

A POTENTIAL NEW BRAIN-SCANNING AGENT:

4-⁷⁷Br-2,5-DIMETHOXYPHENYLISOPROPYLAMINE (4-Br-DPIA)

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A centrally active drug containing bromine has been synthesized with ⁸²Br and ⁷⁷Br and appears to concentrate in normal human brain tissue, suggesting its potential use as a brain-scanning agent.

The detection of brain tumors and the localization of cerebral vascular disease depends on the enhanced uptake of tracer by abnormal brain tissues resulting from increases in vascular permeability and other incompletely understood phenomena. Normal brain is relatively, if not completely, impermeable to the radiopharmaceuticals most commonly employed for brain scanning. An agent that, conversely, concentrates in normally functioning brain tissues might be a useful adjunct to present scanning techniques.

In the course of a study of the human in vivo pharmacodynamics of 4-bromo-2,5-dimethoxyphenylisopropylamine (4-Br-DPIA), we have discovered that it accumulates in the brain. We had anticipated that this compound might be found in the brain because it is a central nervous system stimulant. Its pharmacodynamics were of interest because of this action and because of its structural relationship to dopamine metabolites and their possible involvement in schizophrenia. The complete details of the synthesis—in vivo distribution in the human body measured with the Anger Mark II whole-body scanner and a Hewlett-Packard 5047A computer, excretion measured with a whole-body counter, and urine analysis—are described elsewhere (1). Those aspects that are pertinent to possible application in nuclear medicine are presented here so that this or similar agents may be evaluated by other laboratories.

The compound, 4-Br-DPIA, is synthesized by direct bromination of 2,5-dimethoxyphenylisopropylamine (Fox Chemical Co., Los Angeles). We used ⁸²Br (New England Nuclear, spec. act. 4 mCi/mg) with a 35-hr half-life, and in one experiment ⁷⁷Br with a 57-hr half-life, made at the Lawrence Berkeley Laboratory 88-in. cyclotron with 25-MeV alpha

particles utilizing the ⁷⁵As (α 2n) ⁷⁷Br reaction. The 4-Br-DPIA was purified by solvent extraction, ion exchange, TLC separation, and passage twice through sterile Millipore filters. Animal studies indicated that the compound concentrated in the liver and had a low toxicity (mouse LD₅₀ 100 mg/kg). Pharmacologically, 4-Br-DPIA is a psychodysleptic with a minimal effective dose in humans of 0.2 mg. Our doses were, therefore, adjusted so that the chemical dose was well below this level, approximately 0.03 mg with 20–30 μ Ci of ⁸²Br or ⁷⁷Br. Based on the average maximum fraction of the administered dose observed in each organ (whole body 100%, liver 20%, brain 2%, and lung 12%) and the maximum observed biologic T_{1/2} of 17 hr, the radiation dose to each of these organs in millirads per microcurie was calculated. The dose to the bladder was calculated on the basis of 100% of the dose in the bladder for a mean time of 1 hr. For ⁸²Br the results were: whole body 0.5 mrad, liver 2.2 mrad, brain 0.22 mrad, lung 3.2 mrad, and bladder 2.0 mrad; for ⁷⁷Br the results were: whole body 0.21 mrad, liver 1.4 mrad, brain 0.16 mrad, lung 1.6 mrad, and bladder 1.0 mrad. In each of our experiments, therefore, the maximum dose to any organ was less than 100 mrad. We performed six experiments on four subjects, three of them intravenous and three oral.

Representative scintiscans with the Mark II whole-body scanner are shown in Figs. 1 and 2. When 4-⁸²Br-DPIA was given intravenously to Subject B (Fig. 1), the compound concentrated within 30 sec in the lung. At about 1 hr the concentration in the liver reached a maximum, and at 3½ hr it reached maximum concentration in the brain. A very slow scan (44 min) of just the head at this time showed

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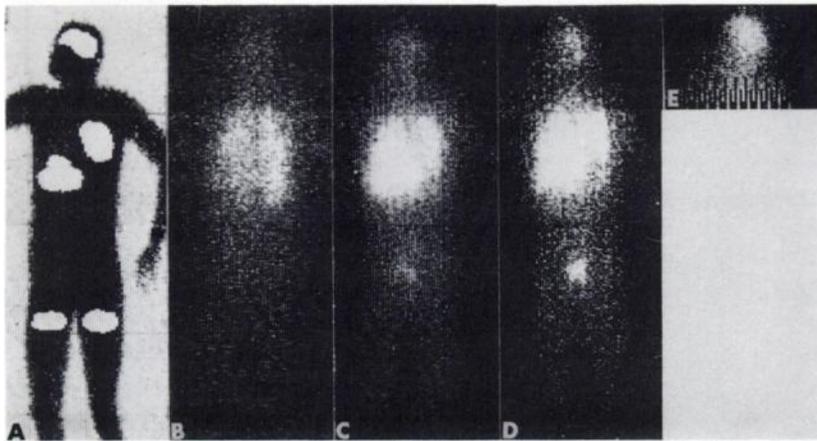


