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Carrier-Free ^{11}C-Labeled Catecholamines in Nuclear Medicine and Biochemical Research

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INTRODUCTION

The catecholamines--dopamine, norepinephrine and epinephrine--are synthesized and secreted by tissues such as brain, sympathetic nerve endings and chromaffin cells. Dopamine and norepinephrine are primarily neurotransmitters while epinephrine functions mainly as a hormone. The biosynthesis of the catecholamines from tyrosine is shown in Figure 1.

Abnormalities in the quantities and metabolism of these compounds are associated with many pathological conditions such as hypertension, Parkinsonism and chromaffin tissue tumors.[1]

Many studies such as those which deal with the effects of drugs on the biosynthesis, storage and metabolism of catecholamines[2] are providing a firm foundation of knowledge applicable to the solution of problems of fundamental and practical importance.

We have recently been engaged in a program designed to devise rapid synthetic methods leading to ^{11}C-labeled catecholamines and to explore the potential use of these catecholamines as organ scanning agents and as unique tracers in biochemical research.

The following topics are discussed: 1) The Use of Carbon-11 as a Tracer; 2) The Use of ^{11}C-Labeled Catecholamines as Scanning Agents; 3) Preliminary Evaluation of the Catecholamines as Scanning Agents; and 4) The Pharmacological Interaction of Catecholamines and the Metabolites of Alcohol.

THE USE OF CARBON-11 AS A TRACER

Carbon-11 is a short-lived ($t_{\frac{1}{2}}$ = 20.4 min) radioactive isotope of carbon which, although it requires a nearby cyclotron for its production and depends on the development of rapid labeling techniques, nonetheless offers the following unique advantages as a label for radiopharmaceuticals used in scanning and metabolic studies.

1. Carbon-11, unlike carbon-14 or tritium, decays by positron emission resulting in the emission of two 511 keV gamma annihilation photons per decay event. These can be detected outside the body barrier. High resolution imaging is achieved by coincidence detection of the two photons using the positron camera. Thus dynamic in vivo tissue distribution studies can be carried out using external imaging.
2. Carbon-11 can be prepared "carrier-free" resulting in exceedingly high specific activity compounds (with carrier-free ^{11}C-dopamine·HCl, 1 mCi = 0.02 nanogram). With the inherent low specific activity available with carbon-14, there is a probable risk of physiological effects of the drug if, by administering the tracer, one adds a significant quantity of compound to the existing body pool of this compound.[3] This could result in side reactions and metabolic changes.
3. Although the short half life of carbon-11 (20 minutes) presents some problems in its rapid incorporation into molecules of interest much progress has been made in this area.[4] The advantage of the short half life of carbon-11 is in its potential use for in vivo tracer experiments in humans where

substantial amounts of radioactivity can be administered with a low radiation risk to the patient. For this reason this tracer should be of value in diagnosis of diseases in children. Furthermore, serial imaging studies can be made.

4. Carbon-11 can be easily produced using compact medical cyclotrons and other small accelerators.

THE USE OF ^{11}C-LABELED CATECHOLAMINES AS SCANNING AGENTS

Catecholamines have an inherent tissue specificity which is a result of specific mechanisms which the body has for removing them from the bloodstream. The most important mechanisms of terminating the action of circulating catecholamines are uptake into sympathetic nerve endings and enzymatic inactivation by catecholamine-O-methyltransferase (COMT).[5] Uptake of circulating catecholamines occurs in organs which have extensive sympathetic innervation or chromaffin cells[6] while enzymatic degradation occurs in tissues which have high levels of COMT such as the liver. Thus catecholamines can be expected to localize rapidly and in a predictable fashion.

Adrenal Medulla: At present, there is no radiopharmaceutical available to image the adrenal medulla. Tumors such as pheochromacytoma and neuroblastoma are associated with the adrenal medulla and chromaffin tissue.[7] The adrenal medulla is a site for the synthesis of catecholamines and previous work with ^{14}C-labeled tracers in dogs[8] has shown that, of the catecholamines, dopamine concentrates most avidly in the adrenal medulla. Furthermore, labeled dopamine has been shown to concentrate in human neuroblastoma[9] and pheochromacytoma.[10] The distribution

of intravenously administered catecholamines is to a great extent determined by blood distribution and density of sympathetic nerve endings or chromaffin granules.[11] The tissue distribution of intravenously administered labeled dopamine would be expected to be high in the adrenal medulla since it is composed of chromaffin cells and is one of the most vascular organs in the body, receiving 6-7 ml of blood per gram of tissue per minute.[12]

