

Dopamine in Drug Abuse and Addiction

Results of Imaging Studies and Treatment Implications

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Imaging studies have provided new insights on the role of dopamine (DA) in drug abuse and addiction in the human brain. These studies have shown that the reinforcing effects of drugs of abuse in human beings are contingent not just on DA increases per se in the striatum (including the nucleus accumbens) but on the rate of DA increases. The faster the increases, the more intense the reinforcing effects. They have also shown that elevated levels of DA in the dorsal striatum are involved in the motivation to procure the drug when the addicted subject is exposed to stimuli associated with the drug (conditioned stimuli). In contrast, long-term drug use seems to be associated with decreased DA function, as evidenced by reductions in D2 DA receptors and DA release in the striatum in addicted subjects. Moreover, the reductions in D2 DA receptors in the striatum are associated with reduced activity of the orbitofrontal cortex (region involved with salience attribution and motivation and with compulsive behaviors) and of the cingulate gyrus (region involved with inhibitory control and impulsivity), which implicates deregulation of frontal regions by DA in the loss of control and compulsive drug intake that characterizes addiction. Because DA cells fire in response to salient stimuli and facilitate conditioned learning, their activation by drugs will be experienced as highly salient, driving the motivation to take the drug and further strengthening conditioned learning and producing automatic behaviors (compulsions and habits).

Arch Neurol. 2007;64(11):1575-1579

Dopamine (DA) is the neurotransmitter that has been classically associated with the reinforcing effects of drugs of abuse and may have a key role in triggering the neurobiological changes associated with addiction. This notion reflects the fact that all of the drugs of abuse increase the extracellular concentration of DA in the nucleus accumbens. Increases in DA levels have an important role in coding reward and prediction of reward, in the motivational drive to procure the reward, and in facilitating learning.¹ It is also believed that DA codes not just for reward but for saliency, which, in addition to reward, includes aversive, novel, and unexpected stimuli. The diversity of DA effects is likely translated by the specific

brain regions (limbic, cortical, and striatal) it modulates.

Herein, we summarize findings from imaging studies that used positron emission tomography (PET) to investigate the role of DA in the reinforcing effects of drugs, the long-term brain changes in drug-addicted subjects, and the vulnerability to addiction. Though most of the PET studies on addiction have focused on DA, it is clear that drug-induced adaptations in other neurotransmitters (ie, glutamate, γ -aminobutyric acid, opioids, and cannabinoids) are also involved, but the lack of radioligands has limited their investigation.

ROLE OF DA ON THE REINFORCING EFFECTS OF DRUGS IN THE HUMAN BRAIN

The effects of short-term drug exposure on extracellular DA concentrations in the human brain can be studied using PET and

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Table 1. Summary of Findings of PET Studies Comparing Various Targets Involved in DA Neurotransmission Between Substance Abusers^a and Non-Drug-Abusing Control Subjects for Which Statistical Differences Between the Groups Were Identified^b

Target Investigated	Drug Used	Finding
D2 DA receptors	Cocaine	↓ Acute withdrawal ↓ Detoxified
	Alcohol	↓ Acute withdrawal ↓ Detoxified
	Methamphetamine	↓ Detoxified
	Heroin	↓ Active user
	Cocaine	↑ Acute withdrawal 0 Detoxified
DA transporters	Alcohol	↓ Acute withdrawal 0 Detoxified
	Methamphetamine	↓ Detoxified
	Cigarettes	0 Active user
	Methamphetamine	↓ Detoxified
	Cigarettes	↓ Active user
Vesicular transporters-2	Cocaine	↓ Detoxified
Metabolism (MAOB)	Alcohol	0 Detoxified
Synthesis (dopa decarboxylase)	Cocaine	↓ Detoxified
DA release ^c	Cocaine	↓ Detoxified
	Alcohol	↓ Detoxified

Abbreviations: DA, dopamine; MAOB, monoamine oxidase B; PET, positron emission tomography; arrows correspond to lower values (↓) and higher values (↑) than in non-drug-abusing control subjects; 0 indicates no statistical difference.

^aTested during acute withdrawal, detoxification, or active use.

^bDifferences were reported in the striatum for all DA targets except MAOB, for which changes were reported throughout the entire brain (cortical and subcortical areas).