FIG. 1. Subject B. Scintiscans of i.v. ^{82}Br -DPIA with Mark II whole-body scanner, reproduced from data collected on-line and stored in HP 5047A computer. (A) This frame is body outline obtained from external beam of ^{241}Am of 60-keV gammas; it may be superimposed on subsequent scans for organ position reference (B, 1.5-min scan at 52 sec; C, 6-min scan at 60 min; D, 6-min scan at 3 hr, 27 min; and E, 44-min scan at 3 hr, 37 min). These time periods refer to total duration of scanning time, foot to head, begun at time indicated after administration of dose. White patches in B-E are areas of interest declared by light pen on computer for integration and study of time-course dynamics of organ concentration (1). All views are anterior.

clearly that the isotope was concentrated primarily in the brain area and considerably less in the facial muscles, bone, salivary glands, and nasopharyngeal structures. Figure 2 shows the results of oral administration of 4- ^{77}Br -DPIA in Subject D. After the initial appearance in the stomach, it concentrated in the liver at about 1 hr without appearing in lung as in the intravenous dose. Again it is concentrated in brain at about 4 hr. This particular subject excreted the compound rapidly as seen by the large accumulation in the bladder.

Briefly, computer analysis of the declared areas of interest showed that the sequence of peak organ concentrations was, for intravenous doses, lung (30 sec), liver (1 hr), plasma (2 hr), brain (3-4 hr); for oral doses, the sequence was the same with the exception that initial concentration did not occur in the lung. Using the thigh as a reference area for general tissue distribution, the ratio of concentration in brain to thigh was approximately 2.5:1. A complete presentation and analysis of these data are re-

ported elsewhere (1). The sequence just described suggests that the 4-Br-DPIA is metabolized to a secondary compound by the liver after which it is transported to the brain through the plasma. The Br remains organically bound, as evidenced by the fact that less than 5% of the Br in the urine is precipitable by acidic AgNO_3 . The initial uptake by lung is not due to macroaggregates formed in plasma because when 4-Br-DPIA was incubated with plasma at 37°C in vitro, the radioactivity passed completely through a 0.22-micron Millipore filter.

Bromine-82 was used to label 4-Br-DPIA because of its ready availability but the high-energy gammas (0.5-1.5 MeV) are poorly collimated. The gammas of ^{77}Br (principally 0.24 and 0.52 MeV) are somewhat better in this respect but 0.52 MeV is still too high for good collimation with a scintillation camera. Because the labeling chemistry can be done quite rapidly, shorter half-life isotopes of bromine would also be feasible. Bromine-76 with a half-life of 16.2 hr might be useful in a positron

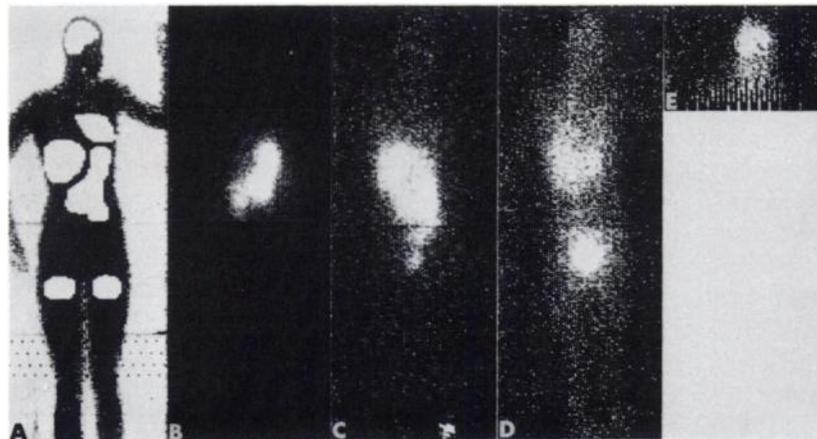


FIG. 2. Subject D. Scintiscans of oral 4- ^{77}Br -DPIA with whole-body scanner of another patient. Body outline (A) may be superimposed on subsequent scans for organ position reference (B, 6-min scan at 4 sec; C, 6-min scan at 1 hr, 14 min; D, 12-min scan at 3 hr, 9 min; and E, 44-min scan at 3 hr, 54 min). All views are anterior.

camera but it has gammas of 0.559 MeV, which would cause spurious coincidences; it is also difficult to produce free of ^{77}Br . Bromine-75 with a 1.7-hr half-life has an excellent 0.285-MeV gamma but also 0.511-MeV positron transformation gammas. Possibly it could be made free of other Br isotopes by the $^{74}\text{Se}(d,n)^{75}\text{Br}$ reaction. With the potential of efficient high-speed positron cameras coming into use, ^{76}Br and ^{75}Br would be the preferred isotopes.

Active accumulation of compounds in brain tissue is a relatively rare phenomenon, the only previous example of which we know being ^{11}C -labeled nitriles and hydantoins (2). The compound 4-Br-DPIA or similar compounds may in the future play a useful role in evaluating brain function and pathology. Localizing areas of decreased cerebral function due to disease and trauma and early detection of cerebral hemorrhage and thrombosis seem possible applications. To what extent brain tumors of various kinds concentrate 4-Br-DPIA is of obvious interest but is not yet known. Work still remains to determine the relative uptake of this drug by brain, and by the bone, muscle, skin, and other tissues of the head,

and to establish whether it will have useful applications as a brain-scanning agent.

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