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THE MEASUREMENT OF THE INFLUENCE OF DRUGS ON VOLUNTARY ACTIVITY IN MICE

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The purpose of the present communication is to describe a method which distinguishes qualitatively between co-ordinated running or walking movements and twitching or convulsive movements in mice, and which yields quantitative information on the former. Winter and Flataker (1951) have used a method very similar to the one to be described in semi-quantitative studies on rats, and Waterman (1947) has briefly reviewed several procedures in common practice.

METHOD

The apparatus consists of a rectangular cage with wooden floor and ends and transparent plastic sides. A beam of light is passed across the cage along the short axis, through the two transparent sides, and on to a photoelectric cell which is adjusted so that when a mouse breaks the beam of light the cell activates a magnetic digital counter. The cage is 42 cm. long, 23.5 cm. wide, and the sides were 8.5 cm. high. These precise dimensions are not critical.

Male albino mice of Carworth Farms CF-1 strain were used throughout. They were allowed free access to food and water until the time they were put in the experimental cage.

Drugs were dissolved in 0.9% sodium chloride solution and were injected intraperitoneally in graded doses to groups of five mice. Dosages of drugs are expressed in terms of drug base. Control groups received 0.9% sodium chloride solution only. Immediately after injection the five mice were put together into the cage, and the number of times the light beam was broken (henceforth called the "count") in 15 minutes was noted.

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RESULTS

Some idea of the reproducibility of the method may be obtained by inspection of the figures for the saline controls in Table I. Each of these figures is the mean of two groups of five mice.

A series of 19 groups of five mice injected with saline were observed over a period of about one month (July–August, 1949). The mean count was 132; the standard deviation of a single count was 19, giving a coefficient of variation $\left(\frac{\text{S.D.}}{\text{mean}} \times 100\right)$ of 15%. There was no evidence of any consistent trend in the counts during the time. During the same period, 11 groups of mice were observed after injection of 1.25 mg./kg. of methamphetamine. The mean count was 325, with a standard deviation of 89, giving a coefficient of variation of 27%. When the responses to methamphetamine were expressed as the ratio of

TABLE I

THE EFFECT OF VARIOUS DRUGS ON CO-ORDINATED ACTIVITY IN MICE

Dose mg./kg.	Epinephrine C	Epinephrine R	Metham-phetamine C	Metham-phetamine R	Strychnine C	Strychnine R	Nicotine C	Nicotine R	Picrotoxin C	Picrotoxin R	Cocaine C	Cocaine R	Amphet-amine C	Amphet-amine R	Ephedrine C	Ephedrine R	Caffeine C	Caffeine R
Saline only	133	1·00	139	1·00	133	1·00	149	1·00	133	1·00	129	1·00	115	1·00	111	1·00	131	1·00
0·0195	131	0·98																
0·039	107	0·80	149	1·07	130	0·97												
0·078	111	0·83	88	0·63	190	1·42												
0·156	39	0·29	183	1·32	142	1·06	123	0·82	130	0·98					108	0·97		
0·312	42	0·31	178	1·28	124	0·93	169	1·13	113	0·85	139	0·95			109	0·98		
0·625	55	0·41	224	1·62	122	0·91	133	0·89	127	0·95	164	1·12	199	1·72	132	1·19		
1·25	15	0·11	367	2·64	66	0·49	7	0·05	11	0·08	164	1·12	152	1·30	165	1·49		
2·50	3	0·02	312	2·24	37	0·28	14	0·09	7	0·05	193	1·40	181	1·57	88	0·79	203	1·54
5·0			386	2·78			14	0·09	13	0·10	190	1·37	309	2·68	62	0·56	165	1·25
10·0			232	1·67					26	0·20	317	2·31	356	3·09	35	0·32	197	1·45
20·0			195	1·41							400	2·92	265	2·29	74	0·67	225	1·71
40·0			96	0·69							639	4·63	109	0·94	37	0·33	220	1·67
80·0											158	1·17	38	0·33	35	0·32	72	0·61
160·0															73	0·66		

C: Number of counts in 15 minutes. R: Ratio of counts after drug to count of saline controls on same day.

the count after methamphetamine to the count of the controls on the same day, the 11 groups gave a mean ratio of 2.49 and the coefficient of variation was 28%. The ratios have been used as ordinates in plotting the dose response curves shown in Fig. 1.

Inspection of Fig. 1 shows that the central nervous stimulant drugs studied may be divided into two groups according to the form of the dose response curve obtained by this method. *Group 1 :* Drugs which, at some dose level, caused an increase in the co-ordinated activity of the mice. This group includes caffeine, cocaine, ephedrine, amphetamine, and methamphetamine. *Group 2 :* Drugs which caused no significant increase in co-ordinated activity in the mice at any dose level. Picrotoxin, nicotine, and strychnine fall into this group, as also do procaine and pyrilamine (not shown in Fig. 1).

It will be noted that the drugs of group 1 are known clinically to prevent sleep and to cause euphoria in man. Evidence of central nervous stimulation by drugs of group 2 was seen with the larger doses in the form of twitchings and convulsions in some mice.

TABLE II

METHODS OF COMPARING THE ACTIVITY OF COCAINE AND EPHEDRINE RELATIVE TO THAT OF METHAMPHETAMINE=1.

(From data of Table I and Fig. 1)

Basis of Comparison	Cocaine	Ephedrine
Reciprocal of doses causing 50% increase in activity over controls ..	0·091	0·36
Reciprocal of doses causing 100% increase in activity over controls ..	0·1	—
Magnitude of effect caused by most active dose	1·6	0·53
Area under dose response curve above control level up to most active dose ..	1·3	0·12

The dose response curves of all the drugs of group 1 showed a peak. In other words, there was a dose level for each drug which caused maximum co-ordinated activity ; doses higher than this, though usually still well below the lethal range, led to less activity. For example, the maximum activity following methamphetamine was obtained with a dose of 5 mg./kg. Higher doses caused less activity, although the LD50 under these conditions was about 100 mg./kg. and only two out of 20 mice were killed by 80 mg./kg.