^cDA release was assessed by measuring changes in specific binding of raclopride labeled with carbon 11 induced by pharmacologic challenge with methylphenidate or amphetamine.

D2 DA receptor radioactive ligands that are sensitive to competition with endogenous DA, such as raclopride labeled with carbon 11 (¹¹C). The relationship between the effects of drugs on DA and their reinforcing properties in the human brain (assessed by self-reports of “high” and “euphoria”) was studied for the stimulant drugs methylphenidate and amphetamine. Methylphenidate, like cocaine, increases DA by blocking DA transporters, whereas amphetamine, like methamphetamine, increases DA by releasing it from the terminal via DA transporters. Intravenous methylphenidate (0.5 mg/kg) and amphetamine (0.3 mg/kg) increased the extracellular DA concentration of DA in the striatum, and these increases were associated with increases in self-reports of high and euphoria.² In contrast, when given orally, methylphenidate (0.75–1 mg/kg) also increased DA but was not perceived as reinforcing.³ Because intravenous administration leads to fast DA changes, whereas oral administration increases DA slowly, the failure to observe the high with oral methylphenidate likely reflects its slow pharmacokinetics. Indeed, the speed at which drugs of abuse enter the brain is recognized as affecting their reinforcing effects.⁴ This association has also been shown in PET studies that evaluated the pharmacokinetics of cocaine (using [¹¹C]cocaine) and MP (using [¹¹C]methylphenidate) in the human brain, documenting that it was the fast uptake of the drug into the brain but not the brain concen-

tration per se that was associated with getting high.⁵ The dependency of the reinforcing effects of drugs on brain pharmacokinetic properties suggests a possible association with phasic DA cell firing (fast-burst firing at frequencies >30 Hz), which also leads to fast changes in DA concentration and whose function is to highlight the saliency of stimuli.⁶ This is in contrast to tonic DA cell firing (slow firing at frequencies around 5 Hz), which maintains baseline steady-state DA levels and whose function is to set the overall responsiveness of the DA system. This led us to speculate that drugs of abuse induce changes in DA concentration that mimic but exceed those produced by phasic DA cell firing.

ROLE OF DA ON THE LONG-TERM EFFECTS OF DRUGS OF ABUSE IN THE HUMAN BRAIN: INVOLVEMENT IN ADDICTION

Synaptic increases in DA concentration occur during drug intoxication in both addicted and nonaddicted subjects. However, a compulsive drive to continue drug taking when exposed to the drug is not triggered in all subjects. Inasmuch as it is the loss of control and the compulsive drug taking that characterizes addiction, the short-term drug-induced DA level increase alone cannot explain this condition. Because drug addiction requires long-term drug administration, we suggest that in vulnerable individuals (because of genetic, developmental, or environmental factors), addiction is related to the repeated perturbation of DA-regulated brain circuits involved with reward/saliency, motivation/drive, inhibitory control/executive function, and memory/conditioning. Herein, we discuss findings from imaging studies on the nature of these changes.

Many radioactive tracers have been used to assess changes in targets involved in DA neurotransmission (**Table 1**). Using 18-N-methylspiroperidol or [¹¹C]raclopride, we and others have shown that subjects with a wide variety of drug addictions (cocaine, heroin, alcohol, and methamphetamine) have significant reductions in D2 DA receptor availability in the striatum (including the ventral striatum) that persist months after protracted detoxification (reviewed in Volkow et al²). We have also revealed evidence of decreased DA cell activity in cocaine abusers. Specifically, we showed that the striatal increases in DA level induced by intravenous methylphenidate (assessed with [¹¹C]raclopride) in cocaine abusers were substantially blunted when compared with DA level increases in control subjects (50% lower).⁷ Because DA concentration increases induced by methylphenidate are dependent on DA release, a function of DA cell firing, we speculated that this difference likely reflects decreased DA cell activity in the cocaine abusers. Similar findings have been reported in alcohol abusers.⁸

These brain-imaging studies suggest 2 abnormalities in addicted subjects that would result in decreased output of DA circuits related to reward; that is, decreases in D2 DA receptors and decreases in DA release in the striatum (including the nucleus accumbens). Each would contribute to the decreased sensitivity in addicted subjects to natural reinforcers. Because drugs are much more potent at stimulating DA-regulated reward circuits than natu-

ral reinforcers, we postulated that drugs are still able to activate these down-regulated reward circuits. The decreased sensitivity of reward circuits would lead to decreased interest in day-to-day environmental stimuli, possibly predisposing subjects to seek drug stimulation as a means to temporarily activate these reward circuits underlying the transition from taking drugs to feel high to taking them to feel normal.

