TERATOLOGY 23:287–291 (1981)

Teratogenic Effects of Mescaline, Epinephrine, and Norepinephrine in the Hamster

KENNETH S. HIRSCH AND H. IRA FRITZ
Department of Biological Sciences, Wright State University, Dayton, Ohio 45435

ABSTRACT Mescaline was administered orally at doses of 16 and 32 mg/kg on the seventh through tenth days of gestation to pregnant cream-strain hamsters. This treatment resulted in a dose-dependent effect on reproductive success and skeletal ossification. The effect of mescaline on reproductive success included an increased number of resorptions resulting in a decreased litter size. The 32 mg/kg dose of mescaline caused 48.8% resorptions, while 16 mg/kg and control animals had 12.0% and 6.4% resorptions, respectively. Litter size was decreased from 12.0 pups in controls to 10.3 (16 mg/kg) and 6.5 (32 mg/kg) pups per litter in treated groups. No gross abnormalities were observed at necropsy; there was, however, a dose-dependent increased delay in the ossification of the skull, sternum, and metatarsals. Both epinephrine and norepinephrine caused a decrease in reproductive success when administered at 500 μg/kg. Epinephrine appeared to cause a trend towards preimplantation wastage as indicated by an increased corpora lutea to implantation site ratio (from 1.3 – 1.9). Norepinephrine, however, caused an increased number of resorptions (29.1% in controls). Both norepinephrine and epinephrine produced similar delays in ossification.

Mescaline has been reported to have adverse effects on the reproductive tract of gravid females. Grace ('34) reported that mescaline induced strong contraction in the uterine muscles of guinea pigs. Patel ('68) demonstrated that mescaline caused vasoconstriction of uterine, placental, and umbilical vessels in man. Taska and Schoolar ('72) reported that ^{14}C-labeled mescaline crossed the placental barrier when administered during the last trimester of pregnancy in the rhesus monkey. The labeled compound was found in the placenta, amniotic fluid, spinal cord, brain, and kidney. Geber ('67) reported that 3 mg/kg of mescaline caused congenital malformations in hamsters when administered on the eighth day of gestation. He reported observing abnormalities of the brain, spinal cord, and liver along with edema and localized hemorrhages. Fetal mortality and resorptions were also higher than controls. In contrast, Strausbaugh ('71) did not find these malformations when 8 mg/kg of mescaline were administered to pregnant hamsters. Strausbaugh found a trend towards increased fetal variability as evidenced by delayed ossification of several specific skeletal sites. More recently, Geber (personal communication) indicated that doses of under 600 mg/kg were ineffective in producing congenital malformations as described in his earlier report.

Some investigators have suggested that the activity of mescaline is associated with the action of the catecholamines. Brodie et al. ('59) attributed the effects observed during the mescaline intoxication to the adrenergic neurotransmitter norepinephrine. Further, the catecholamines have been reported to cause mescaline-like effects in the pregnant female and developing fetus. Auletta ('71) reported that epinephrine influenced ovum transport and impaired implantation in the rabbit. Epinephrine administered twice a day (600 μg/kg) prior to implantation resulted in a reduction in fetal numbers and implantation sites. These effects were suspected to result from fetal anoxia caused by placental vasoconstriction. Embryonic effects were not observed when epinephrine was administered following implantation.

The current study was designed to better define the teratogenicity of mescaline, and to de-

K.S.H.'s current address: Eli Lilly and Co., Box 708, Greenfield, IN 46140.

H.I.F.'s current address: Department of Biological Chemistry, Wright State University, Dayton, OH 45435.

Received August 26, 1977; accepted December 8, 1980.

termine whether epinephrine and norepinephrine, when administered to the gestating hamster, could cause similar teratogenic syndromes to that of mescaline.

MATERIALS AND METHODS

Male and virgin female cream-strain hamsters between the ages of 10 weeks and 12 months were used. The animals were housed individually and maintained under standard laboratory conditions. The animals were provided with Purina Laboratory Chow and water ad libitum. The diet was supplemented with lettuce, apples, and raw peanuts. Room temperature was maintained at 24 ± 2°C.

