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Myocardial Uptake of Cocaine and Effects of Cocaine on Myocardial Substrate Utilization and Perfusion in Hypertensive Rats

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Abstract

Cocaine abuse is a problem causing world-wide concern and the number of deaths following cocaine use is increasing. Cardiovascular complications following cocaine include severe tachyarrythmias, pulmonary edema, myocardial infarction, and acute renal failure, which are major problems confronting emergency facilities. While the studies of cocaine effects on the brain have been given the most attention, it is clear that the effects of cocaine on the cardiovascular system are of great importance, given the increasing number of reports on sudden death and myocardial infarctions in young adults related to cocaine use. The precise mechanisms of cardiotoxic actions of cocaine are unclear. In this project, we investigated the whole-body distribution of C-14-labeled cocaine to determine the cocaine-binding sites, including blocking experiments to determine the nature of regional binding sites, and differential response of the normal vs. diseased heart (hypertensive cardiomyopathy) in an animal model to mimic a potentially "high risk" population. We investigated the acute effects of cocaine on myocardial metabolism using two myocardial energy substrate analogs (fatty acid and glucose) with comparison with regional perfusion.

Introduction

The energy requirements of the normal heart in the basal oxygenation state are met by utilizing free fatty acids (65%) with smaller contributions by lactate and glucose (1). The substrates used to provide energy during persistently increased myocardial work, such as occurs in sustained hypertension or aortic stenosis, however, are less well defined. When the left ventricle is called upon to perform increased pressure work, the myocardium may not respond uniformly (2). In this situation, the effects of increased work may vary on the left ventricular endocardium, epicardium, free wall, and septum. In hypertrophic heart diseases (cardiomyopathy, hypertensive heart disease) catecholamines may also decrease the LV tolerance to ischemia. In order to adequately respond to the increased metabolic demands of the myocardium, the coronary vascular bed in the hypertrophied heart is dilated, even in the basal state. This results in a low coronary reserve (3), especially in the endocardial layers of the left ventricular wall (4,5). The balance of oxygen supply and demand cannot be maintained, especially in the endocardial layers, thus further increasing the vulnerability of the myocardial tissue to ischemic damage (5). A decrease in high energy phosphate compounds was found in severely hypertrophied hearts especially in the endocardial layer (6-8) and was postulated to be the possible

cause for the diminished tolerance of the severely hypertrophic heart to global ischemia (7). We have, however, in the Dahl-strain hypertensive model, recently observed that in severe hypertension regional increase of ATP in the heart, occurs particularly in the endocardial and septal layers (9). It is possible that, in the hypertensive myocardium, there are continuous low-level anoxia-like changes that occur due to high oxygen demand. These ischemic episodes are believed to break down the high energy phosphocreatinine shuttle, resulting in mitochondrial accumulation of ATP (9). It is unknown, however, whether the decreased tolerance to ischemia and/or reperfusion is found only in the hearts of patients with long-standing hypertrophy of the heart or also occurs in less severe hypertrophy, such as in athletes who develop "a physiological hypertrophy", or in hereditary cardiomyopathies (10,11). In such conditions, the LV pump function is believed to be normal or even enhanced.

We investigated the possibility that persistent increase in pressure overload (viz. hypertension) may be associated with alterations in the myocardial utilization of metabolic substrates (viz. fatty acids and glucose) in an animal model of hypertension (rats) (12-14). Using quantitative dual-tracer autoradiography, we evaluated the regional distribution of glucose and free fatty

acid analogs and correlated the results with changes in regional perfusion. We have shown that severe hypertension causes global and regional changes in myocardial perfusion and substrate utilization (12-14). Perfusion and fatty acid utilization were homogeneous in normotensive rats, while in severe, chronic hypertension the perfusion was homogeneous whereas fatty acid utilization was focally decreased mainly in the endocardium and septum (Figs. 1 and 2).

We have also shown that autoradiographic microimaging can be used for the early detection of metabolic changes in the hearts of cardiomyopathic and hypertensive animals (15). Focal reduction in blood flow, glucose, and fatty acid uptake was shown to occur in the myocardium of animals with advanced stage cardiomyopathy (Figs. 3 and 4). However, in the early phase of cardiomyopathy, focal decrease in fatty acid uptake was the only positive indicator of disease even prior to the appearance of histological changes visible by light microscopy. Treatment with a Ca-channel blocker could prevent the development of cardiomyopathy, as shown by homogeneous fatty acid uptake (Fig. 4). These findings suggest that while perfusion tracers (Tl-201) have a role, a myocardial metabolic substrate (fatty acid) can be used to monitor early cardiac pathology.

