Pergamon

Pharmacology Biochemistry and Behavior, Vol. 49, No. 3, pp. 583–588, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)00181-2

Lack of Evidence for Context-Dependent Cocaine-Induced Sensitization in Humans: Preliminary Studies

RICHARD B. ROTHMAN,[1] DAVID A. GORELICK, MICHAEL H. BAUMANN, XIAO Y. GUO, RONALD I. HERNING, WALLACE B. PICKWORTH, TERI M. GENDRON, BONNIE KOEPPL, LESTER E. THOMSON, III AND JACK E. HENNINGFIELD

Clinical Psychopharmacology Section, NIDA/NIH Addiction Research Center, P.O. Box 5180, Baltimore, MD 21224

Received 7 January 1994

ROTHMAN, R. B., D. A. GORELICK, M. H. BAUMANN, X. Y. GUO, R. I. HERNING, W. B. PICKWORTH, T. M. GENDRON, B. KOEPPL, L. E. THOMSON, III AND J. E. HENNINGFIELD. *Lack of evidence for context-dependent cocaine-induced sensitization in humans: Preliminary studies.* PHARMACOL BIOCHEM BEHAV **49**(3) 583–588, 1994.—Cocaine-induced behavioral sensitization is the well-documented phenomenon where repeated doses of cocaine elicit increasingly greater effects on motoric activity in rats. Some observations suggest that behavioral sensitization may provide a model for understanding the mechanisms of drug-craving elicited by environmental triggers or cues. The process of fully validating such an animal model for its ability to detect effective anticraving medicines is a difficult and long-term undertaking. As a first step in that direction, we decided to determine if cocaine can produce conditioned behavioral sensitization in humans using a paradigm fairly similar to that used for rodents. Because humans do not react to cocaine with the pronounced motor activation observed in rodents, we measured a variety of end points, including blood pressure (BP), heart rate (HR), respiratory rate, pupil diameter, hormones (prolactin and cortisol), and subjective responses using the questionnaire for drug-related feelings (QDRF) and the EEG. To mimic the home and test cages used in rodent studies, two rooms were used: a small test chamber and a regular room with a window and furnishings. On day 1 each subject received a drug infusion (either saline or 40 mg cocaine IV) in both locations. On day 2, all subjects received an infusion (saline or 25 mg cocaine IV) in the test chamber. All drug infusions were conducted double blind. The paired group received cocaine on both days in the test chamber. The unpaired group received cocaine in regular room on day 1, and cocaine in the test chamber on day 2. A control-1 group received saline at both locations on day 1, and cocaine on day 2 in the test chamber. A control-2 group [4] received cocaine in the test chamber on day 1 and saline in the test chamber on day 2. Conditioned-sensitization was not observed. However, conditioned tolerance was observed for cocaine-induced changes in plasma prolactin levels and diastolic blood pressure. Because rodent studies use cocaine-naive subjects and this study used cocaine-experienced subjects, these data suggest that prior experience with cocaine may alter it ability to produce sensitization. Viewed collectively, the present investigation suggests caution in the design of both human and animal studies.

Cocaine Behavioral sensitization Classical conditioning Prolactin Cortisol Endocrine effects

COCAINE-INDUCED behavioral sensitization is the well-documented phenomenon where repeated doses of cocaine elicit increasingly greater effects on motoric activity in rats (15,25,28). It is, therefore, a form of reverse tolerance. Although widely studied from a neurochemical point of view (5,10,15,23,30,31), several lines of evidence suggest that behavioral sensitization is a classically conditioned response. For example, cocaine, amphetamine, and apomorphine have been found to serve as effective unconditioned stimuli in a variety of studies that examined changes in the general locomotor behavior elicited by these drugs (4,11,22,24,25,27,29). The conditioning of locomotor activity by psychomotor stimulants follows many of the principles of classical conditioning. For example, the magnitude of the conditioned effect is related to the intensity of the unconditioned stimulus (i.e., the drug dose) as well as the interval between the conditioned and un-

[1] To whom requests for reprints should be addressed.

conditioned stimulus (24,32). The conditioned response decays with time (1), is subject to extinction (1,11,14) and follows the principles of stimulus generalization (35).

