REGIONAL LOCALIZATION OF [14C]MESCALINE IN RABBIT BRAIN AFTER INTRAVENTRICULAR ADMINISTRATION
Effects of Chlorpromazine and Iproniazid Pretreatment

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Albino rabbits of either sex were anesthetized, and a cannula was implanted permanently into the lateral ventricle. About 1 week later, the distribution of [14C]mescaline and its deaminated metabolite, [14C]trimethoxyphenylacetic acid ([14C]TMPA) in 12 brain regions was examined at 15, 60, and 180 min after the intraventricular injection of [14C]mescaline (0.5 μmol in 0.05 ml saline). 14C-radioactivity was rapidly distributed in all regions, reaching peak levels within 15 min. The spinal cord, superior colliculus, pons, hypothalamus, caudate, medulla oblongata, and inferior colliculus contained 23-57 nmol/g of mescaline; the thalamus, tegmentum, and cerebellum, 12-15 nmol/g; and the cerebrum and hippocampus, less than 10 nmol/g; the levels of [14C]TMPA ranged from 0.5 to 5 nmol/g. The levels of [14C]mescaline and of [14C]TMPA in all brain areas were considerably decreased 180 min after its injection. Pretreatment with chlorpromazine (15 mg/kg, i.p., 30 min) lowered [14C]mescaline concentrations in the hippocampus, caudate, thalamus, and cerebrum and elevated them in the spinal cord, medulla oblongata, pons, and tegmentum; [14C]TMPA levels as the percentage of total radioactivity were not affected. Pretreatment with iproniazid (150 mg/kg, i.p., 18 h), on the other hand, uniformly reduced the TMPA levels in

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all brain areas, with the resultant increases in mescaline levels. The CPZ-effect in lowering the mescaline concentrations in the areas belonging to the limbic system may have significance in explaining its antihallucinogenic effect in humans and its ability to block the altered behavior induced by the latter drug in laboratory animals.

INTRODUCTION

The pattern of distribution of a drug in the central nervous system (CNS) may offer a clue to its site and mode of action. A previous study by one of us examined the regional localization of 3,4-dimethoxyphenylethylamine (DMPEA) in the brain of rabbits (1). DMPEA was found to be accumulated in high concentrations in some brain areas belonging to the extrapyramidal system, and a causal relationship was proposed between this pattern of localization and the ability of the drug to induce hypokinetic rigidity syndrome (2-4).

Mescaline, a known hallucinogen in humans (5) and closely related structurally to dopamine and DMPEA, has been extensively studied in humans (6,7), rats (8-10), and mice (11-14). Even though the hallucinogenic site of action of mescaline is the CNS, the drug crosses the blood-brain barrier in the adult rat with difficulty (15). In the present study, our attempts to examine the regional distribution of mescaline in the rabbit brain following the intravenous injection failed mainly because of its poor penetration in the CNS. We, therefore, examined the regional distribution of [14C]mescaline in the rabbit brain after its intraventricular injection. Attempts were also made to study the effects of chlorpromazine (CPZ) and of iproniazid on the regional localization of [14C]mescaline.

EXPERIMENTAL PROCEDURE

[8,14C]mescaline hydrochloride (sp. act. 10 mCi/mmol) and (U)-[14C]sorbitol (sp. act. 8.7 mCi/mmol) were purchased from New England Nuclear Corp., (Boston, Massachusetts) and Amersham/Searle Corp. (Des Plaines, Illinois), respectively. Ketamine hydrochloride was purchased from Parke Davis and Company (Detroit, Michigan). Chlorpromazine hydrochloride and iproniazid phosphate were donated by Smith, Kline and French Laboratories (Philadelphia, Pennsylvania) and Hoffmann-La Roche, Inc. (Nutley, New Jersey), respectively.

Cannulation of Lateral Ventricle. Albino rabbits of either sex weighing 2.5-3.9 kg were used. They were anesthetized by i.m. injection of a mixture of ketamine (55 mg/kg) and CPZ (5 mg/kg). The head was shaved and placed in a stereotaxic instrument (David Kopf Instruments, Tujunga, California) with the bregma 1.5 mm higher than the lambda. The skin overlying the skull was retracted, and burre holes were drilled for the implantation of a