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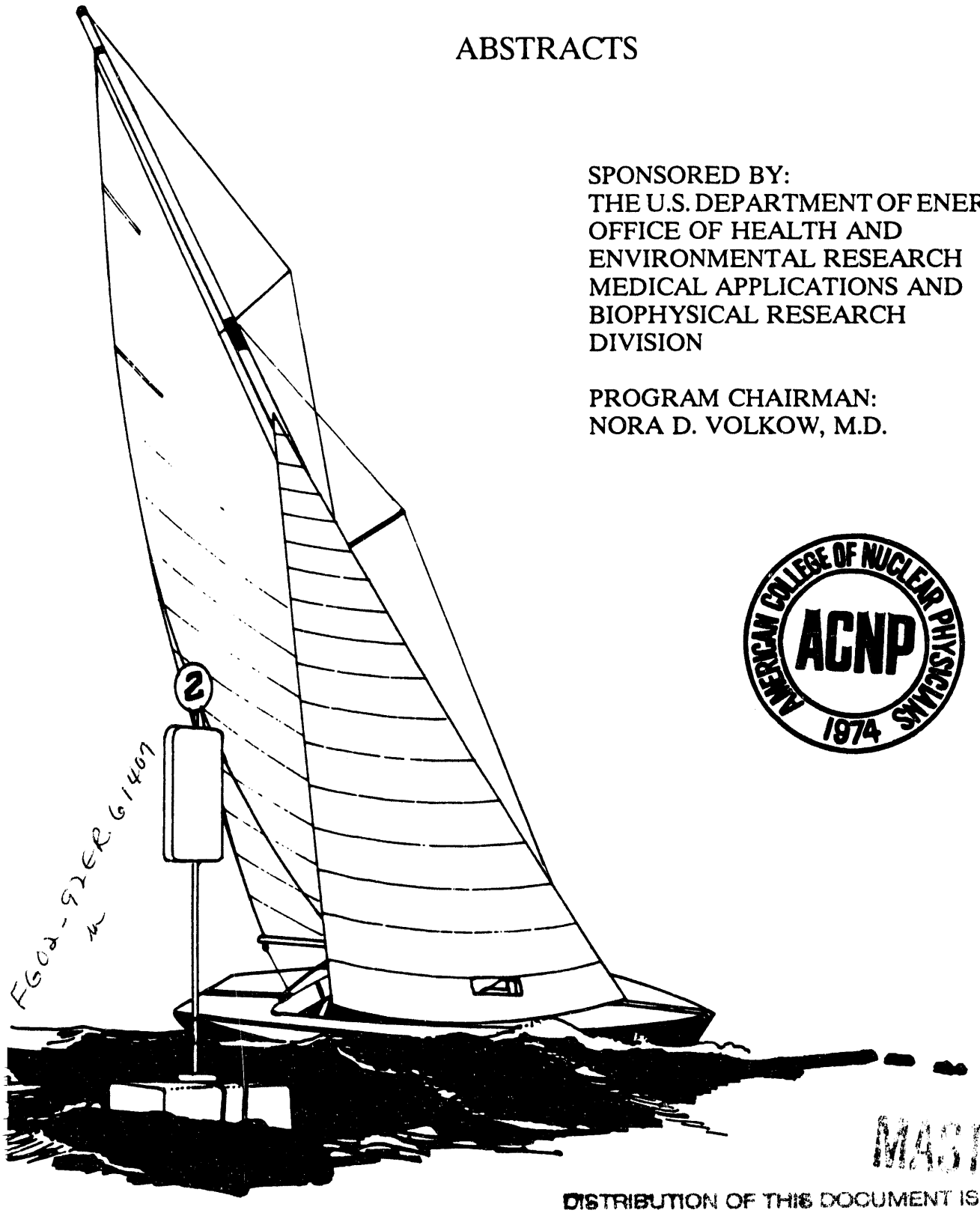
THE AMERICAN COLLEGE OF NUCLEAR PHYSICIANS

18TH ANNUAL MEETING AND SCIENTIFIC SESSIONS

DOE DAY: SUBSTANCE ABUSE AND NUCLEAR MEDICINE

ABSTRACTS



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ABSTRACTS FROM THE

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SUBSTANCE ABUSE AND NUCLEAR MEDICINE

PROGRAM CHAIRMAN: NORA D. VOLKOW, M.D.

