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Functional consequences of acute cocaine treatment depend on route of administration

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Abstract. The 2-[^{14}C]deoxyglucose method was used to compare the effects of the acute administration of cocaine by two different routes, intravenous and intraperitoneal, on rates of local cerebral glucose utilization in freely moving rats. Doses were initially chosen on the basis of their ability to elicit equivalent increases in locomotor activity during the experimental procedure, and the time of cocaine administration relative to 2-[^{14}C]deoxyglucose infusion was chosen so that the maximal behavioral effect occurred during maximal tracer incorporation. Changes in glucose utilization following the intraperitoneal administration of cocaine (10 mg/kg, 10 min before 2-deoxyglucose infusion) were restricted to the nigrostriatal system and related structures involved in the production of movement. Increased activity was observed in the substantia nigra pars reticulata, globus pallidus, and sensorimotor cortex. In contrast, intravenous cocaine administration (1 mg/kg, 2 min before tracer infusion) produced more widespread changes in rates of glucose utilization including portions of both the mesocorticolimbic and nigrostriatal systems. Areas in which metabolic activity was altered included the caudate-putamen, globus pallidus, substantia nigra pars reticulata, sensorimotor cortex, olfactory tubercle, nucleus accumbens, and medial prefrontal cortex. Both intravenous and intraperitoneal cocaine produced similar increases in locomotor activity. Additional studies indicated that the absence of metabolic activation in the mesocorticolimbic system following acute intraperitoneal cocaine was not the result of the specific dose chosen or the length of time between cocaine administration and radiotracer infusion, as no changes in metabolic activity in mesocorticolimbic structures were evident when these parameters were varied. The cerebral metabolic effects of acute intravenous and intraperitoneal cocaine administration are significantly different. These data indicate that pharmacokinetic variables are important determinants of the functional response to cocaine.

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Key words: Cocaine – Psychostimulants – Deoxyglucose – Pharmacokinetics – Locomotor activity

Cocaine is a widely abused drug with powerful reinforcing properties. Its primary mechanism of action in brain is the blockade of the reuptake of the monoamines, dopamine (Moore et al. 1977; Heikkila et al. 1979), norepinephrine (Hertting et al. 1961: Moore et al. 1977), and serotonin (Ross and Renyi 1967). In addition, cocaine is known to have potent local anesthetic properties (Ritchie and Greene 1980). As a drug of abuse cocaine is primarily administered intranasally as a powder or smoked in its free base form, although a small percentage of users do take cocaine intravenously (Johanson and Fischman 1989). These routes of administration have in common relatively rapid onsets of action with peak plasma concentrations achieved within the first 30 min as well as short elimination half-lives (Van Dyke et al. 1976, 1978; Wilkinson et al. 1980; Chow et al. 1985; Fischman 1988). These pharmacokinetic characteristics, particularly the rapid onset of action, have been hypothesized to be in part responsible for the intense subjective effects of cocaine reported within the first few minutes of use (Fischman et al. 1976; Resnick et al. 1977; Javaid et al. 1978).

Studies of the effects of cocaine in laboratory animals, while sometimes using the intravenous route, have more generally utilized the intraperitoneal route of administration. The intraperitoneal route, because of its convenience, is the preferred route in studies of locomotor behavior, schedule-controlled behavior, conditioned place preference, and the discriminative stimulus properties of cocaine. This route is also used in many studies of the neurobiological effects of cocaine, such as neurotransmitter turnover, receptor density, etc. The intravenous route of administration, in contrast, is the route of choice in studies of the reinforcing properties of cocaine utilizing the self-administration paradigm.

The pharmacokinetics of intraperitoneal and intravenous routes of administration differ significantly, however, in that intraperitoneal administration involves the absorption of cocaine from the peritoneal cavity where it enters the portal system and is thereby subject to metabolism in liver before entry into the general circulation and then the brain (Shuster 1992). In contrast, cocaine administered intravenously is delivered directly into the general circulation, allowing it to reach the brain without first-pass metabolism in the liver (Nayak et al. 1976; Wiggins et al. 1989; Shuster 1992). Peak plasma and brain concentrations of cocaine, therefore, occur more rapidly following intravenous administration. Unfortunately, few studies have directly addressed the neurobiological or behavioral consequences of these pharmacokinetic differences.

Metabolic mapping with the 2-[^{14}C]deoxyglucose (2DG) method has been used for the investigation of the neuroanatomical substrates of the effects of the acute administration of cocaine in the central nervous system (London et al. 1986; Porrino et al. 1988; Sharkey et al. 1991). Dose-dependent increases in rates of glucose utilization restricted to components of the nigrostriatal motor system following cocaine treatment have been reported by London and her colleagues (London et al. 1986). A study in this laboratory, however, has demonstrated that cocaine administration produces widespread changes in functional activation, not only in the nigrostriatal motor system, but throughout portions of the dopaminergically innervated mesocorticolimbic system including the nucleus accumbens and medial prefrontal cortex (Porrino et al. 1988). Although there were a number of procedural differences between these two studies, one possible explanation for the discrepancies is the differing routes of administration. The purpose of the present study was to evaluate the potential role of the route of administration in determining the functional consequences of cocaine in brain. The effects of intravenous and intraperitoneal cocaine administration on rates of local cerebral glucose utilization (LCGU) as measured by the 2-[^{14}C]deoxyglucose method were, therefore, compared directly.

Material and methods

Animals. Experiments were performed on male Sprague-Dawley rats (Taconic Farms, Germantown, NY), weighing 300–360 g. Animals were housed in group cages and maintained under standard conditions of temperature and lighting; food and water were available ad libitum.

On the day of the experiment, animals were lightly anesthetized with a mixture of halothane and nitrous oxide, and polyethylene catheters were inserted into one femoral artery and vein, then run subcutaneously to exit at the nape of the neck. This placement of the catheters allows animals to move freely during the experimental procedure (Crane and Porrino 1989). At least 3 h were allowed for recovery from the effects of anesthesia and surgery before the measurement of cerebral metabolic activity was begun.

