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Drug Effects on Discrimination Performance at Two Levels of Stimulus Control

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Abstract. The effects of several doses of *d*-amphetamine, chlordiazepoxide (CDP), chlorpromazine (CPZ), LSD, pentobarbital, and scopolamine were examined in rats trained to respond to the brighter of two keys. On each of the 100 trials during a daily session, the rat pressed the key that was brighter (correct key) and received a food pellet, or pressed the incorrect key and terminated the trial without food, or pressed neither key for 10 s, allowing the trial to terminate. Within a session, trials were mixed randomly such that on 50 trials the incorrect key was not lit (easy trials) and on 50 trials the incorrect key was dimly lit (difficult trials). Amphetamine (0.5–2.0 mg/kg) reduced percent correct responses, with a greater effect on difficult than on easy trials. CDP (4.0–16.0 mg/kg) and pentobarbital (2.0–16.0 mg/kg) reduced percent correct responses on the difficult trials at the highest doses tested. Scopolamine (0.12–1.0 mg/kg) reduced both percent correct (more so on the difficult trials) and percent of trials on which a response was made, in a dose-related fashion. CPZ (1.0–4.0 mg/kg) reduced trial responding at 2.0 and 4.0 mg/kg and reduced percent correct on the difficult trials at 4.0 mg/kg. LSD (0.08–0.32 mg/kg) did not significantly alter behavior in this study.

Key words: Amphetamine – Chlordiazepoxide – Chlorpromazine – LSD – Pentobarbital – Scopolamine – Behavior – Rats

A number of studies over several years of research in behavioral pharmacology have indicated that several variables are important in determining the behavioral effect of a drug. Two such variables are the schedules of reinforcement maintaining the behavior and the discriminative stimuli associated with those schedules. For example, Laties and Weiss (1966) found that pigeons responding under a fixed-interval schedule of reinforcement with no added discriminative stimuli showed large performance changes when scopolamine was administered, but when the pigeons were maintained under a similar schedule with an added clock stimulus, the behavior was much more strongly controlled and was much less influenced by scopolamine. Similar effects have been found under a variety of schedule types, with various species, and with a variety of psychoactive drugs (e. g. McKearney 1970). It is, therefore, a general principle of behavioral pharmacology that an important determinant of the behavioral effect of a drug is the degree of stimulus and schedule control over the behavior (McKearney and Barrett 1978).

While experiments on schedule control are best done by examining rates and patterns of responding using free operant schedules, stimulus control over behavior may best be studied by minimizing the importance of rate and pattern of responding, as in discrete trial procedures. The behavior required for food presentation is usually a single, or another small number of responses, so that it is possible to present a large number of trials in a short period of time. In most free operant procedures, and in some discrete trial procedures, discriminative stimuli are presented successively and a distinctive type of response is appropriate in the presence of each stimulus. In some discrete trial procedures, such as that employed in the present study, discriminative stimuli are presented simultaneously in different locations. The type of response required on each trial is the same, and only its location is controlled from trial to trial by differences between the discriminative stimuli. Drug effects on overall response output would presumably affect both response locations equally, allowing for the possibility of measuring drug effects on discrimination performance somewhat independently of effects on response rate or pattern.

Ksir (1975) demonstrated the relationship between stimulus control and drug effect with rats responding in an operant conditioning chamber containing two keys, one brighter than the other. The rats were given food pellets for pressing the correct key; for some rats this was the brighter key, for some the darker key. No food pellet was presented and the trial was terminated if the incorrect key was pressed. By varying the brightness of the two keys, it was possible to study the interaction between stimulus control and drug effect in a parametric fashion. There was a graded interaction between stimulus control and drug effect, and both *d*-amphetamine and scopolamine showed the same type of interaction. It was concluded from this that the drug-behavior interactions were probably based on the susceptibility of the behavior to drug action in general at lowered levels of stimulus control, rather than to a separate interaction between the behavior and each type of drug.

One question which remains is the extent to which the stimulus control-drug effect interaction may be seen in a single subject and with a single exposure to a drug. The present set of experiments exposed rats to two levels of stimulus control within the same session. This was accom-

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plished by having trials with varying brightness of the two keys mixed in a random pattern within each session.

