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Cocaine Intake by Rats Correlates with Cocaine-Induced Dopamine Changes in the Nucleus Accumbens Shell

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FERRARO, T. N., G. T. GOLDEN, W. H. BERRETTINI, E. GOTTHEIL, C. H. YANG, G. R. CUPPELS AND W. H. VOGEL. *Cocaine intake by rats correlates with cocaine-induced dopamine changes in the nucleus accumbens shell.* PHARMACOL BIOCHEM BEHAV **66**(2) 397–401, 2000.—Extracellular dopamine levels were determined by microdialysis in the core and shell of the nucleus accumbens and the frontal cortex of rats before and after an injection of cocaine (20 mg/kg, IP). After removal of the probes, these same animals were then tested for their voluntary intake of cocaine using the two-bottle, free-choice paradigm. Baseline dopamine levels and their responses to an injection of cocaine differed among the three brain areas. No significant correlations were found between baseline dopamine levels in any of the three brain regions and the voluntary cocaine consumption. A significant negative correlation was found between cocaine-induced increases in extracellular dopamine in the shell of the nucleus accumbens and the voluntary intake of cocaine ($r = -0.73$, $p < 0.01$). No such correlations were observed in the accumbens core region or the frontal cortex. These results provide further evidence of the role of the accumbal shell region in cocaine preference, and indicate that cocaine-induced increases in dopamine levels play a role in oral cocaine self-administration or preference. In addition, this relatively novel approach in using the same animals for both cocaine induced neurotransmitter responses and cocaine preference studies can also be applied for the study of other neurotransmitters and drugs of abuse. © 2000 Elsevier Science Inc.

Cocaine Dopamine Nucleus accumbens Shell of nucleus accumbens Frontal cortex
Cocaine self-administration Intracerebral microdialysis

THE neurobiological substrate for cocaine self-administration by animals and cocaine abuse in humans is believed to involve among other biological substrates the mesocorticolimbic dopamine system. This system originates in the ventral midbrain and projects to the nucleus accumbens, and seems to be primarily responsible for the reinforcing effects of cocaine (2,6,15,21,28–30,35,37). Anatomical, histochemical, and pharmacological studies of the nucleus accumbens indicate that this brain area is heterogeneous and can be divided into subregions termed the "shell" and "core" (9,25,46). Recent evidence suggests that the reinforcing and sensitizing properties of psychostimulants such as cocaine and amphetamine (8,32–34) seem to be differentially regulated in the core region compared to the shell region of the accumbens (32,33). Additionally, other brain areas such as the frontal cortex might also mediate certain effects of cocaine. The frontal cortex receives direct input from midbrain dopamine neurons, but more importantly, rats can be trained to self-administer cocaine into the frontal cortex and lesions of this site can alter cocaine self administration (2,5,7,11,18,23,39,42).

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All studies measuring extracellular dopamine responses to cocaine show marked variations among animals in that some animals respond with smaller and other animals with larger increases in dopamine. Similarly, rats self-administer cocaine intravenously at different rates or quantities (14,41) or voluntarily drink variable, albeit consistent, amounts of a cocaine solution according to individual preferences (1,26,40). Based on these observations, it was hypothesized that there might be an association between cocaine-induced dopamine changes after an acute cocaine challenge and the extent of the voluntary consumption of this drug by rats.

To test this hypothesis, we used a relatively novel approach of correlating cocaine-induced dopamine responses and voluntary cocaine intake in the same animals. First, extracellular dopamine levels in the nucleus accumbens (core and shell) and frontal cortex were determined before and after a cocaine injection. Two weeks later after removal of the probes, the voluntary intake of cocaine or cocaine preference was measured in these same rats.

METHOD

Subjects

Male Sprague–Dawley rats (Harlan), weighing 350–400 g at the beginning of the study, were housed individually and maintained on a 12L:12D cycle, with free access to food and water for at least 1 week prior to these studies. Different groups of rats were used for the study of the individual brain areas (frontal cortex = 10; shell = 17 and core = 20 rats). The experiments reported here were approved by the Institutional Animal Care and Use Committees governing the participating laboratories.

