Cardiotoxic Properties of Cocaine: Studies With Positron Emission Tomography

Nora D. Volkow, Joanna S. Fowler, and Yu-Shin Ding

INTRODUCTION

The frequent use of cocaine in the United States has resulted in a high degree of morbidity and mortality. Although cocaine was initially believed to be a relatively safe drug, there is now evidence that cocaine is one of the most toxic drugs of abuse (Johanson and Fishman 1989). In fact, laboratory animals given free access to cocaine will self-administer until death (Koob and Bloom 1988). Though cocaine is toxic to various organs in the body, the most frequently involved are the brain and the heart (Dackis and Gold 1990).

Cardiac toxicity is the most frequent complication of cocaine abuse. Cocaine use can trigger myocardial infarction (Huester 1987; Isner et al. 1986) and lethal cardiac arrhythmias (Gradman 1988). Both central (Jones and Tackett 1990; Wilkerson 1988) and peripheral mechanisms (Beckman et al. 1991; Hale et al. 1988; Pitts and Marwah 1989) are responsible for cocaine's cardiotoxic properties. Cocaine's peripheral actions involve the release of adrenaline and noradrenaline from the adrenals (Chiueh and Kopin 1978), inhibition of noradrenaline reuptake sites in myocardial tissue (Iversen 1965), and local anesthetic effects in myocardial cells (Seifen et al. 1989).

Cocaine is directly toxic to the myocardium (Peng et al. 1989; Przywara and Dambach 1989), and its anesthetic properties can trigger cardiac asystole (Nanji and Filipenko 1984). There is evidence from postmortem studies in subjects who died of cocaine overdose that there is significant accumulation in myocardial tissue (Poklis et al. 1987). Therefore, it is important to determine the extent to which there is an accumulation of cocaine in the human heart in vivo. One approach is to measure the distribution and behavior of cocaine in the living heart and compare it with that of its distribution in other organs of the human body. Another approach is to assess the effects of cocaine on specific physiologic and neurochemical processes in the heart.

This chapter describes positron emission tomography (PET) studies that investigated the pharmacokinetics of cocaine in the heart and the dynamics for cocaine-induced inhibition of the norepinephrine (NE) transporter. PET was used in two separate studies: One study assessed the pharmaco-kinetics of cocaine in the living heart, and the other evaluated the effects of cocaine in the NE transporter.

PHARMACOKINETICS OF COCAINE IN THE HEART

[11C]Cocaine was used to assess the kinetics and binding of cocaine in the baboon and human heart. Baboon studies were done in order to assess the effects of various pharmacological challenges on the binding of cocaine in heart. This approach was used to characterize the pattern of cocaine binding in myocardial tissue in vivo. [N-11C-methyl] cocaine was prepared by the methylation of nor-cocaine with [11C]methyl iodide (Langstrom and Lundqvist 1976) as previously described (Fowler et al. 1989).

Baboon Studies

Studies were done in adult female baboons (Papio Annubis). For each of the seven paired studies, the baboons were scanned twice, 2-hours apart. The first scan for each animal was always done with no pharmacological intervention and was used as baseline to compare the effects of the interventions on the second scan. The following interventions were done prior to the second scan:

1.   For one of the animals, the second scan was also done with no pharmacological intervention to assess test-retest reproducibility of [11C]cocaine in heart.

2.   The second scan of one animal was done 2 minutes after intravenous (IV) administration of 2 milligrams per kilogram (mg/kg) cocaine to assess the specificity of cocaine's binding to the heart.

3.   For two animals, the second scan was done 30 minutes after IV administration of 0.5 mg/kg desipramine. Another animal was scanned 30 minutes after administration of tomoxetine (0.5 mg/kg) to determine the extent of [11C]cocaine binding to the NE transporter.

4.   For one animal, the second scan was done 30 minutes after IV administration of nomifensine (2mg/kg) to assess binding to dopamine transporters.

5. For one animal, the second scan was done 60 minutes after IV administration of benztropine mesylate (0.1 mg/kg) to assess binding to muscarinic receptors as well as to dopamine transporters.

Human Studies

Ten healthy human volunteers (male, age range 21 to 47 years) were studied. Five of the subjects received two scans with a 2- to 3-hour time interval between doses. For one subject, the scans were done with no pharmacological intervention to assess the reproducibility of the cardiac uptake of [11C]cocaine between measurements. For four subjects, the second scan was done 40 minutes after the IV injection of 2 mg benztropine mesylate (Dewey et al. 1990) to determine the extent to which uptake of cocaine in the heart represented binding to muscarinic receptors and/or dopamine transporters.

