

Cocaine-Induced Reduction of Glucose Utilization in Human Brain

A Study Using Positron Emission Tomography and [Fluorine 18]-Fluorodeoxyglucose

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• We examined the effects of cocaine hydrochloride (40 mg intravenously) on regional cerebral metabolic rates for glucose and on subjective self-reports of eight polydrug abusers in a double-blind, placebo-controlled, crossover study. The regional cerebral metabolic rate for glucose was measured by the [fluorine 18]-fluorodeoxyglucose method, using positron emission tomography. With eyes covered, subjects listened to a tape that presented white noise, "beep" prompts, and questions about subjective effects of cocaine or saline. Cocaine produced euphoria and reduced glucose utilization globally (mean reduction, 14%). Twenty-six of 29 brain regions (all neocortical areas, basal ganglia, portions of the hippocampal formation, thalamus, and midbrain) showed significant decrements (5% to 26%) in the regional cerebral metabolic rate for glucose. No significant effects of cocaine were observed in the pons, the cerebellar cortex, or the vermis. Right-greater-than-left hemispheric asymmetry of regional cerebral metabolic rates for glucose occurred in the lateral thalamus. The findings demonstrate that reduced cerebral metabolism is associated with cocaine-induced euphoria.

(*Arch Gen Psychiatry*. 1990;47:567-574)

Cocaine produces marked behavioral and physiological effects in human subjects. These effects include euphoria, enhanced arousal, reversal of fatigue-induced deficits in performance, and increases in heart rate and blood pressure.^{1,2} The effect on arousal is accompanied by increased fast (beta) activity in the electroencephalogram (EEG)³ and decreased cognitive event-related potentials.⁴ Reinforcing properties of cocaine have been related to inhibition of dopamine up-

take⁵ and may involve the production of euphoria.^{2,6}

Cocaine-induced euphoria might be produced by actions on brain regions that receive input but are remote from primary sites where cocaine binds to receptors on dopamine transporters. Brain areas that show such secondary effects of drugs can be identified by the autoradiographic 2-deoxy-[D-1-carbon 14]-glucose method,^{7,8} which is used to measure the regional cerebral metabolic rate for glucose (rCMRglc), an index of local functional activity in the brain. This method has been used to show cocaine-induced stimulation of rCMRglc in extrapyramidal motor and limbic areas of the rat brain.^{9,10}

The 2-deoxy-[D-1-carbon 14]-glucose method has been adapted for use in humans by the use of positron emission tomography (PET) for visualization and measurement of regional concentrations of radioactivity in the brain after administration of the short-lived radiotracers 2-deoxy-[D-1-carbon 11]-glucose and 2-deoxy-[2-fluorine 18]-fluoro-D-glucose.¹¹⁻¹⁸ Studies in human volunteers have used the [fluorine 18]-fluorodeoxyglucose method to map and quantitate the effects of various drugs on rCMRglc.¹⁴⁻¹⁷ In a previous study by our research group, acute treatment with morphine reduced rCMRglc of the neocortex in polydrug abusers.¹⁸ The findings differed from those obtained in naive rats,¹⁹ possibly reflecting the influence of drug history, drug dosages, or a fundamental difference in the response of the human brain as compared with the rat brain.

The purpose of this study was to assess the effects of an acute, euphorogenic cocaine hydrochloride treatment on rCMRglc in human volunteers. Positron emission tomography has been used previously to demonstrate a decrease in blood flow to the prefrontal cortex (relative to whole brain) in long-term cocaine abusers.²⁰ In addition, preliminary data obtained with the [fluorine 18]-fluorodeoxyglucose method suggest that there is no decrease in normalized rCMRglc in the left lateral prefrontal cortex in nondepressed patients withdrawing from cocaine use.²¹ However, acute effects of cocaine on rCMRglc have not been assessed before in human subjects.

SUBJECTS AND METHODS

Subjects

Ten healthy male volunteers with a history of substance abuse were recruited by newspaper advertisements, and participated in the

Accepted for publication October 18, 1989.

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Presented in part as an abstract at the following annual meetings: Society for Neuroscience, New Orleans, La, November 19, 1987, and Toronto, Canada, November 17, 1988; American Psychiatric Association, Chicago, Ill, May 11, 1987, and San Francisco, Calif, May 10, 1989; Society of Nuclear Medicine, San Francisco, June 17, 1988; and American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 14, 1988.

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study. Naive normal subjects were excluded because of ethical concerns about the administration of cocaine. One subject was rejected from the study because of his unusual sensitivity to 40 mg of cocaine hydrochloride during preliminary training sessions (see below). Another subject did not complete the study because of delays due to equipment failure. Eight subjects between 23 and 40 years of age (mean \pm SD, 33 ± 3.7 years) completed the protocol. They showed no pathological conditions in a complete physical examination and in standard diagnostic tests, including complete blood cell count, serum electrolyte assay, liver function tests, fasting blood glucose level, prothrombin and partial thromboplastin times, thyroid function tests, urinalysis, electrocardiography, and tests for exposure to tuberculosis, viral hepatitis, and human immunodeficiency virus. The subjects demonstrated patency of both radial and ulnar arteries by Allen's test.

Screening Procedures

Subject selection was based on drug experience. A recent history of intravenous (IV) cocaine use was a criterion for admission. Seven of the eight subjects who completed the protocol used cocaine exclusively by the IV route; one also smoked cocaine. Six of the eight subjects reported use of cocaine within the 2 weeks before admission to the study. The reported mean (\pm SD) frequency of cocaine self-administration was 17 ± 8 d/mo, with a mean daily quantity of use of 0.60 ± 0.39 g. All of the participants also used tobacco, opioids, marijuana, and/or amphetamines. Five of the eight subjects reported use of an opioid within the 2 weeks before admission. None reported use of barbiturates or neuroleptics. Four subjects reported using benzodiazepines, with the most recent use within 1 to 7 months before admission. Four subjects had used hallucinogens, including LSD, but not within the 2 years before this study. All eight subjects were right-handed according to Annett's handedness questionnaire.²²

The National Institute on Mental Health Diagnostic Interview Schedule, modified for computerized self-administration,²³ was used to screen for psychiatric disorders. The only acceptable Axis I diagnoses were substance abuse and/or dependence; Axis II diagnoses of borderline and/or antisocial personality disorders were allowed. A score consistent with a sixth-grade education on the Shipley Institute of Living Scale,²⁴ a measure of intellectual function, was used as a minimum criterion for admission. All subjects gave informed consent in compliance with guidelines of the institutional review boards of The Johns Hopkins Hospital and Francis Scott Key Medical Center, Baltimore, Md, where the National Institute on Drug Abuse Addiction Research Center is located.

