Cocaine Alters Cerebral Metabolism within the Ventral Striatum and Limbic Cortex of Monkeys

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The functional consequences of acute cocaine administration in nonhuman primates were assessed using the quantitative 2-[^{14}C]deoxyglucose method. Local rates of cerebral metabolism were determined after an intravenous infusion of 1.0 mg/kg cocaine or vehicle in six awake cynomolgus monkeys (Macaca fascicularis) trained to sit calmly in a primate chair. Cocaine administration decreased glucose utilization in a discrete set of structures that included both cortical and subcortical portions of the limbic system. Glucose metabolism in the core and shell of the nucleus accumbens was decreased markedly, and smaller decrements were observed in the caudate and anterior putamen. In addition, cocaine administration produced significant decreases in limbic cortex. Metabolism was decreased in orbitofrontal cortex (areas 11, 12o, 13, 13a, 13b), portions of the gyrus rectus including area 25, entorhinal cortex, and parts of the hippocampal formation. The cortical regions in which functional activity was altered provide dense projections to the nucleus accumbens, and the decreased activity in these projections may be responsible in part for the large alterations in functional activity within the ventral striatum. Decreased metabolism also was evident in the anterior nuclear group of the thalamus, raphe nuclei, and locus ceruleus. The acute cerebral metabolic effects of cocaine in the conscious macaque, therefore, were contained primarily within a set of interconnected limbic regions, including ventral prefrontal cortex, medial temporal regions, the ventral striatal complex, and anterior thalamus. The decreased rates of glucose metabolism reported here resemble decrements found using positron emission tomography in humans. In the rat, by contrast, metabolic activity increased and changes were focused in subcortical regions. The present results represent an important expansion of the neural circuitry on which cocaine acts in the monkey as compared with the rat, and this in turn implies that cocaine affects a broader spectra of behaviors in primates than in rodents.

Key words: monkey; cerebral metabolism; cocaine; limbic system; ventral striatum; nucleus accumbens; orbital and medial prefrontal cortex

Much of our understanding of the neurobiological basis of cocaine abuse is based on investigations performed in rodents. Rodent models of cocaine use have provided the means to explore the basic mechanisms of cocaine action on both a cellular and a molecular level (Koob and Bloom, 1988; Kalivas et al., 1993; Nestler et al., 1993) and have contributed significant insights into the role of the dopaminergic mesolimbic system in the activating and reinforcing effects of cocaine (Wise, 1978; Koob and Goeders, 1989; Kuhar et al., 1991). Rodent models, however, have important limitations, particularly with respect to questions regarding the neuroanatomical components involved in the response to cocaine. The added complexity of the topographical organization of the ventral striatum and its connections with surrounding brain regions in primates (Lynd-Balta and Haber, 1994a,b; Haber et al., 1995), especially when cortical connections are considered, can make extrapolations from rodent models to primates, including humans, problematic.

The development of in vivo neuroimaging techniques, including positron emission tomography (PET), single-photon emission-computed tomography (SPECT), and magnetic resonance imag-

ing, has made it possible to address some of these questions directly in conscious human drug abusers. A majority of these studies have investigated the withdrawal period during which cocaine is no longer in the bloodstream, concentrating on the long-term consequences of chronic cocaine abuse. Such studies have demonstrated, for example, that functional activation, as measured by changes in cerebral metabolism, increases significantly in cortical regions during the first week of abstinence from cocaine, but then falls below normal levels and remains depressed for at least 3 months (Volkow et al., 1991, 1992, 1993). Less clear, however, is the nature of the functional response to an acute exposure to cocaine in either drug-naive subjects or experienced drug users. Few studies have addressed this issue, primarily because of the difficulties inherent in administering abused substances to humans. In one study in which SPECT imaging of blood flow was used, Pearlson et al. (1993) showed that the acute administration of cocaine reduces blood flow in ventral frontal cortical regions and in basal ganglia. Decreases also have been found in global rates of cerebral metabolism after the administration of intravenous cocaine to a group of experienced polydrug abusers (London et al., 1990). Unfortunately, the interpretation of studies such as these in human cocaine abusers may be confounded by variable and incomplete drug histories, questionable nutritional status, comorbid psychiatric disorders, and the lack of control over psychological variables. Only with reservations, therefore, can these functional changes be attributed directly to cocaine in a population of chronic abusers.

The purpose of the present study was to pursue questions raised by human studies with a nonhuman primate model in which carefully controlled experiments can be conducted without the confounds inherent in human research and with the spatial resolution of autoradiography. The goal was to identify the neuroanatomical substrates of the effects of the administration of a single acute dose of cocaine to cynomolgus monkeys, using the quantitative autoradiographic 2-[^{14}C]deoxyglucose (2-[^{14}C]DG) method (Sokoloff et al., 1977) as adapted for use in nonhuman primates (Kennedy et al., 1978). Because findings in rodents appear to be at odds with those reported in humans (London et al., 1990), a further purpose of this investigation was to compare the cerebral metabolic effects after acute cocaine administration in nonhuman primates with those reported in rodents (London et al., 1986; Porrino et al., 1988; Sharkey et al., 1991; Porrino, 1993) and humans (London et al., 1990; Pearlson et al., 1993).

MATERIALS AND METHODS

Animals and training. Six male cynomolgus monkeys (*Macaca fascicularis*) weighing 5.0–5.9 kg were housed under a 12 hr light/dark cycle with access to food (Purina monkey chow) twice daily and water available *ad libitum*. At the start of the study, all monkeys were naive to cocaine and other psychostimulants. In addition, although previous medication included single doses of clonidine and/or haloperidol, all animals were drug-free for at least 4 months before study, with the exception of ketamine, which was administered approximately once monthly to perform regular veterinary care. All procedures were performed in accordance with established practices as described in the National Institutes of Health guide for care and use of laboratory animals. In addition, all procedures were reviewed and approved by the Animal Care and Use Committee of Wake Forest University.

