# Radiopharmaceuticals. XIX. $^{11}$C-Labeled Octylamine, a Potential Diagnostic Agent for Lung Structure and Function

J. S. Fowler, B. M. Gallagher, R. R. MacGregor, A. P. Wolf, A. N. Ansari, H. L. Atkins, and D. N. Slatkin

*Brookhaven National Laboratory, Upton, New York*

***After intravenous injection, $^{11}$C-octylamine · HCl is rapidly sequestered by the rabbit lung. The initial lung uptake during the first minute was 70 ± 6% of the administered dose, and 40% of the injected dose remained after 15 min. Approximately 12% of the administered radioactivity is exhaled as $^{11}CO_2$ during the first 30 min.***

**J Nucl Med 17: 752–754, 1976**

The lung, in addition to its main role as the organ of external gas exchange, serves as a metabolic regulator of substances circulating in the blood (*1,2*). The lung has been shown to change many circulating vasoactive substances either by activation, inactivation, or removal and storage for subsequent metabolism or release (*3–6*). This function has been established mainly through in vitro studies of isolated perfused lung tissue (*7*). While there has been considerable speculation in the literature as to the importance of this newly discovered pulmonary function in disease states, to date no diseases have been found to be directly related to the failure of this function (*4*). A major barrier to the study of lung function in disease states has been the lack of noninvasive techniques to assess lung function in vivo both in normal subjects and in patients with various abnormal conditions.

For many years the techniques of nuclear medicine have been used for the noninvasive study of pulmonary blood flow and the patterns and dynamics of gaseous diffusion. However, no studies of the metabolic aspects of lung function have been reported. Therefore, we sought to develop a radiopharmaceutical that, in addition to indicating blood perfusion patterns, would be taken up and metabolized by lung tissue. Such an agent could be used to determine the lung's ability to regulate circulating substances and could provide information on regional metabolic activity.

Compounds having an amine function are sequestered by lung tissue (*6*). The site of uptake of biogenic amines by lung has been shown to be the capillary endothelium (*8–11*). In vivo, amines are oxidized by monoamine oxidase to aldehydes that can undergo subsequent metabolism (*12*). Unlike most biogenic amines, which are metabolized to water-soluble products, aliphatic amines are ultimately metabolized to $CO_2$ through the following pathway:

$$R^{11}CH_2NH_2 \rightarrow R^{11}CHO \rightarrow R^{11}CO_2H \rightarrow \rightarrow {}^{11}CO_2.$$

Thus, an aliphatic amine labeled with $^{11}$C could be used both for functional dynamic imaging of the lung and for measuring its metabolic rate by monitoring $^{11}CO_2$ expiration.

In studies of lung selectivity toward aliphatic amines in mice, the pulmonary uptake of aliphatic amines was found to be related to their lipophilicity. The affinity for lung tissue became pronounced at carbon chain lengths greater than seven, whereas the rate of $^{11}CO_2$ expiration was maximized at a chain length of six (*13*). Octylamine ($C_8$) was selected for this study since it showed both high lung affinity and rapid $CO_2$ evolution.

## METHODS

The $^{11}$C-octylamine ($^{11}$C-OA) was synthesized as

Received Sept. 23, 1975; revision accepted March 8, 1976.

For reprints contact: Joanna Fowler, Dept. of Chemistry, Brookhaven National Laboratory, Upton, NY 11973.

follows: $^{11}$C-HCN (*14*) was trapped in 2 ml of 0.05 *M* NaOH and the solution evaporated to dryness. 1-Chloroheptane (0.005 ml in 0.1 ml of dimethylsulfoxide) was added and the mixture was heated and stirred at 130°C for 5 min. Water (0.1 ml) was added and the reaction mixture was extracted with pentane (2 ml). The pentane was dried ($K_2CO_3$ and KOH), and 0.5 ml of ether and 0.3 ml of $LiAlH_4$ (1 *M* solution in THF, Alfa Inorganics, Beverly, Mass.) were added at ambient temperature. After 2 min, 0.075 ml of 2.7% NaOH was added, the mixture was filtered, and the resulting solution extracted with 3 ml of 1 *N* HCl. Evaporation of the HCl extracts (10 mm, 60°C) yielded $^{11}$C-octylamine · HCl, which was dissolved in 0.9% saline for injection. The radiochemical yield was 30%, the synthesis time was 30 min, and the specific activity was about 2,000 Ci/mmole (*14*). Thin-layer chromatography of the product with carrier octylamine · HCl added (silica gel G; n-butanol–acetic acid–water 15:3:5; $R_f = 0.76$) showed that the activity coincided with the spot corresponding to the authentic octylamine · HCl detected by Ninhydrin. The only other basic product that could be produced in this reaction would be $^{11}$C-methylamine (by the reduction of unreacted H$^{11}$CN) and its absence was confirmed by thin-layer chromatography.

