Br. J. Pharmac. (1975), 55, 133-139

A COMPARISON OF THE EFFECT OF MESCALINE ON ACTIVITY AND EMOTIONAL DEFAECATION IN SEVEN STRAINS OF MICE

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1 Mescaline hemi-sulphate (35 mg/kg body weight) was injected intraperitoneally into male mice (*Mus musculus*) from seven genetically diverse laboratory strains.

2 The effect of mescaline was found by comparison of the emotional defaecation and open field activity of mice after mescaline injection with the performance of the same mice after a subsequent saline (0.9% w/v NaCl solution) control injection.

3 In strains A2G, C3H/He, C57BR/cd, CBA/Cam and F/St, mescaline inhibited emotional defaecation and stimulated open field activity. These effects did not occur in strains ICFW and Schneider.

4 A positive relationship was found between the degree of emotional defaecation characteristic of each strain in the saline control experiment and the inhibitory effect of mescaline on emotional defaecation.

5 Pre-treatment of mice with tranylcypromine (20 mg/kg body weight, i.p.) had no effect on emotional defaecation or on its inhibition by mescaline.

Introduction

The genetic resources of the wide variety of strains of the laboratory mouse (*Mus musculus*) have not been much exploited by pharmacologists. One might expect to gain valuable information on the relationship between the different effects of a single drug, or the similar effects of different drugs, by the use of genetic strains which differ in their pharmacological reactions. In spite of the good example set by pharmacogeneticists (Meier, 1963), in much pharmacological work on mice there seems to be an assumption that it is of no great consequence which strain of mice is used, provided it is albino. Indeed, the fascination of the albino gene is so great that some authors regard a phrase such as 'adult male albino mice' as a sufficiently scientific description of the strain they used and give no further details. In the belief that different strains of mice may differ profoundly in their reactions to drugs, I have measured some effects of mescaline on mice from seven different strains. Mescaline has been reported to have a variety of different effects on mice. These include twitching of the hindquarters (Cooper & Walters, 1972) or of the head (Corne & Pickering, 1967), inhibition of aggressiveness (Rewerski, Kostowski, Piechocki & Rylski, 1971), increased motor activity (Shah & Himwich, 1971), decreased motor activity (Cooper & Walters, 1972) and a modification of nest-building behaviour (Schneider & Cheroweth, 1970). I chose to study a version of open field activity, and 'emotional' defaecation. Male mice only were used in order to reduce the biological variables. The scheme was to inject each mouse with mescaline in one experiment, and with saline (0.9% w/v NaCl solution) in a subsequent control experiment, and see if the effect of mescaline showed any interesting differences in different strains.

Methods

The mice and their preparation

Mice from the following seven strains were used: A2G, C57BR/cd, C3H/He, F/St, ICFW (all from the Laboratory Animals Centre, Carshalton), CBA/Cam (from the Department of Genetics, University of Cambridge), and Schneider (from the Imperial Cancer Research Fund Laboratories, London). Strains A2G, ICFW and Schneider are albino. All the strains except Schneider are inbred. Adult (from 12 to 32 weeks old) males were routinely kept in cages (11 cm x 29 cm) with two females which were usually of the same strain as the male. Young litters were sometimes present. All males were kept in their respective cages for at least two weeks before being tested. The cage

floors were covered with beechwood sawdust and the bedding was paper. Water and food (Christopher Hill No. 41B pencils) were supplied *ad libitum*. The ambient temperature of the animal house and the experimental laboratory varied between 19 and 23°C. Mice were left undisturbed during the day before a test and their cages were then brought to the laboratory and left undisturbed for at least 30 min before the test began.

The experimental schedule

The open field consisted of an 87.5 x 87.5 cm square of formica ruled into 49 squares. It was surrounded by a 35 cm high wall of brown cardboard and in the middle was placed an open-topped white cardboard starting enclosure 17 cm high and exactly enclosing the central square. The main illumination apart from diffuse daylight came from an Atlas 80 W 'Daylight' fluorescent tube 1.5 m above the open field. The noise level varied between 50 to 55 dB and came mainly from a window fan. Before each mouse was introduced, the open field and the starting enclosure were cleaned with dilute vinegar and wiped dry in order to remove (for the human nose) any smell left by the previous occupant. A mouse to be tested was gently transferred from its cage to the starting enclosure and allowed to walk off the hand on to the formica surface. After 3 min the enclosure was removed and the mouse left to explore the open field for 2 minutes. The number and the total weight of the faecal boluses produced during the initial 3 min and the number of squares in the open field subsequently entered were recorded.