Dynamic scans were done inmediately after IV administration of 5 to 10millicuries (mCi) of [11C]cocaine to (7 to 13 micrograms (μg) cocaine per injection). In the human subjects, dynamic scans were obtained for a total of 45 minutes, and in the baboons for a total of 54 minutes. The baboons were anesthetized, catheterized, and prepared for the PET study as previously described (Dewey et al. 1990). Details on scanning procedure and preparation have been published both for the human (Volkow et al. 1992) as well as for the baboon studies (Dewey et al. 1990). Arterial blood was sampled to measure total radioactivity concentration as well as unchanged tracer in plasma as previously described. Regions in left atrium, left ventricle, and septum were obtained as described (Fowler et al. 1994; Volkow et al. 1992). Time-activity curves for tissue concentration in heart were plotted for the various interventions.

EFFECTS OF COCAINE ON THE MYOCARDIAL NOREPINEPHRINE TRANSPORTER

[18F]Norepinephrine, a ligand for which uptake in heart reflects the func-tion of the NE transporter, was used to evaluate the function of the NE transporter. The effects of cocaine on the uptake of [18F]norepinephrine in the baboon heart were evaluated with PET (Fowler et al. 1994). Studies were done in two adult female baboons: One was scanned five different times, and the other four different times, with a 9- to 14-day interval between scans. The first scan was

done with no pharmacological intervention and was used as baseline. The experimental strategies were as follows:

1. In one baboon, the four additional [18F]fluoronorepinephrine scans were done 5 minutes, 30 minutes, 66 minutes, and 24 hours after IV administration of 2 mg/kg cocaine.

2. In the second baboon, the three additional [18F]fluoronorepinephrine scans were performed 30 minutes, 78 minutes, and 24 hours after IV administration of 2 mg/kg cocaine.

Dynamic scans were started inmediately after injection of 0.9 to 4.2 mCi of [18F]fluoronorepinephrine (0.17 mg/mCi) and were continued for a total of 100 minutes. Arterial plasma input functions were measured for each study as described previously (Ding et al. 1993). Heart and res-piratory rates were monitored during the PET study. Details on scanning protocol for the [18F]fluoronorepinephrine and synthesis of [18F]norepine-phrine have been published (Ding et al. 1993).

For the analysis of the PET images, regions of interest were drawn directly on the myocardial emission images as previously described (Ding et al. 1993). The activity in these regions of interest was used to obtain the time activity curve for regional tissue concentration. The time-activity curves for tissue concentration and for unchanged tracer in plasma were used to calculate the transport constant between plasma and tissue (K1) and to obtain the retention fraction (ratio of heart radioactivity to integral of plasma radioactivity at 30 minutes) (Ding et al. 1993).

RESULTS

Pharmacokinetics of Cocaine in the Heart

There was high uptake of radioactivity into the human and baboon heart after IV injection of [11C]cocaine (figure 1). Regional analysis of radioactive isotope in the heart showed homogeneous distribution with similar uptake in left ventricle, atrium, and septum.
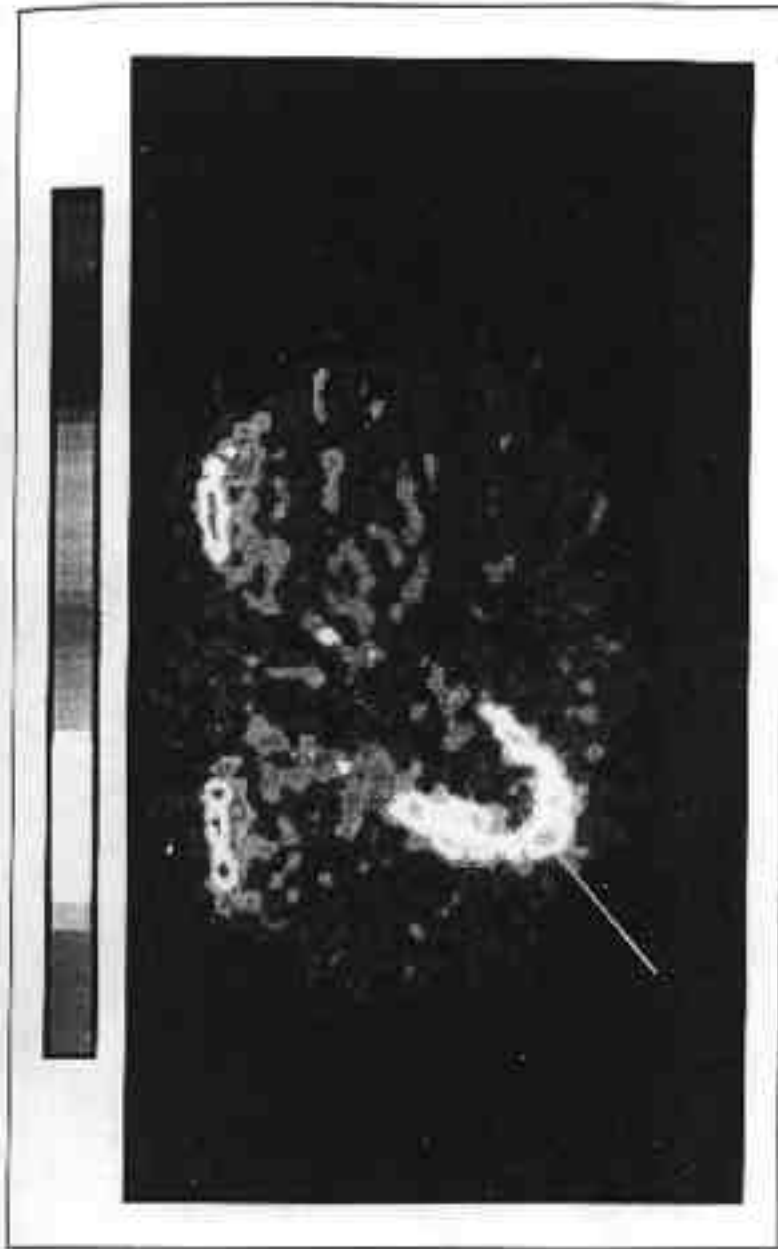
FIGURE 1. *Thoracic images of [¹²³I] ß-CIT-routine taken 2 to 10 minutes after injection. The image corresponds to an axial plane showing the long axis views of the heart.*