The subjects resided on a research ward during the screening procedures and subsequent study to assure compliance and to prevent self-administration of drugs that were not allowed. Random screening of urine samples demonstrated no use of illicit drugs, other than cocaine, which was administered as part of the study protocol. Nicotine (cigarettes), caffeine (beverages), and cocaine (in the study) were the only drugs allowed. Seven to 10 days elapsed between entering the research ward and the first PET simulation (see below). During this period, subjects were observed for symptoms of withdrawal from chemical dependencies; none of these symptoms were noted.

General Experimental Design

The study was designed as a double-blind, placebo-controlled crossover. Each subject completing the study received two PET scans (range, 2 to 10 days apart) in conjunction with either 40 mg of cocaine hydrochloride (diluted in 0.9% saline; total volume, 2.0 mL) or an equal volume of saline, according to a random schedule.

Test Compounds and Radiotracer Preparation

Cocaine hydrochloride (Mallinckrodt, Paris, Ky) was dissolved in saline at a concentration of either 20 or 40 mg/mL as the salt. It was infused IV over about 10 seconds (by D.F.W.) in a volume of 2 mL. Although we could not accurately determine the dosage of cocaine self-administered by users outside the laboratory setting, it has been estimated that single doses range from 20 to 100 mg, considering differences in bioavailability.²⁵ The placebo treatment was 2 mL of saline IV.

[Fluorine 18]-fluorodeoxyglucose was synthesized from fluorine 18 fluoride produced in a biomedical cyclotron (MC-16F, Scanditronix, Uppsala, Sweden) by the (proton, neutron) reaction on 98% enriched

[oxygen 18] water.²⁶ Radiochemical purity of the final product, determined using thin-layer chromatography or high-performance liquid chromatography on an amino column eluted with aqueous acetonitrile, exceeded 98%. All preparations were determined to be sterile and apyrogenic.

Training-Screening Sessions

Subjects participated in four preliminary sessions to achieve the following objectives: (1) training in procedures of the study; (2) reduction of stress and novelty of the test situation; and (3) identification and exclusion of subjects who lacked adequate subjective and EEG responses to cocaine or who showed abnormally strong responses to saline (see criteria below). The first session was for training only; the treatment was always saline (single-blind); EEG data were not collected; and the data were not used. The other sessions occurred at intervals of 24 hours or more. Treatments were administered according to a double-blind, pseudorandom schedule as follows: 20 mg of cocaine hydrochloride preceded the 40-mg dose to reduce the chance of untoward effects, but saline randomly occurred in the sequence. Spontaneous EEG and subjective responses to the treatments were recorded.

For EEG collection, 14 electrodes were attached to the scalp, using all of the International 10-20 System positions on the center line and left side of the scalp.²⁷ The spontaneous EEG was recorded for a 3-minute baseline period and for 30 minutes after test compound injection. Topographic maps of spectral power in the EEG beta band were used to assess effects of cocaine or saline every 3 minutes during the recording session.

The subject sat in an acoustically shielded room. His eyes were covered with cotton gauze patches, and he wore headphones that presented constant white noise and a "beep" prompt every minute to the right ear. He was instructed to respond to each beep with a rating from 0 (no effect) to 4 (extremely) of how much he felt an effect of the test compound. Responses to beep prompts were obtained from shortly before the test compound injection to 30 minutes after injection. At 1, 5, 15, and 20 minutes after injection, the subject was instructed to give similar scores (0 to 4) on a 23-item version of the Cocaine-Sensitive Scale (CSS). Most of the items on this scale have been used in previous studies with IV cocaine.^{28,29} In these studies, the items showed adequate validity when assessed against the Morphine-Benzedrine Group (MBG) subscale of the Addiction Research Center Inventory.³⁰ Principal components analysis and nonparametric analogues of two-way analysis of variance (ANOVA) of data from the present study demonstrated that 8 of the 23 items (ie, feel drug, rush, good, pleasant, high, energetic, powerful, anxious) have predictive power with regard to the test compound given (cocaine vs saline; E. D. L., N. G. C., R. L. P., J. H. J, unpublished observation, 1990). The CSS also was administered at baseline (30 and 60 minutes before the test compound) and at 30 minutes after the test compound. At 30 minutes after injection, the subject was instructed to rate his feelings at the time of peak effect. Blood pressure and heart rate were assessed at 1 and 0.5 hour before the test compound injection and were continuously monitored for 30 minutes after the injection.

Self-reports of subjective effects also were assayed at baseline and 30 minutes after injection using the MBG, the Pentobarbital, Chlorpromazine, and Alcohol Group (PCAG), and the LSD subscales of the Addiction Research Center Inventory.³⁰ The MBG subscale contains 16 items that relate mainly to euphoria; the PCAG subscale contains 15 items that primarily reflect fatigue and low motivation; and the LSD subscale includes 14 items, mainly reflecting feelings of anxiety, tension, depersonalization, and difficulty in concentration.³⁰ At this time, subjects also rated the peak treatment effect on seven 100-mm visual line analogue scales, relating to the following items: "How strong was the treatment effect?" "Did the drug have good effects?" "Did the drug have bad effects?" "How much did you like the drug?" "How high did you feel?" "How much did you want to take the drug again?" and "How energetic did the drug make you feel?" Scores were obtained by summing the distances (in millimeters, from the left end of each line to the point marked) for the 3 items relating to good feelings, how much the subject liked the test compound, and how high he felt.