Characteristic vaginal discharges were used to determine normal estrus cycling (Orsini, '61). Females were mated when the vaginal discharge denoting the first day of the estrus cycle was observed twice, separated by four days. Cycling females were mated at 4:00 PM on the day of estrus. Vaginal smears were made the following morning with the presence of sperm in the smear taken as proof of mating. The day of positive sperm determination was designated as Day 1 of gestation.

The experimental procedures used in this study for the evaluation of the teratogenicity of epinephrine, norepinephrine, and mescaline were taken from the established guidelines developed by the World Health Organization ('67).

Thirty females used in the mescaline teratology study were weighed following a successful mating and again at dosing and necropsy. Animals received either 32 mg/kg, 16 mg/kg, or water by gastric intubation on the seventh through tenth days of gestation. The dosage levels were selected in an attempt to better define mescaline teratogenesis by exaggerating the effect observed by Strausbaugh ('71). The mescaline (Sigma Chemical Co.) solution containing 10 mg of mescaline per ml of water was made just prior to administration. The volume of fluid intubated was held constant by adjusting the intubation volume to 0.6 ml with water.

Thirty-eight females were used for the epinephrine and norepinephrine studies, with separate controls for each of the experiments. The animals were weighed before drug administration to determine the quantity of drug to be administered. Except in the epinephrine study, additional weights were taken at mating and at necropsy to determine the drug's effect on maternal weight gain. The drugs were mixed 30 minutes before dosage at 500 μg/ml of saline. Both epinephrine and norepinephrine were administered by subcutaneous injection on the dorsal surface at 500 μg/kg. The drugs were administered on the seventh through the tenth days of gestation. Control animals were given a similar saline treatment.

Animals were killed by an overexposure to ether on the fifteen day of gestation. The uteri were exposed and implantation sites, and resorptions counted. The fetuses were removed and examined for viability, weight, and sex. The fetuses were then examined for gross external malformations. Approximately 50% of the fetuses were examined for soft tissue defects. The remaining fetuses were eviscerated and skeletal stains made using Alizarin-red S (Dawson, '26). Maternal uteri and ovaries were examined grossly and counts of corpora lutea made.

Data were analyzed by appropriate and various tests based upon the individual data set being considered (Sokal and Rohlf, '69). In all cases the $P < 0.05$ level was chosen to demonstrate statistical significance.

RESULTS

A total of 81 matings were attempted, 68 animals (84%) were successfully impregnated. Animals were assigned to the various treatment groups on the seventh day of gestation at random.

Mescaline-treated dams exhibited a significantly smaller ($P < 0.05$) increase in weight gaining 25.4 gm (32 mg/kg) and 34.2 gm (16 mg/kg) as compared with a gain of 37.0 gm in the control group (Table 1, $P < 0.05$). In addition to the difference in gross weight, treated animals exhibited a significantly smaller ($P < 0.01$) percent increase in weight between the time of drug administration and necropsy (Table 1). The mescaline treatment also resulted in a significant increase ($P < 0.01$) in the number of resorption sites (Table 1). This drug-dependent effect was observed as 48.8% resorptions in the 32 mg/kg group as compared with 12.0% and 6.4% in the 16 mg/kg treated and control animals. Mescaline was also found to significantly reduce ($P < 0.01$) litter size from 12.0 pups in control litters to 10.3 in the 16 mg/kg group and 6.5 in the 32 mg/kg treatment group.