Drug administration. Cocaine hydrochloride (Sigma, St Louis, MO) was dissolved in saline just prior to use, and injected intraperitoneally or intravenously before initiation of the deoxyglucose experimental procedure. Doses were calculated as the salt.

Experimental procedure. In order to compare the effects of intravenous cocaine to those of intraperitoneal cocaine, rats were treated with doses of intravenous or intraperitoneal cocaine chosen on the basis of their ability to elicit equivalent increases in locomotor activity during the experimental test period. Using behavioral equivalence as a basis for effects permits any differences observed between groups to be ascribed to pharmacokinetic differences rather than to differences in behavior itself. Four groups of rats received one of the following treatments: saline vehicle intraperitoneally or intravenously; cocaine, 10 mg/kg, intraperitoneally; or 1.0 mg/kg, intravenously. Each group consisted of five animals with the exception of the group receiving saline intravenously in which four animals were included. Cocaine was injected intraperitoneally 10 min before or intravenously 2 min before initiation of the 2DG procedure. Times were chosen so that the maximum behavioral response occurred within the first 5–10 min following 2DG infusion which is the time of maximal incorporation of radioactive tracer (Sokoloff et al. 1977). In this way the 2DG procedure "records" the maximal effects of each treatment.

The effects of the acute administration of cocaine on locomotor activity were evaluated simultaneously with the measurement of rates of glucose utilization. All experiments were performed in an open-field clear plastic test chamber (42 × 42 × 30 cm). Locomotor activity was measured by electronic counters that detected interruptions of eight independent photocell beams located 2 cm above the floor (Omnitech, Columbus, OH). Each animal was habituated to the cage for 60 min on each of the 2 days prior to the experiment and on the day of the experiment was placed in the chamber 20 min before treatment. Photocell counts were recorded every 10 min after the injection of drug or vehicle and for the 45 minute experimental period.

In order to determine the potential role of cocaine dose in determining patterns of glucose utilization changes, three groups of rats received one of the following treatments: cocaine, 15 or 30 mg/kg, intraperitoneally or saline vehicle 10 min prior to initiation of the 2DG procedure ($N = 3$, 4, and 6, respectively). Experiments were performed in an open-field Plexiglas test chamber (42 × 42 × 30 cm) to which the animals were habituated as described above. Formal measurements of locomotor activity, however, were not conducted in these experiments.

In order to evaluate the contribution of temporal variables to the observed patterns of glucose utilization alterations, four groups of animals received one of the following treatments: cocaine (1 mg/kg; $N = 4$) intravenously, 10 min before 2DG infusion; saline intravenously ($N = 4$); cocaine (10 mg/kg; $N = 4$) intraperitoneally, 2 min before 2DG; or saline intraperitoneally ($N = 5$). These experiments serve as controls for the time points chosen on the basis of equivalent behavioral activation described above. Experiments were performed in an open-field plexiglass test chamber (42 × 42 × 30 cm) to which the animals were habituated as described above. Formal measurements of locomotor activity were not conducted in these experiments.

Measurement of local cerebral glucose utilization. Local cerebral glucose utilization was measured according to the procedures described by Sokoloff et al. (1977) as adapted for freely-moving animals (Crane and Porrino 1989). At times as described above following administration of cocaine or saline intravenously after the injection of cocaine or saline intraperitoneally, a pulse of 2-[^{14}C]deoxyglucose at the dose of 125 μCi/kg (specific activity 50–55 mCi/mmol, New England Nuclear, Boston, MA) was injected through the femoral venous catheter. Timed arterial blood samples were drawn during the next 45 min. Blood samples were centrifuged immediately, and plasma concentrations of 2-[^{14}C]deoxyglucose were determined by liquid scintillation counting (Beckman Instruments, Fullerton, CA). Plasma glucose concentrations were assayed by means of a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA).

Approximately 45 min after 2DG infusion animals were killed by the intravenous administration of sodium pentobarbital. Brains were rapidly removed and frozen in isopentane at −45°C, coated

with embedding matrix, and stored at −70°C until sectioning. Coronal sections of brain (20 μm) were cut in a cryostat maintained at −22°C. Sections were picked up on glass coverslips and dried on a hot plate (60°C). Sections were autoradiographed on Kodak OM1 x-ray film along with a set of calibrated [^{14}C]methylmethacrylate standards (Amersham, Arlington Heights, IL) previously calibrated for their equivalent wet weight ^{14}C concentration in brain sections cut similarly. Films were exposed for 10–12 days and developed by hand in GBX developer (Kodak, Rochester, NY).

Autoradiograms were analyzed by quantitative densitometry with a computerized-image processing system (MCID, Imaging Research, St Catharines, Ontario). Optical density measurements for each structure, identified according to the rat brain atlas of Paxinos and Watson (1982), were made in a minimum of five 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 was then calculated from the local ^{14}C tissue concentrations, the time-courses of the plasma glucose and ^{14}C concentrations, and the appropriate constants according to the operational equation of the method (Sokoloff et al. 1977).

Statistical analysis. Rates of local cerebral glucose utilization were determined in 38 discrete brain regions. Statistical analysis was carried out on each structure individually by means of Dunnett's *t*-test for multiple comparisons or Student's *t*-test for independent samples as appropriate. Total locomotor activity was similarly analyzed by Dunnett's *t*-test for multiple comparisons.

Results

Comparison of the effects of intravenous and intraperitoneal cocaine administration

In the first experiment, the effects of cocaine administered intraperitoneally or intravenously were compared using doses chosen for their ability to elicit similar increases in locomotor activity which was measured simultaneously. No significant differences in locomotor activity were observed between groups administered saline intravenously and intraperitoneally. Data from the saline-treated groups were therefore combined for comparison with cocaine-treated groups. Both intravenous (1 mg/kg) and intraperitoneal (10 mg/kg) cocaine treatment resulted in significant ($P < 0.05$, Dunnett's *t*-test) increases in locomotor activity during the first 5–10 min of the 2DG procedure. Intravenous cocaine produced maximal levels of activity immediately after infusion (Fig. 1A). Although increased significantly, peak levels of activity after intraperitoneal cocaine were not as great as after intravenous cocaine, but remained elevated longer (Fig. 1A). Overall changes in locomotor activity, however, were equivalent in that the mean total number of photocell interruptions recorded during the 45 min experimental period for both cocaine-treated groups were almost identical (see Fig. 1B).