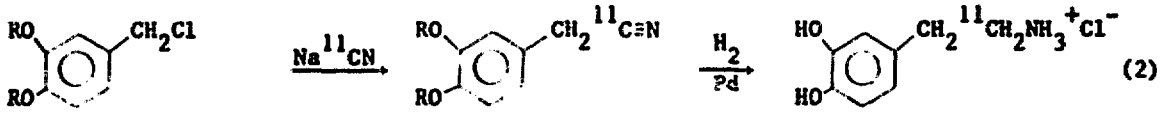
Heart: The importance of heart disease has stimulated the search for a suitably labeled radiopharmaceutical for imaging the myocardium.[13] The diagnosis of myocardial infarction is particularly important. Tracer studies in animals with both carbon-14 and tritium labeled norepinephrine have demonstrated its rapid localization in heart tissue.[14,15] This suggested that norepinephrine labeled with carbon-11 would be potentially useful as a myocardial scanning agent. Furthermore, there is evidence for increased activity of the sympatho-adrenal system in acute myocardial infarction. This is reflected in an increased secretion of dopamine and its metabolite, homovanillic acid during this disease.[16] This suggests the possible diagnostic utility of dynamic studies of myocardial catecholamine uptake.

The potential utility of suitably labeled dopamine and norepinephrine for the diagnosis of diseases associated with the adrenal medulla and heart stimulated the development of new, rapid synthetic routes to carrier-free ^{11}C-labeled dopamine·HCl and norepinephrine·HCl. The synthetic process yields sterile, pyrogen-free radiopharmaceuticals.

Synthesis of ^{11}C-Labeled Dopamine and Norepinephrine: The ^{11}C-labeled precursor used in the synthesis of ^{11}C-labeled dopamine and norepinephrine is carrier-free H^{11}C≡N. This is produced by the irradiation of a N_2/H_2 mixture with protons to give a ^{11}C-methane which is converted to H^{11}C≡N[17] as shown in eq 1. This simple on-line system routinely yields 1-2 Ci of

$$N_2 + H_2 \xrightarrow{p,\alpha} {}^{11}CH_4 \xrightarrow[p+,\ 1000^o]{NH_3} H^{11}CN \qquad (1)$$

H^{11}CN which is used in the synthesis of ^{11}C-labeled catecholamines. ^{11}C-Dopamine·HCl is currently being prepared by a new, higher yield modification (eq 2) of a synthetic method which we have previously reported.[18]



(2)

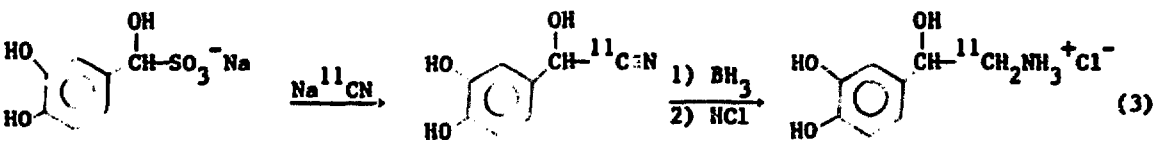
R = $C_6H_5CH_2$–

^{11}C-dopamine·HCl

Radiochemical Yield: 20-30%

Synthesis Time: 65 min

A new synthesis of norepinephrine·HCl has been developed in our laboratory and this has been applied to the carbon-11 labeling of this molecule as shown in eq 3.[19,20]



(3)

^{11}C-norepinephrine·HCl

Radiochemical Yield: 10%

Synthesis Time: 40 min

An important step in the production of carrier-free ^{11}C-dopamine and norepinephrine is the separation of the product from unreacted starting material and various by-products of the synthesis. In both the synthesis of ^{11}C-dopamine·HCl and ^{11}C-norepinephrine·HCl the only source of the amino group is carrier-free H^{11}C≡N. A specially washed cation exchange resin is used in the purification.[21] This absorbs carrier-free ^{11}C-dopamine·HCl, the only basic compound present in the system. Washing the resin with water removes non-basic impurities and pure carrier-free ^{11}C-dopamine·HCl is eluted with hydrochloric acid.

The production of sterile and pyrogen-free product is achieved by a combination of terminal millipore sterilization and the use of a production process which has been demonstrated to yield a pyrogen-free product. The ion exchange column is prepared in advance, sealed and autoclaved. This unit shown in Fig. 2 maintains effectiveness and sterility for at least 6 weeks. Its use requires simply breaking the glass seal, entering the rubber seal with a sterile syringe and needle, and forcing the eluting solvent through the syringe.