Monkeys were trained in daily 1 hr sessions to sit partially restrained in a primate chair (Plastic Labs, Lansing, MI), flanks supported, and with neck and feet loosely secured. Monkeys were free to move head, hands, and arms at all times. Training sessions continued for ~2–3 weeks until signs of distress were minimal. At this point, all animals sat comfortably in the primate chairs without struggling and accepted fruit, juice, and other treats readily from the investigators. Monkeys were randomly assigned to one of two groups: cocaine (1.0 mg/kg, i.v.; *n* = 3), or saline vehicle (0.1 ml/kg, i.v.; *n* = 3).

Drug administration. Cocaine hydrochloride was obtained from the National Institute on Drug Abuse (Research Triangle Park, NC) and dissolved in physiological saline (0.1 ml/kg) immediately before administration. Equivalent volumes of saline were administered to control monkeys. Cocaine (1.0 mg/kg) or saline vehicle (0.1 ml/kg) was administered intravenously via the femoral catheter. This dose was the average cumulative intake of monkeys that maintains peak rates of responding during self-administration sessions in our laboratory (Nader and Reboussin, 1994). The 2-[^{14}C]DG procedure was initiated 2 min after drug injection. Although the 2-[^{14}C]DG method requires a total experimental period of 45 min to allow for clearance of unmetabolized tracer, the uptake and phosphorylation of 2-[^{14}C]DG in brain reflect its metabolism predominantly in the first 5–10 min after its administration. The reason for this is that the tissue concentration of free 2-[^{14}C]DG is highest during the first 5 min after injection (Sokoloff et al., 1977). The time of drug administration and the initiation of the 2-[^{14}C]DG procedure, therefore, were chosen to ensure that maximum incorporation of tracer occurred during the time of peak effects of cocaine.

Measurement of local cerebral glucose utilization. A minimum of 1 d before the measurement of rates of local cerebral glucose metabolism with the 2-[^{14}C]DG method, monkeys were anesthetized briefly with a mixture of ketamine (15 mg/kg, i.m.) and butorphanol (0.18 mg/kg, i.m.). Polyethylene catheters were inserted into a femoral artery and vein to permit subsequent intravenous administration of cocaine, vehicle, and 2-[^{14}C]DG and sampling of arterial blood during the course of the experimental procedure. The catheters then were arranged subcutaneously, and the monkeys were allowed to recover for a minimum of 24 hr.

On the experimental day, each monkey was seated in a primate chair in the testing facility in a manner identical to that used during training. The catheters were exposed, and the monkeys were permitted to sit quietly for ~30 min before drug treatment. During this time, monkeys were offered small amounts of water or fruit juice. Monkeys exhibited no signs of discomfort.

Cocaine hydrochloride (1.0 mg/kg) or saline vehicle (0.1 ml/kg) was infused intravenously over a 15 sec interval. Two minutes after this injection, the experimental procedure was initiated by the injection of an intravenous pulse of 100 μCi/kg 2-deoxy-D-[1-^{14}C]glucose (DuPont NEN, Boston, MA; specific activity 50–55 mCi/mmol) followed by a flush of heparinized saline. Timed arterial blood samples were drawn thereafter at a schedule sufficient to define the time course of the arterial 2-[^{14}C]DG and glucose concentrations. Arterial blood samples were centrifuged immediately. Plasma concentrations of 2-[^{14}C]DG were determined by liquid scintillation spectrophotometry (Beckman Instruments, Fullerton, CA), and plasma glucose concentrations were assessed with a glucose analyzer (Beckman). Approximately 45 min after tracer injection, the animals were killed by an intravenous overdose of sodium pentobarbital (100 mg/kg). Brains were removed rapidly, blocked in three parts, frozen in isopentane (−45°C), and stored at −70°C until processing for autoradiography. Coronal sections (20 μm thick) were cut in a cryostat maintained at −22°C. Four of every ten sections were thaw-mounted on glass coverslips, dried on a hot plate, and autoradiographed with Kodak EMC x-ray film (Rochester, NY) for 15 d, along with a set of [^{14}C]methyl-methacrylate standards (Amersham, Arlington Heights, IL) previously calibrated for their equivalent ^{14}C concentrations in 20 μm brain sections. Autoradiograms were developed by hand in Kodak GBX developer, indicator stop bath, and rapid fix at 68°C.

Autoradiograms were analyzed by quantitative densitometry with a computer-assisted image-processing system (Imaging Research, St. Catharine's, Ontario, Canada). Optical density measurements for each structure were made in a minimum of eight brain sections. Tissue ^{14}C concentrations were determined from the optical densities and a calibration curve obtained by densitometric analysis of the autoradiograms of the calibrated standards. Glucose utilization then was calculated from the local-tissue ^{14}C concentrations, the time course of the plasma 2-[^{14}C]DG and glucose concentrations, and the appropriate kinetic constants (Kennedy et al., 1978) by the operational equation of the method (Sokoloff et al., 1977).

Statistical analysis. Rates of glucose utilization were measured in 67 distinct brain regions. Global rates of cerebral metabolism were estimated as the mean (weighted by region size) of all measured cerebral regions. Statistical analysis was performed on values of rates of local cerebral glucose utilization obtained for each individual cerebral structure by means of a Student's *t* test for independent samples. Comparisons were made between values of rates of glucose utilization in control or saline-treated animals and monkeys receiving cocaine.

