Gradual Tolerance of Metabolic Activity Is Produced in Mesolimbic Regions by Chronic Cocaine Treatment, while Subsequent Cocaine Challenge Activates Extrapyramidal Regions of Rat Brain

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Acute administration of cocaine is known to enhance extracellular dopamine levels in the striatum and to activate immediate-early gene expression in striatal neurons. Regional cerebral metabolic rate for glucose (rCMR_{glc}) reportedly increases in extrapyramidal and mesolimbic brain regions in response to acute cocaine treatment. However, chronic administration attenuates the cocaine-induced enhancement of regional dopamine response and the induction of immediate-early gene expression in these regions. Chronic treatment also produces tolerance to cocaine's reinforcing effects. Thus, differential responses to cocaine occur with increasing length of treatment. Therefore, we examined the time course of effects of repeated daily cocaine treatment on rCMR_{glc} in rat brain. Acute administration of 10 mg/kg cocaine slightly increased rCMR_{glc} in mesolimbic and extrapyramidal regions. However, no significant effects were observed until more than 7 d of treatment, whereupon rCMR_{glc} was reduced compared to saline treatment in the infralimbic portion of the medial prefrontal cortex, nucleus accumbens, olfactory tubercle, habenula, amygdala, and a few other brain regions. In contrast, after 13 d of 10 mg/kg cocaine treatment, challenge with 30 mg/kg cocaine increased rCMR_{glc} in the striatum, globus pallidus, entopeduncular nucleus, subthalamus, substantia nigra pars reticulata, and a few other regions without affecting limbic or mesolimbic regions. Thus, repeated daily treatment with a low dose of cocaine gradually decreased metabolic activity particularly in mesolimbic regions. Subsequent treatment with a higher dose produced metabolic activation mostly in extrapyramidal regions. This effect of chronic treatment could represent tolerance to the initial metabolic response, which can be replicated thereafter but only by increasing the drug dose. These results suggest that tolerance to the metabolic effects of cocaine in selective mesolimbic circuits may contribute to the development of behavioral dependence with repeated exposure.

[Key words: chronic cocaine, 2-deoxyglucose, regional cerebral metabolic rate, psychostimulant activation, tolerance, dependence]

Chronic cocaine exposure produces various behavioral, neurochemical, and pharmacological alterations in rodent brain. Repeated administration produces sensitization of locomotor response to subsequent cocaine treatment (Kalivas et al., 1988; Weiss et al., 1989), which is related to the enhancement of extracellular dopamine levels in the nucleus accumbens (NAc) produced by cocaine (Kalivas et al., 1988; Hurd et al., 1989; Pettit and Justice, 1989). However, chronic treatment attenuates NAc dopamine response compared to that produced by acute cocaine treatment (Hurd et al., 1989), even in the presence of locomotor sensitization (Segal and Kuczenski, 1992; Kalivas and Duffy, 1993). Furthermore, immediate-early gene induction in NAc neurons is desensitized by chronic cocaine treatment compared to acute treatment (Hope et al., 1992). Thus, certain biochemical parameters *decrease* following chronic cocaine exposure.

Acute cocaine treatment increases metabolic activity in various extrapyramidal (London et al., 1986; London, 1990) and mesolimbic (Porrino et al., 1988; Kornetsky et al., 1991) regions of rat brain, which is likely due to cocaine-induced alteration of dopaminergic activity (McCulloch et al., 1982; Trugman and James, 1993). In contrast, regional metabolism is *reduced* during withdrawal following chronic cocaine administration (Clow and Hammer, 1991; Hammer et al., 1993). In addition, recent positron emission tomographic studies of cerebral metabolism (London et al., 1990) and blood flow (Pearlson et al., 1993) in human cocaine abusers demonstrate regional reductions following cocaine administration. Thus, it is possible that cocaine treatment produces different effects in chronically treated animals from those observed in naive animals (as used in acute drug trials). Therefore, we examined the time course of regional metabolic response following repeated daily cocaine treatment using the quantitative ¹⁴C-2-deoxyglucose (2DG) autoradiographic procedure (Sokoloff et al., 1977).

Recent studies have shown that chronic treatment with or self-administration of cocaine increased the frequency of subsequent cocaine self-administration (Emmett-Oglesby et al., 1993) as well as the dose required to support self-administration (Emmett-Oglesby and Lane, 1992), suggesting the development of tolerance to the reinforcing efficacy of the drug. If regional metabolic response following chronic cocaine treatment does differ from the response in naive animals due to the develop-

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ment of tolerance, then a higher dose might activate the affected brain circuits, thereby replicating the initial metabolic response. Therefore, the effect of challenge with a high cocaine dose on regional metabolic response was examined in chronically treated rats.

The results demonstrate that chronic cocaine treatment reduces regional metabolic response primarily in mesolimbic regions of the rodent brain. Furthermore, subsequent challenge with a higher dose of cocaine selectively activates extrapyramidal, but not mesolimbic regions. This suggests that cellular activity in specific circuits is reduced following chronic cocaine treatment. Acute effects can be reproduced thereafter, but only upon administration of a higher cocaine dose. Such effects on selective brain circuits might underlie the development of dependence in response to chronic cocaine exposure.

Materials and Methods

Subjects. Male Sprague–Dawley rats (Simonsen, Gilroy, CA), weighing 250–325 gm at the time of treatment, were housed individually in suspended metal cages in light- (on from 0600–2000 hr) and temperature- (23°C) controlled rooms with ad libitum access to food and water. Animals were allowed to acclimate to these conditions for at least 4 d, after which they were randomly placed into one of six groups in experiment 1, or one of three groups in experiment 2. All studies were carried out in accord with the policies of the *Guide for the Care and Use of Laboratory Animals* (NIH Publication NIH860-23), and were approved by the University of Hawaii Institutional Animal Care and Use Committee.

Treatment paradigm in experiment 1. Animals were weighed and treated daily for 14 d with an intraperitoneal injection (1 ml/kg) of either 0.9% saline vehicle or 10 mg/kg cocaine HCl administered between 1100 and 1200 hr. Animals received either daily saline injections or cocaine injections on the last 1, 3, 7, 10, or 14 d of treatment after initial daily injections of saline.

Treatment paradigm in experiment 2. Animals were weighed daily and received intraperitoneal injections (1 ml/kg) of either saline or cocaine for 14 d. Cocaine treatment groups received 10 mg/kg on each of the first 13 d followed on the last day by either 10 mg/kg or 30 mg/kg. Thus, the saline and 10 mg/kg daily cocaine groups replicated these treatment groups in experiment 1.

