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PLACENTAL TRANSFER AND TISSUE DISTRIBUTION OF MESCALINE-^{14}C IN THE MOUSE[1,2]

NANDKUMAR S. SHAH, A. E. NEELY, K. R. SHAH AND R. S. LAWRENCE

Ensor Research Laboratory, William S. Hall Psychiatric Institute, Columbia, South Carolina

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ABSTRACT

SHAH, NANDKUMAR, S., A. E. NEELY, K. R. SHAH AND R. S. LAWRENCE: Placental transfer and tissue distribution of mescaline-^{14}C in the mouse. J. Pharmacol. Exp. Ther. **184:** 489–493, 1973.

Albino mice (Swiss-Webster) on day 15 of gestation were injected i.p. with a tracer dose of mescaline-^{14}C (36 μc/kg; 8.33 μmol/kg as free base). The distribution of unchanged mescaline-^{14}C was examined in physiological fluids and in tissues on both sides of the placenta. At 15 minutes and 4 hours, the fetal brain levels were 1377 ± 123 and 567 ± 203 pmol/g, respectively; compared with mother brain, they were more than 2 and 4-fold greater. The mescaline contents in plasma (3998 ± 303 pmol/ml) were highest at 15 minutes; those in placenta (4988 ± 535 pmol/g), whole fetus (2166 ± 228 pmol/g) and amniotic fluid (1639 ± 210 pmol/ml) were highest at 1 hour. Several maternal tissues, with the exception of brain, concentrated mescaline rapidly. Fifteen minutes after injection, the levels (as picomoles per gram) were: kidney, 22142 ± 1518; liver, 17626 ± 1347; lung, 16118 ± 1062; spleen, 13635 ± 910; heart, 8619 ± 564. The mescaline content of brain was among the lowest measured (peak 1 hour level, 957 ± 93 pmol/g). Smooth muscle (uterus) retained more mescaline than skeletal or cardiac muscle. At 4 hours, the uterus showed the highest concentration (2561 ± 369 pmol/g) of mescaline of all the tissues examined. About 50% of the injected dose was excreted in the urine during the first 3 hours, which indicates a rapid elimination of the drug.

The mammalian placenta rapidly transports a wide variety of chemical compounds including harmful drugs (Juchau, 1972). One of the pertinent questions regarding hallucinogens concerns the possible deleterious effects on the *in utero* development of the fetus. Low doses of mescaline in pregnant hamster caused teratogenic effects in offspring (Geber, 1967). In her report on "clastogens," Shaw (1970) stated, "In spite of the conflicting chromosome results, there is general agreement that LSD, bromlysergic acid, and mescaline are teratogenic to mice, rats and hamsters." To our knowledge data concerning placental transfer and tissue distribution of mescaline are scarce. In the present investigation, mouse was used because both humans and mice do not have a specific mescaline oxidase and hence resemble each other more closely (Hoffer and Osmond, 1967).

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Send reprint requests to: Dr. Nandkumar S. Shah, Chief, Ensor Research Laboratory, Wm. S. Hall Psychiatric Institute, Columbia, S.C. 29202.

Experimental Procedure

Methods

Preparation of animals. Young adult albino mice (Swiss-Webster) were obtained from the Bureau of Laboratories, South Carolina State Board of Health (Columbia, S.C.). The animals were housed in cages and allowed Purina lab chow food and tap water *ad libitum*. One male and one female mouse were left for mating overnight and examined the following morning for the presence of vaginal plugs. Those with plugs were considered to be in day 1 of pregnancy.

Procedure for drug administration. Pregnant mice on day 15 of gestation were individually housed in metabolic cages. Each animal received i.p. a tracer dose of mescaline-^{14}C (36 μc/kg; 8.33 μmol/kg as free base) in 0.5 ml of saline. At selected times after mescaline, they were sacrificed by decapitation. Maternal tissues, placentae and whole fetuses were removed and frozen on dry ice. Amniotic fluid, maternal plasma and urine as well as frozen tissues were stored at −20°C for 24 hours. In a few instances, the fetal liver and brain were examined for radioactivity.

Extraction and counting of radioactivity. Amniotic fluid, plasma and tissues were homogenized successively with 5 and 3 ml of chilled 0.4 N perchloric acid (Shah *et al.*, 1968). The extracts were adjusted to pH 5.8 with 5 N potassium carbonate solution. The urine samples were used directly. An aliquot of 0.5 ml (perchloric acid extract) or 0.1 ml (urine) was set aside for a count of total radioactivity. Unchanged mescaline was separated from its principal metabolite, 3,4,5-trimethoxyphenylacetic acid (TMPA), on columns containing Dowex 50W-X$_4$ (Charalampous *et al.*, 1966) with some modifications (Shah and Himwich, 1971a). The radioactivity was assayed in a Nuclear-Chicago Mark II liquid scintillation spectrometer using ^{133}Ba as an external standard. The efficiency of the counting system ranged between 85 and 90%. The values are reported as picomoles per gram of wet weight tissue or per milliliter.

