PET Studies of Cerebral Glucose Metabolism: Acute Effects of Cocaine and Long-Term Deficits in Brains of Drug Abusers

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Positron emission tomography (PET) is a nuclear imaging technique that can be employed to assess regional brain function noninvasively. When used with [18F]fluorodeoxyglucose (FDG), a radiotracer for glucose metabolism, it can provide quantitative maps of global and regional cerebral metabolic rates for glucose (Phelps et al. 1979; Reivich et al. 1979). The FDG method has been used to assess changes in regional brain function in a variety of physiological and pathological states (Buchsbaum et al. 1990; Martin et al. 1992; Reiman et al. 1986), including the acute responses to psychoactive drugs (London and Morgan 1993). Measure-ments using PET with FDG also have demonstrated persistent differences in the metabolism of brains of substance abusers as compared with those of control subjects without significant histories of illicit drug abuse (Stapleton et al. 1995; Volkow et al. 1992a, 1992b). This chapter focuses on the acute effects of cocaine on cerebral glucose metabolism and how they relate to other physiological and behavioral states. It also discusses the long-term differences in the brains of substance abusers and the extent to which such differences may relate to cocaine abuse.

Prior to human studies of the effects of cocaine on cerebral metabolism, theacute effects of amphetamine on regional metabolic rate for glucose (rCMRglc) were studied with FDG. An oral dose of d-amphetamine (0.5milligrams per kilogram (mg/kg)) decreased cortical and subcortical rCMRglc in schizophrenic as well as control subjects (Wolkin et al. 1987). The magnitude of amphetamine-induced change was uniform across brain regions, and was related to the concentration of the drug in plasma. These results were in marked contrast to those from a study of subjects with attention deficit-hyperactivity disorder who were given either d-ampheta-mine or methylphenidate (Matochik et al. 1993). Although there were no significant effects on global metabolic rate for glucose, each drug produced differential regional effects. A single oral dose of d-amphetamine (0.25mg/ kg), equal to half the dose given to the

subjects in the study by Wolkin and colleagues (1987), improved performance on an auditory continuous per-formance task (CPT) and significantly increased rCMRglc in anterior medial frontal cortex, right temporal cortex, right caudate nucleus, and right thalamus, but caused decreases in left and right anterior frontal cortices. In contrast, a single oral dose of methylphenidate (0.35mg/kg) did not improve performance on CPT and decreased the rCMRglc in anterior medial frontal, left parietal, and left parietal/occipital cortices. Differences in the effects of the two stimulants on rCMRglc as well as on CPT performance may be attributable to the mechanisms by which the drugs stimulate the release of dopamine and/or norepinephrine (McMillen 1983). Whereas methyl-phenidate promotes the release of catecholamines from reserpine-sensitive vesicular storage pools, amphetamine releases the amines from reserpine-insensitive pools. Both drugs also block amine reuptake. The contrast between results found by Matochik and colleagues (1993) as compared with those of Wolkin and colleagues (1987) for amphetamine-induced changes in rCMRglc may be related to the dose of amphetamine or to the pathology of the respective subject populations.

In a study aimed at elucidating the neuroanatomical substrates of the positive effects of cocaine on mood, the FDG method was used to study the effects of cocaine on cerebral metabolism (London et al. 1990a). Subjects with histories of polysubstance abuse, including intravenous (IV) self-administration of cocaine, were given an IV injection of cocaine hydrochloride (40 mg). They manifested characteristic effects of cocaine, including significant elevations in self-reports of positive mood and cardiovascular stimulation. Cocaine significantly decreased global glucose metabolism by 8.59±3.4 (mean±SEM) percent ($p = 0.02$ by matched pair t-test) and reduced rCMRglc in 35 of 56 regions analyzed ($p< 0.05$ by matched pair t-test) (table 1). Statistically significant decrements ranged in magnitude from 5.8 to 16 percent of values obtained when subjects received placebo. Although the cocaine-induced decrements in cerebral glucose metabolism were global, the magnitude of the metabolic change in the right amygdala was negatively correlated with the positive quality and strength of the subjective response.

