DISPOSITION OF ^{14}C-MESCALINE BY RABBIT LUNG[1]

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ABSTRACT

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Metabolism of mescaline by several rabbit tissues was examined *in vitro*. Mescaline-oxidizing activity (micromoles per milligram of protein/15 min) of lung homogenates was 4 times greater than that of either liver or kidney. Brain and plasma each had comparatively little capacity to metabolize mescaline. Mescaline metabolism *in vitro* was sensitive to inhibition by semicarbazide. Removal of mescaline from the medium perfusing the isolated rabbit lung was explained by intrapulmonary metabolism. Semicarbazide (10^{-3} M) inhibited mescaline metabolism by perfused lung, but metabolism was not decreased by 10^{-5} M pargyline. Semicarbazide-treated lungs accumulated more mescaline than did untreated lungs. Mescaline efflux from lung was slower than that of its metabolite. These results indicate that the intact lung removes perfused mescaline and may be important in the disposition of circulating mescaline *in vivo*.

In the rabbit mescaline is rapidly oxidized *in vivo* to 3,4,5-trimethoxyphenylacetic acid (Slotta and Müller, 1936). It has been generally assumed that the liver is primarily responsible for metabolsim of mescaline (Bernheim and Bernheim, 1938; Zeller *et al.*, 1958; Daly *et al.*, 1962; Denber and Teller, 1968). However, in several species the lung is active in the metabolism of other amines (Gillis, 1973; Fishman and Pietra, 1974; Junod, 1975; Gillis and Roth, 1976). Rabbit lung displays substantial monoamine oxidase (MAO) activity, possessing mitochondrial forms of MAO as well as "plasma" amine oxidase (Roth and Gillis, 1975; Bakhle and Youdim, 1976). Mitochondrial forms of MAO metabolize substrates such as norepinephrine, 5-hydroxytryptamine, tyramine, benzylamine and β-phenylethylamine (Neff and Yang, 1974) and are inhibited by 10^{-5} M pargyline (Youdim, 1972), whereas plasma amine oxidase metabolizes β-phenylethylamine and benzylamine and is selectively inhibited by semicarbazide (McEwen, 1965; McEwen *et al.*, 1966). Mescaline is metabolized *in vitro* by the copper-containing plasma amine oxidase but not by the flavin-containing mitochondrial monoamine oxidase (Bernheim and Bernheim, 1938; Riceberg *et al.*, 1975). It is possible, therefore, that rabbit lung contributes substantially to the disposition of mescaline *in vivo*. For these reasons we compared the mescaline-oxidizing activity of lung with that of other tissues *in vitro* and also examined the disposi-

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tion of this drug by the intact lung using an isolated perfused rabbit lung preparation.

Methods

Preparation of tissue homogenates. Rabbits (2–2.5 kg) were given 1500 U of heparin i.v. after which a 15-ml blood sample was taken from the central artery of the ear. Animals were then anesthetized by i.v. administration of pentobarbital (50 mg/kg). To clear organs of blood, the hepatic portal vein was cannulated and perfused, *in situ*, with cold, heparin-treated (10 U/ml) isotonic saline, and the inferior vena cava was cut below the kidneys to allow drainage of the perfused saline. Organs were then removed, weighed and homogenized in 2 volumes of 0.1 M phosphate buffer containing 0.25 M sucrose in a Waring Blendor and the homogenates were centrifuged at 600 × *g* for 10 minutes. Resulting supernatant fractions were frozen overnight, then rehomogenized by means of a Teflon-glass homogenizer and used for determination of mescaline-metabolizing activity and protein (biuret method).