PRELIMINARY EVALUATION OF THE CATECHOLAMINES AS SCANNING AGENTS

^{11}C-Dopamine·HCl: The tissue distribution ^{11}C-dopamine was determined in dogs and is shown in Table 1. With carrier-free ^{11}C-dopamine, we have observed that the %uptake/gram in the adrenal medulla increased fourfold (from 0.03 to 0.12, avg) compared with the uptake when ^{11}C-dopamine with carrier (0.01 mg/kg) was administered.[18] Since most organs extract most of the catecholamine that perfuses them during a single passage of blood,

almost all of the circulating catecholamine that is not immediately metabolized is taken up within sympathetic-nerve endings or chromaffin tissue. The amount of catecholamine taken up by the sympathetic-nerve endings of a particular organ is a linear function of the dose injected provided the blood levels of catecholamine remain within the physiologic range. Abnormally high concentrations of circulating catecholamines can saturate the uptake mechanism and thus lower the percentage of the administered dose taken up by an organ.[11]

Figure 3 shows the uptake (%/gram) in the adrenal medulla and kidney in dogs as a function of time up to two hours. Since the kidney is the nearest interfering organ it is important that the ratio of medulla:kidney be maximized within the time span for scanning allowed by the 20 minute half-life of carbon-11. This occurs at 1.5-2.0 hours. Using the tissue distribution values obtained in dogs, it can be calculated that for a 10 mCi dose of ^{11}C-dopamine there would be 5.9 μCi in the kidney and 0.16 μCi in the adrenal (medulla + cortex) at 1.5 hours. Phantom studies using the positron camera show that with this ratio imaging is possible using the positron camera. Radiation dosimetry for ^{11}C-dopamine·HCl is given in Table 2.

<u>^{11}C-Norepinephrine·HCl</u>: The uptake of ^{11}C-norepinephrine in dogs (Table 3) was determined at 5, 15, 30, 60 and 90 minutes. The half-time of ^{11}C-norepinephrine·HCl in the blood is less than two minutes as shown in Fig. 4. The heart:liver ratio remained fairly constant ($\sim$ 1) throughout the hour. The heart to lung ratio increased from 1 to 4. Scans were made using the Nuclear Data Radicamera and there was a clear separation between heart and liver and no interference from the lungs (Fig. 5). A detailed dissection of the dog heart showed that the activity

was evenly distributed. Scans of the isolated dog heart using the Positron Camera show an even distribution of activity (Fig. 6). Radiation dosimetry for ^{11}C-norepinephrine·HCl is given in Table 4.

THE PHARMACOLOGICAL INTERACTION OF CATECHOLAMINES AND THE METABOLITES OF ALCOHOL

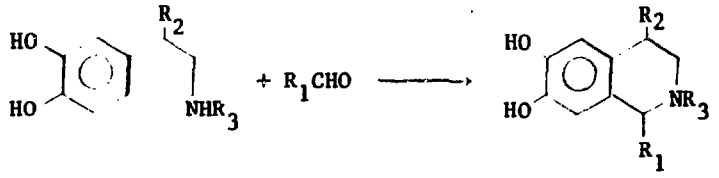
The possible role in the behavioral and biochemical manifestations of alcoholism played by tetrahydroisoquinolines (TIQ's) formed in the reaction of catecholamines with various metabolites of alcohol has been investigated recently.[22-25] Changes in the quantity and chemical structure of catecholamine metabolites during alcohol ingestion and withdrawal have been observed in many laboratories and some of this work has been summarized by Mendelson.[22] Many studies have been concerned with the possible role of tetrahydroisoquinolines in alcohol addiction. Ethanol and methanol[26] (which has been demonstrated to accumulate in the bloodstream of individuals ingesting alcohol) are oxidized *in vivo* to produce acetaldehyde and formaldehyde respectively in the first oxidation step (eq 4). Under

$$R_1CH_2OH + NAD^+ \rightleftharpoons[\text{alcohol dehydrogenase}] R_1CHO + NADH + H^+ \qquad (4)$$

Ia $R_1 = H$ (methanol) IIa $R_1 = H$ (formaldehyde)

b $R_1 = CH_3$ (ethanol) b $R_1 = CH_3$ (acetaldehyde)

physiological conditions both acetaldehyde and formaldehyde have been shown to undergo rapid condensation reactions with catecholamines (III) to yield tetrahydroisoquinolines (IV) (eq 5).[27]



(5)

IIIa $R_2 = R_3 = H$ (dopamine)

b $R_2 = OH$; $R_3 = H$ (norepinephrine)

c $R_2 = OH$; $R_3 = CH_3$ (epinephrine)

IVa $R_2 = R_3 = H$ ($R_1 = H$ or CH_3)

b $R_2 = OH$; $R_3 = H$ ($R_1 = H$ or CH_3)

c $R_2 = OH$; $R_3 = CH_3$ ($R_1 = H$ or CH_3)

Furthermore, tetrahydroisoquinolines have been shown to be formed in mice during methanol metabolism[28,29] and in humans during L-DOPA therapy.[30] They share similar uptake and release mechanisms with catecholamines.[31-33]

In view of the interest in and apparent importance of the pharmacological interaction of the catecholamines and the metabolites of alcohol to form TIQ's during alcohol addiction, we have initiated a program using ^{11}C-tracers to study the physiological disposition of these molecules.

