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REVIEW

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Functional imaging and neurochemical correlates of stimulant self-administration in primates

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Abstract *Rationale:* Recent advances in neuroimaging and in vivo neurochemistry have documented drug-induced functional changes in brain activity under physiologically relevant conditions. These approaches have significant strengths and important limitations that should be considered. *Objectives:* The present review describes current in vivo approaches to characterize drug effects as they relate to behavior, and highlights key contributions derived from each approach in the context of stimulant self-administration in primates. *Methods:* Techniques relating in vitro neurochemistry to behavioral pharmacology are compared to several in vivo approaches, including microdialysis, positron emission tomography (PET) neuroimaging and functional magnetic resonance imaging (fMRI). *Results:* In vitro neurochemical correlates of behavioral pharmacology established a significant relationship between dopamine and the reinforcing effects of abused stimulants. Subsequent in vivo microdialysis studies in behaving animals supported a critical role for nucleus accumbens dopamine in the reinforcing effects of stimulants. PET neuroimaging in monkeys and humans documented a close relationship between dopamine transporter (DAT) occupancy in vivo and the reinforcing effects of stimulants. The effectiveness of selective DAT inhibitors to reduce cocaine self-administration also was linked to DAT occupancy in vivo. Lastly, the measurement of cerebral blood flow and metabolism with PET and fMRI has begun to define the neuronal circuitry influenced by acute and chronic stimulant exposure. *Conclusions:* Collectively, in vivo neurochemistry and functional imaging have complemented in vitro approaches and have enhanced our current understanding of the neurobiology of abused stimulants.

Keywords Neuroimaging · Neurochemistry · Stimulants · Nonhuman primates · Drug self-administration · Dopamine

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Introduction

There has been a long-standing interest in physiological and neurochemical concomitants linked to drug effects on behavior. Among the earlier seminal investigations were studies that documented orderly relationships between the behavioral and cardiovascular effects of drugs (e.g. Herd et al. 1969; Kelleher et al. 1972; Dews and Herd 1974). In parallel, other investigators focused more directly on neurochemical correlates of drug-behavior interactions (e.g. Seiden 1975). More recent approaches directed toward mechanistic accounts of drug-induced changes in behavior represent a logical extension of these pioneering research advances. Efforts focusing on in vitro neurochemical correlates of behavioral pharmacology have identified important neurochemical mechanisms relevant to drug effects on behavior. The extension of these efforts to in vivo analyses has provided direct measures of neurochemistry under physiologically relevant conditions to complement in vitro determinations. Progress in neuroimaging technology has further allowed for noninvasive, functional assessments of brain chemistry and physiology with direct application to human investigations of drug abuse. Each of these approaches has significant strengths and important limitations that should be considered before a given methodology is applied to a specific research question. The present review highlights some of the key contributions that have derived from the use of each approach to study psychomotor stimulant (hereafter referred to as "stimulant") self-administration behavior in nonhuman primates and humans. Collectively, notable advances have been made in our current understanding of the neurobiology of abused stimulants

that may have important implications for medications development to treat stimulant abuse.

In vitro neurochemical correlates of behavioral pharmacology

In a seminal paper, Ritz et al. (1987) reported a significant correlation between the potencies of stimulants in self-administration studies and their binding affinity at the dopamine transporter (DAT). The analysis was based on data derived from a variety of published reports and included stimulants from distinct chemical classes that were studied in rodent and nonhuman primate species. In subsequent studies in nonhuman primates, additional evidence was obtained to link the behavioral effects of cocaine and related drugs to their actions at specific cocaine recognition sites associated with the dopamine uptake system. Specific binding sites for [^{3}H]cocaine were identified in caudate-putamen membranes prepared from cynomolgus and squirrel monkey brains (Madras et al. 1989). [^{3}H]Cocaine was displaced stereoselectively from these sites by enantiomers and diastereoisomers of cocaine, a phenyltropane analog, and by several monoamine uptake inhibitors structurally unrelated to cocaine. In behavioral studies, squirrel monkeys were trained to respond under a fixed-interval schedule of stimulus-shock termination, and dose-effect curves were established for cocaine and the other drugs studied in neurochemical experiments (Spealman et al. 1989). The results demonstrated a strong association between the potencies of 15 different drugs for producing cocaine-like behavioral-stimulant effects and for displacing specifically-bound [^{3}H]cocaine in caudate-putamen.

