

# APPLICATION OF IMAGING TECHNOLOGIES IN THE INVESTIGATION OF DRUG ADDICTION

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Brain imaging can be used to assess the following in the human brain: (a) morphology [computed tomography (CT) and magnetic resonance imaging (MRI)]; (b) electrical and magnetic signals [electroencephalography (EEG) and magnetoencephalography (MEG)]; (c) neurotransmission [positron emission tomography (PET) and single photon emission computed tomography (SPECT)]; (d) tissue composition [magnetic resonance spectroscopy (MRS)]; and (e) blood flow and metabolism [functional MRI (fMRI), PET, SPECT, and dynamic CT]. Table 103.1 summarizes the spatial and temporal resolution and the sensitivity for the various imaging modalities.

This chapter focuses mainly on the application of PET, SPECT, and MRI for the investigation of the effects of drugs of abuse in the human brain and their relationship with their reinforcing, addictive, and toxic effects. A brief description of these imaging techniques follows.

PET and SPECT are nuclear medicine instruments that detect and measure the spatial distribution and movement of radioisotopes in tissues of living subjects. PET measures compounds labeled with positron emitting radioisotopes and SPECT with single photon emitting radioisotopes. An advantage of the positron emitters is that some of these are isotopes for the natural elements of life ( $^{11}\text{C}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$ ), and this feature enables labeling of compounds without affecting their pharmacologic properties. Although labeling an organic compound with a single photon emitter such as  $^{123}\text{I}$  results in a compound that is different from the parent compound, many iodine-substituted radiotracers with high biological selectivity and affinity for specific molecular targets have been developed. The positron emitters used for imaging have shorter half-lives than the single photon emit-

ters. Both types of isotopes can be used to label ligands for specific receptor, transporter, or enzymatic systems to be used with PET or SPECT to quantify these parameters in living human brains. In addition, PET tracers such as  $^{18}\text{F}$  or  $^{11}\text{C}$ -labeled deoxyglucose (FDG, CDG) and  $^{15}\text{O}$ -labeled water can be used to measure regional brain glucose metabolism and cerebral blood flow (CBF), and SPECT tracers such as  $^{99\text{m}}\text{Tc}$  hexamethylpropyleneamineoxime (HMPAO) can be used to measure CBF.

MRI is an imaging instrument that can distinguish elements in tissue on the basis of their magnetic properties. This information can be used to obtain images that reflect brain structure, brain function, or chemical composition. Information on structure in the brain can be obtained on the basis of differences in chemical composition between gray and white matter. For structural brain imaging, this is mostly accomplished by proton analysis, which enables the assessment of the water content of tissues. Information on brain function is derived from the differences in magnetic properties of oxygenated versus deoxygenated hemoglobin (blood oxygenation-dependent or BOLD contrast). During activation of a brain region, an excess of arterial blood is delivered into the area, with concomitant changes in the ratio of deoxyhemoglobin to oxyhemoglobin. Concentration on a wide variety of compounds that reflect metabolic state of the tissue and cell integrity can be obtained with MRS. MRS can also be used to measure the concentration and metabolism of compounds such as  $^{13}\text{C}$ -glucose.

The most widespread application of imaging in the study of drugs of abuse has been its use to assess brain function, which can be done using imaging modalities that measure electrical activity, CBF, or brain metabolism. Of the modalities used for functional imaging, fMRI has the highest spatial resolution. Conversely, MEG and EEG are the imaging technologies with the highest temporal resolution, which enables the examiner to assess the temporal displacement of activation signals as they propagate in brain on the order of a few milliseconds (1).

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**TABLE 103.1. IMAGING MODALITIES USED TO INVESTIGATE THE LIVING HUMAN BRAIN<sup>a</sup>**

	Parameter Measured	Temporal Resolution	Spatial Resolution	Sensitivity
MEG	Function	1 ms	5 mm	
EEG		1 ms	10–15 mm	
CT	Structure	ms		
MRI	Structure	ms	1.0–1.5 mm	10 <sup>-3</sup> molar
	Function	3–5 s	mm	
	Biochemistry	10–20 min	cm	
<sup>b</sup> PET	Function	45 s	4 mm	10 <sup>-2</sup> molar
<sup>b</sup> SPECT	Biochemistry	15 min	4 mm	
	Pharmacokinetics	60 s	4 mm	

<sup>a</sup>The spatial and temporal resolution and the sensitivity cited for PET and MRI correspond to those of currently available commercial instruments. Research instruments have been developed that have better performance.

<sup>b</sup>Require the use of radiotracers and hence repeated studies with these modalities are limited by radiation dosimetry to the subjects.

CT, computed axial tomography; EEG, electroencephalography; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

The effect of drugs of abuse on neurotransmission has also been investigated. This effect depends on biochemical processes that occur at very low concentrations (nanomolar-picomolar range). PET and SPECT have the highest sensitivity of all currently available imaging techniques, and they can measure concentrations in the nanomolar-picomolar range, which are the physiologic concentrations at which neurotransmitter processes occur (2–4).

## PHARMACOLOGIC PROPERTIES OF DRUGS OF ABUSE IN THE HUMAN BRAIN

The investigation of the pharmacologic properties of drugs entails studies of their pharmacokinetics (primarily using PET and the [<sup>11</sup>C]-labeled drug) as well as their pharmacodynamics (using PET or SPECT and a radiotracer with specificity for a particular molecular or biochemical target or using PET, SPECT, and fMRI to assess brain function). Because these studies are done in awake human subjects, one can investigate the relationship between the behavioral effects of drugs and their effects on brain function and neurochemistry.

### Pharmacokinetics

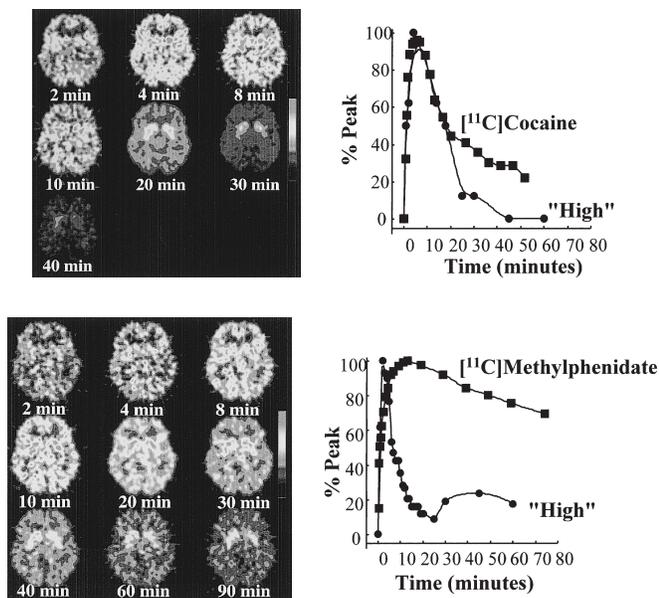
PET can be used to measure the absolute uptake, their regional distribution, and the kinetics of [<sup>11</sup>C]-labeled drugs in the human brain. Moreover, the labeled drug can also be used to determine the target organs for the drug and

thus can provide information on potential organ toxicity. Table 103.2 shows the various addictive drugs that have been labeled with a positron emitter and whose distribution has been evaluated with PET.