Mescaline was also found to be responsible for skeletal changes which were indicative of a delay in skeletal development at a number of specific sites (Table 1). Based on an arbitrary five-point grading system, the mean closure

TABLE 1. Effects of mescaline on maternal weight gain and reproduction

	Mescaline (mg/kg)		
	0	16	32
Females dosed	8	11	11
Maternal weight gain (%)			
Mating to dosing	3.4 ± 2.1[1]	4.8 ± 1.1	6.2 ± 0.8
Dosing to necropsy[2]	30.8 ± 3.0	27.3 ± 1.7	17.5 ± 3.6
Mating to necropsy[3]	35.0 ± 1.8	34.2 ± 2.7	25.1 ± 4.6
Reproduction			
Corpora lutea: animal	13.4 ± 0.8	12.8 ± 0.8	13.2 ± 0.7
Implantation sites: animal	12.9 ± 0.8	11.7 ± 0.8	11.6 ± 0.8
Corpora lutea: Implantation site	1.0 ± 0.0	1.1 ± 0.1	1.2 ± 0.1
Resorptions: litter	0.8 ± 0.0	1.4 ± 0.4	5.2 ± 1.4
Resorptions: %[2]	6.4 ± 2.1	12.0 ± 3.0	48.8 ± 13.0
Embryonic effects			
Pups: litter[2]	12.0 ± 0.9	10.3 ± 0.8	6.4 ± 1.7
Weight range	1.3–2.2	0.7–2.5	1.2–2.2
Fetal weight	1.7 ± 0.3	1.7 ± 0.1	1.7 ± 0.1
Liver fatty infiltration: litter	3.8 ± 0.6	8.7 ± 0.9	9.1 ± 1.0
Liver fatty infiltration: %	32.5 ± 6.3	84.2 ± 5.6	91.0 ± 2.9
Ossification sites[4]			
Pups examined	50	62	37
Mean closure grading[5,6]	4.0 ± 0.3	3.2 ± 0.4	3.0 ± 0.3
Sternal elements[3]	3.9 ± 0.5	3.5 ± 0.5	3.2 ± 0.5
Metacarpals	3.0 ± 0.1	2.0 ± 0.3	3.0 ± 0.0
Metatarsals	2.3 ± 0.4	2.1 ± 0.4	1.8 ± 0.3

[1] + SEM.
[2] $P < 0.01$, regression analysis.
[3] $P < 0.05$, regression analysis.
[4] As observed in alizarin red stained specimens as an index of maturity.
[5] Based on a 1 – 5 scoring system.
[6] $P < 0.05$, regression analysis.

grading of the fetal skull was significantly lower ($P < 0.05$) when the dams received 32 mg/kg of mescaline (3.0) as compared to the 16 mg/kg group (3.2) and controls (4.0). Ossification of the sternal elements was found to be significantly ($P < 0.05$) delayed. The number of sternal elements in the pups from control, 16 mg/kg and 32 mg/kg mescaline-treated animals averaged 3.9, 3.5, and 3.2, respectively. Significant ($P < 0.05$) delays were also found in the ossification of fetal metatarsals. Pups from dams given 32 mg/kg of mescaline had an average of 1.8 ossified metatarsals, while the fetuses from the 16 mg/kg and control dams had 2.0 and 2.3 ossified metatarsals, respectively.

Dams treated with norepinephrine were found to have significantly smaller ($P < 0.05$) increases in weight during gestation (Table 2). Pregnant females treated with norepinephrine had a 22.5% increase in weight, while control animals had an increase of 31.8%.

Epinephrine-treated animals exhibited a possible trend towards an increased corpora lutea to implantation site ratio (Table 2). This increased ratio, indicative of the number of wasted ova, was 1.9 in treated animals as compared with 1.3 in control animals. The number of resorptions was significantly higher ($P < 0.05$) in the norepinephrine-treated animals which had 29.1% resorptions as compared with 2.9% in control animals. Both of the catecholamines caused a nonsignificant reduction in litter size (Table 2).