Microdialysis

Microdialysis probe guide cannulae were implanted under anesthesia stereotaxically using the following coordinates: nucleus accumbens shell region (AP 1.4, ML 0.457, DV 6.2), nucleus accumbens core region (AP 1.04, ML 1.7, DV 6.3), or frontal cortex (AP 3.4, ML 1.5, DV 1.3) at an angle of 35°). The atlas of Paxinos and Watson (27) was used as a reference. Each animal was fitted with a single guide cannula. Microdialysis probes (CMA/11, cuprophane dialysis membrane, 6000 Dalton, 2 mm length) were inserted by hand through the guide cannula in the brain of unanesthetized animals 16 h prior to the start of the microdialysis session. Thus, the tip of the microdialysis probe extended 2 mm below the ventral end of the guide cannula. Before use in vivo, microdialysis probes were calibrated in vitro by dialysis against a warm (37°C) and stirred solution of dopamine (25 pm/ml) prepared in a modified Ringer's buffer. Probe recovery values were used to normalize microdialysate dopamine concentrations, and all reported results are based on levels corrected for individual probe recovery. The microdialysis fluid was a modified Ringer's solution containing NaCl (150 mM), KCI (3.0 mM), $CaCI_2$ (1.4 mM), $MgCl_2$ (0.8 mM) in 10 mM phosphate buffer at pH 7.1. The microdialysis fluid was perfused at a rate of 1.0 μl/min (CMA/100 Microinjection pump) throughout all experiments. Samples were collected at 15-min intervals and injected directly into an HPLC apparatus.

Dopamine Determination

The HPLC method used for measuring levels of dopamine and other monoamines involved reverse-phase chromatography with electrochemical (EC) detection. The analytical column (Rainin Microsorb Short-One 10 cm long) was packed with C-18 resin (3 μm particle size). The mobile phase contained 122 mM citric acid monohydrate, 112 mM sodium acetate, 0.39 mM EDTA, 5.2 mM 1-heptanesulfonic acid, and 15% methanol, with the pH adjusted to 3.50. The mobile phase was pumped at a flow rate of 1 ml/min using a reciprocating piston HPLC pump (Perkin Elmer LC-250). The EC detector (EG&G Instruments, model #400) was set to a working potential of +730 mV, a sensitivity of 0.1 or 0.2 nA, and a time-constant interval of 5 s. Assay sensitivity was about 1.5 pm/ml or about 20 fm/sample. Output was monitored using a strip-chart recorder, and levels of monoamines were calculated by comparing sample peak heights to those generated by chromatographic analysis of external standard solutions containing known concentrations of monoamines. These values were then corrected for probe recovery as described above. Baseline levels of dopamine were defined as the average value in three consecutive samples with less than 10% variation. Typically, this required 1 to 2 h following initiation of perfusion. Mean baseline values as pmol/ml (with SDs and coefficients of variance) were for the frontal cortex 13.2 (18.6 and 1.4), for the core of the nucleus accumbens 77.2 (71.1 and 0.9) and for the shell of the nucleus accumbens 39.7 (28.2 and 0.7). Following the establishment of baseline dopamine levels, animals were given an intraperitoneal injection of cocaine·HCl (20 mg/kg) dissolved in saline and collection of microdialysis samples continued at 15-min intervals. Microdialysis sessions were terminated following reestablishment of baseline dopamine levels. Mean dopamine responses in pmol/ml (with SDs and coefficients of variance) after cocaine injections were for the frontal cortex 103 (59.8 and 0.6), for the core of the nucleus accumbens 116 (62.2 and 0.8) and for the shell of the nucleus accumbens 70 (51.8 and 0.7).