An example of the value of this strategy is its use in the investigation of the pharmacokinetics of cocaine in the human brain, as assessed with [<sup>11</sup>C]cocaine (5), and a comparison with methylphenidate (MP), a drug used in the treatment of attention-deficit disorder that, like cocaine, blocks the dopamine (DA) transporter (DAT) but is much less abused than cocaine, as assessed with [<sup>11</sup>C]MP (6). Cocaine and MP were found to have a large brain uptake (7% to 10% injected dose) and to have an almost identical pattern of distribution in the human brain, where they bound

**TABLE 103.2. DRUGS WITH ABUSE LIABILITY THAT HAVE BEEN LABELED WITH A POSITRON EMITTER (CARBON-11)**

Drug Class	Specific Drug	Reference or Review
Psychostimulants	Cocaine	5,6
	Methylphenidate	113
	Metamphetamine	114
Opiates	Morphine	115
	Heroin	115
	Codeine	115
	Buprenorphine	116
	Methadone	117
Cannabinoids	THC	118
Nicotine	Nicotine	119–120
Caffeine	Caffeine	112
LSD	LSD	121



**FIGURE 103.1.** Left: Images at the level of the striatum obtained with [ $^{11}\text{C}$ ]cocaine and with [ $^{11}\text{C}$ ]methylphenidate at different times after radiotracer injection. Right: Time activity curves for radiotracer concentration in striatum and temporal course for the “high” expressed as a percentage from peak after pharmacologic doses of intravenous cocaine (upper panel) and of intravenous methylphenidate (lower panel). (Modified from Volkow ND, Ding U, Fowler JS, et al. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in human brain. *Arch Gen Psychiatry* 1995;52:456–463, with permission.) See color version of figure.

predominantly to the striatum and where the specific binding for both drugs was to the DATs. Both drugs had a very fast rate of uptake, with peak concentrations in striatum achieved for cocaine between 4 and 6 minutes and for MP between 6 and 10 minutes after injection (6). However, their clearances differed; MP’s clearance from striatum (half-life longer than 90 minutes from peak uptake) was significantly slower than that of cocaine’s (half-life of 20 minutes from peak uptake) (Fig. 103.1). For both drugs, their fast uptake in striatum paralleled the temporal course for the experience of “high” reported by subjects given pharmacologic doses of intravenous cocaine or of MP. However, whereas for cocaine the rate of clearance paralleled the decline in the “high,” for MP the “high” declined while there was still significant binding of the drug in brain (Fig. 103.1). Because it was the “rate of uptake” that was associated with the “high” for both drugs and not the presence of the drug in brain, investigators postulated from this observation that the rate of clearance may affect the propensity of a drug to promote frequent repeated administration. Although the rate at which psychostimulants enter the brain had been recognized as an important variable in their reinforcing effects (7), the relevance of their rate of clearance had not. These pharmacokinetic studies provided evidence that the

rate of drug clearance is relevant in their reinforcing effects. In the case of cocaine, the fast rate of clearance enables repeated, frequent administration that is characteristic of cocaine bingeing (cocaine is taken every 15 to 30 minutes), whereas for MP, its relatively slow clearance from brain is likely to produce accumulation and toxicity that thus prevents frequent repeated administration.

## Pharmacodynamics

Multiple parameters pertaining to the mechanisms of action of the drug of abuse can be investigated with imaging. These include measurement of the efficacy of the drug of abuse at the molecular target that is associated with the reinforcing effects of the drug of abuse (i.e., DAT for cocaine) and assessment on the effects of the drug of abuse on DA concentration and on brain function. These parameters can be assessed both in nonaddicted control subjects and in addicted patients to determine whether there are differences in the responses between them.

## Drug Efficacy

The efficacy of the drug of abuse at the molecular target is illustrated with studies done to investigate the levels of DAT blockade achieved by reinforcing doses of cocaine. With PET and appropriate radiotracers, it is possible to measure the levels of DAT occupancy achieved by drugs that block DAT in human subjects reproducibly (8). The levels of DAT occupancy by different doses of intravenous cocaine were assessed with PET and [ $^{11}\text{C}$ ]cocaine in active cocaine abusers (9). This study showed that cocaine is very effective in blocking DAT; at the doses commonly used by cocaine abusers (0.3 and 0.6 mg/kg), cocaine blocked more than 60% of the DAT. This study also showed that the higher the levels of DAT blockage, the higher the intensity of the “high,” and that for cocaine to induce a “high” it had to block more than 60% of DAT function. A similar study done with intravenous MP showed that the  $\text{ED}_{50}$  (the dose required to block 50% of the DAT) was half that of cocaine (MP, 0.075 mg/kg; cocaine, 0.13 mg/kg) (10). As for cocaine, the magnitude of the DAT occupancy was significantly associated with the intensity of the “high,” a finding corroborating the importance of DAT blockade in the “high.” The differences in the  $\text{ED}_{50}$  between cocaine and MP are compatible with differences in their affinities for DAT (the inhibition constant or  $K_i$  of DA uptake corresponds to 640 and 390 nM, respectively) (11). In analyzing the implications of the similar *in vivo* efficacy for DAT blockade by cocaine and MP, regarding the low abuse potential of MP, it is important to emphasize that the similarities were observed after intravenous administration, which

is not the route of administration used in the treatment of attention-deficit/hyperactivity disorder. Because the rapidity of drug effects is an important variable in the reinforcing effects of drugs of abuse (12) and routes of administration affect drug pharmacokinetics, the results with intravenous MP cannot be extrapolated to oral MP.

The high levels of DAT occupancy achieved by cocaine and MP contrast with the results obtained for other drugs of abuse such as benzodiazepines. SPECT studies measuring the levels of receptor occupancy by the benzodiazepine drug lorazepam showed that only a few receptors are occupied at pharmacologic doses (13), findings that support the notion that in humans there is a “reserve” of benzodiazepine receptors.

### *Effects on Dopamine Concentration*

Because the ability of drugs of abuse to increase extracellular DA concentration is considered crucial for their reinforcing effects, the estimation of DA changes becomes particularly relevant. PET and SPECT enable one to carry such measures in the human brain using radioligands that bind with relatively low affinity to DA D2 receptors (i.e., [<sup>11</sup>C]raclopride, [<sup>123</sup>I]IBZM) and compete with DA for binding to DA receptors. For this purpose, subjects are scanned twice, at baseline and after administration of the drug of abuse, and the difference in the binding of the radioligand between both conditions is mostly a reflection of drug induced changes in extracellular DA. Studies to measure changes in DA concentration induced by drugs of abuse in the human brain have been carried out for amphetamine, cocaine, and MP (14–16). These studies showed that these three psychostimulant drugs significantly increase extracellular DA, and, in the case of intravenous MP, the magnitude of drug-induced DA changes was closely correlated with the intensity of the self-reports of “high.” In fact, for intravenous MP, the changes in DA were a better predictor of the “high” than the levels of DAT blockade, a finding that indicates that the effects of DAT blocker drugs are not only a function of the levels of DAT blockade but also of the amount of DA being released by the terminal (17).