In related studies, there was a close correspondence between the relative potencies of cocaine and related drugs for increasing rates of schedule-controlled responding and for maintaining IV self-administration under a second-order fixed-interval schedule (Bergman et al. 1989). These results suggest that similar neurochemical mechanisms may mediate the behavioral-stimulant and reinforcing effects of cocaine-like drugs in nonhuman primates. Also, the potency relations for self-administered drugs, except GBR 12909, generally corresponded with their relative potencies for displacing [^{3}H]cocaine from striatal binding sites. GBR 12909 was less potent than cocaine in maintaining self-administration behavior, even though it was two-fold more potent than cocaine in displacing [^{3}H]cocaine from monkey caudate-putamen. The authors suggested that the discrepancy in relative potency may have been due to pharmacokinetic factors, and highlighted the importance of in vivo characterization of GBR 12909 bioavailability to determine drug concentration at its central site of action.

Recent studies have used a similar approach to investigate the effects of other drugs that, like cocaine, have local anesthetic properties. These local anesthetics, e.g. procaine, also have been shown to bind to the DAT and inhibit dopamine uptake. Accordingly, it is not surprising that they can exhibit reinforcing effects. When the binding affinities of cocaine and several local anesthetics at the DAT in rhesus monkey brain were compared to their potencies in i.v. self-administration studies, a significant correlation was obtained (Wilcox et al. 1999). In contrast, there was no relationship between their sodium channel affinities, presumed to mediate local anesthetic properties, and self-administration potencies.

Autoradiographic techniques have been used in vitro and ex vivo to map the regional distribution of cocaine binding sites labeled with the cocaine analog [^{3}H]WIN 35,428 in squirrel monkey brain (Canfield et al. 1990; Kaufman and Madras 1992). High densities of [^{3}H]WIN 35,428 binding sites were observed in the caudate-putamen and nucleus accumbens. In all regions, binding was significantly reduced by co-incubation with (–)-cocaine. These results indicated that cocaine binding sites labeled by [^{3}H]WIN 35,428 were localized primarily in dopamine-rich brain regions linked to the behavioral effects of cocaine. In a related study, several additional brain regions exhibited intermediate densities of [^{3}H]WIN 35,428 binding, including the substantia nigra, amygdala and hypothalamus (Kaufman et al. 1991). The latter results raise the possibility that these brain regions, in addition to caudate-putamen and nucleus accumbens, may contribute to the behavioral effects of cocaine. Similarly, neuroanatomical mapping of cocaine distribution in brain after IV administration of [^{3}H]cocaine resulted in the highest accumulation in dopamine-rich brain regions including caudate-putamen and nucleus accumbens (Madras and Kaufman 1994). However, the locus coeruleus, hippocampus and amygdala also accumulated significant quantities of labeled cocaine, consistent with the idea that other prominent targets of cocaine may contribute to its behavioral pharmacology.

Collectively, in vitro neurochemical correlates of behavioral pharmacology have identified important neurochemical mechanisms relevant to the neurobiology of stimulant abuse. A substantial literature has established a significant relationship between dopamine and the reinforcing effects of cocaine and related stimulants. Specific brain regions that may contribute to the behavioral effects of cocaine have been identified, and long-term neurochemical changes associated with chronic stimulant exposure have begun to be characterized. This research has established the foundation of our current knowledge of neurochemical mechanisms underlying the behavioral effects of stimulants. However, it is important to keep in mind that in vitro investigations are necessarily restricted in scope because they cannot mimic physiological conditions in intact animals. For example, ease of passage into the brain or metabolic activity may dictate whether or how much of a drug reaches its sites of action. Longitudinal studies are difficult, and data are often obtained in the absence of functional information. Moreover, because it is difficult to predict the in vitro concentrations that have relevance to actions in vivo, potency relationships established in vitro do not necessarily correspond to those determined in behavioral studies. The development of in

vivo approaches to neurochemical investigations has begun to provide important alternative methodologies for avoiding or resolving these types of problems.

In vivo neurochemistry

In vivo microdialysis has become a widely used technique for sampling extracellular neurochemicals in discrete brain structures. The technique overcomes many of the limitations of in vitro receptor binding and tissue homogenate preparations by providing real-time functional measures of neurochemistry in behaving animals. The approach is well suited for pharmacological studies that characterize dose-response relationships and drug time course of action. Initial studies in rats trained to self-administer cocaine provided convincing evidence that the reinforcing properties of cocaine were mediated primarily by dopamine release in the nucleus accumbens (Pettit and Justice 1989, 1991). Intravenous self-administration of cocaine was shown to be linked to episodic fluctuations in extracellular dopamine. More recent studies have shown a similar relationship between the timing of amphetamine self-administration and dopamine neurochemistry (Ranaldi et al. 1999). Moreover, the context in which cocaine is administered can significantly alter the neurochemical response to equivalent brain concentrations of cocaine, as evidenced by greater increases in nucleus accumbens dopamine when cocaine is self-administered compared to yoked, non-contingent administration (Hemby et al. 1997).