Albino New Zealand rabbits of either sex (4–6 kg), anesthetized with Surital (1.3 mg/kg), were injected in the marginal ear vein with 3–8 mCi of $^{11}$C-octylamine · HCl in 0.9% saline while positioned under a scintillation camera fitted with a pinhole (9-mm) collimator. Data were collected from the time of injection to 20–40 min after. The field of view was either the chest area alone or the entire animal. The activity in the whole body (minus the site of injection) at the time of injection was taken as the injected dose, and the percent sequestered by the lung was calculated from that value. In one experiment, the percent of the injected dose excreted as $^{11}CO_2$ was determined by trapping the expired $^{11}CO_2$ in $Ba(OH)_2$. The precipitated $Ba^{11}CO_3$ accounted for all of the radioactivity in the trap, confirming that the gas involved was $^{11}CO_2$. In some cases, $^{99m}$Tc-MAA (~1 mCi, Squibb, Princeton, N.J.) was administered after the octylamine study and $^{99m}$Tc lung scans were obtained for comparison with the octylamine. Numerical data from all dynamic studies were corrected for radioactive decay.

## RESULTS AND DISCUSSION

After intravenous injection, the $^{11}$C-octylamine · HCl was rapidly concentrated in the lungs. Initial uptakes at 1 min after injection were 70 ± 6% of the administered dose. Lung activity peaked at 40–60 sec and then began to fall, so that at 15 min approximately 40% of the injected dose remained (Fig. 1). The slope of the lung clearance curve shows that the activity is not simply a reflection of activity in the blood, but that the activity is associated with lung tissue. In normal animals the rates of clearance from different areas of the lung were uniform. During the first 30 min after injection, approximately 12% of the administered radioactivity was exhaled as $^{11}CO_2$.

Comparison of activity profiles and contour plots from static images indicated that the initial distribu-

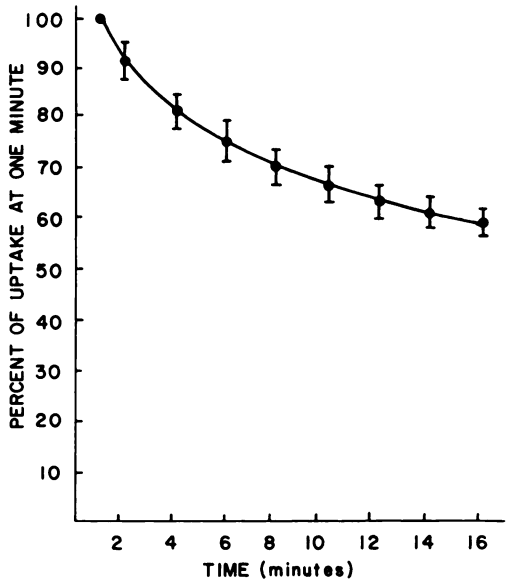


**FIG. 1.** Lung clearance of radioactivity after intravenous injection of $^{11}$C-octylamine · HCl into rabbits (each point represents mean ± s.d. of three rabbits).

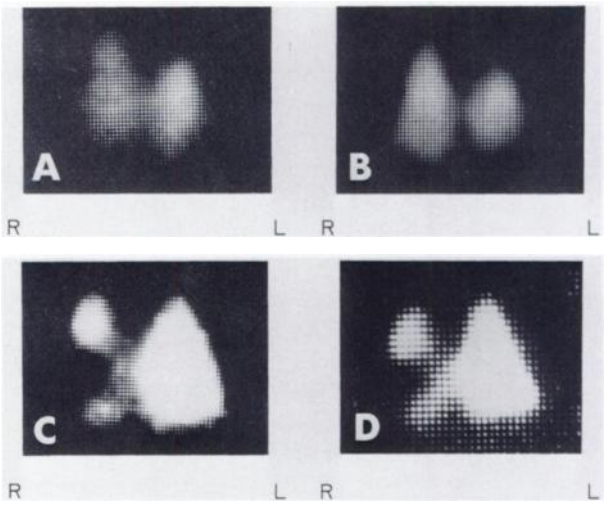


**FIG. 2.** Thoracic images obtained 1 min after injection of $^{11}$C-octylamine · HCl in normal rabbit (A) and rabbit with pleural abscess (C). For comparison, similar images were obtained with $^{99m}$Tc-MAA (B, D).

tion of $^{11}$C-octylamine was essentially the same as that for $^{99m}$Tc-MAA. This suggests that the initial distribution of radioactivity in the lung is mainly dependent upon blood perfusion. Thoracic images (Fig. 2) were obtained with $^{11}$C-octylamine · HCl and $^{99m}$Tc-MAA from a normal rabbit and a rabbit which, after necropsy and histopathologic study, proved to have a 3.5-cm-diam extrapulmonary chronic pleural abscess compressing the adjacent lobe of the right lung toward the midline.