That classical conditioning plays a major role in cocaine-induced behavioral sensitization was elegantly demonstrated by a simple and powerful paradigm [for review see (22)]. Three groups of rats were used. On day 1 of the protocol (the conditioning day), each group received two injections. The paired group received cocaine (40 mg/kg IP) immediately prior to placement in the locomotor activity chamber (the test cage), and saline injections in the home cage. The unpaired group received saline immediately prior to placement in the test cage, and cocaine (40 mg/kg IP) injections in the home cage. A control group was administered saline at both locations. On day 2 of this procedure (the test day), all rats were administered cocaine (10 mg/kg, IP) in the test cage. Unpaired rats had the same motoric activity as the control group, demonstrating an absence of behavioral sensitization. However, the paired group showed an enhanced motoric response to cocaine relative to the unpaired group. Because the only difference between the paired and unpaired groups was the location where they received cocaine the day before, the enhanced motoric response observed in the paired group was attributed to classical conditioning where the test cage is the unconditional stimulus.

Classical conditioning using cocaine as the unconditioned stimulus is readily found in humans (7) as well as animals (22). Some studies suggest that conditioned drug effects play a critical role in the relapse of opiate (21) as well as cocaine addicts (20). Moreover, other studies suggest that drug-related stimuli can precipitate symptoms of withdrawal in abstinent opioid addicts (8) and also induce craving in both opioid- and cocaine-dependent people (7,34). These observations suggest that the rodent behavioral paradigm described above may provide a model for understanding the mechanisms of drug-craving elicited by environmental triggers or cues. The possibility is of more than theoretical interest. The model could be used, for example, to test drugs as possible anticraving medicines. The process of fully validating such an animal model for its ability to detect effective anticraving medicines is clearly a difficult and long-term undertaking. As a first step in that direction, we decided to determine if cocaine can produce conditioned behavioral sensitization in humans using a paradigm fairly similar to that used for rodents. Because humans do not react to cocaine with the pronounced motor activation observed in rodents, we measured a variety of end points including blood pressure (BP), heart rate (HR), respiratory rate, pupil diameter, hormones (prolactin and cortisol), and subjective responses using the questionnaire for drug-related feelings (QDRF) and the EEG.

METHOD

Human Subjects

Physically healthy male and female subjects, age 21 to 45 years, with a history of using intravenous (IV) cocaine at least three times in the month prior to admission were recruited for this study. Twenty-five male subjects enrolled in the study. Subjects provided written informed consent according to guidelines for the protection of human research subjects of the Department of Health and Human Services and were paid for their participation. The study was terminated prior to its completion due to a hold that was placed on all clinical research studies using IV cocaine.

Study Design

The design of the study is illustrated in Table 1. To mimic the home and test cages, two rooms were used: a small test chamber and a regular room with a window and furnishings. On day 1, each subject received a drug infusion (either SAL or 40 mg COC IV) in both locations. One session was run in the morning (AM session) and the second session was held in the afternoon (PM session). On day 2, all subjects received an infusion (SAL or 25 mg COC IV) in the test chamber. All infusions were delivered in a volume of 1 cc over 10 s. All drug infusions were conducted double blind.

As described in Table 1, the paired group [1] received COC on both days in the test chamber. The unpaired group [3] received COC in the regular room on day 1, and COC in the test chamber on day 2. The control-1 group [2] received COC only on day 2 in the test chamber. A control-2 group [4] received COC in the test chamber on day 1 and SAL in the test chamber on day 2. Subjects in all groups were randomly assigned to receive their test chamber session in either the AM or the PM with the limitation that, within each group, the number of AM and PM subjects would be the same. For groups 1, 3, and 4, the session on day 2 was at the same time they received COC on day 1. Group 2 subjects were randomly assigned to receive COC on either the AM or PM, such that the number of AM and PM subjects would be the same.

At each drug-administration session, the end points reported here [systolic and diastolic blood pressure (BP), pulse, respiratory rate, EEG, hormone levels and the QDRF] were measured prior to and at several time points after drug administration (see the Results section).

One hour prior to the beginning of the study, an indwelling heparin-lock was inserted by the study nurse. At the specified times throughout the time line (-20, $+15$, and $+45$) a 5 cc blood sample was drawn from the heparin lock. The sample was immediately transferred into a chilled vacutainer containing the anticoagulant EDTA and subsequently stored on ice. Within 30 min of the blood draw, the sample was spun in a refrigerated Beckman GPR centrifuge (4°C) at 1,800 RPM for

TABLE 1
DESIGN OF STUDY

	Day #1 Test Chamber*	Day #1 Regular Room	Day #2 Test Chamber *
Group 1 (n = 7, paired)	COC†	SAL	COC‡
Group 2 (n = 5, control-1)	SAL	SAL	COC‡
Group 3 (n = 10, unpaired)	SAL	COC†	COC‡
Group 4 (n = 3, control-2)	COC†	SAL	SAL

*There were two drug administration sessions on day #1 (AM and PM). Subjects in all groups were randomly assigned to receive their test chamber session in either the AM or the PM with the limitation that within each group the number of AM and PM subjects would be the same. For groups 1, 3, and 4, the session on day #2 was at the same time they received COC on day #1. Group 2 subjects were randomly assigned to receive COC on either the AM or PM, such that the number of AM and PM subjects would be the same.