2-Deoxyglucose autoradiographic procedures. On the final day of the experiment, animals were anesthetized with halothane, and femoral arterial and venous cannulas were implanted and passed subcutaneously to exit through a small incision on the back. During this procedure, the femoral nerve was carefully preserved to ensure competent motor performance in the affected limb. The 2DG procedure was then performed on freely moving rats as previously described (Crane and Porrino, 1989). Animals were allowed to recover for at least 4 hr, after which the final dose of cocaine or saline was administered. The rats were then placed into a novel environment (shoebox cage lined with benchtop paper), and arterial samples were taken to determine hematocrit and baseline plasma glucose values. Ten minutes after drug treatment, a pulse of ^{14}C -2DG (125 $\mu\text{Ci/kg}$; American Radiolabeled Chemicals, St. Louis, MO) was injected intravenously and timed arterial samples were collected during a 45 min period. Blood pressure was monitored 5 min after 2DG injection. Locomotor behavior was observed and qualitatively assessed during this period, although no quantitative measurements were accomplished. Animals were then given a lethal intravenous injection of 65 mg/kg sodium pentobarbital, and brains were rapidly removed and frozen in -30°C 2-methylbutane. Blood samples were centrifuged and plasma glucose and deoxyglucose values were determined using a glucose analyzer and liquid scintillation spectroscopy, respectively. Brains were sectioned in a -17°C cryostat, and sections were mounted on coverslips that were dried on a 60°C hot plate. Coverslips were mounted on cardboard and apposed to x-ray film (EMC-1, Kodak) together with calibrated acrylic ^{14}C radiostandards (American Radiolabeled Chemicals, St. Louis, MO). Films were developed 12 d later using GBX developer and fixer (Kodak). Autoradiographs were utilized only if optimal labeling (e.g., no visible diffusion of 2DG label and good contrast for regional identification) was present.

The resulting autoradiographs were analyzed using specialized image

analysis software (IMAGE-mg; Wayne Rasband, Gunter Mies; NIMH, Bethesda, MD) on a Macintosh IIfx computer with a frame grabber board (Data Translation, Marlboro, MA) interfaced to a Sony XC-77 CCD camera on a DC-stabilized light table. Regional identification was accomplished when required by superimposing the image of the Nissl-stained section upon its corresponding autoradiograph. Calibrated regional optical density values were measured in 61 individual regions in experiment 1, and 66 regions in experiment 2. Regional cerebral metabolic rate for glucose (rCMR_{glc}) was calculated using the measured values for both plasma ^{14}C -2DG and glucose concentration, the published constants derived using the operational equation of Sokoloff (Sokoloff et al., 1977), and the calibrated regional optical density values.

rCMR_{glc} results from experiment 1 were compared across treatment groups using one-way analysis of variance to examine the main effect of length of cocaine treatment followed by Newman–Keuls post hoc comparisons where appropriate to determine the loci of the effect. In experiment 2, treatment groups were compared using Duncan's multiple range test. The results were determined to be significantly different if $p \leq 0.05$ in all comparisons.

Results

Length of cocaine treatment

Acute cocaine treatment produced a slight but nonsignificant increase of rCMR_{glc} in various regions, especially in structures of the mesolimbic forebrain (Table 1). Additional treatment produced little alteration from control values until 10 consecutive days of treatment (Fig. 1), after which rCMR_{glc} was significantly reduced compared to saline or acute cocaine treatment in the NAc, olfactory tubercle (OT), and piriform cortex (PC). rCMR_{glc} was significantly reduced compared to acute cocaine treatment in the basolateral nucleus of the amygdala (ABL). After 14 d of cocaine treatment, rCMR_{glc} was significantly reduced compared to saline or acute cocaine treatment in the NAc, ABL, PC, as well as the ventromedial caudatoputamen (CP) and cingulate cortex. At this time point, rCMR_{glc} in the OT was significantly reduced compared to acute cocaine treatment. Each of the above regions displayed significant main effects of length of cocaine treatment. No alterations were observed in white matter, as measured in the corpus callosum.

In the test environment, animals were observed to be more active following acute cocaine treatment than after any other treatment examined. Following 3 d or more of cocaine treatment, animals reacted similarly to those receiving saline treatment.

Effect of repeated cocaine treatment and subsequent challenge with a higher dose

Repeated treatment with 10 mg/kg cocaine for 14 d, again, significantly reduced rCMR_{glc} compared to chronic saline treatment in NAc, OT, CP, PC, and amygdala, as well as in the infralimbic portion of the medial prefrontal cortex (MPf_{il}), substantia nigra pars compacta (SNc), habenula, locus ceruleus (LC), and a few other brain regions (Table 2). No significant alterations were observed in white matter.

When 30 mg/kg cocaine was administered on the final treatment day, rCMR_{glc} remained significantly lower compared to chronic saline treatment in some brain regions, including the MPf_{il} , lateral habenula (LH), inferior colliculus, and superior olive. In contrast, rCMR_{glc} increased significantly compared to intermittent treatment with 10 mg/kg cocaine in the CP, globus pallidus (GP), entopeduncular nucleus (EP), subthalamus (STh), substantia nigra pars reticulata (SNr), somatosensory and motor cortices, periaqueductal gray matter (PAG), and LC. This effect was significantly different compared to chronic saline treatment only in the GP, STh, and SNr (Fig. 2).

Figure 1. Regional metabolic effects of repeated daily 10 mg/kg cocaine treatment are dependent upon the length of treatment. Autoradiographs are from sections taken through the rostral portion of the nucleus accumbens (NA) at 1.2 mm anterior to bregma (Paxinos and Watson, 1986). *A*, Saline treatment for 14 d. *B*, Acute cocaine treatment (1 d cocaine following 13 d saline treatment). *C*, Three days cocaine (following 11 d saline treatment). *D*, Seven days cocaine (following 7 d saline treatment). *E*, Ten days cocaine (following 4 d saline treatment). *F*, Fourteen days cocaine treatment. $rCMR_{glc}$ increases slightly with acute treatment (*B*), returns to normal after 3 or 7 d treatment (*C* and *D*), and thereafter decreases significantly in both NA core (*c*) and shell (*s*), as well as in olfactory tubercle (*ot*) and part of the caudatoputamen (*cp*) after 10 and 14 d treatment (*E* and *F*).

Chronic treatment with 10 mg/kg cocaine produced similar locomotor behavior to that observed following saline treatment. In contrast, locomotor activity substantially increased after treatment with 30 mg/kg cocaine on the final treatment day.

Discussion

Effects of chronic cocaine treatment

Cocaine binds to catecholamine transporters, thereby blocking reuptake and increasing extracellular transmitter levels in terminal regions. Thus, acute cocaine treatment in naive rats dramatically elevates extracellular dopamine levels in the NAc (Hurd et al., 1989; Pettit and Justice, 1989). The reinforcing efficacy of cocaine is probably due to its effect on dopamine transporters (Ritz et al., 1987) in the NAc (Roberts et al., 1980). However, the effects of chronic treatment are different from those of acute treatment. For example, the extracellular dopamine response in the NAc is attenuated compared to that produced by acute

cocaine exposure (Hurd et al., 1989), even in the presence of locomotor sensitization (Segal and Kuczenski, 1992; Kalivas and Duffy, 1993). Such attenuated dopamine response to cocaine after chronic exposure could represent a neurochemical manifestation of tolerance.

