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Imaging of Cardiac Neuronal Function After Cocaine Exposure Using Carbon-11 Hydroxyephedrine and Positron Emission Tomography

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Objectives. **The aim of the study was to define the effect of cocaine on the myocardial uptake and retention of C-11 hydroxyephedrine in the anesthetized dog model.**

Background. **Cardiac toxicity of cocaine has been linked to its inhibitory effect on norepinephrine reuptake by the sympathetic nerve terminals of the heart. Carbon-11 hydroxyephedrine is a C-11–labeled norepinephrine analog that has high specific affinity for uptake-1 and thus makes possible the assessment of the effect of cocaine on norepinephrine reuptake by cardiac sympathetic nerve terminals.**

Methods. **The cardiac kinetics of C-11 hydroxyephedrine as assessed by dynamic positron emission tomographic imaging were used to characterize norepinephrine reuptake by the sympathetic nerve terminals. Carbon-11 hydroxyephedrine was injected intravenously before, as well as at 5 min and 2.5 h after, intravenous administration of 2 mg/kg body weight of cocaine in anesthetized dogs. Hemodynamic variables and microsphere-determined cardiac blood flow were also measured before and after cocaine exposure.**

Results. **Intravenous injection of cocaine did not significantly affect hemodynamic variables and myocardial blood flow in the anesthetized animals. Compared with baseline, myocardial retention of C-11 hydroxyephedrine was significantly reduced by 78 ± 3% (mean ± SD) at 5 min and remained significantly reduced (28 ± 17%) at 2.5 h after cocaine injection. Cocaine administration after C-11 hydroxyephedrine injection (30 min) resulted in rapid biexponential clearance of C-11 hydroxyephedrine from myocardium.**

Conclusions. **These results suggest prolonged effects of cocaine on the sympathetic nerve terminals of the heart. Positron emission tomography provides a noninvasive and sensitive means to objectively assess the cardiac pharmacokinetics of drugs such as cocaine.**

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Numerous cocaine-related adverse cardiac events have been reported among occasional and long-term users. Myocardial ischemia, infarction, arrhythmia, sudden death, myocarditis, cardiomyopathy, pulmonary edema and rupture of the aorta have been described (1–11). The action of cocaine on the cardiovascular system is complex. Two essential mechanisms are thought to explain the cardiac toxicity of cocaine: its inhibitory action on catecholamine reuptake by the presynaptic sympathetic nerve endings and its local anesthetic action by blockade of the fast sodium channels (12,13).

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The heart is richly innervated by sympathetic nerve fibers (14–16). On nerve stimulation, norepinephrine is released in the synaptic cleft and interacts with the adrenergic receptors. The termination of norepinephrine effects mainly depends on the recapture of the neurotransmitter by the nerve terminals themselves through an active transport mechanism called uptake-1. Inhibition of this neuronal recapture by cocaine results in an excess of extraneuronal norepinephrine concentration, leading to an overstimulation of postsynaptic receptor sites (17). The norepinephrine overflow may result in smooth muscle contraction and an increase in both heart rate and blood pressure.

The local anesthetic action of cocaine results from its inhibition of transmembranous sodium transport into the neurons, thus preventing the generation and conduction of the nerve impulse. This effect also occurs in the cardiac cells and results in a decrease in the rate of increase of phase zero of action potentials and impairment of conduction, which may contribute to triggering cardiac arrhythmia and contractile depression. Although contributing to the cardiac toxicity of cocaine, the anesthetic effects are usually observed in doses of drug 10 times greater than those necessary to inhibit the norepinephrine recapture (18).

