considered small, .25 is considered medium, and an effect size of .4 is considered large.

Moderating variables—Effect sizes were calculated separately for studies using the adjectives "crave", "desire", and "want" to characterize these responses separately. Similarly, effect sizes were calculated separately for studies employing smoked and IV route of administration, and for low (<48mg) and high (>49mg) cocaine doses (based on a median split of the sample).

Results

Qualitative Review

Cocaine administration increased craving for cocaine in 24 of 38 studies included in this review (Table 1). In contrast, 14 of 38 studies showed that cocaine administration did not affect, or reduced, craving for cocaine.

Quantitative Review

The results from the quantitative review (Table 3) indicate that cocaine administration is associated with a significant increase in craving (Z_{ma} = 5.29, $p \leq .0001$). Moreover, the magnitude of the effect was large (Cohen's d: 1.45±1.04; Pearson's r: 0.53±0.18). The correlation was considered to be robust (Fail-safe n = 86). Table 2 lists the effect sizes for each individual study.

In addition, table 3 shows the impact of potential moderator variables. Responses elicited by the adjectives "desire" and "want" were correlated with significant priming effects whereas "craving" was not correlated with a significant priming effect. Moreover, cocaine administered intravenously was associated with a significant priming effect whereas cocaine administered via smoking was not. Furthermore, priming effects did not appear to be strongly dose related, as doses smaller than 48 mg versus those larger than 49 mg (the median split for all doses specified) produced similar effects.

Discussion

The qualitative review was equivocal with respect to the probability that priming effects occurred subsequent to cocaine administration (24/38 or 63% in the affirmative). In contrast, the quantitative review revealed that cocaine administration was significantly associated with priming effects. It must be emphasized that 83% of the studies included in the meta-analysis demonstrated that cocaine-induced craving exists whereas only 62% of the studies in the qualitative review supported this conclusion. A potential limitation of the meta-analytic method is that studies that do not include statistics cannot be included in the analysis. This can be a cause for concern since details of statistics are very rarely reported when the findings do not reach significance. The quantitative review revealed that methodologies may moderate the outcomes of study (e.g., use of adjectives such as "craving", "desire", or "want"), though the sample was not large enough to permit follow up analyses that would have offered comparisons *within* a class of moderates (i.e., comparing the relative magnitude of the effect for each adjective). It may be that other factors moderate the relationship between cocaine administration and subsequent craving for the drug. These include, but are not limited to, the effects of rate of administration and the effects of administering multiple doses of cocaine. For example, it would be important to know if differences in priming effects occurred when cocaine was smoked or injected (Jeffcoat, Perez-Reyes, Hill, Sadler, & Cook, 1989). From the small number of available studies it appears that smoked administration may produce smaller priming effects than IV administration, but this conclusion is tentative given that only three studies used this route of administration (Table 3).

Furthermore, in studies, where cocaine was administered repeatedly, it was difficult to infer the exact amount administered; therefore, those studies did not meet the inclusion criteria and were omitted from the meta-analysis (however, several of the studies that involved self-administration were able to be included in the meta-analytic review because a "sample session" of cocaine was administered where all participants received a fixed amount of cocaine). The null findings using "craving" and employing smoked cocaine may be due in part to the small number of studies (N=3) using these design features.

The effects of rate of administration may be inferred in a preliminary way by comparing results obtained by Jaffe and colleagues (1989) to those obtained by other authors. In that study, 40 mg of cocaine was administered IV over 1–2 seconds and this produced an average increase in craving of 2.9 on a 0–10 scale (rate of administration for each individual study is reported in Table 1). That was a rapid rate of administration compared to the other studies shown in Table 1, in which the rate of administration ranged from 30 seconds to 2 minutes. The observation that a rapid rate of administration was associated with larger increases in craving is consistent with preclinical studies showing that rapid administration is associated with greater behavioral effects (Samaha et al, 2004;Samaha & Robinson, 2005). In addition, it has been reported that that rapidly administered cocaine preferentially engages mesocorticolimbic circuits, which more readily induces psychomotor sensitization (Samaha & Robinson, 2005). It has also been found that a more rapid rate of onset may enhance a drug's reinforcing effects, but a drug with a slow onset can still maintain self-administration (Lile, 2006). Also, it has been demonstrated that the "rate hypothesis" (the faster the drug reaches the brain, the greater its reinforcing effects) of psychoactive drug action occurs after IV drug administration (Nelson et al., 2006). However, in the current report, there were no significant differences between rate of administration and no significant differences between groups that utilized the smoked route vs. the intravenous route.