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THE AMERICAN COLLEGE OF NUCLEAR PHYSICIANS

18TH ANNUAL MEETING AND SCIENTIFIC SESSIONS

DOE DAY

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Overview of the Problem of Substance Abuse

Nora D. Volkow, M.D.

Drugs of abuse have been consumed for centuries across different types of cultures. The ability of drugs of abuse to change the mental state of the individual via their effects on brain neurotransmitters has also the potential of inducing drug addiction. The consequences of drug addiction are devastating not only to the individual who becomes a slave of the drug, but also to the society who has to incorporate an individual whose behavior is mainly motivated by drug self administration. The magnitude of the problem of abuse is reflected on the large number of individuals which are affected directly or indirectly by drugs of abuse. For example, in the United States it is estimated that at least one out of 7 people abuses or is dependent on alcohol and that an additional 1 out of 20 individuals abuses or is dependent on other drugs (1). The consequences of substance abuse are reflected in the economic costs, and in the morbidity and the mortality associated with their use. The economic cost of substance abuse to the U.S. were estimated to be 177.4 billion dollars as of 1983 (2) and unfortunately those numbers have not be abated. The medical

consequences are various and range from liver dysfunction and dementia in alcoholics, to cardiac arrthymias and infarction in cocaine users to higher incidence of lung cancer in cigarette smokers. The mortality from substance abuse is not only accounted for by the medical complications, but also by the cognitive changes associated with the state of drug intoxication which lead to a much higher incidence of suicides, homicides and accidents (3). Despite the enormous personal and social cost of substance abuse, there is very little knowledge with respect to the mechanisms by which these drugs produce addiction as well as to the mechanisms of toxicity. Similarly, there is a lack of effective therapeutic intervention to treat the drug abusers. In this respect, nuclear medicine could contribute significantly by helping to gather information using brain imaging techniques about mechanisms of drug addiction which, in turn, could help design better therapeutic interventions, and by helping in the evaluation and diagnosis of organ toxicity from the use of drugs of abuse.

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PET STUDIES OF COCAINE DISTRIBUTION IN THE HUMAN BODY

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Cocaine's behavioral and toxic properties have been studied from many perspectives. One important parameter relative to the action of cocaine is the extent to which its distribution and kinetics in the body parallels its behavioral and toxic effects. We have used PET and cocaine labeled with carbon-11 (Fowler et al, 1989) to examine (1) the distribution and kinetics of cocaine in different organs of the human body; (2) the effect of alcohol intoxication on the uptake and residence time of cocaine in the brain and the heart and to examine the distribution of cocaethylene, a metabolite of cocaine which is found in the blood and tissues of individuals using these two drugs in combination (Hearn et al, 1991).

[^{11}C]Cocaine Distribution and Kinetics: The uptake and kinetics of cocaine have been measured in the human brain, heart, lungs, liver, kidneys and adrenals (Fowler et al, 1989 and Volkow et al, 1992). Cocaine's uptake into the normal human brain is rapid (peak uptake, 4-10 minutes) with a clearance to half of peak value by 25 minutes. The highest regional uptake is in the corpus striatum which also shows the longest retention of radioactivity. The total percent of the injected dose in the whole brain at peak is approximately 10 %. The time course of uptake and clearance closely parallels the degree of euphoria reported after cocaine is administered intravenously in pharmacologically significant doses (Cook et al, 1985).