†Dose was 40 mg IV.

‡Dose was 25 mg IV.

10 min. Plasma (500 μl) was pipetted from the spun sample into a Nunc tube prefilled with 50 μl aprotinine (23 TIU/ml). Plasma samples were stored in a −70°C degree freezer until the analysis was performed.

Radioimmunoassay (RIA) Methods

Samples of plasma were thawed. Aliquots of the plasma (50 μl) were assayed for human prolactin (hPRL) by standard double-antibody RIA procedures. Primary antisera and hPRL reference preparation were generously provided by the National Hormone and Pituitary Program and NIDDK (Baltimore, MD) and the [^{125}I]-hPRL was purchased from Hazelton Laboratories (Vienna, VA). Aliquots of the plasma (25 μl) were assayed for cortisol using a commercially available antibody coated-tube [^{125}I]-cortisol RIA kit (ICN Biomedical). All samples were run with the same RIA to avoid interassay variability. The average intraassay coefficients of variation for both RIAs were less than 10%. Only session 3 data obtained from the paired group (n = 6) and from the unpaired group (n = 9) are reported here. There were insufficient numbers of samples from groups 2 and 4 to warrant statistical analysis. The session 1 and 2 data will be presented elsewhere.

EEG Recording and Analysis Procedure

The EEG was recorded from the following International 10/20 scalp sites: F_{p1}, F_{p2}, F_z, F_3, F_4, F_7, F_8, P_3, P_4, T_3, T_4, T_5, T_6, and O_z. The recording reference was the chin. Silver/silver chloride electrodes were used at all locations. The EEG was amplified with Grass (Model 7P511) amplifiers using 1 Hz to 100 Hz half amplitude band pass and a 60 Hz notch filter. The system was calibrated with a 5 Hz, 50 microvolt square wave (Grass Calibrator, Model SWC1B). The calibration signal and EEG signals were recorded via the electrode board in the recording areas. The amplified signal was collected with an IBM/AT personal computer with a Data Translation (Model DT2821-F-SE) analog to digital convertor. Each EEG channel was sampled at 5.0-ms intervals for 2 min. A predrug and a 2-min postdrug recording were obtained. The raw EEG was saved for subsequent analysis.

A fast Fourier transform with a Tukey-Hamming window (6) was calculated on each 512 point sample (2.56 s) of artifact-free EEG data. Eye movement and movement artifact were rejected by a computer algorithm, as in Herning et al. (12,13). Only 16 subjects, who received cocaine, had artifact free EEG on all sessions. The power spectra were resolved into 0.4 Hz increments from 0.0 to 32.8 Hz. The resultant power spectra were averaged for each 2-min period (pre- and 2-minute post). The power spectra were averaged into the delta (0.4–4.0 Hz), theta (4.4–8.0 Hz), alpha (8.4–13.2) and beta (13.6–32.8 Hz) bands. The change scores (2 min postpre) were calculated for EEG spectral power in delta, theta, alpha and beta bands and were analyzed by Analysis of Variance (ANOVA) using the Greenhouse–Geisser adjustment (33).

Other Data Analyses

For the physiological end points, the data were transformed to a percent of the baseline value. For the QDRF, the data were transformed to a difference score relative to the baseline value. The peak effect was determined for each time course, and these values were used for statistical analysis of the data. Differences among groups for each end point were analyzed by one-way analysis of variance (ANOVA) using the program Super ANOVA. Because there were only three subjects in group 4, these data were not included in the analysis.

Regarding the hormone measurements, mean preinjection (t = −20 min) plasma hormone levels were calculated for the paired and unpaired groups. The mean preinjection value was defined as 100% and all data points were normalized to this value using the formula (X/mean value) × 100. These data were analyzed by analysis of variance followed by Duncans' multiple range test for post hoc comparisons. The minimum criterion for statistical significance was set to $p < 0.05$.

RESULTS

Physiological End Points

Figure 1 shows the physiological responses of the paired group [1] to 40 mg IV COC in the actual units of measure. These data demonstrate that COC produced the expected spectrum of physiological effects in these subjects: increased heart rate, increased systolic and diastolic blood pressure, and respiratory rate.