Because no significant differences in rates of glucose utilization were found in the intravenously- and intraperitoneally-treated saline groups, data from the two groups were combined for further analysis as above. The effects of acute intravenous (1 mg/kg; 2 min before 2DG infusion) and intraperitoneal (10 mg/kg; 10 min before 2DG infusion) administration of cocaine on rates of local cerebral glucose utilization in the 38 anatomically discrete brain regions examined are summarized in Table 1. The administration of 10 mg/kg cocaine intraperitoneally significantly increased metabolic activity in the substantia nigra pars reticulata (+17%; Fig. 2), globus pallidus (+16%), and somatomotor cortex (+20%). In contrast, the administration of 1 mg/kg cocaine intravenously produced more widespread changes in rates of glucose utilization, including portions of the dopaminergically-innervated nigrostriatal and mesocorticolimbic systems (Fig. 3). Metabolic activity was significantly altered in the dorsomedial (+12%), dorsolateral (+14%) and ventral (+12%) portions of the caudate, the globus pallidus (+16%), substantia nigra reticulata (+21%; Fig. 2), somatomotor cortex (+17%), and the lateral portion of the lateral habenula (–14%). Glucose utilization was also significantly increased in the olfactory tubercle (+13%), medial prefrontal cortex (+14%), and the nucleus accumbens (+16%) of these rats (Figs 3 and 4).

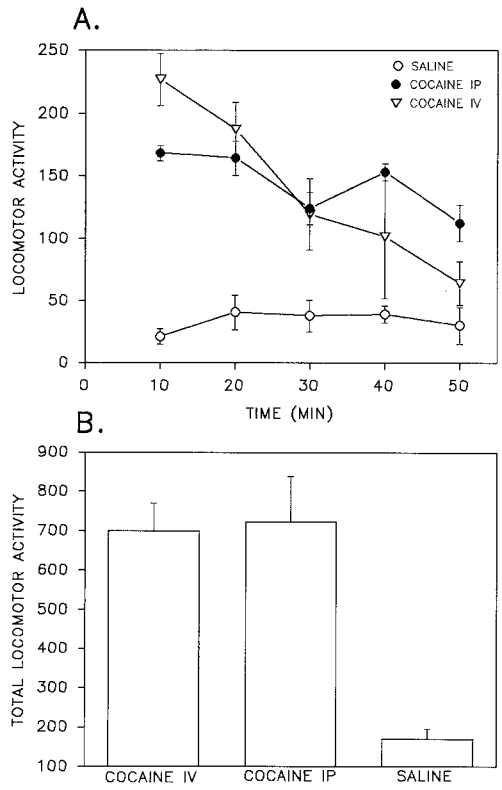

Fig. 1A,B. Effects of acute cocaine administered intravenously (1 mg/kg, 2 min before 2DG) and intraperitoneally (10 mg/kg, 10 min before 2DG) on locomotor activity. **A** Time course of the effects of cocaine on locomotor activity. The 0 time point coincides with the time of 2DG infusion. Values represent means and standard errors of photocell beam interruptions for each 10-minute segment of the experimental period in groups of rats treated with saline ($N = 9$), cocaine IP ($N = 5$) and cocaine IV ($N = 5$). **B** Total locomotor activity during the experimental period of the above groups. *$P < 0.05$, significantly different from saline controls, Dunnett's *t*-test

Dose-dependent effects of cocaine on LCGU

In order to determine whether the failure to detect changes in the dopaminergic mesocorticolimbic system

Table 1. Effects of the acute administration of cocaine on local cerebral glucose utilization (μmol/100 g per min) in rats[a]

Structure	Cocaine		
	Vehicle control $N=9$	Intraperitoneal[b] 10 mg/kg $N=5$	Intravenous[c] 1 mg/kg $N=5$
Mesocorticolimbic system			
Medial prefrontal cortex	67.6±3	68.9±2	77.2±2*
Olfactory tubercle	86.1±5	84.6±3	97.0±4*
Nucleus accumbens	87.8±3	92.3±2	102.2±9*
Anterior cingulate cortex	106.0±3	118.6±4	113.2±3
Basolateral amygdala	82.1±2	76.0±3	79.8±2
Central amygdala	41.9±1	39.2±2	40.2±1
Hippocampus (CA3)	73.2±2	73.3±2	74.3±2
Ventral tegmental area	70.6±3	70.9±3	71.1±1
Nigrostriatal system und related areas			
Dorsomedial caudate	106.5±3	114.8±2	118.0±4*
Dorsolateral caudate	106.9±4	113.9±2	120.5±3*
Ventral caudate	90.9±2	96.3±3	101.8±1*
Globus pallidus	53.8±2	62.7±4*	62.2±4*
Entopeduncular nucleus	52.9±2	55.3±2	57.5±4
Subthalamic nucleus	101.1±3	100.3±4	103.9±5
Substantia nigra pars compacta	75.4±2	74.2±2	77.7±1
Substantia nigra pars reticulata	57.1±1	66.8±3*	69.1±4*
Cerebellum	58.5±0	55.1±3	55.7±3
Neocortical areas			
Somatomotor cortex	87.4±5	104.8±3*	102.4±3*
Auditory cortex	160.1±4	147.8±5	147.6±4
Visual cortex	92.3±2	95.2±8	97.6±2
Thalamus and hypothalamus			
Ventral thalamus	96.5±3	92.7±5	98.8±1
Lateral thalamus	109.2±3	110.4±3	111.5±3
Mediodorsal thalamus	107.6±2	113.3±4	113.8±4
Medial habenula	73.1±3	78.3±3	73.6±1
Lateral habenula (medial)	100.7±4	94.9±7	91.9±2*
Lateral habenula (lateral)	113.3±3	103.5±7	97.6±4
Medial geniculate	121.8±4	125.9±5	120.2±5
Lateral geniculate	96.1±4	99.3±4	94.2±2
Lateral hypothalamus	59.1±2	58.2±2	57.8±3
Mammillary bodies	119.9±2	120.1±4	122.4±3
Myelinated fiber tracts			
Corpus callosum	27.4±1	29.4±1	28.1±1
Internal capsule	33.7±1	32.1±1	34.8±1
Cerebellar white matter	33.5±1	33.7±1	36.3±2