In recent years, several reports were published on incidences of sudden deaths of athletes which were related to addictive substance abuse including cocaine. It may well be that the increased vulnerability of athletes to cocaine-cardiotoxicity and death may be due to their decreased tolerance for global ischemia and abnormalities in cystosolic ATP utilization.

Cocaine is widely recognized as one of the most dangerous abuse substances currently in use, particularly in the chemical form of "crack" (16-18). The reinforcing properties of cocaine are based on its fast effect (depending on the route of administration) and its relatively short biological half-life which lead to a pattern of compulsive, repetitive use. The use of cocaine by frequent repetitive intravenous injections by various age groups may be the reason for the increased risk of cardiovascular toxic effects of cocaine (19). Statistics indicate that most deaths related to cocaine intake appear to be caused by cardiac complications. Despite the increasing frequency of cardiovascular complications reported in recent years, very little is known concerning the cardiovascular hemodynamic effects of cocaine (20-21). Tachycardia, fatal arrhythmias, dangerous elevations in blood pressure, systemic and coronary vasospasm have been reported in cocaine abusers (22-29). Angina, myocardial infarction, left ventricular failure and ventricular arrhythmias

have been described in individuals with normal coronary arteries and in subjects with various degrees of pre-existing coronary artery diseases (22-26).

Although the detailed mechanisms of cocaine cardiotoxicity are unknown, there is evidence showing that the cardiotoxic effect involves sympathetic stimulation, adrenal stimulation, as well as direct action on myocardium resulting in severe vasoconstriction and sympathomimetic effects (24). The cardiotoxic effects of cocaine are similar to those of dextroamphetamine (increased heart rate and elevation of blood pressure) causing increased cardiac work and higher oxygen demand. Tyrosine-like effects involving sympathomimetic stimulation by blocking norepinephrine binding sites on adrenergic nerve endings have also been reported (23). The sudden increase in myocardial oxygen demand cannot be met by coronary dilatation because of severe epicardial and intramural vasospasm resulting in relative ischemia (27).

A clear temporal relationship between cocaine intake and myocardial ischemia or infarction has been recently documented (23, 26, 28-31). Cocaine may elicit coronary vasospasm that may in turn result in cardiac ischemic episodes even in patients with normal coronary arteries (26, 32). Even though isolated cases of cocaine-induced myocardial infarction (MI) were reported in patients with normal coronary arteries (26, 29), most patients

developing acute MI have pre-existing coronary disease, but some had substantial narrowing of coronaries (23, 33, 35). It appears that cocaine poses a higher risk in people with underlying fixed narrowings of coronary arteries, and results in higher morbidity and mortality rates. In these patients the sudden increase of myocardial oxygen demand after cocaine, caused by the increase in blood pressure and heart rate beyond the ability of the narrowed coronary circulation to provide adequate blood flow, causes ischemic episodes.

A similar situation occurs in hypertensive individuals. Although the hypertrophic myocardium of patients with hypertensive heart disease has a proportional increase in myocardial perfusion, the capillary density is decreased and the myocardial perfusion reserve is lower than normal, rendering LV more susceptible to ischemia (36).

The goals of these studies were as follows:

1. To determine the time-course whole body distribution of cocaine;
2. To elucidate the sites of cocaine binding;
3. To evaluate the effects of cocaine on myocardial metabolic substrate utilization and perfusion.

Materials and Methods

The time-course whole body distribution of [carboxy-^{14}C-benzoyl] cocaine (Research Triangle Park, NC) was studied in 36 naive, female Fischer rats (average weight 150-200 g). Radiolabeled cocaine 5-15 μCi (specific activity = 5.88 mCi/mMol) was administered i.v. in a tail vein and animals were killed with an ether overdose 2, 4, 6, 10, 15, and 30 min after injection. Whole body quantitative autoradiography was performed as described earlier (37-39).