In vivo assessment of the cocaine-induced inhibition of norepinephrine recapture by the presynaptic sympathetic

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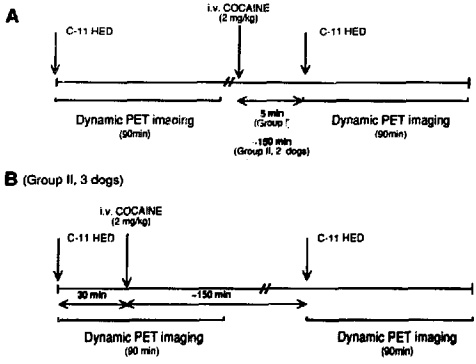

Figure 1. Experimental protocol. A, The first dynamic positron emission tomographic (PET) imaging was performed to evaluate the presynaptic neuronal function before intravenous (i.v.) cocaine injection. Reassessment of the presynaptic neuronal function was performed with C-11 hydroxyephedrine (HED) dynamic positron emission tomographic imaging started 5 min (group I, n = 5) and ~150 min (group II, n = 2) after cocaine exposure, respectively. B, Modified scanning protocol for three group II dogs. Cocaine was administered 30 min after initiation of the first dynamic positron emission tomographic imaging. The second C-11 hydroxyephedrine positron emission tomographic imaging was initiated ~150 min after cocaine injection, as in the two other group II dogs.

nerve endings of the heart has not yet been reported. Carbon-11 hydroxyephedrine has been developed in our laboratory as a C-11–labeled norepinephrine analog (19). This radiotracer showed a high specific affinity for uptake-1 (20) and accumulated in the heart proportionally to the norepinephrine tissue concentration (21). The combined use of this radiotracer and positron emission tomography offers a unique approach to characterize noninvasively the catecholamine uptake mechanism by cardiac presynaptic sympathetic nerve endings.

Therefore, the purpose of this study was to define the effect of short-term cocaine exposure on the myocardial kinetics of C-11 hydroxyephedrine by positron emission tomography. The tracer uptake as well as its retention were assessed by dynamic imaging to probe the pharmacologic effect of cocaine on uptake-1.

Methods

The study was approved by the Committee for Animal Research at the University of Michigan and was performed in accordance with the "Position of the American Heart Association on Research Animal Use" adopted by the Association in November 1984.

Animal preparation. Ten mongrel dogs (mean weight 15 ± 2 kg) of both genders were selected and fasted for 24 h before the study. The dogs were anesthetized with intravenous sodium pentobarbital (30 mg/kg body weight), intubated and ventilated with oxygen-enriched room air (Harvard Apparatus). Venous access was obtained through a femoral vein for C-11 hydroxyephedrine injection as well as for the administration of fluids and sodium pentobarbital to maintain anesthesia. Both femoral arteries were catheterized for aortic pressure monitoring and arterial blood sampling. The heart was exposed by a left thoracotomy in the fifth intercostal space to insert a catheter into the left atrium for microsphere injection. The chest was subsequently closed. After completion of surgery, aortic pressure and the electrocardiogram were monitored continuously (multichannel recorder, model 53-G2682-10, Gould Inc.).

Study protocol. The study protocol (Fig. 1) was designed to evaluate and compare uptake-1 activity of sympathetic nerve endings of the heart at two different times after the bolus intravenous injection of a dose of 2 mg/kg of cocaine hydrochloride. For this purpose, the dogs were divided into two groups (I and II), each of five animals. For each dog in both groups, the first dynamic positron emission tomographic study with C-11 hydroxyephedrine was performed to define baseline presynaptic sympathetic function. Then, the presynaptic neuronal function was reassessed with C-11 hydroxyephedrine, and dynamic positron emission tomography was started at 5 min and ~150 min (range 131 to 187) after cocaine administration in groups I and II, respectively. As described in Figure 1B, the protocol design was modified in three group II dogs. In these dogs, cocaine was injected after 30 min of data acquisition of C-11 hydroxyephedrine baseline kinetics. This protocol of cocaine injection was used to evaluate the effect of cocaine on C-11 hydroxyephedrine tissue retention, which is known to depend on the uptake-1 mechanism (22). In these three dogs, the second injection of C-11 hydroxyephedrine was normally given ~150 min after cocaine, as in the two other group II dogs.