Determination of mescaline metabolism. Reaction mixtures used to measure mescaline metabolism in the 600 × *g* supernatant fraction contained 1 μmol of ^{14}C-mescaline and, where appropriate, 2 μmol of semicarbazide (as an inhibitor of plasma amine oxidase) in a total of 2 ml of 0.05 M potassium phosphate buffer. Aliquots (0.2 ml) of 600 × *g* tissue supernatant fractions were added to the reaction flask, then incubated for 15 minutes at 37°C. This volume of tissue supernate contained the following amounts of protein (mg): lung, 5; liver, 15; kidney, 7; brain, 4; and plasma, 11. The rate of metabolism for this volume of tissue supernatant was constant for the 15-minute incubation period. The reaction was stopped by addition of 0.2 ml of 0.2 M $ZnSO_4$ followed by 0.2 ml of 0.2 M $BaSO_4$. The mixture was then centrifuged at 3000 × *g* for 10 minutes to remove the precipitate formed, and the supernatant fraction was analyzed for ^{14}C-mescaline and metabolite.

Aliquots (0.5 ml) of supernatant fluids were applied to columns (0.5 × 1 cm) of Bio-Rex 70 (sodium form; pH 6.0) cation exchange resin to separate unchanged ^{14}C-mescaline from its acid metabolite. Neutral and anionic products were removed from the column by 2.5 ml of water which was combined with the 0.5-ml column effluent resulting from application of the sample. Amine was subsequently eluted with 3.0 ml of 0.2 N HCl. The radioactivity of each 3.0-ml sample was measured after addition of 10 ml of ACS in a Packard Tri-Carb model 3320 liquid scintillation spectrometer. Recovery of radioactivity from the columns was consistently 90% or greater. From the radioactivity measurements the number of micromoles of mescaline metabolized during the incubation period was calculated.

Mescaline metabolism by perfused rabbit lung. The isolated perfused rabbit lung preparation used was described previously (Gillis and Iwasawa, 1972). Left and right lungs were perfused independently at a rate of 10 ml/min with Krebs-bicarbonate medium for a 10-minute stabilization period. Subsequently, both lungs were perfused with Krebs medium containing ^{14}C-mescaline (0.1–10.0 μM) *via* the first branches of the pulmonary artery, and the effluent from each lung was collected separately using a fraction collector. Where appropriate, the MAO inhibitors, pargyline (10^{-5} M) and semicarbazide (10^{-3} M), were added to the medium perfusing one lung while the other lung was simultaneously perfused with inhibitor-free medium. There was considerable variation in the magnitude of amine removal and metabolism observed among different lung preparations although changes in these parameters produced by MAO inhibitors were quantitatively similar in all lungs tested. Since interpreparation variability tended to obscure consistent treatment effects when the data were expressed as "average" values, we have chosen, in some cases, to present data of representative experiments. Results were analyzed statistically by a paired, two-tailed Student's *t* test (Snedecor and Cochran, 1967).

Mescaline and metabolite retained in lung tissue were measured after perfusing lungs for 30 seconds with ^{14}C-mescaline-free perfusion medium to remove radioactivity from the vascular space. Lungs were then rinsed with perfusion medium, blotted and homogenized in 0.6 N perchloric acid. Homogenates were centrifuged at 10,000 × *g* for 10 minutes and the supernatant solution was adjusted to pH 6.0 with 1 N KOH and recentrifuged to remove the resulting precipitate, and the content of ^{14}C-mescaline and metabolite was determined as described above.

Calculations. Percent removal (%R) of perfused amine was calculated as:

$$\%R = \left[\frac{C_{a,i} - C_{a,o}}{C_{a,i}}\right] \times 100$$

where $C_{a,i}$ and $C_{a,o}$ represent concentrations of ^{14}C-amine in the inflow and outflow perfusion medium, respectively. Percent metabolite (%M) in lung effluent was calculated as:

$$\%M = \frac{C_{m,o}}{C_{t,o}}(100)$$

where $C_{m,o}$ is the concentration of ^{14}C-metabolite in the outflow perfusion fluid and $C_{t,o}$ is the total molar concentration of ^{14}C-mescaline plus ^{14}C-metabolite in the effluent.