### *Effects on Regional Brain Function*

The most widely used imaging approach for the investigation of drugs of abuse has been to assess the effects of acute drug administration on brain glucose metabolism or CBF. This allows analysis of the brain regions that are most sensitive to the effects of the drug, and because the studies are done in awake human study subjects, it allows an analysis of the relation between regional changes in metabolism or flow and the behavioral effects of the drug. Although most drugs of abuse decrease regional brain glucose metabolism, their effects on CBF are increased by some drugs and decreased by others. This discrepancy between metabolism and CBF is probably an indication of the vasoactive proper-

ties of many of these pharmacologic agents, a property that is relevant for understanding their toxicity as it relates to cerebrovascular disease. The discrepancy could also reflect the finding that changes in metabolism reflect an average of the changes that occur over the uptake period of FDG (30 to 35 minutes), whereas those from blood flow reflect activity that occurs between 2 and 5 seconds for fMRI and 60 seconds for PET and [<sup>15</sup>O]water.

## **CHRONIC EFFECTS OF DRUGS OF ABUSE IN THE HUMAN BRAIN**

Imaging studies have been done to assess neurochemical and functional changes in the brain of addicted subjects that are associated with the process of addiction as well as changes associated with drug toxicity. Functional imaging strategies have also been used to assess the brain region involved in drug-related states such as drug craving. (See Chapter 110.)

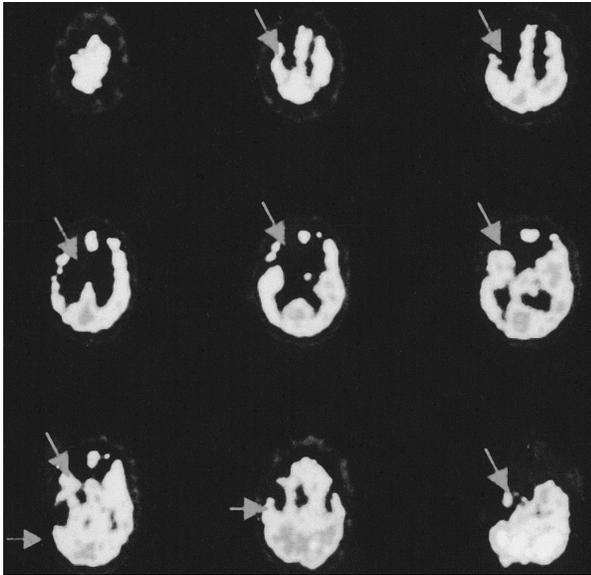
### **Drug Toxicity**

Drug toxicity can be assessed with imaging techniques for brain as well as for other organs. Toxicity from drugs has been documented in abusers of cocaine, methamphetamine, and ecstasy, and the findings from these studies are covered under the subsection of the drug class. In addition, the ability to label the drug with a positron emitter and to follow its distribution in the human body and the availability of radiotracers that allow one to monitor organ function provide a mechanism for evaluating potential toxicity of drugs to organs other than brain. For example, PET studies done with [<sup>11</sup>C]cocaine have shown significant accumulation in human heart (18), a finding leading to the question whether this could be associated with cocaine’s cardiotoxic properties. Cocaine was shown to induce a long-lasting inhibition of the norepinephrine transporter in heart using 6-[<sup>18</sup>F]fluoronorepinephrine or [<sup>11</sup>C]hydroxyephedrine (19,20). Cocaine is a local anesthetic, and its accumulation in heart could result in direct myocardial toxicity. At the same time, inhibition of the norepinephrine transporter by cocaine interferes with a protective mechanism of the heart to remove circulating catecholamines. Thus, these two separate mechanisms operating in parallel are likely to contribute to the highly cardiotoxic properties of cocaine.

### **Cocaine**

#### *Toxicity*

Studies using PET and [<sup>15</sup>O]-labeled water provided the first documentation of abnormalities in CBF in cocaine abusers



**FIGURE 103.2.** Brain images obtained with PET and [ $^{15}\text{O}$ ]water to measure cerebral blood flow in a cocaine abuser. Note the regional decreases in blood flow (arrows). (Modified from Volkow ND, Mullani N, Gould KL, et al. Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. *Br J Psychiatry* 1988;152:641–648, with permission.) See color version of figure.

(Fig. 103.2) (21). The patchy distribution of these CBF defects in brain suggested that they were secondary to cocaine's vasoactive effects (e.g., vasoconstriction, and platelet aggregation), rather than its regional neuroactive properties. These imaging findings, which appeared as defects seen with small strokes and hemorrhages, corroborated clinical reports of strokelike symptoms associated with cocaine use. These PET findings were subsequently replicated in several SPECT studies of CBF in chronic cocaine abusers (reviewed in ref. 22). More recent studies with MRI documented hyperintense lesions in white matter suggestive of subclinical anoxic vascular events in cocaine abusers that were also ascribed to the vasoactive effects of cocaine (23,24). The vasoconstricting effects of cocaine in human brain were corroborated by MRI studies showing significant reductions in cerebral blood volume (23%) (25) and CBF after acute cocaine administration (26).

Using MRS, it is possible to assess tissue composition differentially for neurons and glial cells in brain. This information can be used, in turn, to determine whether there is neuronal damage or glial proliferation. In cocaine abusers, MRS studies reported increases in total creatine (+7%) and myoinositol (+18%) in white matter but no changes in *N*-acetyl aspartate, which is a marker for neuronal content (27). This finding was interpreted as reflecting alterations of nonneuronal but not of neuronal cells in cocaine abusers.

### Brain Glucose Metabolism and Function

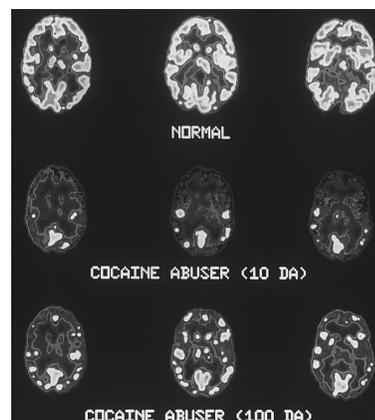
In contrast to the marked defects in CBF reported in cocaine abusers, the functional changes as assessed with brain glu-

cose metabolism are not as pronounced and vary significantly as a function of detoxification. Also different from the patchy distribution of the CBF defect are the decrements in metabolism that tend to localize to cortical projections of the DA system. In recently detoxified cocaine abusers (less than 1 week), brain glucose metabolism was reported to be significantly higher in orbitofrontal cortex and in striatum than in control subjects (28). Metabolic activity was highest in subjects tested during the initial 72 hours after withdrawal, and cocaine abusers who had the highest brain metabolic values had also the highest subjective ratings for craving. In contrast, cocaine abusers tested between 1 and 4 months of detoxification showed significant reductions in metabolic activity in prefrontal cortex, orbitofrontal cortex, and anterior cingulate gyrus (Fig. 103.3) (29). Thus, the orbitofrontal cortex, which is hypermetabolic during early cocaine discontinuation, becomes hypometabolic with protracted cocaine withdrawal.