Chronic treatment also produced tolerance to the reinforcing efficacy of cocaine, whereby repeated exposure increased the rate of self-administration and the threshold dose required to support self-administration in rats (Emmett-Oglesby and Lane, 1992; Emmett-Oglesby et al., 1993). Continuous cocaine infusion produced the same effect in rhesus monkeys (Woolverton and Kleven, 1988); however, differential behavioral responses to continuous and intermittent cocaine treatment have been observed in rats (King et al., 1992) and mice (Reith et al., 1987). Such a behavioral demonstration of tolerance could result from a physiological condition of dependence.

Continuous cocaine treatment also produced tolerance to the

Figure 2. Challenge with 30 mg/kg cocaine following chronic treatment increases $rCMR_{glc}$ in extrapyramidal efferent regions. Autoradiographs in *A–C* illustrate the entopeduncular nucleus (*ep*) and the adjacent lateral hypothalamus (*lh*) at 2.3 mm posterior to bregma (Paxinos and Watson, 1986), while *D–F* show the substantia nigra pars reticulata (*snr*) at 5.6 mm posterior to bregma (Paxinos and Watson, 1986). Compare the autoradiographs produced following saline treatment (*A* and *D*) to those produced after chronic daily 10 mg/kg cocaine treatment following either 10 mg/kg (*B* and *E*) or 30 mg/kg (*C* and *F*) administered on the final treatment day. $rCMR_{glc}$ in the entopeduncular nucleus and substantia nigra pars reticulata increase significantly after challenge with 30 mg/kg cocaine.

Table 1. Regional cerebral metabolic rate ($\mu\text{mol}/100\text{ gm}/\text{min}$ glucose $\pm$ SEM) following 14 daily injections of saline vehicle or 10 mg/kg cocaine on the final 1, 3, 7, 10 or 14 treatment days