The rate of uptake of cocaine varied among other organs with peak uptakes occurring in lungs, in heart, in kidneys, in adrenals and in liver at 45 sec, 2-3 minutes, 2-3 minutes, 7-9 minutes and 10-15 minutes respectively. Clearance rates also varied with the time for clearance to half of peak value being 1.5 minutes for lungs, 10 minutes for the heart and 22 minutes for the adrenals. The liver activity plateaued at 10-15 minutes after injection and remained constant thereafter. The significant accumulation of cocaine in the human heart, kidneys, adrenals and liver could contribute to its toxicity especially when the drug is administered repeatedly.

Cocaine and Alcohol: The concurrent use of cocaine and alcohol is a frequent pattern of combined drug use and recent epidemiological evidence suggests that this combination may be synergistically toxic (Hearn et al, 1991). We have used PET and [^{11}C]cocaine to assess if the

distribution and and clearance of cocaine are affected by the presence of alcohol resulting in altered tissue exposure to the drug. Each subject received two PET studies with [^{11}C]cocaine, one before and one after alcohol intoxication (1g/kg). Alcohol intoxication did not change the steady state distribution volume for brain (striatum, thalamus and cerebellum) or for heart suggesting that the enhanced toxicity associated with the combined use of cocaine and alcohol is not due to an alteration in cocaine distribution and may be related the direct actions of each of these drugs.

In a second part of this study, PET was used to compare the regional distribution and kinetics of cocaine with cocaethylene (the ethyl homologue of cocaine), a metabolite of cocaine found in individuals using cocaine and alcohol in combination (Hearn et al, 1991). [^{11}C]Cocaine and [^{11}C]cocaethylene were compared in baboon brain in a serial study protocol where each drug was compared in the same animal. The uptake and distribution of the two tracers was very similar. However, cocaethylene had a significantly slower clearance from all brain regions relative to cocaine. This could contribute to a greater tissue exposure for cocaethylene than for cocaine and to a greater risk when these two drugs are repeatedly used in combination.

Summary: The substitution of stable carbon (^{12}C) in organic molecules with the short lived positron emitter carbon-11 (^{11}C) offers the potential of measuring the spatial and the temporal distribution of drugs and their metabolites in the living body. We have described the use of [^{11}C]cocaine and PET to measure the distribution of of cocaine in the human body and the effect of alcohol intoxication on the distribution. The significant concentration of cocaine in the brain, heart, kidneys and the adrenals could contribute to toxicity to these organs and indirect effects on other organ systems. These effects may be exacerbated repeated administration of the drug. This strategy has also been used to show that the distirbution and kinetics of cocaine is not altered during alcohol intoxication and that cocaethylene, a metabolite of cocaine has a longer residence time in brain relative to cocaine itself. Although we are presenting a specific example of the use of PET to study cocaine in the human body, the same general strategy can be applied to the study of other drugs of abuse and the pathology that results from their use.
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SPECT STUDIES OF THE EFFECTS OF DRUGS OF ABUSE ON NEUROTRANSMITTER FUNCTION

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I. SPECT Measurement of Stimulant-induced Dopamine Release

We used the reversibly binding D2 dopamine receptor radioligand [123I]IBZM (iodobenzamide) to test whether the endogenous neurotransmitter dopamine competes in vivo for radiotracer binding measured with single photon emission computed tomography (SPECT). In a series of non-human primate experiments (n=27), the effects of temperature, amphetamine, haloperidol, and reserpine on brain uptake of [123I]IBZM were measured. Specific brain uptake of [123I]IBZM reached a peak by 100 min post injection of radioligand and demonstrated a gradual, apparent "steady-state" washout over the next 2 hr. Brain uptake was temperature dependent, with rates of washout of specifically-bound radioligand greater under normothermic conditions (26%/hr: core body temperature 35-37 C) than under conditions of controlled hypothermia (11%/hr; 32-34 C). Given the greater retention of radioactivity, low temperature conditions were used in all other experiments. Administration of haloperidol (0.02 mg/kg iv) during the period of apparent steady state resulted in a dramatic increase in washout (60%/hr; $p<0.0001$), consistent with its potent D2 receptor antagonist properties. d-Amphetamine (1.0 mg/kg iv), which has negligible affinity for the D2 receptor, but

