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SHORT COMMUNICATIONS

2,5-Dimethoxy-4-methyl-amphetamine—Tissue distribution and neurochemical action

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2,5-DIMETHOXY-4-METHYLAMPHETAMINE (STP, DOM) has a hallucinogenic effect in humans. It is about 50–100 times more potent than mescaline, but is 30–50 times less active than lysergic acid diethylamide (LSD).[1, 2] In cats it antagonizes ether anesthesia and causes first a catatonic stage terminating in a violent aggressive reaction with growling, hissing, biting and clawing.[3] We have studied the absorption, tissue distribution and elimination of ^{3}H-labeled STP in mice, using total body autoradiography and chromatography, and the effect of STP on brain amines.

STP was synthesized and labeled with tritium* in positions 3 and 6 using a tritium–hydrogen exchange reaction as reported earlier.[3, 4] The chemical and radiochemical purity of the compound (sp. act., 360 μc/mg) was ascertained by thin-layer chromatography (Silica gel G) and infrared spectroscopy. The chromatograms were developed in three systems: (A) chloroform–butanol (1:1, v/v); (B) butanol–acetic acid–water (4:1:1, v/v); (C) isopropanol–butanol–acetic acid–water (10:1:1:1, v/v). Autoradiograms and ultraviolet fluorescence were used to detect STP-^{3}H on the plates.

Sixteen male (22–24 g) and six pregnant female (42–46 g) mice (Yale–Swiss) received i.v. doses of 10 μc/g (28 mg/kg; male mice) or 5 μc/g (female mice) of STP-^{3}H. The animals were sacrificed at 5 and 20 min, and at 1, 2, 6 and 24 hr after the injection by dropping them into a mixture of hexane and solid carbon dioxide at approximately $-70°$. Ten male mice received STP-^{3}H (10 μc/g) orally and were decapitated at different time intervals. Sagittal sections, 30–60 μ thick, through the whole frozen animals were cut with a Jung model K microtome in the freezer at $-10°$. The autoradiography of the total body sections and the evaluation of the results were performed as previously described.[5–7] The sections were exposed both on Kodak RP/S X-omat Medical X-ray films and on Ilford Nuclear Research Plates G5 (emulsion thickness 50 μ) for 20 weeks.

To obtain quantitative measurements, the frozen organs were dissected and homogenized with methanol (100 mg tissue/ml of homogenate) and their radioactivities were counted by liquid scintillation. The amount of unchanged STP-^{3}H was identified by thin-layer chromatography using the solvents systems described above. The amount of labile tritium in tissue homogenates varied from 0·4 to 0·6 per cent. The identity of the isolated compound with authentic STP was ascertained by the isotope dilution method and by mixed melting point.

To study the effect of STP on brain amine levels, 44 female (20–22 g) mice (Yale–Swiss) were injected intraperitoneally with 10 or 50 mg/kg of STP while 12 control mice received only saline. The animals were decapitated at 30, 60 and 120 min after administration; the brains were removed and homogenized with 0·01 N HCl. Norepinephrine (NE) and 5-hydroxytryptamine (5-HT) were extracted from the homogenates and the amounts of these amines were measured spectrophotofluorometrically as described earlier.[8–10] Recovery of added amines was satisfactory and the presence of STP in the solutions did not interfere with the fluorometric assay.

The whole body tremor, later noted only in the legs, was the major pharmacological effect recorded with STP. The motor activity of the animals was slightly increased, and they showed a special sensitivity to external auditory stimuli and to the touch. These sympathomimetic effects lasted up to 3–4 hr. Absorption of the compound from the gastrointestinal tract declined rapidly, indicating a complete absorption (Fig. 1, right panel).

Five minutes after i.v. administration, the brain had twice the radioactivity of the blood. The

* The 2,5-dimethoxy-4-methyl-amphetamine (STP,DOM) as well as the tritiated STP was synthesized and provided to us by Dr. Beng T. Ho and Wayne Tansey, M.S., to whom we are greatly indebted.