While in vivo microdialysis has been used extensively in rodents to examine the neurochemical effects of cocaine, only recently has the technique been extended into behavioral studies in nonhuman primates. In view of the expense of this type of work in primates, such studies generally are undertaken as long-term neurochemical studies involving repeated experiments in the same subject. Also, verification of accurate probe placement is obtained with MRI rather than histology, obviating the need to sacrifice valuable subjects (Bradberry et al. 2000; Czoty et al. 2000). The ability to utilize a repeated-measures, within-subjects design has been proven crucial to the success of this line of research (Iyer et al. 1995; Czoty et al. 2000, 2002). For example, recent studies were conducted to document longitudinal changes in neurochemical responses to self-administered cocaine in rhesus monkeys (Bradberry 2000). Subjects were trained under fixed-ratio schedules of IV cocaine delivery and allowed to receive two injections per session. During individual cocaine self-administration sessions, acute tolerance developed to cocaine-induced elevations in extracellular dopamine in the striatum. However, long-term exposure to cocaine self-administration enhanced the neurochemical response to a fixed dose of cocaine in a time-dependent manner. Hence, in vivo microdialysis has been used effectively in nonhuman primates to document both acute tolerance and long-term sensitization to self-administered cocaine.

In vivo microdialysis protocols also have been implemented in conscious squirrel monkeys to identify neurochemical correlates of drug interactions during cocaine self-administration behavior (Czoty et al. 2002). In these studies, a serotonin uptake inhibitor, alaproclate, and a serotonin direct agonist, quipazine, were used to suppress cocaine self-administration under a second-order schedule of IV cocaine delivery. These effects were produced by doses of the serotonergic agents that did not have nonspecific behavioral suppressant actions, as evident in companion studies of behavior maintained by an identical schedule of stimulus termination. Importantly, the same pretreatment doses that decreased cocaine self-administration significantly attenuated cocaine-induced increases in extracellular dopamine in a separate group of awake monkeys used for in vivo microdialysis. Hence, in vivo measures effectively identified ongoing neurochemical actions on extracellular dopamine that likely were related directly to the behavioral effects of the serotonergic agonists.

In vivo microdialysis techniques have provided a means to measure ongoing neurochemical activity, augmenting other types of in vivo approaches that can be used to characterize neurochemical mechanisms underlying drug effects on behavior and their roles in drug addiction. The electrophysiological studies of Schultz and colleagues are particularly noteworthy and have elegantly illuminated the role of dopamine neuronal activity in reward processing in behaving nonhuman primates (Schultz et al. 1997; Martin-Soelch et all 2001; Watanabe et al. 2001). Nevertheless, technical considerations still limit the scope of investigation for these methodologies. They involve invasive surgical preparations that require significant effort to maintain effectively over extended periods, and they are restricted to limited target structures defined a priori as being relevant to the research question. For microdialysis, the technical features are uniquely challenging: analyses are limited to small molecules that can effectively diffuse across the dialysis membrane; absolute quantitation of basal levels of neurochemicals depends on a problematic correspondence between in vitro and in vivo probe recovery; and temporal resolution is on the order of minutes rather than moment to moment.

Functional neuroimaging

Functional imaging provides an alternative, noninvasive approach toward understanding CNS function and neural mechanisms underlying drug-induced changes in behavior. Current technologies include positron emission tomography (PET), single-photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI). In PET, ligands of interest are radiolabeled with unstable atoms that emit positrons. When positrons collide with electrons, dual photons are emitted which are recognized by a detector array in the tomograph. A computer algorithm then uses this information to map the source and concentration of the radiotracer.

SPECT imaging uses different radiotracers that emit a single photon. Due to methodological differences in single versus dual photon detection, SPECT imaging has lower sensitivity and resolution compared to PET imaging. A number of radiotracers have been developed for use in PET and SPECT imaging that enable the in vivo measurement of brain neurochemistry and physiology. Since radiotracers can be used to label compounds without influencing their pharmacology, functional imaging can also measure drug distribution and pharmacokinetics in brain. In contrast to PET imaging and SPECT imaging, fMRI does not require the use of radiotracers. Instead, the subject is placed into a homogeneous magnetic field where presentations of radiofrequency pulses cause transient energy changes. Current fMRI studies rely on changes in signal intensity due to blood oxygenation levels, thereby quantifying hemodynamic responses associated with neuronal activity. Collectively, these neuroimaging techniques have been used to identify the neural substrates and target systems that mediate the reinforcing effects of stimulants.