mediates the release of endogenous stores of dopamine, also enhanced washout (34%/hr; $p<0.0005$). Reserpine pretreatment at doses (1.0 mg/kg) sufficient to cause greater than 90% depletion of striatal dopamine levels blocked this amphetamine-enhanced washout (10%/hr; $p<0.05$). Reserpine did not block the increased washout induced by the direct acting D2 receptor antagonist haloperidol. These results are consistent with the hypothesis that endogenous dopamine may effectively compete for radioligand binding in vivo in neuroreceptor imaging studies using PET and SPECT.

II. SPECT Studies of Benzodiazepine Receptor Pharmacology.

[123I]-labeled iomazenil is a high affinity, reversibly binding radiotracer for the benzodiazepine (BZ) receptor. Brain uptake of this radioligand was relatively stable and showed high ratios of specific to non-specific uptake, with greater than 90% displaced by iv administration of BZ receptor agents. Repeated injections of increasing doses of each of five BZ drugs (iomazenil, flumazenil, clonazepam, alprazolam, and diazepam) yielded stepwise displacement curves, which were analyzed to measure the in vivo potencies of these agents. The relatively long half-life of [123I] and the stable biological uptake of the radiotracer allowed such potency estimations in just one experiment following a single injection of radioligand. The in vivo potencies of these five agents were highly correlated with their affinities for the BZ receptor determined with in vitro homogenate binding. A single crystal

probe provided potency measurements virtually identical to simultaneously performed SPECT imaging studies. In conclusion, stepwise displacement by agents administered following the injection of the radioligand [123I]iomazenil provided a reliable means of measuring the in vivo potencies of BZ receptor agents. This in vivo determination may better predict the clinical potency of BZ drugs than in vitro homogenate estimations, because the in vivo measure provides the summed effects of receptor affinity, plasma protein binding, penetration of the blood brain barrier, and metabolism of the displacing agent.

Effects of acute exposure to drugs of abuse on regional brain metabolism

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ABSTRACT

The epidemic of substance abuse in the United States has fostered scientific investigations on the substrates in brain for the psychoactive, and particularly the euphorigenic, effects of abused drugs. The reason for this focus is the observation that all drugs of abuse produce a positive affective state, termed "euphoria". Acute effects of abused drugs on brain function have been assessed using positron emission tomography (PET) to measure regional rates of blood flow and glucose metabolism in the human brain. In general, acute administrations of drugs of abuse reduce cerebral glucose utilization. This statement is based on studies that have been performed using opioids, stimulants, benzodiazepines, and ethanol. In contrast, delta-9-tetrahydrocannabinol does not generally reduce cerebral glucose utilization, but stimulates glucose metabolism in the cerebellum.

In studies with morphine and cocaine, reduced glucose utilization accompanies self-reports of euphoria. Furthermore, the magnitude of the effect of either drug on measures of positive mood is related negatively to glucose metabolism in the temporal cortex. Therefore, function in this brain region appears to be an important determinant of subjective responses to abused drugs that differ widely in their spectrum of action, but share the property of producing euphoria.

The effects of abused drugs on cerebral metabolism may reflect a common neurochemical action of these drugs. In this regard, studies in animals have suggested that drugs of abuse share the property of enhancing dopaminergic neurotransmission in the mesolimbic reward system. Thus, drugs of abuse, which produce reward/reinforcement, may produce a generalized reduction of cerebral metabolism as a consequence of dopaminergic activation.

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PET Studies on the Effects of Chronic Drug Abuse on Brain Metabolism and Neurotransmission

Nora D. Volkow, M.D., Joanna S. Fowler, Ph.D., and Alfred P. Wolf, Ph.D.

