EFFECTS OF METHYLPHENIDYLACETATE AND CHLORPROMAZINE ON CERTAIN COMPONENTS OF GENERAL ACTIVITY[1]

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Investigators interested in psychopharmacology have frequently used some measure of general activity as an indicator of the behavioral effects of drugs. However, little attention has hitherto been paid to the effects of drugs on the various specific components of an animal's activity, that is, on the particular responses or acts that make up "general activity." Some recent studies have shown that certain components of the rat's general activity, such as sniffing, walking, grooming, lying, and sitting, are readily quantifiable (Bindra & Blond, 1958), and are meaningfully related to other psychological variables, such as stimulus change or novelty (Bindra & Spinner, 1958) and response decrement in a stimulus-generalization situation (Claus, 1959). These studies suggest the possibility that drugs may differentially affect the occurrence of different components of general activity. This paper reports an investigation of the effects of three dosages of each of two drugs, methylphenidylacetate[2] and chlorpromazine[3], on sniffing, lying, and grooming responses of the rat.

METHOD

Subjects

Thirty-two naive male hooded rats, about 90 days old at the beginning of the experiment, were used as subjects. Two animals were housed in each of several wire-mesh cages, in which food and water were available at all times.

Apparatus and Materials

Four identical observation boxes were placed on a table with a glass surface. Each observation box was made of plywood, measuring 12 by 12 by 12 inches. Each of two opposite walls of the box was extended vertically by attaching a triangular piece 12 by 8 by 8 inches at its top. These triangular pieces supported a two-way slanting roof, one side of which was made of wire mesh and the other of glass. The animal was placed in the box by removing the wire mesh and was observed through the glass pane. All the boxes were painted grey on the inside. The windows in the experimental room and the fluorescent lights on the ceiling provided light for observation.

For recording the time that the animal spent in each activity, six ordinary kitchen clocks were mounted on a panel. Each clock could be made to register time if a key was pressed and held down. The experimenter sat with the six keys in front of him and pressed the key corresponding to a particular class of activity for as long as the animal engaged in that activity, thus accumulating the time spent in a given activity on one of the clocks. At the end of the observation period, the experimenter recorded the total time spent in each class of activity. In the present experiment, only three of the keys (and clocks) were used.

Each time a different key was pressed, a magnetic counter registered the event. The total number of key presses (i.e., switches from one activity to another) was read off at the end of the observation period.

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[2]Supplied by Ciba, Montreal, as Ritalin.

[3]Supplied by Poulenc, Montreal, as Largactil.

The drugs, methylphenidylacetate and chlorpromazine, were available in a number of concentrations. At the appropriate concentration, the volume injected could be kept below 1 cubic centimeter regardless of the drug dosage.

Procedure

Eight of the 32 animals served as a control group, S (saline); and two groups of 12 animals each served as the two experimental groups, M (methylphenidylacetate) and C (chlorpromazine). Four animals, one from the control group and three from one of the experimental groups, were tested on any one day, each being placed in one of the observation boxes. Every animal was tested on three consecutive days.

Each control-group animal received an intraperitoneal injection of 0.5 cubic centimeter of physiological saline on each of the three test days, while the experimental-group animals received a different dosage of a drug each day. The three dosages used for the M group were 0.5, 2.0, and 7.0 milligrams per kilogram of methylphenidylacetate; those for the C group were 2.0, 5.0, and 10.0 milligrams per kilogram of chlorpromazine. The order of days on which any one of the three dosages was administered was balanced among the 12 animals of each experimental group.

The behavior of each animal was recorded during six 5-minute observation periods, spread over a test session of roughly 3.5 hours. The first observation period started 15 minutes after the animal had been introduced into the box. Immediately after the end of the first observation period, the animal was injected with the appropriate fluid and quickly placed back in the box. The second observation period started 5 minutes after the injection, and the remaining four observation periods started 30, 60, 120, and 180 minutes after the injection. Each observation period was only 5 minutes; therefore, by staggering the time of initiating the test session, one experimenter could take complete records from four animals, one in each observation box.