[a] Results are expressed as the means±SEM
[b] Cocaine administered 10 min before 2DG infusion
[c] Cocaine administered 2 min before 2DG infusion
* $=P<0.05$ different from control (Dunnett's statistic)

following intraperitoneal cocaine administration was due to the choice of cocaine dose, rates of cerebral metabolism were measured in the mesocorticolimbic and nigrostriatal systems of rats following the administration of higher doses of cocaine, 15 and 30 mg/kg administered intraperitoneally (Table 2). Dose-dependent alterations in LCGU were present throughout the nigrostriatal system, including the globus pallidus, substantia nigra reticulata (Fig. 2), entopeduncular nucleus, subthalamic nucleus, and the lateral habenula. In contrast, LCGU was not significantly changed in *any* portion of the mesocorticolimbic system including the nucleus accumbens (Fig. 3), olfactory tubercle, and medial prefrontal cortex.

Time-dependent effects of cocaine on LCGU

In order to determine the role of the length of time between cocaine administration and 2DG infusion in producing the patterns of LCGU changes in rats treated with cocaine intraperitoneally and intravenously, rates of cerebral metabolism were measured in the mesocorticol-

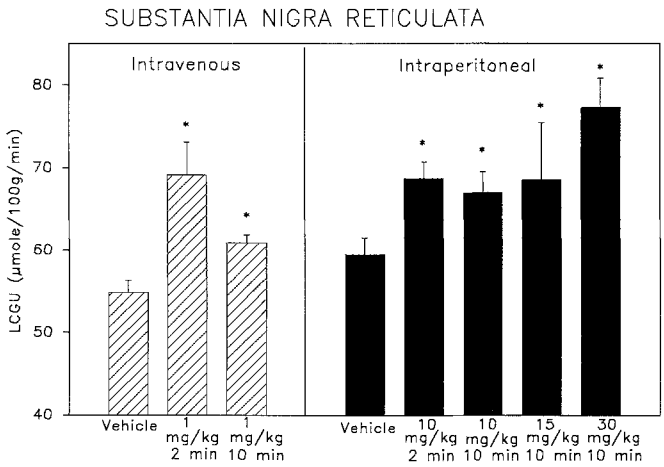

Fig. 2. Effects of acute cocaine treatment on metabolic activity in the substantia nigra reticulata. Values represent means and standard errors of rates of local cerebral glucose utilization in rats treated with cocaine intravenously (*left*; vehicle, $N=4$; cocaine, 1 mg/kg, 2 min, $N=5$ or 10 min, $N=4$ prior to 2-deoxyglucose infusion) or intraperitoneally (*right*; vehicle, $N=5$; cocaine, 10, 15, or 30 mg/kg, 10 min before 2-deoxyglucose infusion, $N=5$, 3, 4, respectively; or 10 mg/kg, 2 min before infusion, $N=4$), $^*P < 0.05$, significantly different from appropriate saline controls

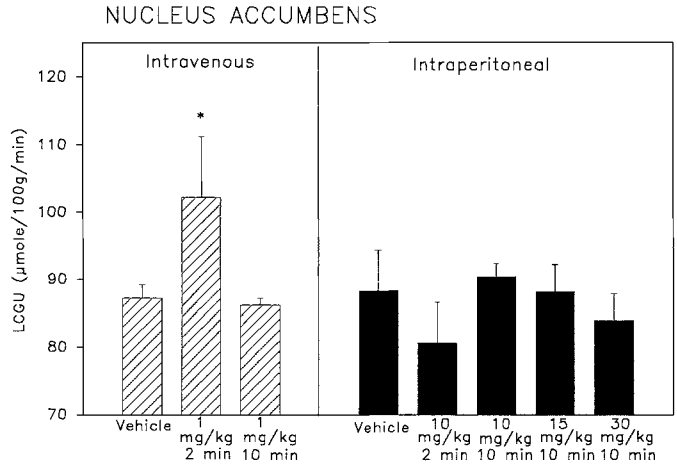

Fig. 3. Effects of acute cocaine treatment on metabolic activity in the nucleus accumbens. Values represent means and standard errors of rates of local cerebral glucose utilization in rats treated with cocaine intravenously (*left*; vehicle, $N=4$; cocaine, 1 mg/kg, 2 min, $N=5$ or 10 min, $N=4$ prior to 2-deoxyglucose infusion) or intraperitoneally (right; vehicle, $N=5$; cocaine, 10, 15, or 30 mg/kg, 10 min before 2-deoxyglucose infusion, $N=5$, 3, 4, respectively; or 10 mg/kg, 2 min before infusion, $N=4$), $^*P < 0.05$, significantly different from appropriate saline controls

Table 2. Dose-dependent effects of cocaine administered intraperitoneally on rates of local cerebral glucose utilization