Voluntary Cocaine Consumption

After the microdialysis experiment, probes were removed and the animals were returned to their home cages in which they were individually housed. Following a 2-week "washout" period, rats were entered into a two-bottle, free-choice protocol. In this paradigm, two drinking bottles were placed into each cage—one containing 0.2% saccharin, and the other containing 0.2% saccharin/0.002% cocaine hydrochloride. The bottles were rotated daily. Weights of the animals and total fluid intake (about 125 ml/kg/day) were not different for the three groups. Total fluid intake and cocaine intake were determined daily for 12 days and, after plateau cocaine intake was reached after 7 days, and only the intake of cocaine consumed at days 8–12 was used.

Histology

At the end of the drinking interval, rats were sacrificed and brains were prepared for histology to confirm the location of the microdialysis probe. Preparation of brain tissue for histological study began with transcardial perfusion of a formalin solution (10%) at the time of euthanasia. Brains were removed and allowed to stand in formalin fixative for at least 1 week prior to vibratome sectioning. Coronal brain sections (100 μm) were stained with cresyl violet and evaluated by light microscopy. Data are reported from only those rats in which appropriate probe placement could be documented.

Statistical Analyses

Statistical evaluation of data was carried out using a Spearman regression analysis. Three sets of associations were eval-

uated: 1) baseline microdialysate dopamine levels vs. peak cocaine-induced dopamine levels; 2) baseline microdialysate dopamine levels vs. voluntary cocaine intakes; and 3) peak cocaine-induced dopamine level vs. voluntary cocaine intakes. These associations were examined in all three brain regions studied. Voluntary cocaine intake was defined as the total amount of cocaine consumed during days 8 to 12, at which time cocaine intake had stabilized. Mean cocaine intake (mg/rat) (with SDs and coefficients of variance) were for the frontal cortex group 5.8 (3.0 and 0.5), for the shell of the nucleus accumbens 4.5 (1.9 and 0.5), and for the core of the nucleus accumbens 4.5 (1.7 and 0.5).

Baseline dopamine levels were calculated as the mean absolute values of dopamine from three consecutive microdialysate samples exhibiting less than 10% variation. Peak cocaine-induced dopamine levels were taken from the microdialysate sample with the greatest increase in response to acute cocaine injection. This peak level typically occurred in the first or second sample collected following cocaine injection. Increases are calculated as percentage increases over baseline values assuring that smaller baseline values did not result in larger percentage changes which could distort the results.

RESULTS

No significant correlations were observed in all three regions between baseline levels of extracellular dopamine and cocaine-induced increases of dopamine levels. Similarly, no significant correlations were observed between baseline levels of extracellular dopamine and the voluntary intake of cocaine for any of the regions studied.

Figure 1 shows the correlations between voluntary cocaine intake and peak dopamine levels elicited by an acute cocaine injection for the three brain regions investigated. No significant correlations were found between cocaine intake and increases in extracellular dopamine levels in the core of the nucleus accumbens or the frontal cortex. However, a significant negative correlation ($r = -0.73$, $p < 0.0004$) was found for the shell of the nucleus accumbens.

DISCUSSION

Consistent with the pharmacological action of cocaine as a competitive inhibitor of brain catecholamine uptake (12,36), cocaine has been shown to cause transient but significant elevations of extracellular dopamine levels in the striatum, nucleus accumbens, and frontal cortex (16,19,24). These brain regions mediate functions consistent with the behavioral effects of cocaine (3,18). However, the precise relationship between changes in extracellular dopamine and specific cocaine-related behaviors remains to be elucidated. Previous studies investigating the reinforcing effects of cocaine have focused upon changes in dopamine levels during self-administration in rats trained to respond in an operant fashion (20,31,44). Our study utilized individual differences as a means to gain insight into the mechanisms mediating self-administration behavior by correlating voluntary drug-intake with dopamine responses to acute cocaine injection. Additionally, we studied subregions of the nucleus accumbens (core and shell) as well as the frontal cortex in an attempt to further decipher the exact location of the processes mediating cocaine seeking behavior.