The data were initially analyzed to determine if the groups differed in regards to their baseline responses to SAL or COC. An ANOVA indicated that there were no significant differences in the SAL responses or in the COC responses among groups 1-3 on day 1. Moreover, within each group, comparison of the responses of the AM and PM subjects showed no significant differences. Therefore, for subsequent analyses, the data of the AM and PM subjects were pooled. To verify that there was an effect of COC, the responses of the paired group on day 1 (40 mg IV COC) were compared to the responses of the unpaired group on day 1 (SAL IV). As shown in Fig. 2, COC produced highly significant increases in all physiological measures and the QDRF drug effect scale as well.

The cocaine-induced responses of groups 1 and 2 (unpaired vs. control-1) on session 3 were analyzed by ANOVA to determine if sensitization developed. The only significant difference occurred in the diastolic BP measurement, where the effect of cocaine in group 1 was decreased relative to group 2 (Fig. 3). The cocaine-induced responses of groups 1 and 3

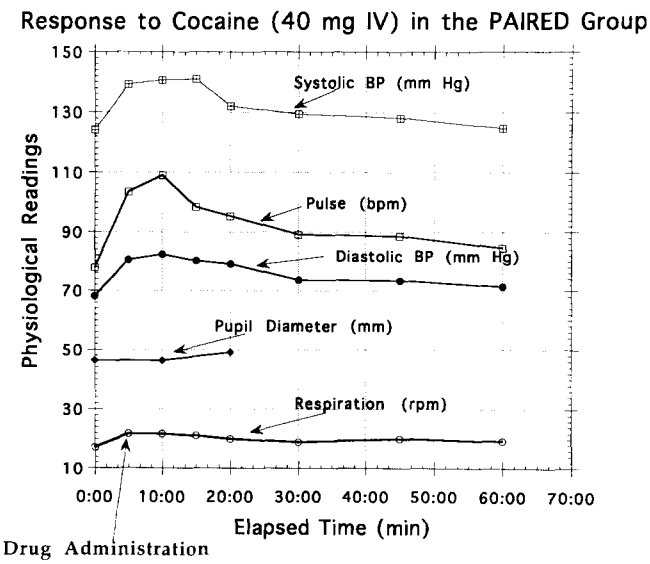

FIG. 1. Effect of 40 mg cocaine on physiological end points. Each point is the mean responses.

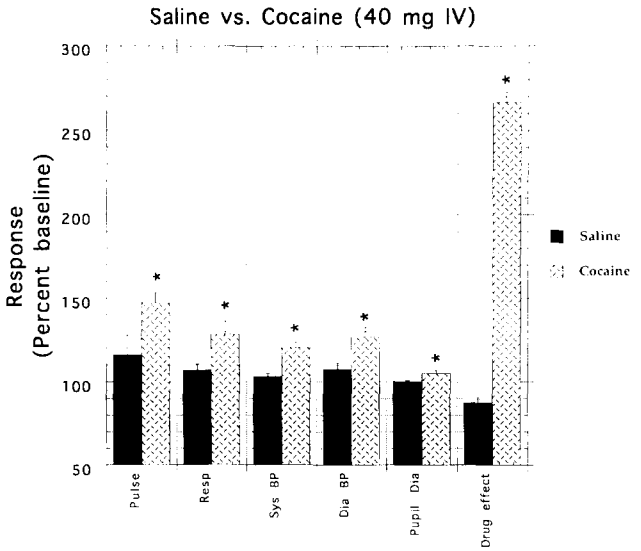

FIG. 2. Effect of cocaine (40 mg iv) on physiological end points and the drug effect scale of the QDRF. Each point is the mean ± SD (n = 7). *p < 0.05 when compared (ANOVA).

on day 3 (paired vs. unpaired) were analyzed by ANOVA to determine if conditioned sensitization developed. There were no significant differences across all end points. Moreover, there were no significant differences, between the baseline values, across all end points, of groups 1 and 3 on day 3 (paired vs. unpaired). The data of each subject in the paired and unpaired groups were also expressed as a ratio of the responses observed at session 3 (25 mg COC IV) and those observed at either session 1 or session 2 (40 mg COC IV). An ANOVA showed no statistically significant differences across all end points between the two groups when the data were normalized in this way.