In the human heart, peak carbon-11 concentrations for the left ventricle, septum, and atrium corresponded to 0.007 (standard deviation (SD) 0.001), 0.006 (SD 0.002), and 0.007 percent (SD 0.001) dose/cc of tissue respectively. The peak uptake is equivalent to that observed for the basal ganglia, which also corresponded to 0.007 percent dose/cc tissue. Peak uptake of carbon-11 in the heart occurred 2 to 3 minutes after admini-stration of the tracer. The clearance of [11C] cocaine from the heart was also very fast, with half-peak activity seen 10 minutes after injection (figure 2). In contrast, there was no retention of radioactivity by the lung, where the activity paralleled that of the tracer in plasma. Figure 2 shows the kinetics of carbon-11 uptake in heart, lung, and arterial plasma for one representative subject.

Benztropine mesylate, a drug that binds to muscarinic receptors and dopamine transporters, did not change binding of [11C]cocaine in the human heart (figure 3).
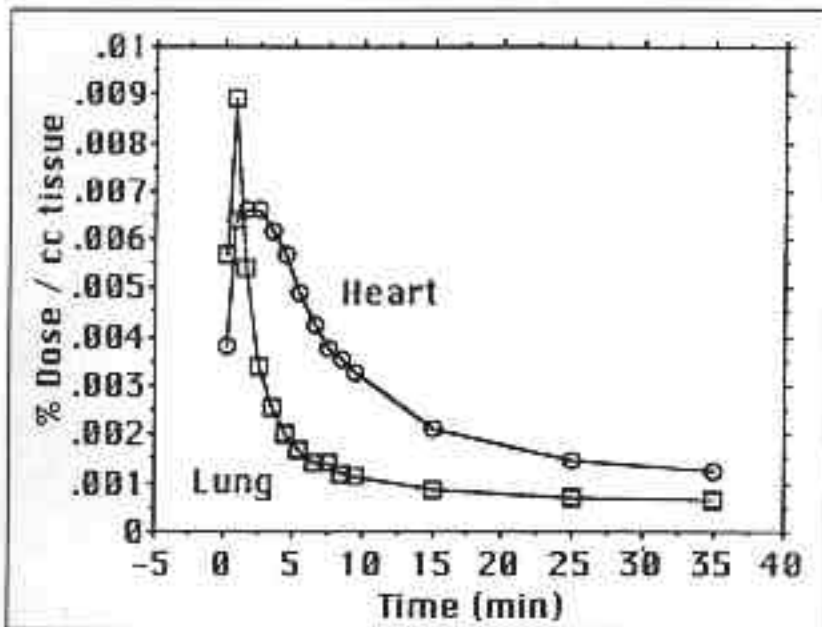

FIGURE 2. *Average time-activity curves of [^{11}C]cocaine in heart and lung for the baseline studies in the normal contt· ls. Uptake in lung paralleled the radioactivity of plasma. In the heart, peak uptake occurred 2 to 3 minutes after injection. Half of the peak activity remained at 10 minutes.*
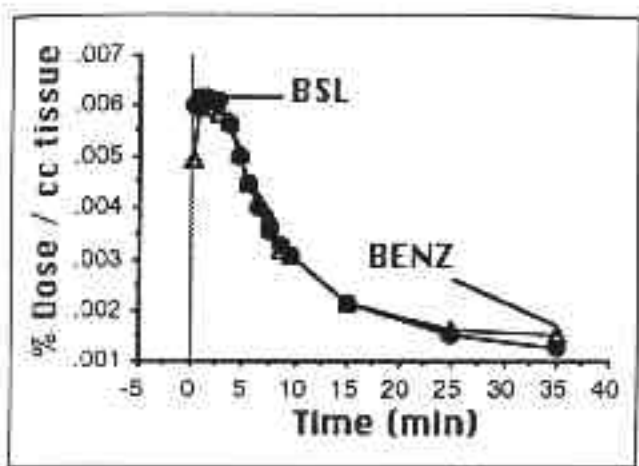
FIGURE 3. Time-activity curves of [¹¹C]cocaine in heart for a normal control tested at baseline (BSL) and after pretreatment with benztropine mesylate (BENZ). benztropine did not affect [¹¹C]cocaine binding.