Paper chromatography. Extracts from organs were prepared for paper chromatograms using two solvent systems: *n*-butanol–acetic acid–water (4:1:1 by volume) and *n*-butanol–isopropanol–ammonia–water (3:1:1:1 by volume). The details are reported elsewhere (Shah and Himwich, 1971a).

The efficiency of recovery. A solution containing 1 mg of nonlabeled mescaline HCl and 222,000 dpm of mescaline-^{14}C was added to brain tissue. The procedure for extraction and separation of mescaline is similar to that reported for 3,4-dimethoxyphenylethylamine (Shah *et al.*, 1972). Paper chromatography performed on a fraction eluted with 7 ml of ethanol–ammonia solution revealed a single radioactive spot with R_f value 0.63 identical to the authentic nonlabeled mescaline; the recovery was 93%. Insignificant amounts of radioactivity were present in effluent, four water washes and two ethanol–ammonia washes.

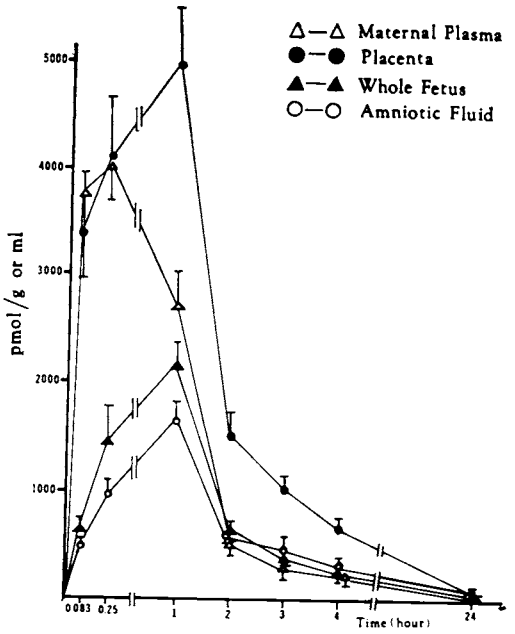

FIG. 1. The concentrations of unchanged mescaline-^{14}C in the maternal plasma, amniotic fluid, placenta and whole fetus at various times after i.p. injection of a tracer dose of mescaline-^{14}C (36 μc/kg; 8.33 μmol/kg) to a pregnant mouse on day 15 of gestation. Each value is an average of data from four to five animals. The bars indicate the standard deviation of the mean.

Materials

Chemicals. Mescaline-8-^{14}C-HCl (specific activity, 4.53 mc/mmol) was purchased from New England Nuclear Corporation (Boston, Mass.). The chemical and radiochemical purity was ascertained by column and paper chromatography and found to be approximately 97%.

Statistics. The values are the mean ± standard deviation of the mean. The statistical significance of differences between mean values was determined with a two-tailed Student's *t* test; P values are given at appropriate places.

Results

Plasma concentrations of mescaline increased with time and reached highest levels (3998 ± 303 pmol/ml) at 15 minutes (fig. 1). At four

TABLE 1

The levels of mescaline-^{14}C in maternal tissues

The results are averages of four to five separate experiments ± S.D. The time interval indicates the time of sacrifice after i.p. administration of a tracer dose of mescaline-^{14}C (36 μc/kg; 8.33 μmol/kg).

Tissue	Mescaline-^{14}C Levels at:				
	15 min	1 hr	3 hr	4 hr	24 hr
	pmol/g wet wt. tissue				
Kidney	22142 ± 1518	14119 ± 1670	2012 ± 651	852 ± 89	130 ± 14
Liver	17626 ± 1347	12414 ± 1020	1151 ± 183	772 ± 191	140 ± 32
Lung	16118 ± 1062	9723 ± 901	1190 ± 332	704 ± 149	62 ± 14
Spleen	13635 ± 909	7475 ± 769	713 ± 130	471 ± 118	81 ± 12
Heart	8619 ± 563	3534 ± 461	398 ± 161	259 ± 90	71 ± 18
Brain	617 ± 46	957 ± 93	298 ± 63	145 ± 32	23 ± 10
Uterus		7547 ± 600		2561 ± 369	
Eye		2349 ± 217		352 ± 44	
Skeletal muscle		5105 ± 444		778 ± 238	
Fat		1994 ± 242		181 ± 26	