Positron emission tomography. *Radiochemistry.* A detailed description of the synthesis of C-11 hydroxyephedrine has been published elsewhere (19). Briefly, C-11 hydroxyephedrine was produced by direct *N*-methylation of metaraminol with C-11 methyl iodide in dimethyl formamide/dimethyl sulfoxide and purified by reversed-phase high

Table 1. Hemodynamic Variables at Baseline and After Cocaine Administration in All Dogs

	Baseline	1 min	2 min	3 min	4 min	5 min
HR (beats/min)	140 ± 21	141 ± 28	137 ± 28	132 ± 26	132 ± 27	137 ± 22
p value*		NS	NS	NS	NS	NS
SBP (mm Hg)	130 ± 18	131 ± 20	133 ± 20	128 ± 18	128 ± 18	130 ± 21
p value*		NS	NS	NS	NS	NS
DBP (mm Hg)	94 ± 15	102 ± 12	100 ± 14	97 ± 14	96 ± 16	95 ± 17
p value*		NS	NS	NS	NS	NS
PRP (× 100)	183 ± 46	189 ± 64	185 ± 60	170 ± 52	170 ± 54	180 ± 52
p value*		NS	NS	NS	NS	NS

*Versus baseline. Data presented are mean values ± SD. DBP = diastolic blood pressure; HR = heart rate; PRP = rate-pressure product; SBP = systolic blood pressure.

performance liquid chromatography in an isotonic aqueous buffered system. The specific activity was >1,000 mCi/mmol at the end of synthesis, and radiochemical and chemical purities were >95%.

Data acquisition. Each dog was imaged using the scanner (PCT 4600 A, TCC Corporation) of the positron emission tomography facility at the University of Michigan. This scanner acquires coincidence data that are reconstructed into five transverse section planes of 1.1-cm thickness (three direct and two cross planes) with a transaxial resolution of 12.5 mm. Placement of the dog within the gantry was adjusted using a N-13 ammonia scout scan. A 10-min transmission scan was acquired with an external ring source to correct for attenuation in the emission scans. At the time of each C-11 hydroxyephedrine injection, dynamic image acquisition was initiated with varying frame duration for 90 min (six 10-s frames, three 20-s frames, three 60-s frames, two 150-s frames, six 300-s frames and six 600-s frames). A modified 90-min dynamic image acquisition protocol was used for group II baseline study, with frames of 120-s duration after cocaine injection (six 10-s frames, three 20-s frames, three 60-s frames, two 150-s frames, four 300-s frames and 30 120-s frames). An arterial input function for C-11 hydroxyephedrine was obtained by serial 1-ml arterial blood sampling until the completion of the imaging protocol. Carbon-11 blood radioactivity was counted in a well counter (EG&G Ortec) and automatically corrected for background and decay to generate time-activity curves. The arterial input function was then individually corrected for carbon-11 blood metabolite activity using a rapid solid-phase extraction of carbon-11 metabolites from C-11 hydroxyephedrine as described previously (19).

Data analysis. Midventricular images were selected for positron emission tomographic data analysis. Myocardial regions of interest were defined in the anterior, septal, inferior and lateral walls of the myocardium. Each of these regions of interest was automatically propagated over the entire sequence of images, and time-activity curves for the myocardium were generated. The retention of C-11 hydroxyephedrine in the myocardium was used as an index of norepinephrine uptake into the nerve terminals. A retention index, having units of inverse minutes, was calculated for each region of interest by dividing the tissue activity at 30 min after tracer injection by the integral of the activity in arterial blood from zero to 30 min.