Three mutually exclusive categories of activities were recorded. The definition of each activity was roughly the same as that used in earlier studies (e.g., Bindra & Blond, 1958); however, in the present investigation the response categories were not jointly exhaustive.

Sniffing: rapid movement of whiskers, sound of sniffing, with head directed at a particular object or place; usually accompanied by neck stretching, rearing, or walking.

Lying: rat lies with abdomen resting on the floor of the cage in a relaxed and motionless state; or sleeps.

Grooming: rat licks, scratches, or "washes" any part of its body.

One other response measure was also derived from the recorded data.

Activity changes: the number of times the animal switched from one activity to another (of the three activities: sniffing, lying, and grooming), or repeated the same activity following a "no-activity" period. This number is a rough measure of the lack of stability in the over-all behavior of the animal.

RESULTS

The results are described in terms of the total time, in seconds, for which the animal engaged in each of the three activities during a 5-minute observation period, and of the number of behavior changes in each observation period. Where tests of significance between the groups appeared desirable, the rank-sums test was used. Unless otherwise mentioned, the

scores for this test were obtained during the second postinjection observation period (30 minutes postinjection).

Sniffing

Figure 1 shows the mean times spent sniffing by the S group (saline, N = 8), M group (methylphenidylacetate, N = 12), and C group (chlorpromazine, N = 12). Compared with the mean of the mean three-day sniffing scores of animals in Group S, the sniffing scores are, in general, higher for M group and lower for C group. For both drugs, the smallest dosage used seems to have had little or no effect (M: $p < 0.10$; C: $p < 0.09$). In both cases, however, the deviation from the S group with the two higher dosages is significant (M: medium dosage, $p < 0.01$; high dosage, $p < 0.007$; C: medium dosage, $p < 0.06$; high dosage, $p < 0.03$). The effects of both the drugs seem to have reached their maximum values

