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Cocaine Addiction:

Nora D. Volkow MD ^a, Yu-Shin Ding PhD ^b, Joanna S. Fowler PhD ^b & Gene-Jack Wang MD ^b

^a Department of Psychiatry, State University of New York Stony Brook, Medical and Chemistry Departments, Brookhaven National Laboratory, Upton, NY, 11973, United States

^b Medical and Chemistry Departments, Brookhaven National Laboratory, Upton, NY, United States

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Cocaine Addiction: Hypothesis Derived from Imaging Studies with PET

Nora D. Volkow, MD
Yu-Shin Ding, PhD
Joanna S. Fowler, PhD
Gene-Jack Wang, MD

SUMMARY. Analysis of the behavior of cocaine in the human brain with Positron Emission Tomography reveals that it is not only its affinity for the dopamine transporter that gives it its unique properties but also its fast pharmacokinetics. Its very fast uptake and clearance

Nora D. Volkow, Yu-Shin Ding, Joanna S. Fowler, and Gene-Jack Wang are affiliated with the Medical and Chemistry Departments, Brookhaven National Laboratory, Upton, NY. Nora D. Volkow is also affiliated with the Department of Psychiatry, State University of New York Stony Brook, Stony Brook, NY.

Address correspondence to: Nora D. Volkow, MD, Medical Department, Brookhaven National Laboratory, Upton, NY 11973.

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from the brain contrasts with that of methylphenidate, another drug that inhibits the DA transporter. Methylphenidate clears from the brain at a much slower rate and is less addictive than cocaine. We postulate that periodic and frequent stimulation of the dopaminergic system secondary to chronic use of cocaine favors activation of a circuit that involves the orbitofrontal cortex, cingulate gyrus, thalamus and striatum. This circuit is abnormal in cocaine abusers and we postulate that its activation by cocaine perpetuates the compulsive administration of the drug and is perceived by the cocaine abuser as a intense desire resulting in the loss of control over the drive to take more cocaine. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: getinfo@haworth.com]

INTRODUCTION

The problem of cocaine addiction has to be understood both with respect to the properties of cocaine that make it such a reinforcing drug as well as the characteristics of the individuals who becomes addicted to it. Though it is well recognized that cocaine is among the most reinforcing of the drugs of abuse,^{1,2} only 10-15% of those who initially try cocaine intranasally become cocaine abusers.³ This highlights the importance of individual biological as well as environmental factors in cocaine addiction. Though it is also true that under experimental conditions where cocaine is freely available most animals will self-administer it at the exclusion of other behaviors,³ these conditions are rarely those encountered in our society where cocaine is not only a illegal drug but is also expensive. Thus the question that remains to be answered is what are the mechanisms that will make an individual overcome the normal positive and negative societal reinforcers in favor of cocaine sometimes even at the expense of his or her own conscious will.⁴

In this paper we postulate that the unique pharmacological properties of cocaine serve as the link that triggers a pathological activation of a cerebral circuit that enables maintenance of behaviors that are required in order to achieve a targeted biological goal. This circuit which includes the orbitofrontal cortex, thalamus and striatum is involved in behaviors that require a repetitive pattern to achieve fulfillment of their biological goal such as eating, drinking, grooming and mating.⁵ These behaviors are terminated either by satiety and/or competing distracting stimuli with consequent deactivation of this circuit. We hypothesize that cocaine addicts have a lower threshold for activation of this circuit by cocaine and that disruption of dopaminergic neurotransmission is in part responsible for

this abnormality. Dysfunction of this circuit could result from either chronic use of cocaine or as a resultant of a biological characteristic that places subjects at risk for drug addiction. In this paper we discuss the results obtained from positron emission tomography (PET) studies that have led us to this hypothesis. PET studies were done to investigate the properties of cocaine in the living human brain and to assess brain function and dopamine brain activity in cocaine abusers.