In the baboon, peak [11C]cocaine concentration ranged from 0.036 to 0.055percent dose/cc tissue, which (as in humans) was also similar to peak uptake in basal ganglia (0.05 percent (SD 0.01) dose/cc tissue). Serial PET studies showed a test-retest variability of less than 5 percent for the uptake of [11C]cocaine in heart. The time-activity curves for both studies were super-imposable on each other (data not shown). Preadministration of cocaine prior to tracer injection decreased the clearance of [11C]cocaine (half-life (t_): 12.3 minutes (cocaine) versus 9 minutes (baseline)) (figure 4).

Slowing of the clearance may have reflected a higher plasma concentra-tion of [11C] cocaine throughout the study, when the animal was pre-administered pharmacological doses of cocaine (figure 5). This plasma increase probably reflects a larger bioavailability of [11C]cocaine, as a result of the occupation by cocaine of its binding sites.

Neither tomoxetine, desipramine, nomifensine, nor benztropine mesylate inhibited the uptake of [11C]cocaine in the heart, nor did they change its pharmacokinetics (figure 6 shows the time-activity curves for the tomoxetine study).
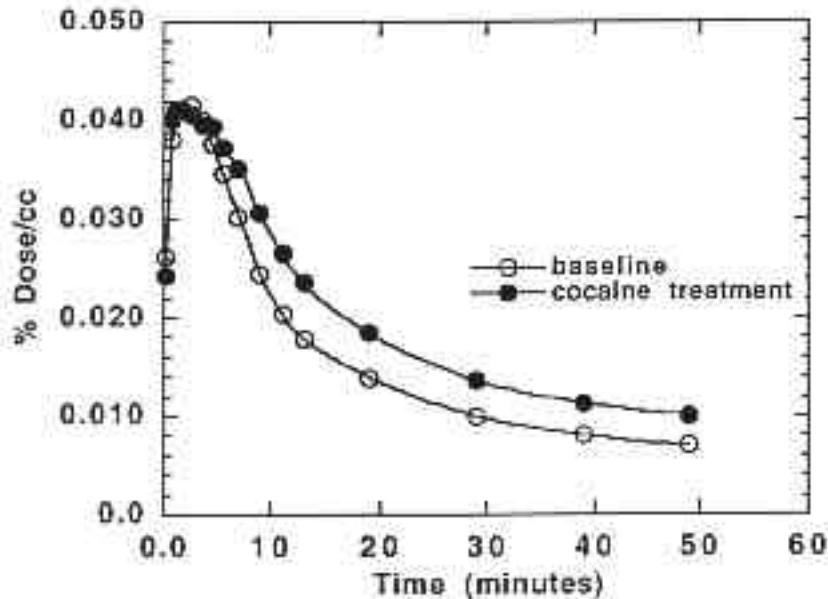
FIGURE 4. *Time activity curves for [11C]cocaine in baboon heart at baseline and after administration of cocaine (2 mg/kg IV). Cocaine preadministration decreased uptake of [11C]cocaine in heart.*

Effects of Cocaine on the Myocardial Norepinephrine Transporter

Studies with [18F]norepinephrine revealed the characteristic pattern of high uptake of radioactive isotope into the heart that peaks almost immediately after injection and plateaus thereafter (Ding et al. 1993). Cocaine preadministration inhibited [18F]norepinephrine uptake into the heart by 90 percent when the studies were done 5 minutes after cocaine administration. This profound inhibition of [18F]norepinephrine uptake is equivalent to that observed after pretreatment with desipramine using doses that had failed to inhibit [11C]cocaine in heart (Ding et al. 1993). In contrast to the fast pharmacokinetics of cocaine in the heart, cocaine-induced inhibtion of the NE transporter was prolonged. Sixty-six minutes after cocaine administration, the retention fraction for [18F]norepinephrine was 29 percent of the baseline value for one baboon. At 78minutes after cocaine administration, the retention fraction for [18F]norepinephrine was 57 percent of the baseline value for the other baboon. By 24 hours, the retention fraction for [18F]norepinephrine approached baseline values.
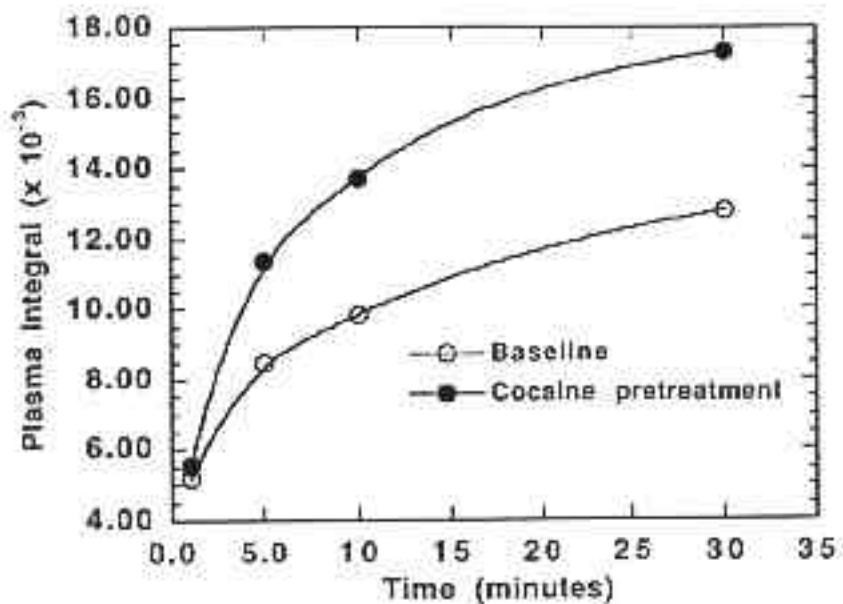
FIGURE 5. *Plasma integrals for the concentration of [^{11}C]cocaine (nCi/cc minute) for the study done at baseline and after cocaine preadministration (2 mg/kg IV).*

