jnm / PRELIMINARY NOTE

SYNTHESIS AND PRELIMINARY EVALUATION IN ANIMALS OF CARRIER-FREE ^{11}C-1-DOPAMINE HYDROCHLORIDE: X

Joanna S. Fowler, Azizullah N. Ansari, Harold L. Atkins, Patrick R. Bradley-Moore, Robert R. MacGregor, and Alfred P. Wolf

Brookhaven National Laboratory, Upton, New York

Carrier-free ^{11}C-labeled dopamine hydrochloride was synthesized using carrier-free H^{11}CN as a precursor. Tissue distribution studies on five dogs showed a specific localization in the adrenal medulla. Tissue distribution studies with ^{11}C-labeled noradrenaline are in progress.

We have prepared carrier-free dopamine hydrochloride labeled with short-lived ^{11}C($T_{1/2}$ = 20 min) for evaluation as an agent for scanning the adrenal gland and chromaffin tissue tumors. We previously reported a method for labeling dopamine hydrochloride using Na^{11}CN which was not carrier free (*1*). Specific activities at delivery were only ~3 μCi/mg which was too low for animal studies. The recent development in our laboratory of a simple, reliable method for the routine production of 1–2 Ci of carrier-free H^{11}CN (*2*) and the modification of the dopamine synthesis to a microscale has made it possible to deliver routinely 10–20 mCi of carrier-free ^{11}C-dopamine hydrochloride for animal experiments.

The potential use of ^{11}C-labeled dopamine for scanning was suggested by previous studies with ^{14}C-labeled dopamine in which an avid uptake of dopamine by human adrenal medulla and neuroblastoma was observed (*3,4*). We report here the results of tissue distribution studies in dogs which show a specific uptake of ^{11}C-labeled dopamine by the adrenal medulla.

METHODS

Carrier-free H^{11}CN is produced using the Brookhaven 60-in. cyclotron and the ^{14}N(p,α)^{11}C nuclear reaction according to the following equation.

$$N_2 + H_2 \xrightarrow{p,\alpha} {}^{11}CH_4 \xrightarrow[NH_3]{Pt,\ 1,000°C} H^{11}CN$$

This material is trapped during the cyclotron bombardment and is used as described below.

Carrier-free ^{11}C-1-dopamine · HCl. The H^{11}CN was transferred on a vacuum line into 50 λ of 0.05 *M* NaOH, the reaction vessel was warmed to room temperature, and the solution stirred for 1 min and evaporated to dryness to remove excess NH_3 formed by radiolysis in the target. The sodium bisulfite adduct of 3,4-dihydroxybenzaldehyde (*1*) (0.0235 m*M*) in 25 λ of H_2O was added and the mixture heated at 70° for 5 min. This was extracted with 1.5 ml of ether (total) in four portions and the ether extracts passed through a filter containing $CaCl_2$ into a specially constructed vessel for hydrogenation. The ether was completely removed using a stream of nitrogen, ~5 mg of 10% palladium on carbon and 0.2 ml of a 2% solution of conc. HCl in ethanol was added and the mixture was hydrogenated on a Paar shaker at 60 psi for 20 min. The reaction mixture was filtered onto a 1 × 0.5 cm column of Dowex 50W X-8 (H^+ form) which had previously been washed as described by Häggendal (*5*). Unreacted starting material and other nonbasic impurities were washed from the column with 15 ml of 0.001 *N* HCl and discarded. The ^{11}C-labeled dopamine · HCl was washed from the column with 15 ml of 3 *N* HCl, and the HCl solvent was rapidly removed by rotary evaporation at 80° (10 mm). The product was washed from the flask with 3 ml of H_2O and was delivered for animal experiments. The entire procedure required 60 min and ~10% of the initial H^{11}CN activity was incorporated into the ^{11}C-labeled dopamine · HCl.

Demonstration of the chemical form of the ^{11}C-product. Since the amount of dopamine produced was too small to detect chemically (20 mCi of carrier-free ^{11}C-dopamine = 0.39 ng), carrier dopamine hydrochloride was added and the following experi-

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For reprints contact: J. S. Fowler, Chemistry Dept., Brookhaven National Laboratory, Upton, N.Y. 11973.

TABLE 1. DISTRIBUTION OF ^{11}C-1-DOPAMINE HYDROCHLORIDE (%/gm)

Experiment No.	Dose	Time after injection (hr)	Blood	Urine	Heart	Liver	Kidney	Adrenal medulla	Adrenal cortex
1	0.01 mg/kg (7.54 mCi)	2	0.0014	0.028	0.009	0.0065	0.0075	0.028	0.013
2	Carrier free (1.29 mCi)	2	0.0028	0.31	0.020	0.014	0.023	0.13	0.031
3	Carrier free (1.04 mCi)	2	0.0020	0.29	0.013	0.010	0.015	0.094	0.024
4	Carrier free (6 mCi)	2	0.0017	1.59	0.016	0.020	0.019	0.15	0.035
5	Carrier free (6 mCi)	1.5	0.0023	1.24	0.019	0.012	0.026	0.091	0.041

ments were made to confirm the chemical form: thin-layer chromatography (tlc) [butanol:acetic acid: water (15/3/5) on silica gel G and butanol:pyridine: acetic acid:water (15/2/3/5) on silica gel G] showed all of the radioactivity coincident with the spot corresponding to dopamine hydrochloride ($R_f = 0.5$ and 0.6, respectively). The material with carrier added was recrystallized five times. The specific activity of a sample from each recrystallization was measured, and it remained constant. The correspondence of the activity and dopamine hydrochloride on the tlc plate also remained unchanged.

