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OXIDATIVE METABOLISM OF MESCALINE IN THE CENTRAL NERVOUS SYSTEM—II

OXIDATIVE DEAMINATION OF MESCALINE AND 2,3,4-TRIMETHOXY-β-PHENYLETHYLAMINE BY DIFFERENT MOUSE BRAIN AREA *IN VITRO*

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Abstract—The oxidative deamination of mescaline (3,4,5-trimethoxy-β-phenylethylamine) and 2,3,4-trimethoxy-β-phenylethylamine was studied using mouse brain homogenates. The deamination of these phenylethylamines is slow. It is inhibited by inhibitors of MAO and not by inhibitors of DAO. High concentrations of mescaline and chlorpromazine inhibit the deamination of 2,3,4-trimethoxy-β-phenylethylamine. Mescaline oxidation is depressed by its 2,3,4-isomer, but not by chlorpromazine. The ratio of oxidation velocities of the two trimethoxy-β-phenylethylamines is fairly constant with tissue from many brain structures, with the exception, that mescaline is relatively more actively deaminated by cerebellar homogenates than its 2,3,4-isomer.

IN A PAPER published recently from our laboratory[2] it was demonstrated by autoradiography, that mescaline (3,4,5-trimethoxy-β-phenylethylamine) is localized nearly exclusively in the hippocampus of mice, 6 hr after the administration of this psychotomimetic compound. In the meantime other findings have been recorded on the regional distribution of hallucinogenic substances in the brain (LSD-25, psilocin, 2,4-dimethoxy-4-methylamphetamine) and on compounds, which influence hallucinations in man (chlorpromazine, oxypertine etc).[3–10] These observations suggest a significant role of the hippocampus in the storage, and possibly in the mode of action of the hallucinogens.

There appears to be no experimentally based theory to account for the ability of the hippocampus to store structurally very dissimilar substances, though differences in the cerebral capillarization and in metabolic parameters have been discussed.[3]

We have started a series of attempts to clarify mescaline storage and metabolism in mouse brain. It could not be excluded in advance, that differences in oxidation activities of the various regions of mouse brain caused the different velocities of mescaline elimination from brain. Though it seemed not very promising, we nevertheless tested this hypothesis, especially since mescaline metabolism by brain tissue was scarcely examined hitherto.[11] In parallel to the oxidation of mescaline we studied the oxidative degradation of 2,3,4-trimethoxy-β-phenylethylamine by brain homogenates. This latter substance, though very closely related to mescaline, is according

to a remark of Slotta[12] not hallucinogenic in normal persons, but has more hallucinogenic potencies than mescaline in schizophrenics. This compound was found to be inactive in two behavioural indices for psychotomimetic agents in animal experiments as well.[13] The metabolism of 2,3,4-trimethoxy-β-phenylethylamine seems to be entirely uninvestigated.

MATERIALS AND METHODS

Male albino mice (NMRI, Gesellschaft für Versuchstierzucht, Hannover) (25–30 g) were used in all experiments.

8-[^{14}C]mescaline.HCl (specific activity 4·5 mc/mM) was purchased from New England Nuclear Corporation, Boston. 2,6-[^{3}H]mescaline.HCl (specific activity 24·2 mc/mM) and 5,6-[^{3}H]2,3,4-trimethoxy-β-phenylethylamine.HCl (specific activity 15·5 mc/mM) was obtained by electrophilic substitution of 3,4,5-trimethoxy-β-phenylethylamine sulfate (3,4,5-TMPEA) and 2,3,4-trimethoxy-β-phenylethylamine hydrochloride (2,3,4-TMPEA) respectively with BF_3 saturated phosphoric acid in tritium water, according to Seiler *et al.*[14] In analogy to this method 3,4,5-trimethoxyphenylacetic acid (3,4,5-TMPAA) was also labelled (specific activity 64·2 mc/mM). The purity of these compounds was controlled by thin-layer chromatography on silica gel G; solvent system: tert. butanol–2-oxobutane–25% ammonia–water (4:3:2:1 by vol.), and by mass spectrometry.