Brain region	14 days saline (<i>n</i> = 5)	Acute cocaine (<i>n</i> = 5)	3 days cocaine (<i>n</i> = 6)	7 days cocaine (<i>n</i> = 5)	10 days cocaine (<i>n</i> = 4)	14 days cocaine (<i>n</i> = 3)
Mesolimbic structures						
Medial prefrontal cortex	101.2 $\pm$ 3.0	99.2 $\pm$ 7.4	94.2 $\pm$ 7.4	108.2 $\pm$ 4.1	82.7 $\pm$ 11.9	80.7 $\pm$ 12.0
Nucleus accumbens, rostral pole	92.8 $\pm$ 4.3	81.7 $\pm$ 2.9	84.7 $\pm$ 5.9	95.0 $\pm$ 6.4	78.7 $\pm$ 10.6	71.3 $\pm$ 13.7
Nucleus accumbens, core (rostral)	82.8 $\pm$ 3.4	90.6 $\pm$ 3.6	83.2 $\pm$ 6.0	84.2 $\pm$ 4.4	62.0 $\pm$ 7.4*†	68.7 $\pm$ 9.5*†
Nucleus accumbens, core (caudal)	78.6 $\pm$ 3.1	90.6 $\pm$ 7.0	81.7 $\pm$ 4.9	87.6 $\pm$ 6.5	65.5 $\pm$ 9.2	62.7 $\pm$ 14.5
Nucleus accumbens, shell (rostral)	76.8 $\pm$ 3.9	86.8 $\pm$ 2.1	79.8 $\pm$ 5.9	80.2 $\pm$ 3.8	60.0 $\pm$ 6.7*†	65.3 $\pm$ 10.1*†
Nucleus accumbens, shell (caudal)	69.4 $\pm$ 1.9	73.0 $\pm$ 4.6	69.2 $\pm$ 5.6	71.4 $\pm$ 5.2	57.2 $\pm$ 6.5*†	56.3 $\pm$ 9.3
Olfactory tubercle (rostral)	100.4 $\pm$ 3.8	96.3 $\pm$ 4.8	98.8 $\pm$ 7.2	109.6 $\pm$ 4.0	82.7 $\pm$ 13.1	89.0 $\pm$ 14.0
Olfactory tubercle (mid)	87.4 $\pm$ 5.6	94.2 $\pm$ 2.5	89.3 $\pm$ 7.0	94.6 $\pm$ 4.4	65.7 $\pm$ 9.7*†	77.0 $\pm$ 7.0†
Olfactory tubercle (caudal)	81.0 $\pm$ 3.4	92.0 $\pm$ 8.6	89.7 $\pm$ 5.3	90.0 $\pm$ 7.1	65.5 $\pm$ 8.5	71.3 $\pm$ 5.9
Islands of Calleja (rostral)	97.4 $\pm$ 4.3	97.7 $\pm$ 5.0	100.6 $\pm$ 9.2	107.2 $\pm$ 4.5	79.7 $\pm$ 13.3	87.3 $\pm$ 10.4
Islands of Calleja (caudal)	80.6 $\pm$ 4.8	89.5 $\pm$ 1.8	86.0 $\pm$ 8.1	88.2 $\pm$ 4.9	64.7 $\pm$ 11.0	75.7 $\pm$ 5.5
Ventral tegmental area	76.6 $\pm$ 2.9	73.0 $\pm$ 3.9	78.0 $\pm$ 5.3	78.6 $\pm$ 5.3	60.7 $\pm$ 7.1	70.0 $\pm$ 6.5
Extrapyramidal structures						
Caudatoputamen, dorlat. (rostral)	115.6 $\pm$ 4.6	116.0 $\pm$ 4.9	114.5 $\pm$ 8.5	120.2 $\pm$ 5.9	94.7 $\pm$ 11.1	80.5 $\pm$ 9.7
CP, dorsolateral (mid)	113.4 $\pm$ 3.1	119.4 $\pm$ 7.6	115.2 $\pm$ 8.8	125.0 $\pm$ 8.6	98.2 $\pm$ 13.4	80.5 $\pm$ 9.6
CP, dorsolateral (caudal)	104.8 $\pm$ 2.4	108.2 $\pm$ 13.5	109.2 $\pm$ 8.7	110.0 $\pm$ 7.3	96.5 $\pm$ 10.7	68.0 $\pm$ 9.4
CP, ventromedial (rostral)	110.6 $\pm$ 5.5	111.0 $\pm$ 5.0	109.3 $\pm$ 7.9	113.6 $\pm$ 7.1	88.7 $\pm$ 10.8	71.5 $\pm$ 10.1*†
CP, ventromedial (mid)	108.4 $\pm$ 3.2	114.8 $\pm$ 8.4	106.0 $\pm$ 10.3	117.2 $\pm$ 7.8	90.2 $\pm$ 13.1	71.0 $\pm$ 12.2
CP, ventromedial (caudal)	91.2 $\pm$ 4.3	90.2 $\pm$ 10.2	92.5 $\pm$ 7.1	92.5 $\pm$ 6.7	62.5 $\pm$ 9.5	47.0 $\pm$ 14.0
Globus pallidus	69.0 $\pm$ 4.0	70.0 $\pm$ 3.6	74.3 $\pm$ 6.5	76.0 $\pm$ 9.1	62.5 $\pm$ 9.5	47.0 $\pm$ 14.0
Entopeduncular nucleus	70.8 $\pm$ 2.7	82.0 $\pm$ 5.5	74.7 $\pm$ 6.4	81.8 $\pm$ 6.9	62.2 $\pm$ 6.3	70.0 $\pm$ 11.2
Subthalamus	96.4 $\pm$ 2.6	93.4 $\pm$ 8.9	103.2 $\pm$ 10.3	101.2 $\pm$ 7.2	88.2 $\pm$ 10.7	74.0 $\pm$ 10.5
Substantia nigra pars compacta	64.4 $\pm$ 4.1	70.2 $\pm$ 4.6	72.0 $\pm$ 5.7	72.2 $\pm$ 3.6	59.5 $\pm$ 6.3	63.7 $\pm$ 11.1
Substantia nigra pars reticulata	78.0 $\pm$ 2.7	76.4 $\pm$ 4.5	80.2 $\pm$ 5.9	80.2 $\pm$ 4.0	63.2 $\pm$ 6.0	67.0 $\pm$ 15.5
Diencephalic structures						
Medial habenula	84.2 $\pm$ 2.4	78.8 $\pm$ 3.6	81.0 $\pm$ 7.5	79.8 $\pm$ 5.9	66.0 $\pm$ 9.3	67.3 $\pm$ 9.6
Lateral habenula (medial)	96.8 $\pm$ 3.3	86.2 $\pm$ 4.6	89.3 $\pm$ 7.4	87.6 $\pm$ 5.7	76.2 $\pm$ 9.9	75.3 $\pm$ 11.8
Lateral habenula (lateral)	107.6 $\pm$ 3.0	97.0 $\pm$ 6.9	99.8 $\pm$ 7.8	98.8 $\pm$ 6.8	84.7 $\pm$ 10.7	76.0 $\pm$ 11.5
Ventral thalamus (VPM/VPL)	96.6 $\pm$ 6.7	97.2 $\pm$ 5.7	103.2 $\pm$ 8.8	108.6 $\pm$ 8.1	86.3 $\pm$ 14.8	89.7 $\pm$ 15.1
Laterodorsal thalamus	107.0 $\pm$ 3.9	114.6 $\pm$ 8.8	115.5 $\pm$ 10.4	125.2 $\pm$ 7.5	90.5 $\pm$ 14.4	91.7 $\pm$ 12.4
Dorsomedial thalamus	115.2 $\pm$ 4.2	128.2 $\pm$ 7.0	130.5 $\pm$ 11.0	132.0 $\pm$ 8.7	109.5 $\pm$ 15.2	96.0 $\pm$ 16.6
Ventral pallidum (whole)	65.8 $\pm$ 3.4	69.2 $\pm$ 7.9	64.0 $\pm$ 4.0	71.2 $\pm$ 6.8	58.2 $\pm$ 7.2	55.0 $\pm$ 11.9
Substantia innominata	64.0 $\pm$ 3.8	63.2 $\pm$ 4.8	62.5 $\pm$ 5.0	66.2 $\pm$ 8.2	54.0 $\pm$ 8.2	47.5 $\pm$ 2.5
Medial preoptic area	58.2 $\pm$ 3.5	57.0 $\pm$ 5.7	54.7 $\pm$ 5.0	53.4 $\pm$ 4.8	45.2 $\pm$ 6.4	46.0 $\pm$ 5.0
Lateral preoptic area	71.8 $\pm$ 3.5	75.2 $\pm$ 5.8	70.8 $\pm$ 5.6	77.2 $\pm$ 8.1	57.2 $\pm$ 7.5	53.0 $\pm$ 9.3
Lateral hypothalamus (rostral)	73.0 $\pm$ 0.5	76.2 $\pm$ 4.7	69.7 $\pm$ 4.8	76.0 $\pm$ 6.4	57.5 $\pm$ 6.2	66.3 $\pm$ 5.2
Lateral hypothalamus (caudal)	70.0 $\pm$ 2.0	69.8 $\pm$ 5.0	69.8 $\pm$ 6.6	72.4 $\pm$ 5.2	59.2 $\pm$ 8.0	50.0 $\pm$ 12.8
Arcuate nucleus	50.5 $\pm$ 4.9	50.4 $\pm$ 3.9	46.5 $\pm$ 4.8	54.5 $\pm$ 6.3	37.7 $\pm$ 3.8	50.7 $\pm$ 2.7
Limbic regions						
Medial septal nucleus	89.2 $\pm$ 1.8	77.0 $\pm$ 11.6	86.2 $\pm$ 6.0	81.7 $\pm$ 6.6	67.7 $\pm$ 6.6	57.7 $\pm$ 12.4
Lateral septal nucleus	53.6 $\pm$ 2.4	56.7 $\pm$ 8.6	55.2 $\pm$ 4.6	57.6 $\pm$ 3.8	49.5 $\pm$ 6.6	48.7 $\pm$ 7.0
Basolateral amygdala	89.0 $\pm$ 2.7	97.2 $\pm$ 5.6	90.8 $\pm$ 7.9	92.6 $\pm$ 6.7	71.0 $\pm$ 8.4†	58.0 $\pm$ 9.9*†
Central amygdala	60.0 $\pm$ 2.3	65.2 $\pm$ 3.8	58.5 $\pm$ 4.8	61.8 $\pm$ 6.3	48.2 $\pm$ 5.4	52.5 $\pm$ 8.5
Piriform cortex (rostral)	119.0 $\pm$ 5.4	113.0 $\pm$ 5.1	123.0 $\pm$ 10.1	130.6 $\pm$ 9.5	101.2 $\pm$ 15.3	99.0 $\pm$ 11.3
Piriform cortex (mid)	117.2 $\pm$ 8.0	120.8 $\pm$ 5.7	116.3 $\pm$ 7.3	123.4 $\pm$ 8.5	85.5 $\pm$ 12.1*†	92.6 $\pm$ 10.0*†
Piriform cortex (caudal)	108.2 $\pm$ 4.4	120.6 $\pm$ 6.1	115.2 $\pm$ 6.5	127.8 $\pm$ 10.0	87.0 $\pm$ 13.3	88.3 $\pm$ 17.7
Cingulate cortex (rostral)	103.2 $\pm$ 4.8	100.8 $\pm$ 4.6	99.2 $\pm$ 6.7	107.2 $\pm$ 6.1	83.5 $\pm$ 11.4	66.0 $\pm$ 12.4*†
Cingulate cortex (caudal)	100.2 $\pm$ 3.5	100.2 $\pm$ 7.1	97.3 $\pm$ 7.3	105.8 $\pm$ 7.5	82.5 $\pm$ 13.0	77.0 $\pm$ 13.1
Entorhinal cortex (superficial)	81.8 $\pm$ 6.7	77.5 $\pm$ 4.8	88.2 $\pm$ 6.5	76.0 $\pm$ 5.7	62.7 $\pm$ 9.3	78.0 $\pm$ 4.5
Entorhinal cortex (deep)	87.0 $\pm$ 9.1	87.2 $\pm$ 5.7	92.8 $\pm$ 7.9	74.2 $\pm$ 3.6	67.7 $\pm$ 8.7	78.0 $\pm$ 6.7
Cortical regions						
Agranular motor cortex	95.8 $\pm$ 3.4	104.0 $\pm$ 8.4	102.5 $\pm$ 6.4	106.2 $\pm$ 6.3	78.7 $\pm$ 10.1	72.0 $\pm$ 9.4
Somatosensory cortex	97.4 $\pm$ 3.5	99.8 $\pm$ 7.7	100.0 $\pm$ 7.2	105.2 $\pm$ 7.9	79.2 $\pm$ 10.8	71.0 $\pm$ 8.0
Visual cortex	103.4 $\pm$ 5.1	101.4 $\pm$ 7.4	103.5 $\pm$ 8.1	105.4 $\pm$ 4.8	90.7 $\pm$ 11.0	78.5 $\pm$ 13.5
Auditory cortex	138.8 $\pm$ 10.4	136.8 $\pm$ 7.5	134.5 $\pm$ 11.4	138.2 $\pm$ 11.6	110.7 $\pm$ 14.1	114.0 $\pm$ 7.1