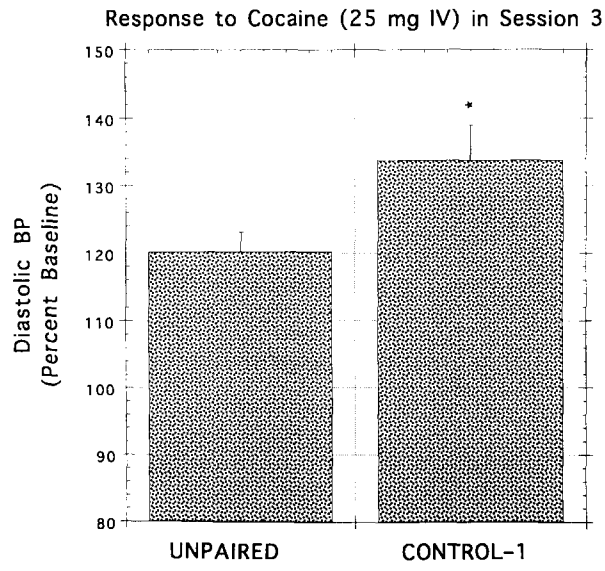

FIG. 3. The diastolic BP response to cocaine (25 mg IV) on the test day: unpaired group compared with the control-1 group on session 3 diastolic BP. *p < 0.05 when compared (ANOVA).

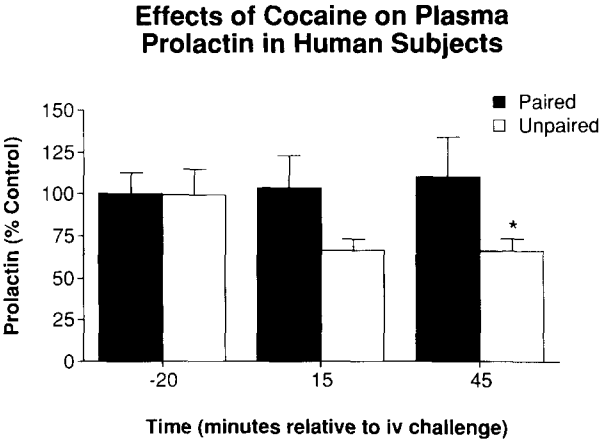

FIG. 4. Effect of cocaine (25 mg IV) on plasma prolactin. Each point is the mean ± SD (n = 6–9). *p < 0.05 when compared (ANOVA).

Hormonal End Points

Blood samples were taken at −20, +15, and +45 min after the administration of COC at session 3. Basal pretreatment levels of circulating prolactin were 13.2 ± 1.8 ng/ml (n = 15) and cortisol were 229 ± 34 ng/ml (n = 14). There were no significant differences in baseline endocrine measures between paired and unpaired groups. As shown in Fig. 4, administration of COC produced a statistically significant decrease in plasma hPRL in the unpaired group, but not the paired group. In contrast, COC increased plasma cortisol in both groups (Fig. 5).

EEG End Points

Few significant differences were noted in the EEG data. To evaluate whether cocaine had an effect on the EEG, the cocaine and saline sessions on the conditioning day were compared for all subjects with both sessions (n = 16). Cocaine tended to increase EEG beta power, $F(1, 14) = 2.605$, p =

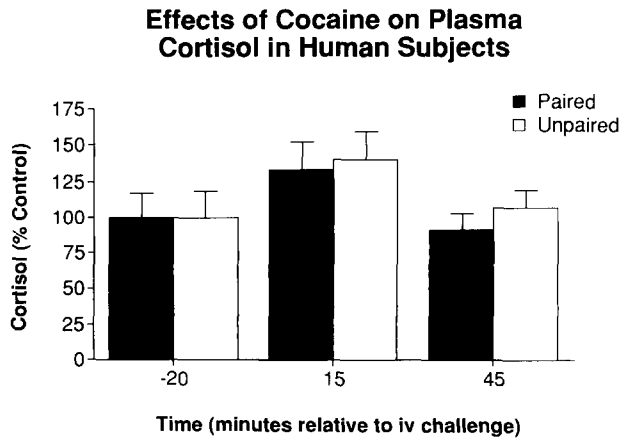

FIG. 5. Effect of cocaine (25 mg IV) on plasma cortisol. Each point is the mean ± SD (n = 6–9). *p < 0.05 when compared (ANOVA).

0.12. To test for conditioned sensitization, the increase in EEG beta was compared on the test day for groups 1 and 3. A ratio of the increase in EEG beta on the test day divided by the increase the conditioning day was calculated. An ANOVA showed no significant differences between groups on this measurement [group effect: $F(1, 10) = 0.30, p = 0.60$; group by electrode interaction: $F(10, 140) = 1.28, p = 0.25$]. The mean for ratios for groups 1 and 3 are shown in Fig. 6. There was no evidence for sensitization because the ratio for group 1 was near 1. Group 3 had a larger increase in beta power when cocaine was administered in a novel environment, but difference in ratios was not statistically significant since the variability in group 3 was large.