PET is an imaging technique which allows the measurement of the concentration of positron-emitter labeled compounds in the living brain noninvasively.⁶ Because the short-lived positron emitters such as carbon-11 (half-life: 20.4 minutes) can be used to label organic compounds without affecting their pharmacological properties, PET can be used to assess neurochemistry and pharmacology of the human brain. For example, PET has been used to evaluate the effects of acute cocaine on brain glucose metabolism⁷ and the effects of chronic cocaine on cerebral blood flow,⁸ glucose metabolism during early⁹ and late¹⁰ cocaine withdrawal, DA metabolism,¹¹ and DA D₂ receptor availability^{12,13} as well as to assess the pharmacokinetics and distribution of cocaine¹⁴ and cocaethylene (a metabolite from cocaine and ethanol) in the human brain¹⁵ with and without alcohol intoxication,¹⁶ and to compare it with the pharmacokinetics of methylphenidate¹⁷ and to assess the distribution of ¹¹C cocaine in the human body.¹⁸

MATERIALS AND METHODS

Pharmacological Studies of Cocaine

Two strategies were used. The first strategy was to characterize cocaine binding in the baboon brain and to investigate its pharmacokinetics in the human brain.¹⁴ The second strategy was to compare its behavior with that of methylphenidate,¹⁷ a drug which, like cocaine, inhibits the dopamine transporter, (K_i for inhibition of dopamine uptake corresponds to 640 nM for cocaine and 390 nM for methylphenidate)¹⁹ but which is abused in humans much less frequently than cocaine.²⁰

Studies characterizing the binding of cocaine and methylphenidate were done in anesthetized baboons using PET and ¹¹C-cocaine and ¹¹C-methylphenidate, respectively. Details about the procedures have been published.^{14,21} Briefly, baboons were scanned twice; first at baseline and then after preadministration of drugs that inhibit one of the monoamine transporters. Studies were also done with preadministration of pharmaco-

logical doses of cocaine (2 mg/kg iv.) and of methylphenidate (0.5 mg/kg iv.) to assess the ability of each one of these drugs to inhibit the binding of the other.

Studies on the pharmacokinetics of ^{11}C -cocaine and ^{11}C -methylphenidate were done in 10 and 8 healthy controls, respectively. One subject was tested twice, once with ^{11}C -cocaine and the second time with ^{11}C -methylphenidate. Details and procedures have been published.^{14,17}

Studies on Cocaine Addicts

Two studies were done; one evaluated subjects during early cocaine withdrawal (<1 week) and involved studies in 15 outpatient chronic cocaine abusers and 14 normal controls^{9,12} and the other was a longitudinal study that assessed the effects of protracted withdrawal at ~1 month and then after 4 months of detoxification and involved studies in 22 inpatient cocaine abusers and 24 normal controls.^{10,13}

These studies involved chronic cocaine addicts that fulfilled DSM-III-R criteria for cocaine addiction as well as healthy non-abusing subjects as controls. Cocaine addicts had to consume at least 4 grams of cocaine a weeks for at least the 6 months that preceded the investigation and were excluded if they were dependent on other drugs of abuse (except caffeine and nicotine).

Subjects were tested with ^{18}F FDG to measure regional brain glucose metabolism and with ^{18}F -NMS to assess dopamine D_2 receptors. For the longitudinal studies the scans were repeated 3 months after completion of an inpatient rehabilitation program. Details on scanning procedures as well as subjects characterization have been published.^{9,10}

RESULTS

Pharmacological Studies

Cocaine binding in the brain was heterogeneous with the highest concentration in the striatum. Pretreatment with pharmacological doses of cocaine inhibited binding in the striatum but not in the cerebellum. Binding in the striatum was also inhibited by drugs that inhibited the dopamine transporter but not by drugs that inhibited the norepinephrine or the serotonin transporter.¹⁴

Studies of its pharmacokinetics in the human brain revealed a very fast uptake in the brain which occurred approximately 4-6 minutes after injection.