Table 1. Continued.

Brain region	14 days saline (n = 5)	Acute cocaine (n = 5)	3 days cocaine (n = 6)	7 days cocaine (n = 5)	10 days cocaine (n = 4)	14 days cocaine (n = 3)
Brainstem and other regions						
Medial geniculate nucleus	122.0 ± 4.9	120.6 ± 9.2	117.2 ± 9.8	121.4 ± 7.6	98.5 ± 10.4	92.7 ± 14.5
Periaqueductal gray matter	75.6 ± 4.3	80.4 ± 4.6	78.2 ± 5.8	82.2 ± 6.2	66.7 ± 8.7	67.0 ± 13.1
Superior colliculus	84.4 ± 5.9	86.2 ± 4.1	82.0 ± 7.4	93.6 ± 7.8	65.2 ± 10.3	66.0 ± 8.9
Dorsal raphe nucleus	90.4 ± 10.9	90.7 ± 11.2	92.2 ± 3.5	99.0 ± 7.1	77.0 ± 10.3	85.0 ± 3.0
Median raphe nucleus	108.2 ± 9.7	104.0 ± 14.2	102.2 ± 7.9	92.7 ± 4.8	79.2 ± 10.6	95.0 ± 5.0
Inferior colliculus	152.2 ± 9.2	133.8 ± 11.6	123.7 ± 5.5	127.2 ± 8.7	102.7 ± 16.5	127.0 ± 8.0
Cerebellar cortex	62.8 ± 2.8	66.2 ± 4.2	77.3 ± 6.3	68.0 ± 3.3	52.7 ± 6.8	53.7 ± 9.5
Locus ceruleus	114.8 ± 13.2	105.2 ± 9.4	117.4 ± 5.7	100.2 ± 7.4	82.7 ± 11.5	83.3 ± 16.2
Superior olive	115.8 ± 8.3	117.6 ± 11.3	108.0 ± 7.6	123.0 ± 13.9	100.2 ± 13.5	93.0 ± 14.5
Corpus callosum	39.0 ± 4.3	40.2 ± 3.2	37.8 ± 6.4	38.2 ± 3.6	36.0 ± 5.2	46.7 ± 6.3

* Significantly ($p \leq 0.05$) different compared to saline treatment by one-way ANOVA followed by Newman-Keuls post hoc test.

† Significantly ($p \leq 0.05$) different compared to acute 10 mg/kg cocaine treatment by ANOVA followed by Newman-Keuls test.

inhibitory effect of cocaine on dopamine uptake in the NAc (Izenwasser and Cox, 1992), while repeated treatment at high levels reduced ^3H -mazindol binding to dopamine transporters in the NAc during subsequent cocaine withdrawal (Sharpe et al., 1991). Furthermore, studies of immediate-early gene expression reveal that the levels of NAc *c-fos* and *c-jun* mRNA do not change in response to cocaine challenge following chronic treatment (Hope et al., 1992), and *zif/268* mRNA basal levels are suppressed in response to cocaine challenge after chronic treatment (Bhat et al., 1992). In contrast, acute cocaine treatment induced expression of each of these immediate-early genes (Hope et al., 1992; Moratalla et al., 1992, 1993). Thus, the induction of immediate-early gene expression reflecting cellular activity also becomes tolerant in response to chronic cocaine treatment.

The present data show that regional brain metabolic activity exhibits a time-dependent pattern in response to repeated daily treatment with 10 mg/kg cocaine (Table 1). Whereas acute treatment slightly increased rCMR_{glc} , subsequent treatment had no effect until more than 7 d of treatment, whereupon the same cocaine dose reduced rCMR_{glc} in mesolimbic forebrain compared to saline treatment. This gradual shift from initial activation to eventual reduction of rCMR_{glc} after chronic cocaine treatment could represent tolerance of metabolic response to cocaine in selective brain regions. However, the exact time course and magnitude of these effects could be dependent upon the specific dose and paradigm of drug administration.