An investigator (N. G. C.) who did not attend the sessions evaluated data from the training-screening sessions to determine whether the subject met inclusion criteria for PET study. The criteria were based on EEG data and responses on the visual analogue scale. The EEG

criterion for a response to 40 mg of cocaine hydrochloride was a 25% increase in beta power. The same response to saline was an exclusionary criterion. The EEG criterion was based on previous EEG effects of cocaine in substance abusers.³⁴ An acceptable response to cocaine was defined by a score of 20 mm or more on four of the five following items of the visual analogue scale: "How strong was the drug effect?" "Did the drug have good effects?" "How much did you like the drug?" "How high did you feel?" and "How energetic did the drug make you feel?" No subject was rejected on the basis of these criteria.

PET Scan Procedures

Before PET scanning, a molded plastic head-stabilization device for PET and roentgenographic computed tomographic (CT) scans was prepared as described previously.¹⁸ The CT scan was used to verify the absence of brain disease and to help identify regions of interest (ROIs) in PET scans.

On each PET day, subjects received a standard nonketogenic breakfast and then were deprived of food for 4 to 6 hours before the [fluorine 18]-fluorodeoxyglucose injection, which occurred between noon and 3:30 PM. They were not allowed to smoke for 2 hours before the [fluorine 18]-fluorodeoxyglucose injection or during the [fluorine 18]-fluorodeoxyglucose uptake and scanning. An IV infusion of 0.45% sodium chloride was initiated in a forearm vein of each arm. A radial arterial catheter was inserted after the administration of local anesthetic (0.5% lidocaine hydrochloride, subcutaneously). Thirty minutes before test compound injection, four of the subjects were seated with eyes covered and earphones in place. The other four subjects were in a supine position for the [fluorine 18]-fluorodeoxyglucose uptake period to allow estimation of the rate constants for [fluorine 18]-fluorodeoxyglucose transport and phosphorylation (work in progress). Subjective and physiological responses were sampled as in the training-screening sessions.

Simultaneous with the test compound injection, 0.0185 Bq of [fluorine 18]-fluorodeoxyglucose in 5 mL of saline was infused through a forearm vein catheter over about 30 seconds, followed by 20 mL of saline. Arterial blood samples were drawn for the assay of glucose concentration, radioactivity, and blood gas analysis (baseline and 30 minutes after test compound injection), as previously described.¹⁸ Arterial blood samples were collected in heparinized tubes for assay of plasma cocaine levels (baseline and 30 minutes after test compound injection).

Cocaine levels were assayed by gas chromatography-mass spectrometry. Mean within-run coefficients of variation for cocaine standards of 25 and 100 ng/mL ($n=6$) were 15.6% and 7.1%, respectively. Accuracy of the measurement for 25- and 100-ng/mL control samples was within about 3% and 2% of the target concentrations, respectively (mean \pm SD for 25 and 100 ng/mL, 24.2 ± 3.8 and 101.9 ± 7.2 ng/mL, respectively).

For four of the subjects, PET scanning began 45 minutes after [fluorine 18]-fluorodeoxyglucose injection, using a Neuro-ECAT PET scanner (Computers Technology and Imaging, Knoxville, Tenn) in the high-resolution mode. The resolution of the scanner was 8 mm within-plane and 15 mm axially. The PET scanning began immediately with the injection of [fluorine 18]-fluorodeoxyglucose for the four subjects in whom rate constants for [fluorine 18]-fluorodeoxyglucose transport and phosphorylation were determined (data not given). For all eight subjects, data used in the present study were from four 15-minute consecutive scans, beginning 45 minutes after [fluorine 18]-fluorodeoxyglucose injection, each comprising a set of three planes on 32-mm centers. Twelve images, which were on 8-mm centers and parallel to the inferior orbitomeatal line (IOM), were obtained. The lowest plane was 16 mm above the IOM, and the highest was 104 mm above the IOM. There were approximately 2 million true coincidence counts per image. The PET scanner and the well counter were cross-calibrated daily, PET images were reconstructed from the raw data, and attenuation correction was performed as described previously, using an ellipse and a uniform attenuation coefficient ($\mu=0.088/\text{cm}$, measured for water).¹⁸ For seven of the eight subjects, those seven consecutive planes, beginning with 32 mm above the IOM and continuing at 8-mm increments until 80 mm above the IOM, were selected for assessment of global CMRglc. For one subject, sampling began with 48 mm above the IOM and continued by 8-mm increments so that seven levels were sampled. Measures of CMRglc reflected glucose utilization in the telencephalon, diencephalon, and midbrain but not the remaining brain stem and cerebellum.

Measures of brain radioactivity were converted into metabolic rates from PET data, plasma radioactivity, and glucose concentrations using standard values of the rate constants for the transport of [fluorine 18]-fluorodeoxyglucose (between brain and plasma), [fluorine 18]-fluorodeoxyglucose phosphorylation and dephosphorylation in brain (k_1 , k_2 , k_3 , and k_4 , respectively), and the lumped constant, as well as the operational equation of Huang et al.³¹ We also used the model of Hutchins et al.³² because of concern that cocaine-induced cerebral vasoconstriction might dramatically reduce cerebral blood flow and thereby affect determination of rCMRglc. This model is insensitive to changes in perfusion, and thereby in k_1 , on rCMRglc measurements. Although no systematic study on the effects of cocaine on cerebral vessels has been done, the sympathomimetic effects of cocaine can produce vasoconstriction.⁶

ROI Analysis

Data from PET scans were analyzed using a PET image analysis system (LOATS Associates Inc, Westminster, Md) and an analysis program developed at the National Institute on Drug Abuse Addiction Research Center. A standard template of ROIs was constructed with reference to an anatomical atlas³³ as previously described.¹⁸ For ROI analysis, CT and PET scans from each study were compared with the atlas to select those seven planes that best matched the planes in the reference set (standard template).