RESULTS

Behavioral observations

The acute administration of a moderate dose of cocaine to monkeys produced mild behavioral activation. Monkeys displayed "lip smacking," head turning, and some small increases in upper limb movement. No changes in lower limb movement were noted. Although activation began immediately after cocaine infusion and persisted for ~10 min, the degree of movement was in essence relatively small. Monkeys remained quiet and alert for the remainder of the experimental period. Vehicle-treated monkeys sat quietly during the entire 2-[^{14}C]DG procedure and displayed none of the behavioral characteristics observed after cocaine infusions.

Rates of local cerebral glucose utilization

Rates of local cerebral glucose utilization for the 67 brain regions examined are shown in Tables 1–3. Global rates of cerebral metabolism in the cocaine- and vehicle-treated groups did not differ from one another significantly (saline, 41.5 ± 1; cocaine, 36.1 ± 1). Significant changes in rates of local cerebral glucose utilization were observed in 21 regions ($p < 0.05$), all of which displayed decreases in cerebral metabolic rates after the administration of cocaine (1.0 mg/kg).

Table 1. Local cerebral metabolic rates (μmol · 100 gm^{-1} · min^{-1}) for glucose in subcortical limbic regions of cynomolgus monkeys after i.v. saline or 1.0 mg/kg i.v. cocaine

	Saline Mean ± SEM ($n = 3$)	Cocaine Mean ± SEM ($n = 3$)	Percentage change
Mesolimbic system and related structures			
Medial accumbens (shell)	39 ± 2	28 ± 1*	−28
Lateral accumbens (core)	41 ± 2	29 ± 1*	−29
Olfactory tubercle	38 ± 3	29 ± 2	−23
Ventral pallidum	28 ± 3	27 ± 1	−4
Bed nucleus stria terminalis	25 ± 2	23 ± 1	−8
Lateral hypothalamus	31 ± 2	29 ± 2	−10
Ventral tegmental area	27 ± 2	30 ± 3	−15
Mammillary bodies	65 ± 3	55 ± 4	−15
Hippocampal formation			
Hippocampus, CA1	30 ± 1	26 ± 1*	−13
Hippocampus, CA3	30 ± 1	27 ± 1	−10
Dentate gyrus	33 ± 2	28 ± 1	−15
Subicular complex	38 ± 1	30 ± 1*	−21
Amygdala			
Central nucleus	23 ± 3	22 ± 1	−4
Medial nucleus	26 ± 4	29 ± 2	12
Accessory nucleus	28 ± 2	27 ± 2	−4
Mediobasal nucleus	29 ± 2	25 ± 2	−14
Basolateral nucleus	36 ± 3	35 ± 2	−3

*Indicates a significant difference from saline (Student's t test, $p < 0.05$).

Mesolimbic system and related structures

Acute cocaine administration significantly reduced glucose utilization in both subdivisions of the nucleus accumbens (core, −29%; shell, −28%) (Table 1, Fig. 1). These changes were among the largest noted in any brain region. In contrast, cocaine treatment did not alter glucose utilization in the lateral septum, bed nucleus of the stria terminalis, or any portion of the amygdala (Table 1). The latter subcortical limbic areas similar to the ventral striatum receive dopaminergic inputs from the ventral midbrain but showed no metabolic response to cocaine.

Basal ganglia and related structures

Changes in glucose utilization were restricted to highly discrete portions of the nigrostriatal system and related basal ganglia structures (Table 2). Acute cocaine administration significantly decreased cerebral metabolism in the dorsal extent of the anterior caudate nucleus (−18%) and the anterior portions of the putamen (−22%). Reduced rates of glucose utilization also were observed in the subthalamic nucleus (−20%). Significant changes were not observed in any other portion of this system.

Cerebral cortex

The most striking response to acute cocaine administration in monkeys occurred in limbic prefrontal cortex, particularly within portions of orbitofrontal cortex and along the medial wall of the frontal lobe (Table 3). To establish the exact topography of the response to cocaine in these areas, prefrontal cortex was further subdivided according to the boundaries determined by Ray and Price (1993). Figure 2 shows the response to cocaine on a flattened map of the prefrontal cortex in the monkey. Cocaine had its most intense effects in areas 11 (−24%), 12o (−25%), 13

Table 2. Local cerebral metabolic rates (μmol · 100 gm^{-1} · min^{-1}) for glucose in basal ganglia, thalamus, brainstem, cerebellum, and white matter of cynomolgus monkeys after i.v. saline or 1.0 mg/kg i.v. cocaine

	Saline Mean ± SEM ($n = 3$)	Cocaine Mean ± SEM ($n = 3$)	Percentage change
Basal ganglia and related structures			
Dorsal caudate	54 ± 3	44 ± 2*	−18
Anterior putamen	51 ± 3	40 ± 1*	−22
Posterior putamen	52 ± 4	45 ± 1	−13
Globus pallidus, external	31 ± 2	30 ± 1	−3
Globus pallidus, internal	33 ± 1	32 ± 3	−3
Subthalamus	61 ± 2	49 ± 3*	−20
Red nucleus	46 ± 2	40 ± 2	−13
Substantia nigra, compacta	41 ± 1	39 ± 3	−5
Substantia nigra, reticulata	35 ± 1	37 ± 2	6
Thalamus			
Anteroventral/antero- medial	61 ± 1	53 ± 2*	−13
Ventroanterior	43 ± 1	35 ± 3*	−19
Paraventricular	38 ± 3	32 ± 4*	−16
Reuniens	36 ± 3	35 ± 3	−3
Mediodorsal, magno- cellular	54 ± 1	52 ± 5	−4
Mediodorsal, parvi- cellular	57 ± 2	54 ± 3	−5
Ventrolateral	43 ± 3	35 ± 2	−19
Medial habenula	39 ± 3	32 ± 1	−18
Lateral habenula	41 ± 2	29 ± 1*	−29
Brain stem and cerebellum			
Dorsal raphe	38 ± 1	32 ± 1*	−16
Medial raphe	34 ± 1	28 ± 1*	−18
Locus ceruleus	38 ± 2	30 ± 1*	−21
Cerebellar cortex	36 ± 1	42 ± 2	17
White matter			
Anterior commissure	16 ± 3	12 ± 1	−25
Corpus callosum	17 ± 2	13 ± 1	−24
Internal capsule	20 ± 3	17 ± 2	−15

*Indicates a significant difference from saline (Student's t test, $p < 0.05$).