DISCUSSION

To our knowledge, this is the first study to determine the occurrence of cocaine-induced sensitization in humans under conditions similar to that used in a well-characterized rodent model. Unlike the data readily obtained with rats, a single conditioning session was not sufficient to produce either conditioned or unconditioned sensitization to a spectrum of cocaine-induced effects in humans, including blood pressure, heart rate, respiratory rate, subjective effects, and EEG. These data support earlier observations that two IV injections of 40 mg cocaine administered 2 weeks apart showed no significant differences in cardiovascular or subjective responses that might have been indicative of tolerance or sensitization development (19).

Based on rodent studies (3,17,26), we did not expect to observe sensitization to the endocrine effects of COC in humans. We found that acute COC increased plasma cortisol. This finding agrees with the data of Mendelson et al. (18) who showed that administration of COC (30 mg IV) increased plasma ACTH in cocaine-dependent men. Also analogous to the data of Mendelson et al. (18), we failed to observe COC-induced decreases in plasma prolactin in sessions 1 or 2 where subjects received either saline or COC (40 mg IV). Interestingly, the unpaired group responded in session 3 to lower dose of COC (25 mg IV) with a decrease in plasma levels of hPRL. This finding is consistent with the development of noncontext-dependent sensitization to COC. Paradoxically, this failed to occur in the paired group, suggesting that context-dependent tolerance to the PRL-decreasing effects of COC develops in the PAIRED group.

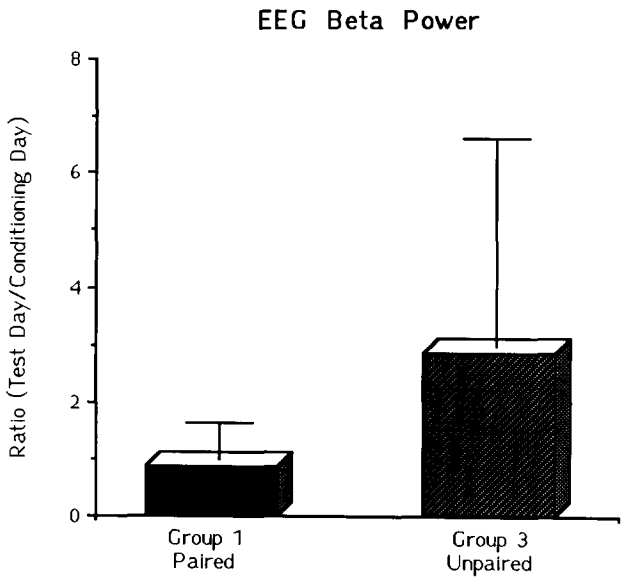

FIG. 6. The increases in EEG beta power (2 min post-pre value) are plotted for group 1 (paired) and group 3 (unpaired). The saline and cocaine doses on the conditioning day and cocaine dose on the test day are shown for each group. The beta power values are the mean over electrode sites and the error bars are standard errors.

Cocaine tended to produce an increase EEG beta, but no conditioned sensitization was observed. The increases in EEG beta power were more robust in previous studies (12,13). This experimental paradigm with the numerous experimental measures collected after the cocaine administration increased the variability of the EEG data. In spite of the increased variability, the subjects who received cocaine in a novel environment on the test day (group 3) tended to have a larger increase in EEG beta than those who previously received cocaine in the same room (group 1). Thus, there was a trend toward conditioned tolerance.

Although the finding of context-dependent tolerance seems at odds with the expected finding of context-dependent sensitization, this is not necessarily the case. For example, Kandel (16) has shown that tolerance development to a presynaptic inhibitory action is the major mechanism responsible for postsynaptic behavioral sensitization (16). Similarly, others have shown in the rat that the occurrence of stimulant-induced sensitization parallels the development of tolerance-development to the DA-synthesis inhibiting effects of COC (2) and amphetamine (36). Thus, the same underlying process may lead to tolerance development in one end point and sensitization in another (9).

There are several possible reasons for the difference between our results and those in rodent studies. First, rodent studies use cocaine-naive subjects, whereas this study used cocaine-experienced subjects. It is possible, in other words, that prior experience with cocaine alters its ability to produce sensitization. Second, the stimulus properties of the two environments may not have been different enough. For example, the subjects may not have associated the cocaine administration with the room, but, perhaps, with the medical personnel in attendance. Three, there may not have been enough conditioning sessions to facilitate such an association to form. Recent studies (Elmer et al., manuscript in preparation) have demonstrated considerable differences, among genetically inbred strains of mice, in the number of conditioning trials required to produce sensitization. Thus, it is also likely that there will be considerable heterogeneity in the responses among the humans who volunteered for this study. In this case, the number of subjects may have been too small to detect small changes. Four, the end points we can measure in humans may be only weakly associated with the primary events underlying conditioned sensitization. In future studies, we plan to increase the number of training sessions to four and to maximize the differences between environments.