The template was displayed on the PET images from the first PET study of a given subject, and was adjusted, without reference to the identity of the test compound, by one of us (N.G.C.) until it corresponded with the location of the brain areas on the PET and corresponding CT scans. Adjustments were minimized by fixing region size; only global template and individual region shifts were used (in succession). The ROI template in the second study was aligned with that of the first study by an automated technique that minimized variations between the two studies.

In general, after preliminary alignment using reconstruction software, the ROI template required an adjustment of 8 to 15 mm within the transverse plane. The visual display readily identified subjects where misalignment in the z axis was appreciable. Misalignment in the z axis was appreciable only in two subjects. In one case, the misalignment was small and could be safely ignored, while in the other case it was nearly one slice wide and was corrected by using adjacent slices.

Using an edge-finding algorithm, average CMRglc for each entire image was determined by the same analysis used to calculate rCMRglc in ROIs and was multiplied by the area of the image in pixels, the resultant values having the dimension milligrams of glucose per 100 g of tissue per minute multiplied by pixels. Values were summed for seven images (see above); the sum was divided by the total area analyzed, giving average CMRglc.

Statistical Analysis

Values of rCMRglc were subjected to two-way (saline vs cocaine, right vs left hemisphere, excluding midline structures) ANOVAs with repeated measures on the drug treatment factor and hemisphere as a grouping factor. Values of rCMRglc from midline structures and global CMRglc were analyzed by one-way (saline vs cocaine) ANOVA with repeated measures. We made no correction for the number of comparisons.

Cardiovascular values (systolic and diastolic blood pressure, heart rate), plasma glucose concentrations, and arterial blood gases (PaCO_2 and PaO_2) and pH were analyzed by two-way ANOVA, with drug treatment (saline, cocaine) and time of measurement as the factors. When significant F values were obtained for cardiovascular measures, individual means were compared by post hoc paired t tests to determine if (and at what times) the change from baseline was statistically significant on cocaine and saline treatment days. The Bonferroni correction for multiple comparisons was used. The criterion for significance at the .05 level was $P < .005$.

Plasma glucose concentrations were averaged over the PET measurement period for each subject under saline and cocaine conditions. The data were analyzed by Student's paired t test.

Self-reported responses on CSS, subscales of the Addiction Research Center Inventory, and visual analogue scales were analyzed by two-way ANOVA, with drug and time as repeated measures.

All tests of significance were performed using BMDP programs.³⁴ Statements of significance used $P < .05$ as the criterion.

RESULTS

Cocaine Levels

Plasma samples taken before test compound administration, and at 30 minutes after the injection of saline or cocaine, were assayed. Samples obtained before cocaine or saline injection, or after the injection of saline, were negative for cocaine. The mean (\pm SD) cocaine level 30 minutes after cocaine hydrochloride injection was 213 ± 47.3 ng/mL ($n=6$; samples were not obtained from two subjects).

Physiological Parameters

Although cocaine did not alter arterial PaO_2 and pH, PaCO_2 increased significantly, by 2 to 3 mm Hg, at 30 minutes after the test compound injection as compared with baseline levels in both the saline and cocaine conditions (baseline: saline, 38.2 ± 1.9 mm Hg; cocaine, 37.8 ± 2.5 mm Hg; 30 minutes: saline, 41.2 ± 2.0 mm Hg; cocaine, 39.9 ± 2.1 mm Hg; $F[1,14]=11.51$, $P<.005$ for time effect). There were no statistically significant effects of time of measurement on arterial blood PaO_2 or pH (mean PaO_2 , 95.8 ± 14 mm Hg; $F[1,14]=0.10$, $P=.75$; mean pH, 7.40 ± 0.02 ; $F[1,14]=2.04$, $P=.17$).

Cardiovascular values revealed statistically significant time-dependent effects on systolic blood pressure (drug, $F[1,92]=25.0$, $P<.0001$; time, $F[7,92]=11.7$, $P<.0001$; interaction, $F[7,92]=1.98$, $P<.05$) and heart rate (drug, $F[1,99]=59.8$, $P<.0001$; time, $F[7,99]=4.32$, $P<.001$; interaction, $F[7,99]=2.80$, $P<.011$). Effects on diastolic blood pressure were not statistically significant ($P>.05$; Fig 1). The effects of cocaine on systolic blood pressure and heart rate were similar to those observed previously after a similar treatment.³⁵

Saline increased mean systolic blood pressure slightly and nonsignificantly above baseline values. The greatest increase occurred 3 minutes after the injection (mean of differences from baseline, 17.8 ± 5.69 mm Hg). However, cocaine produced significant differences from baseline at 1 to 10 minutes after injection (greatest increase, calculated as the mean of individual changes, was 42.1 ± 15.2 mm Hg [$P<.01$] at 1 minute after injection; greatest increase, calculated as the change in the means, was at 3 minutes; Fig 1).

Heart rate did not increase significantly above baseline at any of the measurement times after saline injection (largest mean increase was 13.9 ± 13.6 beats per minute at 1 minute after injection). Cocaine produced significant elevations over baseline at 1 through 10 minutes after the drug injection ($P<.05$, .01, .02, and .025 for 1, 3, 5, and 10 minutes, respectively; greatest mean increase of 28.8 ± 15.3 beats per minute [$P<.01$], at 10 minutes after injection).

Plasma glucose concentrations, averaged over the PET measurement period for each subject, were 93 ± 2.6 and 94 ± 4.1 mg/dL (mean \pm SD for eight subjects) under saline and cocaine conditions, respectively. The values did not differ significantly (paired t test, $P>.05$).