The complete experimental schedule for each mouse began with the procedure described above. The mouse was then removed from the open field, weighed and injected intraperitoneally with mescaline hemi-sulphate (Sigma Ltd.) 35 mg/kg in saline. The volume injected was 0.1 ml per 10 g body weight. The mouse was then returned to its cage and the test repeated (without any injection) 1 h later, and 1 h later again. As a control the schedule was then repeated with the same mice between 7 and 10 days later, injecting normal saline in place of mescaline. Two batches of six males (each male kept with two females) were tested from each strain. Three males of each batch were tested in the forenoon and three in the afternoon. Data from all seven strains were collected in the course of one year and the testing of the two batches from each strain was separated by at least three months. The Walsh two-tailed test for paired non-parametric data (Siegel, 1956) was used to calculate the significance of the effect of mescaline on defaecation and open field activity. To find the effect of a monoamine oxidase inhibitor some mice were injected intraperitoneally with tranylcypromine (Smith, Kline & French) 20 mg/kg in saline 16 to 24 h before the mice were tested as described above.

Results

The total number of boluses produced by each batch of six mice in the mescaline experiment and in the subsequent saline control experiment are shown in Table 1. In the first five strains mescaline inhibited defaecation, moreover the degree of inhibition of the two batches within each strain was in no case significantly different. (The second batch of A2G and C3H mice were pre-treated with tranylcypromine but since this had no significant effect on their defaecation or on its inhibition by mescaline they have been included in the general comparison. Tranylcypromine had been expected to modify the effect of mescaline for reasons which are explained later.) With ICFW and Schneider mice the number of boluses produced after mescaline was not significantly different from the number produced after saline, and there was therefore no evidence of any effect of mescaline in these two strains. However, it is clear that ICFW and Schneider mice defaecate much less than the other five strains, and it is arguable that they defaecate so little that their occasional defaecation is not an emotional reaction but a physiological necessity which is not amenable to inhibition by mescaline. This would mean that some other measure of the effect of mescaline is needed for these two strains, and such a measure is fortunately provided by open field activity.

Table 2 shows the mean activity of each strain before injection and 1 h after injection with mescaline or saline. Two hours after injection the effect of mescaline on activity was much reduced, and more variable. The data from both batches have been pooled in all strains except A2G and C3H. In most strains there was an increase in activity after mescaline and a decrease in activity after saline; the effect of mescaline is therefore calculated as shown in Table 2. With ICFW and Schneider mice mescaline was followed by reduced activity, indeed in both these strains the reduction in activity after mescaline was not significantly different from the reduction in activity after saline. Therefore with both defaecation and activity measurements the conclusion is that mescaline had no measurable effect on ICFW or Schneider mice. In C57BR, CBA and F/St mice the effect of mescaline was a significant increase in activity. In batch 1 of both A2G and C3H

Table 1 Numbers of faecal boluses produced by each batch of six mice in each test

Strain:	*A2G*		*C57BR/cd*		*C3H/He*		*CBA*		*F/St*		*ICFW*		*Schneider*		*Totals*
Batch:	*1*	*2**	*1*	*2*	*1*	*2**	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2*	
							Mescaline experiment								
Before injection	20	25	11	18	17	17	23	20	21	22	0	0	3	0	197
1 h after injection	0	3	6	0	4	7	4	0	4	8	0	0	1	1	38
2 h after injection	5	4	3	9	3	4	11	10	10	6	2	3	4	1	75
Total after mescaline	5	7	9	9	7	11	15	10	14	14	2	3	5	2	113
							Saline experiment								
Before injection	22	29	14	27	19	13	19	22	18	20	0	0	3	0	206
1 h after injection	24	25	15	18	16	17	9	10	16	13	2	1	3	0	169
2 h after injection	26	20	22	23	25	18	17	16	11	15	4	4	4	0	205
Total after saline	50	45	37	41	41	35	26	26	27	28	6	5	7	0	374
†Effect of mescaline	45	38	28	32	34	24	11	16	13	14	4	2	2	−2	
Probability less than	0.011		0.011		0.011		0.011		0.048		NS		NS		
Mean age at mescaline expt. (wks)	24	26	21	19	27	30	20	25	25	24	30	18	28	21	
Mean body weight (g)	24	24	21	26	27	27	21	25	16	20	29	24	29	33	

* Pre-treated with tranylcypromine. † The total number of boluses after saline minus the total after mescaline. NS = not significant.

Table 2 Mean numbers of open field squares entered

Strain:	*A2G*		*C57BR/cd*	*C3H/He*		*CBA*	*F/St*	*ICFW*	*Schneider*	*Totals*
Batch:	*1*	*2**	*1 & 2*	*1*	*2**	*1 & 2*	*1 & 2*	*1 & 2*	*1 & 2*	
						Mescaline experiment				
Before injection (A)	22	6	78	50	28	26	52	41	88	391
1 h after injection (B)	40	20	104	62	42	51	49	32	61	
						Saline experiment				
Before injection (C)	25	14	90	52	40	41	48	68	69	447
1 h after injection (D)	5	13	59	40	41	27	22	48	49	
Effect of mescaline (B–A) + (C–D)	38	15	57	24	13	39	23	11	–7	
s.e. mean	10.9	6.9	9.6	7.3	13.3	10.5	6.1	7.5	8.9	
Probability less than	0.094	0.094	0.011	0.031	NS	0.011	0.011	NS	NS	
	0.011			0.048						

* Pre-treated with tranylcypromine. NS = not significant. s.e. mean = standard error of the mean of the effect of mescaline.