tion. At peak the concentration in the brain corresponded to 8-10% of the injected dose. The distribution in the brain was as for the baboon with the highest concentration in the striatum followed by the thalamus, cingulate gyrus, temporal cortex, frontal and occipital cortexes and cerebellum. Cocaine cleared very rapidly from the brain with a half-peak clearance in basal ganglia of approximately 20 minutes.¹⁴

Characterization studies with ¹¹C-methylphenidate revealed a similar binding profile to that observed with ¹¹C-cocaine (Figure 1). Maximal uptake was observed in the striatum where binding was inhibited by drugs that inhibited the DA transporter but not by drugs that inhibited the norepinephrine or the serotonin transporter.²¹

To assess binding overlap at the dopamine transporter between cocaine and methylphenidate we assessed the effects of pharmacological doses of methylphenidate on ¹¹C-cocaine binding and the effects of pharmacological doses of cocaine on ¹¹C-methylphenidate binding in the baboon brain. Both of these drugs inhibited the binding of the other in the striatum but not in the cerebellum indicating binding to the same or to an overlapping site.¹⁷

Studies on the pharmacokinetics of ¹¹C-methylphenidate revealed a fast uptake into the brain, with peak occurring 8-10 minutes after injection. At peak the concentration in brain corresponded to 7-9% of injected dose. Following the peak, the concentration of methylphenidate in basal ganglia plateaued for approximately 20-30 minutes and then cleared slowly for a half-life of approximately 90 minutes.¹⁷

To compare the kinetics of these two drugs in human brain we averaged the time activity curves for ¹¹C-cocaine and for ¹¹C-methylphenidate in striatum and cerebellum in the subjects investigated, (Figure 2). The values for peak uptake of ¹¹C-cocaine and of ¹¹C-methylphenidate in whole brain (global), in striatum and in cerebellum are shown in Table 1 along with the times to reach peak uptake and half peak clearance. Both drugs showed a similar rate of uptake in the brain but a much slower rate of clearance for ¹¹C-methylphenidate than for ¹¹C-cocaine. Despite the significant rate of clearance between these two drugs the duration of the high after their intravenous injection was of similar duration.¹⁷

In the case of cocaine the "high" as reported by Cook et al.²² followed a parallel temporal course to that of ¹¹C-cocaine in the striatum (Figure 3). The "high" after intravenous injection of methylphenidate (0.5 mg/kg iv.) paralleled the fast rate of uptake of the drug in the brain of ¹¹C-methylphenidate but it declined rapidly despite the continuous binding of ¹¹C-methylphenidate in the brain (Figure 3).¹⁷

Studies in Cocaine Addicts

Regional brain glucose metabolism in recently detoxified cocaine abusers (< 1 week) was significantly higher in the orbitofrontal cortex and in the striatum than in healthy non-abusing controls and it was also (though not significant) higher than in the 5 cocaine abusers tested 2-4 weeks after withdrawal (Figure 4).⁹ The metabolic activity in these brain regions was found to be correlated with the days since last use of cocaine. The highest values were observed in subjects tested during the initial 72 hours. Metabolic activity in the orbitofrontal cortex and in the striatum was significantly correlated with the intensity of cocaine craving. Cocaine abusers who had the highest subjective ratings for craving were those with the highest metabolic values in orbitofrontal cortex and striatum.⁹ Studies done with ¹⁸F-NMS on these same cocaine abusers revealed decreases in dopamine D₂ receptor availability.