Subjective Responses to Cocaine

Subjective responses to cocaine and saline are given in Table 1. The MBG scores showed a statistically significant drug-by-time interaction ($F[2,12]=11.55$, $P=.0016$), reflecting an increase in score under cocaine but not saline conditions. The LSD score increased over time, irrespective of drug treatment ($F[2,12]=6.05$, $P<.0153$); the PCAG subscale showed no statistically significant effects. The CSS scores, obtained by summing the scores for those eight items that showed predictive power with regard to the test compound, showed a significant effect of cocaine ($F[1,5]=9.43$, $P<.0278$). The visual analogue scale showed statistically significant effects of drug ($F[1,42]=14.3$, $P=.0005$) and time ($F[2,42]=20.9$, $P<.0001$) and a significant interaction ($F[2,42]=14.8$, $P<.0001$). The integrated beep prompt responses to the question "How much do you feel the effect of the test compound?" showed a statistically significant effect of drug, reflecting higher scores under the cocaine condition, primarily at the earliest times after injection (0 to 5 minutes). However, when the score was integrated from 0 to 30 minutes after cocaine injection, there was no significant difference from 0, reflecting greater variance at later times after cocaine injection.

Analysis of those eight items of CSS that showed predictive value of a cocaine effect (Fig 2) showed no significant effects on the following items: "feel good," "energetic," and "anxious." "Feel drug" showed a significant effect of drug ($F[1,6]=14.7$, $P<.01$) but not time

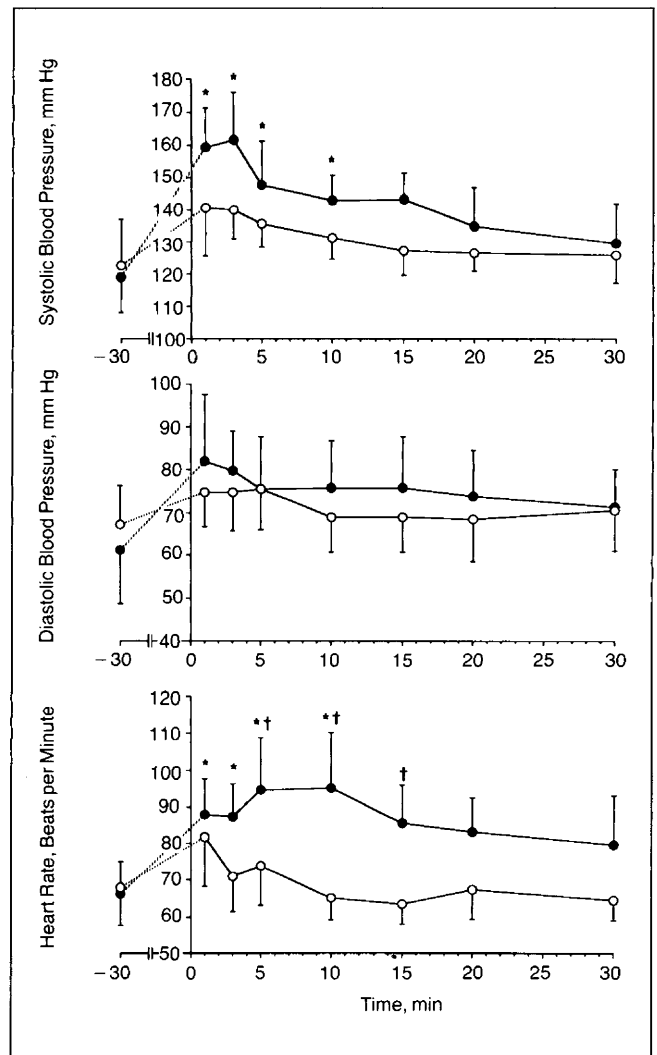


Fig 1.—Time course of effects of cocaine hydrochloride (closed circles) and saline (open circles) on cardiovascular measures. Each point indicates the mean \pm SD for eight subjects at each of the times indicated relative to the injection of test compound. Asterisk indicates significant difference from baseline mean; dagger, significant difference from corresponding mean in the saline condition.

or the interaction of drug with time. "Rush" showed significant effects of drug ($F[1,6]=12.8$, $P=.01$), time ($F[3,18]=4.0$, $P<.05$), and the interaction ($F[3,18]=3.45$, $P<.05$). "Pleasant" showed no significant main effects of drug or time but a significant interaction ($F[3,18]=5.37$, $P<.01$), reflecting a transient increase after cocaine but not saline. Using the Bonferroni correction, individual means at the various times showed no statistically significant differences from baseline, and no differences between cocaine and saline treatments. Despite greater reports of being "high" in response to cocaine vs saline, this measure showed no statistically significant effects of drug or drug-by-time interaction, owing to variation in the response to cocaine. A significant effect of time ($F[3,18]=5.59$, $P<.01$) was due to a rapid, transient increase in the "high" score after cocaine but not saline injection. There was a significant drug effect on "powerful" ($F[1,5]=7.95$, $P<.05$), with no significant effects of time or the interaction.

Regional Cerebral Glucose Utilization

Table 2 gives mean \pm SD values of rCMRglc in the 50 ROIs analyzed and global CMRglc in response to saline and cocaine (Fig 3). No brain region showed a statistically significant cocaine-induced increase of mean rCMRglc . However, cocaine significantly reduced cerebral glu-

Table 1.—Effects of Cocaine on Subjective Responses*

Score	Saline			Cocaine Hydrochloride		
	-60 min	-30 min	30 min	-60 min	-30 min	30 min
MBG†	4.3±3.1	4.1±3.7	4.3±3.0	4.6±4.3	4.1±4.2	9.6±3.2
LSD‡	2.3±0.95	3.6±1.9	4.0±2.3	3.0±1.4	3.3±2.2	5.4±2.4
PCAG	2.7±9.95	3.0±1.6	2.7±0.95	3.0±1.3	3.4±1.3	2.5±1.3
CSS§	...	6.8±3.3	6.2±3.6	...	7.2±4.3	16±7.7
VAS, mm†‡§	14±31	14±36	39±74	14±38	12±34	304±168
Integrated "beep" prompt response§	0±0 (5)	0±0 (30)	...	7.8±4.2 (5)	29±30 (30)	...