These findings were extended in a study by Morgan and colleagues (1993) that investigated the relationship between subjective responses to cocaine and ventricle-to-brain ratio (VBR), an index of cerebral atrophy (Ron 1983; Wilkinson 1982). In subjects with histories of polydrug abuse, this parameter of ventriculomegaly has been correlated with the amount of alcohol consumed during the period of peak alcohol use (Cascella et al. 1991). The results from Morgan and colleagues (1993)

TABLE 1. Effect of cocaine on rCMRglc.

	Placebo		Cocaine	
	Left	Right	Left	Right
Neocortex				
Superior frontal gyrus	8.18±1.38	8.67±1.35	7.75±0.81	8.14±1.27
Orbitofrontal cortex (19)	8.93±1.43	8.83±1.41	8.57±1.15	8.34±1.03
Insula	10.26±1.56	10.70±1.72	9.15±1.66*	9.23±2.01*
Temporal pole (19)	5.83±1.01	5.90±1.01	5.40±0.82*	5.60±0.78
Primary visual cortex	9.50±1.82	10.10±1.78	8.53±1.56*	9.06±1.72*
Lateral occipital gyrus	7.94±1.34	6.40±1.41	7.27±0.90*	7.60±1.20*
Basal ganglia				
Caudate nucleus	8.44±1.28	8.85±1.19	7.91±1.28*	7.76±1.47*
Putamen	9.47±1.21	10.10±1.36	8.57±1.27*	8.35±1.57

Each value is the mean±SD regional cerebral metabolic rate for glucose (rCMRglc, mg/100g/min) for 20 subjects, except where indicated in parentheses.

KEY: * = Statistically significant effect of cocaine as determined by t-test using the difference between rCMRglc measured in cocaine and in placebo conditions, uncorrected for the number of comparisons, $p<0.05$.

indicated that selective measures of the effects of cocaine, including self-report ratings of intensity of drug effect, scores on the morphine-benzedrine group subscale of the Addiction Research Center Inventory, and several items on visual analog scales of subjective self-reports were negatively correlated with VBR. VBR also differed significantly between subjects who were grouped according to scores (rush and crash) on the cocaine sensitive scale (larger VBR in subjects with weaker responses). Changes in global and regional cerebral metabolic rates for glucose were not significantly related to VBR. Thus, the effects of cocaine on mood but not cerebral glucose metabolism were related to the structural integrity of the brain.

Findings that cocaine and other stimulants reduce cerebral glucose metabolism seem inconsistent with the behavioral effects of these drugs in humans, and they are at variance with reported effects of d-ampheta-mine (Wechsler et al. 1979) and l-cocaine on rCMRglc in rats (London et al. 1986). However, the effects of stimulants on rCMRglc in the human brain are consistent with observations that other drugs which produce positive affective states, such as diazepam (De Wit et al. 1990; Foster et al. 1987), ethanol (De Wit et al. 1990; Volkow et al. 1992a), morphine (London et al. 1990b), nicotine

(Stapleton et al. 1992), and buprenor-phine (Walsh et al. 1994) also reduce rCMRglc, particularly in cortical areas. The mechanism for producing decreases in cerebral glucose metabolism may be related to the interaction between euphoriant drugs and the mesolimbic dopamine system (Gardner 1992; Koob and Bloom 1988; London and Morgan 1993). Thus, the reduced cortical metabolism seen in response to euphoriants may be a consequence of an action on mesolimbic areas that are important to reward and that provide the reinforcement for continued drug self-administration. Alternatively, decrements in rCMRglc may be a response to positive affect induced by drugs of abuse.