Placebo administration has been reported to produce cocaine-like subjective effects (Muntaner et al., 1989). It is likely that expectancy can alter responses to active cocaine administration, as well. For example, in the study by Fischman and colleagues (Fischman et al., 1990), participants reported very high baseline craving (95 of 100), which limited the extent to which subsequent cocaine administration could increase craving. That research group had many active ongoing cocaine administration studies, and this may have produced an atmosphere of expectation in their participants. Similarly, the magnitude of priming effects reported in studies of Walsh and Ward (Walsh et al., 2000;Ward et al., 1997) may have been influenced by expectancies. Participants in these studies were aware that they would subsequently receive multiple doses of cocaine, and this expectancy may have contributed to the robust priming effects observed. The contrast between the low baseline levels of craving in those studies (mean baseline craving < 5 on a scale of 100) remains unclear when compared to that specified in the earlier study by Fischman and colleagues (Fischman et al., 1990).

The available literature does not allow examination of several other factors that may affect priming effects. For example, the role played by contingent compared to non-contingent cocaine administration may be important (Leri & Stewart, 2002), but has not been systematically evaluated in clinical studies. A recent investigation of priming effects utilized self-administration using patient-controlled analgesia (PCA) pumps. This study allowed non-treatment seeking cocaine dependent individuals to self-administer cocaine during a two-hour session (Sughondhabirom et al., 2005) . The authors reported that Visual Analog Scale (VAS) assessments of "want cocaine" did not differ as a function of dose. However, the response rate on the PCA device appeared as a classical "inverted U" dose-response function. Maximal response rates were supported by 8 mg cocaine, with placebo and higher doses of cocaine eliciting fewer responses. Moreover, study participants often administered approximately 50% of the cocaine available to them during a given study session. Further research is needed to determine if higher doses of cocaine suppress cocaine responding, as observed in preclinical investigations, though these initial data raise questions as to the relationship between cocaine dose, craving, and drug-seeking behavior. For example, one particular study found that higher doses of cocaine suppress cocaine responding (# injections/session), though total cocaine intake remains similar (mg/kg/session) (Edwards et al, 2006).

Other factors that could moderate priming effects include genetics, personal history of cocaine or polysubstance use, and comorbid psychiatric illnesses. For example, we recently reported

that cocaine-induced craving was moderated by the level of reported symptoms of apathy, a distinct neuropsychiatric syndrome (Newton, Kalechstein, De La Garza, Cutting, & Ling, 2005). Recently, we have also noted that craving produced by non-contingent administration of cocaine is positively correlated with the number of days in which the drug was used in the month prior to the study (Newton and De La Garza, *unpublished findings*).

In interpreting these outcomes, several limitations should be noted. While most of the studies reported the years of cocaine use, most studies did not report the amount used nor the days used in the past month of previous cocaine exposure participants had *outside* of the laboratory, and this may affect the magnitude of cocaine priming effects observed in the laboratory. Paradoxically, repeated exposure to cocaine outside of the relevant laboratory context might *reduce* priming effects observed in the laboratory, a phenomenon referred to as the "Unconditioned Stimulus-pre-exposure effect" (Randich & LoLordo, 1979;Saladin, 1986). As specified previously, the simple visual analogue scales used to assess craving are unlikely to fully reflect the multifaceted and complex nature of craving in cocaine-addicted patients (Robbins, Ehrman, Childress, & O'Brien, 1997;Tiffany & Drobes, 1991;Tiffany, Singleton, Haertzen, & Henningfield, 1993). As such, the studies surveyed provide a limited assessment of factors impacting craving. Factors affecting craving for drugs other than cocaine (e.g. alcohol, nicotine, methamphetamine) may differ from those identified above. Finally, elucidation of the mechanisms by which drug administration alters both subjective mood states and behavior requires additional research.