Structure	Cocaine (mg/kg, intraperitoneal)		
	0.0 $N=6$	15.0 $N=3$	30.0 $N=4$
Mesocorticolimbic system			
Medial prefrontal cortex	76.6±5	72.9±7	66.2±2
Olfactory tubercle	86.9±5	87.5±7	82.8±3
Nucleus accumbens	87.8±4	88.2±6	83.8±3
Basolateral amygdala	80.4±4	78.2±2	77.8±5
Central amygdala	47.3±3	41.5±3	43.6±3
Hippocampus (CA3)	65.5±2	64.3±3	60.8±3
Ventral tegmental area	71.5±4	72.8±4	67.0±4
Nigrostriatal system and related areas			
Dorsomedial caudate	100.8±5	116.6±4	113.8±6
Dorsolateral caudate	112.6±7	108.2±7	118.3±10
Ventral caudate	101.8±2	98.4±4	114.5±6*
Globus pallidus	53.1±3	61.3±6*	69.5±2*
Entopeduncular nucleus	56.1±3	69.2±6*	69.8±3*
Subthalamic nucleus	92.8±5	102.0±4	115.0±8*
Medial habenula	74.9±3	64.7±5	67.2±4
Lateral habenula (medial)	99.7±2	67.1±5**	74.6±6**
Lateral habenula (lateral)	116.3±5	82.4±7**	84.2±8**
Substantia nigra compacta	82.7±5	79.8±4	82.2±3
Substantia nigra reticulata	58.5±3	71.9±7*	79.8±3**

* $=P<0.05$ Dunnett's t-test
** $=P<0.01$ Dunnett's t-test

imbic and nigrostriatal systems of rats following intraperitoneal administration of cocaine 2 min before 2DG (Table 3) or intravenous administration of cocaine 10 min before 2DG (Table 4). These experiments served as controls for the time points chosen on the basis of equivalent behavioral activation as described above. Intraperitoneal administration of cocaine 2 min prior to the initiation of the 2DG procedure did not alter cerebral metabolic rates in any portion of the mesocorticolimbic system (Fig. 3), nor were portions of the nigrostriatal system affected with the exception of the substantia nigra reticulata (Fig. 2) in which LCGU was increased (+11%). Measurement of rates of glucose utilization 10 min following intravenous administration of cocaine re-

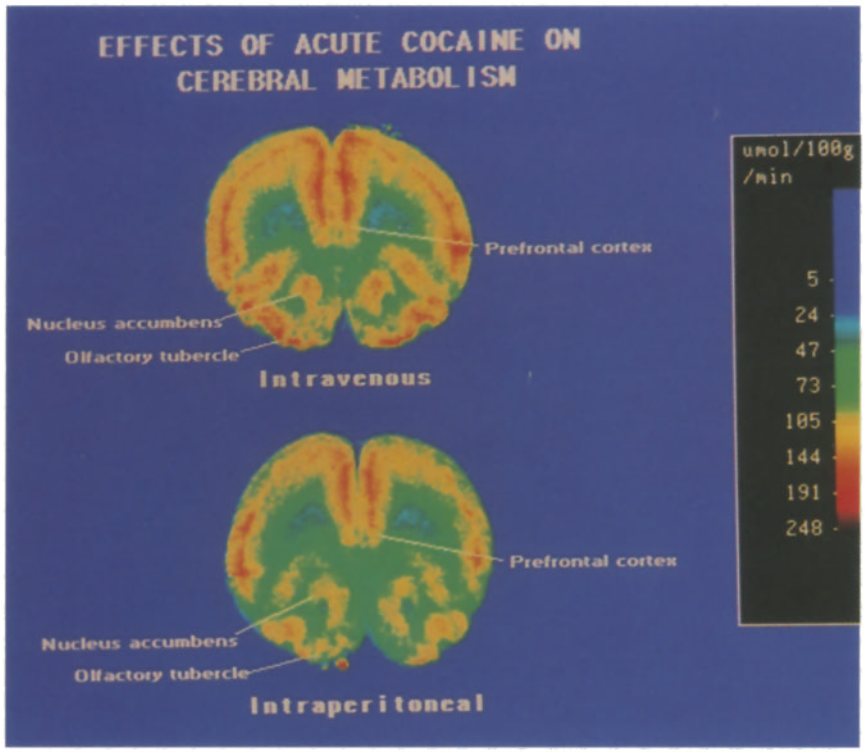

Fig. 4. Effects of acute administration of intravenous (1 mg/kg) and intraperitoneal (10 mg/kg) cocaine on local cerebral glucose utilization in rats. Shown are color-coded transformations of autoradiograms of coronal sections of rat brain at the level of the nucleus accumbens in which each color represents a range of rates of local cerebral glucose utilization in μmol/100 g per min according to the calibration scale to the right of the autoradiograms. Note that rates of glucose utilization are elevated in the nucleus accumbens, olfactory tubercle, and prefrontal cortex of the rat receiving intravenous cocaine as compared to the rat receiving intraperitoneal cocaine

Table 3. Cerebral metabolic effects of cocaine (10 mg/kg) as measured 2 min after intraperitoneal administration

Structure	Cocaine (10 mg/kg, IP)	
	Control $N=5$	$N=4$
Mesocorticolimbic system		
Medial prefrontal cortex	69.1±5	65.5±3
Olfactory tubercle	87.7±9	80.5±2
Nucleus accumbens	88.3±7	80.6±6
Basolateral amygdala	84.7±3	82.3±3
Central amygdala	43.6±1	37.6±4
Hippocampus (CA3)	75.4±2	71.2±3
Ventral tegmental area	64.4±1	64.6±3
Nigrostriatal system and related areas		
Dorsomedial caudate	106.0±6	110.5±4
Dorsolateral caudate	110.8±8	114.6±5
Ventral caudate	91.0±5	92.0±4
Globus pallidus	52.5±3	60.5±6
Entopeduncular nucleus	53.7±2	55.4±4
Subthalamic nucleus	102.2±5	102.3±7
Medial habenula	71.2±4	75.5±7
Lateral habenula (medial)	102.2±8	95.2±5
Lateral habenula (lateral)	111.7±5	110.0±7
Substantia nigra compacta	78.6±2	76.5±5
Substantia nigra reticulata	59.4±2	65.7±2*

* $P<0.05$ Student's t-test

Table 4. Cerebral metabolic effects of cocaine (1 mg/kg) as measured 10 min after intravenous administration