The term "steady state" as used in this paper implies that radioactivity in the inflow perfusion medium is equal to that of the effluent. Initial rate of mescaline removal refers to removal prior to establishing the steady-state condition, that is, when inflow ^{14}C > outflow ^{14}C.

Estimation of initial rates of ^{14}C-mescaline re-

moval. In order to determine which effluent fractions best reflected the initial rates of removal, it was necessary, in preliminary experiments, to determine the rate of equilibration of an extracellular marker, ^{14}C-inulin, during four successive perfusion periods, each of 4 minutes duration. These preliminary experiments showed that the third 30-second fraction after inulin perfusion was begun reflects 84 to 90% recovery of inulin in the effluent (*i.e.*, almost complete equilibration of the inulin space) during each of the four perfusion periods. These data suggested that initial removal of amine should be calculated as [amine infused in 30 seconds − amine recovered in fraction 3]. In order to increase accuracy of calculated initial removal rate, however, we determined the average removal for fractions 3, 4 and 5, for which removal values were similar.

To measure the initial rates of amine removal, lungs were perfused for 5 minutes with Krebs medium containing ^{14}C-mescaline. Amine perfusion was repeated three times in the same lung with increasing concentrations of ^{14}C-mescaline. Between each period of amine perfusion, lungs were washed for 5 minutes with amine-free Krebs medium to clear them of accumulated ^{14}C-mescaline. Lung effluent fractions were collected for 30-second periods and the third, fourth and fifth fractions (collected as indicated above) after ^{14}C-mescaline perfusion was begun were used to determine removal. This method eliminates much of the variability in removal among different lung preparations, since removal at several different perfused lung concentrations is measured in the same lung.

Thin-layer chromatography. Aliquots of lung effluent were applied to Baker-flex 1B silica gel chromatographic sheets (J. T. Baker Chemical Co., Phillipsburg, N.J.) and carrier amounts of mescaline, 3,4,5-trimethoxyphenylacetic acid and N-acetylmescaline were added. Plates were developed in three solvent systems: ethyl acetate–methanol–ammonium hydroxide (65:35:11), butanol–acetic acid–water (2:1:1), or 2.5% methanol in chloroform (developed twice). Marker compounds were visualized with iodine, and radioactivity was localized by cutting the chromatographic sheets into 0.5 cm sections and measuring the radioactivity as described above. In each solvent system, radioactivity from lung effluent chromatographed with mescaline and marker 3,4,5-trimethoxyphenylacetic acid. Radioactivity in effluent from semicarbazide-treated lungs chromatographed with mescaline only. Less than 1% of applied radioactivity was associated with N-acetylmescaline, even in effluent from lungs treated with semicarbazide.

Drugs and isotopes. Mescaline HCl[8-^{14}C] (21 mCi/mmol) was purchased from New England Nuclear Corp., Boston, Mass.; mescaline and semicarbazide were from Sigma Chemical Co., St. Louis, Mo. Pargyline·HCl was a gift from Abbott Laboratories, North Chicago, Ill. Bio-Rex 70 cation exchange resin (100–200 mesh) was purchased from Bio-Rad Laboratories, Richmond, Calif.

Results

Tissue homogenates. The mescaline-metabolizing activity of 600 × *g* supernatant fractions of several tissues is shown in table 1. The lung, liver and kidney metabolized more mescaline per gram of tissue than did plasma and brain. Also, the specific activity (metabolism per milligram protein) of lung was almost 4 times that of kidney and 5 times that of liver. Despite the high specific activity found in lung tissue, liver has greater total enzymatic capacity for mescaline metabolism *in vitro* due to its greater organ mass (table 1).

