TOXICITY AND EFFECTS OF INCREASING DOSES OF MESCALINE

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Mescaline, (3,4,5-trimethoxyphenylethylamine), is one of the nine alkaloids found in the peyote cactus (Henry, 1949). Administered to man either orally or intravenously, it produces colored visions, synesthesias, and functional alterations of the autonomic nervous system (Hoch, 1951). Psychiatrists have used mescaline experimentally to induce a temporary psychosis with the hope of gaining insight into the nature of certain mental disorders. The effect on the autonomic nervous system and the chemical similarity to epinephrine and norepinephrine suggested that the mode of action of mescaline may involve a disturbance in the activity of the adrenergic substances.

The present work was undertaken to investigate the physiological effects of increasing doses of mescaline, of chronic administration, and of the influence of certain drugs on the action of mescaline. The possibility that mescaline competes for certain epinephrine receptors was considered and this phase of the investigation was emphasized.

METHODS. An inbred, local strain of Sprague-Dawley rats was used. Male animals 160 to 230 grams in weight were used in the experiments. No animal was used more than once in the acute experiments. Unless otherwise stated, the rats were permitted to feed *ad lib.* until the time of the experiment.

The intraperitoneal LD_{50} of mescaline was determined by a method using probit analysis and groups of ten animals per dose (Litchfield and Wilcoxon, 1949).

The effects of mescaline on the heart rate, blood sugar, and behavior were observed for intraperitoneal doses ranging from 5 mgm. to 400 mgm. per kgm. body weight. A pair of electrodes made from phonograph needles—one in the anterior part of the brain and the other in the tail—was used to record the electrocardiogram. The rats were unanesthetized.

Blood glucose was determined by the Nelson variation of the Somogyi method (Nelson, 1944). Blood samples were collected from the tail before and after the administration of the drugs. All drugs were given intraperitoneally unless otherwise specified.

Synthetic mescaline sulfate (Hoffmann-La Roche) was used. The crystals were dissolved in distilled water immediately before use.

The effects of chronic administration of mescaline were studied. A group of ten rats was given daily intraperitoneal injections of 50 mgm. of mescaline sulfate per kgm. body weight. A group of control rats received daily injections of an equal volume of sterile Ringer's solution. The injections were given five days a week and the experiment was continued for one and one-half months. Weights were recorded weekly. Before sacrifice, at the end of the experiment, blood sugars were determined before and after the final injection of mescaline.

All results were calculated in terms of the means of all the animals in a group and the standard deviation.

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RESULTS. *Acute Toxicity.* The intraperitoneal LD_{50} for unfasted, male, albino rats was found to be 370 mgm./kgm. body weight with upper and lower confidence limits of 410 and 330 mgm./kgm. for 19/20 probability. These results are within the ranges given by other authors for white mice, guinea pigs, and frogs (Grace, 1934; Delay *et al.* 1950). Death was accompanied by flexor convulsions and respiratory arrest, followed in several minutes by cardiac arrest. All doses of mescaline over 700 mgm./kgm. resulted in the death of the animal after a short period of hyperactivity and flexor convulsions. It was not possible to block the terminal convulsions with curare or decamethonium.

Effects of Increasing Doses of Mescaline. Mescaline sulfate produced bradycardia and hypoglycemia. The results are seen in table 1. It should be noted that only the lowest dose is within the range of those taken by human beings. The bradycardia was maximal at thirty minutes and the heart rate had returned to normal at the end of an hour. The two deaths at the 120 mgm./kgm. dose occurred after great acceleration of heart rate. One animal had a heart rate of 550/min. thirty minutes after injection, while the other rat had an initial depression of rate followed by a rise to 490/min. shortly before death at one hour. This particular dose is of special interest because in all other rats of the group, bradycardia and vasoconstriction was maximal. Vasoconstriction was estimated from color of ears and tail and difficulty in taking a blood sample from the tail. At this dose the reaction to pain and touch appeared to be depressed as evidenced from the indifference to pinprick, tail snip, and touch on body. The deaths at 411 mgm./kgm. occurred less than thirty minutes after injection with respiratory arrest and tonic flexor convulsions. Transient cyanosis, apparently related to the period of maximal cardiac slowing was observed at all doses.

Hypoglycemia became more severe as the dose was increased. The depression of blood sugar appeared during the first thirty minutes after injection, became

TABLE 1

Effect of various doses of mescaline on blood glucose and heart rate in fasted and unfasted rats

Means of all animals in group.