Carrier-free ^{11}C-labeled dopamine is readily converted to ^{11}C-DAIQ (IVa, R_1=H) and ^{11}C-salsolinol (IVa, R_1=CH_3) by reaction with 37% formaldehyde solution or acetaldehyde. We have studied the tissue distribution of these TIQ's in normal mice and present evidence that they (or their ^{11}C metabolites), when compared with ^{11}C-dopamine, shows enhanced capability to cross the blood-brain barrier. A comparison of the tissue distribution of ^{11}C-DAIQ and ^{11}C-salsolinol to ^{11}C-dopamine at different sacrifice times if presented in Table 5. The uptake (%/organ) of ^{11}C-DAIQ (or its ^{11}C-metabolites) into the brain was measured at 1, 5, 10, 15, 30 and 60 minutes and is shown graphically in Fig. 7. A striking difference in the uptake of the two compounds is revealed in the 4-fold increase in brain uptake of the ^{11}C-DAIQ

over ^{11}C-dopamine. The brain uptake was rapid and remained constant over the time period of the study. The brain uptake (%/organ) of ^{11}C-dopamine is shown on the same graph. The half life of the ^{11}C-DAIQ or its metabolites in the blood is less than 2 minutes, as shown in Fig. 8.

In view of our results it is interesting to speculate that the effects of the TIQ alkaloids might arise from their enhanced uptake in the brain which could cause alterations in the normal catecholamine levels. While our initial program involves the studies in normal mice experiments using alcohol addicted animals are planned. Information concerning fundamental changes in the physiological disposition of these compounds which could lead to alcohol addiction and its associated behavioral and biochemical characteristics is sought.

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Table 1. Tissue uptake (%/g) of carrier-free ^{11}C-Dopamine·HCl in dogs at different times.

Sacrifice Time (hr)	Number of Dogs	% uptake/gram							
		Blood	Heart	Liver	Kidney	Spleen	Lung	Adrenal Medula	Adrenal Cortex
0.5	2	0.004 ±0.001	0.0031 ±0	0.0028 ±0.005	0.045 ±0.003	0.051 ±0.005	0.0075 ±0.0005	0.094 ±0.014	0.048 ±0.016
1.0	2	0.0035	0.015 ±0.002	0.018 ±0.0016	0.060 ±0.03	0.0132 ±0.0007	0.0046 ±0.0003	0.176 ±0.09	0.040 ±0.003
1.5	3	0.0017 ±0.0004	0.017 ±0.002	0.017 ±0.002	0.021 ±0.003	0.030 ±0.003	0.0032 ±0.0003	0.124 ±0.03	0.037 ±0.002
2.0	3	0.0021 ±0.0004	0.016 ±0.002	0.015 ±0.003	0.019 ±0.003	0.059	0.0028	0.124 ±0.02	0.030 ±0.004
2.0	1[a]	0.0014	0.009	0.0065	0.0075			0.028	0.013

[a] Carrier dopamine·HCl was added (0.01 mg/kg).

Table 2. Estimated Radiation Doses[a] for ^{11}C-Dopamine·HCl/mCi Activity

Tissue	Dose β (rad)	Dose γ (rad)	Dose Total (rad)
Liver	0.06	0.03	0.09
Kidney	0.08	0.01	0.09
Adrenal[b] (total)	0.16	0.02	0.18
Spleen	0.11	0.02	0.13
Pancreas	0.04	0.005	0.045
Heart	0.06	0.01	0.07
Testes	0.01	0.001	0.011
Total Body	0.005	0.005	0.01

a) Doses were calculated using equations and information supplied in the MIRD Supplements 1, 3 and 4 (J. Nucl. Med., 1968-70). The fraction of administered dose/organ was obtained from dog tissue distribution data.

b) No ϕ_1 value was supplied in the MIRD tables and the ϕ_1 value for the testicle was used as an approximation.

Table 3. Tissue uptake (%/g) of ^{11}C-norepinephrine·HCl in dogs at different times.

Sacrifice Time (min)	Number of dogs	% uptake/gram							
		Blood	Heart (avg)	Liver	Kidney	Spleen	Lung	Adrenal Medulla	Adrenal Cortex
5	2	0.007 ±0.001	0.025 ±0.001	0.023 ±0.001	0.060 ±0.007	0.034 ±0.018	0.018 ±0.007	0.132 ±0.04	0.032 ±0.001
15	1	0.003	0.016	0.024	0.042	0.050	0.010	0.093	0.026
30	2	0.004 ±0.001	0.026 ±0.001	0.024 ±0.001	0.037 ±0.005	0.035 ±0.008	0.010 ±0.004	0.084 ±0.038	0.020 ±0.003
60	3	0.0025 ±0.0005	0.016 ±0.007	0.014 ±0.003	0.023 ±0.003	0.027 ±0.018	0.004 ±0	0.063 ±0.02	0.017 ±0.003
90	1	0.002	0.023	0.010	0.019	0.024	0.005	0.06	0.023