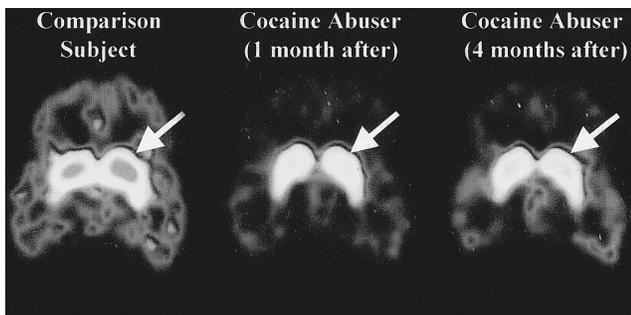
In addition to the studies measuring resting metabolism or CBF, the effects of pharmacologic challenges in cocaine abusers have been compared with controls. Intravenous cocaine was found to reduce brain glucose metabolism in cortical and subcortical brain regions as measured by FDG PET (30). In contrast, an fMRI study of acute cocaine administration revealed widespread activation in various cortical and subcortical brain regions, and the temporal course paralleled that of cocaine-induced "rush" (31). Because other acute pharmacologic interventions used to study cocaine abusers were for the most part chosen to target a specific neurotransmitter system, these aspects are discussed under the appropriate neurotransmitter headings.

### Dopamine System

It has been hypothesized that decreased DA activity could underlie cocaine addiction (32). PET studies done to assess whether there are changes in DA brain activity in cocaine



**FIGURE 103.3.** Images at the level of the striatum obtained with PET and FDG to measure regional brain glucose metabolism in a control subject and in a cocaine abuser tested at two different time points of the detoxification. Notice the marked reduction in metabolism in the frontal cortex. See color version of figure.



**FIGURE 103.4.** Images at the level of the striatum obtained with PET and [ $^{18}\text{F}$ ]NMSP to measure dopamine D2 receptors in a control subject and in a cocaine abuser tested at two different time points of the detoxification. Notice the marked reduction in dopamine D2 receptors during both early and protracted detoxification. See color version of figure.

abusers have used a multitracer approach to assess the relationship between levels of DA D2 receptors and regional brain metabolism in cocaine abusers during early cocaine withdrawal and after cocaine detoxification. Studies in cocaine abusers tested during early cocaine withdrawal (less than 1 week) revealed significant decreases in DA D2 receptor availability when compared with controls (Fig. 103.4) (33).

Studies in cocaine abusers tested between 1 and 4 months of detoxification also showed significant reductions in DA D2 receptor availability as assessed with [ $^{11}\text{C}$ ]raclopride (34). The reductions in DA D2 receptor availability persisted on repeated testing 3 months after completing the inpatient detoxification program. In these patients, the reductions in DA D2 receptors were significantly correlated with metabolic activity in prefrontal cortex, orbitofrontal cortex, and cingulate gyrus (34). Lower values for D2 receptors were associated with lower metabolism in orbitofrontal cortex, cingulate gyrus, and prefrontal cortex, a finding suggesting an association between DA activity and the function of these frontal brain regions. The persistence of the decreased D2 function raise the question of long-term cocaine-induced changes versus preexisting DA system deficits that could increase vulnerability to cocaine dependence.

Abnormalities in orbitofrontal cortex and cingulate gyrus have also been reported for patients with obsessive-compulsive disorders (35), with whom cocaine abusers share the compulsive quality of their behaviors. In patients with obsessive-compulsive disorders, this feature manifests itself in specific behavioral rituals, and in cocaine abusers, it manifests as an obsession to procure the drug and in the repetitive pattern of cocaine self-administration. In laboratory animals, destruction of the orbitofrontal cortex leads to the emergence of repetitive behaviors that cannot be easily terminated (36), and a similar syndrome can be generated by the destruction of the mesocortical DA pathway (37). Thus, it has been postulated that DA-mediated dysregulation of the orbitofrontal cortex and the anterior cingulate gyrus may

be one of the mechanisms responsible for the compulsive administration of cocaine during a “binge” and for the loss of control experienced by the drug abusers when exposed to cocaine or cocaine-related cues (38).

Studies in cocaine abusers to assess the DA terminal have mostly used ligands for the DAT. The results from studies are not consistent; PET studies done with [ $^{11}\text{C}$ ]cocaine as a DAT ligand in actively abusing as well as in detoxified cocaine abusers have failed to show changes in DAT availability (reviewed in ref. 39), whereas SPECT studies done with [ $^{123}\text{I}$ ]β-CIT showed significant DAT increases (17% to 25%) during states of acute (up to 96 hours) drug abstinence (40). Studies with [ $^{18}\text{F}$ ]6-fluorodopa (6-FDOPA), which is an index of DA synthesis that also serves as a marker of the DA terminal, revealed significant reductions in recently detoxified cocaine abusers (11 to 30 days) when compared with control subjects or early abstinent cocaine addicts (1 to 10 days) (41). Reasons for the disparity between these studies are likely to reflect not only differences in the subjects studied but also differences in the effects of cocaine on the targets studied (i.e., it is possible that cocaine increases the expression of DAT while decreasing the synthesis of DA in the terminal). The discrepancies between the two types of DAT studies could reflect differences between the radiotracers and the models used. Because of the disparities, the effects of cocaine on the DA terminal are still not clear. However, because no study has documented reductions in DAT in cocaine abusers, this provides with evidence that cocaine does not induce degeneration of the DA terminal in humans.

Studies in cocaine abusers to assess DA release by the DA terminal have been done using PET and the DA D2 radioligand [ $^{11}\text{C}$ ]raclopride. Studies to assess DA release were performed with and without administration of MP, which is a drug that, like cocaine, blocks DAT. In humans, the measures of MP-induced DA changes are reproducible (42), and they are similar in magnitude to those induced by equivalent doses of cocaine (43). Studies comparing the changes in [ $^{11}\text{C}$ ]raclopride binding between cocaine abusers and control subjects showed that the response of cocaine abusers was 50% lower than that of controls. The “high” induced by intravenous MP was also more intense in controls than in cocaine abusers, whereas in cocaine abusers but not in controls, MP induced intense cocaine craving. This finding indicates that cocaine-dependent patients release less DA in the striatum and have a blunted “high” relative to controls when they are given MP. These results provide evidence that cocaine addiction does not imply an enhanced pleasurable response nor is there a sensitized DA response to the drug. Rather, the reduced DA release and blunted “high” are compatible with cross-tolerance between cocaine and intravenous MP.

The marked decrease in DA brain function in the cocaine abusers (reduction in DA D2 receptors, DA synthesis, and release) may lead to a decrease in activation of DA-modu-

lated reward circuits that are important in drive and motivation. Thus, one could postulate that the decreased in DA activity in cocaine abusers may make normal reinforcers less effective, and these patients may be taking the drug to compensate for the decreased stimulation of DA reward pathways. The decrease in DA function may also contribute to the dysphoria and the anhedonia experienced by these patients during cocaine withdrawal. Thus, strategies to enhance DA brain function in cocaine abusers may help these individuals to engage in activities that may help them to avoid a relapse.