hours, the level had dropped to 267 ± 107 pmol/ml which was about 6 to 7% of the peak value. An insignificant amount (22 ± 8 pmol/ml) was measured at 24 hours. Plasma concentrations of TMPA at 15 minutes, 1, 2, 3, 4 and 24 hours were 839 ± 276, 1405 ± 298, 372 ± 119, 250 ± 80, 169 ± 63 and 19 ± 6 pmol/ml, respectively. Mescaline contents in placenta, whole fetus and amniotic fluid were highest at one hour (fig. 1). Placenta contained significantly more mescaline than amniotic fluid or whole fetus. The placental levels increased from 3385 ± 435 pmol/g at five minutes to 4988 ± 535 pmol/g at one hour. The disappearance was rapid; at two and four hours the levels were declined to 30 and 13% of peak values. At one hour mescaline content of whole fetus was 2166 ± 228 pmol/g whereas that of the amniotic fluid was 1639 ± 210 pmol/g. After one hour, the mescaline levels in whole fetus and amniotic fluid were virtually identical. At 24 hours, the mescaline contents in placenta, whole fetus and amniotic fluid were 25 ± 11, 36 ± 13 and 30 ± 16 pmol/g or /ml, respectively.

Among maternal tissues studied, the highest concentrations of mescaline were measured in the kidney (22142 ± 1518 pmol/g) and the lowest were in the brain (957 ± 93 pmol/g) (table 1). The mescaline concentrations in the brain were highest at one hour and were highest in the kidney, liver, lung, spleen and heart at 15 minutes. Compared with kidney, the percent levels in the liver, lung, spleen and heart at 15 minutes were 80, 73, 61 and 40, respectively. By 24 hours, all tissues contained minute quantities. Mescaline levels in smooth (uterus), skeletal and cardiac muscle were compared. One hour after injection, uterus levels of 7547 ± 600 pmol/g were about 1½ and 2 times more than skeletal and cardiac muscle. The disappearance from the latter two tissues was relatively rapid; that from uterus was comparatively slow. At four hours, the uterine muscle contained the highest level among the tissues examined. Fat accumulated less than one-half of the mescaline level of skeletal muscle at one hour and less than one-fourth at four hours. Mescaline levels in the eye were compared with brain; the former accumulated almost twice as much as the latter at one and four hours.

Compared with maternal brain, the fetal tissue demonstrated more rapid accumulation and higher concentration of mescaline (table 2); at 15 minutes, the levels were more than twice that of maternal brain (1377 ± 123 *vs.* 617 ± 46 pmol/g; $P < .001$). The disappearance was less rapid; at four hours, the fetal brain level was 4 times that of mother (567 ± 203 *vs.* 145 ± 32 pmol/g; $P < .001$). Small amounts of TMPA were present in both maternal and fetal brain. Fifteen minutes and four hours after the injection, the fetal liver mescaline contents were 2268 ± 242 and 664 ± 116 pmol/g, respectively; compared with maternal liver, these levels were 13 and 86%, respectively.

TABLE 2

Comparison of levels of mescaline-^{14}C and TMPA in maternal and fetal brain and liver at 15 minutes and at four hours

The values are the mean ± S.D. with number of separate determinations in parentheses.

Tissue	15 Minutes			4 Hours		
	TMPA	Mescaline	TMPA/ mescaline	TMPA	Mescaline	TMPA/ mescaline
	pmol/g wet wt. tissue			*pmol/g wet wt. tissue*		
Maternal						
Brain	44 ± 10 (4)	617 ± 46 (4)	6.7:93.3	17 ± 8 (4)	145 ± 32 (4)	8.4:91.6
Liver	1734 ± 303(4)	17626 ± 1347(4)	9.0:91.0	362 ± 29(4)	772 ± 191(4)	31.9:68.1
Fetal						
Brain	54 ± 33 (12)	1377 ± 123 (12)[a]	3.8:96.2	81 ± 9 (12)	567 ± 203(12)[b]	12.6:87.4
Liver	136 ± 45 (12)	2268 ± 242 (12)[c]	5.7:94.3	181 ± 20(12)	664 ± 116(12)[d]	21.4:78.6

[a] Significantly different from maternal brain for corresponding time period, $P < .001$.
[b] Significantly different from maternal brain for corresponding time period, $P < .001$.
[c] Significantly different from maternal liver for corresponding time period, $P < .001$.
[d] Not significantly different from maternal liver for corresponding time period, $P > .1$.