Semicarbazide (1 mM) has been shown to inhibit the plasma form of amine oxidase selectively (Zeller *et al.*, 1958; McEwen, 1965). In all tissues tested except brain, mescaline metabolism was almost completely inhibited by semicarbazide (table 1). In brain tissue one-third of mescaline-oxidizing activity was semicarbazide-insensitive, confirming data of Riceberg *et al.* (1975) who reported that mescaline-

TABLE 1

^{14}C-mescaline metabolism by 600 × g supernatant fractions of organ homogenates[a]

Tissue	^{14}C-mescaline Metabolized in 15 Min			% Inhibition by Semicarbazide (10^{-3} M)
	μmol/g wet tissue	*μmol/mg protein*	*μmol/whole organ*	
Lung	4.25 ± 0.66	0.0413 ± 0.0079	42.0 ± 4.9	98.4 ± 0.2
Liver	1.90 ± 0.18	0.0087 ± 0.0014	156.8 ± 25.5	97.8 ± 0.3
Kidney	1.41 ± 0.14	0.0116 ± 0.0016	26.0 ± 3.3	97.1 ± 0.8
Brain	0.06 ± 0.02	0.0005 ± 0.00001	0.4 ± 0.1	66.6 ± 9.1
Plasma	0.08 ± 0.01	0.0014 ± 0.0002		96.2 ± 2.2

[a] Aliquots of 600 × *g* supernatant fraction were incubated at 37°C for 15 minutes with 0.5 mM ^{14}C-mescaline. Analysis of mescaline and metabolite was performed as described in "Methods." Results are expressed as mean ± S.E.M., $N = 4$.

metabolizing activity of brain is low, variable and only partially sensitive to an inhibitor of plasma amine oxidase.

Metabolism by perfused lung. Since studies *in vitro* indicated that the lung may be important in the disposition of mescaline *in vivo*, studies were undertaken in the isolated perfused rabbit lung to characterize further the removal and metabolism of mescaline by this organ. Figure 1 depicts results from a typical experiment in which both lungs were perfused with ^{14}C-mescaline (2 μM) for 10 minutes, after which the treated lung was perfused for a further 15-minute period with medium containing pargyline (10^{-5} M) and ^{14}C-mescaline. Finally, the treated lung was perfused with semicarbazide (10^{-3} M) as well as pargyline and ^{14}C-mescaline for an additional 15-minute period. During the entire experiment the untreated lung was perfused only with ^{14}C-mescaline. After the first 3 minutes, during which time the amine was probably equilibrating with extracellular fluids, percent mescaline removal reached a steady-state level (which averaged 45.4 ± 5.1% in four experiments) and remained constant in the untreated lung for the duration of the experiment (fig. 1). Pargyline, an inhibitor of mitochondrial monoamine oxidase (Neff and Yang, 1974), significantly ($P < .05$) increased the removal of mescaline by 9%. Semicarbazide markedly depressed percent removal of mescaline by the inhibitor-treated lung (fig. 1) to 8.2 ± 0.9% at minute 40.

Figure 2 (data from the same lungs as in fig. 1) shows the percentage of total radioactivity appearing in the effluent as mescaline metabolite, ^{14}C-3,4,5-trimethoxyphenylacetic acid (TMPA). This averaged 42.8 ± 5.5% in untreated lungs during steady-state conditions. These data indicate that the small increase in mescaline removal resulting from pargyline administration was caused by elevated metabolism of the drug. Semicarbazide, an inhibitor of plasma amine oxidase, markedly reduced the percent metabolite appearing in lung effluent, reflecting inhibition of mescaline metabolism in the perfused lung. The data suggest that under control conditions, or during exposure to pargyline, steady-state mescaline removal is due largely to metabolism of the amine, since percent removal is numerically equal to the percent metabolite in the effluent. After exposure to semicarbazide, however, percent metabolite decreases to 1.5 ± 0.3% while percent removal, although depressed, remains significantly higher (8.2 ± 0.9%). Thus, during semicarbazide treatment the lung continues to remove some ^{14}C-mescaline although metabolism is almost completely inhibited.

Retention of mescaline by perfused lung.