(−24%), 13a (−35%), 13b (−29%), and 25 (−34%). The effect was less intense lateral to areas 13 and 12o and disappeared completely in the lateral prefrontal cortex.

The effects of the acute administration of cocaine in limbic cortex were in marked contrast to those in other neocortical areas. Acute cocaine did not alter rates of glucose utilization in any measured sensory, motor, or association region, including area 46 in the banks of the principal sulcus, area 12 on the inferior prefrontal convexity, the forelimb region of area 4 on the anterior bank of the central sulcus and the same representation in area 3b on the posterior bank of the central sulcus, the lateral portion of striate cortex, and V2 immediately adjacent to it (Table 3). The effects of cocaine administration, therefore, were clearly localized to anterior limbic cortical areas.

The acute administration of cocaine also decreased rates of local cerebral glucose utilization within the hippocampal complex (Table 1, Fig. 1). Metabolism decreased in the CA1 subfield of
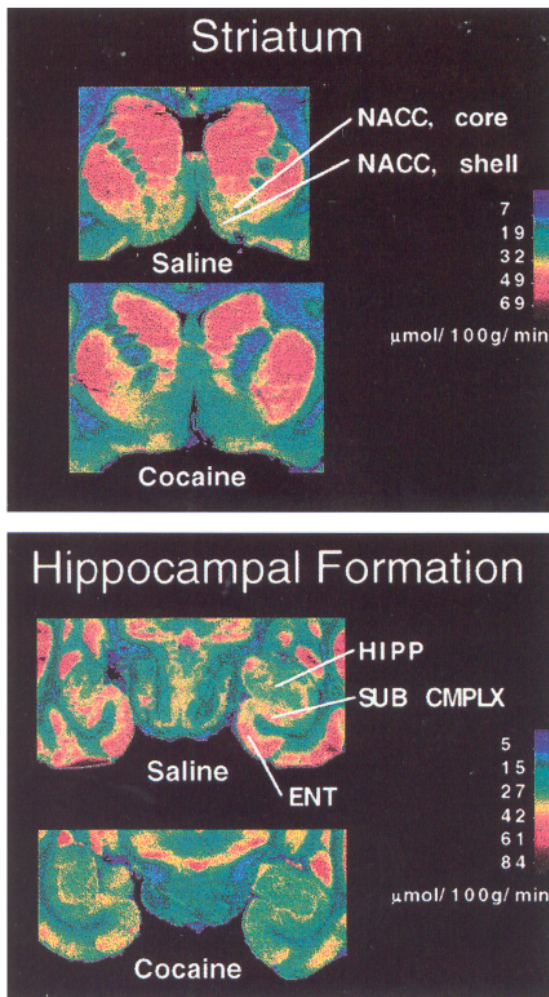
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Figure 1. Effects of the acute intravenous administration of cocaine (1.0 mg/kg) and saline (0.1 ml/kg) on rates of local cerebral glucose utilization in the ventral striatum (*top panel*) and in the hippocampal formation (*bottom panel*). Shown are color-coded transformations of autoradiograms of coronal sections of cynomolgus monkey brain at the level of the ventral striatum (*top panel*) and the hippocampus (*bottom panel*) in which each color represents a range of rates of glucose utilization (μmol $\cdot$ 100 gm^{-1} $\cdot$ min^{-1}) calculated from calibrated standards exposed along with the brain sections. Autoradiograms were normalized to saline controls. Note in the *top panel* the significant reduction in rates of glucose utilization in each of the subdivisions of the nucleus accumbens in the cocaine-treated monkeys. In the *bottom panel* note the significant reduction in rates of glucose utilization within portions of the hippocampus and the entorhinal cortex in the cocaine-treated monkeys. *ENT*, Entorhinal cortex; *HIPP*, hippocampus; *NACC*, nucleus accumbens; *SUB CMPLX*, subicular complex.

hippocampus (-13%), subicular complex (-21%), and entorhinal cortex (-21%) (Table 3).

No changes in cerebral metabolism were noted in the regions of the primary somatosensory and motor areas of cortex in which the hand and face are represented. This lack of changes reflects the small degree of movement elicited by cocaine administration (Table 3).