rCMR_{glc} in the NAc shell, wherein dopamine turnover is increased by stress (Deutch and Cameron, 1992), was reduced by chronic 10 mg/kg cocaine treatment in both experiments (Tables 1, 2). The NAc shell receives afferent projections from the MPF_{ii} (Berendse et al., 1992), which also exhibited reduced rCMR_{glc} upon selective regional analysis (Table 2). Glucose utilization is known to be relatively greater in synaptic terminals than in somata due to their increased surface-to-volume ratio (Schwartz et al., 1979; Kadekaro et al., 1987). Therefore, a specific mesocorticolimbic forebrain circuit extending from the MPF_{ii} to the NAc shell might be preferentially affected, exhibiting reduced activity following chronic cocaine treatment. In fact, projections from the NAc shell to the subnucleus extended amygdala (Heimer et al., 1991) have been implicated in the modulation

of cocaine reinforcement (Robledo and Koob, 1993). The olfactory tubercle, in which rCMR_{glc} may be related to cocaine reinforcement or expression of stereotypic behavior (Kornetsky et al., 1991), consistently exhibited reduced rCMR_{glc} after chronic cocaine treatment. The ABL, which together with the NAc may be necessary for expression of locomotor sensitization (Post et al., 1987), and the PC also exhibit consistent metabolic deficits compared to chronic saline treatment. The NAc core, the rostral portion of which was affected by chronic cocaine treatment (Table 1), innervates the SNc (Zahm and Brog, 1992), wherein rCMR_{glc} was reduced by chronic cocaine treatment. Few other extrapyramidal regions showed any reduction of rCMR_{glc} following chronic cocaine treatment. Interestingly, rCMR_{glc} in the LC, a source of noradrenergic innervation, was also reduced after chronic cocaine treatment in experiment 2, revealing a potential effect on synaptic activity in this brain region. These results suggest that the cocaine-induced reduction of metabolic activity, which was largely limited to mesocorticolimbic brain regions, might be related to stereotypy and drug reinforcement regulated by these circuits rather than to motor output, unless such locomotor activity is also affected by mesolimbic projections. Such regional reduction could function to decrease the expression of these behaviors. Alternatively, the same level of behavioral expression might require less synaptic stimulus following chronic drug treatment. Further studies that correlate behavioral and metabolic response are required to elucidate this question.

It should be noted that these experiments examined rCMR_{glc} response to cocaine treatment, rather than basal metabolic activity present prior to terminal drug treatment. Therefore, we cannot determine whether the final dose of 10 mg/kg cocaine actually increased or decreased rCMR_{glc} compared to basal values. The resulting rCMR_{glc} values were significantly reduced compared to regional values from saline-treated animals, which could occur either by a reduction of basal rCMR_{glc} , a reduction of rCMR_{glc} in response to cocaine treatment, or both. Previous studies have shown that rCMR_{glc} is reduced in mesolimbic forebrain at various times during withdrawal following chronic contingent (Hammer et al., 1993) and noncontingent (Clow and Hammer, 1991) cocaine treatment. Since the basal metabolic state prior to terminal cocaine treatment resembles that of 24

Table 2. Regional cerebral metabolic rate ($\mu\text{mol}/100 \text{ gm}/\text{min}$ glucose $\pm$ SEM) following repeated daily saline or 10 mg/kg cocaine injection with or without 30 mg/kg cocaine treatment on the final day

Brain region	Saline (<i>n</i> = 5)	Chronic cocaine (daily 10 mg/kg treatment) (<i>n</i> = 6)	Challenge with 30 mg/kg after chronic treatment (<i>n</i> = 7)
Mesolimbic structures			
Medial prefrontal cx., prelimbic	113.8 $\pm$ 5.0	102.7 $\pm$ 5.0	101.7 $\pm$ 3.1
Medial prefrontal cx., infralimbic	98.2 $\pm$ 4.9	85.2 $\pm$ 3.5*	87.3 $\pm$ 2.0*
Nucleus accumbens, rostral pole	100.4 $\pm$ 5.1	93.2 $\pm$ 5.1	101.4 $\pm$ 2.6
Nucleus accumbens, core (rostral)	97.4 $\pm$ 5.0	84.0 $\pm$ 4.1	87.6 $\pm$ 3.8
Nucleus accumbens, core (caudal)	89.0 $\pm$ 5.1	78.0 $\pm$ 4.2	83.4 $\pm$ 4.1
Nucleus accumbens, shell (rostral)	98.2 $\pm$ 5.2	82.7 $\pm$ 4.6*	81.4 $\pm$ 4.9
Nucleus accumbens, shell (caudal)	80.2 $\pm$ 3.9	67.8 $\pm$ 1.7*	71.6 $\pm$ 2.8
Olfactory tubercle (rostral)	123.8 $\pm$ 6.1	110.5 $\pm$ 5.4	112.6 $\pm$ 4.2
Olfactory tubercle (mid)	109.4 $\pm$ 4.0	94.5 $\pm$ 4.9*	101.6 $\pm$ 5.0
Olfactory tubercle (caudal)	99.2 $\pm$ 4.5	89.7 $\pm$ 3.4	95.3 $\pm$ 4.1
Islands of Calleja (rostral)	121.8 $\pm$ 4.7	108.7 $\pm$ 4.0	114.9 $\pm$ 4.9
Islands of Calleja (caudal)	104.2 $\pm$ 4.6	90.3 $\pm$ 4.3	97.4 $\pm$ 5.2
Ventral tegmental area	86.8 $\pm$ 3.6	83.5 $\pm$ 5.7	98.6 $\pm$ 3.1
Extrapyramidal structures			
Caudatoputamen (CP) dorsolateral (rostral)	117.6 $\pm$ 4.3	101.5 $\pm$ 5.3*	114.1 $\pm$ 3.5
CP, dorsolateral (mid)	116.4 $\pm$ 4.4	103.0 $\pm$ 4.3*	118.6 $\pm$ 3.4†
CP, dorsolateral (caudal)	109.8 $\pm$ 3.7	97.7 $\pm$ 5.1	117.7 $\pm$ 4.3†
CP, ventromedial (rostral)	114.2 $\pm$ 4.2	99.7 $\pm$ 5.7	109.1 $\pm$ 3.3
CP, ventromedial (mid)	111.6 $\pm$ 4.3	100.3 $\pm$ 3.3	111.6 $\pm$ 2.0†
CP, ventromedial (caudal)	98.8 $\pm$ 2.9	90.7 $\pm$ 3.7	102.0 $\pm$ 2.8
Globus pallidus	75.0 $\pm$ 4.0	69.0 $\pm$ 4.6	86.9 $\pm$ 2.5*†
Entopeduncular nucleus	80.2 $\pm$ 3.8	69.3 $\pm$ 5.8	91.6 $\pm$ 3.4†
Subthalamus (rostral)	96.0 $\pm$ 4.7	88.8 $\pm$ 6.4	98.6 $\pm$ 4.2
Subthalamus (caudal)	97.6 $\pm$ 4.5	92.2 $\pm$ 6.6	114.3 $\pm$ 4.5*†
Substantia nigra pars compacta	86.8 $\pm$ 4.0	75.5 $\pm$ 3.3*	88.6 $\pm$ 3.4†
Substantia nigra pars reticulata	76.2 $\pm$ 4.7	69.5 $\pm$ 4.6	98.9 $\pm$ 4.7*†
Diencephalic structures			
Medial habenula	97.4 $\pm$ 4.7	76.3 $\pm$ 5.8*	86.3 $\pm$ 4.1
Lateral habenula (medial)	109.0 $\pm$ 5.3	84.2 $\pm$ 6.2*	86.0 $\pm$ 4.4*
Lateral habenula (lateral)	118.4 $\pm$ 4.8	88.3 $\pm$ 6.8*	90.4 $\pm$ 4.7*
Ventral thalamus (VPM/VPL)	109.6 $\pm$ 6.2	92.5 $\pm$ 6.2	107.4 $\pm$ 4.6
Laterodorsal thalamus	117.4 $\pm$ 5.4	102.0 $\pm$ 8.4	122.0 $\pm$ 5.7
Dorsomedial thalamus	115.6 $\pm$ 4.6	105.5 $\pm$ 7.7	121.6 $\pm$ 5.5
Ventral pallidum, dorsolateral	75.8 $\pm$ 4.3	65.8 $\pm$ 2.8	76.7 $\pm$ 3.0
Ventral pallidum, ventromedial	82.4 $\pm$ 5.7	70.3 $\pm$ 4.0	79.0 $\pm$ 2.9
Substantia innominata	67.0 $\pm$ 3.6	59.3 $\pm$ 3.9	63.7 $\pm$ 2.0
Diagonal band, horizontal limb	87.6 $\pm$ 4.4	82.8 $\pm$ 4.6	82.1 $\pm$ 2.8
Bed nucleus of the stria terminalis	63.2 $\pm$ 3.3	55.2 $\pm$ 3.2	58.9 $\pm$ 2.2
Medial preoptic area	66.6 $\pm$ 3.5	56.5 $\pm$ 2.8	60.9 $\pm$ 1.9
Lateral preoptic area	86.0 $\pm$ 7.5	71.0 $\pm$ 4.7	77.9 $\pm$ 3.2
Lateral hypothalamus (rostral)	82.2 $\pm$ 2.9	69.8 $\pm$ 4.9	76.4 $\pm$ 3.8
Lateral hypothalamus (caudal)	78.2 $\pm$ 3.6	71.8 $\pm$ 5.1	76.0 $\pm$ 2.8
Arcuate nucleus	63.0 $\pm$ 3.2	56.8 $\pm$ 4.4	63.3 $\pm$ 2.1