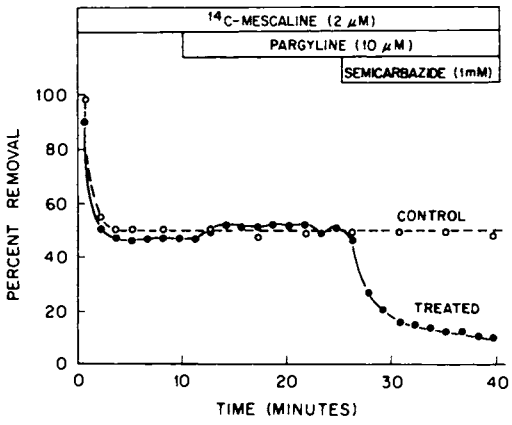

FIG. 1. Effect of 10^{-5} M pargyline and 10^{-3} M semicarbazide on removal of ^{14}C-mescaline by perfused rabbit lungs. Krebs medium containing ^{14}C-mescaline (2 μM) alone, ^{14}C-mescaline and pargyline or ^{14}C-mescaline, pargyline and semicarbazide was perfused sequentially at times indicated by the appropriate bars. Control (right) lung received no MAO inhibitors. Note: percent removal is 100% (by definition) where effluent concentration is zero.

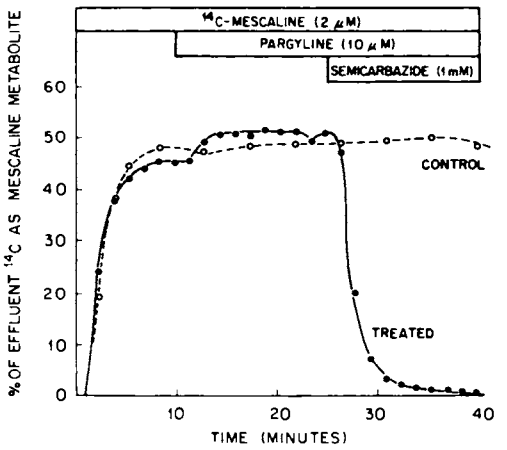

FIG. 2. Effect of 10^{-5} M pargyline and 10^{-3} M semicarbazide on the percentage of total radioactivity appearing as metabolite in effluents from rabbit lungs perfused with 2 μM ^{14}C-mescaline. Krebs medium containing ^{14}C-mescaline alone, ^{14}C-mescaline and pargyline or ^{14}C-mescaline, pargyline and semicarbazide was perfused sequentially at times indicated by the appropriate bars. Control (right) lung received no MAO inhibitors. Data from same set of lungs as figure 1.

The accumulation of ^{14}C-mescaline and its acid metabolite by the perfused rabbit lung after a 10-minute perfusion with ^{14}C-mescaline is shown in figure 3. In untreated lungs 71% of the accumulated radioactivity was TMPA metabolite. Semicarbazide-treated lungs accumulated more than twice as much radioactivity as untreated lungs, almost all in the form of unchanged ^{14}C-mescaline. Inhibitor-treated lungs accumulated 7 times as much ^{14}C-mescaline as did untreated lungs.

Efflux of mescaline. Efflux of ^{14}C-mescaline and TMPA from the perfused lung after a 10-minute perfusion with 2 μM ^{14}C-mescaline was studied. Results of a typical experiment are presented in figure 4. This protocol was repeated four times with identical results. Mescaline is rapidly lost from untreated lungs. The rapid loss may represent washout from vascular and extracellular space. In the inhibitor-treated lung the initial (11–13 minutes, fig. 4) mescaline washout rate was also high, but decreased during the remainder of the washout. As was anticipated, virtually no TMPA appeared in effluent from the treated lung during perfusion with drug or during the washout period. The loss of metabolite from the untreated lung was faster than that of mescaline from treated lungs after the initial rapid phase of loss. Thus mescaline appears to be less readily released from lung tissue than its acid metabolite.