*MBG indicates Morphine-Benzadrine Group, LSD, lysergic acid diethylamide, and PCAG, Pentobarbital, Chlorpromazine, and Alcohol Group subscales of Addiction Research Center Inventory; CSS, Cocaine-Sensitive Scale; and VAS, visual analogue scale. Values are mean ± SD for eight subjects. The CSS score was obtained by summing the scores for those eight items that were shown to have predictive power with regard to the test compound administered (saline vs cocaine hydrochloride). The visual analogue scale score was obtained by summing the scores (in millimeters from the left end of the scale to the point marked by the subject) for all seven items of the questionnaire. The response to the item "Did the drug have bad effects?" was always 0 mm under saline and cocaine conditions. The integrated "beep" prompt response was calculated as the area under the time-action curve using the method of trapezoids. Integrated time after injection is noted in parentheses and expressed in minutes.

†Statistically significant interaction, $P = .002$ for MBG, $P < .0001$ for VAS.

‡Statistically significant main effect of time, $P = .015$ for LSD, $P < .0001$ for VAS.

§Statistically significant main effect of cocaine, $P = .028$ for CSS, $P = .0005$ for VAS, and $P = .016$ for integrated beep score.

cose utilization by 14% in whole brain and by up to about 26% in all of the 23 telencephalic areas sampled. Also, the caudate nucleus (13% and 16%), putamen (15% and 12%), amygdaloid nucleus (12% and 10%), hippocampus (14% and 9%), and parahippocampal gyrus (10% and 11%) showed statistically significant decreases. In subtelencephalic areas, cocaine significantly reduced rCMRglc in the medial thalamus (10%), the lateral thalamus (9% and 11%), and the midbrain (13%). No significant effects were noted in the pons, cerebellar cortex, or vermis.

Values of rCMRglc calculated using standard values of the rate constants for the transport, phosphorylation, and dephosphorylation of [fluorine 18]-fluorodeoxyglucose, and the model of Hutchins et al³² (data not given), generally were similar ($\pm 13\%$) to those obtained by the model of Huang et al,³¹ and the effects of cocaine were the same using both models. Cocaine caused significant decrements in rCMRglc and CMRglc irrespective of the model used for calculating metabolic rates.

COMMENT

This article is the first indicating that acute, euphorogenic doses of cocaine reduce rCMRglc and CMRglc in humans. The decrease occurs throughout the telencephalon and extends into the thalamus and midbrain. Of the ROIs sampled, only the pons and cerebellum were spared. The effect on rCMRglc apparently is not due to a reduction of cerebral blood flow, as it occurs when rCMRglc is calculated by a model that is insensitive to ischemia.³²

While we demonstrate a cocaine-induced decrease in rCMRglc in humans, cocaine generally stimulates rCMRglc in naive rats. Inconsistencies may reflect species differences or the dependence of subjective responses on the mode of drug administration (eg, passive injection to rats vs injection to humans who choose to receive cocaine in a research setting). Another factor may be the lack of spatial resolution provided by the PET [fluorine 18]-fluorodeoxyglucose method as compared with the [carbon 14]-deoxyglucose method, which has been used in rats. Effects of prior drug experience on rCMRglc responses also must be considered, as behavioral and pharmacological history can influence drug effects.^{36,37} Therefore, the present findings cannot be generalized to subjects without a history of drug use.

Hemispheric asymmetry of rCMRglc was seen in the lateral thalamus, where rCMRglc was greater on the right. Although this observation was consistent with a previous report that verbal stimuli produced significant activation of the right thalamus,³⁸ we previously observed a nonsignificant trend for

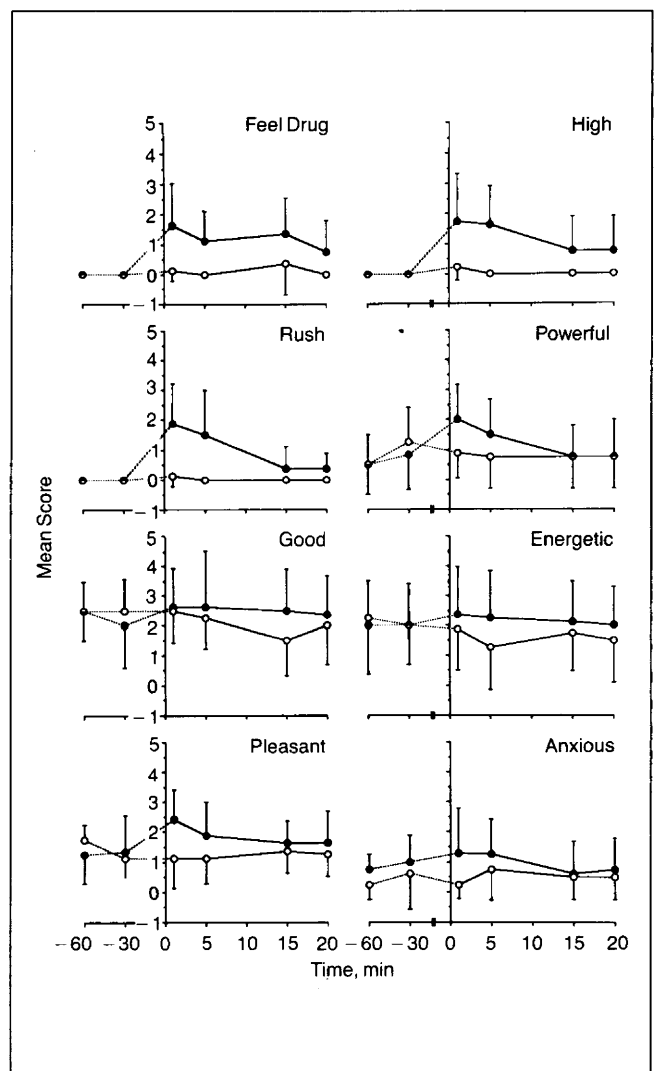


Fig 2.—Time course of effects of cocaine hydrochloride (closed circles) and saline (open circles) on self-reports on Cocaine-Sensitive Scale. Each point indicates the mean ± SD for eight subjects at each of the times indicated relative to the injection of the test compound.