hr cocaine abstinence, it is likely that basal rCMR_{glc} was reduced following chronic cocaine treatment.

Effect of subsequent cocaine challenge

We observed that rCMR_{glc} increased following 30 mg/kg cocaine challenge in CP, GP, EP, STh, and SNr, as well as in sensorimotor cortex, PAG, and LC compared to chronic treatment

with 10 mg/kg cocaine alone. Moreover, rCMR_{glc} was significantly greater after 30 mg/kg cocaine challenge than after chronic saline treatment in GP, STh, and SNr, as has been observed in these regions following acute cocaine treatment with the same cocaine dose (London et al., 1986). Therefore, striatal efferent neurons might be activated in response to cocaine challenge, since these neurons innervate the affected extrapyramidal regions.

Table 2. Continued.

Brain region	Saline (n = 5)	Chronic cocaine (daily 10 mg/kg treatment) (n = 6)	Challenge with 30 mg/kg after chronic treatment (n = 7)
Limbic regions			
Medial septal nucleus	82.2 ± 5.0	77.5 ± 4.3	82.0 ± 2.5
Lateral septal nucleus	71.4 ± 2.0	67.2 ± 4.7	81.6 ± 4.2
Basolateral amygdala	103.8 ± 3.9	84.5 ± 5.6*	92.7 ± 3.8
Central amygdala	69.4 ± 3.6	56.3 ± 3.6*	63.4 ± 2.4
Piriform cortex (rostral)	135.0 ± 5.1	122.0 ± 6.9	125.6 ± 3.4
Piriform cortex (mid)	128.6 ± 4.1	112.3 ± 5.4*	117.6 ± 3.6
Piriform cortex (caudal)	125.6 ± 4.7	105.8 ± 6.1*	118.3 ± 3.4
Cingulate cortex (rostral)	114.6 ± 5.2	100.7 ± 5.7	103.9 ± 2.4
Cingulate cortex (caudal)	108.8 ± 5.2	95.0 ± 3.9	101.7 ± 1.7
Entorhinal cortex (superficial)	86.8 ± 4.5	82.2 ± 4.0	89.3 ± 2.8
Entorhinal cortex (deep)	87.6 ± 5.1	79.3 ± 4.1	87.7 ± 2.5
Cortical regions			
Agranular motor cortex	102.8 ± 3.6	91.8 ± 4.8	109.4 ± 2.9†
Somatosensory cortex	105.8 ± 4.1	89.0 ± 3.2*	100.7 ± 2.5†
Visual cortex	102.8 ± 6.4	92.0 ± 5.8	109.4 ± 4.0
Auditory cortex	129.8 ± 4.5	122.0 ± 5.8	136.4 ± 4.2
Brainstem and other regions			
Medial geniculate nucleus	125.0 ± 6.0	112.3 ± 3.3	118.6 ± 7.2
Periaqueductal gray matter	84.2 ± 4.9	77.0 ± 2.9	88.6 ± 1.7†
Superior colliculus	94.4 ± 2.7	90.7 ± 4.1	100.0 ± 2.5
Dorsal raphe nucleus	90.6 ± 6.2	81.3 ± 4.3	89.4 ± 3.4
Median raphe nucleus	99.4 ± 9.6	80.5 ± 5.6	86.7 ± 6.4
Inferior colliculus	138.8 ± 3.3	119.2 ± 4.6*	121.0 ± 3.8*
Cerebellar cortex	72.2 ± 4.8	68.3 ± 7.8	83.9 ± 3.4
Locus ceruleus	123.0 ± 5.6	98.5 ± 4.2*	117.3 ± 6.8†
Superior olive	128.2 ± 3.2	103.0 ± 5.8*	106.2 ± 5.8*
Corpus callosum	39.8 ± 3.0	37.5 ± 3.6	41.0 ± 3.3

* Significantly ($p \leq 0.05$) different compared to saline treatment by Duncan's multiple range test.† Significantly ($p \leq 0.05$) different compared to chronic 10 mg/kg cocaine treatment by Duncan's multiple range test.