Dose—I.P.	Unfasted			24-hr. Fasted		
	1 hr. Glucose	H.R./min.	Deaths	1 hr. Glucose	H.R./min.	Deaths
mgm./kgm.	*mgm. %*			*mgm. %*		
0.9% NaCl	97 ± 10†	348 ± 54†	0/103	71 ± 17†	431 ± 42†	0/51
5.8 mescaline*	82 ± 22	322 ± 25	0/12	63 ± 18	440 ± 24	0/23
58 mescaline	50 ± 8	206 ± 37	0/12	62 ± 18	309 ± 49	0/13
116 mescaline	40 ± 12	217 ± 42	2/14	57 ± 12	258 ± 30	0/11
205 mescaline	25 ± 17	318 ± 29	0/10	47 ± 18	310 ± 29	0/12
411 mescaline	26 ± 7‡	267 ± 37‡	10/17	45 ± 5	—	2/4

* Dose taken by human beings.

† The figures in all instances are the means of the group and the standard deviation.

‡ Only survivors included.

maximal at one hour, remained low for four hours after injection, and returned to normal or was slightly elevated at the end of twenty-four hours. In spite of the severe depression of blood sugar, the rats did not appear comatose or have clonic-tonic convulsions.

In the fasting animal it was found that, although the blood sugar level was lower before injection, mescaline did not reduce the glucose as much as it did in the unfasted rats (table 1). Maximum slowing of the heart was again found at an intermediate dose although twice as much mescaline was required to produce the effect. The fasting rats appeared to be protected against the hypoglycemia and bradycardia produced by mescaline.

After the animals were returned to their cages, they groomed themselves, huddled, stood on their hind legs without moving for 10 to 20 minutes when threatened, and were hyperreactive to noises for several hours after the injection. Weakness of the hind limbs, exophthalmos, trembling, and hyperreactivity to a tap on the spine were frequently seen. Chewing, sniffing, and sneezing was noted in all the animals given mescaline. There appeared to be a resemblance between the effects of mescaline and the effects reported by Gellhorn for DFP (1953). The following day the rats were drowsy and slept much of the time. By the third day they were normal in behavior.

Effects of Certain Drugs on The Action of Mescaline. The effects of 5, 10, and 20 units of insulin per kilogram body weight given subcutaneously were determined for groups of six animals. These doses were tolerated by the unfasted, male, adult rat. Each of the previously tested insulin doses was given one hour before an intraperitoneal mescaline dose of 6, 30, 60, and 100 mgm./kgm. to groups of six animals. It was found that the hypoglycemia produced by the combination of the drugs was equal to the sum of the effects of the substances alone at the lower dose of mescaline. The hypoglycemia at the higher dose of mescaline was greater than the sum of the individual actions. Doses of insulin of 10 units/kgm. caused death when combined with 30 mgm./kgm. doses of mescaline. The 100 mgm./kgm. dose of mescaline was lethal in the presence of any of the tested doses of insulin. The results may be seen in table 2. The hypoglycemia produced by insulin and mescaline may be a result of two independent processes although there may be some potentiation of the drugs at the higher dose of mescaline. It should be noted that the lethal dose of mescaline in the presence of insulin has been moved toward the range of doses taken by human beings.

The effects of subcutaneous and intraperitoneal doses of 0.12 mgm./kgm. of epinephrine on heart rate, blood sugar, and survival were determined for unfasted rats. These doses were non-lethal and produced marked tachycardia and hyperglycemia as determined one-half and one hour respectively after administration. Since the values were more consistent after the subcutaneous doses the latter route was chosen for the experiment. It was determined experimentally that a fifteen-minute interval after the subcutaneous epinephrine injection was long enough to allow for absorption. Mescaline doses of 100, 200, and 400 mgm./kgm. were given intraperitoneally to groups of six or more rats fifteen minutes after a subcutaneous injection of 0.12 mgm./kgm. of epinephrine. As before,

TABLE 2

Synergistic effect of insulin on the hypoglycemia produced by mescaline

Rats were unfasted, 5 units/kgm. insulin given one hour subcut. before mescaline.

Dose	Glucose 1 hr. After Mescaline	Deaths
mgm./kgm.		
0.9% NaCl	97 ± 10†	0/103
Insulin 5 units	45 ± 4	0/16
6 mgm. Mes. + 5 units Ins	38 ± 5	0/6
30 mgm. Mes. + 5 units Ins	24 ± 6	0/6
60 mgm. Mes. + 5 units Ins	10 ± 2‡	2/6
100 mgm. Mes. + 5 units Ins	—	6/6

† The figures are the means of the groups and the standard deviation.