### GABA System

Cocaine enhances DA brain activity, and DA signals are transferred by  $\gamma$ -aminobutyric acid (GABA)ergic pathways (44). These make the GABA pathways a particularly susceptible target for cocaine's effects. PET studies have shown significant reductions in striatal DA D2 receptors in cocaine abusers (33–34). Because D2 receptors are predominantly located on GABA cells (45), reductions of these receptors suggest involvement of GABA pathways in cocaine abusers. The GABA system has been evaluated in cocaine abusers with functional imaging techniques. These studies assessed the brain regional responsivity to GABA stimulation in cocaine abusers and controls (46). Brain responsivity to GABA stimulation was assessed by measuring the brain metabolic responses to lorazepam, a drug that facilitates GABA neurotransmission. Although plasma lorazepam concentration was significantly higher in controls than in drug abusers, lorazepam-induced sleepiness in cocaine abusers was significantly more intense than in controls. Lorazepam reduced whole-brain metabolism, the decrements were greater in drug abusers ( $21 \pm 3$  %) than in controls ( $13 \pm 7$  %), and the differences were largest in striatum, thalamus, and parietal cortex. Because lorazepam-induced sleepiness was correlated with changes in thalamic metabolism, this finding suggests that the increased sedation in cocaine abusers results from the enhanced sensitivity of the thalamus to lorazepam. These results support the notion of disruption of GABA activity in the brain of cocaine abusers. The extreme sedative effects observed for some of the cocaine abusers after lorazepam administration should alert clinicians to potential untoward reactions in the use of these drugs in active cocaine abusers.

MRS was used to assess the concentration of GABA levels in brain comparing cocaine abusers and controls (47). GABA measurements were localized to the occipital cortex (volume, 9 cc). The cocaine abusers showed a significant decrease (23%) in GABA in comparison with controls. In contrast, macromolecule levels were not significantly different between controls and cocaine abusers. These data corroborate an involvement of cerebral GABA levels in cocaine abusers.

### Opioid System

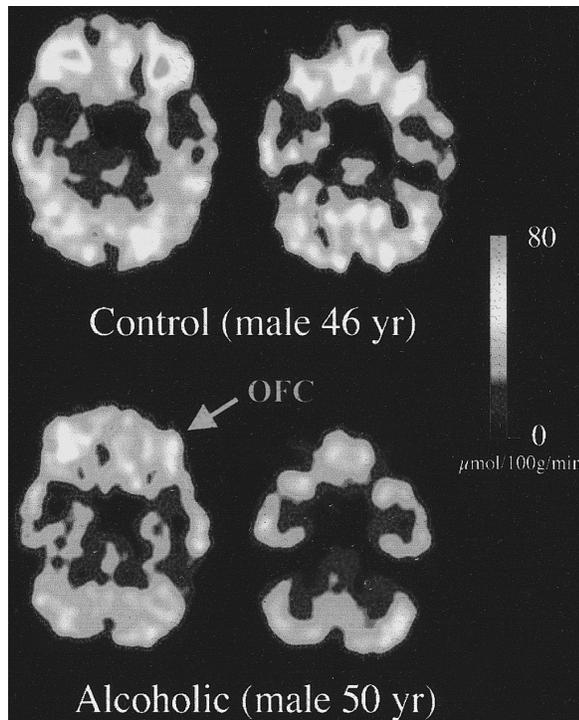
The endogenous opioid system has been implicated in the reinforcing actions of cocaine and other addictive drugs.  $\mu$ -Opioid receptor binding was measured in cocaine-dependent subjects using PET and [ $^{11}\text{C}$ ]carfentanil (48).  $\mu$ -Opioid binding was increased in several brain regions of the cocaine addicts in proportion to the severity of cocaine craving experienced at the time. The up-regulation of  $\mu$ -opioid receptor binding persisted after 4 weeks of detoxification. These findings provide evidence for the involvement of the opioid system in cocaine addiction.

### Alcohol

Imaging studies in patients with alcoholism have been done to measure CBF, brain glucose metabolism (baseline and with pharmacologic challenges), benzodiazepine receptors, DA D2 receptors, and DATs and serotonin transporters in brain.

### Brain Metabolism and Cerebral Blood Flow

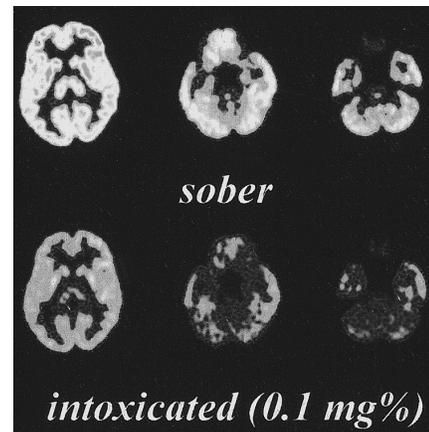
Most of the nonstructural imaging studies have been done to investigate brain metabolic and CBF changes in patients with chronic alcoholism with and without neurologic impairment (reviewed in refs. 49 and 50). Patients with alcoholism and Korsakoff encephalopathy showed decreased metabolism in prefrontal, parietal, and temporal cortices, and patients with alcoholism and neurologic symptoms other than Korsakoff encephalopathy showed decreased metabolism in frontal and parietal cortices. Studies in patients with alcoholism who have no evidence of neurologic impairment have also consistently shown evidence of frontal abnormalities (reviewed in ref. 51). Decrements in metabolism were most accentuated in the older patients with alcoholism with longer histories of alcohol consumption. The degree of brain metabolic recovery with detoxification was evaluated with PET in patients with alcoholism who were evaluated at different times of the detoxification (52,53). These studies showed that brain metabolism increased significantly during detoxification, predominantly during the first 16 to 30 days of detoxification. However, decreased metabolic activity in orbitofrontal cortex persisted (Fig. 103.5) (9). Most PET studies in patients with alcoholism have been done in male patients, and little is known about changes in female patients with alcoholism. One PET study measured regional brain metabolism in recently detoxified female patients with alcoholism and compared it with that in age-matched female controls (54). This study showed no differences between patients with alcoholism and female control subjects. These results did not support a higher toxicity for the effects of alcohol in the female than in the male brain, in which most studies have consistently reported lower metabolism in the frontal region. However, this study was con-



**FIGURE 103.5.** Images at the level of the orbitofrontal cortex obtained with PET and FDG to measure regional brain glucose metabolism in a control subject and in detoxified patient with alcoholism. Notice the reduction in metabolism in the orbitofrontal cortex. See color version of figure.

founded by the finding that the severity of alcohol use in these female patients with alcoholism was less than that of the male patients with alcoholism previously investigated in PET studies. The female subjects in this study were mostly premenopausal, and thus the lack of metabolic abnormalities may have reflected not only the lower alcohol severity but also the protective effects of estrogens.