Determinations of the oxidation velocities of mescaline and 2,3,4-trimethoxy-β-phenylethylamine by brain homogenates: Determinations of oxidation velocities of the β-phenylethylamines were achieved by means of tritiated substrates and measurement of the reaction products formed. The procedure was as follows: The animals were killed by decapitation and the brains were quickly removed from the skull. For preparation of different parts, the mouse brains were frozen with dry ice and the following parts were dissected at −15° with a small scalpel: Neocortex, hippocampus, the region around *N.* amygdalae, thalamus, hypothalamus, cerebellum. The different preparations were controlled by histological methods and found to be sufficiently pure for the intended experiments. Whole brain homogenates and homogenates of the different parts of the brain were prepared with 3 vol. of ice cold 0·06 M phosphate buffer pH 7·2 with a Potter–Elvehjem glass homogenizer. Three-ml portions of these homogenates were frozen and stored at −20° up to 7 days. Before use these homogenates were brought to 2° and rehomogenized.

Incubation. To 0·3 ml of homogenate 0·1 ml of substrate solution (2,5-[^{3}H]3,4,5-TMPEA.HCl and 5,6-[^{3}H]2,3,4-TMPEA.HCl respectively in the same buffer) was added. Forty μl samples of these mixtures were incubated in test tubes (12 × 60 mm). Filter paper strips saturated with 1 N KOH were fixed above the reaction mixture, in order to absorb the CO_2 generated during incubation. The sealed test tubes were shaken at 38° in a water bath. The reaction was stopped by addition of 0·2 ml 0·2 N $HClO_4$ at different time intervals (0, 3, 6, 12 and 18 hr). The perchloric acid reaction mixtures were neutralized with 20 μl 2 N K_2CO_3 and then 1 ml ethanol was added. In order to accomplish the precipitation of proteins and $KClO_4$, the samples were stored for 12 hr at 4°. Neutral and anionic substances were separated from the cationic compounds of the reaction mixture by ion exchange chromatography on cellulose phosphate in the following manner: Glass tubes (7 × 140 mm) with one tipped end were filled with a suspension of cellulose phosphate (SP-7, Mikrotechnik,

Miltenberg or Whatman P 11) in water–methanol (1:2, v/v). After the cellulose phosphate had sedimented, the column end was sealed by a cotton plug, as was the tipped end before. These columns could be stored in a jar with methanol–water vapor saturated atmosphere. The wide ends of the columns were directly inserted into the test tubes with the above described samples. Then the contents of the test tubes were transported through the columns with a velocity of 1 ml/hr by suction directly into sample vessels for liquid scintillation counting. Proteins and $KClO_4$ were retained by the cotton plug. Elution of the anionic and the neutral components ("anion fraction") of the reaction mixture was accomplished by successive washings with 3 × 3 ml methanol.

The eluate was evaporated in a stream of air to approximately 1 ml. For radioactivity measurement 1 ml of methanol and 10 ml of a liquid scintillator (50 g naphthalene, 7 g PPO and 50 g POPOP per l. dioxane) were added. Radioactivity was measured with a Packard Tri-Carb model 3375. Average counting efficiency: 10–15 per cent. Recovery of 2,6-[^{3}H]3,4,5-TMPAA: 97·6 ± 2 per cent.

The column effluents contained no radioactive cationic compounds, as was demonstrated by thin-layer electrophoresis on silica gel thin-layers; buffer pH 4·8: 40 ml pyridine, 30 ml acetic acid and 12 g citric acid per 930 ml water. Main reaction products of 3,4,5-TMPEA and 2,3,4-TMPEA deaminations were in accordance with earlier findings on mescaline oxidation by brain homogenates *in vitro*[1] 3,4,5-TMPAA and 2,3,4-TMPAA respectively. These substances were esterified to a large extent on the cellulose phosphate columns during their elution with methanol, as was proven in addition to electrophoresis by thin-layer chromatography (method see above).