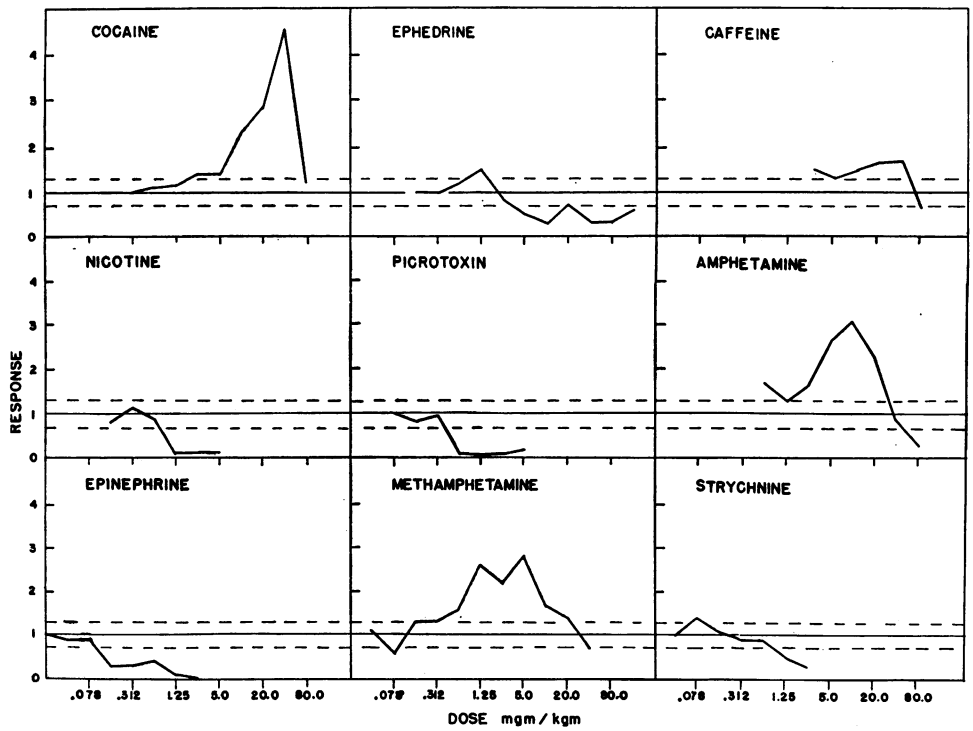

FIG. 1.—The effect of various drugs on co-ordinated activity of mice. Ordinate—response expressed as ratio of count after drug to count of controls on same day. Two dotted lines indicate ± two standard deviations of control counts over whole period of observation.

The method gives quantitative information on the action of drugs of group 1. Table II illustrates some ways in which the relative activities of such drugs may be compared.

Discussion

Obviously only walking or running activity which leads to a mouse breaking the light beam is measured by the apparatus; similar activity confined to the ends of the cage is not detected. However, it seems reasonable to expect that the number of times the beam is broken will be proportional to the total amount of movement of translation of the mice. A larger proportion of the total activity could be measured directly by reflecting the beam across the cage one or more times before it reaches the photo cell; such an arrangement was tried, but resulted in no real advantage.

The counts given by groups of five mice showed a smaller coefficient of variation than those given by groups larger or smaller than five. When more than one mouse is in the cage at the same time, the activity of any one mouse is affected by the activity of the others. In practice, the net effect of such interactions has been to reduce the variability of the counts of groups of five mice in the cage simultaneously below that found for the totals or means of five mice put in the cage consecutively.

The rate of counting of groups of control mice was found to remain quite constant for the first 15–20 minutes after their introduction into the cage. Subsequently, the rate of counting decreased, sometimes steeply. Under the conditions used, counts taken for a period of 15 minutes showed a smaller coefficient of variation than those obtained with any other reasonable period.

Sufficiently large doses of the drugs of group 1 led to a marked decrease in co-ordinated movements around the cage and the production of twitchings and convulsions. These effects were certainly the main reason for the fall in measured activity. It is interesting to note that Schulte, Tainter, and Dille (1939) found that their "jiggle cage" indicated little increase in activity in rats with subconvulsive doses of picrotoxin or metrazole. However, convulsive doses led to a considerable increase in measured total activity. The method here described distinguishes more clearly, at least with the drugs studied, between central nervous stimulating drugs which are used as "psychomotor stimulants" and those which are either used for the production of convulsions or counteraction of states of central nervous depression, or whose central nervous actions are usually unsought side-effects. It is suggested that the test might be useful in the search for better drugs of the former kind.

For screening purposes it is suggested that the testing of drugs at two dose levels at 10% and 50% of their LD50 will give maximum economy with little risk of missing potentially useful drugs. For definitive evaluation of a drug, construction of the whole dose response curve is necessary; if from this a single numerical index of activity is required, the area under the dose response curve above control level and up to the most active dose summarizes most information. Experience to date indicates that, using mice of the same strain and sex, it is not necessary to repeat the whole dose response curve for the standard drug every time such an evaluation is performed.

Summary

A method of measuring running and walking activity in mice by counting the number of times they interrupt a beam of light has been described. It has been found that psychomotor stimulants such as cocaine and methamphetamine cause a great increase in such activity, while other central nervous stimulant drugs such as picrotoxin and strychnine cause no change or a decrease in activity.

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