In addition to the studies measuring resting metabolism or CBF in patients with alcoholism, multiple studies have been done comparing regional brain metabolic and CBF responses to various pharmacologic challenges between control subjects and patients with alcoholism. Because most of the pharmacologic interventions were chosen to target a specific neurotransmitter system, we will discuss the findings from these studies under the neurotransmitter heading. In the case of alcohol, which is believed to exert its effects through multiple neurotransmitter systems, its effects on brain glucose metabolism (55,56) and CBF (57) were evaluated with PET. Such studies showed that acute alcohol administration decreased brain glucose metabolism (Fig. 103.6). When compared with controls, patients with alcoholism showed a significantly larger reduction in metabolism despite showing less subjective response to the intoxicating properties of ethanol (55). In control subjects but not in patients with alcoholism, the subjective response to



**FIGURE 103.6.** Images at the level of the striatum and of the orbitofrontal cortex and cerebellum obtained with PET and FDG to measure the effects of acute alcohol administration (1 g/kg orally) on brain glucose metabolism in a control subject. Notice the marked reduction in metabolism during alcohol intoxication. See color version of figure.

the intoxicating effects of ethanol was significantly correlated with the brain metabolic decrements (55). This seemingly paradoxical response in patients with alcoholism was interpreted as reflecting their tolerance to ethanol-induced decrements in metabolism.

### GABA System

The effects of benzodiazepines, which facilitate GABA neurotransmission, on brain glucose metabolism (58–60) and CBF (61) have also been evaluated with PET. Such studies have shown that, similar to ethanol, benzodiazepines decrease brain glucose metabolism, and the effects are more pronounced in the occipital cortex, the area of the brain with the highest density of benzodiazepine receptors (62). Benzodiazepines also decrease CBF, and as for metabolism, the largest changes are observed in the occipital cortex. Studies comparing the response to benzodiazepines between control subjects and patients with alcoholism showed a significantly lower response in the orbitofrontal cortex in patients with alcoholism than in controls (46,53). The blunted response to lorazepam in orbitofrontal cortex persisted after detoxification, a finding suggesting that it was not the result of withdrawal and that hypoactivity in this brain region may in part reflect abnormal GABAergic function (benzodiazepines facilitate GABAergic neurotransmission).

Imaging studies have also been done to measure changes in benzodiazepine receptors using PET and [ $^{11}\text{C}$ ]flumazenil in patients with alcoholism. One study showed that although there were no changes in the levels of receptor between controls and patients with alcoholism, the latter had a significantly larger variability for  $B_{\text{max}}$  (receptor concentration) measures than controls (63). However, more recent studies have consistently reported significant decreases in

benzodiazepine receptors in patients with alcoholism, predominantly in frontal brain regions including cingulate gyrus and orbitofrontal cortex (64,65), but also in cerebellum (66). The reductions in benzodiazepine receptors in patients with alcoholism reported by these imaging studies are consistent with postmortem studies and may indicate either a toxic effect of alcoholism on benzodiazepine receptors or a vulnerability factor for developing alcoholism. The reductions in benzodiazepine receptors in the orbitofrontal cortex of patients with alcoholism could account for the blunted response to benzodiazepines reported in this brain region (53,59).

### Dopamine System

DA D2 receptors were evaluated in patients with alcoholism with PET and [<sup>11</sup>C]raclopride and showed significant reductions in DA D2 receptor availability when compared with controls (67,68). No significant correlations were found between DA D2 receptor availability and days of detoxification (1 to 68 weeks). One of these studies also measured DATs in a subgroup of the alcoholics in whom reductions in DA D2 receptors were detected and reported no changes in DAT availability (68). This finding was interpreted as evidence of GABAergic involvement in patients with alcoholism because DA D2 receptors in striatum are mainly localized in GABA cells.

DAT availability in patients with alcoholism has been measured by various PET and SPECT studies. The results have not been consistent. SPECT studies with [<sup>123</sup>I]β-CIT reported that a group of violent patients with alcoholism had increases (8%) and nonviolent patients with alcoholism had decreases in DATs (25%) when compared with controls (69). SPECT studies in nonviolent patients with late-onset alcoholism have also reported a reduction in DATs (70). However, a PET study done with [<sup>11</sup>C]D-threo-MP and a SPECT study done with [<sup>123</sup>I]β-CIT showed no changes in DATs in patients with alcoholism (71,68). These discrepancies are likely to reflect in differences in the time since detoxification. One SPECT study showed that whereas DAT levels were significantly reduced in patients with alcoholism within the first few days of last alcohol use, the levels returned to normal 4 weeks after detoxification (72). PET studies with 6-[<sup>18</sup>F]-FDOPA (a marker for the DA synthesis in the DA terminal) in patients late-onset (type 1) alcoholism showed higher striatal 6-[<sup>18</sup>F]-FDOPA uptake in the patients with alcoholism than in the controls, a finding that was interpreted as a compensatory mechanism to low postsynaptic DA function (73).

### Serotonin System

The effects of m-chlorophenylpiperazine (mCPP), a mixed serotonin agonist-antagonist drug, on brain glucose metabolism was compared in patients with alcoholism and in con-

trols. This study showed that mCPP-induced activation in thalamus, orbitofrontal cortex, caudate, and middle frontal gyrus was significantly blunted in patients with alcoholism when compared with controls (74). This finding was interpreted as reflecting a hyporesponsive striatalthalamoorbitofrontal circuit in patients with alcoholism. The abnormal response to mCPP suggests an involvement of the serotonin system in the abnormalities seen in this circuit in patients with alcoholism.

The availability of serotonin transporters, which serve as markers for the serotonin terminals, was measured with SPECT and [<sup>123</sup>I]β-CIT in patients with alcoholism. This study showed a significant reduction in the availability of brainstem serotonin transporters in patients with alcoholism that was significantly correlated with lifetime alcohol consumption and with ratings of depression and anxiety during withdrawal (75). As for the prior study, this finding provides evidence of a role for serotonin in alcoholism and in its involvement with depressive symptoms during withdrawal.

### Opioid System

The effects of an oral naltrexone challenge on CBF in patients with alcoholism during detoxification was studied with SPECT and HMPAO. At baseline, patients with alcoholism showed lower CBF in left orbitofrontal cortex and prefrontal cortex than controls. After naltrexone, a significant regional CBF decrease was found in basal ganglia and the left mesial temporal region, which are structures rich in opioid receptors. These results were interpreted as supporting the involvement of the opioid system in alcohol dependence (76).

### Spectroscopic Studies

Patients with alcoholism had a significant reduction of the cerebellar *N*-acetylaspartate-to-creatine ratio, which was interpreted as reflecting neuronal loss and a reduction of the choline-to-creatine ratio, which was interpreted as reflecting cell membrane modification or myelin alterations (77).