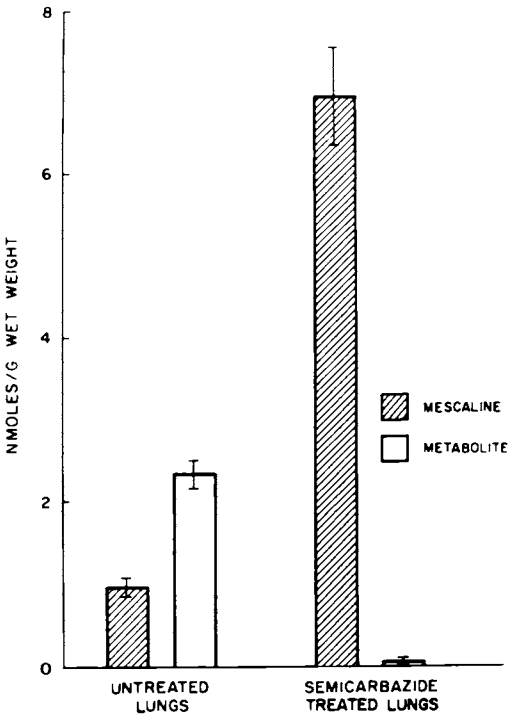

FIG. 3. Accumulation of ^{14}C-mescaline and mescaline metabolite by perfused rabbit lung. Untreated lungs were perfused with only ^{14}C-mescaline (2 μM) for 10 minutes. Treated lungs were preperfused with semicarbazide (1 mM) for 15 minutes, then perfused with semicarbazide plus ^{14}C-mescaline for 10 minutes. After perfusion with ^{14}C-mescaline all lungs were perfused with mescaline-free perfusion medium for 30 seconds then homogenized and analyzed for accumulated mescaline and metabolite as described in "Methods."

Concentration dependence of mescaline removal. The manner in which initial ^{14}C-mescaline removal (see "Methods") changes with inflow ^{14}C-mescaline concentration is shown in figure 5. The relationship appears to depart from linearity only slightly at the highest mescaline concentration perfused (8.5 μM).

Removal of ^{14}C-mescaline approximated steady-state conditions after 3 to 5 minutes of perfusion (fig. 1). The effect of ^{14}C-mescaline concentration on steady-state removal and metabolism of the amine by perfused lung is shown in table 2. Decreasing the inflow drug concentrations from 2 to 1 μM increased steady-state percent removal by one-third. A further decrease in concentration of perfused amine to 0.1 μM did not significantly change percent removal from the 1 μM level. Concentration-dependent changes in percent metabolite appearing in the effluent paralleled alterations in drug removal.

Neither phenoxybenzamine (10^{-5} M) nor ouabain (10^{-5} M) decreased the removal or metabolism of perfused ^{14}C-mescaline (1 μM).

Discussion

This study compares the mescaline-metabolizing capabilities of serveral tissues *in vitro* (table 1). In the peripheral tissues tested, the metabolism of mescaline was almost completely inhbited by semicarbazide. This agrees with the results of others in the rabbit (Riceberg *et al.*, 1975) and indicates that mescaline is metabolized by the copper-containing "plasma" form of the amine oxidase and not by mitochondrial MAO. Other species apparently differ in this regard, since in the mouse semicarbazide has been reported to be without effect on mescaline metabolism (Shah and Himwich, 1971).