The effects of desipramine (DES) (Sidmak, East Hanover, NJ) and GBR 12909 (Research Biochemicals, Inc., Natick MA) on the distribution of [carboxy-^{14}C-benzoyl]cocaine was studied. Despiramine, 10 mg/kg i.p. was given to rats 60 min before cocaine and rats were sacrificed at 2, 4, 6, 10, 15, and 30 min after cocaine injection. GBR 12909 4 mg/0.5 ml (20 mg/kg) i.p. or 2 mg/0.25ml (10 mg/kg) given to rats i.v. followed by ^{14}C-cocaine one minute after intravenous injection and one hour after intraperitoneal injection of GBR.

The acute effects of cocaine in a rat model of hypertension (Dahl strain salt-sensitive) mimicking the "high-risk" group were also studied. Cocaine (4 mg/kg i.v.) on myocardial perfusion (Tl-201, 5 min), glucose (C-14-2DG, 20 min) and fatty acid utilization

(I-131 BMIPP, 30 min) i.v. was studied. The RV, septum (SPT), and endocardium (ENDO), and epicardium (EPI) of the LV were analyzed.

Results

In rats, ^{14}C-cocaine injected i.v. showed very fast and intense binding in the brain, spinal cord, nuchal brown fat pad, and adrenals and heart (Fig. 5). In the brain, peak concentration occurred at 2-4 min with highest concentration in the cortex, followed by striatum and cerebellum. The uptake in the cortex was much more intense than in subcortical structures. The clearance of cocaine from the brain was very fast and was more rapid from the cerebellum than from the cortex and striatum. ^{14}C-cocaine activity in the brain reached soft tissue background levels 15-20 min after injection. In the heart, maximal concentration was seen in the left ventricle, reaching a peak at about 4 min after injection (Fig. 6A) and washing out at the same rate as from the brain. The adrenal medulla showed almost immediate uptake (2 min) followed by rapid washout. Uptake in the kidney parenchyma with gradual accumulation in the collecting system by 15 min was observed. In contrast, accumulation of cocaine in the liver was gradual, peaking at 15-30 min when the activity in the primary target organs, i.e., the heart, brain, spinal cord, and adrenals had mostly cleared out.

In the bowel and collecting system of the kidneys, ^{14}C activity accumulated later. The activity in the lungs was negligible, about one-fifth of the maximal activity in the brain.

Pre-treatment with desipramine (DES) did not significantly affect uptake of ^{14}C-cocaine in the brain, but caused decreased uptake in the heart and adrenals (Fig. 6). In the kidneys of rats pre-treated with DES prior to ^{14}C-cocaine, the uptake pattern became non-uniform. It appears that the mottled pattern was caused by decreased uptake in the renal pyramids.

GBR 12909 caused decreased ^{14}C-cocaine uptake in the brain (cortex and striatum) heart, and adrenals. Maximal decrease was seen in the striatum with minimal decrease in the cerebellum. The decreased uptake of ^{14}C-cocaine in the heart by the GBR pre-treatment was 34% and in the kidneys ~46-48%. The liver showed an increase in ^{14}C-cocaine which probably represents the increased excretion induced by the lesser binding by other organs.

Increased perfusion in the myocardium of hypertensive (21.9±4.0%) as compared to normotensive was noted. Higher 2DG (227±9.6%) and lower fatty acid (17.6±17.5%) uptake in HT rats was seen, indicative of a shift from aerobic to anaerobic substrate utilization. The global changes in saline (control) vs. cocaine-treated rats is shown in Table 1. Fig. 7 depicts the autoradiographic microimages of the heart showing the effects of cocaine in the normotensive and hypertensive heart. In cocaine-treated normotensive rats, a generalized decrease in perfusion and fatty acid uptake and increased glucose metabolism was seen. In

cocaine-treated hypertensive rats, increased global perfusion was more pronounced in SEP and EPI. Glucose uptake was also higher, but to a lesser degree than in the normotensive heart, especially in ENDO and EPI.