It is known, for example, that *c-fos* expression is induced by acute cocaine in striatal neurons (Moratalla et al., 1993), and this effect is blocked by dopamine D_1 antagonist pretreatment (Young et al., 1991). Expression of *c-fos* is thought to be related to neuronal activity as illustrated by local 2DG uptake (Sharp et al., 1989), although additional factors might induce *c-fos* expression without affecting neuronal activity. Since the striatal neurons that project to GP, EP, and SNr (Kawaguchi et al., 1990) probably contain D_1 receptors (Gerfen et al., 1990), their activation by cocaine could increase $rCMR_{glc}$ in regions containing their efferent terminals. Such cocaine-induced activation might also involve synergistic regulation of both D_1 and D_2 receptors, as treatment of intact rats with a selective dopamine D_1 agonist increases $rCMR_{glc}$ only in SNr (Trugman and James, 1993).

Although challenge with 30 mg/kg cocaine increased $rCMR_{glc}$ in extrapyramidal regions, such treatment had little effect in mesolimbic structures. Instead, $rCMR_{glc}$ remained depressed in the NAc shell and was significantly reduced in MPf_{li} after 30 mg/kg cocaine treatment compared to saline treatment. The present study did not compare the regional metabolic response of cocaine challenge to that of acute administration; however,

several studies using the acute paradigm have reported similar results to those observed herein. Acute intraperitoneal treatment with 30 mg/kg cocaine did not affect $rCMR_{glc}$ in mesolimbic regions (London et al., 1986, 1990), although acute intravenous cocaine increased $rCMR_{glc}$ in the MPf and NAc (Porrino et al., 1988). Hence, the route of administration might contribute to the magnitude and location of metabolic effects. The preferential activation of extrapyramidal efferent circuits by cocaine challenge following chronic treatment might be related to cocaine-induced locomotor activity (i.e., sensitization). This relationship is complex, however, since treatment with 30 mg/kg cocaine increased $rCMR_{glc}$ only in the SNr of naive, gallamine-paralyzed animals (London et al., 1990). In any case, this effect seems unrelated to the prior induction of metabolic tolerance in mesolimbic circuits.

Challenge with 30 mg/kg cocaine also produced metabolic activation in primary somatosensory and motor cortices and LC. Cortical activation could be a consequence of the increased motor activity (and sensory feedback) observed. It is possible that cocaine has direct effects on synaptic terminals in the LC, and this could be related to the effects of this drug on noradrenergic transporters. The reduction of $rCMR_{glc}$ in the LH fol-

lowing 30 mg/kg cocaine challenge is consistent with the effect on this brain region of the same dose administered acutely (London et al., 1986). Repeated administration of 10 mg/kg cocaine reduced $rCMR_{glc}$ (Table 2), and subsequent challenge with 30 mg/kg cocaine produced no further change. The LH receives extensive projections from the EP (Herkenham and Nauta, 1977; van der Kooy and Carter, 1981) as well as dopamine innervation from the medial VTA (Skagerberg et al., 1984). Thus, cocaine-induced activation of GABAergic terminals in EP could inhibit firing of neurons projecting to the habenula, or dopamine could have direct effects on synaptic activity, either of which could result in reduced $rCMR_{glc}$ in this region.

Mechanisms of chronic cocaine effects

Although the cause of these differential metabolic responses following chronic treatment is unclear, the induced reduction of $rCMR_{glc}$ apparently does not involve a reduction of regional drug availability. In fact, pharmacokinetic analyses show that regional brain cocaine concentration is *elevated* after chronic treatment (Pettit et al., 1990; Cass and Zahniser, 1993), perhaps due to increased absorption of the drug following intraperitoneal injection (Pan et al., 1991). Cocaine levels are higher in the NAc than in striatum during the first 20 min following a 10 mg/kg intraperitoneal injection (Javaid and Davis, 1993), which represents the period during which most uptake of 2DG and its intracellular trapping in the form of 2DG-6-phosphate occur (Sokoloff et al., 1977). Thus, the relatively greater effect of cocaine challenge on $rCMR_{glc}$ in extrapyramidal than mesolimbic regions is probably not due to higher striatal cocaine levels.

The effect of chronic cocaine on $rCMR_{glc}$ resembles the pattern of altered mesolimbic dopamine response to chronic cocaine. Repeated daily intraperitoneal administration of 10 mg/kg cocaine for 10 d has been shown to increase basal dopamine level in the NAc while attenuating the relative dopamine response to cocaine challenge (Weiss et al., 1992), which could further reduce NAc neuronal firing, thereby decreasing $rCMR_{glc}$ in regions containing the efferent terminals of NAc neurons, since iontophoretic application of either dopamine (Henry et al., 1989) or dopamine D_1 agonists (Henry and White, 1991) reportedly enhances inhibition of NAc neuronal firing in anesthetized animals after repeated cocaine treatment. This may occur even in the absence of increased D_1 receptor number (Kleven et al., 1990; Peris et al., 1990; Mayfield et al., 1992) due to a postreceptor increase of adenylate cyclase and cAMP-dependent protein kinase activity in NAc (Terwilliger et al., 1991). However, the predominant inhibitory action of dopamine on NAc neurons in anesthetized animals might not occur in freely moving animals, which exhibit dopaminergic excitation in the NAc (West et al., 1992). Moreover, the effect of chronic cocaine on basal dopamine level is somewhat controversial, as 10 mg/kg administered twice daily reportedly increases basal dopamine level in NAc over the first 3 d before returning to baseline on days 4 and 5, and significantly decreases NAc basal dopamine level thereafter (Imperato et al., 1992). Indeed, this putative time course of altered basal dopamine level is remarkably similar to that of $rCMR_{glc}$ which we observed in the same region after repeated treatment. It is possible that the resulting dopamine basal level affects the activity of cortical neurons that project to the NAc or of local circuit neurons located therein, thus altering $rCMR_{glc}$ in these sites.

Although few previous studies have examined $rCMR_{glc}$ response to chronic cocaine treatment in experimental animals,

recent positron emission tomographic studies using ^{18}F -2DG in humans show that $rCMR_{glc}$ *decreases* in the cerebral cortex, basal ganglia, and thalamus following cocaine administration in cocaine abusers (London et al., 1990). Cocaine administration also reduced regional cerebral blood flow, which is tightly coupled to $rCMR_{glc}$ even after cocaine administration (Sharkey et al., 1991), in frontal cortex and basal ganglia of cocaine abusers (Pearlson et al., 1993). These results are consistent with a differential effect of cocaine on $rCMR_{glc}$ in naive subjects versus those experienced with cocaine, as we have observed in animals. Thus, animal studies would appear to provide an appropriate model for human brain response to chronic cocaine administration. Furthermore, the results suggest that regional metabolic responses to cocaine administration in naive subjects might be quite different from those observed in cocaine (or polydrug) abusers. The resulting $rCMR_{glc}$ pattern suggests that chronic use can produce tolerance to the acute metabolic response. Moreover, the cellular, chemical, and molecular alterations that contribute to this regional metabolic response apparently last for days to weeks after cessation of cocaine self-administration, in both rats (Hammer et al., 1993) and humans (Volkow et al., 1992).

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