Fetuses from pregnant females treated with either of the catecholamines exhibited delayed ossification of specific skeletal sites (Table 2). Fetuses from animals treated with epinephrine and norepinephrine had closure

TABLE 2. Effect of catecholamines on maternal weight gain and reproducton

	Epinephrine (μg/kg)		Norepinephrine (μg/kg)	
	0	500	0	500
Females dosed	10	10	8	10
Maternal weight gain (%)				
Mating to dosing[1]			5.0 ± 1.2[2]	3.0± 0.7
Dosing to necropsy[1]			25.5±4.2	18.7± 2.5
Mating to necropsy[3]			31.8±2.5	22.5± 3.3
Reproduction				
Corpora lutea: animal	13.7± 1.4	13.3± 0.7	12.6±0.4	13.4± 0.5
Implantation sites: animal	10.7± 1.1	8.2± 2.5	11.4±0.6	11.2± 0.7
Corpora lutea: implantation site	1.3± 0.1	1.9± 0.3	1.1±0.0	1.2± 0.1
Resorptions: litter	1.7± 0.1	2.2± 1.1	0.5±0.2	3.4± 1.1
Resorptions: %[4]	18.2±10.1	29.4±13.4	3.4±2.1	29.1±10.8
Embryonic effects				
Pups: litter	9.4± 0.2	6.4± 1.5	10.9±0.6	8.7± 1.3
Weight range	0.7− 2.0	1.0− 2.1	1.1−2.3	0.9− 2.4
Fetal weight	1.6± 0.1	1.5± 0.1	1.7±0.7	1.7± 0.1
Liver fatty infiltration: litter	0.1± 0.1	0.0± 0.0	0.0±0.0	3.7± 1.6
Liver fatty infiltration: %[5]	0.0± 0.0	0.0± 0.0	0.0±0.0	37.1±12.4
Ossification sites[6]				
Pups examined	43	34	36	46
Mean closure grading[7,8]	4.4± 0.3	2.8± 0.4	4.0±0.3	3.0± 0.3
Sternal elements[9]	3.6± 0.4	2.7± 0.4	3.9±0.5	3.3± 0.6
Metacarpals[10]	2.9± 0.1	2.5± 0.3	2.9±0.3	3.0± 0.2
Metacarpals[11,12]	2.2± 0.4	1.6± 0.3	2.8±0.2	2.0± 0.5

[1]Data was not collected for the epinephrine-treated animals.
[2]± 1 SEM.
[3]Norepinephrine, $P < 0.05$, analysis of variance.
[4]Norepinephrine $P < 0.05$, Mann-Whitney U test.
[5]Norepinephrine $P < 0.024$, Mann-Whitney U test.
[6]As observed in Alizarin Red stained specimens as an index of maturity.
[7]Based on a 1−5 scoring system.
[8]Epinephrine and Norepinephrine, $P < 0.005$ analysis of variance.
[9]Epinephrine, $P < 0.01$, analysis of variance.
[10]Epinephrine, $P < 0.01$, Mann-Whitney U test.
[11]Epinephrine, $P < 0.05$, analysis of variance.
[12]Norepinephrine, $P < 0.005$, Mann-Whitney U test.

gradings which were significantly lower ($P < 0.005$) than their respective controls. Closure gradings were 2.8 and 3.0 in fetuses from dams treated with epinephrine and norepinephrine, while control animals had closure gradings of 4.4 and 4.0, respectively. Ossification was also reduced in the sternums of fetuses from epinephrine-treated dams. These fetuses averaged 2.7 ossified sternal elements while control fetuses had 3.6. A similar although nonsignificant trend was exhibited in the norepinephrine-treated group. Metacarpal ossification was also reduced ($P < 0.01$) in fetuses from epinephrine-treated females. Upon examination the fetuses from treated females had an average of 2.5 ossified metacarpals while control fetuses averaged 2.9 Epinephrine and norepinephrine also caused a significant reduction in the number of ossified metatarsals. While the number of metatarsals in control fetuses was 2.2, fetuses from treated feamles had 1.6. Fetuses from norepinephrine-treated dams had 2.0 ossified metatarsals which represented a significnat reduction ($P < 0.005$) in ossification from the 2.8 metatarsals observed in control fetuses.