The consequences of chronic use of drugs of abuse can now be investigated using positron emission tomography (PET) and appropriate radiotracers. Investigation of the changes in brain metabolism, cerebral blood flow, and neurotransmitter function brought about by chronic substance abuse is of relevance in understanding toxic properties of drugs of abuse as well as mechanisms of addiction. We have applied PET to investigate brain functional and neurochemical changes in cocaine addicts, chronic marijuana users, and alcoholics.

Cocaine:

We have investigated the effects of chronic use of cocaine on cerebral blood flow, regional brain glucose metabolism, dopamine receptors, and presynaptic dopamine terminals. Studies done with $H_2{}^{15}O$ to measure cerebral blood flow in cocaine abusers revealed profound changes in brain perfusion in these patients (1). Cerebral blood flow defects were found scattered

throughout the brain, predominantly in cortical areas, and affecting more the left hemisphere and frontal cortex of these patients. Changes in cerebral blood flow persisted after 10 days of cocaine detoxification, suggesting that they were independent of cocaine withdrawal and probably reflected the direct effects of cocaine on cerebral blood vessels. These changes probably represent both the vasoconstricting effects of cocaine as well as small strokes and hemorrhages brought about by its vasoactive properties.

Investigation of the effects of chronic use of cocaine in regional brain glucose metabolism showed that cocaine abusers tested after the initial period of cocaine withdrawal (10 days) have evidence of decreased glucose metabolism in the frontal cortex involving the medial area, dorsolateral, and orbito-frontal gyrus (2). The left frontal cortex was more affected than the right. The extent of decrease in brain metabolism was correlated with the dose of cocaine utilized, suggesting that these changes were related to their past history of cocaine use. The rate of decrease of left frontal metabolism was also associated with the intensity of depressive symptoms in these patients. Seven of the 21 patients investigated, were retested three months later after they had been detoxified in an

inpatient unit. These patients continued to show decreased metabolic activity in the frontal cortex. Persistence of frontal changes with protracted cocaine withdrawal suggests that these effects are long-lasting and their association with depressive symptoms implicates them in the clinical phenomenology seen in the cocaine abuser.

Studies on postsynaptic dopamine receptors in cocaine abusers using 18-F-N-methylspiroperidol binding showed that cocaine abusers have marked decreases in dopamine receptors which are more accentuated when tested within one week of last use of cocaine (3). When subjects are tested for longer periods after withdrawal (10 days to 3 months), their values are higher than during the first week, but are still significantly lower than those seen in the normal subjects (unpublished data). The rate of decrease in dopamine receptors is significantly correlated to the rate of changes in frontal brain metabolism, (unpublished data) suggesting that changes in dopamine receptor availability translate into metabolic changes in those areas that are neuroanatomically connected with the dopamine system.

Investigation of changes in presynaptic terminals of cocaine abusers using carbon-11 cocaine also showed reductions in carbon-11 cocaine binding in cocaine abusers located in basal

ganglia and thalamus. These changes could represent either downregulation of cocaine binding sites (monoamine transporters) and/or degeneration of presynaptic terminals (unpublished data).

Alcoholics

Studies done on healthy, neurologically intact alcoholics have shown that these patients have global decreases in whole brain metabolism that are more accentuated in the frontal and parietal cortices (4). In contrast, subcortical structures appeared to be relatively spared. The extent of decrease in brain metabolic activity was correlated to the period of alcohol withdrawal, suggesting that, in part, it represents the adaptation of the brain to chronic alcohol administration and discontinuation. In contrast, the changes in frontal and parietal metabolism were independent of the days of alcohol withdrawal, suggesting that there were consequences of alcohol on brain metabolism. Studies designed to investigate differences between normals and alcoholics in response to the effects of a benzodiazepine agonist (lorazepam) on regional brain glucose metabolism have also been done. These studies have demonstrated decreased responsiveness of the brain of alcoholics to challenge with a benzodiazepine drug (5). These changes were regional and involved the thalamus, the orbito-frontal cortex, and the basal

ganglia. The latter brain regions form part of a circuit which has been implicated in the emergence of repetitive behaviors. Inability of the alcoholics to inhibit these regions as when challenged with a drug that enhances inhibitory neurotransmission such as lorazepam or alcohol could explain their compulsive use of alcohol. Decreased responsiveness to benzodiazepine was independent of the period of alcohol withdrawal, suggesting that it represents a phenomenon that is either associated with alcohol use or which antedated the use of alcohol and may relate to alcohol predisposition.