Materials and Methods

Eight adult male Long-Evans-derived hooded rats, approximately 90 days of age at the beginning of training, were individually housed and maintained at approximately 80% free-feeding weight by supplemental postsession feedings. Water was continuously available in the home cages. Daily sessions were conducted in a standard operant conditioning chamber which contained two Gerbrands (model B) response keys mounted on either side of a pellet chute. Each key could be transilluminated from behind by a 7.5 W white light bulb operated either at 110 V or 60 V. The pellet chute was the location for the delivery of 45 mg Noyes Lab animal food pellets. Events in the chamber were controlled and recorded by a Texas Instruments 960 A minicomputer system located in an adjacent room.

Procedure. Each rat was trained to press the response keys by presenting a food pellet for each response on either key, with both keys illuminated. They were then trained to press only an illuminated key. The lighted key was on either the left or right, according to a random sequence. A response on the unlit key terminated the trial without producing a food pellet, whereas a response on the lighted key produced a food pellet and then terminated the trial. Trials lasted a maximum of 10 s if no response was made, then terminated without a food pellet. The intertrial interval (ITI) was always 20 s (ITI). Each daily session consisted of 100 trials. After more than 30 sessions on this schedule, on half the trials the incorrect key was lit at 40 V. After two sessions this was changed to 60 V. Thus, the rat always received a food pellet after a response on the brighter of the two keys. On half the trials the incorrect key was lit dimly, on half it was not lit.

After 18 sessions on this final schedule, drug injections were begun. All injections were given IP 30 min before the session in a volume of 1 ml/kg body weight. Injections were given on Tuesdays and Fridays of each week. For each drug, the first injection was saline, followed by an increasing dose series, another saline injection, and a decreasing dose series. Scopolamine hydrobromide (0.12, 0.25, and 1.0 mg/kg) was given first. LSD tartrate was then given, but only in a single, increasing dose series (0.08, 0.16, and 0.32 mg/kg). *d*-Amphetamine sulfate (0.5, 1.0, and 2.0 mg/kg) followed, then sodium pentobarbital (2.0, 4.0, 8.0, and 16.0 mg/kg), chlordiazepoxide (CDP) HCl (4.0, 8.0, and 16.0 mg/kg), and chlorpromazine (CPZ) HCl (1.0, 2.0, and 4.0 mg/kg). Since over 4 months of drug testing had by then been done using these rats, another series of scopolamine doses (0.25, 0.50, and 1.0 mg/kg) was given for comparison with the first series. All drug quantities are given as the salt weights.

Results

Nondrug Performance. The three measures calculated were as follows: (1) percent correct choices (number of correct responses/number of correct plus number of incorrect responses), done separately for each level of discrimination difficulty; (2) percent of trials on which a response was made (percent trial responses), also calculated separately for each level of difficulty; (3) number of ITI responses, which, since these were between trials, were not separated by difficulty level.

On the percent correct measure, performances on saline days showed that most of the rats responded correctly on all the easy trials, on which the incorrect key was not lit. One or two rats occasionally made one or two errors, but the mean percent correct was always near 100%. During the initial scopolamine series the saline days showed a mean of 99.86% correct for the easy discrimination. During the final scopolamine series the corresponding value was 99.87%. All saline mean values for this measure during the intervening drug series over a 5-month period were 99.5 – 100%. On the difficult trials, during which the incorrect key was dimly lit, most rats made one or two errors on a given session, though some rats on some sessions made no errors. The mean percent correct scores on saline days during the first and last scopolamine series were 96.60% and 96.44%, with intervening values of 95.3 – 97.7%. Thus, each of these measures remained stable over the 5-month testing period. There was a clear and consistent effect of the dimly lit incorrect key on difficult trials so that, even though the rats showed over 95% correct performance on these trials, the demonstration of reduced stimulus control over behavior was made in the absence of drug treatments.

The percent trial response measure was also quite stable on saline days, ranging between 96 – 98% over the entire drug treatment period. There was no difference between easy and difficult trials for this value.

ITI responses were highly variable from rat to rat and session to session. The saline day mean values were 29 – 322, with the most common values being near 100.