In contrast to the marked increases in metabolism observed during early cocaine withdrawal, the study done in patients tested between 1 and 4 months of detoxification showed significant reductions in metabolic activity. These patients showed significant decrements in metabolism of the prefrontal cortex, orbito frontal cortex, temporal cortex and cingulate gyrus.¹⁰ There were no changes in metabolic activity of the striatum. Measures of dopamine D₂ receptor availability showed a significant reduction as had been observed for the study in the patients tested during early detoxification.¹³ Measures for D₂ receptors were not found to correlate with intensity of cocaine craving.¹³ However, they were found to show a significant negative correlation with the subjective experience of dysphoria as assessed with the Beck depression inventory (Figure 5).¹³ The measures of dopamine D₂ receptors in the cocaine abusers were also significantly correlated with measures of metabolic activity in the orbito frontal cortex, cingulate gyrus and prefrontal cortex (Figure 6).¹³

The decrements in regional brain metabolism as well as the reductions in dopamine D₂ receptor availability persisted in the follow up studies performed 3 months after completing the inpatient detoxification program.

DISCUSSION

These studies reveal the unique pharmacokinetics of cocaine when compared with that of methylphenidate, a drug with a similar affinity for the dopamine transporter but which is infrequently abused.²⁰ These differences were not in their rate of uptake but in their rate of clearance. Cocaine

FIGURE 1. Brain images obtained with ^{11}C -cocaine and with ^{11}C -methylphenidate. Images are from a normal control that was tested twice with both tracers. From Volkow et al.¹⁷

FIGURE 2. Average time activity curves for ^{11}C -methylphenidate ($n = 8$) and ^{11}C -cocaine ($n = 10$) in striatum (circles) and cerebellum (triangles).

TABLE 1. Regional uptake and kinetics for ^{11}C -cocaine ($n = 8$) and for ^{11}C -methylphenidate ($n = 8$). Peak uptake is expressed as % injected dose per cc of tissue and kinetics correspond to the time required to reach peak uptake and the time required for half peak clearance for the various brain regions (GLB = Global, ST = Striatum, CB = Cerebellum). Modified from Volkow et al.¹⁷

Regions	^{11}C -Cocaine			^{11}C -Methylphenidate		
	Peak Uptake % Dose/cc	Time to Peak Uptake	Half Peak Clearance	Uptake % Dose/cc	Time to Peak Uptake	Half Peak Clearance
GLB	$0.005 \pm .002$	2-8 min	15 min	$.005 \pm .001$	4-10 min	75 min
ST	$0.008 \pm .002$	2-9 min	25 min	$.008 \pm .001$	4-10 min	90 min
CB	$0.007 \pm .002$	2-6 min	15 min	$.006 \pm .001$	4-8 min	50 min

FIGURE 3. Time activity curves for ^{11}C -cocaine in striatum ($n = 10$) and for ^{11}C -methylphenidate ($n = 4$) superimposed with the temporal changes on the "high" experienced after intravenous cocaine. The "high" from intravenous cocaine followed a parallel temporal course to that of ^{11}C -cocaine in the striatum. The "high" after intravenous methylphenidate paralleled the fast rate of uptake of ^{11}C -methylphenidate in the brain but it declined rapidly despite the continuous binding of ^{11}C -methylphenidate in the striatum. From Volkow et al.¹⁷

FIGURE 4. Individual regional brain metabolic values in the orbitofrontal cortex and in the striatum in 14 healthy controls (NML) and 14 cocaine abusers. Nine of the cocaine abusers were tested within one week of last use of cocaine ($< 1\text{W}$) and five between 2 and 4 weeks of last cocaine use (2-4W). Cocaine abusers tested during early cocaine withdrawal showed significantly higher metabolic values in the orbitofrontal cortex and striatum than normal controls.

FIGURE 5. Correlation between the measures of dopamine D₂ receptors (Ratio Index) as assessed with PET and ¹⁸F-NMS and the subjective experience of dysphoria as assessed with the Beck depression inventory in 17 of the cocaine abusers tested between 4 and 6 weeks after last cocaine use; $r = 0.7$ $p < 0.002$.