In these preliminary studies with rabbits and in previous studies with mice (*13*), $^{11}$C-octylamine has been shown to be avidly sequestered by lung tissue and ultimately metabolized to $^{11}CO_2$. Therefore, its potential usefulness as a tool for studying the regulation of circulating amines is twofold. First, lung uptake of circulating amines can be assessed by radionuclide imaging after the injection of $^{11}$C-octylamine. Secondly, enzymatic oxidation by monoamine oxidase can be measured by collecting $^{11}CO_2$ expired during the imaging procedure. Although the pulmonary extraction of circulating amines has been discussed in general and an altered pulmonary uptake of biogenic amines has been found in pulmonary hypertension (*15*), the importance of this function of the lung is largely unknown. Similarly, abnormalities in monoamine oxidase activity have been implicated but not conclusively proven in such diverse disease states as hypertension (*16*), schizophrenia (*17*), depression (*18*), and migraine (*19*).

Further work is in progress to explore the usefulness of $^{11}$C-octylamine · HCl in the evaluation of pulmonary metabolic function and the assessment of monoamine oxidase activity in vivo.

## ACKNOWLEDGMENTS

This work was presented in part at the 22nd Annual Meeting of the Society of Nuclear Medicine, held in Philadelphia, June, 1975. The research was performed under the auspices of the U.S. Energy Research and Development Administration.

We thank David Christman for the preparation of the $^{11}$C-labeled cyanide used in this study, and Donald Sacker for technical assistance. We thank Jean Laissue for his help in the necropsy study.

## REFERENCES

*1.* HEINEMANN HO, FISHMAN AP: Nonrespiratory functions of mammalian lung. *Physiol Rev* 49: 1–47, 1969

*2.* TIERNEY DF: Lung metabolism and biochemistry. *Annu Rev Physiol* 36: 209–231, 1974

*3.* SAID SI: The lung in relation to vasoactive hormones. *Fed Proc* 32: 1972–1976, 1973

*4.* FISHMAN AP, PIETRA GG: Handling of bioactive materials by the lung. *N Engl J Med* 291: 889–890, 1974

*5.* GILLIS CN: Metabolism of vasoactive hormones by lung. *Anesthesiology* 39: 626–632, 1973

*6.* BROWN EAL: The localization, metabolism and effects of drugs and toxicants in lung. *Drug Metab Rev* 3: No. 1, 33–87, 1974

*7.* BAKHLE YS, VANE JR: Pharmacokinetic function of the pulmonary circulation. *Physiol Rev* 54: 1007–1045, 1974

*8.* STRUM JM, JUNOD AF: Radioautographic demonstration of 5-hydroxytryptamine-$^{3}$H uptake by pulmonary endothelial cells. *J Cell Biol* 54: 456–467, 1972

*9.* IWASAWA Y, GILLIS CN, AGHAJANIAN G: Hypothermic inhibition of 5-hydroxytryptamine and norepinephrine uptake by lung: Cellular location of amines after uptake. *J Pharmacol Exp Ther* 186: 498–507, 1973

*10.* NICHOLAS TE, STRUM JM, ANGELO L, et al.: Site and mechanism of uptake of $^{3}$H-norepinephrine by isolated perfused rat lungs. *Circ Res* 35: 670–680, 1974

*11.* ALABASTER VA, BAKHLE YS: The removal of noradrenaline in the pulmonary circulation of rat isolated lung. *Br J Pharmacol* 47: 325–331, 1973

*12.* BLASCHKO H: Amine oxidase and amine metabolism. *Pharmacol Rev* 4: 415–458, 1952

*13.* FOWLER JS, GALLAGHER BM, MACGREGOR RR, et al.: Carbon-11 labeled aliphatic amines in lung uptake and metabolism studies: Potential for dynamic measurements in vivo. *J Pharmacol Exp Ther*: to be published

*14.* CHRISTMAN D, FINN RD, KARLSTROM KI, et al.: The production of ultra-high activity $^{11}$C-labeled hydrogen cyanide, carbon dioxide, carbon monoxide, and methane via the $^{14}N(p,\alpha)^{11}C$ reaction. XV. *Int J Appl Radiat Isot* 26: 435–442, 1975

*15.* GILLIS CN, CRONAU LH, GREENE NM, et al.: Removal of 5-hydroxytryptamine and norepinephrine from the pulmonary vascular space of man: Influence of cardiopulmonary bypass and pulmonary arterial pressure on these processes. *Surgery* 76: 608–616, 1974

*16.* AXELROD J, WEINSHILBOUM R: Catecholamines. *N Engl J Med* 287: 237–242, 1972

*17.* WYATT RJ, MURPHY DL, BILMAKER R, et al.: Reduced monoamine oxidase activity in platelets: A possible genetic marker for vulnerability to schizophrenia. *Science* 179: 916–918, 1973

*18.* BOCKAR J, ROTH R, HENINGER G: Increased human platelet monoamine oxidase activity during lithium carbonate therapy. *Life Sci* 15: 2109–2118, 1975

*19.* SANDLER M, YOUDIM MB, HARRINGTON E: A phenylethylamine oxidizing defect in migraine. *Nature* 250: 335–337, 1974