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Table 1

Studies included in the qualitative and quantitative reviews

First author	Year	Sample	ROUTE[1]		Dose (mg)	RATE	Adjective	Measure to Assess Craving[2]	Effect of Cocaine[3]
			Usual	Study					
Collins	1998	8M/0F	Smk	Smk	12, 25, and 50	*	Want	100 mm (line)	+
De La Garza	2005	7M/0F	Smk or IV	IV	40	40	Craving	100 mm (line)	0
Donny	2003	7M/1F	Smk or IV	IV	12.5, 25, 50	60	Desire	100 mm (line)	+
Donny#	2004	8M/4F	Smk or IV	IV	15 and 30	60	Desire	100 mm (line)	0
Donny	2006	8M/2F	Smk or IV	IV	20 and 40	60	Desire	100 mm (line)	0
Fischman#	1990	6M/0F	NR	IV	8, 16, and 32	60	Want	50 mm (line)	+
Foltin	2000	6M/2F	Smk	Smk	25	NR	Want	100 mm (line)	0
Foltin	2003	11M/3F	Smk	Smk	12, 25, 50	NR	Want	100 mm (line)	−
Foltin	2004	10M/0F	Smk	Nasal	4, 24, 48, 96	60	Want	100 mm (line)	0
Haney	1998	7M/5F	Smk or IV	IV	8, 16, 32	30	Want	100 mm (line)	+
Haney	1999	8M/1/F	Smk	Smk	12 and 50	*	Want	100 mm (line)	0
Haney	2001	8M/2F	Smk	Smk	12, 25, and 50	*	Want	100 mm (line)	+
Haney	2005	8M/0F	Smk	Smk	6, 12, 25, 50	*	Want	100 mm (line)	0
Haney	2006	9M/1F	Smk	Smk	12, 25, and 50	*	Want	100 mm (line)	+
Hart	2004	6M/1F	Smk	Smk	12, 25, and 50	*	Want	100 mm (line)	+
Houtsmuller	2004	10M/2F	Smk or IV	IV	20 and 40	60	Desire	100 mm (line)	+
Jaffe#	1989	9M/0F	IV	IV	40	2	Craving	0 –5	+
Johnson#	2004	12M/6F	IV	IV	22.75 and 45.5	NR	Craving	100 mm (line)	0
Johanson	2006	9M/1F	Smk or IV	IV	10, 20, and 40	60	CCQ-Now	NR	+
Kosten	1992	4M/1F	Smk or IV	IV	8.75, 17.5, 35	NR	Desire	10 point	+
Leyton	2005	8M/0F	Nasal	Nasal	42, 105, and 210	**	Multiple	10 point	+
Nann-Vernotica#	2001	9M/1F	Smk or IV	IV	25, 50	60	Desire	100 mm (line)	+
Nelson	2005	17M/F	Smk or IV	IV	10, 25, 50	10, 30, 60	Want	100 mm (line)	+
Preston#	1992	8M/0F	IV	IV	12.5, 25, and 50	60	Desire	100 mm (line)	+
Preston#	1993	8M/0F	IV	IV	12.5, 25, and 50	60	Desire	100 mm (line)	+
Roache	2005	11M/1F	IV	IV	22.75 and 45.5	60	Crave	100 mm (line)	+
Romach	1999	11M/0F	IV	IV	30	60	Desire	100 mm (line)	0
Rush	1999	8M/1F	Smk	Oral	50, 100, 200, 300	Immediate	Want	100 mm (line)	0
Sofuoglu	1999	6M/3F	Smk	Smk	28	25	Crave	100 mm (line)	0
Sofuoglu#	2000a	9M/3F	NR	Smk	28	25***	Crave	100 mm (line)	+
Sofuoglu	2000b	9M/3F	NR	Smk	28	25***	Crave	100 mm (line)	+
Sofuoglu	2003	25M/19F	Smk	Smk	28	25***	Desire	100 mm (line)	0
Sofuoglu	2005	5M/2F	Smk or IV	IV	11 and 21	60	Crave	100 mm (line)	+
Walsh#	2000	7M/1F	IV	IV	25, 50	60	Desire	100 mm (line)	+
Ward#	1997a	7M/0F	IV	IV	32	30	Want	100 mm (line)	+
Ward#	1997b	7M/0F	Smk	Smk	50	*	Want	100 mm (line)	+
Ward#	1998	7M/1F	Smk	Smk	12 and 50	*	Want	100 mm (line)	+
Winhusen	2006	7M/F	IV	IV	20, 40	120	Desire	100 mm (line)	0