Table 1: Effects of Cocaine on Myocardial Perfusion and Substrate Uptake*

	Tl-201	2DG	BMIPP
Normotensive (NT)	-29.4±3.7%	+74.4±6.8%	-5.6±5.0%
Hypertension (HT)	+22.0±15.6%	-24.0±20.0%	+9.3±8.1%

*Data expressed as percent changes from saline-treated animals

Discussion

We have described three stages of [carboxy ^{14}C benzoyl] cocaine whole body distribution. Our data showed: 1) an initial localization in the brain, spinal cord, heart, adrenals, and kidneys occurring over the first 2-5 min post injection; 2) a second stage of gradual accumulation in the liver at 5-10 min post injection with washout from organs showing early localization; and 3) a third phase of excretion into the urine and bowel at 15-20 min post injection. This sequence of cocaine kinetics correlates with the description of cocaine users as well as with the timing of the pharmacologic effects of cocaine and its metabolism. We are probably presenting the first report of early whole body pharmacokinetics of intravenously administered cocaine. The observation of the transient nature of uptake in the brain and heart and the correlation with the well-known observations in cocaine users of transient euphoria, sympathetic stimulation and cardiovascular effects following i.v. cocaine administration suggests that the whole body distribution kinetic data may provide important information related to understanding the mechanisms underlying drug addiction and toxicity and possibly help in developing strategies for therapy.

<u>In vitro</u> studies have demonstrated that cocaine binds to norepinephrine (NE), dopamine (DA), and serotonin (SE)

transporters. This binding prevents reuptake of neurotransmitters and a rising level of neurotransmitters in the synaptic cleft. We have investigated the characterization of cocaine binding sites in vivo using specific neurotransmitter reuptake blockers: desipramine, to block the SE/NE and GBR to block the DA transporters. In the brain, binding of cocaine was not affected by desipramine, suggesting that it probably binds to a site DA associated transporter. In contrast, binding of cocaine in the heart and adrenals was decreased by both desipramine and GBR, suggesting binding of cocaine in these organs to the NE and DA transporter. In addition, desipramine also decreased cocaine binding to the kidneys (renal pyramids). Liver and gut uptake is probably non-specific, since it was not prevented by desipramine or GBR and probably represents metabolites of labeled cocaine. These findings of specific binding of cocaine to certain organs correlates with the multi-organ toxic effects described in cocaine abusers.

In addition to the above studies, we have also performed studies on the acute effect of i.v. administered cocaine on the heart in anesthetized dogs (40). Several observations were made during these experiments which included marked S-T depressions which started immediately after cocaine injection. The pulse rate did not increase significantly, possibly because of the effects of

general anesthesia. No other changes could be observed clinically. Regional ischemia, as evidenced by Tl-201 studies of various degrees, was also striking. Global left ventricular (LV) Tl-201 activity after cocaine injection was 30% less than in the baseline state.

These imaging experiments indicate that the deleterious effects of cocaine on the heart are probably due to spasm of the coronaries and decreased myocardial perfusion. Since the degree of spasm of the large subpericardial vessels after cocaine cannot explain the marked increased coronary resistance and decreased coronary flow described in the literature (28), it is suggested that microvascular spasm of the intramural vessels plays the major role in the temporary decrease in perfusion. The data also suggest that severe temporary myocardial ischemia is probably the initiating factor of most cardiac perturbations induced by cocaine.

Preliminary studies in normal dogs showed that I-123 BMIPP uptake was also decreased after acute cocaine, possibly due to coronary vasospasm (Som, Oster, Knapp, et al., unpublished data, 1993).

Uptake of cocaine by the human heart and adrenals has also been shown with PET and ^{11}C-cocaine (41). High cocaine

accumulation in the heart supports the relevance of direct toxic effect of cocaine on the myocardium.

In normotensive rats, cocaine caused a generalized decrease in myocardial perfusion and a concomitant increase in the glucose uptake and decrease in I-131 BMIPP uptake. In hypertensive rats, however, there was a generalized increase in global myocardial perfusion which was more pronounced in the septum and epicardium, which may be due to increased heart mass (hypertrophy). There was only a slight increase in I-131 BMIPP uptake. Glucose uptake was also increased, but to a lesser degree than in the normotensive heart, especially in the endocardium and epicardium. It may well be that the hypertensive cardiomyopathic heart is unable to respond to the increased cardiac work caused by cocaine by increasing metabolic processes. These data seem to indicate that hypertension may also increase the risk of cardiac complications related to cocaine. The cardiovascular effects of cocaine seem to last longer than indicated by the fast kinetics of cocaine in the heart, indicating that probably other factors may participate to the cardiovascular perturbations initiated by cocaine. Multiple mechanisms involving both central and peripheral components may play an important role. The intense rapid binding of ^{14}C-cocaine to the heart indicates probably that cocaine has a peripheral action. The high binding of ^{14}C-cocaine to the adrenal medulla

may explain the contribution of increased catecholamine release which probably further amplifies the cardiotoxicity of cocaine.