Marijuana:

We have studied regional brain glucose metabolism in chronic marijuana users under baseline conditions and upon challenge with THC (the main psychoactive component of marijuana) (6). When compared with normal controls, marijuana abusers showed significantly lower brain metabolic activity in the cerebellum. The cerebellum was also the region that was most sensitive to the effects of acute marijuana administration both in normals and in the marijuana abusers. This is of interest in that the cerebellum has a very high density of cannabinoid

receptors, suggesting that the effects of marijuana on brain metabolism are mediated by its interaction with these receptors and that chronic use of marijuana could lead to cerebral dysfunction in those brain regions with high concentrations of cannabinoid receptors. In addition, marijuana abusers differ from normal controls with respect to their response to acute marijuana administration. Marijuana users showed less cerebellar activation upon marijuana intoxication than the normal controls and showed, in addition, activation of the prefrontal cortex. The sensitivity of the cerebellum to marijuana for acute and chronic conditions could explain the marked disturbances in motor coordination observed during marijuana intoxication as well as the impaired function in tasks that require motor coordination reported in the marijuana users.

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SPECT Studies of the Deleterious Effects of Drugs on the Brain

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NUCLEAR MEDICINE IN THE EVALUATION OF CARDIAC TOXICITY SECONDARY TO DRUG ABUSE

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With increasing use of recreational drugs in our society, the cardiovascular complications of drug abuse has been widely recognized. Various forms of cocaine abuse are associated with cardiac arrhythmias, myocardial infarction, sudden cardiac death and cardiomyopathy. The pathophysiologic mechanism of cardiac toxicity is primarily related to the increase of circulating and tissue catecholamine levels. Cocaine inhibits the reuptake of amines into sympathetic nerve terminals. Nuclear medicine procedures such as radionuclide ventriculography, can be used to assess sequalae of cardiac toxicity of drugs, such as myocardial infarction or cardiomyopathy. In addition, blood flow studies can be employed to differentiate true coronary artery disease from cocaine induced vascular spasm. With the advent of positron emission tomography, the physiology and pathophysiology of abused drugs such as cocaine can be studied in detail. Work of the group at Brookhaven National Laboratories has focused on the definition of pharmacokinetics of radiolabeled cocaine. This compound is taken up by the myocardium, suggesting specific binding of cocaine to the sympathetic nervous system of the heart. The pharmacological affect of this drug correlated with the kinetics of the tracer in the CNS and

plasma. Recent studies in our laboratory concentrate on the characterization of sympathetic nerve terminals using radiolabeled norepinephrine analogs such as C-11 hydroxyephedrine. This compound specifically delineates sympathetic nerve terminals by tracing uptake and storage of norepinephrine in the sympathetic nerve terminals. Validation studies in patients with recent cardiac transplantation indicated the high specificity of this tracer for the autonomic nervous system. Our recent animal studies employed C-11 hydroxyephedrine to study the effect of intravenous cocaine application on the myocardial uptake of catecholamines. The animals were studied at baseline and following exposure to the drug. Blood flow was measured with microspheres at the same time. Initial results reveal that in the absence of significant changes in myocardial blood flow, there was a marked decrease in C-11 hydroxyephedrine retention in the myocardium following cocaine exposure. These results confirm the known pharmacological effect of cocaine and indicate the potential of this approach to quantitatively characterize the drug effect in vivo. Current research focuses on the assessment of chronic effects of cocaine exposure in animal and human heart. PET in combination with tracers of the autonomic nervous system allow for the sophisticated assessment of the acute and chronic effect of drug abuse, which may give us insights into the better understanding of cardiovascular complications.

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