Although it is sometimes assumed that humans and rodents have essentially the same responses to cocaine, the data reported here suggest that animal models do not always extrapolate to humans in a straightforward manner. Because effective pharmacotherapeutic treatments for cocaine addiction are likely to come from a better understanding of cocaine's mechanisms of action, our findings emphasize the critical role that human research must play in the effort to develop new medications for the treatment of cocaine addiction.

REFERENCES

1. Barr, G. A.; Sharplus, N. S.; Cooper, S.; Schiff, S. R.; Paredes, W.; Bridger, W. H. Classical conditioning, decay and extinction of cocaine-induced hyperactivity and stereotypy. Life Sci. 33: 1341-1351; 1983.
2. Baumann, M. H.; Raley, T. J.; Partilla, J. S.; Rothman, R. B. Biosynthesis of dopamine and serotonin in rat brain after repeated cocaine injections: A microdissection mapping study. Synapse 14:40-50; 1993.
3. Borowsky, B.; Kuhn, C. M. Chronic cocaine administration sensitizes behavioral but not neuroendocrine responses. Brain Res. 543:301-306; 1991.
4. Bridger, W. H.; Schiff, S. R.; Cooper, S. S.; Paredes, W.; Barr, G. Classical conditioning of cocaine's stimulatory effects. Psychopharmacol. Bull. 18:210-214; 1982.
5. Cador, M.; Dumas, S.; Cole, B. J.; Mallet, J.; Koob, G. F.; Le Moal, M.; Stinus, L. Behavioral sensitization induced by psychostimulants or stress: Search for a molecular basis and evidence for a CRF-dependent phenomenon. Ann. NY Acad. Sci. 654:416-420; 1992.
6. Chamberlin, H. Musical applications of microprocessors. Hasbrook Height, NJ: Hayden; 1993.
7. Childress, A. R.; McLellan, A. T.; Ehrman, R. N.; O'Brien, C. P. Extinction of conditioned responses in abstinent cocaine or opioid abusers. NIDA Res. Monogr. 76:189-195; 1986.
8. Childress, A. R.; McLellan, A. T.; O'Brien, C. P. Abstinent opiate abusers exhibit conditioned craving, withdrawal and reduction in both through extinction. Br. J. Addict. 81:655-660; 1986.
9. De Montis, M. G.; Devoto, P.; Meloni, D.; Gambarana, C.; Giorgi, G.; Tagliamonte, A. NMDA receptor inhibition prevents tolerance to cocaine. Pharmacol. Biochem. Behav. 42:179-182; 1992.
10. Farfel, G. M.; Kleven, M. S.; Woolverton, W. L.; Seiden, L. S.; Perry, B. D. Effects of repeated injections of cocaine on catecholamine receptor binding sites, dopamine transporter binding sites and behavior in rhesus monkey. Brain Res. 578:235-243; 1992.
11. Hayashi, T.; Ohashi, K.; Tadokara, S. Conditioned drug effects of *d*-amphetamine- and morphine-induced motor acceleration in mice: Experimental apporach for placebo effect. Jpn. J. Pharmacol. 30:93-100; 1980.
12. Herning, R. I.; Glover, J.; Keoppl, B.; Phillips, R. L.; London, E. D. Cocaine-induced increases in EEG alpha and beta activity: Evidence for reduced cortical processing. Neuropsychopharmacology (in press).
13. Herning, R. I.; Jones, R. T.; Hooker, W. D. Cocaine increases EEG beta: A replication of Hans Berger's historic experiments. Electroencephalogr. Clin. Neurophysiol. 60:470-477; 1985.
14. Hinson, R. E.; Poulos, C. X. Sensitization to the behavior effects of cocaine: Modification by Pavlovial conditioning. Pharmacol. Biochem. Behav. 15:559-562; 1981.
15. Kalivas, P. W.; Striplin, C. D.; Steketee, J. D.; Klitenick, M. A.; Duffy, P. Cellular mechanisms of behavioral sensitization to drugs of abuse. Ann NY Acad Sci 654:128-135; 1992.
16. Kandel, E. R. Cellular mechanisms of learning and the biological basis of individuality. In: Kandel, E. R.; Schwartz, J. H., eds. Principles of neural science. New York: Elsevier; 1985:816-833.