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Legends for Figures

Figure 1. Dual tracer autoradiography using Tl-201 (perfusion) and C-14-BMHDA (fatty acid) utilization in normotensive and hypertensive rat hearts. Notice C-14-BMHDA uptake is severely diminished in severe hypertension while perfusion (Tl-201) has not significantly decreased.

Figure 2. Dual tracer autoradiography of I-131 BMIPP (left panel) and C-14-DG (right panel) of hypertensive rat heart. Notice fatty acid utilization is decreased, especially in the endocardium and free wall of LV with a concomitant increase in glucose uptake in the same areas.

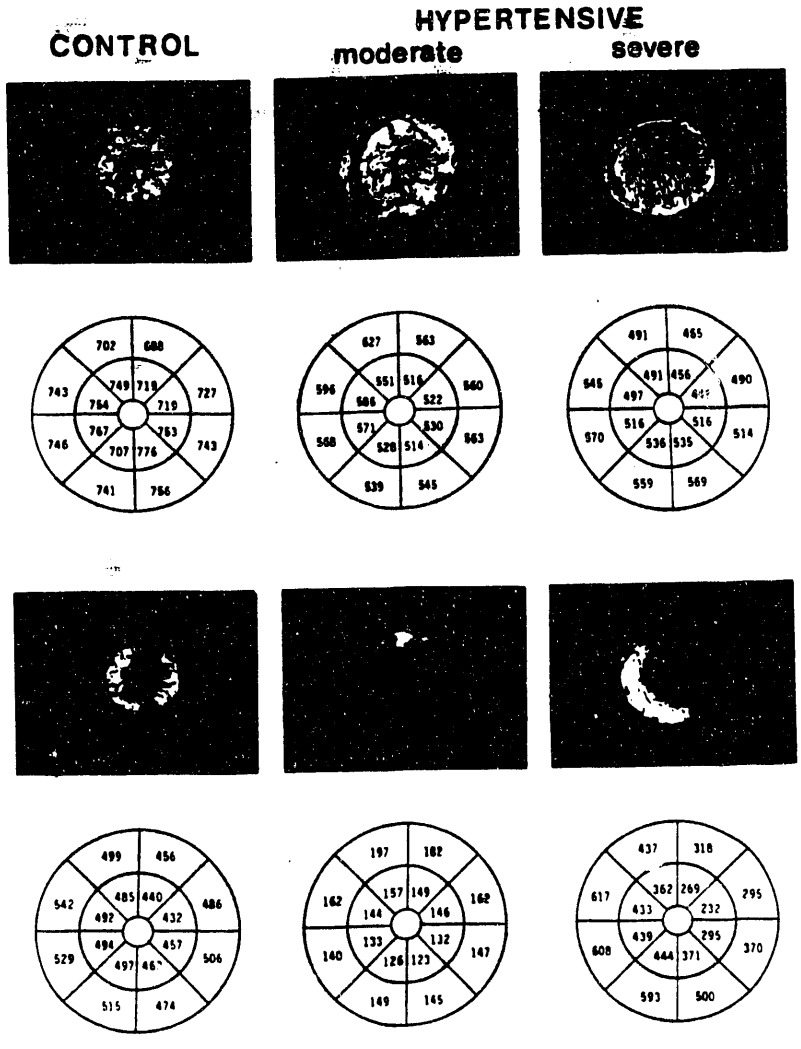
Figure 3. Fatty acid (I-131 DMIPP) glucose (C-14-FDG) utilization and perfusion Tl-201 in advance cardiomyopathy in hamsters (top) and normal hamster heart (bottom). Notice both DMIPP uptake is decreased in the free wall and septum and FDG uptake is increased in the septum.

Figure 4. I-131 DMIPP uptake in control hamsters and hamsters with early and late stage cardiomyopathy (top). Effect of treatment with verapamil caused reversal of the disease process (bottom).

Figure 5. ^{14}C-cocaine autoradiographs (ARG), coronal sections in control rats. A and B, 2 minutes after injection. A is a more dorsal section showing intense uptake in the olfactory bulbs, cerebrum and cerebellum, adrenals and renal parenchyma. B is a more ventral section showing high uptake in the myocardium. C and D are 10 and 15 minute sections showing washout from brain, heart and adrenals, and high uptake in liver, renal collection system, and bowel.