Currently, functional imaging techniques are being used in nonhuman primates and human subjects to study the neurochemical actions of cocaine and cocaine-like drugs that can be related to their behavioral effects. For example, recent PET imaging studies to characterize the interaction of cocaine and candidate medications were conducted with the new DAT radioligand 8-(2-[^{18}F]fluroethyl)2β-carbomethoxy-3β(4-chlorophenyl) nortropane ([^{18}F]FECNT) (Goodman et al. 2000). DAT occupancy by cocaine was determined by displacement of FECNT using a reference tissue method of kinetic modeling in rhesus monkeys (Votaw et al. 2002). Doses of 0.1 and 1.0 mg/kg cocaine occupied 53% and 87% of the transporters, respectively. These results confirmed that FECNT labels a cocaine-sensitive binding site, and that high levels of DAT occupancy are associated with behaviorally active doses of cocaine.

In a related study, the reinforcing effects of cocaine were compared to its phenyltropane analog, RTI-113, in rhesus monkeys responding under a second-order schedule of IV drug self-administration (Wilcox et al. 2002). Both drugs reliably and equipotently maintained self-administration behavior, with DAT occupancies of 65–76% and 94–99% for optimum doses of cocaine and RTI-113, respectively. When administered as a pretreatment, RTI-113 dose-dependently reduced responding maintained by cocaine, with DAT occupancies ranging between 72 and 84% for pretreatment doses of RTI-113 that effectively suppressed cocaine self-administration. The relationship between DAT occupancy and the effectiveness of selective DAT inhibitors to reduce cocaine self-administration extends to the phenylpiperazine, GBR 12909. GBR 12909 is a high-affinity ligand that has a cocaine-like profile of behavioral effects (Rothman 1990; Rothman et al. 1992). In rhesus monkeys, IV administration of GBR 12909 was found to suppress cocaine self-administration dose-dependently under multiple fixed-ratio schedules of cocaine and food delivery (Glowa et al. 1995). The same doses of GBR 12909 that decreased cocaine self-administration in rhesus monkeys were subsequently tested in baboons to quantify DAT occupancy during PET neuroimaging with [^{11}C]WIN 35,428 (Villemagne et al. 1999). The results indicated that, like RTI-113, doses of GBR 12909 that decrease cocaine self-administration in nonhuman primates also occupy a substantial fraction (>50%) of dopamine transporters.

With regard to pharmacokinetic profile, PET neuroimaging studies with [^{11}C]WIN 35,428 have confirmed that, compared to cocaine, GBR 12909 has a slower onset and longer duration of DAT occupancy in conscious rhesus monkeys (Tsukada et al. 2000). Of interest, the time course of effects for DAT occupancy in these studies closely paralleled drug-induced increases in extracellular dopamine measured with in vivo microdialysis in rhesus monkeys or, in separate studies, squirrel monkeys (Czoty et al. 2000). Moreover, the time-course and potency differences in neurochemical effects paralleled differences in the behavioral-stimulant effects of these drugs in monkeys performing under fixed-interval schedules of stimulus termination (Howell et al. 1997, 2000). Taken together, these data offer compelling evidence that DAT occupancy measures obtained with PET neuroimaging are closely linked to functional changes in dopamine neurochemistry and behavior.

PET neuroimaging with [^{11}C]cocaine has been used to describe the distribution and pharmacokinetics of cocaine in humans. Studies with [^{11}C]cocaine at tracer doses in the human brain yielded results similar to those reported in baboons, with a rapid uptake in the striatum and a clearance half-life of about 20 min (Fowler et al. 1989). Subsequently, a direct relationship was established between self-reports of “high” induced by cocaine and the time course for striatal uptake (Volkow et al. 1997). The description of cocaine’s rapid uptake and reversible kinetics in the human brain illustrated how neuroimaging techniques in human subjects could be expanded to quantify DAT availability, and DAT occupancy by drugs that target the dopamine transporter (Fowler et al. 2001). Indeed, functional imaging studies in human drug users have begun to relate the acute neurochemical effects of stimulants to their reinforcing effects, and the results obtained are in close agreement with preclinical studies conducted in nonhuman primates (Table 1). A good example is provided by recent studies with methylphenidate.