A recent study by Herning and colleagues (1994) that used a group of subjects drawn from the same population studied with FDG and cocaine (London et al. 1990a; Morgan et al. 1993) indicated that acute cocaine significantly increased frontal and central electroencephalographic (EEG) activity in the beta range (13.6 to 32.8 hertz (Hz)). Although increased beta activity is usually considered to be indicative of increased brain activ-ity, the finding that other drugs of abuse, such as barbiturates (Benowitz et al. 1980) and benzodiazepines (Manmaru and Matsura 1989), also increase EEG beta activity while reducing rCMRglc (Buchsbaum et al. 1987; deWit et al. 1990; Foster et al. 1987; Theodore et al. 1986) suggested that increases in beta activity may be related to decreased cortical function and metabolic demand (Bunney and Aghajanian 1978; Siggins 1978).

Aside from assessment of the acute effects of cocaine, recent investi-gations have been directed at determining if the brains of substance abusers manifest deficits that may reflect long-term consequences of the use of cocaine or other drugs of abuse. A study of VBR, determined volumetrically by magnetic resonance imaging, demonstrated that relative to normal controls, subjects with histories of polydrug abuse did not have larger VBR, nor was there any tendency toward relative ventriculomegaly (Liu et al. 1995). In contrast, patterns of rCMRglc differed in polydrug abusers as compared with those in controls (Stapleton et al. 1995). Comparisons of absolute values of rCMRglc indicate that polydrug abusers have statistically lower metabolism in the visual association cortex than controls. When values of rCMRglc were normalized for global glucose metabolism (a technique used to reduce the effect of interindividual differences on group comparisons of rCMRglc), rCMRglc was significantly higher in the orbitofrontal cortex in the drug abuse group as compared with controls. These metabolic differences, which are more robust than

structural deficits in the brains of substance abusers, may represent long-term consequences of the self-administration of cocaine or other drugs of abuse. Nonetheless, the degree to which these differences predate drug abuse is not known.

Other studies have been designed specifically to test the effects of cocaine withdrawal on rCMRglc. A study of two groups of male polydrug abusers, who used an average of 4 grams (g) of cocaine per week, indicated that abstinence from cocaine for less than 1 week was associated with increased rCMRglc in orbitofrontal cortex and basal ganglia, whereas abstinence for 2 to 4 weeks was associated with a return to normal rCMRglc (Volkow et al. 1991). The subjects were polydrug abusers who were dependent on nicotine and cocaine, but not other drugs of abuse. Cocaine dependence was established using criteria from the "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. revised (DSM-III-R), and all but three of the cocaine-dependent patients had depressive symptoms at the time of the study. In a second study by the same group, male cocaine-dependent volunteers were recruited from a detoxification unit. This study revealed lower levels of rCMRglc in the frontal cortex of cocaine abusers after 1 to 6 weeks of abstinence as compared with values in controls. The difference persisted in a subset of subjects who were retested after 3 to 4 months (Volkow et al. 1992b). A more recent, preliminary study of cocaine absti-nence involved three groups of six subjects each, studied with FDG on three occasions relative to cocaine withdrawal (Flowers et al. 1994). Factor analysis indicated that early cocaine abstinence (7 to 20 days) was asso-ciated with increased metabolism in ventral striatum, orbitofrontal cortex, and amygdala, with a decline in rCMRglc to these regions during middle abstinence (21 to 41 days). In addition, the dorsal caudate and putamen were less activated early in abstinence, but rCMRglc in these regions showed peak rCMRglc in middle abstinence. Finally, rCMRglc in the anterior cingulate and dorsolateral frontal cortex declined only late in abstinence (100 days to 10 years). Data from these studies indicate that the early stage of cocaine withdrawal (1 to 3 weeks) appears to be associated with increased rCMRglc in orbitofrontal cortex and basal ganglia. This hypermetabolic condition is followed by decreased rCMRglc in frontal cortex at a later stage (> 4 weeks). Furthermore, the decrease in rCMRglc of the frontal cortex persists for at least 3 to 4 months.