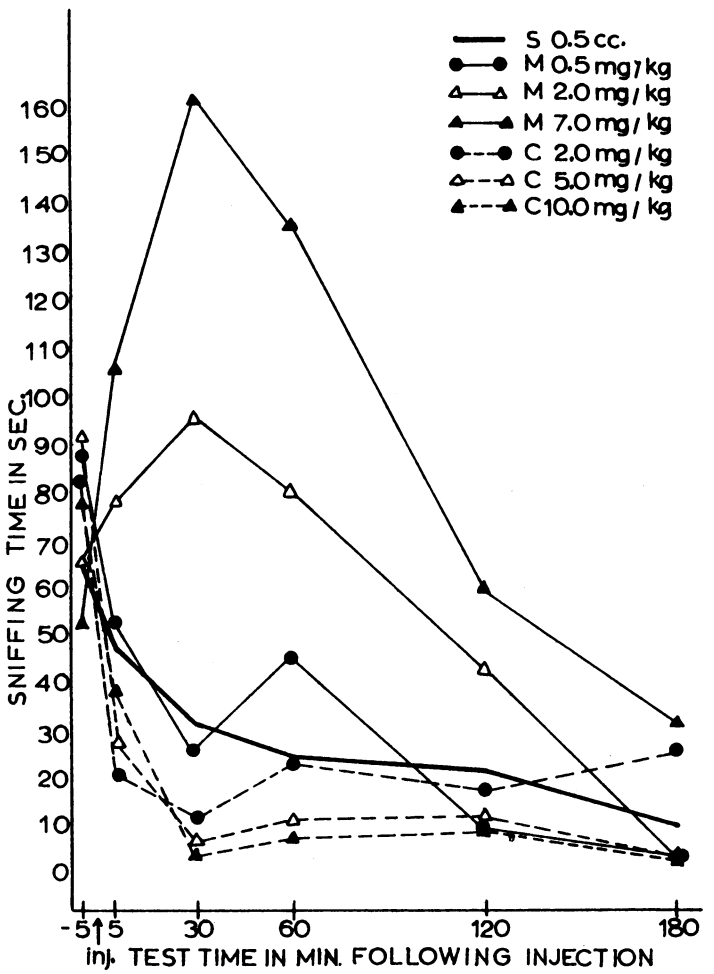

Figure 1. Mean time spent sniffing by the control (S) group and by the methylphenidylacetate (M) and chlorpromazine (C) groups (under each of three dosages) in six 5-minute observation periods spread over 3.5 hours. Eight rats were in the control group, and 12 each in the two experimental groups.

about 30 minutes after the injection; at the end of 3 hours the ranges of M and C groups closely resemble the range of the S group.

Lying

The M group spent less time lying relaxed with abdomen resting on the floor than did the S group. (See Fig. 2.) The decrease in lying is not significantly different from the control-group scores for the smallest dosage, but is significant at less than 0.01 level for the other two groups. None of the dosages of chlorpromazine significantly affected lying. The animals in the C group spent a great deal of time *sitting* motionless, a type of activity that was not recorded in the present experiment.

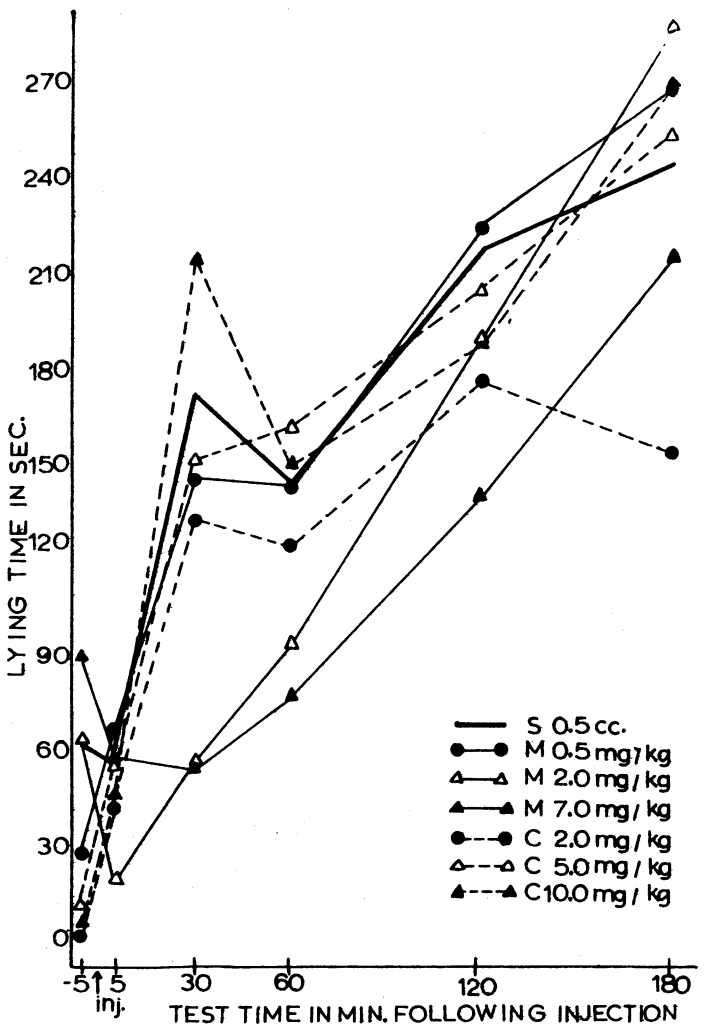

Figure 2. Mean time spent lying by the control (S) group and by the methylphenidylacetate (M) and chlorpromazine (C) groups (under each of three dosages) in six 5-minute observation periods spread over 3.5 hours. Eight rats were in the control group, and 12 each in the two experimental groups.