Preclinical studies have demonstrated a prominent role of DA in motivation that seems to be mediated in part via a DA-regulated circuit involving the orbitofrontal cortex (OFC) and the anterior cingulate gyrus (CG).⁹ In imaging studies in human subjects using the radioactive tracer fludeoxyglucose F 18, we and others have shown decreased activity in the OFC and CG in different classes of addicted subjects (reviewed in Volkow et al²). Moreover, in both cocaine- and methamphetamine-addicted subjects, we have shown that the reduced activity in the OFC and CG is associated with decreased availability of D2 DA receptors in the striatum (reviewed in Volkow et al⁷) (**Figure**). Because the OFC and CG participate in the assignment of value to reinforcers as a function of context, their disruption in the abuser could interfere with their ability to change the saliency value of the drug as a function of alternative reinforcers, becoming the main drive motivating behavior. In contrast to the pattern of decreased OFC and CG activity when drug-free, addicted subjects show increased activation in these regions when presented with the drug or drug-related stimuli, consistent with the enhanced saliency values of drugs or drug reinforcers in these subjects. Moreover, the enhanced activation of the OFC and CG was associated with the intensity of desire for the drug. This has led us to speculate that the hypermetabolism in the OFC and CG triggered by drugs or drug cues underlies the compulsive drug intake, just as it underlies the compulsive behaviors in patients with obsessive-compulsive disorders.¹⁰ This dual effect of disruption of the OFC-CG brain circuit is consistent with the behavior of the drug addict, whose compulsion to take the drug overrides competing cognitive-based tendencies not to take the drug; just as in patients with obsessive-compulsive disorders, the compulsion persists despite cognitive attempts to stop the behaviors.

The CG and the OFC are also involved with inhibitory control, which led us to postulate that disrupted DA modulation of the OFC and CG also contributes to the loss of control over drug intake by drug-addicted subjects.¹⁰ Inhibitory control is also dependent on the dorsolateral prefrontal cortex, which is also affected in addiction (reviewed in Volkow et al²). Abnormalities in the dorsolateral prefrontal cortex are expected to affect processes involved in executive control including impairments in self-monitoring and behavior control, which have an important role in the cognitive changes that perpetuate drug self-administration.¹⁰

Circuits underlying memory and learning, including conditioned-incentive learning, habit learning, and declarative memory (reviewed in Vanderschuren and Everitt¹¹), have been proposed to be involved in drug addiction. The effects of drugs on memory systems suggest ways that neutral stimuli can acquire reinforcing properties and motivational salience, that is, through