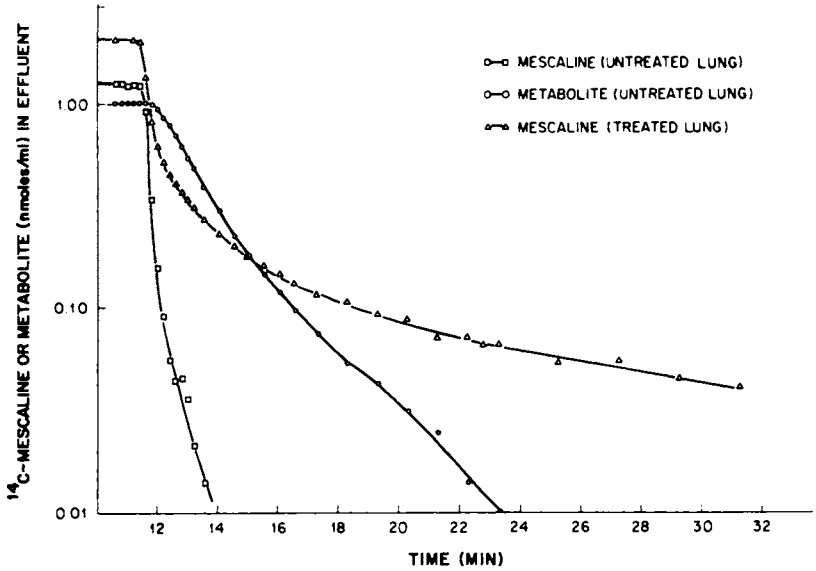

FIG. 4. Washout of ^{14}C-mescaline and mescaline metabolite from isolated perfused rabbit lungs. Treated (left) lung was pre-perfused with 1 mM semicarbazide for 10 minutes then with semicarbazide plus ^{14}C-mescaline (2 μM) for an additional 10 minutes. Untreated (right) lung was perfused only with ^{14}C-mescaline. After ^{14}C-mescaline perfusion (starting at minute 11 in this figure) the untreated and treated lungs were perfused with Krebs medium and with Krebs medium plus semicarbazide, respectively. Amine and metabolite in effluent during the washout period were analyzed as described in "Methods."

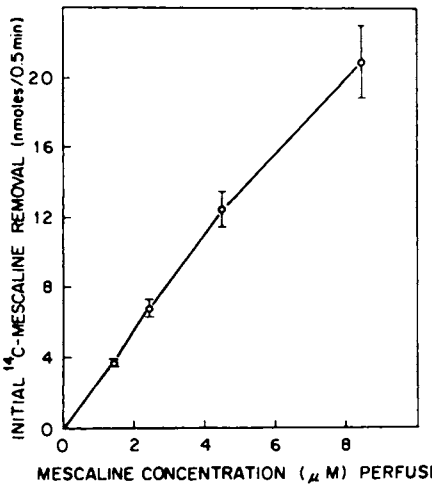

FIG. 5. Concentration dependence of initial removal of perfused ^{14}C-mescaline by rabbit lung. Removal is the rate of delivery to lung minus the rate of appearance of ^{14}C-mescaline in lung effluent. Points represent mean ± S.E.M.; N = 4.

TABLE 2

Concentration dependence of steady-state ^{14}C-mescaline disposition by isolated perfused rabbit lung[a]

^{14}C-Mescaline in Perfusion Medium	N	% Metabolite in Effluent	% Removal of Amine
μM			
0.1	6	58.5 ± 1.5	59.8 ± 1.5
1.0	4	55.8 ± 2.2	57.4 ± 2.1
2.0	7	41.0 ± 2.3[b,c]	43.2 ± 2.1[b,c]
10.0	12	47.4 ± 1.6[b,c]	49.0 ± 1.6[b,c]

[a] Values represent mean ± S.E.M. for left lungs from separate experiments perfused as described in "Methods" with Krebs medium at a flow of 10 ml/min.

[b] Significantly different from 0.1 μM value ($P < .05$, Student's t test).

[c] Significantly different from 1.0 μM value ($P < .05$, Student's t test).

Previously, Zeller *et al.* (1958), using unlabeled mescaline, reported the absence of mescaline-oxidizing activity in rabbit brain homogenate. Our results and those of others (Shah, 1971; Riceberg *et al.*, 1975) reveal the presence of low levels of mescaline-metabolizing activity by rabbit brain. Weak metabolizing activity has also been reported in homogenates of human brain (Zeller *et al.*, 1958) as well as mouse and rat brain (Shah, 1971). Our present findings and these earlier results indicate that brain amine oxidases play an insignificant role in the inactivation of circulating mescaline.