Grooming

As Fig. 3 indicates, the grooming scores do not show any clear, consistent pattern, even in the S group. In spite of the great variability, certain group differences are noticeable. At the two higher dosages, the C group had significantly ($p < 0.03$) lower grooming scores at the third postinjection (60-minute) test.

Activity changes

Figure 4 shows that under the two higher dosages, the M group changed from one activity to another much more frequently than did the S group (medium dosage: $p < 0.0002$; high dosage: $p < 0.008$). However, there is no clear difference between the two high-dosage conditions. Group C deviated from the saline group in the opposite direction, showing fewer

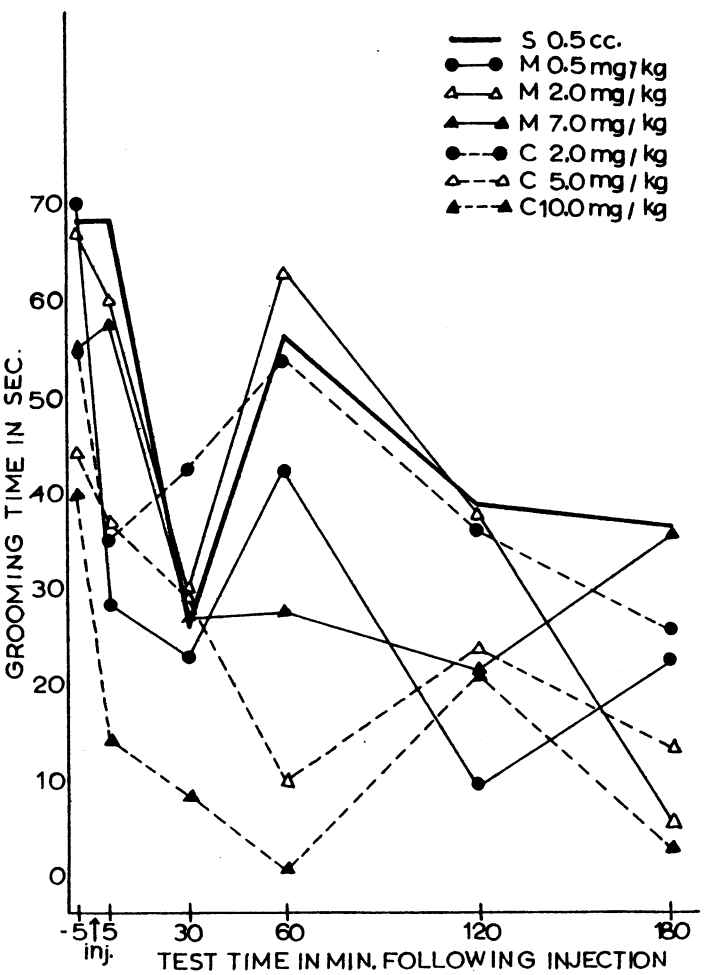

Figure 3. Mean time spent grooming by the control (S) group and by the methylphenidylacetate (M) and chlorpromazine (C) groups (under each of three dosages) in six 5-minute observation periods spread over 3.5 hours. Eight rats were in the control group, and 12 each in the two experimental groups.

activity changes. Though this deviation is quite consistent for the first 60 minutes of the postinjection time, the differences reach a significant level ($p < 0.03$) only for the two higher dosages and at the third postinjection test.