The method described for the measurement of deamination of phenylethylamines is based on the determination of the radioactivity present in the neutral and anionic derivatives of these compounds after their incubation with tissue homogenates. Though we have shown, that under the conditions of incubation with brain homogenates main reaction products of the phenylethylamines were the respective phenylacetic acids, it cannot be excluded completely, that small amounts of acylated phenylethylamines are formed during incubation. But the formation of non-deaminated neutral derivatives in small amounts would only feign somewhat higher reaction velocities, as compared to the true deamination velocities, without influencing the results basically.

In the reaction mixtures, in which the oxidation reaction was stopped immediately after the addition of the radioactive substrates 0·14 per cent in case of 2,6-[^{3}H]3,4,5-TMPEA and 0·2 per cent in case of 5,6-[^{3}H]2,3,4-TEMPEA of the total radioactivity added was found in the anion fraction. This amount of radioactivity ("zero value") was subtracted from the radioactivity measured in the anion fraction of each incubated reaction mixture.

The exchange of tritium from [^{3}H]TMPEA and from [^{3}H]TMPAA under the conditions of our procedure could be excluded by double label experiments. Details will be described elsewhere.

Inhibition of the oxidative deamination of mescaline and 2,3,4-trimethoxy-β-phenylethylamine: Inhibitors were dissolved in 0·06 M phosphate buffer pH 7·2. Twenty μl aliquots of the inhibitor solutions were added to 0·3 ml of brain homogenate and preincubated for 5 min at room temperature. (To controls 20 μl buffer solution

was added.) After 0·1 ml of the substrate solution had been mixed with the pre-incubated homogenate sample, 40 μl aliquots were incubated for 3 hr at 38°. The further procedure was as described above.

RESULTS

Oxidative deamination of the phenylethylamines was at constant velocity for at least 12 hr under substrate saturated conditions.

Figure 1 demonstrates the dependence of oxidation velocity from substrate concentration for mescaline and for 2,3,4-trimethoxy-β-phenylethylamine. Substrate saturation of the enzymatic reaction was observed at concentrations above 10 mM/l. in case of mescaline. Under the conditions described, the maximal reaction rate was round 5 nM/g fresh weight/min.

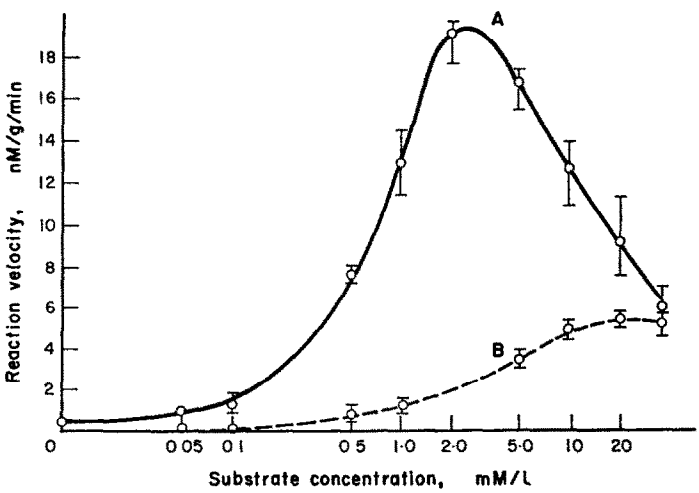

FIG. 1. Dependence of deamination velocities by whole mouse brain homogenates of 2,3,4-trimethoxy-β-phenylethylamine (A) and 3,4,5-trimethoxy-β-phenylethylamine (mescaline) (B) from substrate concentration. Reaction conditions: 0·06 M phosphate buffer pH 7·2; 38°. Ordinate: reaction velocity nM/g fresh weight/min; abscissa: substrate concentration mM/l. (logarithmic scale).