Methylphenidate has affinity for the DAT comparable to cocaine, and behaviorally-relevant doses of methylphenidate can block the uptake of [^{11}C]cocaine. Likewise, doses of cocaine that induce euphoria can block the uptake of [^{11}C]methylphenidate. In human cocaine abusers, subjective ratings of “high” have been correlated with percent DAT occupancy measured with PET neuroimaging and [^{11}C]cocaine following acute administration of cocaine (Volkow et al. 1997) or methylphenidate (Volkow et al. 1999b). Approximately 50% occupancy of striatal DAT was required for subjects to

Table 1 Dopamine and the reinforcing properties of stimulants. *mg/kg* mg/kg per injection

Cocaine and DAT inhibitors maintain IV self-administration	
Nader et al. 1997	Rhesus monkeys; fixed-interval schedule; cocaine (0.03 and 0.1 mg/kg), PTT (0.003–0.1 mg/kg)
Wilcox et al. 2002	Rhesus monkeys; second-order schedule; cocaine (0.003–1.0 mg/kg), RTI-113 (0.01–0.3 mg/kg)
Bergman et al. 1989	Squirrel monkeys; second-order schedule; cocaine (0.01–0.56 mg/kg), bupropion (0.1–3.0 mg/kg), GBR 12909 (0.03–1.0 mg/kg), methylphenidate (0.01–0.3 mg/kg), nomifensine (0.01–0.3 mg/kg)
Howell and Byrd 1991	Squirrel monkeys; second-order schedule; GBR 12909 (0.3–1.0 mg/kg)
Howell et al. 2000	Squirrel monkeys; second-order schedule; cocaine (0.03–1.0 mg/kg), RTI-113 (0.1–0.3 mg/kg)
Reinforcing/euphoric doses of cocaine and DAT inhibitors require high DAT occupancy (>50%)	
Volkow et al. 1997	Human cocaine-dependent; PET imaging – [^{11}C]cocaine; cocaine (0.3–0.6 mg/kg, IV)
Volkow et al. 1999b	Human normal-controls; PET imaging – [^{11}C]cocaine; methylphenidate (0.05–0.5 mg/kg, IV)
Votaw et al. 2002	Rhesus monkeys; PET imaging – [^{18}F]FECNT; cocaine (0.1–1.0 mg/kg, IV)
Wilcox et al. 2002	Rhesus monkeys; PET imaging – [^{18}F]FECNT; cocaine (0.1–0.3 mg/kg, IV), RTI-113 (0.03–0.17 mg/kg, IV)
DAT inhibitors suppress cocaine self-administration at high DAT occupancy (>50%)	
Villemagne et al. 1999	Baboons; PET imaging – [^{11}C]WIN 35,428; GBR 12909 pretreatment (1.0–10.0 mg/kg, IV)
Glowa et al. 1995	Rhesus monkeys; multiple fixed-ratio schedule (food/cocaine); cocaine self-administration (0.01–0.1 mg/kg, IV); GBR 12909 pretreatment (0.1–3.0 mg/kg, IV)
Wilcox et al. 2002	Rhesus monkeys; second-order schedule; cocaine self-administration (0.1–0.3 mg/kg, IV); RTI-113 pretreatment (0.1–0.3 mg/kg, IM); PET imaging – [^{18}F]FECNT
Howell et al. 2000	Squirrel monkeys; second-order schedule; cocaine self-administration (0.1–0.3 mg/kg, IV); RTI-113 pretreatment (0.03–0.3 mg/kg, IM)
Dopamine D_2 receptor density predicts reinforcing/euphoric effects of cocaine and methylphenidate	
Volkow et al. 1999d	Human normal-controls; methylphenidate (0.5 mg/kg, IV); PET imaging – [^{11}C]raclopride
Morgan et al. 2002	Cynomolgus monkeys; fixed-ratio schedule; cocaine self-administration (0.003–0.1 mg/kg, IV); PET imaging – [^{18}F]FCP

identify cocaine delivered as an IV injection (Volkow et al. 1997). Therapeutic doses of methylphenidate commonly used in the treatment of attention deficit disorder also resulted in approximately 50% DAT occupancy. A subsequent study compared the levels of DAT occupancy by cocaine via different routes of administration (Volkow et al. 2000). Although similar levels of DAT occupancy were obtained across all routes of administration, smoked cocaine with the most rapid onset to action induced significantly greater self-reports of "high" than intranasal cocaine, highlighting the importance of pharmacokinetic factors in the subjective effects of cocaine.