The long-term changes in brain function seen during active drug use and during periods of abstinence also may include alterations that underlie behavioral responses to conditioned cues. It has been

suggested that stimuli which reliably signal drug use may come to elicit conditioned responses (Siegel 1979; Stewart et al. 1984). For example, heroin users manifest decreased skin temperature and skin resistance, as well as increased self-reported craving and withdrawal, when presented with stimuli related to heroin use, but not during presentation of cues that are not related to drug abuse (Childress et al. 1986; O'Brien et al. 1986). Several studies have examined whether stimuli associated with cocaine use produce different responses in cocaine abusers compared with subjects with no history of cocaine use (Bauer and Kranzler 1994; Childress et al. 1988; Ehrman et al. 1992; O'Brien et al. 1990). These studies indicate that patients who have abused cocaine show increased physiological and subjective responses to cocaine-related stimuli when compared to subjects who have no history of cocaine use.

A prominent response to presentation of cocaine-related stimuli is an increase in subjective reports of craving for cocaine. Although craving has been difficult to define precisely (Kozlowski et al. 1989; Markou et al. 1993; Newlin 1992; Tiffany et al. 1993), it has been conceptualized as an intervening variable that motivates continued drug use or resumption after abstinence. In particular, increased craving during withdrawal from chronic cocaine use is believed to contribute substantially to relapse (Gawin and Kleber 1986). Although the physiological responses to cocaine-related stimuli are believed to be the product of a Pavlovian conditioning process that generates craving, the neural substrates of craving are largely unknown (Koob 1992).

Preliminary data from a PET study using the FDG method suggest a potential neural mechanism for the long-term changes in brain that underlie the production of craving (Grant et al. 1994). Consistent with previous studies, polydrug abusers who are currently using cocaine show an increase in self-reports of craving and overall EEG arousal during presentation of visual cocaine-related stimuli. PET scans reveal increases in rCMRglc in portions of the prefrontal cortex and the occipital lobe. These cortical responses to conditioned cues point to a potential dif-ference between polydrug abusers and individuals who have no histories of drug abuse, and may reflect cerebral substrates that are targets for therapies aimed to antagonize drug craving and relapse.

In conclusion, cocaine abuse is associated with a number of acute and long-term effects that are both behavioral and physiological. To summarize, acute cocaine administration produces a constellation of

effects that are similar to those produced by other euphoriant drugs. These physiological effects include decreases in regional and global metabolic rates for glucose and increases in EEG beta power. Current literature suggests that a common brain mechanism, which may be attributable to an interaction with the mesolimbic dopaminergic system, underlies the euphoriant actions of these drugs.

The data presented in this chapter also indicate that cerebral functional differences in the brains of substance abusers include reduced rCMRglc of visual association cortex and increased rCMRglc in orbitofrontal cortex and basal ganglia in polydrug abusers relative to nonabusing controls. In addition, rCMRglc in several brain regions in cocaine abusers seems to be related to the length of abstinence from cocaine. Furthermore, long-term cocaine use is associated with the development of conditioned responses that may include craving, a behavioral state which may contribute to relapse. Preliminary data indicate that these condi-tioned responses include specific changes in rCMRglc. Thus, metabolic mapping with PET and FDG has been useful in providing information on brain function in several states of the cycle of cocaine addiction, from acute euphorigenic responses to persistent differences in brain function after cessation of drug use. The major challenge of the human studies described has been the lack of control over drug history and other envi-ronmental factors that may confound the interpretation of the findings. Such problems could be obviated in studies of primates, and the develop-ment of PET scanners with improved spatial resolution would enhance such efforts.

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ACKNOWLEDGMENT

The Brain Imaging Facility of the NIDA Intramural Research Program is supported in part by funding from the Counterdrug Technology Assessment Center, Office of National Drug Control Policy.

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