17. Levy, A. D.; Li, Q.; Alvarez Sanz, M. C.; Rittenhouse, P. A.; Kerr, J. E.; Van de Kar, L. D. Neuroendocrine responses to cocaine do not exhibit sensitization following repeated cocaine exposure. Life Sci. 51:887-897; 1992.
18. Mendelson, J. H.; Teoh, S. K.; Mello, N. K.; Ellingboe, J.; Rhoades, E. Acute effects of cocaine on plasma adrenocorticotropic hormone, luteinizing hormone and prolactin levels in cocaine-dependent men. J. Pharmacol. Exp. Ther. 263:505-509; 1992.
19. Nagoshi, C.; Kumor, K. M.; Muntaner, C. Test-retest stability of cardiovascular and subjective responses to intravenous cocaine in humans. Br. J. Addict. 87:591-599; 1992.
20. O'Brien, C. P.; Childress, A. R.; Arndt, I. O.; McLellan, A. T.; Woody, G. E.; Moany, I. Pharmacological and behavioral treatments of cocaine dependence: Controlled studies. J. Clin. Psychiatry 49:17-22; 1988.
21. O'Brien, C. P.; Ehrman, R. N.; Towes, J. W. Classical conditioning in human opioid dependence. In: Goldberg, S. R.; Stolerman, J. P., eds. Behavioral analyses of drug dependence. Orlando, FL: Academic Press; 1986:329-356.
22. Pert, A.; Post, R. M.; Weiss, S. R. B. Conditioning as a critical determinant of sensitization induced by psychomotor stimulants. NIDA Res. Monogr. 97:208-241; 1990.
23. Pettit, H. O.; Pan, H. T.; Parsons, L. H.; Justice, J., Jr. Extracellular concentrations of cocaine and dopamine are enhanced during chronic cocaine administration. J. Neurochem. 55:798-804; 1990.
24. Pickens, R. W.; Crowder, W. F. Effects of CS-US interval on conditioning of drug response, with assessment of speed of conditioning. Psychopharmacologia 11:88-94; 1967.
25. Pickens, R. W.; Dougherty, J. D. Conditioning of the activity effects of drugs. In: Thompson, T.; Schuster, C., eds. Stimulus properties of drugs. New York: Appelton-Century-Crofts; 1971: 39-50.
26. Pilotte, N. S.; Sharpe, L. G.; Dax, E. M. Multiple, but not acute, infusions of cocaine alter the release of prolactin in male rats. Brain Res. 512:107-112; 1990.
27. Post, R. M.; Lockfeld, A.; Squillace, K. M.; Contel, N. R. Drug-environment interaction: Control dependency of cocaine-induced behavioral sensitization. Life Sci. 28:755-760; 1981.
28. Post, R. M.; Weiss, S. R.; Pert, A. The role of context and conditioning in behavioral sensitization to cocaine. Psychopharmacol. Bull. 23:425-429; 1987.
29. Schiff, S. R. Conditioned dopaminergic activity. Biol. Psychol. 17:135-154; 1982.
30. Segal, D. S.; Kuczenski, R. Repeated cocaine administration induces behavioral sensitization and corresponding decreased extracellular dopamine responses in caudate and accumbens. Brain Res. 577:351-355; 1992.
31. Striplin, C. D.; Kalivas, P. W. Correlation between behavioral sensitization to cocaine and G protein ADP-ribosylation in the ventral tegmental area. Brain Res. 579:181-186; 1992.
32. Tilson, H. A.; Rech, R. H. Conditioned drug effects and absence of tolerance to *d*-amphetamine induced motor activity. Pharmacol. Biochem. Behav. 1:149-153; 1973.
33. Vasey, M. W.; Thayer, J. F. The continuing problem of false positives in repeated measures ANOVA in psychophysiology: A multivariate solution. Psychophysiology 24:479-486; 1987.
34. Wallace, B. Psychological and environmental determinants of relapse in crack cocaine smokers. J. Subst. Abuse Treat. 6:95-100; 1989.
35. Weiss, S. R. B.; Post, R. M.; Woodward, R.; Murman, D. Role of conditioning in cocaine-induced behavioral sensitization. Pharmacol. Biochem. Behav. 34:655-661; 1989.
36. Wolf, M. E.; White, F. J.; Nassar, R.; Brooderson, R. J.; Khansa, M. R. Differential development of autoreceptor subsensitivity and enhanced dopamine release during amphetamine sensitization. J. Pharmacol. Exp. Ther. 264:249-255; 1993.