Time-activity curves for [18F]norepinephrine are shown in figure 7 for [18F]fluoronorepinephrine scans done at baseline and at 5 minutes, 30minutes, 66 minutes, and 24 hours after administration of cocaine to one baboon.

Discussion

This study documented significant uptake of [11C] cocaine by the human heart. In a heart weighing 350 gm, 2.5 percent of the injected dose was in the heart 2 to 3 minutes after IV administration. The uptake and clearance of carbon-11 from the heart were faster than in the brain (Fowler et al. 1989). In the heart, the time for clearance to 50percent of maximum uptake was 10 minutes, whereas in the brain it was 25 minutes (Fowler et al. 1989). The 2- to 3-minute postinjection peak corresponds with the time required to reach maximal chronotropic response after IV cocaine (Rowbotham et al. 1987). However, the kinetics of cocaine clearance from the heart do not correspond to the longer lasting chronotropic effects of cocaine (Foltin
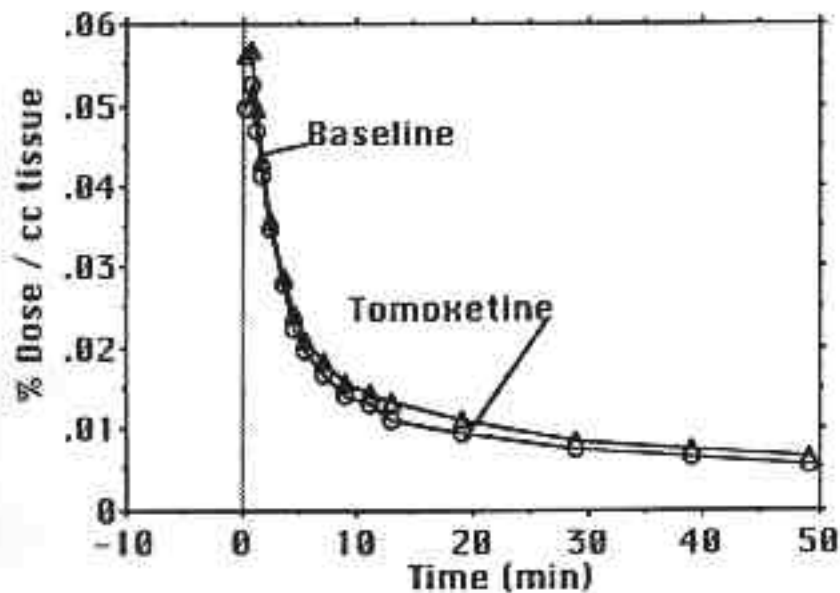
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FIGURE 6. *Time activity curves for [^{11}C]cocaine in baboon heart at baseline and after administration of tomoxetine. Tomoxetine did not affect [^{11}C]cocaine binding in heart.*

and Fischman 1991). Similarly, the chronotropic effects of cocaine are of much longer duration than the kinetics of cocaine in brain.

The discrepancy in the duration of the chronotropic effects of cocaine and the kinetics of cocaine in heart or brain suggests either that cocaine induces a prolonged change in the transporters and/or receptors with which it inter-acts or that the actions are indirect. Indirect chronotropic effects on the heart could be due to central effects and/or to catecholamine release from the adrenal (Nahas et al. 1991). Alternatively, these effects could be the results of a cocaine metabolite.