Drug Effects. Due to the large variability of the ITI response measure it was impossible to detect significant drug effects on it. Therefore, those data are not shown. Reliable dose-related effects were found on the percent correct and percent trial response measures, as shown in Figs. 1 and 2. Analyses of variance for repeated measures tested the significance of dose, difficulty, and dose- × -difficulty interaction effects for each drug for each measure. Due to the large number of independent statistical tests carried out on these data, effects are not reported as significant unless $P < 0.01$.

Reflecting the effect of discrimination difficulty on nondrug performance, the difficulty factor was highly significant for the percent correct measure during every drug series, but was not significant for the percent trial response measure during any drug series.

CPZ (Fig. 1) reduced trial responding in a dose-related fashion ($F = 17.1$, df 3,21, $P < 0.001$). The percent correct measure was reduced on difficult, but not on easy trials ($F = 7.9$, df 3,21, $P < 0.005$ for dose effect; $F = 35.3$, df 1,7, $P < 0.001$ for difficulty effect; $F = 11.7$, df 3,21, $P < 0.001$ for dose- × -difficulty). Figure 1 indicates that the reduction in trial responding began at a lower dose than did the effect on percent correct. CDP had no significant overall effect on trial responses, but did reduce percent correct responding on the difficult trials at the highest dose tested (for percent correct measure $F = 5.6$, df 3,21, $P < 0.01$ for dose effect; $F = 22.5$, df 1,7, $P < 0.005$ for difficulty effect; $F = 8.2$, df 3,21, $P < 0.001$ for dose- × -difficulty). Pentobarbital produced a dose-related decrease in percent correct responses on the difficult trials ($F = 12.4$, df 4,28, $P < 0.001$ for dose; $F = 35.8$, df 1,7, $P < 0.001$ for difficulty; $F = 12.3$, df 4,28, $P < 0.001$ for dose- × -difficulty). There was not a significant

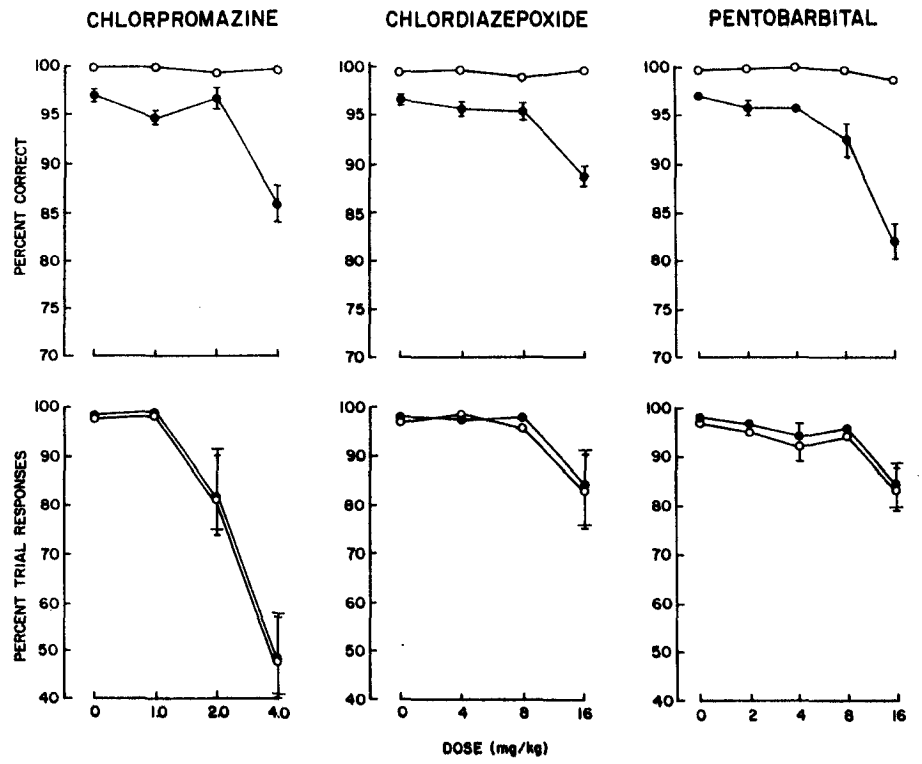

Fig. 1
Chlorpromazine, chlordiazepoxide, and pentobarbital effects on percent correct responses (upper panels) and on percent of trials on which a response was made (lower panels): easy discrimination trials (○); difficult discrimination trials (●). Points at 0 mg/kg are means for placebo (saline) sessions. Bars above and below points represent SEM, and are not shown if SEM is smaller than the range covered by the circle