Competition between radiolabeled ligands and endogenous neurotransmitters for receptor binding can provide an effective means to assess drug-induced changes in the extracellular concentration of neurotransmitters. For example, PET studies with the dopamine D_2 receptor ligand, [^{11}C]raclopride, showed significant reductions in D_2 receptor binding by [^{11}C]raclopride in baboons following drug administrations that elevate extracellular dopamine (Dewey et al. 1993). Ostensibly, the reductions in [^{11}C]raclopride binding reflected greater occupancy of D_2 receptors by endogenous dopamine. More recently, [^{18}F]4'-fluoroclebopride (FCP) was developed as a reversible D_2 receptor ligand and used to characterize stimulant-induced dopamine release in rhesus monkeys (Mach et al. 1997). Intravenous administration of cocaine, amphetamine, methylphenidate and methamphetamine all increased the rate of washout of FCP from the basal ganglia in a manner consistent with the ability of each drug to elevate extracellular dopamine. The effects of cocaine, amphetamine and methylphenidate were replicated in subsequent studies using the D_2 receptor ligand, [^{11}C]raclopride, in baboons (Villemagne et al. 1999; Volkow et al. 1999a). However, only one study has directly compared D_2 binding potential of a radioactive ligand with quantitative measures of extracellular dopamine (Laruelle et al. 1997). Using a D_2 receptor ligand and SPECT neuroimaging, a positive correlation was observed between D_2 receptor binding and peak dopamine release measured with microdialysis following several doses of amphetamine. Unfortunately, the microdialysis studies were limited to a single vervet monkey, whereas the SPECT imaging studies were conducted in baboons. This is an area of investigation where direct measures of extracellular neurotransmitter levels are clearly needed to interpret and validate the functional imaging data. Once validated, the methodology could provide a noninvasive approach toward quantifying neurotransmitter levels in vivo.

Clinical studies that have used functional imaging to characterize the CNS effects of stimulants have focused primarily on long-term changes in individuals with a complex history of multidrug use. PET studies have documented decreased blood flow in the prefrontal cortex of chronic cocaine users (Volkow et al. 1988), and additional studies with PET and SPECT have confirmed those results, demonstrating that brain perfusion defects occur with high frequency (Holman et al. 1991, 1993;

Strickland et al. 1993; Levin et al. 1994). Local perfusion deficits have been linked closely to changes in cerebral metabolism. Measures of brain glucose metabolism with fluorodeoxyglucose (FDG) in chronic cocaine users showed transient increases in metabolic activity in brain regions associated with dopaminergic systems during cocaine withdrawal (Volkow et al. 1991) and persistent decreases in frontal brain metabolism after months of detoxification (Volkow et al. 1992). The same pattern of decreased glucose metabolism (Reivich et al. 1985) and perfusion deficit (Volkow et al. 1988) was observed in the prefrontal cortex in a subset of cocaine users who were imaged on multiple occasions.

Chronic exposure to stimulant drugs in humans may also lead to significant reductions in neuronal markers of dopaminergic function. For example, dual-tracer PET neuroimaging with FDG and [^{11}C]raclopride to measure brain metabolism and D_2 receptor binding, respectively, has documented both reduced frontal metabolism and decreased dopamine D_2 receptor availability in cocaine or methamphetamine abusers (Volkow et al. 1993, 2001a). Moreover, D_2 receptor availability was associated with metabolic rate in the orbitofrontal cortex. Based on such findings, the authors speculated that D_2 receptor-mediated dysregulation of the orbitofrontal cortex could underlie compulsive drug taking. This is an intriguing suggestion, but it awaits further experimental evidence. In other PET neuroimaging studies with [^{11}C]WIN-35,428 as the ligand, reduced DAT density in nucleus accumbens, striatum and prefrontal cortex was documented in methamphetamine users (Sekine et al. 2001). Importantly, the reduction in DAT binding in these studies was significantly correlated with the duration of drug use and the severity of persistent psychiatric symptoms. Subsequent PET studies with [^{11}C]d-threo-methylphenidate as the DAT ligand found partial recovery of DAT binding in methamphetamine abusers during protracted abstinence (Volkow et al. 2001b). However, neuropsychological function did not improve to the same extent, leading the authors to suggest that recovery of DAT density was not sufficient for complete recovery.