Figure 6. ^{14}C-cocaine ARG after pre-treatment with desipramine and GBR 12909. Desipramine caused decreased uptake in the heart and adrenals and non-uniform renal uptake. GBR 12909 decreased uptake in the striatum, cerebellum, heart. (A = control, B = DES, C - GBR).

Figure 7. Distribution of Tl-201, ^{14}C-2-deoxyglucose (2-DG) and I-131 BMIPP in the heart of normotensive and hypertensive rats after administration of normal saline or cocaine. NS: normotensive rats injection with saline; HS: hypertensive rats injected with saline; HC: hypertensive rats injected with cocaine; NC: normotensive rats injected with cocaine


CONTROL
HYPERTENSIVE
moderate
severe
1
2
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4
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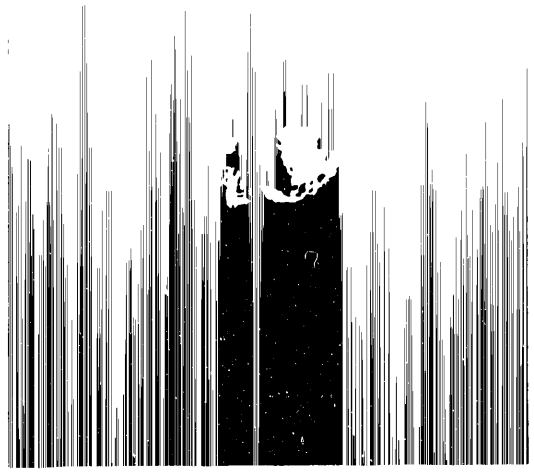
Fig 2



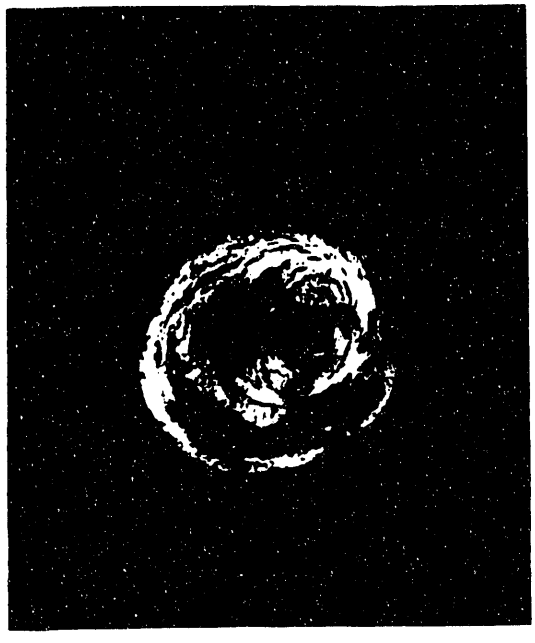
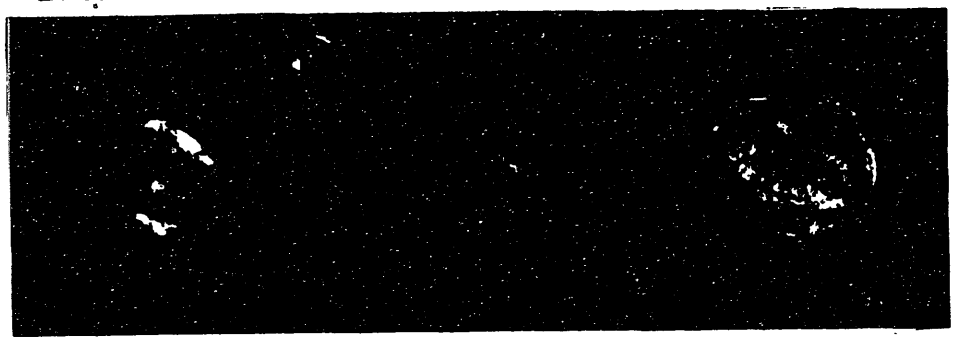