Abbreviations and Notes: M = female, F = female, IV =intravenous, NR = not recorded, Smk = smoked

[1] – Usual = route of administration participant uses in their natural environment, Study = route of administration participant received in the laboratory study described.

[2] – 0 – 100 mm (line) = VAS where participant marks along a 100-point line labeled “not at all” to “extremely” 0 – 5 = participant marks between 0 and 5

* = participant told to inhale similarly to outside the laboratory and/or finish the smoke inside the pipe

** = participant told to insufflate at own pace

*** = participant told to inhale for 10 second and then hold for 15 seconds

3 + = increase in craving after cocaine administration (and/or stated as a significant increase within the paper)

0 = no change in craving after cocaine administration (and/or stated as a nonsignificant change within the paper)

– = decrease in craving after cocaine administration (and/or stated as a nonsignificant decrease within the paper)

= study also included in the quantitative, meta-analytic review

Table 2

Effect sizes of individual studies included in the quantitative review

First author	Year	Sample	Effect Size		Effect on Craving
			Pearson's r	*Cohen's d*	
Donny	2004	8M/4F	0.28	0.58	0
Fischman	1990	6M/0F	0.76	2.34	+
Jaffe	1989	9M/0F	0.55	1.32	+
Johnson	2004	12M/6F	0.26	0.54	0
Nann-Vernotica	2001	9M/1F	0.62	1.58	+
Preston	1992	8M/0F	0.39	0.85	+
Preston	1993	8M/0F	0.47	1.06	+
Sofuoglu	2000a	9M/3F	0.49	1.12	+
Walsh	2000	7M/1F	0.91	4.39	+
Ward	1997a	7M/0F	0.6	1.5	+
Ward	1997b	7M/0F	0.48	1.09	+
Ward	1998	8M/0F	0.49	1.12	+

Table 3

Variables that moderate the intensity of cocaine-induced craving

Domain	Pearson's r Mean (SD)	Cohen's d Mean (SD)	Number of Comparisons	Meta-Analytic Z-Score	*p*-value	Fail-safe N_{fs}
Overall Effect of Priming	0.53 (0.18)	1.45 (1.04)	12	5.29	<0.0001	86.41
Adjectives Used to Define Priming Effect						
Craving	0.48 (0.16)	1.14 (0.44)	4	1.92	NS	2.84
Desire	0.51 (0.28)	1.72 (1.8)	4	2.05	<0.005	3.38
Want	0.58 (0.13)	1.51 (0.58)	4	2.32	<0.01	4.60
Route of Administration						
Smoked	0.49 (0.01)	1.10 (0.02)	3	1.46	NS	0
IV	0.54 (0.21)	1.57 (1.20)	9	4.84	<0.0001	53.89
Dose						
<48	0.54 (0.17)	1.37 (0.64)	5	2.68	<0.005	8.35
>49	0.49 (0.19)	1.23 (0.67)	7	3.43	<0.001	20.44