The finding that there is significant accumulation of cocaine in the human heart suggests that cocaine could affect myocardial tissue directly via its interaction with noradrenergic transporters in myocardial cells (Lew and Angus 1981) or via its local anesthetic properties at this site (Boni et al. 1991). Both of these properties may act synergistically to enhance cocaine's toxic effects. Although the cardiac accumulation of cocaine is

TABLE 1.   [^{18}F]Norepinephrine ([^{18}F]NE) heart uptake after cocaine pretreatment (2 mg/kg) at different times prior to tracer injection. Heart uptake is expressed as retention fraction (the ratio of the heart uptake to the arterial plasma integral for [^{18}F]NE at 30 minutes). The peak uptake of the tracer in heart for this study (0.060 percent dose/cc tissue) was 10percent lower than that for the baseline (0.067 percent dose/cc tissue).

	Intervention	Intervention time prior to [18F]NE	Retention fraction (RF)	% inhibition
			0.41	100
Baboon 1	baseline	NA		
	cocaine	5 minutes postcocaine	0.032	92
	cocaine	30 minutes postcocaine	0.090	78
	cocaine	66 minutes postcocaine	0.12	71
	cocaine	1440 minutes postcocaine	*	*
Baboon 2	baseline	NA	0.28	100
	cocaine	30 minutes postcocaine	0.089	68
	cocaine	78 minutes postcocaine	0.16	43
	cocaine	1440 minutes postcocaine	0.24	14

KEY: * = Blood measurements lost due to technical error; NA = not applicable.

transient after a single administration, under conditions of repeated administration (as in the cocaine abuser), one would expect high concentrations throughout the period of drug administration.

Pretreatment with desipramine, nomifensine, and benztropine did not affect the binding of [11C]cocaine to the heart. These results could be interpreted as showing no binding of cocaine to NE transporters, dopa-mine transporters, or to muscarinic receptors, but it is unlikely since postmortem studies have demonstrated binding of cocaine to NE trans-porters (Lew et al. 1981) and to muscarinic receptors (Sharkey et al. 1988) in the heart. It is more likely that these results reflect insufficient sensitivity of PET to detect binding when the concentration (Bmax) or the affinity (Kd) of the transporters or the receptors is low.
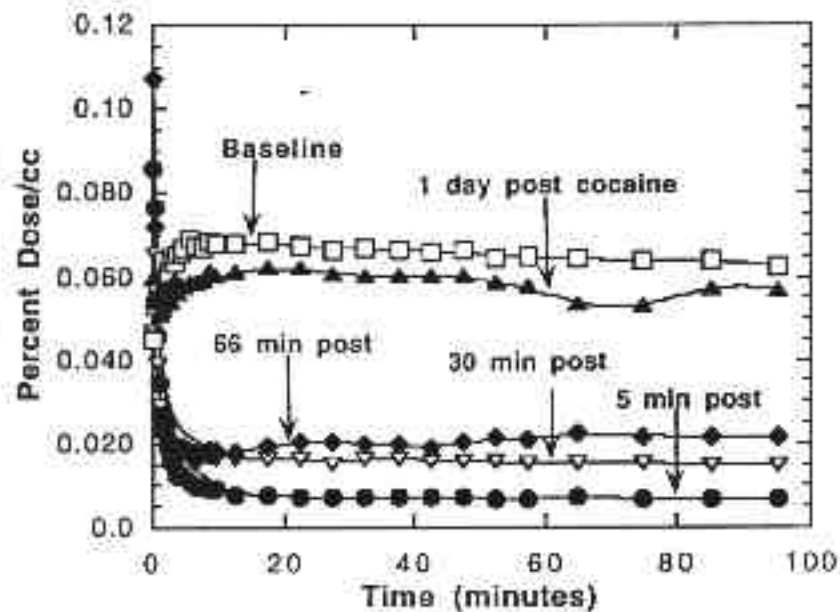
FIGURE 7. *Time-activity curves for five different PET studies with (·)-6[¹⁸F]FNE in one of the baboons at baseline, and at 5 minutes, 30 minutes, 66 minutes, and 24 hours after pretreatment with cocaine (2 mg/kg IV).*

Even though the authors were unable to document binding of cocaine into the NE transporter as assessed by the inability of desipramine to block [11C]cocaine uptake, inhibition of the NE transporter by cocaine was demonstrated by the blockade of [18F]norepinephrine uptake. This apparent discrepancy could be due to the lack of PET sensitivity to detect binding sites with relatively low concentration per cc of tissue, but it may also indicate different sites of interaction of desipramine and cocaine at the NE transporter site. These results highlight the importance of com-bining more than one tracer in imaging studies that investigate the actions of a given drug in a receptor or transporter.

Another interesting finding from this investigation was the discrepancy between the short pharmacokinetics of cocaine in heart and the long-lasting cocaine-induced inhibition of the NE transporter. At 66 minutes, when there was no [11C]cocaine left in the myocardium, there was still 71percent inhibition of the transporter. Even 24 hours after adminis-tration of cocaine, there still appeared to be some functional inhibition of the NE transporter. The long-lasting inhibition of the NE transporter by cocaine despite its short

pharmacokinetics could represent competition for the transporter by circulating catecholamines induced as a result of cocaine's actions in the adrenals (Powis et al. 1989). However, it is also possible that the long-lasting NE transporter inhibition reflects a cocaine-induced change in the conformation of the transporter. Further work is required to evaluate if acute cocaine administration does in fact alter the conformation of the NE transporter.