‡ Only survivors included.

TABLE 3

Protective effect of epinephrine on hypoglycemia produced by mescaline

Rats were unfasted, 0.12 mgm./kgm. epinephrine subcut. given 15 min. before or 30 min. after mescaline as indicated.

Dose	Glucose 1 hr. after Mescaline	Heart Rate ½ hr. after Mescaline	Deaths
mgm./kgm.			
0.9% NaCl	97 ± 10†	348 ± 54†	0/103
0.12 mgm. Epi	170 ± 16	420 ± 35	0/12
100 mgm. Mes. after 0.12 mgm. Epi	131 ± 10	250 ± 49	0/6
200 mgm. Mes. after 0.12 mgm. Epi	130 ± 18	231 ± 18	0/6
400 mgm. Mes. after 0.12 mgm. Epi	83 ± 30‡	332 ± 45‡	7/12
200 mgm. Mes. before 0.12 mgm. Epi	79 ± 21	—	1/10

† All figures are means of the group and the standard deviation.

‡ Only survivors included.

determination of heart rate was made one-half hour and blood sugar one hour after injection of mescaline. It was found that the hypoglycemic action was almost completely blocked (table 3). Maximal bradycardia again appeared at an intermediate dose but three and one-half times as much mescaline was required to produce the effect as compared to mescaline alone. In spite of the protective effect of a previous dose of epinephrine, the LD_{50} was not increased. Respiratory failure was the terminal event. The character of the terminal convulsion was modified from a tonic-flexor type to a clonic type. When epinephrine was given one-half hour after mescaline the hyperglycemic action of epinephrine was partially blocked.

During the course of the experiment, cardiac puncture sometimes had to be resorted to for blood samples because of the severe vasoconstriction. The difference in blood sugar from the tail vein and the heart was determined on groups of six animals for no medication, mescaline, and epinephrine alone, and in combination. A 15 mgm. per cent difference was found for the normal and mes-

caline groups, while a 20 mgm. per cent difference was found for the epinephrine and combination group. It was felt that this represented approximately an arterial-venous difference and showed that the hypoglycemia of mescaline was not the result of an increased uptake of glucose by the tissues.

An analeptic action of mescaline which resulted in the dramatic arousal of animals previously anesthetized with pentobarbital was noted early in the study. When the analeptic effect was investigated, it was found that even 50 mgm./kgm. doses of mescaline caused death in fifty per cent of deeply anesthetized animals, although the survivors awakened in one-half the usual time. The investigation into the possible use of mescaline as an analeptic in barbiturate poisoning was discontinued because of the toxicity.

Physostigmine when given in doses of 1 mgm./kgm. body weight did not cause death. Since physostigmine frequently caused muscular twitch, a previous subcutaneous 2 mgm./kgm. dose of decamethonium was given to prevent muscle artifact in the EEG recordings which are described in another paper. Mescaline given in a dose of 30 mgm./kgm. after the injection of the sublethal dose of physostigmine and decamethonium, resulted in the death of all the animals. The rats died rapidly with gasping respiration and marked cyanosis. These findings are consistent with Gellhorn's (1953) report of synergism between mescaline and anticholinesterases.

Chronic Experiments. The results of the chronic experiments are shown in table 4. At the end of the experiments all of the animals which had received mescaline had ruffled coats, squealed when handled, and generally seemed more apprehensive. Auditory stimuli, *e.g.* key jangling, produced excitement but not

TABLE 4

Results of chronic administration of mescaline

50 mgm./kgm. daily—1.5 months.

Means of All Animals in Groups	Controls	Experimentals
Deaths	0/10	2/11
Body weight	240 ± 40 gm.†	214 ± 30 gm.†
Weight gain during experiment	144 ± 17 gm.	128 ± 14 gm.
Weight liver	10.8 ± 2 gm.	11.2 ± 1 gm.
Weight liver/body weight	0.046 ± .005	0.053 ± .004
Weight adrenals (pair)	0.052 ± .020 gm.	0.072 ± .014 gm.
Weight adrenals/body weight	0.00022 ± .00007	0.00034 ± .00006
Weight heart	0.92 ± .04 gm.	0.83 ± .05 gm.
Weight heart/body weight	0.0039 ± .0003	0.0040 ± .0004
Heart rate at end of experiment before injection	360 ± 35/min.	418 ± 28/min.
Blood glucose at end of experiment before injection	95 ± 21 mgm.%	110 ± 19 mgm.%
Heart rate at end of experiment ½ hour after injection	360 ± 29/min.	228 ± 15/min.
Blood glucose at end of experiment 1 hour after injection	93 ± 20 mgm.%	76 ± 12 mgm.%