It is becoming increasingly accepted that behavior, brain chemistry and neuronal function can be readily influenced by environmental conditions as well as by pharmacological challenge. Neuroimaging techniques have proven especially useful in studying dynamic changes in neuronal activity that may be associated with environmental variables. For example, differences in housing conditions and the dominance rank among socially housed nonhuman primates recently have been associated with differential levels of dopamine D_2 receptors. An initial study using PET neuroimaging with [^{18}F]FCP in socially-housed female cynomolgus monkeys documented reduced availability of D_2 receptors in subordinate monkeys compared to the dominant group members (Grant et al. 1998). However, it was unclear whether the observed differences in D_2 binding reflected a predisposition that determined dominance rank or neurochemical alterations in response to dominance rank. In a subsequent series of experiments in cynomolgus monkeys, subjects were first scanned using PET neuroimaging with [^{18}F]FCP while individually-housed and again after they were placed in social groups and allowed to establish a stable social hierarchy (Morgan et al. 2002). The monkeys did not differ in the availability of D_2 receptors during individual housing. However, social housing increased the availability of D_2 receptors in dominant monkeys without producing any changes in subordinate group members. The alterations in dopaminergic function were apparently a consequence of change in dominance rank and related changes in social interactions. Importantly, the neurochemical changes had a significant influence on vulnerability to cocaine use. Intravenous cocaine delivery reliably functioned as a reinforcer in subordinate subjects but failed to maintain self-administration in dominant group members. Subordinate monkeys reliably self-administered cocaine across a range of doses, and the shape of the dose-effect curve was characterized as an inverted U-shaped function typical of stimulant self-administration in nonhuman primates. In contrast, cocaine failed to maintain rates of responding higher than saline rates in dominant monkeys, indicating that cocaine did not function as a reinforcer in these subjects. During self-administration sessions, subordinate monkeys also had significantly higher cocaine intakes compared to dominant monkeys. These provocative findings obtained with repeated PET neuroimaging in individual subjects document rapid neurochemical changes in response to environmental conditions, and subsequent alterations in propensity to self-administer cocaine.

Analogous relationships between dopamine receptor densities and the behavioral effects of stimulants also have been reported in studies with human subjects. PET neuroimaging with [^{11}C]raclopride was used to measure dopamine D_2 receptor occupancy as an indirect measure of stimulant-induced elevations in extracellular dopamine (Volkow et al. 1999c). Parallel measures for self-reported "high" were obtained and related to methylphenidate-induced changes in brain dopamine. The intensity of "high" was significantly correlated with estimated levels of released dopamine. In a related study, dopamine D_2 receptor levels were determined in healthy men who had no history of drug abuse (Volkow et al. 1999d). Subjects who reported liking the effects of methylphenidate had significantly lower D_2 receptor levels in striatum compared to subjects who disliked the drug. In addition, there was a direct relationship between the intensity of unpleasant effects and D_2 receptor levels. The results indicated that subjective responses to stimulants in humans may be correlated with D_2 receptor levels, and that low levels of D_2 receptors may contribute to stimulant abuse. Note the parallels between these findings and those in nonhuman primates described earlier (Morgan et al. 2002). The ability to manipulate D_2 receptor density environmentally in nonhuman primates provides especially strong support for orderly relationships between such variables and the reinforcing effects of cocaine.

Table 2 Acute effects of cocaine on cerebral metabolism and blood flow

Decreases in cerebral metabolism	
London et al. 1990	Human polydrug abusers; PET imaging – [^{18}F]FDG; 40 mg (IV) cocaine
Decreases in cerebral blood flow	
Johnson et al. 1998	Human cocaine-dependent; SPECT – technetium-99-m-bicisate; 0.325 and 0.650 mg/kg (IV) cocaine
Pearlson et al. 1993	Human cocaine-dependent; SPECT – technetium-99-m-exametazine; 48 mg (IV) cocaine
Wallace et al. 1996	Human cocaine-dependent; SPECT – technetium-99-m-exametazine; 40 mg (IV) cocaine
Transient regional increases in cerebral blood flow	
Breiter et al. 1997	Human cocaine-dependent; fMRI (BOLD); 0.6 mg/kg (IV) cocaine
Mathew et al. 1996	Human cocaine-dependent; laser Doppler – 133 xenon; 0.3 mg/kg (IV) cocaine
Howell et al. 2002	Rhesus monkeys; PET – [^{15}O]water; 0.3 and 1.0 mg/kg (IV) cocaine

The noninvasive measurement of cerebral blood flow with PET neuroimaging and [^{15}O] water provides another in vivo functional measure to characterize drug-induced changes in brain activity. However, the high incidence of polydrug use among human cocaine users complicates the identification of functional changes in CNS activity due specifically to the direct pharmacological effects of cocaine. As with other types of neuroimaging techniques, the use of nonhuman primates can provide the experimental control necessary to obtain and document the effects of cocaine exposure independent of major confounding variables. Initial studies have been conducted to examine this possibility. Functional changes in cerebral blood flow measured by PET were determined in conscious, drug-naive rhesus monkeys following acute IV administration of cocaine (Howell et al. 2001, 2002). Repeated baseline determinations of cerebral blood flow prior to drug administration were stable. In contrast, cocaine had significant dose-related effects on cerebral blood flow at 5 min postinjection that diminished markedly by 15 min postinjection. Brain activation maps normalized to global flow showed prominent cocaine-induced activation of prefrontal cortex localized primarily to dorsolateral regions. The brain activation effects were blocked by pretreatment with the selective serotonin uptake inhibitor, alaproclate. Importantly, the same dose of alaproclate that blocked cocaine-induced brain activation was effective in attenuating cocaine self-administration and cocaine-induced elevations in extracellular dopamine in squirrel monkeys (Czoty et al. 2002). Hence, there appeared to be a close concordance among in vivo measures of behavior, neurochemistry and functional imaging.