Table 2. — Effects of Cocaine on Regional Cerebral Metabolic Rates for Glucose*

Brain Region	Saline		Cocaine Hydrochloride	
	L	R	L	R
Frontal gyrus				
Superior†	8.53 ± 0.78	8.82 ± 0.55	7.49 ± 1.31	7.60 ± 1.12
Middle†	9.29 ± 1.06	9.84 ± 1.80	8.16 ± 1.38	8.54 ± 1.38
Gyrus				
Precentral†	8.47 ± 0.96	8.87 ± 1.04	7.20 ± 0.77	7.47 ± 1.01
Postcentral†	8.47 ± 0.95	8.25 ± 2.11	7.08 ± 1.00	6.91 ± 0.80
Paracentral lobule†	8.12 ± 1.37		6.65 ± 0.99	
Anterior cingulate cortex†	9.72 ± 1.09		8.38 ± 1.13	
Superior parietal gyrus†	8.40 ± 1.32	8.49 ± 1.85	7.22 ± 0.91	6.83 ± 0.77
Gyrus supramarginalis†	8.96 ± 1.59	9.29 ± 1.50	8.08 ± 0.82	8.21 ± 0.88
Temporal pole (5)†	5.93 ± 0.76	5.18 ± 0.71	4.38 ± 0.43	4.35 ± 0.42
Temporal gyrus				
Superior (7)†	7.57 ± 1.03	7.10 ± 1.32	6.35 ± 0.78	6.16 ± 0.62
Middle (7)†	8.59 ± 0.97	7.82 ± 0.89	7.55 ± 1.15	7.20 ± 0.71
Inferior (7)†	8.15 ± 0.80	8.19 ± 1.11	7.21 ± 0.92	7.74 ± 1.30
Primary visual cortex†	9.13 ± 1.60	9.63 ± 1.82	7.75 ± 0.90	8.29 ± 1.10
Lateral occipital gyrus†	7.51 ± 0.85	7.23 ± 0.65	5.70 ± 1.03	6.07 ± 1.35
Precuneus†	11.0 ± 1.75		9.61 ± 1.12	
Cuneus†	8.02 ± 1.19	8.49 ± 1.17	6.68 ± 0.53	7.40 ± 0.68
Gyrus rectus (7)†	8.77 ± 1.08		7.50 ± 0.68	
Insula†	8.74 ± 1.05	9.06 ± 1.24	7.57 ± 0.74	7.47 ± 0.75
Caudate nucleus†	8.86 ± 1.03	8.82 ± 0.53	7.66 ± 0.99	7.37 ± 0.93
Putamen†	9.39 ± 0.90	9.10 ± 1.22	8.01 ± 0.84	7.97 ± 0.76
Amygdaloid nucleus†	5.36 ± 0.83	5.04 ± 0.50	4.72 ± 0.68	4.51 ± 0.70
Hippocampus (7)†	5.97 ± 0.69	5.58 ± 0.72	5.12 ± 0.35	5.08 ± 0.55
Parahippocampal gyrus (7)†	6.48 ± 1.26	5.83 ± 1.21	5.80 ± 0.86	5.17 ± 1.16
Thalamus				
Medial	7.33 ± 0.54		6.54 ± 1.08	
Lateral†	7.65 ± 0.50	8.63 ± 0.59	6.94 ± 1.12	7.67 ± 1.10
Midbrain (7)†	6.42 ± 0.57		5.56 ± 0.36	
Pons (5)	4.89 ± 0.21		4.20 ± 0.98	
Cerebellum				
Cortex (5)	7.88 ± 0.84	7.40 ± 0.71	7.07 ± 1.07	7.01 ± 0.87
Vermis (5)	6.21 ± 0.53		6.40 ± 0.85	
Whole brain†	6.81 ± 0.81		5.88 ± 0.45	

*Each value is the mean ± SD for eight subjects, in milligrams per 100 g per minute, except where indicated in parentheses. In those cases in which $n < 8$, measurement of the ROI was not possible because of equipment failure or improper placement of the subject in the scanner.

†Statistically significant main effect of cocaine by two-way analysis of variance, uncorrected for the number of comparisons, $P < .05$.

‡Statistically significant main effect of hemisphere, $P < .05$.

right-greater-than-left asymmetry in the lateral thalamus in a study of long-term substance abusers.¹⁸ In our earlier study, the subjects were not presented with verbal stimulation. As normal control subjects have shown left-greater-than-right asymmetry in this brain region,³⁹⁻⁴¹ the reversal observed in our studies may reflect a biological difference in substance abusers.

Many studies have suggested importance of dopaminergic systems to the effects of cocaine,^{6,42-45} and a decrease of cortical rCMRglc is consistent with a dopaminergic action. Supporting the view that cocaine would decrease cortical rCMRglc is the finding that D-amphetamine, another indirect dopaminergic agonist, reduces rCMRglc in chronic schizophrenic and control subjects.¹⁷ In addition, haloperidol, a D₂-dopamine receptor antagonist, increases cortical rCMRglc in schizophrenic patients.⁴⁶

One of our objectives was to determine cerebral metabolic correlates of cocaine-induced euphoria. While only one dose of cocaine was tested, the dose is an effective euphoric dose

for about 90% of the population sampled at our research center³⁵ and is within the range of common street usage.²⁶ Subjective self-reports (MBG scores, responses on CSS items relating to euphoria) indicate that euphoria was achieved in the sample studied.