Structure	Cocaine (1 mg/kg, IV)	
	Control $N=4$	$N=4$
Mesocorticolimbic system		
Medial prefrontal cortex	66.2±3	70.9±1
Olfactory tubercle	84.5±5	92.4±2
Nucleus accumbens	87.2±2	86.2±1
Basolateral amygdala	79.4±2	84.1±1
Central amygdala	40.2±2	46.8±4
Hippocampus (CA3)	71.0±3	66.2±4
Ventral tegmental area	66.7±3	64.4±4
Nigrostriatal system and related areas		
Dorsomedial caudate	107.1±2	113.7±7
Dorsolateral caudate	103.0±1	114.1±7
Ventral caudate	90.8±1	108.0±6**
Globus pallidus	55.1±1	49.6±3*
Entopeduncular nucleus	52.1±3	53.7±1
Subthalamic nucleus	100.0±4	103.1±2
Medial habenula	75.0±4	79.9±8
Lateral habenula (medial)	99.2±3	98.8±9
Lateral habenula (lateral)	114.9±2	117.5±12
Substantia nigra compacta	72.3±2	69.7±4
Substantia nigra reticulata	54.8±1	61.4±3*

* $=P<0.05$ Student's t-test
** $=P<0.01$ Student's t-test

vealed significant changes in metabolism in the ventral caudate (+19%), substantia nigra reticulata (+12%; Fig. 2) and the globus pallidus (–10%). Once again, LCGU was unchanged in the mesocorticolimbic system (Fig. 3).

Discussion

The present study clearly demonstrates that the route of administration of cocaine is an important determinant of its neurobiological consequences. Despite the similarities

in the locomotor activating effects of intravenous and intraperitoneal cocaine, the cerebral metabolic effects of the acute intravenous administration of cocaine were significantly different from the effects of intraperitoneal cocaine administration. The similarity in the degree of behavioral activation is important, because differences in the amount of cocaine-induced locomotor activity alone would be reflected in differing rates of metabolism, particularly in motor structures as seen here when higher doses of cocaine were administered. The choice of a common or equivalent behavioral endpoint as the basis for comparison in this study, therefore, allows the differences in the patterns of functional activation to be attributed to pharmacokinetic variables rather than the behavior itself. Intraperitoneal cocaine treatment resulted in changes in neuronal activity, as reflected in changes in rates of cerebral glucose utilization, mainly within the nigrostriatal system, including the substantia nigra reticulata and globus pallidus, known to be involved in the production of motor behavior. Intravenous administration, on the other hand, resulted in altered functional activity not only in these brain regions, but in all portions of the caudate nucleus, the nucleus accumbens, olfactory tubercle, and the medial prefrontal cortex. The patterns of glucose utilization changes elicited by each route of administration are consistent with those reported in previous studies of the effects of cocaine administered either intravenously (Porrino et al. 1988) or intraperitoneally (London et al. 1986). These data therefore confirm the findings of these studies and provide an explanation for the discrepancies between them. The present data support the conclusion that cocaine activates different neuronal circuits depending on the route by which it is administered. As a result, pharmacokinetic variables must be considered important determinants of neurochemical, behavioral, and physiological responses to cocaine.

One possible reason for the rather circumscribed effects of intraperitoneal cocaine as compared to those of intravenous cocaine was the relatively low dose chosen for study. Higher cocaine doses, however, did not alter rates of glucose utilization in any portion of the mesolimbic system (Table 2, Fig. 2) including the nucleus accumbens, olfactory tubercle or medial prefrontal cortex, structures in which glucose utilization was increased when cocaine was administered intravenously (Porrino et al. 1988; present study). The present findings are similar to those reported by London and colleagues (1986). Dose therefore does not appear to be a sufficient explanation for the differential distribution of changes in functional activity. These higher doses did, however, elevate energy metabolism in portions of the caudate nucleus and other components of the nigrostriatal motor system in a dose-dependent manner. These changes probably reflect the greater levels of behavioral activation that are elicited by higher doses of cocaine. Conversely, lower doses of intravenous cocaine have been shown to selectively increase metabolism in the nucleus accumbens without significantly affecting most structures within the nigrostriatal system (Porrino et al. 1988). The effects in the mesocorticolimbic system, then, appear to be route-dependent rather than dose-dependent. These data suggest that the measurable metabolic effects of intraperitoneal cocaine administration are limited to brain regions more likely to be associated with the control of motor behavior and do not involve structures within the dopaminergically innervated mesocorticolimbic system that are generally associated with the reinforcing effects of psychostimulants (cf Koob and Goeders 1989).

When compared to the intraperitoneal route, cocaine administered intravenously rapidly reaches peak concentrations in both plasma and brain. Estimates vary, but peak plasma concentrations are achieved within the first 5–10 min following intravenous administration, but do not occur until 10–40 min after intraperitoneal administration (Nayak et al. 1976; Lau et al. 1991; Shuster 1992). Peak behavioral activating effects tend to coincide with peak plasma cocaine concentrations regardless of the route of administration. In the present study, therefore, when locomotor activity was used as the index of comparison, maximal 2DG incorporation occurred during the time of peak plasma cocaine levels. When, however, maximal incorporation occurred at times other than peak plasma concentrations, e.g., 10 min after intravenous administration (when concentrations of cocaine are declining) or 2 min after intraperitoneal administration (well before peak cocaine concentrations), significantly different patterns of changes in LCGU were obtained. When cocaine was administered intravenously ten min before 2DG infusion, rates of cerebral metabolism were altered only in the ventral caudate, globus pallidus, and substantia nigra reticulata, whereas when cocaine was administered intraperitoneally 2 min before 2DG infusion, glucose utilization was increased only in the substantia nigra reticulata. The only instance in which cerebral metabolic activity was altered in portions of the mesocorticolimbic system was when cocaine was administered intravenously and peak plasma cocaine concentrations occurred during maximal tracer incorporation, e.g., cocaine administration 2 min before 2DG infusion. A unique and rather limited set of circumstances appears necessary for metabolic activation of the nucleus accumbens and other mesocorticolimbic structures.