The significant inverse correlation which we observed between voluntary oral cocaine intake and peak cocaine-induced dopamine increase in the shell of the accumbens is consistent with the idea that animals will self-administer psychostimulant drugs to produce a constant level of dopa-

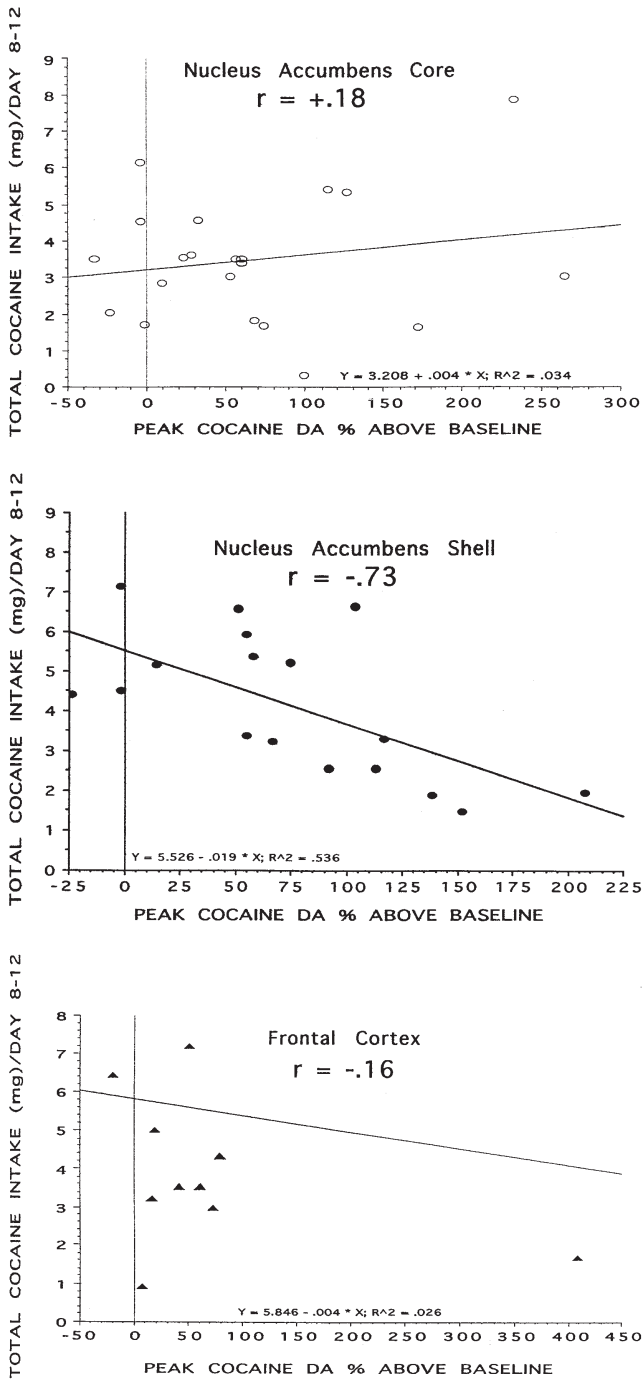

FIG. 1. Graphs show correlations of voluntary cocaine intakes and increases in extracellular dopamine levels in the nucleus accumbens core region ($n = 20$), the nucleus accumbens shell region ($n = 17$), and the frontal cortex ($n = 10$) induced by acute cocaine injection of individual animals. Intracerebral microdialysis was used to monitor increases in dopamine levels induced by an acute cocaine challenge (20 mg/kg, IP). Dopamine levels are given as the peak percentage increases over the baseline levels. After a 2-week "wash-out" period, voluntary cocaine intake was taken as the total amount of cocaine consumed in a two-bottle, free-choice paradigm over days 8–12. Spearman correlation coefficients are shown.