Table 4. Estimated Radiation Doses[a] for ^{11}C-Norepinephrine·HCl/mCi Activity

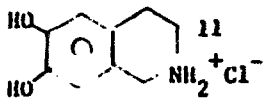
Tissue	Dose β (rad)	Dose γ (rad)	Dose Total (rad)
Liver	0.056	0.023	0.079
Kidney	0.090	0.017	0.107
Adrenal[b] (total)	0.091	0.011	0.102
Spleen	0.195	0.039	0.234
Pancreas	0.062	0.007	0.069
Heart	0.091	0.018	0.109
Testes	0.0068	0.0008	0.0076
Total Body	0.005	0.0045	0.0095

a) Doses were calculated using equations and information supplied in the MIRD Supplements 1, 3 and 4 (J. Nucl. Med., 1968-70). The fraction of administered dose/organ was obtained from dog tissue distribution data.

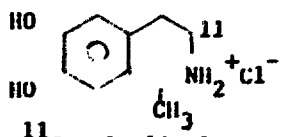
b) No ϕ_i value was supplied in the MIRD tables and the ϕ_i value for the testicle was used as an approximation.

Table 5. Comparison of the organ uptake (%/organ) in mice after the intravenous injection of carrier-free ^{11}C-labeled dopamine (^{11}C-DA, IIIa) and 3-^{11}C-6,7 dihydroxy-1,2,3,4-tetrahydroisoquinoline (^{11}C-DAIQ, IVa (R_1 = H)) and ^{11}C-salsolinol (IVa (R_1 = CH_3)).

^{11}C-DA·HCl

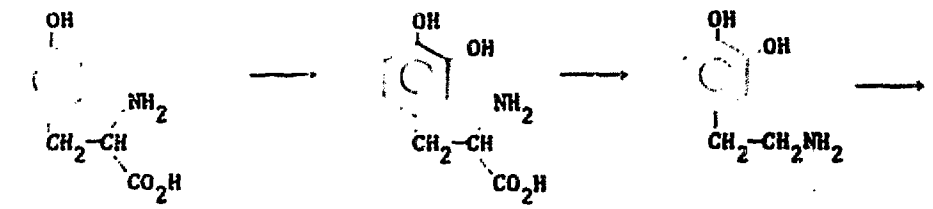


^{11}C-DAIQ·HCl



^{11}C-salsolinol

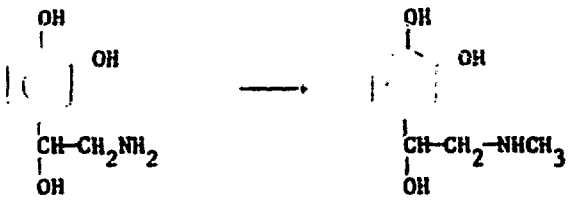
Tissue	Sacrifice Time (min)	Number of Mice, DA (DAIQ)[sal]	^{11}C-DA %/organ	^{11}C-DAIQ %/organ	^{11}C-salsolinol %/organ
Blood	15	3(3)	--	--	
	30	2(3)	--	--	
	60	(3)			
Heart	15	4(3)[3]	1.3 ± 0.6	0.41 ± 0.02	0.29 ± 0.01
	30	5(3)[3]	1.2 ± 0.3	0.23 ± 0.01	0.21 ± 0.02
	60	(3)		0.15 ± 0.02	
Lung	15	3(3)[3]	1.1 ± 0.3	0.84 ± 0.09	0.56 ± 0.06
	30	5(3)[3]	0.6 ± 0.1	0.42 ± 0.03	0.35 ± 0.03
	60	(3)		0.26 ± 0.01	
Pancreas	15	4(3)[3]	0.35 ± 0.11	0.82 ± 0.06	0.45 ± 0.004
	30	5(3)[3]	0.5 ± 0.2	0.58 ± 0.08	0.31 ± 0.03
	60	(3)		0.44 ± 0.1	
Spleen	15	3(3)[3]	0.56 ± 0.14	0.67 ± 0.1	0.24 ± 0.01
	30	5(3)[3]	0.6 ± 0.1	0.43 ± 0.02	0.15 ± 0.02
	60	(3)		0.28 ± 0.03	
Kidneys	15	4(3)[3]	3.0 ± 0.6	4.7 ± 0.8	3.6 ± 0.6
	30	5(3)[3]	1.6 ± 0.4	3.6 ± 1.4	2.5 ± 1.0
	60	(3)		2.8 ± 0.4	
Liver	15	4(3)[3]	10.7 ± 2.9	19.3 ± 2.9	16.2 ± 1.2
	30	4(3)[3]	8.7 ± 2.1	24.0 ± 7.8	18.2 ± 4.8
	60	(3)		20.7 ± 2.8	
Adrenals	15	3(2)[3]	0.05 ± 0.013	0.06 ± 0.005	0.023 ± 0.004
	30	5(3)[3]	0.04 ± 0.01	0.06 ± 0.02	0.015 ± 0.001
	60	(3)		0.06 ± 0.003	
Brain	15	4(3)[3]	0.053 ± 0.006	0.21 ± 0.02	0.15 ± 0.03
	30	2(3)[3]	0.036 ± 0.002	0.19 ± 0.02	0.11 ± 0.01
	60			0.17 ± 0.03	