Microsphere-determined myocardial blood flow. Myocardial blood flow was determined using the standard technique with microspheres (23). Myocardial blood flow was measured before and 10 min after cocaine. In group II, myocardial blood flow was also measured at the time of the second C-11 hydroxyephedrine injection. Microspheres labeled with either niobium-95 (765 keV), cerium-141 (150 keV) or tin-113 (393 keV) (DuPont-NEN Products) were injected into the left atrium. An arterial input function was obtained for each microsphere injection by arterial blood collection using a Harvard pump (Harvard Apparatus) at a rate of 14.8 ml/min for 2 min.

At the end of image acquisition, the dogs were killed by injection of a saturated solution of potassium chloride. The heart was then excised, and the left ventricle was cut into samples ~1 g. The microsphere radioactivity in the myocardial and blood samples was counted using a multicaannel well counter (model 5780, Packard) and preselected energy windows (niobium-95 710 to 820 keV, cerium-141 127 to 175 keV, tin-113 360 to 440 keV).

Statistical analysis. Results are given as mean values ± SD. Significance levels for changes in heart rate, blood pressure, rate-pressure product and blood flow from before to after cocaine exposure were determined by repeated-measures analysis of variance, followed by the Bonferroni modified t test when a significant difference was indicated by analysis of variance. Values of cardiac C-11 hydroxyephedrine retention before and after cocaine exposure were compared using a paired t test. Values at $p \leq 0.05$ were considered significant.

Results

Hemodynamic variables and myocardial blood flow. Intravenous injection of 2 mg/kg of cocaine hydrochloride was well tolerated, and the experimental protocol was completed in all dogs. The effect of cocaine on systolic and diastolic blood pressure, heart rate and rate-pressure product are presented in Table 1. Values of myocardial blood flow

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Table 2. Blood Flow Expressed in ml/min per 100 g at Baseline and After Cocaine Administration

	Baseline	5 min	148 ± 23 min
Group I	90 ± 24	97 ± 19 p = NS*	—
Group II	70 ± 32	79 ± 24 p = NS*	69 ± 21 p = NS*

*Versus baseline. Data presented are mean value ± SD.

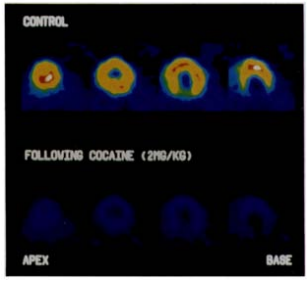
measured before and after cocaine exposure are shown in Table 2. Intravenous injection of cocaine did not significantly affect heart rate, blood pressure, rate-pressure product or blood flow in these anesthetized animals.

Carbon-11 hydroxyephedrine cardiac retention. In each dog, the input function was corrected for the presence of carbon-11 metabolites. Nonmetabolized C-11 hydroxyephedrine represented 97 ± 1%, 95 ± 2%, 92 ± 3%, 89 ± 3% and 85 ± 5% of the blood radioactivity at 1, 5, 10, 20 and 40 min after tracer injection, respectively.

The C-11 hydroxyephedrine images obtained before and after cocaine exposure in one group I dog is shown in Figure 2. Homogeneous myocardial retention of the tracer reflects the normal distribution of the sympathetic nerve terminals throughout the left ventricle. Measurements at 5 min after cocaine administration demonstrated significant reduction in tracer retention in the heart. Changes were homogeneous among the four myocardial regions of interest. The results of regional myocardial C-11 hydroxyephedrine retention in groups I and II are shown in Table 3. In group I, a reduction in C-11 hydroxyephedrine retention by 78 ± 3% was observed 5 min after cocaine administration. In group II, the average value of C-11 hydroxyephedrine retention remained significantly reduced by 28 ± 17% compared with the baseline value.

Effects of cocaine on a C-11 hydroxyephedrine-preloaded heart. Figure 3 shows the time-activity curve for C-11 hydroxyephedrine obtained from a region of interest placed over the left ventricle in a dog before cocaine injection. After initial uptake, carbon-11 activity decreased and then remained essentially constant for the remaining time of data acquisition. Figure 4 shows an example of a tissue time-activity curve of carbon-11 activity after cocaine administration in a C-11 hydroxyephedrine-preloaded heart. After intravenous cocaine injection, carbon-11 tissue radioactivity cleared biexponentially in all three dogs, with an average half-life of 6 ± 3 and 145 ± 41 min for the rapid and slow components of the curve, respectively.

