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# HUMAN PHARMACODYNAMICS OF THE PSYCHODYSLEPTIC 4-BROMO-2,5-DIMETHOXY-PHENYLISOPROPYLAMINE LABELLED WITH $^{82}$Br

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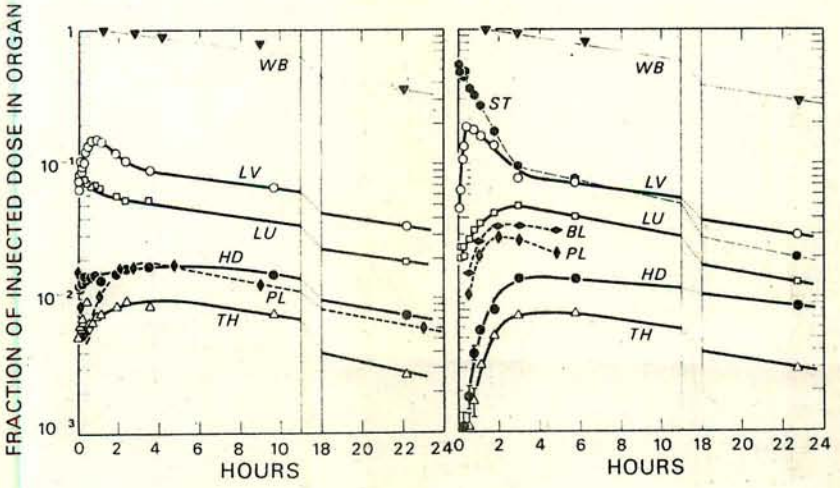
A centrally active psychodysleptic, 4-Bromo-2,5-dimethoxy-phenylisopropylamine (4-Br-DPIA) (1) was synthesized with $^{82}$Br ($T_{1/2}$ = 35 hr) at a specific activity of 1 mCi/mg and administered orally or intravenously to 4 human subjects in 6 experiments. The gamma radiation was measured externally *in vivo* with the Anger Mark II Whole-Body Scanner combined with a Hewlett Packard 5047A scintigraphic data computer, yielding both whole-body scan photos and digital data for specific organ areas.

A whole-body counter was used to measure the biological half life and the solvent extracted urinary metabolites of 4-$^{82}$Br-DPIA. Urinary metabolites were also studied by thin layer chromatography. Organ areas were outlined by light pen on the computer. Digital data analysis showed a striking first-pass accumulation of the intravenously injected compound in the lung. After release from lung, radioactivity accumulated in the liver, with a peak at one hour. Plasma radioactivity reached a braod peak at about two hours, and concentration in the brain reached a maximum at 3 hours, subsequently declining at the same rate as the total body activity.

When given orally, the organ concentration pattern was the same with the exception that early accumulation in the lung did not occur. Radioactivity concentrated in the lung at a rate parallel to that in the brain, after first reaching a peak in the stomach and then liver. The results of one i.v. and one oral experiment in the same subject are shown in the figure.




*Organ retention of 4-$^{82}$Br-DPIA after i.v. (left) and oral (right) administration. WB = whole body, ST = stomach, LV = liver, LU = lung, BL = whole blood, PL = plasma, HD = head, TH = thigh.*

Maximum excretion rate in all urine fractions was found at 2-3 hours. From 60% to 92% of the radioactivity was excreted in a form that was water-soluble and highly polar, but was not inorganic bromide ion (not precipitable with acidic silver nitrate). The $^{82}$Br can thus be assumed to have remained organically bound and hence serves as a tracer for 4-Br-DPIA and its various metabolites. Extraction of urine gave a free base fraction containing 2-30% of the radioactivity and unchanged 4-Br-DPIA. The biological half-life, as measured by whole-body counting, varied from 4 to 23 hours in the various human subjects, the shorter half-life correlating with greater excretion of water-soluble metabolites. TLC analysis of dansylated urinary excretion products showed several radioactive spots: (a) one identical with the original compound; (b) another, possibly a β-hydroxylated metabolite; and (c), two others highly polar, believed to be O-conjugated metabolites. The striking accumulation of this compound in the lung, shown here for the first time in humans, corresponds with the finding of Eichelbaum et al. (2) for chlorphentermine in the lung of rats, rabbits and pigs. The sequence of organ peak times (lung–liver–blood–brain) suggests that the active psychodysleptic may be a metabolite rather than the original compound.

The potential of 4-Br-DPIA as a diagnostic scanning agent for human brain and lung visualization in Nuclear Medicine is being explored.

1. Shulgin, A.T., Sargent, T. and Naranjo, C. (1971) *Pharmacology* **5**, 103
2. Eichelbaum, M., Hengstmann, J.H. and Dengler, H.J. (1970) *Naunyn-Schmiedebergs Arch. Pharmak.* **267**, 446

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