Animal experiments. To date, tissue distribution studies on five mongrel dogs have been made. Four animals were sacrificed after 2 hr and one after 90 min by injection of a rapidly acting lethal solution. Four animals were given the carrier-free ^{11}C-dopamine and one was given ^{11}C-dopamine with carrier (0.01 mg/kg). A standard from the delivered ^{11}C-dopamine hydrochloride solution was retained. After sacrifice, samples of blood, urine, kidney, liver, heart, adrenal medulla, and adrenal cortex were taken and counted in a NaI(Tl) well counter. The samples were weighed and percent uptake of the administered dose per gram, (%/gm) was calculated (Table 1).

RESULTS AND DISCUSSION

As can be seen from the data in Table 1, ^{11}C-1-dopamine hydrochloride concentrates specifically in the adrenal medulla. Since this localization effect is sufficiently rapid to be useful with ^{11}C (2 hr or less) and since tumors associated with the adrenal medulla are actively involved in the metabolism of catecholamines, it appears that carrier-free ^{11}C-dopamine will be a useful scanning agent. The ratios (%/gm) of carrier-free ^{11}C-dopamine hydrochloride in the adrenal medulla versus blood, liver, kidney, and heart (values with carrier are in parentheses) are 61 (20), 8.7 (4.3), 6.6 (3.7), and 7.7 (3.1), respectively. Since our interest lies in visualizing the adrenal medulla, the information of most concern is to have the ratios of %/gm of ^{11}C-dopamine in the adrenal medulla to the %/gm in the contiguous organs. These ratios are expressed in the unusual but preferred form of Fig. 1.

With carrier-free ^{11}C-dopamine, we have observed that the %/gm in the adrenal medulla increased fourfold (from 0.028 to 0.117, avg) compared with the uptake when ^{11}C-dopamine hydrochloride with carrier (0.01 mg/kg) was administered. A similar dependence of tissue uptake as a function of loading dose was observed in the localization of ^{18}F-labeled 6-fluorotryptophan in the pancreas (*6*). The advantage of the carrier-free radiopharmaceutical as demonstrated in this study is that it is physiologically insignificant and further increases the uptake in the specific target organ.

Although most of the tissue distributions were measured at 2 hr, one recent experiment showed

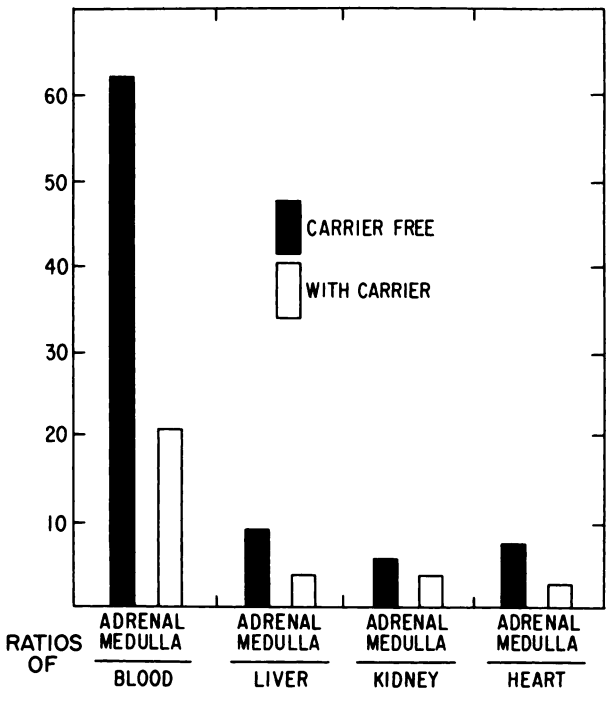

FIG. 1. ^{11}C-dopamine tissue radioactivity at 2 hr expressed as ratio of adrenal medulla to blood, liver, kidney, and heart.

tissue uptake to be not significantly different at 90 min (Table 1, No. 5). The uptake as a function of time is presently being investigated. In addition, studies have been initiated on the tissue distribution of ^{11}C-dopamine on animals pretreated with various agents which inhibit the in vivo enzymic degradation of catecholamines (7). These results and the results of imaging experiments will be reported in a full paper.

We have recently prepared ^{11}C-noradrenaline hydrochloride by a related synthetic pathway and have begun tissue distribution studies. The results of this study will be reported later.

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