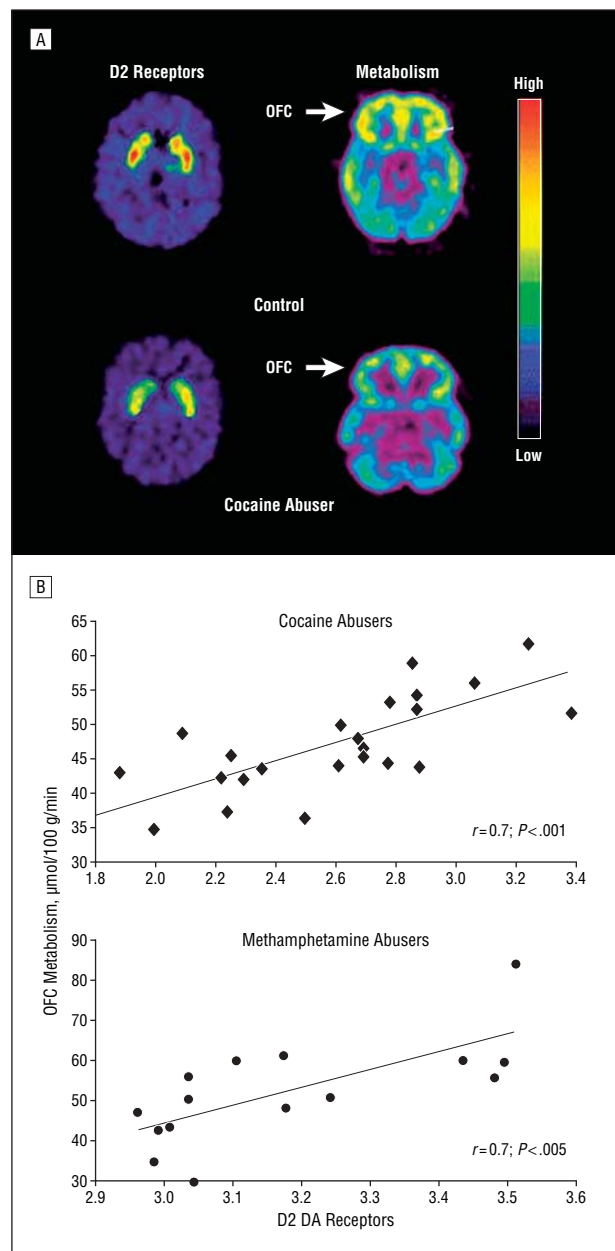


Figure. A, Images of D2 dopamine receptors (raclopride labeled with carbon 11) and of brain glucose metabolism (fludeoxyglucose), which is used as an indicator of brain function in a control subject and a cocaine abuser. Cocaine abusers have lower D2 dopamine receptor availability in the striatum and lower metabolism in the orbitofrontal cortex (OFC) than do control subjects. B, Correlations between D2 dopamine (DA) receptors and orbitofrontal cortex (OFC) metabolism in detoxified cocaine abusers and detoxified methamphetamine abusers. Note that the subjects with the lowest measures of D2 DA receptor availability have the lowest metabolism in the OFC.

conditioned-incentive learning. In research on relapse, it has been important to understand why drug-addicted subjects experience an intense desire for the drug when exposed to places where they have taken the drug, to persons with whom previous drug use occurred, and to paraphernalia used to administer the drug. This is clinically relevant because exposure to conditioned cues (stimuli associated with the drug) is a key contributor to relapse. Because DA is involved with prediction of reward (reviewed in Schultz⁹), we hypothesized that DA might underlie conditioned responses that trigger craving. Stud-

Table 2. Proposed Medications for Treatment of Drug Addiction^a

Proposed Circuit	Proposed Mechanism	Target and Effectiveness for
Reward	Substitution therapies	Nicotine replacement therapies Nicotine (<i>patch, chewing gum</i>) ¹⁶
		$\alpha_4 \beta_2$ Partial agonist Nicotine (<i>varenicline</i>) ¹⁷
	Immunization	μ Opiate partial agonists Heroin (<i>methadone, buprenorphine</i>) ¹⁸
		Vaccines Nicotine, cocaine ¹⁹
	Modulators	Antibodies Methamphetamine ¹⁹ μ Opiate receptor antagonists Alcohol (<i>naltrexone</i>) ²⁰ Heroin (<i>naltrexone</i>) ²¹ Nicotine (<i>naltrexone</i>) ²² Cannabinoid antagonists (CB1) Alcohol, nicotine, marijuana ²³
Conditioning/learning	Glutamate	Aldehyde dehydrogenase inhibitor Alcohol (<i>disulfiram</i>) ²⁰
		Alcohol (<i>acamprosate</i>) (mixed results ^{24,25}) Cocaine (<i>N-acetylcysteine</i>) ²⁶
Motivation/drive	GABA enhancers	Some antiepileptic drugs ^b Alcohol (<i>topiramate</i>) ²⁷ Cocaine (GVG), ²⁸ (<i>topiramate</i>) ²⁹ Methamphetamine (GVG) ²⁸
		GABA B receptor agonists Cocaine (<i>baclofen</i>) ³⁰
		DA enhancers DAT blockers: nicotine (<i>bupropion</i>) ¹⁶ Multiple targets: cocaine (<i>modafinil</i>) ^{31c} MAOB inhibitors: nicotine (<i>deprenyl</i>) ³²

Abbreviations: DA, dopamine; DAT, dopamine transporter; GABA, γ -aminobutyric acid; GVG, γ -vinyl- γ -aminobutyric acid; MAOB, monoamine oxidase B.

^aMedications for which there is proved benefit are identified in italics to differentiate them from those for which there is preliminary clinical data showing benefit. In addition to these mechanisms, medications to treat withdrawal are used in the treatment of acute alcohol withdrawal.