Figure 2. Carbon-11 hydroxyephedrine images of the heart obtained from a group I dog. The images represent a 5-min data collection performed 25 min after C-11 hydroxyephedrine injection and are normalized to maximal activity (**red** in the color scale). The images obtained before and after cocaine administration are displayed in the **upper and lower rows**, respectively. The apex of the heart is on the **left**, and the base is on the **right**.



Discussion

Cocaine is one of the most widely abused drugs in the United States (24). The large popularity of the drug is related to its potent euphorigenic effects. Compared with other drugs, the psychologic sensations have a short duration. These effects peak ~10 min after intravenous injection of cocaine hydrochloride or smoking of cocaine free base and are resolved 30 min after initiation of drug exposure (25,26). Sympathomimetic response as reflected by heart rate and blood pressure variations parallels the subjective sensations (26,27). After intranasal administration of cocaine, subjective and hemodynamic changes peak at 15 to 20 min and disappear within 60 to 90 min (27). The recurrence of arrhythmias, myocardial infarction or ischemia during repetitive use of cocaine has confirmed the cardiac toxicity of the drug (1,2,5,28–30). The imbalance between cardiac oxygen demand (increase in heart rate and blood pressure) and delivery (constriction of coronary vessels) in relation to the stimulation of the sympathetic nervous system is thought to explain the ischemic events (31,32). However, the latency between the absorption of cocaine and the onset of symptoms has been very variable (3,5,29,33,34). It has not been infrequent that acute myocardial infarction or ischemia occurred several hours after peak cardiovascular effects or blood and cardiac concentrations of cocaine had been reached.

The delayed toxic effects are consistent with the scintigraphic observations in this study, which demonstrated for the first time the prolonged effect of cocaine on sympathetic nerve terminals.

The dose of cocaine associated with cardiovascular accidents varies from study to study. According to available data, the amount of cocaine may vary from 0.15 to 2 g, with the largest doses usually taken by regular, long-term users. On the basis published toxicologic data, the dosage of 2 mg/kg of cocaine, as used in this study, may reflect an amount of drug frequently absorbed during recreational use. Daily consumption from 0.5 up to 4 g of cocaine has been

Table 3. Regional Carbon-11 Hydroxyephedrine Cardiac Retention Before and After Cocaine Administration

	Anterior		Inferior		Lateral		Septal	
Dog No.	Before	After	Before	After	Before	After	Before	After
Group I								
1	0.242	0.037	0.280	0.037	0.274	0.039	0.260	0.032
2	0.252	0.075	0.265	0.071	0.248	0.072	0.245	0.066
3	0.231	0.061	0.216	0.054	0.205	0.052	0.216	0.052
4	0.270	0.056	0.396	0.075	0.369	0.076	0.313	0.063
5	0.209	0.050	0.213	0.048	0.207	0.055	0.242	0.048
Mean	0.241	0.056	0.274	0.057	0.260	0.059	0.250	0.052
±SD	±0.023	±0.014	±0.074	±0.016	±0.068	±0.015	±0.040	±0.040
p value	0.0001		0.0019		0.0019		0.0004	
Group II								
6	0.207	0.132	0.207	0.160	0.230	0.146	0.217	0.157
7	0.242	0.137	0.271	0.171	0.263	0.163	0.237	0.129
8	0.268	0.255	—	—	0.264	0.239	0.283	0.244
9	0.276	0.235	0.266	0.222	0.278	0.271	0.245	0.224
10	0.257	0.151	0.303	0.144	0.264	0.142	0.315	0.167
Mean	0.250	0.182	0.268	0.175	0.257	0.190	0.259	0.189
±SD	±0.027	±0.058	±0.030	±0.034	±0.024	±0.056	±0.039	±0.048
p value	0.020		0.033		0.041		0.032	