Thalamus

Acute cocaine administration had few significant effects on rates of glucose utilization in the thalamus (Table 2). Reduced glucose metabolism was evident only in the ventral and medial nuclei of the anterior group (-13%), the paraventricular nucleus (-16%), and the ventral anterior nucleus (-19%). Despite the widespread changes in the orbitofrontal cortex, there was only a trend toward reduced glucose metabolism in any portion of the mediodorsal nucleus of the thalamus.
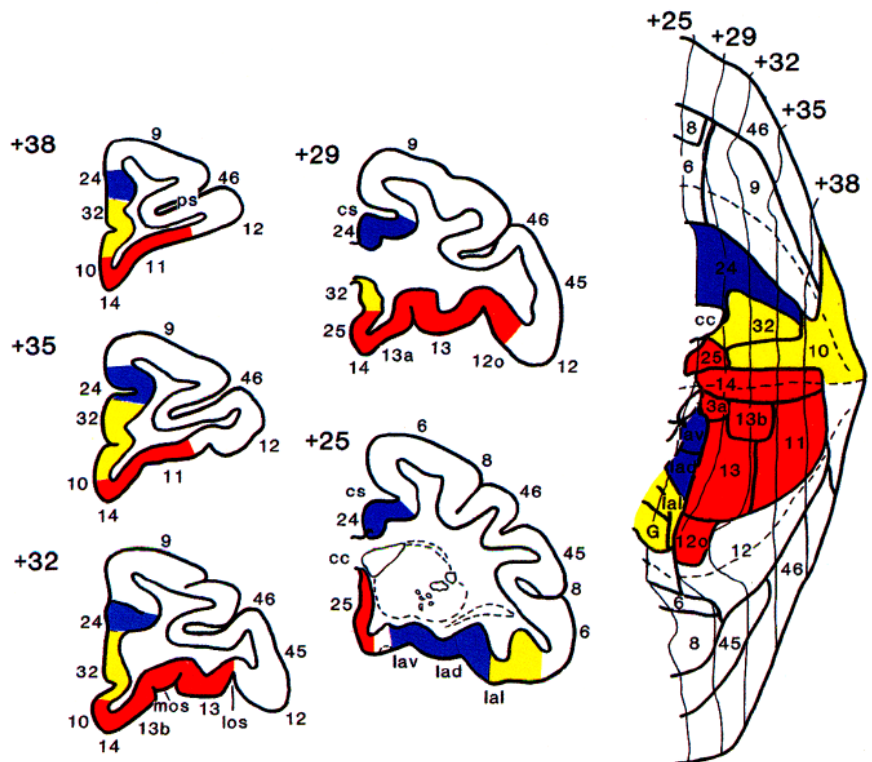
Figure 2. Distribution of changes in rates of local cerebral glucose metabolism in prefrontal cortex. Four coronal sections adapted from the atlas of Szabo and Cowan (1984) are shown on the *left*. A representative unfolded two-dimensional map of the prefrontal cortex of cynomolgus monkey adapted from Ray and Price (1993) appears on the *right*. The color coding indicates differing degrees of decreases in glucose utilization in prefrontal areas caused by cocaine administration. *Red*, >20% decreases; *yellow*, >15% decreases; *blue*, >10% decreases.

Table 3. Local cerebral metabolic rates (μmol · 100 gm^{-1} · min^{-1}) for glucose in cortex of cynomolgus monkeys after i.v. saline or 1.0 mg/kg i.v. cocaine

	Saline Mean ± SEM ($n = 3$)	Cocaine Mean ± SEM ($n = 3$)	Percentage change
Neocortex			
Frontal pole (area 10)	46 ± 2	39 ± 3	−15
Principal sulcus (area 46)	53 ± 3	49 ± 2	−8
Inferior prefrontal			
convexity (area 12)	46 ± 1	47 ± 4	2
Motor cortex (area 4)	52 ± 4	48 ± 1	−8
Somatosensory cortex			
(area 3)	60 ± 1	59 ± 1	−2
Prestriate cortex			
(area 18)	58 ± 3	56 ± 2	−3
Limbic cortex			
Gyrus rectus (area 14)	42 ± 2	33 ± 4	−21
Entorhinal cortex			
(area 28)	39 ± 2	31 ± 1*	−21
Perirhinal cortex			
(area 20)	36 ± 2	31 ± 2	−14
Prepiriform olfactory			
cortex	44 ± 3	38 ± 2	−14
Orbital cortex			
Area 11	51 ± 3	39 ± 1*	−24
Area 13a	46 ± 2	30 ± 1*	−35
Area 13b	48 ± 1	34 ± 1*	−29
Area 13	50 ± 1	38 ± 2*	−24
Area 12o	52 ± 1	39 ± 2*	−25
Cingulate			
Area 23	46 ± 3	37 ± 3	−20
Area 24	43 ± 2	38 ± 3	−12
Area 24	48 ± 2	42 ± 2	−12
Area 25	44 ± 3	29 ± 3*	−34
Area 32	42 ± 1	34 ± 4	−19
Anteroventral insula			
Iapm/Iai	33 ± 3	30 ± 3	−9
Ia1	38 ± 3	30 ± 3	−21
G	44 ± 4	35 ± 4	−20
Temporal pole			
Medial	37 ± 2	32 ± 3	−14
Lateral	39 ± 2	32 ± 3	−18

*Indicates a significant difference from saline (Student's *t* test, $p < 0.05$).

Brainstem regions

Brainstem structures comprising monoamine-containing neuronal cell bodies were examined in the present investigation (Table 2). Acute cocaine administration significantly reduced glucose utilization in the dorsal (−15%) and median (−18%) raphe nuclei and in the locus ceruleus (−20%).

DISCUSSION

The results of the present metabolic mapping study demonstrate that the acute intravenous administration of a moderate dose of cocaine (1.0 mg/kg) to cocaine-naive cynomolgus monkeys produced a highly discrete pattern of decreases in cerebral metabolism restricted to specific components of the limbic system. These changes in functional activity, measured with the quantitative autoradiographic 2-[^{14}C]DG method, were most robust within the

ventral striatum and within a subset of the limbic areas that project to it. The affected regions include the nucleus accumbens (core and shell), portions of the hippocampal formation, entorhinal cortex, orbitofrontal cortex, and anterior portions of the cingulate cortex. This array of affected structures suggests that corticostriatal activity, originating in limbic cortex and projecting to ventral striatum, plays an important role in the acute actions of cocaine in primates. In contrast to the intense changes in functional activity evident within the limbic system, cocaine administration at this dose had few effects on cerebral metabolism within cortical and subcortical sensory and motor systems.