tyrosine

3,4-dihydroxyphenylalanine
(DOPA)

dopamine



norepinephrine

epinephrine

Fig 1. Biosynthesis of the catecholamines.

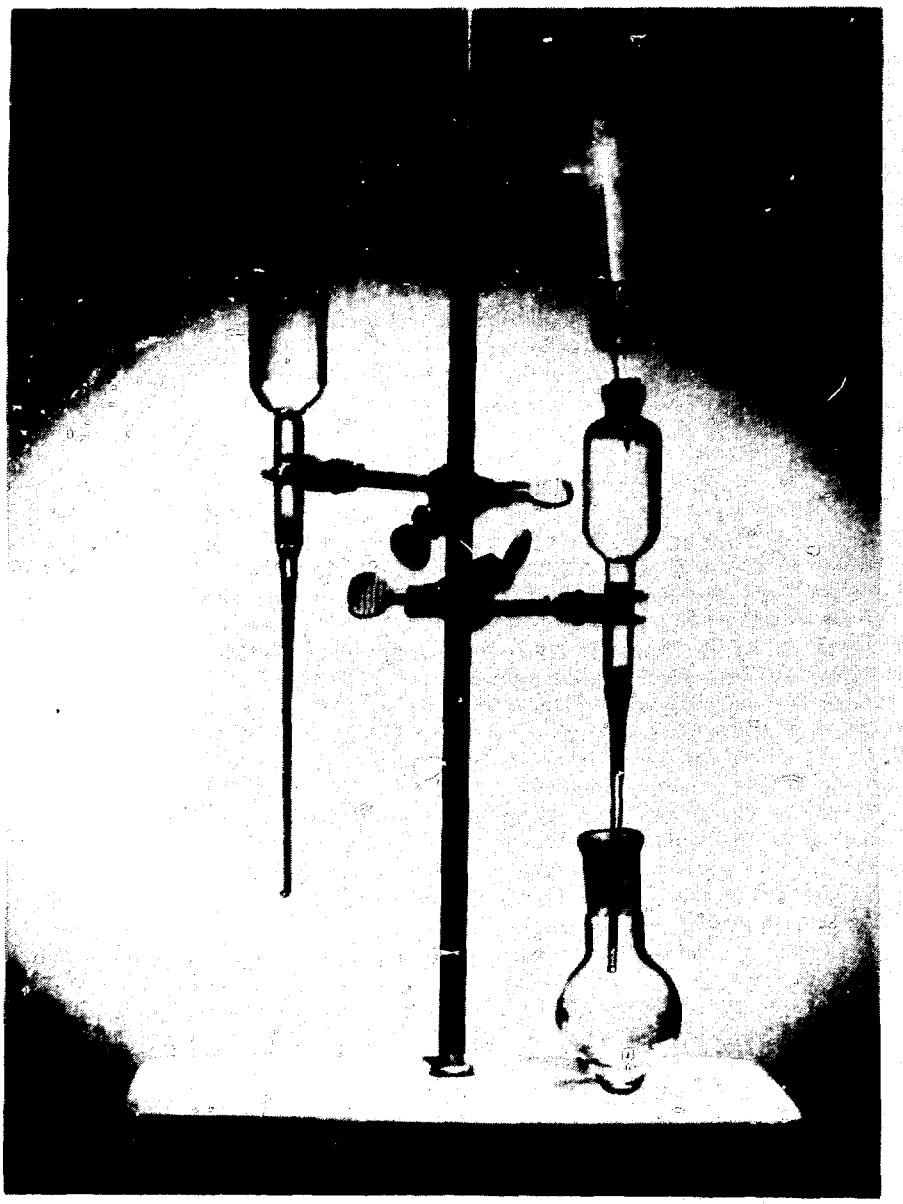


Fig 2. Sterilized resin columns used in the preparation of carrier-free ^{11}C-dopamine·HCl and norepinephrine·HCl for injection.