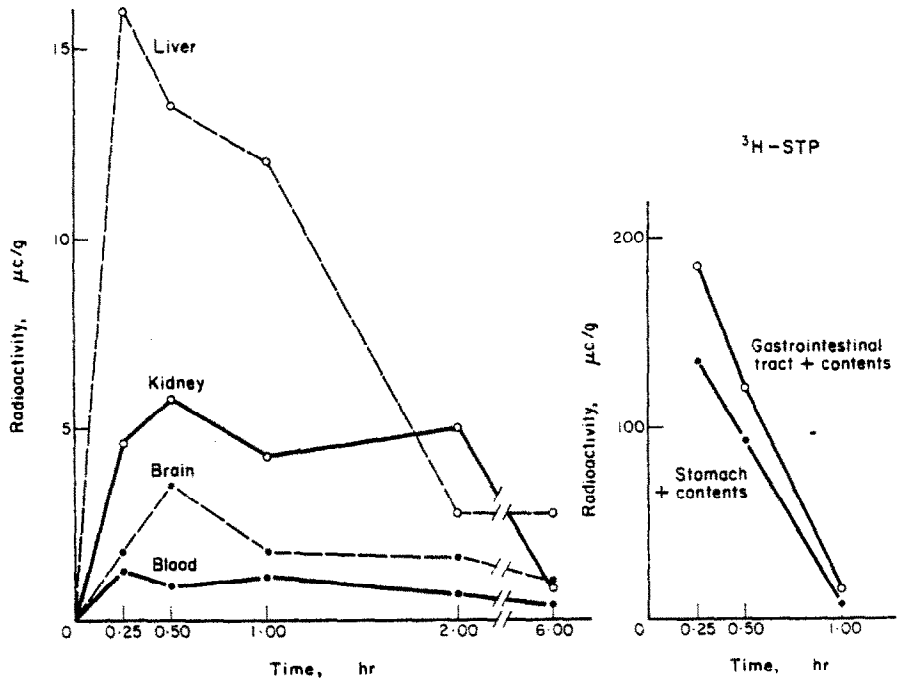

FIG. 1. Radioactivity in mouse organs after oral administration of STP-^{3}H. The dose was 10 μc/g (28 mg/kg). Note the sharp decline in the radioactivity of the gastrointestinal tract in the graph on the right, indicating fast and complete absorption.

TABLE 1. DISTRIBUTION OF RADIOACTIVITY IN MOUSE TISSUES AFTER AN I.V. INJECTION OF STP-^{3}H*

Sample	Radioactivity present at postmedication intervals of†		
	20 min	1 hr	6 hr
Blood	1·74 (53·6)	0·74 (32·2)	0·03 (17·2)
Brain	6·37 (39·7)	6·03 (26·6)	0·18 (13·2)
Liver	14·03 (36·2)	12·28 (30·5)	0·06 (10·2)

* The dose of STP-^{3}H was 10 μc/g (28 mg/kg).
† The mean value of three animals is given in μc/g of tissue or in μc/ml of blood. The values in parentheses represent the percentage of radioactivity present as unchanged STP.

highest concentration was obtained at 20 min (Table 1) and this level remained up to 2 hr. These results indicate that STP penetrates the blood–brain barrier rapidly and has a relatively high affinity for the brain tissue, where the concentration remained continuously higher than that in the blood up to 6 hr (Table 1). First the cortex, then later both the white matter and thalamus, showed remarkable accumulations. At 1 hr, however, the hippocampus exhibited the highest content of radioactivity in the brain and kept this up to 6 hr. The same observation has been made earlier in cats with STP[3] and with LSD in mice.[11]

Next to urine, kidney and liver showed the highest concentration of radioactivity (Fig. 2). At 24 hr, 61 per cent of the injected radioactivity had been excreted in urine, indicating that this is the main