Topography

The pattern of metabolic alterations observed in the present study is particularly noteworthy because the cortical regions in which metabolism was altered by cocaine form a subset of those forebrain domains sending projections to the nucleus accumbens. This is shown schematically in Figure 3, in which the inputs to the nucleus accumbens and surrounding ventral striatum, as demonstrated by anatomical tracing techniques, are compared with the changes in cerebral metabolism observed in the present study. Because changes in glucose utilization in a specific brain region are thought to be attributable primarily to changes in the afferent inputs to that region (Schwartz et al., 1979; Kadekaro et al., 1985; Sokoloff, 1985), the striking overlap reported here between the territories projecting to the ventral striatum and the location of the metabolic changes in the cerebral cortex suggests that the projections arising in the orbitofrontal cortex, anterior cingulate cortex, and the hippocampal formation are responsible, at least in part, for the significant changes in glucose utilization in the ventral striatum. This overlap also may reflect a potential neural substrate by which the reinforcing effects of cocaine are mediated, in part, by limbic cortical structures.

All of the cortical sites that displayed decreased glucose utilization project to the nucleus accumbens, but not all regions that project to the nucleus accumbens exhibited a metabolic effect. In particular, the amygdaloid complex, which provides dense input to the nucleus accumbens (Russchen et al., 1985; Amaral et al., 1992), showed no detectable changes in glucose metabolism. The lack of an effect in the amygdala was unexpected from an anatomical perspective and because of its reported involvement in motivated behaviors (Weiskrantz, 1956; Robbins et al., 1989; Aggleton, 1992; Gaffan, 1992). Neurons within the amygdala of the monkey, for example, increase their firing rates in the presence of stimuli once those stimuli have been paired with positive reinforcers (Nishijo et al., 1988). The failure of acute cocaine to alter functional activity in the amygdala, therefore, may be attributable in part to the lack of any conditioned context of drug administration in the present study. In self-administration paradigms or after the motivational significance of cocaine has become established after conditioning, the involvement of the amygdala may be revealed.

The primate nucleus accumbens, like that of the rodent, may be subdivided into the core and the shell based on afferent and efferent projections (Haber et al., 1990; Berendse et al., 1992; Friedman et al., 1992; Zahm and Brog, 1992; Meredith et al., 1993), as well as on the distribution of calbindin binding (Friedman et al., 1992; Meredith et al., 1993). Recent evidence in the rodent suggests that in certain contexts cocaine treatment has preferential effects in shell compared with the core of the nucleus accumbens (Pulvirenti et al., 1994; Pontieri et al., 1994), but this distinction was not apparent in the present study. Cocaine induced equivalent decreases in metabolism
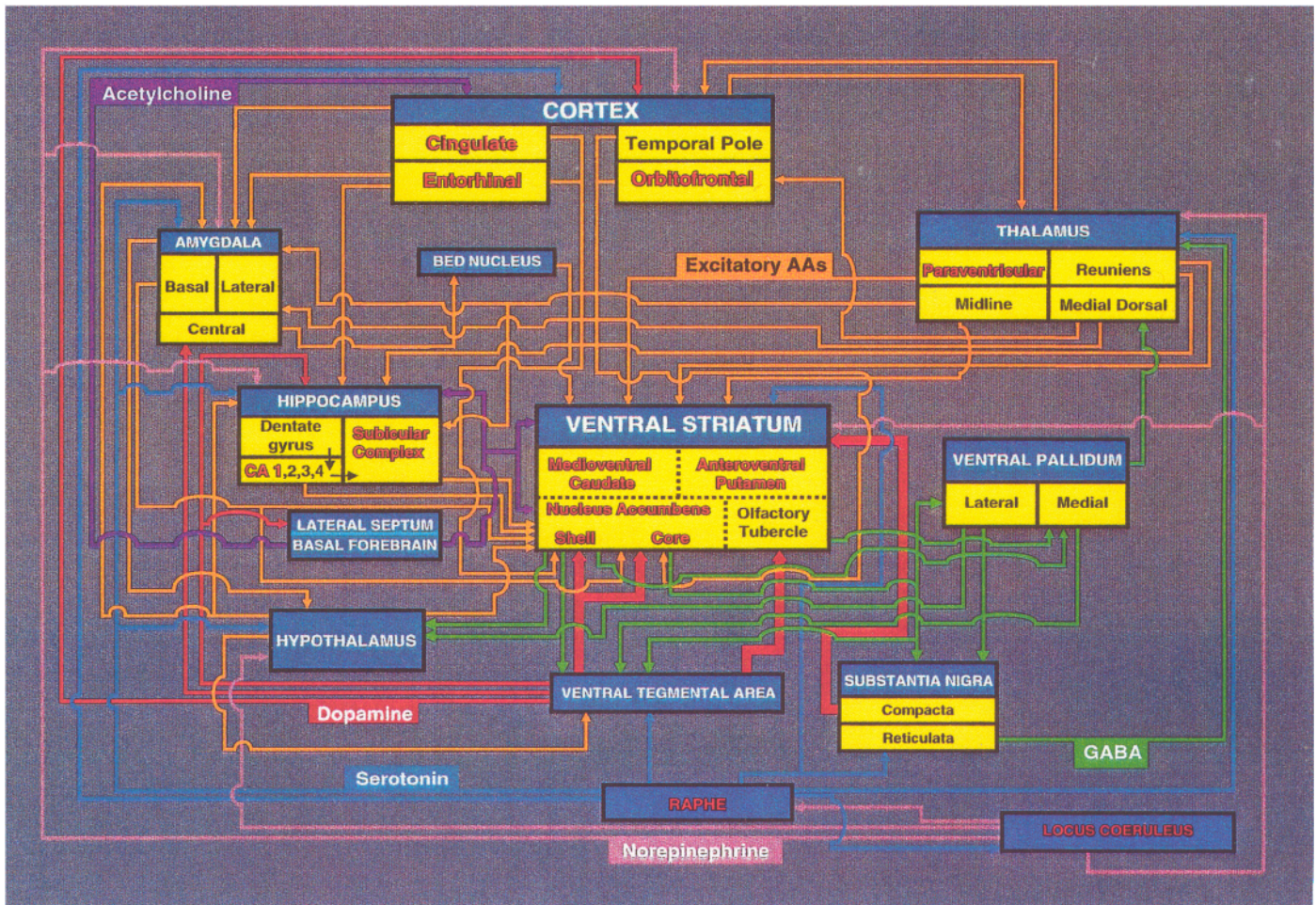
Figure 3. Schematic diagram of the connections of ventral striatum within the limbic system. Areas in which glucose utilization was altered by the administration of an acute dose of cocaine (1.0 mg/kg) are indicated in *red*, and they include portions of the ventral striatum, cortex, hippocampus, thalamus, the raphe, and the locus ceruleus. Note that cocaine produced discrete changes in functional activity within a subset of cortical and subcortical regions that project to the ventral striatum.