The rate of delivery of cocaine to its binding sites in brain is often considered to be an important determinant of the powerful reinforcing effects of cocaine and the reason that routes of administration that result in the fastest onsets of action produce the most intense euphoria and other subjective effects as reported by human users (Fischman et al. 1976; Resnick et al. 1977; Javaid et al. 1978). Certain brain sites such as the nucleus accumbens may be more sensitive to rapidly rising cocaine concentrations than other brain areas such as the caudate nucleus that also bind significant concentrations of cocaine. Such differential sensitivity may be the reason that alterations in functional activity are seen in the nucleus accumbens only when there is an extremely rapid rate of change of cocaine concentrations on the ascending limb of the curve. The importance of rates of change is supported by the results of a study of monkeys trained to self-administer cocaine intravenously, in which the duration of infusions of a constant drug dose was varied systematically

(Balster and Schuster 1973). Response rates declined precipitously as the infusion duration increased regardless of the dose, supporting the view that the rate of change of cocaine concentrations in brain is critical in determining its functional consequences.

The levels of cocaine delivered to the nucleus accumbens, as measured by in vivo microdialysis, may also vary depending on the route of administration (Pettit et al. 1990; Pan et al. 1991). Peak cocaine concentrations in brain were more than twice as high following the intravenous administration of 7.5 mg/kg cocaine than following the intraperitoneal administration of 30 mg/kg. The slower absorption after intraperitoneal administration also resulted in significantly lower peak plasma cocaine levels (Pan et al. 1991). These differences may also contribute to the functional differences between intravenous and intraperitoneal cocaine observed in the present study.

Both intravenous and intraperitoneal cocaine administration, however, increase the concentration of extracellular dopamine in the nucleus accumbens (Bradberry and Roth 1989; Pettit and Justice 1989; Kuczenski et al. 1991; Pan et al. 1991). The present data suggest that increases in dopamine concentrations alone are not sufficient to produce measurable metabolic changes in this structure in all cases. Dopamine increases, however, do appear to be sufficient to produce transynaptic increases in functional activity in brain regions which receive efferent projections from the accumbens, e.g. pallidum and substantia nigra reticulata. The increased metabolic rates seen following intravenous cocaine are thus likely to be the result of changes in inputs to the nucleus accumbens other than the dopaminergic inputs from the ventral tegmental area or from changes in intrinsic activity within the accumbens itself.

Pharmacokinetics also play an important role in determining the behavioral effects of cocaine. Differences in the effectiveness of the administration by various routes have been documented in a number of studies which in general have shown that higher doses of cocaine administered by routes such as oral or intragastric, that lead to slow absorption, have been required to produce equivalent effects on behavior as compared to routes associated with more rapid absorption. Intraperitoneal cocaine, for example, was approximately two to three times more potent than intragastric cocaine in suppressing food intake in rats (Bedford et al. 1980; Downs et al. 1980; Foltin et al. 1983; Vee et al. 1983;). Similarly, cocaine administered by the intraperitoneal route was more effective than intragastric cocaine in stimulating locomotor activity (Lau et al. 1991), and the intragastric route more effective than subcutaneous administration (Dow-Edwards et al. 1989).

Few studies, however, have directly compared the intravenous route to other routes. In one such study, Nomikos and Spyraki (1988) examined the influence of route of administration on the development of cocaine-induced conditioned place preferences in rats. They found that preference developed rapidly for an environment paired with cocaine administered intravenously, but that higher doses and twice the number of training trials were needed before preference for an environment paired with intraperitoneal cocaine was induced. Furthermore, the preference that developed for the environment paired with intraperitoneal cocaine appeared to be far less robust than for intravenous cocaine. Thus, the development of preference with intraperitoneal cocaine was highly dependent not only on the drug, but also on other procedural variables such as the rats' environmental preference prior to training and the number of pairings. The characteristic patterns of glucose utilization changes associated with the two routes seen in the present study, particularly within the nucleus accumbens, provide a neurochemical basis for these behavioral differences. Nomikos and Spyraki (1988) further concluded that conditioned place preference with intraperitoneal cocaine, in contrast to preference with intravenous cocaine, may *not* reflect the rewarding properties of the drug, but may result from the pairing of the environment with other effects of cocaine. Again, this is consistent with the lack of activation with intraperitoneal administration of the nucleus accumbens an area implicated in the mediation of the rewarding properties of cocaine (Roberts et al. 1977, 1980).

In summary, given the range of doses and post-treatment time points tested, the cerebral metabolic consequences of cocaine administration have been shown to be dependent on the route of administration. Structures within the mesocorticolimbic system, in particular the nucleus accumbens and olfactory tubercle, were activated only when cocaine was administered intravenously. Activation following acute intraperitoneal cocaine was restricted to structures involved in the production of movement. These data therefore demonstrate the importance of pharmacokinetics as a determinant of the functional effects of cocaine. Effects observed with one route of administration do not necessarily apply to other routes or paradigms and broad generalizations cannot be made on the basis of data obtained with a single route of administration, particularly with respect to the rewarding effects of cocaine. Although these data relate only to cocaine, similar findings may obtain with other drugs as well.

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References

Balster RL, Schuster CR (1973) Fixed-interval schedule of cocaine reinforcement: effect of dose and infusion duration. J Exp Anal Behav 20:119–129

Bedford JA, Lovell DK, Turner CE, Elsolly MA, Wilson MC (1980) The anorexic and actometric effects of cocaine and two coca extracts. Pharmacol Biochem Behav 13:403–408

Bradberry CW, Roth RH (1989) Cocaine increases extracellular dopamine in rat nucleus accumbens and ventral tegmental area as shown by in vivo microdialysis. Neurosci Lett 103:97–102

Chow MJ, Ambre JJ, Ruo TI, Atkinson AJ Jr, Bowsher DJ, Fischman MW (1985) Kinetics of cocaine distribution, elimination, and chronotropic effects. Clin Pharmacol Ther 38:318–324

Crane AM, Porrino LJ (1989) Adaptation of the quantitative 2-[^{14}C]deoxyglucose method for use in freely moving rats. Brain Res 499:87–92

Dow-Edwards DL, Fico TA, Osman M, Gamagaris Z, Hutchings DE (1989) Comparison of oral and subcutaneous routes of cocaine administration on behavior, plasma drug concentration and toxicity in female rats. Pharmacol Biochem Behav 33:167–173