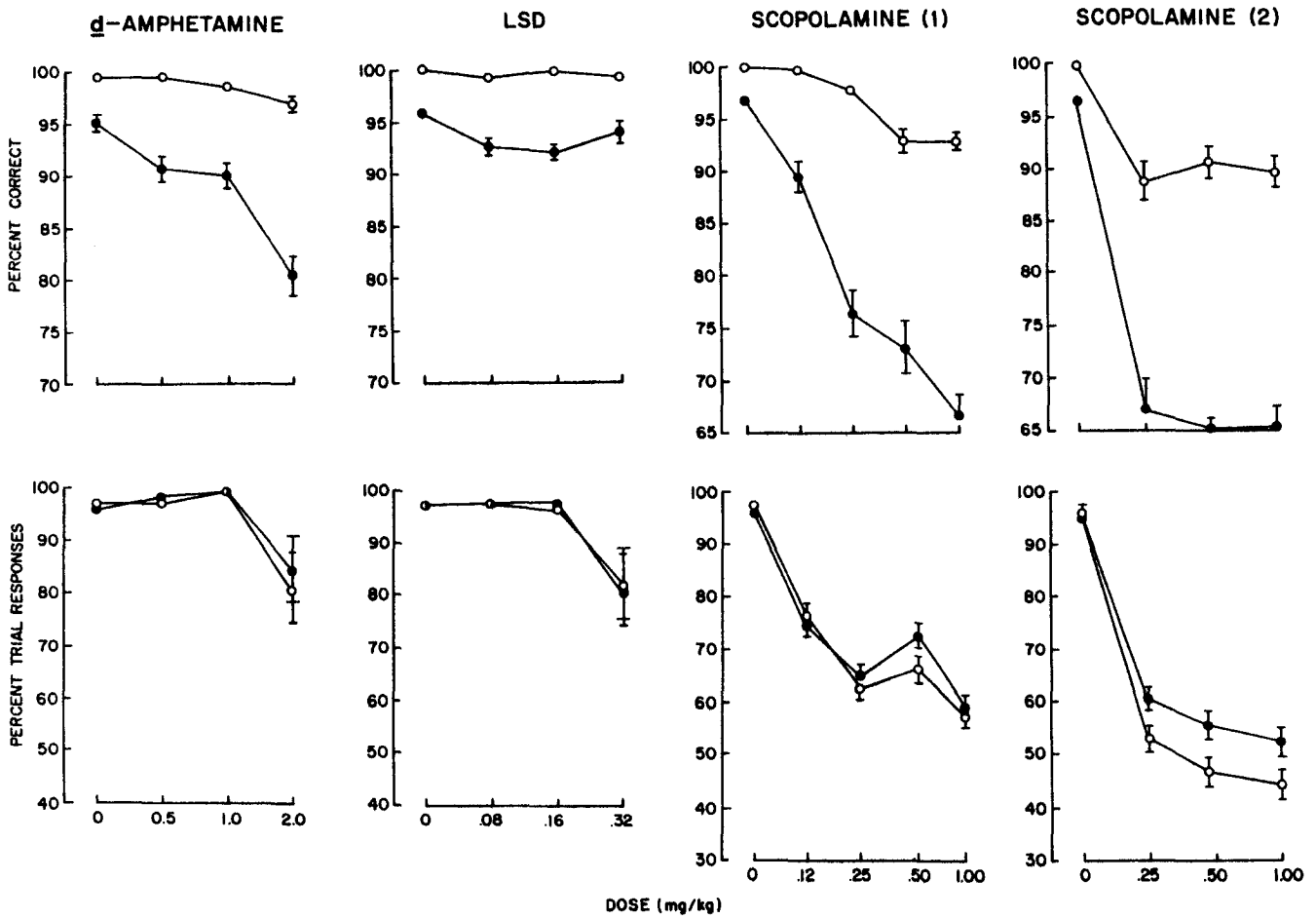

Fig. 2. Amphetamine, LSD, and scopolamine effects on percent correct responses (upper panels) and on percent of trials on which a response was made (lower panels). Scopolamine (*1*) represents the initial series of scopolamine injections, scopolamine (*2*) the second series of scopolamine injections. Symbols as in Fig. 1

effect of pentobarbital on trial responses, even though the highest dose appeared to slightly reduce this measure.