in both the shell and the core of the monkey. Moreover, functional activity in the cortical inputs specific to these subdivisions was not differentially altered.

Although the function of the caudate and putamen is considered to be primarily sensorimotor or cognitive in nature, the cortical inputs to portions of the anterior caudate and putamen suggest a role more characteristic of limbic function. This idea is supported by the decreased metabolism caused by cocaine administration observed in the present study. In addition, neurons contained within these striatal regions increase their firing rates in response to the presentation of rewarding stimuli or stimuli that predict the presentation of reward (Apicella et al., 1991; Schultz et al., 1992). This further supports the limbic nature of these regions and their involvement in the processing of reward-relevant information.

Role of limbic cortex

Based largely on data generated in the rodent, the mesolimbic dopamine system, particularly the pathway from the ventral tegmental area to the nucleus accumbens, has been widely recognized as a critical substrate for the reinforcing and activating properties of cocaine and other drugs of abuse (Wise, 1978; Koob and Goeders, 1989; Kuhar et al., 1991). The present data confirm the role of the nucleus accumbens in subserving the effects of

cocaine. Although electrophysiological studies in primates have shown that the neurons of the ventral striatum are sensitive to reward presentation (Apicella et al., 1991; Schultz et al., 1992), few studies have addressed the role of the nucleus accumbens in drug action in monkeys. The present data serve to extend the importance of this nucleus to the primate in the action of cocaine.

There are a number of lines of evidence showing that the orbitofrontal cortex is intimately involved in the mediation of positive reinforcement in primates (Rolls and Baylis, 1994). It has been shown, for example, that neurons in this region respond best to the presentation of rewarding stimuli, such as food and water, and shift their responsiveness depending on the motivational state of the organism (Rolls et al., 1980). Furthermore, the orbitofrontal cortex supports electrical self-stimulation in primates (Mora and Myers, 1977; Phillips et al., 1979), and orbitofrontal neurons increase their firing rates during rewarding electrical stimulation to other brain regions (Mora et al., 1980; Rolls et al., 1980). Lesions of this cortical region also have been shown to reduce the ability of monkeys to ascribe positive reinforcing value to stimuli (Baylis and Gaffan, 1991). Finally, the significance of orbitofrontal cortex to cocaine abuse is underscored further by PET studies of abstinent cocaine addicts in whom depressed rates of glucose metabolism in the orbitofrontal cortex were shown to persist for

up to 3 months of withdrawal, an effect positively correlated with changes in D_2-receptor availability in this region (Volkow et al., 1993). Thus, the changes in functional activity within the orbitofrontal cortex and adjacent cortical areas that accompany acute cocaine administration are clearly consistent with a role for these areas as potential substrates for the modification and modulation of the central representation of reward in the monkey.

Relationship of metabolic changes to the distribution of cocaine-binding sites

Although cocaine equipotently inhibits the transport of dopamine, serotonin, and norepinephrine (Koe, 1976; Ritz et al., 1990), the behavioral effects of cocaine have been attributed chiefly to its actions at the dopamine transporter (DeWit and Wise, 1977; Colpaert et al., 1978; Miczek and Yoshimura, 1982; Ritz et al., 1987). The relationship of cocaine to dopamine synapses is emphasized by numerous binding studies using radiolabeled cocaine or labeled cocaine analogs that have shown that the greatest levels of binding are found within the dopamine-rich regions of the striatum. In postmortem human tissue, the highest density of [^{3}H]cocaine binding was observed in caudate and putamen (Biegon et al., 1992, 1995). Infusions of [^{11}C]cocaine *in vivo* reveal a similar distribution in basal ganglia to that observed autoradiographically (Fowler et al., 1989, 1995). The binding of high-affinity tropane analogs such as [^{3}H]WIN-35,428 (CFT) and [^{123}I]RTI-55, which have high affinity for the DA transporter, also has been shown to be densest in caudate and putamen. The ventral midbrain, nucleus accumbens, and olfactory tubercle contain fewer of these binding sites, and amygdala, hippocampus, and cerebral cortex contain fewer still (Kaufman et al., 1991; Madras and Kaufman, 1994). Although cocaine has been shown to bind to other amine transporters, the regional densities of cocaine-binding sites closely parallel the regional densities of the dopamine transporter and include many of the structures in which decreases in metabolic activity were identified in the present study.