Downs DA, Miller LE, Wiley JN, Johnston DE (1980) Oral vs parenteral drug effects of schedule-controlled behavior in rhesus monkeys. Life Sci 26:1163–1168

Fischman MW (1988) Behavioral pharmacology of cocaine. J Clin Psychiatry 49:7–10

Fischman MW, Schuster CR, Rosnekov L, Shick JFE, Krasnegor NA, Fennel W, Freedman DX (1976) Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch Gen Psychiatry 33:983–990

Foltin RW, Woolverton WL, Schuster CR (1983) Effects of psychomotor stimulants, alone and in pairs, on milk drinking in the rat after intraperitoneal and intragastric administration. J Pharmacol Exp Ther 226:411–418

Heikkila RE, Cabbot FS, Manzino L, Duvoisin RC (1979) Rotational behavior induced by cocaine analogs in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra: dependence upon dopamine uptake inhibition. J Pharmacol Exp Ther 211:189–194

Hertting G, Axelrod J, Whitby LG (1961) Effect of drugs on the uptake and metabolism of ^{3}H-norepinephrine. J Pharmacol Exp Ther 134:146–153

Javaid JI, Fischman MW, Schuster CR, Dekirmenjian H, Davis JM (1978) Cocaine plasma concentration: relation to physiological and subjective effects in humans. Science 202:227–228

Johanson C-E, Fischman MW (1989) The pharmacology of cocaine related to its abuse. Pharmacol Rev 41:3–52

Koob GF, Goeders NE (1989) Neuroanatomical substrates of drug self-administration. In: Liebman JM, Cooper SJ (eds) The neuropharmacological basis of reward. Clarendon, Oxford, pp 139–156

Kuczenski R, Segal DS, Aizenstein ML (1991) Amphetamine, cocaine, and fencamfamine: relationship between locomotor and stereotypy response profiles and caudate and accumbens dopamine dynamics. J Neurosci 11:2703–2712

Lau CE, Imam A, Ma F, Falk JL (1991) Acute effects of cocaine on spontaneous and discriminative motor functions: relation to route of administration and pharmacokinetics. J Pharmacol Exp Ther 257:444–456

London ED, Wilkerson G, Goldberg SR, Risner ME (1986) Effects of L-cocaine on local cerebral glucose utilization in the rat. Neurosci Lett 68:73–78

Moore KE, Chiueh CC, Zeldes G (1977) Release of neurotransmitters from the brain in vivo by amphetamine, methylphenidate and cocaine. In: Ellinwood EH, Kilbey MM (eds) Cocaine and other stimulants. Plenum, New York, pp 143–160

Nayak PK, Misra AL, Mulé (1976) Physiological disposition and biotransformation of [^{3}H]cocaine in acutely and chronically treated rats. J Pharmacol Exp Ther 196:556–569

Nomikos GG, Spyraki C (1988) Cocaine-induced place conditioning: importance of route of administration and other procedural variables. Psychopharmacology 94:119–125

Pan H-T, Menacherry S, Justice JB Jr (1991) Differences in the pharmacokinetics of cocaine in naive and cocaine-experienced rats. J Neurochem 56:1299–1306

Paxinos G, Watson C (1982) The rat brain in stereotaxic coordinates. Academic, New York

Pettit HO, Justice HB Jr (1989) Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. Pharmacol Biochem Behav 34:899–904

Pettit HO, Pan H-T, Parsons LH, Justice JB Jr (1990) Extracellular concentrations of cocaine and dopamine are enhanced during chronic cocaine administration. J Neurochem 55:798–804

Porrino LJ, Domer FR, Crane AM, Sokoloff L (1988) Selective alterations in cerebral metabolism within the mesocorticolimbic dopaminergic system produced by acute cocaine administration in rats. Neuropsychopharmacology 1:109–118

Resnick RB, Kestenbaum RS, Schwartz LK (1977) Acute systemic effects of cocaine in man: a controlled study by intranasal and intravenous routes. Science 195:696–698

Ritchie JM, Greene NM (1980) Local anesthetics. In: Goodman LS, Gilman A (eds) The pharmacological basis of therapeutics. Macmillan, Toronto, pp 300–320

Roberts DCS, Corcoran ME, Fibiger HC (1977) On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacol Biochem Behav 6:615–620

Roberts DCS, Koob GF, Klonoff P, Fibiger HC (1980) Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacol Biochem Behav 12:781–878

Ross SF, Renyi AL (1967) Inhibition of the uptake of tritiated catecholamines by antidepressants and related agents. Eur J Pharmacol 2:181–186

Sharkey J, McBean DE, Kelly PAT (1991) Acute cocaine administration: effects on local cerebral blood flow and metabolic demand in the rat. Brain Res 548:310–314

Shuster L (1992) Pharmacokinetics, metabolism and disposition of cocaine. In: Lakowski JM, Galloway MP, White FJ (eds) Cocaine: pharmacology, physiology, and clinical strategies. CRC Press, Boca Raton, pp 1–14

Sokoloff L, Reivich M, Kennedy C, DesRosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M (1977) The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure and normal values in the conscious and anesthetized albino rat. J Neurochem 28:897–916

Van Dyke C, Barash PG, Jatlow P, Byck R (1976) Cocaine plasma concentrations after intranasal application in man. Science 191:859–861

Van Dyke C, Jatlow PF, Ungerer J, Barash PG, Byck R. (1978) Oral cocaine: plasma concentrations and central effects. Science 200:211–213

Vee GL, Fink GB, Constantine GH Jr (1983) Anorexic activity of cocaine and coca extract in naive and cocaine tolerant rats. Pharmacol Biochem Behav 18:515–517

Wiggins RC, Rolsten C, Ruiz B, Davis CM (1989) Pharmacokinetics of cocaine: basic studies of route, dosage, pregnancy and lactation. Neurotoxicology 10:367–382

Wilkinson P, Van Dyke C, Jatlow P, Barash P, Byck R (1980) Intranasal and oral cocaine kinetics. Clin Pharmacol Ther 27:386–394