Amphetamine (Fig. 2) produced a dose-related decrease in the percent correct measure which was greater for the difficult than for the easy trials ($F = 9.5$, df 3,21, $P < 0.001$ for dose; $F = 28.4$, df 1,7, $P < 0.005$ for difficulty; $F = 9.0$, df 3,21, $P < 0.001$ for dose- × -difficulty). Although there is an appearance of an increase in trial responding at 0.5 and 1.0 mg/kg and a decrease at 2.0 mg/kg, these effects were not statistically significant. LSD, at the doses tested in the current study, did not significantly alter either measure shown in Fig. 2. At the completion of all other drug testing, test doses of LSD were again given, and the measures were not altered until a very large dose (1.28 mg/kg) was given. That dose did significantly reduce both trial responding and percent correct. Scopolamine produced a dose-related decrease in percent correct that was greater for the difficult than for the easy trials ($F = 21.6$, df 4,28, $P < 0.001$ for dose; $F = 106.0$, df 1,7, $P < 0.001$ for difficulty; $F = 18.0$, df 4,28, $P < 0.001$ for dose- × -difficulty). This result was replicated almost 5 months later when the second scopolamine series was run ($F = 33.4$, df 3,21, $P < 0.001$ for dose; $F = 171.3$, df 1,7, $P < 0.001$ for difficulty; $F = 9.6$, df 3,21, $P < 0.001$ for dose- × -difficulty). Scopolamine also caused a dose-related decrease in trial responding during both series ($F = 15.5$, df 4,28, $P < 0.001$ for dose in the first series and $F = 28.9$, df 3,21, $P < 0.001$ for dose in the second series). There were no significant difficulty effects or dose- × -difficulty interactions for the trial response measure on either series, in spite of the appearance of a slightly greater reduction in easy trial responding in the second series.

Discussion

Because the relationship between degree of stimulus control and drug effect has been noted in a variety of experimental procedures and with various psychoactive drugs, the development of a sensitive standard test to examine this interaction could be a useful basic tool for the behavioral pharmacologist. The current procedure has been employed to examine the effects of drugs from a variety of psychoactive drug classes. The advantage of this procedure is that two levels of stimulus control can be tested within a single session. It is also apparent that it provides stable measures and repeatable drug effects for at least 5 months. Every drug tested in this experiment except LSD produced a highly significant decrease in the percent correct measure and a highly significant interaction between that drug effect and the difficulty, or stimulus control effect.

The different drugs may be categorized according to their relative effectiveness in altering percent correct on the difficult trials and percent trial responses. Amphetamine decreased percent correct at doses that may have slightly increased trial responses, and certainly at doses well below those at which the first hint of trial response decrease was seen. This effect of amphetamine is consistent with a previous report of amphetamine action on a similar task (Ksir 1975) and with other reports of disruption by amphetamine of learned discriminations (e.g. Heise and Lilie 1970). However, Eckerman et al. (1980) reported that scopolamine (0.1 – 1.0 mg/kg), but not *d*-amphetamine (0.3 – 3.0 mg/kg) or pentobarbital (1 – 10 mg/kg), disrupted rats' performance in a radial arm maze. Another recent experiment (Grilly et al. 1980), using a visual discrimination task in a T-maze with about 80% correct performance under nondrug conditions, found that morphine (2 or 4 mg/kg), but not *d*-amphetamine (0.5 or 1.0 mg/kg) or pentobarbital (6 or 12 mg/kg), reduced percent correct responses. The functional differences among these procedures that produce disparate drug effects remain to be revealed, but one possible feature may be the strong spatial stimuli provided by the maze situations.