The 2,3,4-isomer of mescaline is oxidized more rapidly than 3,4,5-TMPEA, at least by a factor 3. And, interestingly enough, the enzymatic degradation of this compound is inhibited by high substrate concentrations. Michaelis–Menten constants K_m were found to be approximately 0·5–0·7 mM/l. for 2,3,4-TMPEA and 3 mM/l. for 3,4,5-TMPEA. In Table 1 the influence of some inhibitors of amine oxidases on the oxidation velocity of mescaline and 2,3,4-TMPEA by mouse brain homogenates are shown. In accordance with our previous findings[1] mescaline oxidation by brain homogenates is inhibited by typical MAO inhibitors, but not by inhibitors of diamine oxidase.

Under the standardized reaction conditions applied, the inhibition of 2,3,4-TMPEA deamination in comparison to the deamination of mescaline was more pronounced by non-hydrazinic MAO inhibitors and by chlorpromazine. The latter

TABLE 1. INHIBITION OF THE OXIDATIVE DEAMINATION BY WHOLE MOUSE BRAIN HOMOGENATES OF MESCALINE (3,4,5-TRIMETHOXY-β-PHENYLETHYLAMINE; 3,4,5-TMPEA) AND 2,3,4,-TRIMETHOXY-β-PHENYLETHYLAMINE (2,3,4-TMPEA). REACTION CONDITIONS: pH 7·2 (0·06 M PHOSPHATE BUFFER); 38°; SUBSTRATE CONCENTRATION: 10 mM/l. (AVERAGE VALUES OF TWO DETERMINATIONS)

Inhibitor	Inhibitor concentration (mM/l.)	Mescaline Inhibition % of control value	2,3,4-TMPEA Inhibition % of control value
Iproniazid (N_2-isopropyl-iso-nicotinic acid hydrazide phosphate)	1·0	56	23
Semicarbazide.HCl	1·0	14	1
Tranylcypromine (trans-2-amino-1-phenyl-cyclopropane sulfate)	1·0	68	83
Pargyline (*N*-methyl-*N*-benzyl-propargylamine.HCl)	1·0	56	87
n-Octanol	saturated solution	0	16
Potassium cyanide	1·0	0	11
Chlorpromazine (2-Chloro-10-(3'-dimethyl-1'-propyl)phenothiazine)	1·0	0	41
	0·1	—	0

compound lowered the oxidation velocity of 2,3,4-TMPEA at 1 mM/l. to approximately 60 per cent of the control value, while the oxidation of mescaline was not influenced at this concentration.

Hydrazine derivatives were more potent inhibitors of mescaline deamination than of the oxidative deamination of 2,3,4-TMPEA.

A further analysis of the inhibitory action of chlorpromazine on the oxidative degradation of 2,3,4-TMPEA by brain homogenates showed interesting relations: While at a concentration of 1 mM/l. chlorpromazine inhibited the oxidation of

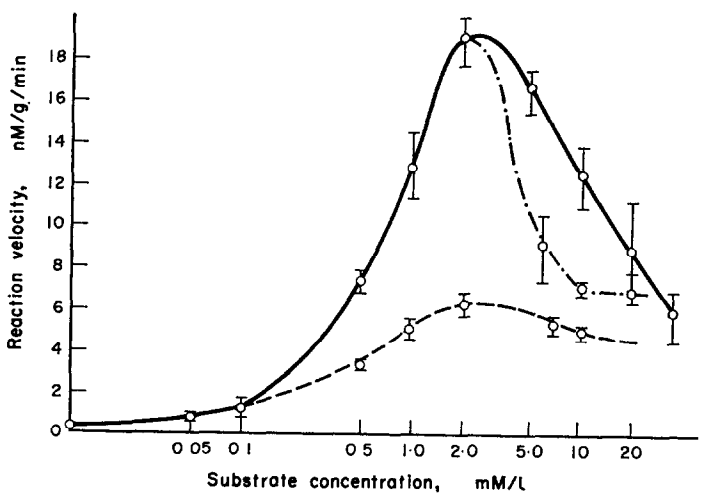

FIG. 2. Inhibition of oxidative deamination of 2,3,4-trimethoxy-β-phenylethylamine by chlorpromazine (CPZ). ———— without CPZ; –.–.–.–.–. 1 mM/l. CPZ; ---------- 5 mM/l. CPZ. (Reaction conditions see Fig. 1 and Material and Methods.)