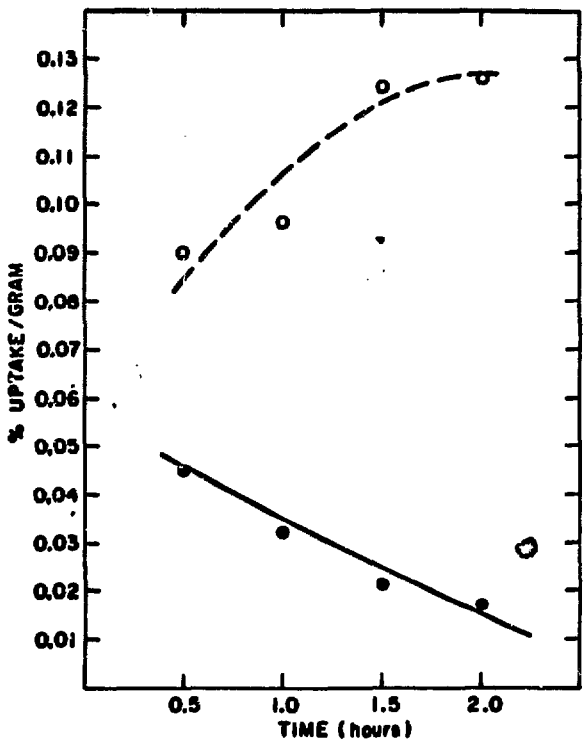


Fig 3. Uptake (%/gram) of carrier-free ^{11}C-dopamine·HCl in the dog adrenal medulla (O---O---O) and kidney (●——●——●) as a function of time.

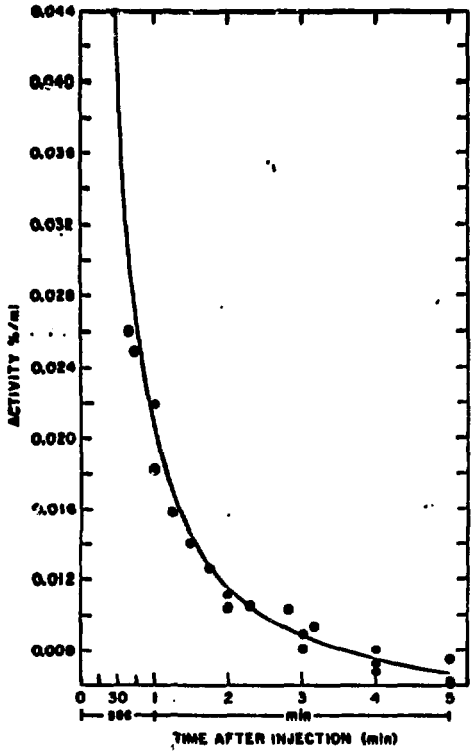


Fig 4. Blood clearance of carrier-free ^{11}C-norepinephrine·HCl in dogs (3 dogs).

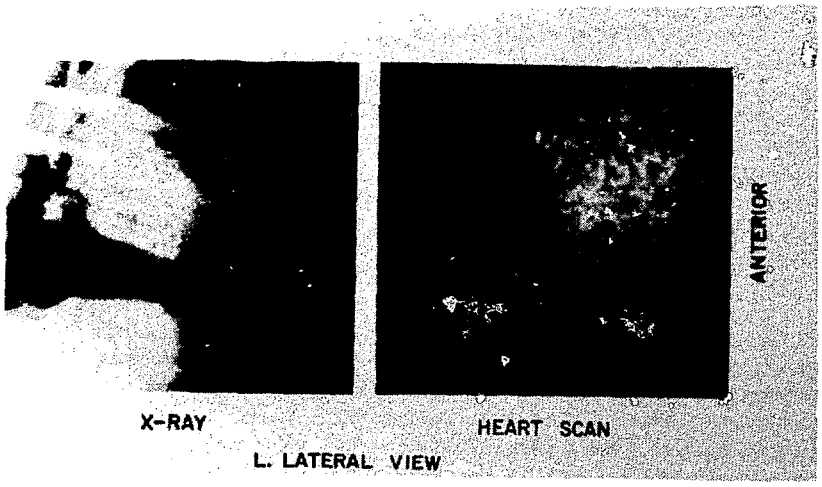


Fig 5. Scan of the chest area of a dog compared with an x-ray, 15 minutes after intravenous injection of carrier-free ^{11}C-norepinephrine·HCl.