Retention is expressed in min^{-1}.

reported in long-term abusers (35). Previous reports have shown that smaller doses of intravenous cocaine were required to produce a similar pharmacologic response to doses of snorted or smoked cocaine. It has been reported that the pharmacologic response of an intravenous dose of 16 mg of cocaine corresponded to an intranasal dose of 96 mg (27), and 50 mg of cocaine smoked as free base to 20 mg intravenous cocaine hydrochloride (26).

Effects of cocaine on hemodynamic variables and myocardial blood flow. The intravenous injection of cocaine did not significantly change heart rate, blood pressure or myocardial blood flow in this study. These results are in agreement with previous investigations that have reported hemodynamic responses to cocaine varying with the animal model. Wilkerson (36) demonstrated that hemodynamic changes were dependent on a fully functional peripheral and central nervous system. In that study, long-term administration of cocaine resulted in a significantly smaller increase in heart rate and blood pressure in pentobarbital-anesthetized animals than in conscious dogs. Fraker et al. (37) did not observe any increase in rate-pressure product after intravenous injection of 4 mg/kg of cocaine in pentobarbital-sedated dogs. In pentobarbital-anesthetized animals, Hayes et al. (38) observed a significant reduction in microsphere-determined blood flow after intravenous cocaine administration. Conversely, coronary blood flow increased after cocaine administration in a group of conscious dogs studied by Fraker et al. (37). Thus, the hemodynamic responses to

Figure 3. Typical C-11 hydroxyephedrine decay-corrected cardiac time-activity curve obtained before cocaine injection in one group I dog.

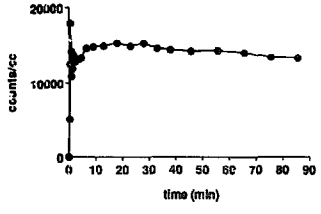
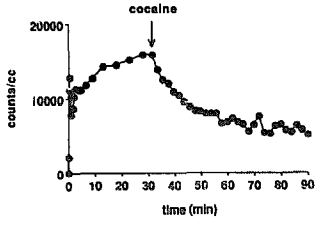


Figure 4. Effect of intravenous injection of 2 mg/kg of cocaine on C-11 hydroxyephedrine–preloaded heart. After intravenous injection, C-11 hydroxyephedrine rapidly accumulates in the heart. Intravenous injection of cocaine at 30 min after injection of C-11 hydroxyephedrine induces a biexponential clearance of carbon-11 activity from the heart.



cocaine are different in anesthetized and awake animals. This implies that cocaine may have distinct effects on the heart in anesthetized and awake states. However, the positron emission tomographic protocol, which requires rigorous immobility of animals within the gantry of the scanner, prevents studies of conscious or lightly sedated dogs.

Effects of cocaine on cardiac norepinephrine reuptake. This study demonstrates that 2 mg/kg of cocaine severely inhibits norepinephrine reuptake by the cardiac sympathetic nerve terminals. The reduction of C-11 hydroxyephedrine retention by 78 ± 3% suggests nearly complete blockade of norepinephrine reuptake. Inhibition of uptake-1 by the intraperitoneal injection of 10 mg/kg of desipramine produced a 92% reduction of myocardial C-11 hydroxyephedrine retention in the rat model. Furthermore, chemical sympathectomy by hydroxydopamine resulted in a similar reduction of C-11 hydroxyephedrine and tritiated norepinephrine concentration in the left ventricle of rats (39,40).