Although the cocaine-induced reduction of rCMRglc was widespread, cortical decrements may relate to reinforcing effects of the drug. The medial prefrontal cortex has been implicated in rewarding effects of cocaine, as rats can be trained to self-administer cocaine intracranially into this brain area.⁴⁷ Reduced cortical rCMRglc has also been observed in humans given acute treatments with various euphoricants, including benzodiazepines,^{15,16} barbiturates,¹⁴ and amphetamine.¹⁷ Furthermore, we noted previously that, when corrected for the contribution from hypercapnia, a euphoric dose of morphine reduced rCMRglc in cortical areas.¹⁸ A common role of the cortex in euphoria, induced by various drugs that act through different mechanisms, is in harmony with a theory proposed by Cannon,⁴⁸ that emotions enter

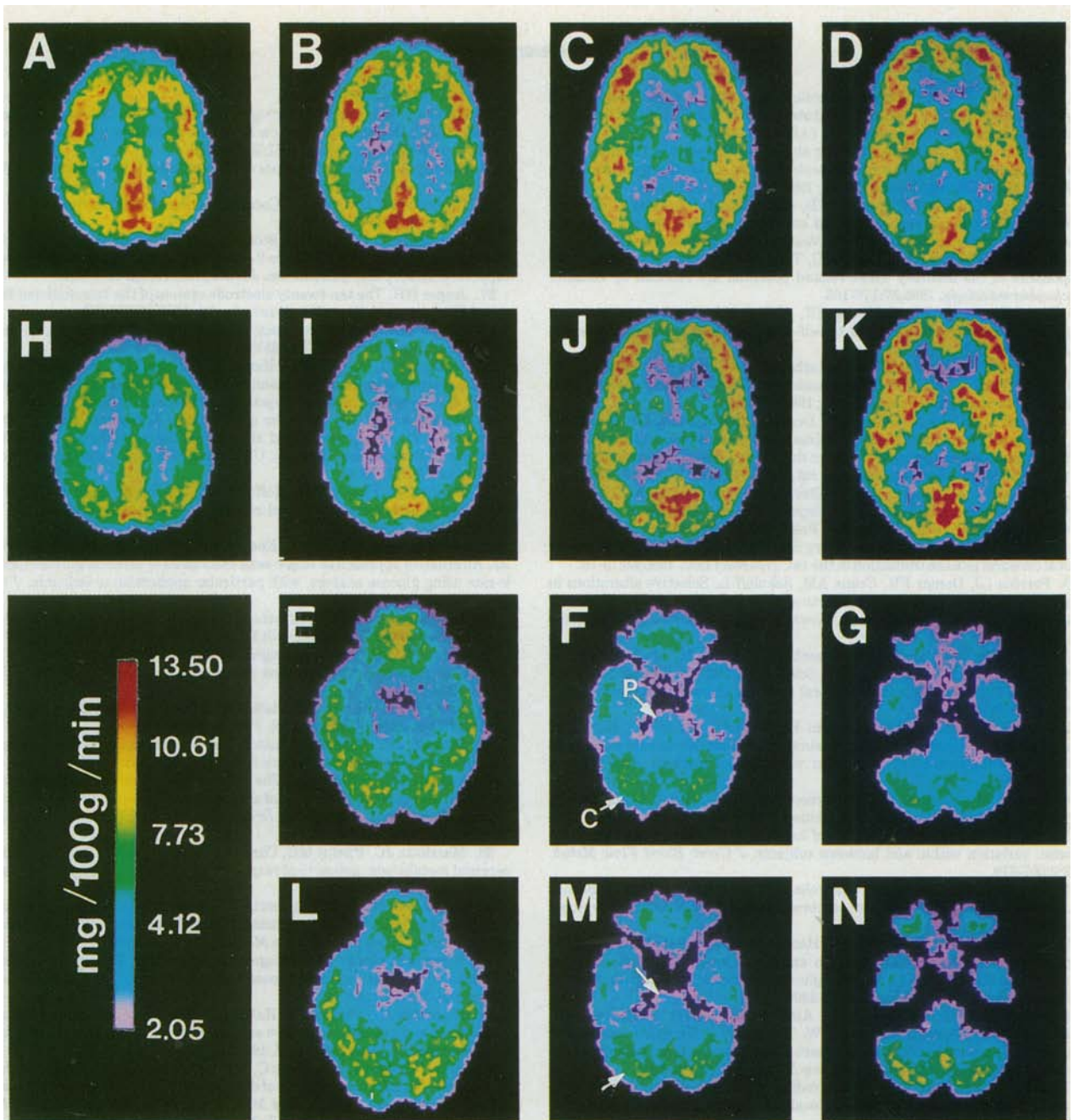


Fig 3.—Color-coded transforms of positron emission tomographic scans showing regional cerebral metabolic rates for glucose (rCMRglc) in a selected subject after treatment with saline (A to G) or 40 mg of intravenous cocaine hydrochloride (H to N). Cocaine produced statistically significant reductions in rCMRglc (mean for eight subjects) in all regions of interest sampled except the pons (P) and cerebellum (C).

consciousness only if cortical inhibition is abolished.

A mechanism by which abused drugs, particularly cocaine and opioids, might reduce cortical rCMRglc by an action on limbic areas important to reward (eg, nucleus accumbens and ventral tegmental area) can be hypothesized on the basis of corticostriatopallidothalamic circuitry. According to a model put forth by Swerdlow and Koob,⁴⁹ an action of cocaine to increase dopaminergic inhibition in the nucleus accumbens would disinhibit neurons in the ventral pallidum, increasing inhibition of neurons that stimulate limbic cortex by afferents from the dorsomedial thalamic nucleus. An interaction of opioids with dopaminergic neurons of the ventral tegmental area could produce the same effect by afferents to the nucleus accumbens. Therefore, although current PET instruments

lack the spatial resolution to visualize the ventral tegmental area or nucleus accumbens, they can be used to image brain regions, such as the limbic cortex, into which these areas project, and which may play a fundamental role in drug-induced reward.

This study was supported in part by US Public Health Service grants NS-15080 (Drs Links, Wong, Dannals, and Wagner) and NS-15080 and MH-42821 (Dr Wong), and by a grant from the Council on Tobacco Research, New York, NY (Dr Wong).

We thank Alan A. Wilson, PhD, Hayden T. Ravert, PhD, and Robert Smoot for radiotracer synthesis; Trevor Young, MD, for assistance in performing some of the PET studies; Elizabeth Dax, MD, and Robert Lange, MD, for medical coverage; Edward Cone, PhD, for providing assays of cocaine levels; Lillian R. Rippetoe, RN, for nursing services; and Geraldine Hill, Gershman Wilkerson, David Yousefnejad, and David Clough, CNMT, for technical services.

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