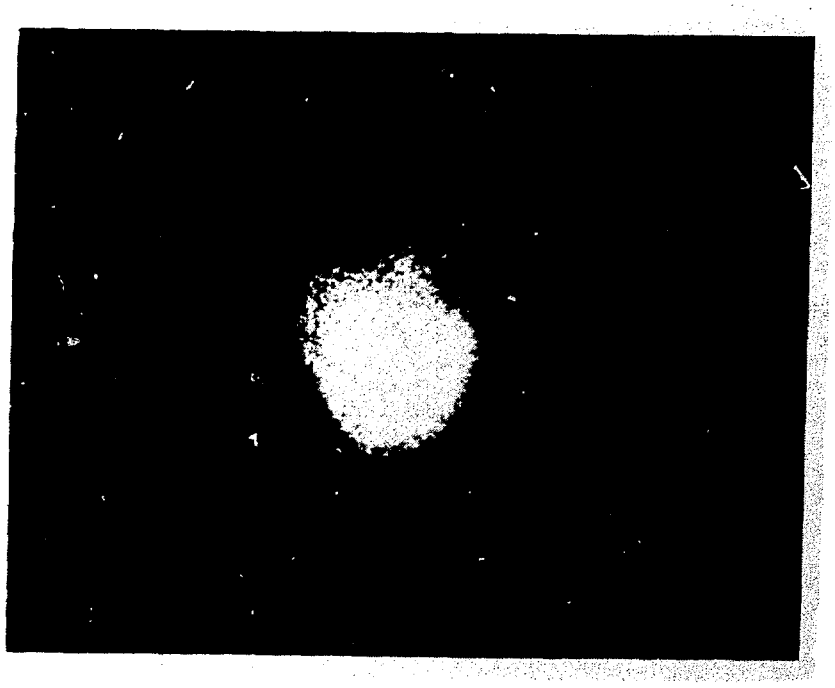


Fig 6. Image of the isolated dog heart using the Nuclear Chicago Pho Gamma (HP) Camera with Positron Attachment.

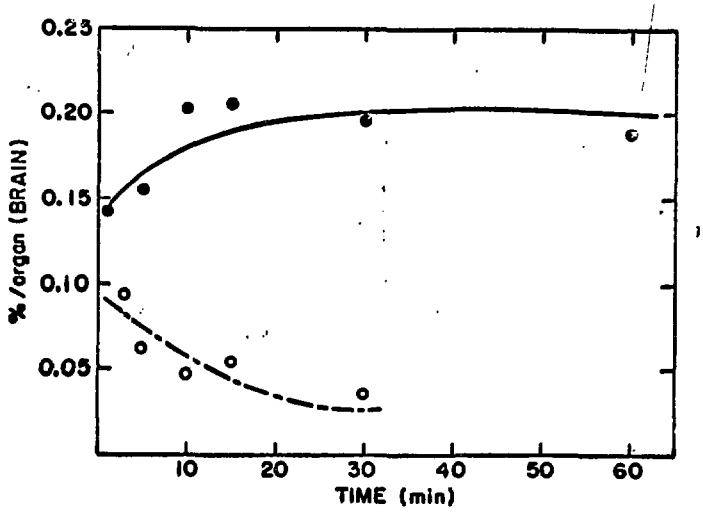


Fig 7. Comparison of the brain uptake (%/organ) of ^{11}C-DAIQ, IVa (R_1=H) (●——●——●) and ^{11}C-DA, IIIa (O- - -O- - -O) in mice.

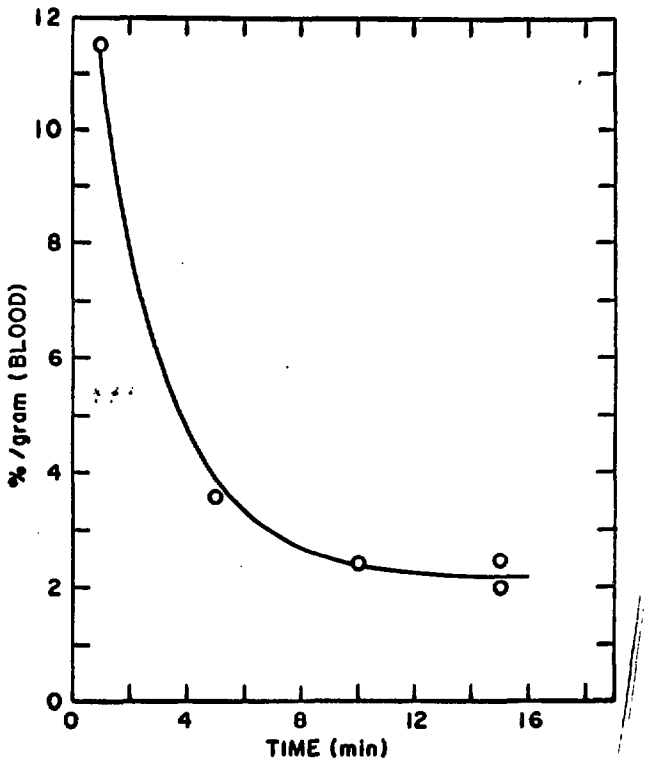


Fig 8. Blood clearance of ^{11}C-DAIQ, IVa(R_1=H) in mice.