Pentobarbital and CDP decreased percent correct slightly less effectively than did amphetamine and only at the higher doses tested. Those were also doses with nonsignificant tendencies to reduce trial responding. McKearney (1970) reported that operant behavior in pigeons was more affected by amobarbital, another barbiturate, under conditions of weak rather than stronger stimulus control, and the current finding with pentobarbital is consistent with that result. The apparent lack of pentobarbital effect found by both Eckerman et al. (1980) and Grilly et al. (1980) on other types of discrimination tasks have already been mentioned. However, neither of those reports used a dose of pentobarbital as large as the 16 mg/kg dose, which produced the largest effect in the present experiment.

With respect to CDP, it has been reported that both the performance by monkeys (Hasegawa et al. 1973) and the learning by rats (Iwasaki et al. 1976) of a visual discrimination were disrupted by CDP (20 mg/kg) when the discriminative stimuli were presented on successive trials (successive discrimination), but not when the stimuli were simultaneously present on each trial (simultaneous discrimination as in the current study). In spite of efforts in each study to equate difficulty of the two types of tasks, it does not appear that this was entirely successful. The present study points out that small, but consistent differences in nondrug performance may result in profound differences when drugs are given.

The current procedure seems to be particularly well-suited to demonstrating a large dose-related effect of scopolamine. This was the only drug tested which produced decreases in both percent correct and percent trial responses. This result agrees completely with our previous report (Ksir 1975) that also showed a reduction in trial responding with methylscopolamine, which enters the brain poorly. Thus, the trial responding effect may be through non-CNS actions, whereas the percent correct effect is mediated through the CNS. Analogous results have been reported by others; e.g. Heise and Lilie (1970).

CPZ showed a highly significant reduction of trial responses, and in fact a clear reduction in percent correct was not seen until the largest dose (1.0 mg/kg) was given and the rats were responding on less than half the trials on both difficult and easy trials. Frontali et al. (1976), in a review of drug effects on differential responding, points out that psychomotor depression is consistently seen with CPZ, whereas effects on stimulus control over behavior are seen in only some of the reports. The present results would suggest that the effect on stimulus control is less pronounced and occurs at higher doses than the reduction in responding.

LSD, at least in reasonable doses, did not alter either measure. Given that rats can detect LSD at doses lower than those used in this study (Hirschhorn and Winter 1971), and that such doses also produce a profound effect on electrical activity in the raphe nuclei (Aghajanian et al. 1970), this lack of effect would seem surprising. However, others have failed to find effects of LSD on discrete trial auditory and visual discriminations using procedures that were sensitive to the effects of other drugs (Appel and Dykstra 1977). The Frontali

et al. (1976) review also points out the variety of confused and contradictory findings reported for the behavioral effects of LSD in rats, including many reports of failures to demonstrate effects. In the current study, as in many of the others, the demonstration that the procedure is sensitive to the effects of a variety of psychoactive drugs, but not sensitive to reasonable doses of LSD, may be seen as a meaningful failure; not simply due to an insensitive test procedure.

The fact that most psychoactive drugs decrease percent correct responding in this test, and also demonstrate an interaction of this decrease with the difficulty of the discrimination, implies that this behavioral effect is pharmacologically quite nonspecific. Another example of such a nonspecific behavioral effect is the rate-dependent effect many drugs have on operant responding under a fixed-interval schedule. The positively accelerated pattern of responding produced by this schedule is readily altered by most drugs, but Ksir and Nelson (1977) reported that LSD failed to produce significant rate-dependent changes in fixed-interval responding under conditions that clearly allowed amphetamine to have such an effect. McKim (1981) has recently reviewed the concept that such nonspecific behavioral effects may reflect a common mechanism: The administration of a psychoactive drug produces a stimulus and, thus, has an effect similar to that of altering environmental stimuli during the performance of an operant schedule or a discrimination. If this is so, the failure of LSD to produce similar behavioral effects will need to be explained.

It is important that these nonspecific effects of psychoactive drugs be understood for two reasons. First, experimenters unfamiliar with the ubiquity of these nonspecific effects may be tempted, on the basis of experiments on only a single drug or a single class of drugs, to speculate on neurochemical mechanisms when similar behavioral effects might have been obtained from virtually any psychoactive agent. Second, there may be organizing principles of a general nature, such as that suggested by McKim (1981), which could be discovered through study of these phenomena and which could lead to understanding and predicting the occurrence of nonspecific drug effects in future experiments.

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