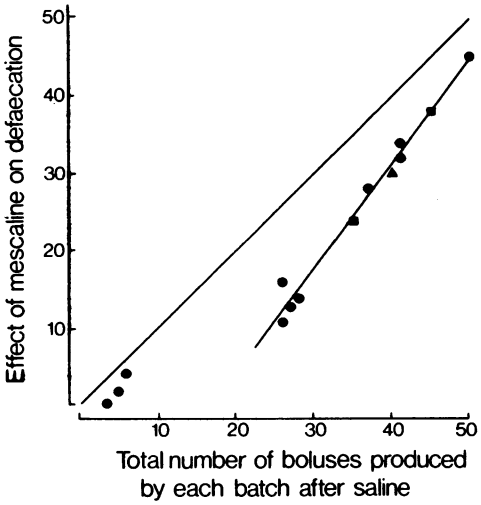

Figure 1 Display of data in Table 1 to show the relationship between defaecation after saline and the effect of mescaline on defaecation. Each symbol represents one batch of six mice, except in the Schneider strain in which the two batches have been pooled and then halved to give an average value for a batch of six Schneider mice. (▲) CBA batch 3; (■) tranylcypromine-treated batch 2 of A2G and C3H/He.

mescaline also increased activity significantly. In both the tranylcypromine-treated second batches of A2G and C3H the effect of mescaline was less marked although not significantly different from the untreated batches. The effect of tranylcypromine was not investigated further. Among the five strains in which mescaline had an effect on both activity and defaecation there was no correlation in the size of the effect on the two measurements. This is not surprising when one reflects that open field activity is a more complex activity than defaecation, and the effect of mescaline on activity is therefore subject to a wider range of influences, both genetic and environmental, than is its effect on defaecation. Nevertheless it seems that the ICFW and Schneider mice are so much less responsive to mescaline than are the other five strains that the difference can be seen in both the defaecation and the activity measurements. The totals on the right of Table 2 show that the mice were on average less active before the mescaline injection than they were before the subsequent saline injection, however the tendency was not statistically significant (Walsh test, $P > 0.1$).

If the effect of mescaline on defaecation is examined in greater detail (Table 1) among the five high-defaecating strains an inverse relationship between the number of boluses produced after mescaline and after saline can be discerned. This relationship means that the inhibitory effect of mescaline is greatest in those strains which defaecate most after saline. This is shown in Figure 1, in which a batch which was completely inhibited by mescaline would be plotted on the diagonal line drawn from the origin. The greater the number of boluses produced by a batch after mescaline the greater the vertical distance it falls below the diagonal. The two batches in each strain fall fairly near to each other along the regression line ($b = 1.35$, $P < 0.001$) which is to be expected if genetical factors are important in determining their position. The ICFW and Schneider data clearly do not fall on the regression line, but as we have already seen they can be regarded as extreme examples of the same tendency in that they defaecated very little after saline and were not significantly inhibited by mescaline. These two strains each defaecated significantly less after mescaline than any of the other five strains except A2G. The regression line in Figure 1 cuts the abscissa scale at 16.5 boluses. One would therefore expect mescaline not to inhibit strains which produced less than about 16 boluses after saline under the conditions used in these experiments.

Effect of dosage Perhaps the few boluses produced by ICFW and Schneider mice were not amenable to inhibition by mescaline, even at a higher dosage. This possibility was not tested, but a dose-response experiment was carried out with batch 2 from each of strains C57BR and CBA. These were the two available batches which had previously given the highest post-mescaline defaecation scores and

Table 3 The effect of dosage on inhibition of defaecation by mescaline

Dosage of mescaline (mg/kg)	*17.5*	*35.0*	*70.0*
		C57BR/cd (Batch 2)	
Before injection	18	18	20
1 h after injection	1	0	0
2 h after injection	9	9	2
Total after mescaline	10	9	2
		CBA (Batch 2)	
Before injection	18	20	21
1 h after injection	7	0	3
2 h after injection	9	10	4
Total after mescaline	16	10	7
Pooled totals	26	19	9

(The data for the standard dose of 35 mg/kg are taken from Table 1)

which were therefore expected to respond most readily to an increase and a decrease of mescaline dosage. C57BR batch 2 was tested with mescaline at half the normal dosage and subsequently at twice the normal dosage. CBA batch 2 was tested with the same dosages but in the reverse order. The results are shown in Table 3 where it can be seen that each batch responded to the changes in dosage. The effect is statistically significant if the data from both batches are pooled ($\chi^2 = 8.10$, $P < 0.025$).