The acute effects of stimulants on cerebral blood flow and metabolism have been examined more frequently in human subjects and especially in studies to evaluate the neuronal basis of drug-induced euphoria. The acute IV administration of cocaine in human users resulted in significant blood flow decreases in selected frontal and basal ganglia regions as measured by SPECT (Pearlson et al. 1993; Wallace et al. 1996; Johnson et al. 1998). Cocaine-induced euphoria following acute IV administration also has been associated with regional decreases in cerebral metabolism (London et al. 1990). Other investigators have reported cocaine-induced increases in blood flow mainly in the frontal and parietal regions after acute drug administration in humans (Mathew et al. 1996). Similarly, a study using fMRI reported dynamic patterns of brain activation following cocaine administration in cocaine-dependent subjects (Breiter et al. 1997). Some regions showed short duration of activation that was correlated with ratings of "rush", whereas other regions showed sustained activation associated with measures of "craving".

The transient pattern of brain activation induced by cocaine in humans is consistent with that reported in conscious rhesus monkeys imaged 5 min postinjection (Howell et al. 2001, 2002). It is noteworthy that the majority of studies have measured drug effects at later time points (up to 45 min postinjection) and have found cocaine-induced decreases in cerebral blood flow and metabolism in chronic cocaine users. Not surprisingly, the time of measurement appears to be a major determinant of experimental outcome, especially with a rapid-acting drug like cocaine. Notwithstanding such differences in experimental procedures and outcomes, however, enough collective evidence has accumulated to consider acute drug effects on cerebral blood flow and metabolism as a means to characterize the functional neuroanatomy underlying the etiology of stimulant abuse (Table 2).

In summary, functional neuroimaging offers several notable advantages for drug abuse research. The procedures are noninvasive and, thus, well suited for human studies. The capability to conduct similar studies in nonhuman primates and human subjects provides a powerful tool for linking findings in human and laboratory animal research efforts. Longitudinal designs can be implemented to characterize the consequences of chronic drug exposure and potential recovery of brain function. Hence, analyses are not restricted to between-subject comparisons at single time point determinations. This consideration is particularly important in human studies where terminal endpoints are not an option, and in nonhuman primate studies where significant resources are committed to individual subjects. Functional imaging can be used to study drug distribution and pharmacokinetics of binding to relevant substrates in vivo. The information that can be derived from such studies is especially

valuable for the determination of dosing regimens where bioavailability is a significant concern. Lastly, the measurement of cerebral blood flow changes coupled to cerebral metabolism is beginning to establish the integrated neuronal circuitry underlying drug effects on behavior in real time. Despite the many advantages, however, there currently are important limitations to the use of imaging technology. It is very expensive and time-consuming, and there are limited resources with high demand for use. There also are limits to anatomical and temporal resolution that dictate the appropriate application of imaging technology. Lastly, functional imaging in nonhuman primates requires anesthetic agents that alter brain function or, alternatively, the implementation of extensive behavioral training protocols to restrain awake subjects. The potential impact of the technology is considerable, but the resources required can be prohibitive for many research applications.

Summary

Recent advances in neuroimaging and in vivo neurochemistry have documented drug-induced functional changes in brain activity under physiologically relevant conditions. Current in vivo approaches allow for simultaneous measures of behavioral activity and brain function, providing an analysis of integrated systems in the intact organism that are relevant to drug abuse. Neuroimaging of cerebral blood flow changes coupled to cerebral metabolism measured with PET and fMRI is particularly well suited to define the neuronal circuitry underlying drug effects on behavior. The ability to study drug interactions with specific neurochemical targets in vivo also can be used to identify pharmacokinetic considerations that are critical in medications development. Lastly, the ability to conduct within-subject, longitudinal assessments of neurochemistry and brain function could greatly enhance our ability to document long-term changes due to chronic drug exposure and potential recovery during prolonged abstinence or during treatment interventions. A review of the literature shows close concordance among functional measures of behavior, neurochemistry and neuroimaging. Moreover, the clinical relevance of information derived from nonhuman primates has been established in the outcome of functional imaging studies in humans. These complementary and integrative approaches should have important implications for medications development to treat stimulant abuse.

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