Fig. 3

cardiomyopathy. advanced

DMIPP FDG 201Tl



Control hamsters

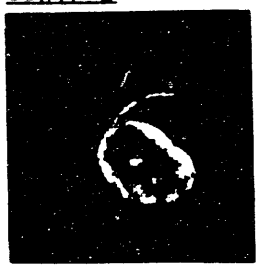
DMIPP FDG 201Tl

Fig. 4

FATTY ACID UTILIZATION IN CARDIOMYOPATHY

AUTORADIOGRAPHY OF CARDIOMYOPATHY (CM) HAMSTERS WITH ^{131}I-DMIPP

CONTROL

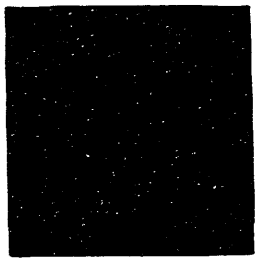


CM EARLY STAGE

CM ADVANCED

VERAPAMIL TREATMENT EFFECT ON CARDIOMYOPATHY

SALINE TREATMENT



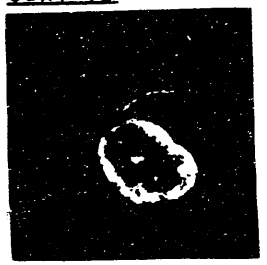
VERAPAMIL TREATMENT

Fig. 3