### Subjects at Risk of Alcoholism

The regional brain metabolic response to lorazepam was evaluated in subjects with a positive family history of alcoholism (FHP) and was compared with that of subjects without a family history of alcoholism (FHN) (78). At baseline, FHP subjects showed lower cerebellar metabolism than FHN, and when challenged with lorazepam, they also showed a blunted response in cerebellum and in anterior cingulate gyrus. Lorazepam-induced changes in cerebellar metabolism were significantly correlated with motor impairment. The blunted cerebellar sensitivity to benzodiazepines in FHP could account for the decreased sensitivity to the motor effects of alcohol and benzodiazepines in FHP sub-

jects. The decreased cerebellar baseline metabolism in FHP subjects as well as the blunted cerebellar response to lorazepam challenge may reflect disrupted activity of benzodiazepine-GABA receptors in cerebellum of FHP subjects.

## Opiates

The effects of morphine on brain glucose metabolism were evaluated in polydrug abusers (79). This study showed that morphine reduced glucose metabolism by 10% in whole brain and by about 5% to 15% in telencephalic areas and the cerebellar cortex. Morphine-induced metabolic decrements were not significantly related to subjective measures of euphoria. The effects of acute fentanyl, a synthetic opiate, on CBF were measured with PET and [ $^{15}\text{O}$ ]water. Fentanyl administration was associated with significant increases in regional CBF in cingulate, orbitofrontal, and medial prefrontal cortices, as well as caudate nuclei, areas known to be involved in reward and addiction (80).

Resting CBF was measured with SPECT and  $^{99\text{m}}\text{Tc}$ -HMPAO in heroin abusers tested 1 week after opiate discontinuation and then retested 2 weeks later (81). The initial scans demonstrated significant CBF defects in the frontal, parietal, and temporal cortices. Two weeks later, the SPECT scans showed improvement. The results from this study provide evidence that long-term use of opiates results in perfusion abnormalities that are partially reversible with short-term abstinence.

## Dopamine System

Using PET and [ $^{11}\text{C}$ ]raclopride, opioid-dependent subjects were found to have lower DA D2 receptor availability than controls. Naloxone-induced withdrawal in opioid-dependent subjects did not change [ $^{11}\text{C}$ ]raclopride binding, a finding indicating that withdrawal does not alter synaptic DA in the striatum as measured by this method (82).

## Opioid System

To date, there have been no published studies of opioid abusers using these opiate receptor radioligands to study heroin abusers (see earlier).

## Spectroscopic Studies

Phosphorus magnetic resonance spectroscopy ( $^{31}\text{P}$  MRS) at 1.5 T was performed on polysubstance abusing men (cocaine and heroin dependence) (83). The phosphorus metabolite signal expressed as a percentage of total phosphorus signal was 15% higher for phosphomonoesters, 10% lower for nucleotide triphosphates ( $\beta$ -NTP), and 7% lower for total nucleotide phosphates in polydrug abusers compared with controls. These findings were interpreted as suggesting that long-term drug abuse or withdrawal results in changes

in cerebral high-energy phosphates and in phospholipid metabolites.

## Marijuana

Marijuana is the most widely used illicit drug of abuse in the United States. Despite its widespread use, the mechanisms by which  $\Delta^9$ -tetrahydrocannabinol (THC) (the main psychoactive substance of marijuana) exerts its psychoactive effects are still not known. Relatively few imaging studies have been done to assess the effects of acute and chronic marijuana use in the human brain.

### *Brain Metabolism and Cerebral Blood Flow*

SPECT studies assessed the effect of THC intoxication on CBF in chronic marijuana users (84,85). Acute marijuana administration led to decreases in CBF in subjects who were not experienced marijuana smokers, whereas it increased CBF in subjects who were experienced smokers. In a more recent study, these investigators extended these findings to a larger group of subjects and documented increases in CBF in anterior cingulate gyrus and in the insula in marijuana users (86). Interpretation of the effects of THC on CBF is confounded by the vasoactive properties of THC (87). Thus, it is difficult to separate the effects of THC that are related to its action on nervous tissue from those that are related to its vasoactive effects. This problem is obviated when using deoxyglucose to measure brain glucose metabolism because this agent is insensitive to fluctuations in CBF (88).

The effects of THC on regional brain glucose metabolism have been evaluated in nonabusing controls (89) as well as in marijuana abusers (90). The whole-brain metabolic response to the effects of THC was variable among individuals; some subjects had increases, some had decreases, and some did not show change. Despite these variable responses in whole-brain metabolism, there was a very consistent pattern of metabolic activation by THC. That is, under THC intoxication, most of the subjects showed activation of the cerebellum. The cerebellar activation by THC was significant both for the absolute and for the relative measures. In marijuana abusers, THC also increased metabolism in the anterior cingulate gyrus and in the orbitofrontal cortex. A more recent study assessing the effects of marijuana on CBF also reported an increase in cerebellar flow during intoxication (91). The highly localized concentration of cannabinoid receptors in the cerebellum (92) supports involvement of the cannabinoid receptors in the metabolic and CBF response during THC intoxication. Activation of the cerebellum by THC could explain the disruption in motor coordination and proprioception during THC intoxication. Cannabinoid receptors are also localized in other discrete areas, namely, hippocampus, substantia nigra, pars reticu-

lata, and globus pallidus. These are too small to be measured with the spatial resolution of the PET instrument used.

SPECT studies compared CBF in subjects with attention-deficit disorder who had a history of marijuana abuse with those who did not (93). Decreased perfusion in the prefrontal cortex was seen in both marijuana users and non-users. However, the marijuana users also demonstrated marked decreased activity in the temporal lobes, which was ascribed to chronic marijuana use.

### Cannabinoid Receptors

Attempts to investigate THC in the living brain with PET by using the labeled drug with a positron emitter have been unsuccessful because of the highly lipophilic nature of THC. This was also a limitation for  $\Delta^8$ -tetrahydrocannabinol, an analog of  $\Delta^9$ -THC, which was labeled with  $^{18}\text{F}$ . Its uptake and distribution showed widespread uptake in the baboon brain with no particular pattern of localization (94). This pattern of distribution mainly reflected nonspecific binding because pretreatment with  $\Delta^8$ -THC did not affect the uptake of [ $^{18}\text{F}$ ] $\Delta^8$ -THC in brain. A promising alternative may be the use of THC antagonists with high receptor affinities (95).

### Cigarettes and Nicotine

Even though there are 45 million cigarette smokers in the United States and there are 400,000 deaths per year associated with smoking, surprisingly little is known about the neurochemical actions of tobacco smoker exposure on the human brain, and very few imaging studies have been performed. The acute administration of intravenous nicotine has been reported to reduce brain glucose metabolism (96). In addition, PET studies with [ $^{11}\text{C}$ ]nicotine have shown that cigarette smokers have increased binding in brain that could reflect the up-regulation in nicotinic receptors sites reported in smokers (97).