2,3,4-TMPEA to the mentioned extent at substrate concentrations above 5 mM/l., there was no substantial inhibition to be seen at substrate concentrations below 2 mM/l. (Fig. 2). Further increase of chlorpromazine concentration in the incubation mixture to 5 mM/l. effected the depression of the oxidation rate of 2,3,4-TMPEA to a maximal rate of approximately 5 nM/g/min, i.e. to reaction velocities, as were measured for the degradation of mescaline without any inhibitor; with the only difference, that considerable oxidative deamination of 2,3,4-TMPEA could be demonstrated already at relatively low substrate concentrations, whereas mescaline is oxidized with an appreciable velocity only at substrate concentrations above 0·5 mM/l. (Fig. 1).

A similar situation is observed, if mescaline is present in the incubation mixture together with radioactive 2,3,4-TMPEA. But even higher concentrations of mescaline are necessary for the depression of the 2,3,4-TMPEA oxidation rate to the level of maximal mescaline oxidation velocity, as have been needed of chlorpromazine (Fig. 3).

Reversedly, 2,3,4-TMPEA inhibits the oxidative degradation of mescaline by brain tissue *in vitro* at high concentrations. The Lineweaver–Burk plot[15] in Fig. 4 shows, that this inhibition is of the reversible type.

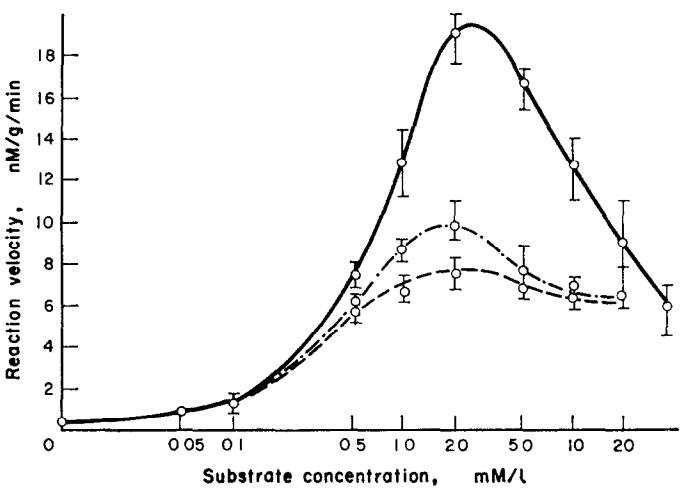

FIG. 3. Inhibition of oxidative deamination of 2,3,4-trimethoxy-β-phenylethylamine by mescaline. HCl (3,4,5-TMPEA). ———— without 3,4,5-TMPEA; –.–.–.–.–.– 5 mM/l. 3,4,5-TMPEA; ---------- 10 mM/l. 3,4,5-TMPEA. (Reaction conditions see Fig. 1 and Material and Methods.)

In Table 2 regional differences of oxidation capacities of mouse brain are shown for 2,3,4-TMPEA and 3,4,5-TMPEA as substrates under standardized conditions. The highest oxidation activity was found with tissue samples from the hypothalamic region, the lowest activities with samples from hippocampus and neocortex, among the brain regions so far studied. Most of the brain regions had lower oxidation capacities as compared to whole brain. The ratio between the oxidation velocity of 3,4,5-TMPEA and 2,3,4-TMPEA was fairly constant with one 'exception: the cerebellar oxidation rate of mescaline is relatively higher than that of 2,3,4-TMPEA.