SUMMARY

This study documented marked accumulation of cocaine in the human and baboon heart, which was not inhibited by desipramine pretreatment. However, cocaine inhibited 6-[18F]fluoronorepinephrine uptake in heart to the same degree as did desipramine (Fowler et al. 1994). Since uptake of [18F]norepinephrine in the heart is a function of its uptake by the NE transporter (Fowler et al. 1994), its inhibition by cocaine corroborates in vivo a significant interaction of cocaine with this transporter.

REFERENCES

Beckman, K.J.; Parker, R.B.; Hariman, R.J.; Gallastegui, J.L.; Javaid,J.J.; and Bauman, J.L. Hemodynamic and electrophysiological actions of cocaine. Circulation 83:1799-1807, 1991.

Billman, G.E., and Hoskins, R.S. Cocaine-induced ventricular fibrillation: Protection afforded by the calcium antagonist verapamil. FASEB J 2:2990-2995, 1988.

Boni, J.P.; Barr, W.H.; and Martin, B.R. Cocaine inhalation in the rat: Pharmacokinetics and cardiovascular response. J Pharmacol Exp Ther 257:307-315, 1991.

Chiueh, C.C., and Kopin, I.J. Endogenous epinephrine and norepinephrine from the sympathoadrenal medullary system of unanesthetized rats. JPharmacol Exp Ther 205:148-154, 1978.

Dackis, C.A., and Gold, M.S. Medical, endocrinological and pharmacological aspects of cocaine addiction. In: Volkow, N.D., and Swann, A.C., eds. Cocaine in the Brain. New Brunswick: Rutgers University Press, 1990. pp. 135-154.

Dewey, S.L.; MacGregor, R.R.; Brodie, J.D.; Bendriem, B.; King, P.T.; Volkow, N.D.; Schlyer, D.J.; Fowler, J.S.; Wolf, A.P.; Gately, S.J.; and Hitzemann, R. Mapping muscarinic receptors in human and baboon brain using N-11C-methyl benztropine. Synapse 5:213-223, 1990.

Ding, Y.S.; Fowler, J.S.; Dewey, S.L.; Schlyer, D.; Gatley, J.; Volkow,N.D.; King, P.T.; and Wolf, A.P. Comparison of high specific activity (+) and (-) 6-18F fluoronorepinephrine and 6-18F fluorodopamine in baboon: Heart uptake, metabolism and the effect of desipramine. J Nucl Med 34:619-629, 1993.

Foltin, R.W., and Fischman, M.W. Smoked and intravenous cocaine in humans: Acute tolerance, cardiovascular and subjective effects. J-Pharmacol Exp Ther 257:247-261, 1991.

Fowler, J.S.; Ding, Y.S.; Volkow, N.; Martin, T.; MacGregor, R.; Dewey,S.L.; King, P.; Pappas, N.; Alexoff, D.; Shea, C.; Gatley, J.; Schlyer, D.; and Wolf, A. PET studies of cocaine inhibition of the myocardial norepinephrine uptake. Synapse 16:312-317, 1994.

Fowler, J.S.; Wolf, A.P.; and Volkow, N.D. New directions in positron emission tomography—Part II. Ann Reports Med Chem 25:261-269, 1990.

Fowler, J.S.; Volkow, N.D.; Wolf, A.P.; Dewey, S.L.; Schlyer, D.J.; MacGregor, R.R.; Hitzemann, R.; Logan, J.; Bendriem, B.; Gatley,S.J.; and Christman, D. Mapping cocaine binding sites in human and baboon brain in vivo. Synapse 4:371-377, 1989.

Gradman, A.H. Cardiac effects of cocaine: A review. Yale J Biol Med 61:137-141, 1988.

Grant, B.F., and Harford, T.C. Concurrent and simultaneous use of alcohol with cocaine: Results of national survey. Drug Alcohol Depend 25:97-104, 1990.

Hale, S.L.; Alker, K.J.; Reskalla, S.; Figures, G.; and Kloner, R.A. Adverse effects of cocaine on cardiovascular dynamics, blood flow and coronary artery diameter in an experimental model. Am Heart J 118:927-933, 1988.

Hayes, S.N.; Moyer, T.; Moyer, P.; Morley, D.; and Bove, A.A. Intravenous cocaine causes epicardial coronary vasoconstriction in the intact dog. Am Heart J 121:1639-1648, 1991.

Huester, D.C. Cardiovascular effects of cocaine. JAMA 257:979-980, 1987.

Isner, J.; Estes, M.; Thompson, P.D.; Subramanian, R.; Miller, G.; Katsas,G.; Sweeney, K.; and Sturner, W.Q. Acute cardiac events temporarily related to cocaine abuse. N Engl J Med 315:1438-1443, 1986.