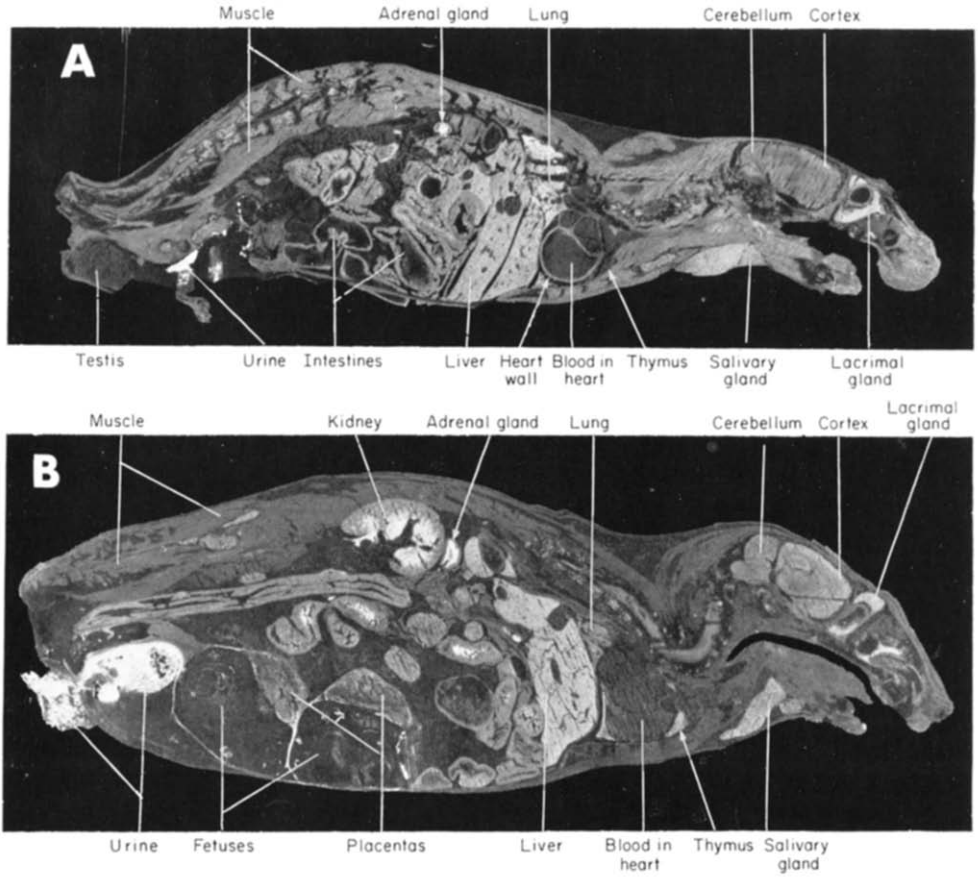

FIG. 2. The total body distribution of radioactivity (light areas) in mice 20 min (A) and 1 hr (B) after STP-^{3}H was injected into the tail vein. Note the high accumulations in urine, kidney, liver and adrenals, and in lacrimal and salivary glands.

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elimination route. There was a remarkable concentration of radioactivity in the liver which was long-lasting. Little accumulation, however, was evident in the intestinal contents, indicating the relatively minor role of biliary excretion of STP and its metabolites (Table 1, Fig. 2).

The high uptake of radioactivity in salivary and lacrimal glands (Fig. 2), which was constant up to 6 hr, may indicate the excretion of STP through these organs. The same observation earlier with LSD by one of us[11] suggests the possibility of utilizing saliva for the clinical detection of abuse of these hallucinogenic compounds.

Pituitary, thymus, ovaries and testes all accumulated a considerable amount of radioactivity, but so far there has been no report of the effect of STP on endocrine function. In adrenals, a high and long-lasting accumulation was observed both in the cortex and medulla (Fig. 2). At 6 hr, the adrenal medulla showed the highest radioactivity of all the mouse tissues in autoradiograms.

STP crossed the placenta slowly and only traces of radioactivity were found in fetuses 5 and 20 min after i.v. injection. The peak concentration was obtained at 1 hr (Fig. 2B). The placental radioactivity was constantly two to three times higher than the maternal blood concentration.

A dose level of 10 mg/kg of STP did not change significantly the brain amines in mice. At a dose of 50 mg/kg, brain norepinephrine was increased by 22·5 per cent 1 hr after i.p. injection, whereas 5-HT showed only a slight elevation of 5·0 per cent. At 2 hr, no detectable change was noted in brain amines.

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