For the first time, this study describes the time course of cocaine effects on the sympathetic nerve terminals of the heart. The results show sustained reduction of C-11 hydroxyephedrine retention at 2.5 h after injection of cocaine, suggesting prolonged effects of the drug on the sympathetic nerve terminals. Previous human studies have shown that cocaine-related subjective sensations of tachycardia and hypertension last ~30 min after injection of the drug (25,26). Using carbon-11 cocaine and positron emission tomography, Volkow et al. (41) have also shown that the accumulation of cocaine is transient in the human heart, as reflected by the clearance of 50% of carbon-11 activity from the cardiac tissue at 10 min after radiotracer injection. The combined use of C-11 hydroxyephedrine and positron emission tomography in humans may be helpful to correlate these results about the general and cardiac effects of cocaine with the duration of the inhibitory effect of the drug on the cardiac sympathetic nerve terminals.

DeGrado et al. (22) have previously shown that increasing norepinephrine concentration in the perfusate of the isolated heart model decreased cardiac retention of C-11 hydroxyephedrine. Plasma norepinephrine levels were not evaluated in the present study. However, it is unlikely that increased norepinephrine plasma concentration influenced C-11 hydroxyephedrine cardiac uptake measured at 2.5 h after drug exposure. Hayes et al. (38) have shown a transient increase in plasma norepinephrine concentration after cocaine injection and a rapid return to baseline levels using a similar anesthetized dog model.

Mechanism of C-11 hydroxyephedrine neuronal localization. The intravenous injection of cocaine produced a biexponential clearance of carbon-11 activity from the C-11 hydroxyephedrine-preloaded heart. This experiment demonstrates a direct relation between cardiac C-11 hydroxyephedrine retention and functional uptake-1 mechanism.

The neuronal vesicles concentrate and store the neurotransmitter norepinephrine. This storage mechanism protects the neurotransmitter from metabolic degradation by the mitochondrial monoamine oxidase. In contrast, C-11 hydroxyephedrine is not a substrate for monoamine oxidase by virtue of its alpha-methyl group, and, thus, it is not metabolized in the cytosol. Under normal conditions, passive diffusion of C-11 hydroxyephedrine from vesicles and cytosol into the synaptic cleft might occur. The efficient uptake-1 mechanism recaptures the tracer before it diffuses into the interstitial space. Our results suggest the presence of such a mechanism in the canine myocardium and confirm the results of rat studies performed in our laboratory. Using isolated working rat hearts loaded with C-11 hydroxyephedrine, DeGrado et al. (22) have shown that the tracer clears rapidly after inhibition of uptake-1 by desipramine (22). In the C-11 hydroxyephedrine-preloaded hearts desipramine accelerated clearance of the tracer (~3 min half-life), indicating that neuronal reuptake of C-11 hydroxyephedrine represents the primary mechanism by which the tracer is retained in the tissue.

The two phases of tracer tissue clearance observed in this study correspond to radiotracer exchanges from different cellular compartments. On inhibition of uptake-1 by cocaine, the rapid phase of carbon-11 radioactivity clearance from the heart is likely to represent the extracellular leakage of cytosolic C-11 hydroxyephedrine. The second slow phase of the biexponential curve may reflect exchange of stored C-11 hydroxyephedrine between the cytosol and other cellular compartments. Consequently, C-11 hydroxyephedrine primarily traces norepinephrine transmembranous uptake by sympathetic neurons. The identification of norepinephrine vesicular storage will require the use of radiotracers either binding to the storage vesicles, like tetrabenazine, or displaying high affinity for the vesicular uptake (42).

Conclusions. Positron emission tomography in combination with C-11 hydroxyephedrine provides a noninvasive and sensitive means to objectively define the cardiac pharmacokinetics of drugs such as cocaine. Prolonged inhibition of the presynaptic sympathetic nerve terminals of the heart has been identified after a single intravenous injection of cocaine.

This noninvasive technique is a promising tool for evaluation of effects of other drugs on the catecholamine uptake by cardiac sympathetic nerve terminals. Future clinical protocols with C-11 hydroxyephedrine may allow better understanding of the pharmacokinetics of cocaine in the human heart.

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