Iversen, L.L. Inhibition of noradrenaline uptake by drugs. J Pharm Pharmacol 17:62-64, 1965.

Johanson, C.E., and Fishman, M.W. The pharmacology of cocaine related to its abuse. Pharmacol Rev 41:3-52, 1989.

Jones, L.F., and Tackett, R.L. Central mechanisms of action involved in cocaine-induced tachycardia. Life Sci 46:723-728, 1990.

Koob, G.F., and Bloom, F.E. Cellular and molecular mechanisms of drug dependence. Science 242:715-723, 1988.

Langstrom, B., and Lundqvist, H. The preparation of 11C-methyl iodide and its use in the synthesis of 11C-methyl-L-methionine. Int J Appl Radiat Isot 27:357-363, 1976.

Lew, M.J., and Angus, J.A. Disadvantages of cocaine as a neuronal uptake blocking agent: Comparison with desipramine in guinea-pig right atrium. J Auton Pharmacol 3:61-71, 1981.

Logan, J.; Fowler, J.S; Volkow, N.D.; Wolf, A.P.; Dewey, S.L.; Schlyer,D.; MacGregor, R.R.; Hitzemann, R.; Bendriem, B.; Gatley,-S.J.; and Christman, D.R. Graphical analysis of reversible radioligand binding time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. JNeurochem 10:740-747, 1990.

Nahas, G.; Trouve, R.; Manger, W.; and Latour, C. Cocaine and sympathoadrenal system. In: Nahas, G.G., and Latour, G., eds. Physiopathology of Illicit Drugs: Cannabis, Cocaine Opiates. Oxford: Pergamon Press, 1991. pp. 151-164.

Nanji, M.B., and Filipenko, D.J. Asystole and ventricular fibrillation associated with cocaine intoxication. Chest 85:132-133, 1984.

Peng, S.-K.; French, W.J.; and Pelikan, P.C.D. Direct cocaine cardiotoxicity demonstrated by endomyocardial biopsy. Arch Pathol Lab Med 113:842-845, 1989.

Pitts, O.K., and Marwah, J. Autonomic actions of cocaine. Can J Physiol Pharmacol 67:1168-1176, 1989.

Poklis, A.; Maginn, D.; and Barr, J.L. Tissue disposition of cocaine in man: A report of five fatal poisonings. Forensic Sci Int 33:83-88, 1987.

Powis, D.A.; O'Brien, K.J.; and Torok, T.L. Multiple effects of cocaine upon evoked secretions in bovine adrenal medullary chromaffin cells. Arch Pharmacol 339:272-280, 1989.

Przywara, D.A., and Dambach, G.E. Direct actions of cocaine on cardiac cellular activity. Circulation Res 65:185-192, 1989.

Rowbotham, M.C.; Hooker, W.D.; Mendelson, J.; and Jones, R.T. Cocaine-calcium channel antagonist interactions. Psychopharmacology 93:152-154, 1987.

Sands, B.F., and Ciraulo, D.A. Cocaine drug-drug interactions. J Clin Psychopharm 12:49-55, 1992.

Seifen, E.; Plunkett, L.M.; and Kennedy, R.H. Cardiovascular and lethal effects of cocaine in anesthetized dogs and guinea pigs. Arch Int Pharmacodyn 300:241-253, 1989.

Sharkey, J.; Ritz, M.; Schenden, J.A.; Hanson, R.C.; and Kuhal, M.J. Cocaine inhibits muscarinic cholinergic receptors in heart and brain. JPharmacol Exp Ther 246:1048-1052, 1988.

Urbano-Marquez, A.; Estruch, R.; Navarro-Lopez, F.; Grau, J.M.; Mont,L.; and Rubin, E. Effects of alcoholism on skeletal and cardiac muscle. N Engl J Med 320:409-415, 1989.

Volkow, N.D.; Fowler, J.S.; Wolf, A.P.; Wang, G.-J.; Logan, J.; MacGregor, R.; Dewey, S.L.; Schlyer, D.J.; and Hitzemann, R. Distribution of [11C]cocaine in human heart, lungs, liver and adrenals. A dynamic PET study. J Nucl Med 33:521-525, 1992.

Wilkerson, R.D. Cardiovascular effects of cocaine in conscious dogs: Importance of fully functional autonomic and central nervous system. J Pharmacol Exp Ther 246:466-471, 1988.

AUTHORS

Nora D. Volkow, M.D.
Director, Nuclear Medicine
Associate Chief of Staff
Clinical Research Center
Brookhaven National Laboratory
and
Associate Professor
Department of Psychiatry
State University of New York at Stony Brook
Stony Brook, NY 11794-8101

Joanna S. Fowler, Ph.D.
Director, PET Program
Chemistry Department

Yu-Shin Ding, Ph.D.
Chemist
Chemistry Department

Brookhaven National Laboratory
Building 490
30 Bell Avenue
Upton, NY 11793

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