† The figures are the means of the groups and the standard deviation.

convulsions during the first week. After the first week, there did not appear to be any increased sensitivity to noise. The experimental rats had heart rates and blood sugars in the upper normal ranges at the end of the experiments before the daily injection of mescaline. No tolerance was developed to the hypoglycemia and bradycardia following the injection of the mescaline.

Gross examination of the viscera showed only an increase in weight of the livers and adrenals. Small hemorrhages were noted in some of the lungs and livers. Samples of heart, liver, kidney, and adrenals were sectioned and stained with Gomori's tricolor process (Gomori, 1950). No changes were seen in the hearts and kidneys. The livers of the rats receiving mescaline showed some fatty infiltration. The increased weight of the adrenals appeared to be due to hyperplasia of the cortex.

Discussion. So far as it is known, no human being has died as a result of taking mescaline. The LD_{50}'s of mescaline are within the same range for a number of species of animals. It is not known how these may relate to man. Physostigmine, insulin, and barbiturates in high doses increase the toxicity of mescaline. The dose of mescaline which caused death when combined with insulin is closer to the range of doses taken by human beings. It is possible that the presence of hyperinsulinism might result in the death of a person taking mescaline. It is interesting that thiamin has been reported to increase the toxicity of mescaline (Dessi and Labo, 1950) as well as of insulin (Burke and McIntyre, 1938).

Previous injection of epinephrine prevented the hypoglycemia and decreased the bradycardia produced by mescaline but did not prevent death. Twenty-four-hour fasting also had a significant effect in decreasing the degree of hypoglycemia and bradycardia. It is possible that the protective action of the fasting might be due to endogenous epinephrine since these animals were alert, had low voltage fast EEG patterns, and fast heart rates.

It has been reported that arylalkyl amines with the catechol groups blocked, such as mescaline, can compete for epinephrine receptors in the liver and prevent a hyperglycemic response (Ellis and Anderson, 1951). Such a mechanism is consistent with our findings of hypoglycemia which can be prevented by a previous injection of epinephrine, and conversely, a previous injection of mescaline can partially block the hyperglycemic response of epinephrine. Although knowledge of how mescaline acts is far from complete, it is probable that competition for epinephrine receptors is a factor. Such a blockade of some epinephrine receptors may then result in the disturbance of adrenergic mechanisms which have been suggested by several investigators (Hoch *et al.*, 1953; Hoch, 1955; Marrazzi and Hart, 1955). The apparent potentiation of parasympathetic effects may be due to an unmasking effect as a result of depression of some epinephrine actions.

The results of the chronic experiments suggest that mescaline has a nonspecific stressing effect on the organism. No tolerance to the effects of mescaline were observed.

SUMMARY

The intraperitoneal LD_{50} of mescaline sulfate for the unfasted, male, albino rat was found to be 370 mgm./kgm. body weight with upper and lower confidence

limits of 410 and 330 mgm./kgm. body weight for 19/20 probability. Flexor convulsions and respiratory arrest were the terminal events.

Bradycardia and hypoglycemia occurred after injection of varying doses of mescaline.

Fasting has a protective action against the hypoglycemia and bradycardia produced by mescaline.

Previous injection of epinephrine protects against the heart slowing and decrease of blood sugar, but not death. A previous injection of mescaline partially prevents the hyperglycemia produced by epinephrine.

Mescaline has an analeptic effect against the usual anesthetic dose of pentobarbital but appears to be too toxic to be useful in barbiturate poisoning.

Insulin potentiated the hypoglycemia produced by mescaline and brought the lethal dose closer to the range of doses taken by human beings.

Mescaline appeared to have a nonspecific stressing effect on animals when given daily for one and one-half months. No tolerance was noted to the hypoglycemia or bradycardia produced by an injection of mescaline at the end of the experiment.

The mode of action of mescaline is still unsolved, but it appears probable that competition for some epinephrine receptors may be involved. Such a blockade of receptors may result in a disturbance of adrenergic mechanisms.

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