In studies by Madras and Kaufman (1994), the intravenous infusion of both behaviorally active (0.1 and 0.3 mg/kg) and tracer doses (0.001 mg/kg) of radiolabeled cocaine to anesthetized squirrel monkeys also identified a set of structures known to contain high concentrations of the dopamine transporter. Of more importance, levels of cocaine binding were found to be highly correlated ($r_{xy} = 0.90$) with changes in rates of glucose utilization in rats receiving a behaviorally activating dose of cocaine. This strong correlation was interpreted by these authors to suggest that the functional changes associated with acute cocaine exposure are caused directly by the actions of cocaine at its binding sites on the dopamine transporter.

Although metabolic changes in the present study were evident in many of the regions in which high levels of cocaine binding have been found, the structures in which the largest decreases in functional activity were observed did not correspond to the regions with the highest densities of cocaine-binding sites. Specifically, the densest accumulation of labeled cocaine is observed in the dorsal striatum, but the largest changes in cerebral glucose metabolism were found instead in the ventral striatum, particularly the nucleus accumbens. Other regions, such as the orbitofrontal cortex and hippocampal formation, which have far fewer cocaine-binding sites than the dorsal striatum, had equivalent or greater changes in glucose utilization. Finally, some structures, particularly the substantia nigra compacta and the amygdaloid complex, which clearly have dopamine transporters, had no changes in metabolism in response to cocaine exposure. Although methodological differences exist between the study of cocaine-

binding sites described above and the present study in terms of dose, time, and species of primate, it remains clear that the relative density of cocaine-binding sites in monkey brain is not sufficient to predict the intensity of the metabolic response to cocaine. Our results are consistent with the hypothesis that the disparities between the magnitude of the functional response to cocaine administration reported here and the density of cocaine-binding sites are more likely to be due to differences in the distributions of receptor subtypes expressed by the target neurons than to differences in the distribution of amine transporters to which cocaine binds.

Relationship to metabolic mapping studies in the rat

A number of clear similarities between the metabolic response to acute cocaine administration in rat and monkey are important to note. In particular, the ventral striatum is profoundly affected in both monkeys and rats (Porrino et al., 1988; Porrino, 1993). Furthermore, in both monkey and rat, cocaine appeared to have a more profound effect on metabolism in the ventral striatum than in the dorsal striatum. This difference in the magnitude of metabolic responses between dorsal and ventral striatum may reflect a greater sensitivity of the ventral striatum to stimulants across species (Porrino and Lucignani, 1987; Porrino et al., 1988; Porrino et al., 1995).

Despite these similarities, a larger number of brain regions responded to acute cocaine administration in the monkey than in the rat (Porrino et al., 1988; Porrino, 1993). Not only is the topography of altered brain metabolism different in monkeys and rats, the directions of the metabolic responses are different as well. After the administration of cocaine, rates of cerebral glucose utilization are depressed in primates, whereas they are elevated in rodents. The source of this discrepancy is unclear, but may stem directly from differences in the structures involved and their organization. Further research clearly is needed to understand the basis of the differences in the direction of the metabolic response in primates and rodents to cocaine administration.

The present study showed that glucose metabolism is altered in a number of brain regions in the monkey, in which it is unaffected in rats, regardless of the dose of cocaine tested or the regimen of cocaine administration. In rat, metabolic effects generally have been restricted to dopaminergic circuits (Porrino et al., 1988), but in the primate, cocaine depressed metabolism in the dorsal and median raphe nuclei and the locus ceruleus, sources of forebrain serotonergic and noradrenergic innervation, respectively. These effects are consistent with the actions of cocaine at serotonin and norepinephrine transporters and with its more widespread actions in monkey compared with rat.

Relationship to metabolic mapping studies in humans

In PET and SPECT studies, the acute administration of stimulants such as cocaine or amphetamine to human subjects generally has been found to cause widespread reductions in rates of cerebral metabolism or blood flow (Mathew and Wilson, 1985; Wolkin et al., 1987; Kahn et al., 1989; London et al., 1990; Pearlson et al., 1993). Thus, both humans and nonhuman primates respond to cocaine with reductions in cerebral metabolism. The metabolic changes that follow acute cocaine administration in humans, however, were apparent throughout the entire expanse of cerebral cortex and were not restricted to limbic cortex as reported here in the monkey (Wolkin et al., 1987; London et al., 1990). It is difficult to explain why metabolic rates were unchanged in parietal and occipital cortices of monkeys, whereas in humans these posterior

cortical regions showed decreases in metabolism as large as those found elsewhere in the human cortex (London et al., 1990). Although the reasons for these differences across species are not known, they may be due to differences in drug histories or expectations inherent in the design of human studies. Whereas the monkeys studied here had no history of drug self-administration, the human subjects studied previously had a wide range of experience with a variety of psychoactive drugs, including caffeine, nicotine, alcohol, cocaine, opiates, and psychedelics, among others. The influence of previous drug experiences and the expectations that they produce have not been investigated, but it may represent an important variable in determining the response to cocaine.

In summary, the acute intravenous administration of a moderate dose of cocaine to monkeys produces a discrete pattern of functional changes restricted to the ventral striatum and a subset of its limbic projection fields, including orbitofrontal and cingulate cortex, along with portions of the hippocampal formation. In addition, cocaine produced alterations in the metabolism of medial and dorsal raphe nuclei and the locus ceruleus. The decreased cerebral metabolism found in nonhuman primates more closely resembles data on functional activity in humans than rodents and supports the use of nonhuman primates as a model for the study of the neurobiological consequences of cocaine abuse. Furthermore, the involvement of cerebral cortex in the response to cocaine in primates suggests a means by which cocaine can influence directly the integration of the complex sensory and limbic information that is processed in these areas, not only in terms of their immediate emotional and motivational value, but in terms of their conditioned or remembered significance as well.

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