At one hour, kidney levels of TMPA ranged from 35 to 38% of total radioactivity. The fat, heart, liver and whole fetus levels followed that of the kidney. TMPA levels in the amniotic fluid, placenta, uterus, lung and eye ranged from 12 to 16% and, in skeletal muscle, spleen, maternal and fetal brain and fetal liver, they ranged from 6 to 12%. Of particular interest is the observation on the brain. Both *in vivo* and *in vitro* studies (Shah and Himwich, 1971a,b; Seiler and Demisch, 1971) have shown that very small but measurable amounts of mescaline are oxidatively deaminated to TMPA by mouse brain.

Radioactivity was rapidly eliminated through the kidney. About 50% of the injected dose was excreted in the urine during first three hours and from 70 to 89% was excreted in 24 hours. The urinary levels of mescaline were always higher than those of TMPA at all time periods. The relative concentration ratios of TMPA/mescaline at one and four hours were 36:64 and 43.5:56.5, respectively.

Discussion

The exchange of drugs between the mother and the fetus has been the subject of innumerable reports. Several studies have indicated transfer of a wide range of chemical compounds across the mammalian placenta. In this report, the distribution pattern of mescaline-^{14}C has been presented. Mescaline crosses the placenta and enters the fetus in readily measurable amounts. However, there appears to be some restriction to the passage of mescaline into the fetus as the amount found in the whole fetus at one hour was only two-fifths of that measured in the placenta. It is also evident that once the mescaline enters the fetus, there is no restriction to its distribution to the central nervous system since the brain tissue rapidly accumulated mescaline in high concentrations. This is probably due to a partially developed blood-brain barrier in the fetus. Another point of interest is the slow disappearance of mescaline from the fetal brain. It is likely that the fetal brain, unlike adult brain, has a less efficient mechanism for the disposition of the drug. In the discussion to follow, major emphasis is placed on the comparison of mescaline levels in the adult and fetal brain. Shah and Himwich (1971a) have reported that the gross behavioral effects of mescaline in adult mice were greatest when brain mescaline had attained peak levels, *i.e.*, one hour after i.p. injection. It is noteworthy that the brain concentration of mescaline at the time of maximal behavior was 0.002% of the injected dose. Thus, the amount of mescaline required to induce behavioral changes is only a very small fraction of the injected hallucinogen. This is highly significant, particularly when the fetal brain is exposed to prolonged and dangerously higher concentrations of mescaline than the maternal brain (table 2). The fact that the accumulation of a significantly higher concentration of mescaline

than that required to induce behavioral changes in adult animals occurs in fetal brain emphasizes a potential hazard to the fetal brain specifically at a period when neural tissue is highly susceptible to the actions of a variety of chemical agents. Among the biochemical effects, mescaline was shown to inhibit the oxidation of glucose, pyruvate, lactate and glutamate by isolated brain tissue (Quastel and Wheatley, 1933). Our laboratory is currently investigating this effect of mescaline in fetal brain after the mother is exposed to 25 and 50 mg/kg of mescaline. Such biochemical, as well as microscopic, examination will eventually determine whether mescaline in amounts that accumulate in fetal brain would have any adverse effect on the brain during development.

The rapid tissue distribution of mescaline is evidenced by the fact that 15 minutes after i.p. injection, several maternal tissues, with the exception of brain, showed high levels. Among the tissues that had high concentrations are the kidney, liver, lung and spleen. The selective absorption of mescaline in these organs seems to be due to a high affinity of mescaline for parenchymal tissues. It is interesting that, although mescaline acts as a psychotomimetic agent, the levels of mescaline in the brain were the lowest of all maternal tissues studied. The brain is protected by the blood brain barrier. This barrier and the physicochemical nature of mescaline, such as poor binding to subcellular structures (Shah, 1971), could be responsible for the significantly lower amounts of mescaline found in the maternal brain. Thus, the passage of mescaline across the barrier may be an important event in mescaline-induced responses.

The uterus is capable of storing mescaline for longer periods of time than other tissues studied. This selective retention may be due either to greater affinity of mescaline for the uterine smooth muscle or to secretion of mescaline by the fetus in the uterine lumen. The ability of the nonpregnant uterus to accumulate approximately an equivalent amount of mescaline for the corresponding time period (unpublished observations) emphasizes that the uterine smooth muscle has a greater affinity for mescaline.

Disappearance of mescaline from all organs with the exception of the uterus was rapid. This phenomenon might be explained from the results of subcellular studies (Shah, 1971) which showed a poor binding of mescaline to cell particles. The urinary data further support this conclusion. The 24-hour urine contained from 70 to 89% of the administered radioactivity of which 50% was recovered from the three-hour urine samples. The urinary excretion pattern of mescaline-^{14}C in humans (Charalampous *et al.*, 1966) was similar to that reported for mice. An average of 87% of the orally administered dose was excreted in the first 24 hours; the amounts of mescaline and TMPA ranged from 55 to 60% and 27 to 30%, respectively.

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