FATTY ACID UTILIZATION IN CARDIOMYOPATHY

AUTORADIOGRAPHY OF CARDIOMYOPATHY (CM) HAMSTERS WITH ^{131}I-DMIPP

CONTROL

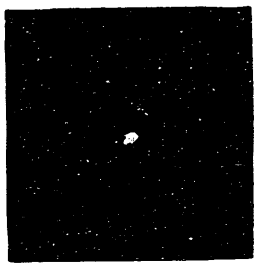


CM EARLY STAGE

CM ADVANCED

VERAPAMIL TREATMENT EFFECT ON CARDIOMYOPATHY

SALINE TREATMENT



VERAPAMIL TREATMENT

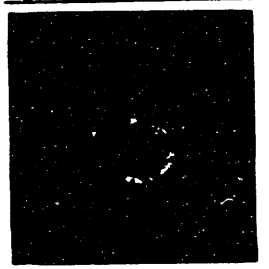


FIG. 6

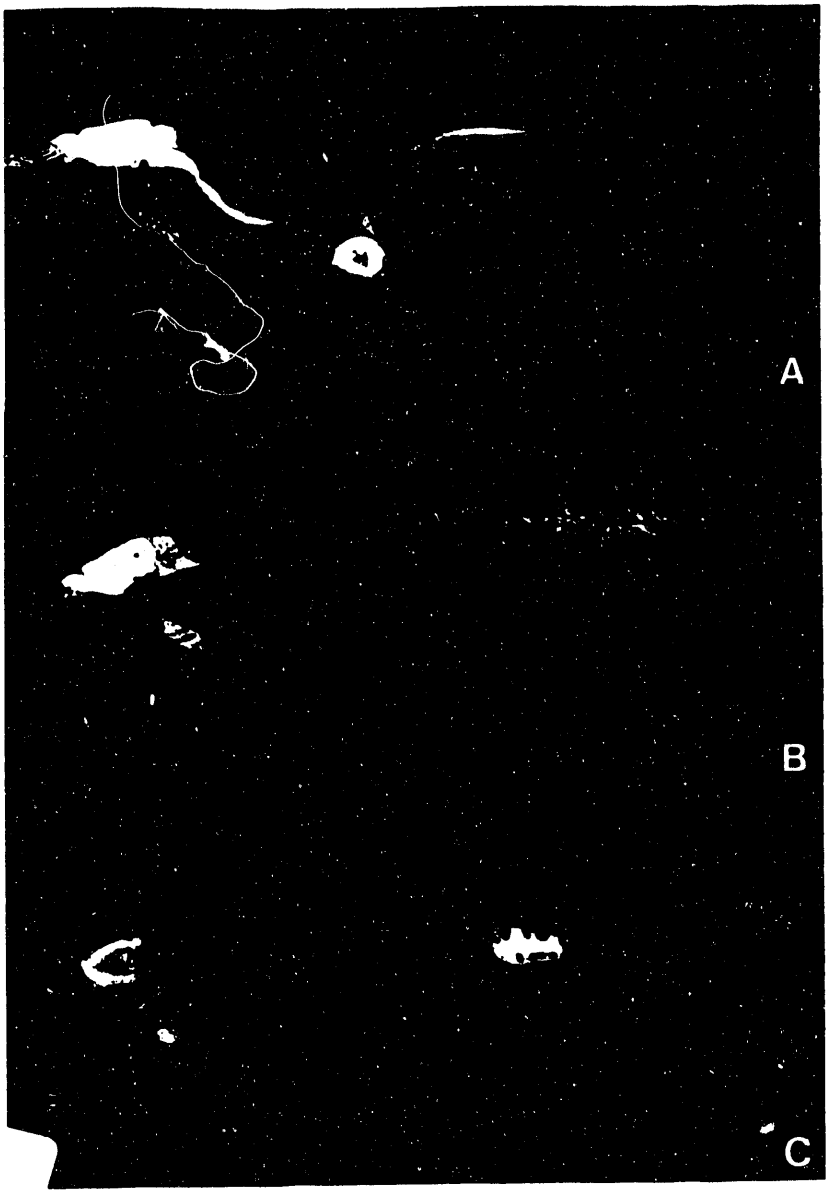
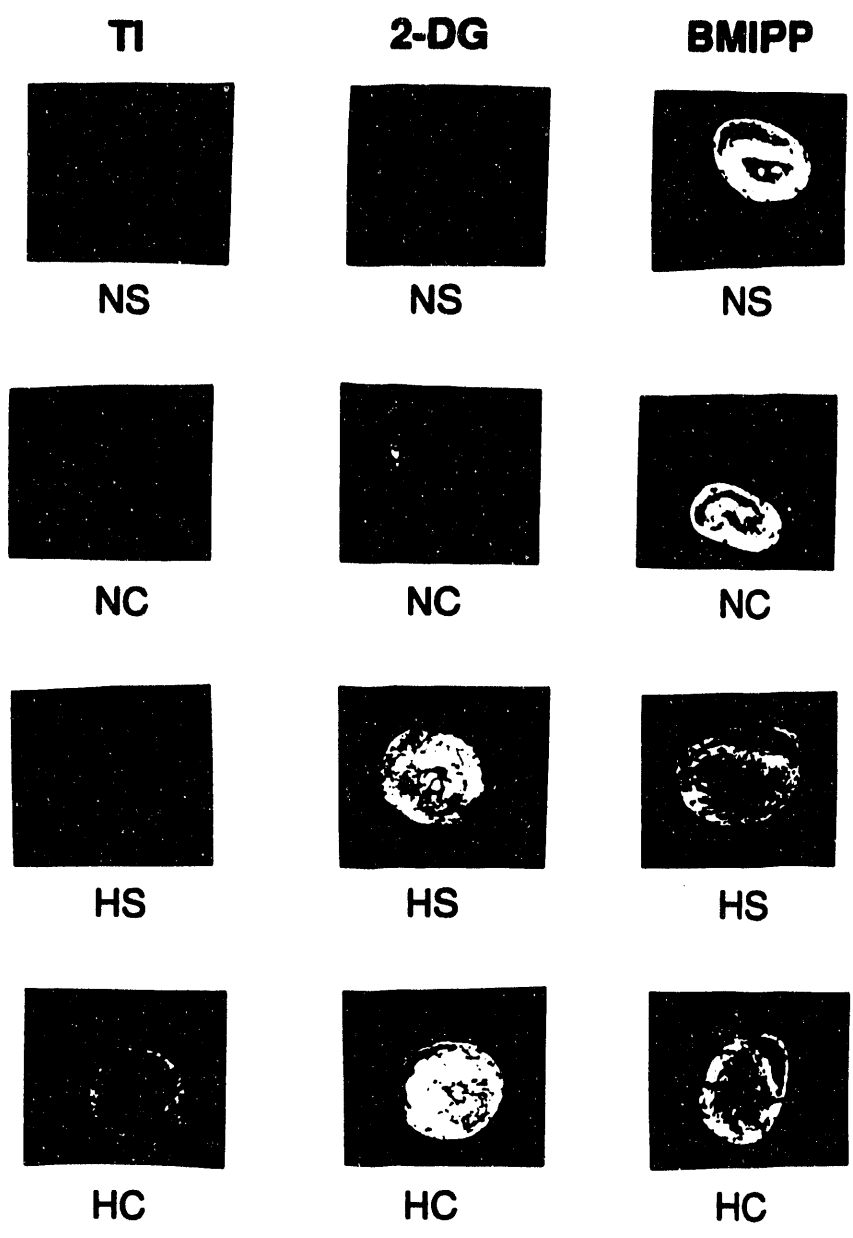


Fig. 7



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