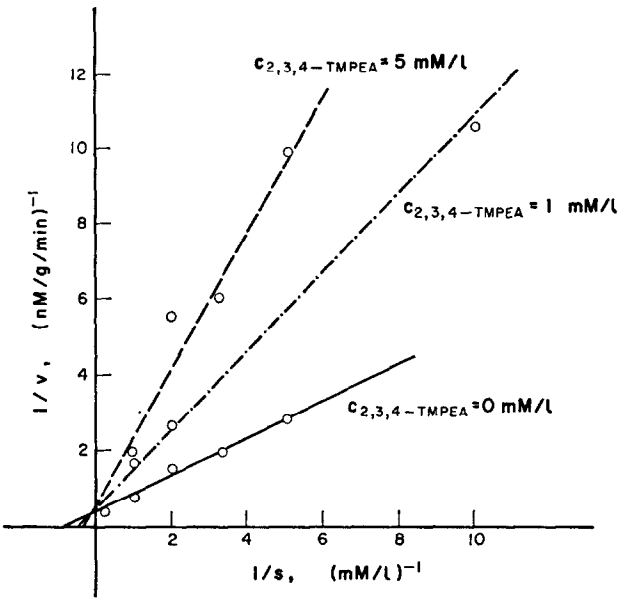

FIG. 4. Lineweaver–Burk-plot of the inhibition of oxidative deamination of mescaline by 2,3,4-trimethoxy-β-phenylethylamine (2,3,4-TMPEA). ———— without 2,3,4-TMPEA; –.–.–.–.–.–. 1 mM/l. 2,3,4-TMPEA; ---------- 5 mM/l. 2,3,4-TMPEA. (Reaction conditions see Fig. 1 and Material and Methods.)

DISCUSSION

Our present results confirm our earlier findings concerning the oxidation of mescaline by brain tissue *in vitro* with a different analytical procedure. In contrast to current view[16] mescaline is deaminated by brain tissue to a small but measurable extent. The enzymes involved in this reaction have different properties as the comparable liver enzymes. The oxidative degradation of mescaline by brain tissue is not inhibited by

TABLE 2. OXIDATIVE DEAMINATION OF MESCALINE. HCl (3,4,5-TRIMETHOXY-β-PHENYLETHYLAMINE. HCl; 3,4,5-TMPEA) AND 2,3,4-TRIMETHOXY-β-PHENYLETHYLAMINE. HCl (2,3,4-TMPEA) BY HOMOGENATES OF DIFFERENT REGIONS OF MOUSE BRAIN. REACTION CONDITIONS: pH 7·2 (0·06 M PHOSPHATE BUFFER); 38°; SUBSTRATE CONCENTRATION: 10 mM/l.

Region	Deamination velocity $v_{3,4\ 5-TMPEA}$ (nM/g/min)	Relative deamination velocity* of 3,4,5,-TMPEA	Deamination velocity $v_{2,3,4,-TMPEA}$ (nM/g/min)	Relative deamination velocity* of 2,3,4,-TMPEA	$\frac{v_{3,4,5-TMPEA}}{v_{2,3,4-TMPEA}}$
Neocortex	2·5 ± 0·5	0·56	8·1 ± 0·7	0·67	0·30
Hippocampus	2·3 ± 0·2	0·53	9·0 ± 0·3	0·76	0·25
Amygdala region	3·7	0·84	11·9 ± 0·1	0·99	0·30
Thalamus	3·8	0·87	12·1 ± 0·7	1·01	0·31
Hypothalamus	5·2 ± 0·2	1·41	13·7	1·14	0·44
Cerebellum	4·6 ± 0·4	1·03	6·3 ± 0·5	0·52	0·70
Whole brain	4·3 ± 0·5	1·00	12·0 ± 1·0	1·00	0·36

* Relative deamination velocity is related to the deamination velocity of whole brain homogenate = 1·00.

diamine oxidase (DAO) inhibitors, but by typical MAO inhibitors, both by hydrazine derivatives and by non-hydrazine compounds, quite in contrast to the findings with liver preparations.[17–19]

During the past years numerous speculations have been published on mescaline induced behavioural changes in experimental animals, which were based on findings of the influence of MAO inhibitors on mescaline metabolism by liver mitochondria. Conclusions of this type must be misleading as far as they concern involvement of mescaline oxidation by brain tissue.