minergic activation (10). Furthermore, these results suggest that cocaine-induced increases in extracellular dopamine in the accumbens shell explain the amount of cocaine consumed or cocaine preference. Assuming that the response of extracellular dopamine to IP administration of cocaine is similar to the response during oral self-administration in the two-bottle, free-choice paradigm (i.e., rats exhibiting a relatively small increase in accumbens shell level of extracellular dopamine in response to acute cocaine injection also experience a small increase in dopamine level in response to oral self-administration of a given dose), results of the present study provide further evidence that rats self-administer cocaine to achieve an individually specific level of extracellular dopamine elevation in the nucleus accumbens shell region. Rats that exhibited the larger increases in accumbens shell extracellular dopamine after acute cocaine injection consumed less cocaine in a two-bottle, free-choice situation, suggesting that the amount they consumed produced a level of dopaminergic activation similar to that of rats who consumed more oral cocaine but who, based upon their response to acute cocaine injection, achieved proportionately smaller increases in extracellular dopamine levels. Thus, it can be hypothesized that a smaller response to an initial acute exposure to cocaine predisposes rats to greater cocaine consumption. It is noteworthy, however, that increases in extracellular dopamine were measured in response to intraperitoneally administered cocaine, whereas self-administration employed the oral route. However, the oral route can discriminate consistently between high and low consuming animals (1,26,40), serve as a reinforcer (17) and consistently deliver cocaine (5) into the blood stream. As expected, it has been recently demonstrated that oral cocaine achieves lower serum concentrations than injected cocaine (e.g., 1000 μg/ml vs. 100 μg/ml), but was found to be behaviorally more effective than injected cocaine (22).

Initial work on the anatomical areas involved in mediating the reinforcing effects of cocaine has indicated that the nucleus accumbens is critical (42). Investigations in the past on the effects of cocaine on extracellular dopamine in the nucleus accumbens did not distinguish between the shell and core subdivisions (25,32,38,44). However, the presence of anatomical subterritories in the rat nucleus accumbens (26,46) has prompted a more precise examination of the mechanism of action of cocaine and other psychostimulants. More recent work strongly indicated that accumbal dopamine responses to cocaine are significantly more pronounced in the shell as compared to the core (32,33). Furthermore, the dopamine transporter is more sensitive to cocaine in the shell compared to the core (8) and psychostimulant drugs increase selectively glucose utilization in this area (34). These findings are consistent with the fact that anatomical connections of the shell are related more to limbic structures, whereas those of the core are related more to motor structures (13,45). Results of this study are consistent with this line of reasoning, and support the general idea that the anatomical distinctions within the nucleus accumbens have functional correlates (9,32,33). More specifically, our results clearly support the notion (32,33) that dopamine responses within the shell, and not the core, are related to cocaine self-administration, suggesting a crucial role of dopamine for this brain area in mediating motivational drug-seeking effects.

Our study did nor reveal a correlation between basal levels of dopamine and cocaine-induced increases of this neurotransmitter (43). We also did not find an association between voluntary cocaine intake and frontal cortex dopamine responses to acute cocaine. The latter may be explained by the fact that A10 midbrain dopamine neurons project to more medial portions of the prefrontal cortex (4), whereas our microdialysis probe placements were more lateral. Thus, it is still possible that specific sites within the medial prefrontal cortex participate in cocaine self-administration.

In conclusion, the known individual differences in dopamine responses to a cocaine injection and the voluntary cocaine self-administration in rats has been used to provide further evidence that the dopaminergic neurons of the shell of the nucleus accumbens, and not of the core of this nucleus or the lateral frontal cortex, participate in cocaine-seeking behavior. Results also indicate that rats titrate their cocaine preference or intake on the increases of cocaine-induced dopamine levels in this area. It is suggested that individual differences among rats can be used successfully to identify other brain areas or neurotransmitters involved in cocaine or other drug abusing behaviors and, thus, to provide a better understanding of human drug abuse or addiction.

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