The data reported in Tables 1 and 2 attempt to present teratological evidence from separate experiments comparing the similar effects of mescaline and the catecholamines

when they are administered during organogenesis. These data do not indicate direct relationships between the different treatments nor have they been tested statistically. They merely represent a comparison of effects.

DISCUSSION

The results obtained in the present study fail to confirm the observations of Geber ('67) who reported low doses of mescaline (3 mg/kg) caused severe abnormalities of the brain. In this study the effects of mescaline were characterized by decreased reproductive success, including a decreased maternal weight gain and a delay in skeletal ossification. These findings are similar in many respects to those observed following a subcutaneous injection of either epinephrine or norepinephrine. In all cases these agents appear to affect the embryo during the early stages of development. There do appear to be some differences with respect to the time of embryonic death. In the case of epinephrine, death appears to occur prior to implantation as indicated by the increased corpora lutea to implantation site ratio. This effect may be related to an increase in the rate of tubal transport, since these results parallel those reported by Auletta ('71) and Adamson ('71) in the rabbit. On the other hand, norepinephrine and mescaline cause an increase in resorptions along with a decrease in litter size. This effect is probably related to events which occur during the early stages of placentation which occurs between Days 5 and 7 of gestation (Boyer, '68; Ward, '48). This is based upon the absence of fetal bodies with the resorption site.

These experiments which examined the teratogenicity of mescaline and the catecholamines were undertaken because of the suggestion by Brodie et al. ('59) that epinephrine and norepinephrine may have a role in the mechanism of action of mescaline. Evidence based on the similarities in teratogenic response would tend to indirectly support this conclusion and suggest that further studies be undertaken aimed at determining the mechanism of action of mescaline.

LITERATURE CITED

Adamson, K., E. Mueller-Heubach, and R.E. Myers (1971) Production of fetal asphyxia in the rhesus monkey by the administration of catecholamines to the mother. Am. J. Obstet. Gynecol, *109*:248–269.

Auletta, F.J. (1971) Effects of epinephrine on implantation and fetal survival in the rabbit. J. Reprod. Fertil, *127*:281–282.

Boyer, C.C. (1968) The Golden Hamster. Iowa State University Press. R.A. Hoffman et al., eds, pp. 73–90.

Brodie, B., S. Spector and PA. Shore (1959) Interactions of drugs with nor-epinephrine in the brain. Symposium on the catecholamines. O. Krayer (ed.). Baltimore: Williams and Wilkins.

Dawson, A.B. (1926) A note on the staining of the skeleton of cleared specimens with alizarin red S. Stain. Techniques, 1:*123*.

Geber, W. (1967) Congenital maformations induced by mescaline, L.S.D., and bromolysergic acid in the hamster. Science, *158*:265–267.

Grace, G.S. (1934) The action of mescaline and some related compounds. J. Pharmacol. Exp. Ther., *50*:359–371.

Orsini, M.W. (1961) The external vaginal phenomena characterizing the stages of the estrous cycle, pregnancy, pseudopregnancy, lactation, and the anestrous hamster *Mesocricetus auratus*. Proc. Anim. Care Panel, *11*:183–206.

Patel, A.R. (1968) Mescaline and related compounds. Arnemittel Forschung, *11*:11–47.

Sokal, R.R. and F.J. Rohlf (1969) Biometry, The Principles and Practices Statistics in Biological Research. W.H. Freeman and Company, San Francisco.

Strausbaugh, L.D. (1971) Mescaline teratology in the hamster. Wright State University, Undergraduate Honors Thesis (unpublished).

Taska, R.J., and J.C. Schoolar (1972) Placental transfer and fetal distribution of mescaline-C^{14} in monkeys. J. Pharmacol. Exp. Ther., *183*:427–432.

Ward, M.C. (1948) The early development and implantation of the golden hamster cricetus auratus, and the associated endometrial changes. Am. J. Anat., *82*:231–276.

World Health Organization (1967) Principles for the testing of drugs for teratogenicity. Report of a WHO group. WHO Technical Report Series, No. 364. Geneva. pp. 5–18.