^bSome antiepileptic drugs may also interfere with conditioned responses.

^cMechanism of action for modafinil is unclear, but it requires DAT for its pharmacologic effects. It is also believed to exert effects on orexins and glutamate.

ies in laboratory animals support this hypothesis: when neutral stimuli are paired with a drug, they will, with repeated associations, acquire the ability to increase DA in the nucleus accumbens and dorsal striatum, becoming conditioned cues. Furthermore, these neurochemical responses are associated with drug-seeking behavior (reviewed in Vanderschuren and Everitt¹¹). In human beings, PET studies with [¹¹C]raclopride recently confirmed this hypothesis by showing that, in cocaine abusers, drug cues (cocaine-cue video of scenes of subjects taking cocaine) substantially increased DA in the dorsal striatum and that these increases were associated with cocaine craving.^{12,13} Because the dorsal striatum is implicated in habit learning, this association likely reflects the strengthening of habits as chronicity of addiction progresses. This suggests that a basic neurobiologic disruption in addiction might be a DA-triggered conditioned response that results in habits leading to compulsive drug consumption. It is likely that these conditioned responses reflect adaptations in corticostriatal glutamatergic pathways that regulate DA release (reviewed in Vanderschuren and Everitt¹¹).

DA AND VULNERABILITY TO DRUG ABUSE

A challenging question in the neurobiology of drug abuse is why some individuals are more vulnerable than oth-

ers to becoming addicted to drugs. Imaging studies suggest that preexisting differences in DA circuits may be one mechanism underlying the variability in responsiveness to drugs of abuse. Specifically, baseline measures of striatal D2 DA receptors in nonaddicted subjects have been shown to predict subjective responses to the reinforcing effects of intravenous methylphenidate treatment; individuals describing the experience as pleasant had substantially lower levels of D2 DA receptors compared with those describing methylphenidate as unpleasant (reviewed in Volkow et al⁷). This suggests that the relationship between DA levels and reinforcing responses follows an inverted U-shaped curve: too little is not optimal for reinforcement but too much is aversive. Thus, high D2 DA receptor levels could protect against drug self-administration. Support for this was provided by preclinical studies that showed that up-regulation of D2 DA receptors in the nucleus accumbens dramatically reduced alcohol intake in animals previously trained to self-administer alcohol¹⁴ and by clinical studies showing that subjects who, despite having a dense family history of alcoholism, were not alcoholics had substantially higher D2 DA receptors in the striatum compared with individuals without such family histories.¹⁵ In these subjects, the higher the D2 DA receptors, the higher the metabolism in the OFC and CG. Thus, we postulate that high

levels of D2 DA receptors may protect against alcoholism by modulating frontal circuits involved in salience attribution and inhibitory control.

TREATMENT IMPLICATIONS

Imaging studies have corroborated the role of DA in the reinforcing effects of drugs of abuse in human beings and have extended traditional views of DA involvement in drug addiction. These findings suggest multicomponent strategies for the treatment of drug addiction that include strategies to (1) decrease the reward value of the drug of choice and increase the reward value of nondrug reinforcers, (2) weaken conditioned drug behaviors, (3) weaken the motivational drive to take the drug, and (4) strengthen frontal inhibitory and executive control (**Table 2**).

Accepted for Publication: January 17, 2007.

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Author Contributions: *Study concept and design:* Volkow. *Acquisition of data:* Volkow, Wang, Swanson, and Telang. *Analysis and interpretation of data:* Volkow, Fowler, Wang, and Telang. *Drafting of the manuscript:* Volkow and Swanson. *Critical revision of the manuscript for important intellectual content:* Volkow, Fowler, Wang, Swanson, and Telang. *Statistical analysis:* Volkow. *Obtained funding:* Volkow, Fowler, and Wang. *Administrative, technical, and material support:* Volkow, Fowler, Wang, and Telang. *Study supervision:* Volkow, Wang, and Telang. **Financial Disclosure:** None reported.

Funding/Support: This study was supported in part by the intramural program of the National Institute on Alcohol Abuse and Alcoholism; grants DA 06891, DA 09490, DA 06278, and AA 09481 from the National Institutes of Health; and the US Department of Energy, Office of Biological and Environmental Research.

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