Although the specific mescaline-oxidizing activity was much higher in lung than other tissues, the liver has a greater total capacity to metabolize mescaline *in vitro* due to its larger organ mass (table 1). *In vivo*, however, delivery of drug substrate is many-fold greater to lung than to liver, since the lung receives all of the cardiac output while liver blood flow is only one-fifth this value (Korner *et al.*, 1967; Slater *et al.*, 1972; Nies *et al.*, 1973; Branch *et al.*, 1973c). The flow dependence of drug clearance has been demonstrated in perfused organ preparations (Branch *et al.*, 1973a; Roth and Rubin, 1974; Shand *et al.*, 1975) and *in vivo* (Branch *et al.*, 1973b, c, 1974; Nies *et al.*, 1973; Ohnhaus *et al.*, 1971) for other drugs which are moderately or extensively removed from the circulation. Therefore, *in vivo* the greater total mescaline-metabolizing capacity of the liver may be offset by the slow delivery of the drug to this tissue relative to lung. These results suggest that the lung may play an important role in the disposition of circulating mescaline.

Although other studies *in vivo* have suggested the possibility, this study represents the first demonstration of mescaline removal by the intact lung. The steady-state removal of mescaline from the perfusion medium may be explained entirely by metabolism of the amine. Results indicate that in the intact organ, as in tissue homogenates, mescaline in metabolized by a semicarbazide-sensitive amine oxidase (fig. 2). This amine oxidase is probably associated with endothelial cells (Roth and Gillis, 1975) and may be identical to rabbit "plasma" amine oxidase (McEwen *et al.*, 1966). An amine oxidase from rabbit aorta has been isolated and demonstrates properties similar to plasma amine oxidase (Rucker and Goettlich-Riemann, 1972). Mescaline is not metabolized by mitochondrial MAO since 10^{-5} M pargyline, which completely inhibits this form of MAO in lung (Roth and Gillis, 1975), failed to inhibit metabolite formation. It is of interest to note in this regard that structurally similar phenylethylamine is metabolized by both mitocondrial MAO and plasma amine oxidase in the perfused rabbit lung (Roth and Gillis, 1975). The mechanism by which parglyine infusion produced a small but significant increase in removal of mescaline is presently unclear.

The accumulation of mescaline by perfused lung was markedly increased when metabolism of the amine was inhibited (fig. 3). These data agree with those of Riceberg *et al.* (1975), which showed that, after its systemic administration, mescaline accumulates in tissues to a greater extent in the presence than in the absence of an inhibitor of metabolism. The extensive organ accumulation also explains the low levels of plasma mescaline found *in vivo* in animals treated with a plasma amine oxidase inhibitor. The observation that total accumulated radioactivity also increased as a result of inhibition of metabolism suggests that the metabolite (TMPA) is released from lung tissue more readily than the parent drug. This was confirmed by the results of washout studies (fig. 4), which indicated that, after an initially rapid efflux probably representing amine loss from extracellular space, cellular washout of the acid metabolite was more rapid than cellular washout of mescaline. Although the efflux of TMPA could be resolved into two components, the washout of mescaline was obviously more complex.

Initial amine removal as measured by the method employed in this study likely reflects primarily uptake of amine into lung cells. No substantive evidence for a saturable component was found for initial ^{14}C-mescaline removal over the range of concentrations (1.4–8.5 μM) tested (fig. 5). In addition, neither phenoxybenzamine nor ouabain, both of which inhibit pulmonary removal of other amines (Gillis, 1976), decreased the rate of mescaline removal by lung. Accordingly, mescaline uptake into cells may be a passive process not involving facilitated transport. The fact that initial ^{14}C-mescaline removal at the highest mescaline concentration perfused (fig. 5) deviates slightly from linearity could reflect the existence of a facilitated transport mechanism. However, if a facilitated component indeed exists it is of very low affinity (large K_m) or is minor compared to passive cellular uptake.

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