Monoamine oxidase A and B (MAO A and B) have been examined in the human brain (98,99). MAO breaks down neurotransmitter amines like DA, serotonin, and norepinephrine, as well as amines from exogenous sources. It occurs in two subtypes, MAO A and MAO B, which can be imaged *in vivo* using [ $^{11}\text{C}$ ]clorgyline and [ $^{11}\text{C}$ ]L-deprenyl-D2 and PET. Using these ligands, it was shown that cigarette smokers have a reduction in brain monoamine oxidase B (MAO B) of about 40% relative to nonsmokers and former smokers, and smokers have a 28% reduction in brain MAO A relative to nonsmokers. It is known that nicotine does not inhibit MAO B at physiologically relevant levels. MAO A and B inhibition is associated with enhanced activity of DA, a neurotransmitter involved in reinforcing and motivating behaviors and in movement as well as decreased production of hydrogen peroxide, a source of reactive oxy-

gen species. Inhibition of MAO by cigarette smoke could be one of the mechanisms accounting for the lower incidence of Parkinson disease in cigarette smokers. MAO A and B inhibition by smoke may also account for some of the epidemiologic features of smoking that include a higher rate of smoking in persons with depression and addiction to other substances. In this regard, it is noted that MAO A inhibitors are effective in the treatment of depression.

### Ecstasy

The toxicology of the popular illicit drug ecstasy, 3,4-methylenedioxyamphetamine (MDMA), is covered in Chapter 108. Studies in laboratory animals have shown that ecstasy induces neurotoxicity to serotonergic neurons. Ecstasy users imaged with the PET ligand [ $^{11}\text{C}$ ]McN-5652 (for 5-hydroxytryptamine transporters), showed decreased global and regional brain 5-hydroxytryptamine transporter binding compared with controls (100). SPECT studies with [ $^{123}\text{I}$ ] $\beta$ -CIT (a radioligand for DAT and serotonin transporters) confirmed the reductions in serotonin transporters in ecstasy users (101) and provided preliminary evidence of serotonergic neurotoxicity by ecstasy in humans.

Because the cerebrovasculature is regulated partly by the serotonergic system, it was questioned whether ecstasy would affect CBF in humans. For this purpose, CBF was measured with SPECT in ecstasy users tested at baseline and after receiving MDMA (102). Abstinent ecstasy users showed no baseline CBF changes when compared with controls. However, within 3 weeks after MDMA administration, CBF remained decreased in the visual cortex, the caudate, and the superior parietal and dorsolateral frontal regions compared with baseline values. These reductions were interpreted as reflecting transient effects of MDMA on the serotonergic system or the indirect effects of its metabolites on the DA system.

PET and FDG were also used to measure regional brain glucose metabolism in ecstasy users (103). Ecstasy users showed altered activity in amygdala, hippocampus, and Brodmann's area II, findings interpreted as suggesting a long-term effect of ecstasy on brain function.

Spectroscopic studies with proton MRS done in ecstasy users showed normal *N*-acetyl compounds in all brain regions but showed increases in myoinositol concentration (+16.3%) and the myoinositol-to-creatine ratio (+14.1%) in parietal white matter (104). The finding of a normal *N*-acetyl concentration was interpreted as a lack of neuronal injury in recreational ecstasy users, and the increase in myoinositol was seen as an increase in glial content.

### Methamphetamine

Methamphetamine is a particularly problematic drug not only in that it is highly addictive but also because animal

studies have shown that it is neurotoxic to DA cells (105). Because the pattern and doses of methamphetamine administered to laboratory animals differ from those used by drug abusers, imaging studies have been performed to determine whether similar pathologic features occur in human methamphetamine abusers. The data in humans are very limited: a postmortem study of 12 methamphetamine abusers (106) and two PET studies, one of six (107) and the other of 15 methamphetamine abusers (108). Both reported reductions in brain DATs. Moreover, for one of the studies, the reductions in DAT were associated with motor slowing and memory impairment and were present even in patients who had been detoxified for more than 11 months (108). These results provide evidence that methamphetamine, at the doses administered by humans, damages the DA terminals, that these effects are long lasting, and that the damage from methamphetamine is functionally significant.

Spectroscopic studies were done with proton MRS in abstinent methamphetamine abusers and showed that the concentration of *N*-acetylaspartate, a neuronal marker, was reduced significantly (−5 to −6%) in the basal ganglia and frontal white matter of methamphetamine users compared with controls (109). The frontal white matter (*N*-acetylaspartate) correlated inversely with the logarithm of the lifetime methamphetamine use. The methamphetamine users also showed significantly reduced total creatine in the basal ganglia (−8%) and increased choline-containing compounds (+13%) and myoinositol (+11%) in the frontal gray matter. These findings were interpreted as providing evidence of long-term neuronal damage in abstinent methamphetamine users.

## Caffeine

Caffeine is an antagonist of the G-protein–linked adenosine receptors. Caffeine is a mild stimulant when taken orally, but it has marked effects when administered intravenously, including olfactory hallucinations.

Despite the widespread consumption of caffeine and the potential for confounding effects in studies of other drugs of abuse, caffeine appears to be the subject of only a single PET CBF study. Caffeine (250 mg), given either intravenously or orally, produced an approximately 30% decrease in global CBF measured using [<sup>15</sup>O]water, without significant regional differences (110). The effect of caffeine lasted for at least 45 minutes. The original purpose of this study was to examine whether patients with panic disorder exhibited a difference response from control subjects, but no differences were found.

The effects of caffeine on regional brain metabolism, as assessed by the changes in brain lactate, were measured with MRS (111). The response of heavy caffeine users was compared with that of caffeine-intolerant persons. Subjects were studied at baseline and 1 hour after caffeine (10 mg/kg).

The caffeine-intolerant group but not the heavy caffeine users showed significant increases in brain lactate. Reexposure of the regular caffeine users to caffeine after a caffeine holiday resulted in rises in brain lactate similar in magnitude to those seen in the caffeine-intolerant group. These results provide evidence of caffeine tolerance in the human brain and do not support the role of lactate as a mediator of caffeine intolerance.

Studies using [<sup>11</sup>C]caffeine showed that its binding in brain was mostly nonspecific, as was expected because of caffeine's low affinity and lack of selectivity for adenosine receptor subtypes (112). Intravenously administered [<sup>11</sup>C]caffeine resulted in very fast uptake and clearance from brain, contrasted with the slow brain uptake when [<sup>11</sup>C]caffeine was given orally through a nasogastric tube (brain uptake was increasing even after 2 hours at the end of the study).

## CONCLUSION

Brain imaging using virtually all available methods has proved useful in evaluating the effects of abused drugs. Much has been learned about the mechanisms of action in human subjects as well as the potential for toxic effects. Among the consistent findings across the various drugs of abuse are the following:

1. The pharmacokinetic properties of drugs of abuse affect their reinforcing effects.
2. Many of the drugs of abuse have vasoactive effects, which, in the case of cocaine, can result in cerebrovascular disease.
3. The orbitofrontal cortex and the anterior cingulate gyrus have consistently been shown to be abnormal in addicted subjects, a finding implicating a role in the process of drug addiction.
4. The availability of DA D2 receptors is reduced in most drug abusers who have been investigated. Because DA D2 receptors modulate reward circuits, this could be one of the mechanisms that contributes to drug self-administration.

As new ligands and new methods are developed, an improved understanding of the mechanisms of addiction can be expected.

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