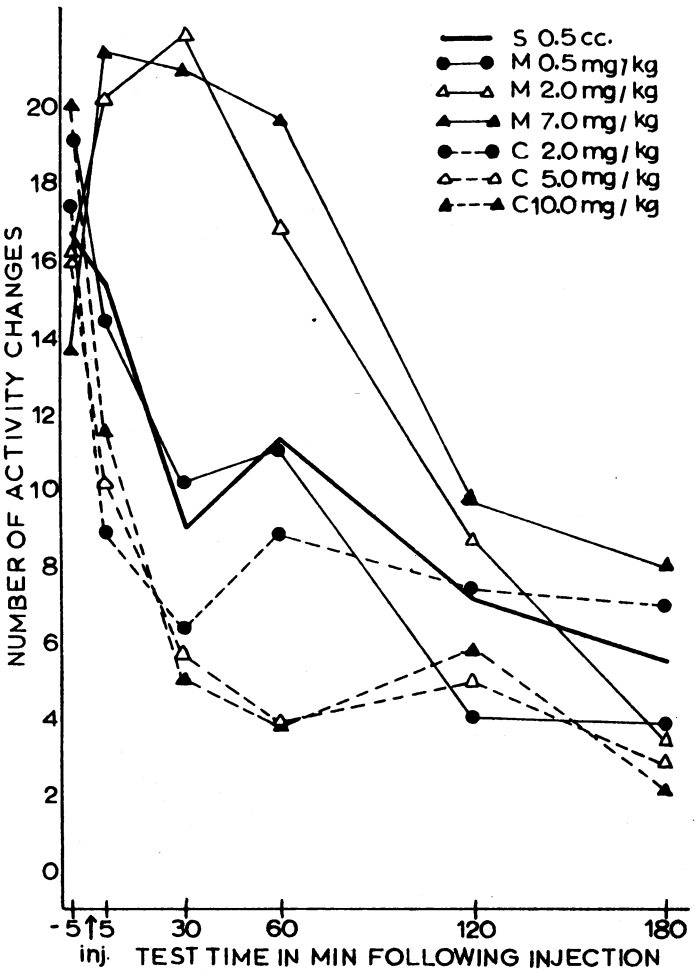

Figure 4. Mean number of changes from one activity to another for the control (S) group and for the methylphenidylacetate (M) and chlorpromazine (C) groups (under each of three dosages) in six 5-minute observation periods spread over 3.5 hours. Eight rats were in the control group, and 12 each in the two experimental groups.

Individual differences

Figure 5 gives the individual sniffing records of six animals; these records indicate the range of individual differences in the effects of the drugs. Though, in general, the curves for various activities in individual animals resembled the group curves shown in Fig. 1 to 4, some remarkable deviations from the norm were also observed. This was particularly true with animals in the M group. For example, at each of the two higher dosages of this drug, 9 of the 12 animals were clearly affected by the drug. One of the three rats not affected by