Validity of saline control experiment

Another possibility to be considered was that mescaline affected defaecation in the saline experiment several days later. In order to test this possibility a third batch of each of the A2G, CBA and F/St strains was set up and taken through the standard experiment with saline. The results are shown in Table 4. The A2G and F/St data agree well with those in Table 1 and support the assumption that the mescaline experiment had no effect on the result of the subsequent saline experiment. The CBA batch 3 gave a total which was much higher than expected. However, when this CBA batch was then tested with mescaline it gave a total of only 10 boluses after injection, which brings it close to the regression line (see Figure 1). The open field data from these three controls were not significantly different from the data of mice previously used in a mescaline experiment.

Bolus weight

In nearly all batches throughout the whole series of experiments described above, the mean bolus weight increased slightly after mescaline injection and decreased slightly after saline injection.

Discussion

The data obtained in these experiments describe a relationship between a normal behaviour in seven strains of mice and the effect of mescaline on that behaviour. Let us suppose that when a mouse is put into the enclosure the immediate result is a release in the body of a chemical substance, perhaps an amine, which predisposes the mouse to defaecate if it rises to a sufficient concentration in some part of the brain. Let us also suppose that the hypothetical amine is released in approximately the same amount in mice of different strains. Now suppose that there is an enzyme which inactivates the amine, and that the enzyme is present in greater activity in some strains than in others. In the strains with high enzyme activity the amine will be rapidly inactivated and therefore prevented from reaching an effective level. In the strains with lower enzyme activity the amine will not be inactivated fast enough to prevent it from reaching an effective level and defaecation will take place. The lower the enzyme activity the more amine will accumulate and the more defaecation will take place. On this hypothesis A2G would have the lowest enzyme activity and Schneider the highest activity. Mescaline is metabolized in the mouse and excreted as a mixture of various metabolites and unchanged drug (Shah & Himwich, 1971). If the same enzyme that inactivates the hypothetical defaecation amine also plays an important part in the inactivation of mescaline, this would explain why the effect of mescaline was greater in the higher-defaecating strains and least in the two lowest-defaecating strains.

Which enzyme might be involved? There is some evidence that monoamine oxidase (MAO) can deaminate mescaline in the mouse (Zeller, Barsky, Berman, Cherkas & Fouts, 1958; Shah & Himwich, 1971). It was for this reason that the second batches of A2G and C3H mice were pre-treated with tranylcypromine before being tested with mescaline or saline. As it turned out these two strains were ill-chosen because the hypothesis predicts that they are relatively deficient in MAO (or some other enzyme) and one would therefore not expect them to be much affected if their MAO were inhibited. Unfortunately one would expect the same result if MAO had nothing to do with defaecation. ICFW or Schneider mice would have been a better choice, however, a smaller trial of tranylcypromine on Schneider mice also had no effect on defaecation either before or after mescaline injection, and one must conclude that MAO is probably not involved. There is good evidence (Zeller *et al.*, 1958) that diamine oxidase can deaminate mescaline in several species, and it would be interesting to see if a diamine oxidase inhibitor such as aminoguanidine (Kapeller-Adler, 1970) has any effect on emotional defaecation in ICFW or Schneider mice.

Table 4 Numbers of boluses produced in saline experiment by mice which had not previously been injected with mescaline

Strain:	*A2G*	*CBA*	*F/St*
Batch	*3*	*3*	*3*
Before injection	23	19	13
1 h after injection	27	21	15
2 h after injection	26	19	9
Total after saline	53	40	24

As an alternative hypothesis one could suppose that the genetical variation between strains is not due to variation in the activity of an enzyme but to variation in the number of available receptor sites. If the hypothetical defaecation amine and mescaline share a common receptor site in the brain then genetical variation in the number of such sites available would be expected to alter the response to both amines in the same direction.

It is clearly imperative that pharmacological work on mice should be done with genetically defined strains. No statement about the species as a whole can be reasonably made until several different strains have been investigated. There is no reason yet to suppose that other experimental animals are less genetically variable than the mouse, with the possible exception of the laboratory populations of the Syrian Hamster (*Mesocricetus auratus*) which are apparently all descended from one breeding pair (Searle, 1968).

Mescaline is not an addictive drug. However, where addiction to a certain drug is thought to be heritable, the method of comparing several different inbred strains with respect to both addiction and also possible biochemical causes of addiction might well be informative.

I am grateful to Dr M.B.H. Youdim for the tranylcypromine, to Miss Jill Ford, A.I.A.T., for her care of the mice, and to the Medical Research Council for financial support.

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(Received April 15, 1974. Revised April 25, 1975.)