The oxidation rates of mescaline and 2,3,4-TMPEA by brain were also quite in contrast to oxidations by liver tissue. While liver mitochondrial enzymes oxidize mescaline somewhat more rapidly than its isomer,[18] brain homogenates metabolize 2,3,4-TMPEA considerably more vigorously to 2,3,4-TMPAA than mescaline to the respective acid. The relations are similar *in vivo* in mouse brain.[20]

The low oxidation rate of mescaline in brain is in analogy to the resistency of the amphetamines against oxidative deamination by mitochondrial enzymes,[16] and in contrast to the metabolic behaviour of its psychotomimetically inactive 2,3,4-isomer. This seems to support the view, that mescaline itself or a non-oxidized metabolite may exhibit the hallucinogenic properties rather than 3,4,5-trimethoxyphenylacetaldehyde or the respective alcohol, as was proposed by Friedhoff and Goldstein[21] on grounds of the absence of behavioural changes after the inhibition of MAO and exaggerated effects after inhibition of dehydrogenation reactions by calcium carbimide. The intensification of behavioural effects of mescaline by MAO inhibition with iproniazid, as reported by Smythies *et al.*[13] are in contrast to the above mentioned findings of Friedhoff and Goldstein. These effects cannot simply be explicated by elevation of mescaline concentration in brain. Preliminary observations demonstrated, that application of hydrazine and of iproniazid to mice, i.e. inhibition of DAO and MAO, did not elevate, but rather slightly lower mescaline concentrations in brain.[22] Iproniazid treated rats excrete increased amounts of *N*-acetylated mescaline, whereas excretion of deaminated metabolites is decreased.[23]

The interesting properties of the oxidative degradation of 2,3,4-TMPEA by brain tissue open questions concerning the mechanism of oxidative deamination of β-arylethylamines by monoamine oxidases, aside from that they demonstrate fundamental differences between the metabolism of mescaline and its psychotomimetically inactive isomer. Our present data on the inhibition of 2,3,4-TMPEA deamination by the substrate itself, by mescaline and by chlorpromazine can be interpreted in different ways. But they are not as complete as to allow to decide whether the oxidation of mescaline and the normal substrates of MAO and 2,3,4-TMPEA respectively is achieved in brain by the same or by different enzymes, or even by different mitochondria. We want to refrain therefore from a detailed discussion of our observations at present. The relatively unspecific interference of chlorpromazine with mitochondrial metabolism is well established.[24,25] But since the concentrations of chlorpromazine and mescaline necessary for the inhibition of 2,3,4-TMPEA degradation are high, it seems not very probable, that the inhibitory properties on MAO have any pharmacological significance in *in vivo* experiments. The different oxidation rates found in various mouse brain regions with mescaline and 2,3,4-TMPEA as substrates *in vitro* resemble similar oxidations of tyramine, dopamine, serotonin and tryptamine by rat brain, as in these experiments the highest oxidation rates were found also with tissue

of the hypothalamic region.[26] But this region was followed in oxidation activity by hippocampal tissue and then by the remaining brain area. Unfortunately cerebellar tissue was not included in these experiments. In dog cerebellar tissue average oxidation velocities were measured.[27] In human cerebellar cortex the oxidase activity was beneath the average of the other brain parts.[28] Though the oxidation activity of hippocampal tissue of mouse brain is low, the slight differences in oxidation activity as compared to the various brain regions with mescaline and 2,3,4-TMPEA as substrates demonstrate clearly, that missing capacity of oxidative deamination in hippocampal structures cannot be the reason for the long lasting storage of mescaline in this archicortical structure.

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