FIGURE 6. Correlation between the measures of dopamine D₂ receptors (Ratio Index) as assessed with PET and ¹⁸F-NMS and measures of metabolic activity in the orbito frontal cortex, cingulate gyrus and prefrontal cortex in 22 cocaine abusers tested after protracted withdrawal (> 1 week, < 6 weeks).

cleared from brain much faster than methylphenidate.¹⁷ We believe that the fast pharmacokinetics of cocaine at the dopamine transporter account for its unique behavior when compared with that of other drugs that inhibit the dopamine transporter. Its high and fast rate of uptake accounts for its highly reinforcing properties and its fast clearance promotes its repeated and frequent self-administration. We believe that the pleasurable response experienced after cocaine and/or methylphenidate use, which is linked to the release of dopamine in the nucleus accumbens,²³ activates the orbitofrontal-thalamo-striatal circuit setting out the drive to continue to self-administer the drug, a state which is subjectively experienced as drug craving.²⁴ Other reinforcing drugs, such as methylphenidate^{25,26,27} which clear slowly from brain,¹⁶ may not be as effective in maintaining rapid and frequent administration and may therefore be less likely to induce bingeing behavior. We postulate that rapid and frequent administration of the drug interferes with the processes involved in terminating the activation of the orbitofrontal-thalamo-striatal circuit. This circuit which we postulate is initially activated by changes in dopamine, then deactivates as a function of time since last use of the drug. This deactivation does not occur in the abuser self-administering cocaine since its short half-life enables periodic administration that perpetuates the activation of the circuit without enabling its deactivation. For drugs with slow clearance kinetics at the dopamine transporter and for which the high decreases rapidly despite the presence of the drug in the brain, the rapid re-administration of the drug will be less effective in changing dopamine concentration (the first dose is still occupying the transporters) and hence in reactivating the circuit until eventually the circuit deactivates.¹⁷ Though this discussion focuses on the relation between the kinetics of the drug at the dopamine transporter and its ability to induce continuous craving that is not satiated, it is also likely that environmental factors also contribute to the intake of the drug and by themselves may also initiate a craving reaction.^{4,28}

The question then remains as to the mechanisms that account for this pathological activation of the orbitofrontal-thalamo-striatal circuit and its relation to enhanced dopaminergic activity induced by the drug. Perception of pleasure is likely to underlie behaviors that need to be repeated in order for species survival.²⁹ Pleasure is used as a natural reinforcer to increase the probability of the animal engaging in a given behavior and maintaining that behavior once it has initiated it.²⁸ Thus the perception of pleasure which gives the stimuli its motivational properties has been associated with increased dopamine activity in the nucleus accumbens and may serve as a trigger for the maintenance of the behavior.³⁰ For physiological stimuli such as eating, drinking, or sex, the incentive motivational

properties of the stimuli which appear to involve dopaminergic neurotransmission are followed by the consummatory response which is terminated by what humans subjectively describe as satiety. The consummatory component of the behavior is likely to involve the activation of neurotransmitters other than dopamine such as central opiates²⁸ as well as activation of frontal cortical areas since these are uniquely activated with reinforcer dependent stimulation and not with reinforcement independent stimulation.³¹ Though the mechanisms underlying the termination of the consummatory component of the behavior (perception of satiety) are not well understood it is likely that they involve participation of the orbitofrontal cortex since its destruction can lead to the emergence of repetitive behaviors that cannot be terminated.³² Dopaminergic regulation is also likely to play a role since a similar syndrome can be generated by the destruction of the mesocortical dopamine pathway.³³ Serotonergic neurotransmission is probably also involved since destruction of the serotonergic system increases the "drive" to self-administer the drug while enhancement of serotonergic activity significantly reduces it.^{34,35} In humans pathology in the orbitofrontal cortex, cingulate gyrus and in the striatum has been linked with obsessive compulsive disorders^{36,37} which share with addiction the compulsive quality of the behavior.⁴ In fact acute intoxication with psychostimulants induces stereotypical behaviors in the user³⁸ and exacerbates compulsive symptomatology in patients with obsessive compulsive disorder,^{39,40} indicating that both of these types of pathology may involve a common cerebral circuit.