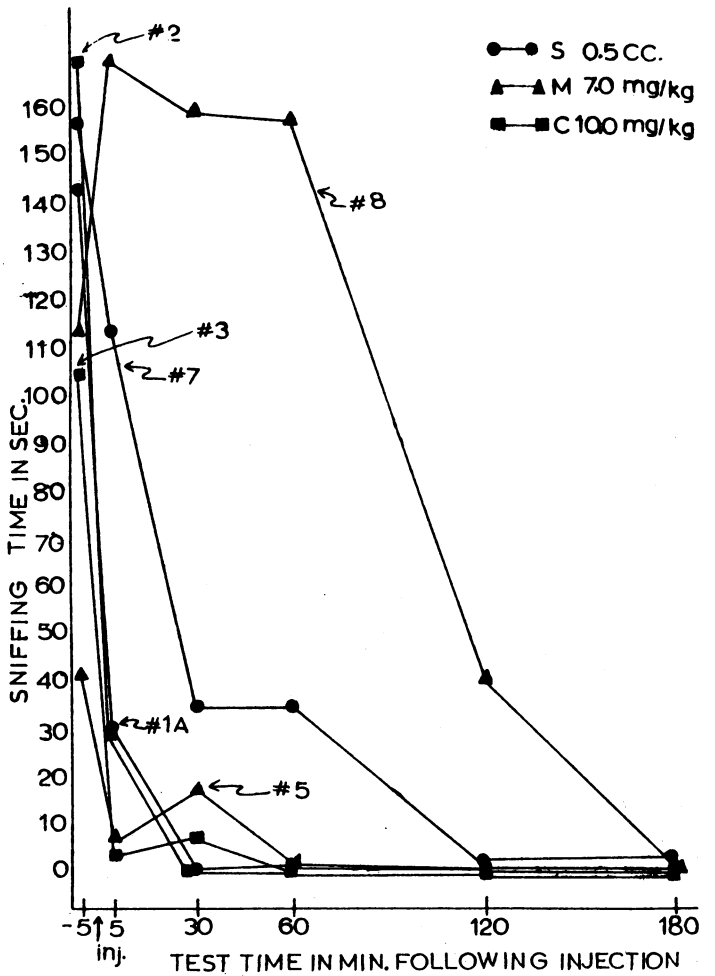

Figure 5. The records of six animals selected to show the range of variation in time spent sniffing within each of the three (saline, S; methylphenidylacetate, M; and chlorpromazine, C) groups.

the medium dosage was also not affected by the largest dosage; but two of the animals not affected by the largest dosage were affected by the medium dosage. Such extreme deviations from the typical pattern were not observed in the C group.

DISCUSSION

The most obvious feature of the results is that various specific activities comprising "general activity" are meaningful dependent variables for studying the effects of drugs on behavior. Because particular classes of activity, such as sniffing, lying, and grooming, are differentially affected by drugs, they yield information that cannot be obtained by gross measures of general activity, such as those obtained with a stabilimeter-type device. For example, lying is not simply the opposite of sniffing (which includes walking-sniffing and rearing-sniffing); although chlorpromazine decreases sniffing, it does not correspondingly in-

crease lying. Similarly, grooming, which often contributes to general-activity scores obtained from a stabilimeter, is not affected by methylphenidylacetate, although this drug greatly increases sniffing scores. The frequency of change from one activity to another is also seen to be a meaningful dependent variable. The impression of some psychiatric workers that methylphenidylacetate facilitates free association in depressed human patients may be related to the increase in activity changes brought about by this drug in the present experiment.

A second point made clear by the present results is that changes in the occurrence of components of general activity are remarkably sensitive indicators of drug effects. Relatively small dosages (2 milligrams per kilogram for M and 5 milligrams per kilogram for C) are sufficient to change the frequencies of occurrence of the selected components; by contrast, we have found that much larger dosages (15 milligrams per kilogram of M and 20 milligrams per kilogram of C) of the drugs fail to affect a well-established running response in the rat. Sensitivity of the components of general activity to drugs is also apparent in the fact that different dosages of the drug yielded different degrees of change in the responses studied. Thus, further investigations of the effects of drugs on specific components of general activity may be rewarding.

SUMMARY

This paper reports an investigation of the effects on rats of three dosages each of two drugs, methylphenidylacetate (0.5, 2.0, and 7.0 milligrams per kilogram) and chlorpromazine (2.0, 5.0, and 10.0 milligrams per kilogram), on the frequency of occurrence of sniffing, lying, grooming, and of changes from one of these activities to another.

Of the 32 animals used, 8 were given injections of physiological saline (S); 12, of methylphenidylacetate (M); and 12, of chlorpromazine (C). Each of the animals in the M and C groups received a different dosage on each of the three test days, the order being determined by a balanced design. For each animal, on each day, the duration of occurrence of the three activities, and of the number of activity changes, in a 5-minute observation period were recorded six times during a test session of about 3.5 hours.

Compared with the control injections, methylphenidylacetate increased sniffing and activity changes, decreased lying, but did not affect grooming; chlorpromazine decreased sniffing and activity changes, but did not affect lying or grooming. The effects of both seemed to reach maximum values in about 30 to 60 minutes. In general, the degree of effect was proportional to the dosage. Marked individual differences in drug effects were observed with methylphenidylacetate.

The results show that the selected components of general activity are sensitive and meaningful dependent variables for the study of behavioral effects of drugs, and yield information that is not obtained by gross measures of general activity.

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