Interestingly, in our studies with cocaine abusers dopamine D₂ receptor availability was found to be correlated with metabolic activity in the orbitofrontal cortex and cingulate gyrus suggesting an association between dopamine activity and function of these cortical brain regions. This association could reflect either a modulation by dopamine of these brain regions⁴¹ or alternatively it could represent modulation of dopamine activity by frontal-striatal circuits.^{31,42} Assuming that changes occurring in the nigro-striatal dopamine pathway (which are the ones measures with PET and D₂ receptor ligands) are similar to those in the meso-cortical dopamine pathway one could interpret the correlation as reflecting dopaminergic activity from the ventral tegmental area modulating activity in the orbitofrontal cortex and cingulate gyrus.^{35,43} However, this relation could also occur indirectly via the striato-pallido-thalamic-cortical circuit.^{44,45} In this model increased dopaminergic activation would change activity in these two frontal regions and the rapid and repeated administration of cocaine would trigger a continuous state of hyperactivity perceived as intense desire for the drug, loss of control and failure to terminate the use

of the drug. This state would take over the behavior of the subject perpetuating drug self-administration despite tolerance to the pleasurable effects of cocaine.⁴⁶ In this respect it is interesting to note that experiments in animals have shown that both the orbitofrontal cortex as well as the medial prefrontal cortex can initiate neuronal activity in circuits that mediate reinforcement.⁴⁷

This still leaves the question unanswered of what are the mechanisms that account for the differences in responses observed between the cocaine addict and the non-addict. Our study shows abnormalities in metabolic activity in the orbitofrontal cortex and cingulate gyrus both during early⁹ and late cocaine withdrawal,¹⁰ which change from hypermetabolic to hypometabolic. The direct association between metabolic activity in these brain regions and dopamine D₂ receptors¹³ indicates that manipulation of dopaminergic circuits may activate or deactivate these brain regions. We believe that cocaine activates these cortical regions by increasing dopamine activity in meso-cortical as well as meso-striatal pathways and that this activation is maintained by its frequent administration. We also postulate that the threshold for activation of this circuit lowers as a function of chronic cocaine exposure and that this is likely to involve changes in receptor-effector signaling mechanisms that initiate the behavior even after small changes in dopamine release as may occur for example when addicts are exposed to drug paraphernalia. With protracted withdrawal the reduction in dopamine D₂ receptors remains but without the use of cocaine there is no longer dopaminergic activation of the orbitofrontal circuit which becomes hypometabolic. However, in these subjects the threshold for activation remains low such that if exposed to stimuli that raise dopamine levels, i.e., stress,⁴⁶ alcohol,⁴⁹ small doses of cocaine and/or memories associated with cocaine, the orbitofrontal-striatal circuit is activated generating the drive and loss of control for consuming cocaine. However, it is also possible that the abnormalities occur at the level of the orbitofrontal cortex and/or cingulate gyrus which then becomes hyper-responsive to dopaminergic stimulation and hyporesponsive to deactivating signals that would normally terminate the behaviors. Dysfunction of the orbitofrontal cortex and/or cingulate gyrus could result, among others, from changes in dopaminergic as well as serotonergic neurotransmission.

In summary, based on results from our PET studies we postulate that cocaine addiction results from the frequent repeated stimulation of meso-cortical and meso-striatal dopaminergic pathways which activates the orbitofrontal-thalamo-striatal circuit that then serves to perpetuate its continuous and repeated administration after tolerance to the pleasurable effects of the drug have occurred and even in the presence of negative side effects.

From this perspective, the pleasurable properties of cocaine serve as a trigger for the activation of a circuit that will then maintain the consummatory behavior. Lower threshold for activation and higher threshold for deactivation of this circuit may be one of the mechanisms accounting for the loss of control and the compulsive drug intake in the addicted individual.

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