Pharmacology Biochemistry and Behavior, Vol. 43, pp. 1155–1159, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Effect of Various Psychotropic Drugs on the Performance of Avoidance and Escape Behaviors in Rats

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Received 11 January 1990

RODRIGUEZ, R. *Effect of various psychotropic drugs on the performance of avoidance and escape behaviors in rats.* PHARMACOL BIOCHEM BEHAV 43(4) 1155–1159, 1992.—The effect of different doses of nine psychotropic drugs upon conditioned avoidance responses (CARs) developed on a stable basis, after appropriate training, was investigated in rats and compared with their capacity to disrupt escape responses (ERs). Haloperidol (HAL), chlorpromazine (CPZ), morphine (MOR), pentobarbital (PENT), chlordiazepoxide (CDP), meprobamate (MPB), and amphetamine (AMPH) dose dependently inhibited both behaviors. Imipramine also disrupted CARs dose dependently, but did not affect ERs at maximal tolerated doses. Significant differences in the minimal effective doses, effective dose range, and time of onset and duration of action, as well as in potency, were observed. The quantitative determination of the level of selectivity, based upon the ratio ED_{50} escape failure/ED_{50} avoidance failure, indicated that all CNS depressants tested caused a selective inhibition of avoidance behavior. HAL was found to be the most specific, followed, in order, by CDP, MOR, CPZ, MPB, and PENT, whose ratio values were not significantly different. AMPH produced a nearly parallel impairment of both behaviors and quipazine only affected CARs at toxic doses. It is concluded that both neuroleptic and nonneuroleptic CNS depressant drugs have selective inhibitory effects on avoidance behavior. Data revealed differences that were more quantitative than qualitative.

Psychotropics Avoidance Escape Rats

DISCRETE avoidance-escape procedures have been traditionally used to analyze the specificity of drug effects on avoidance responding as compared to escape behavior. Most studies have concluded that only certain types of centrally acting drugs, such as neuroleptics (7,9,21,22), narcotic analgesics (21,27), and antidepressants (21), inhibit conditioned avoidance responses (CARs) at doses that do not impair escape responses (ERs). In contrast, other CNS depressants, such as benzodiazepines and barbiturate and nonbarbiturate sedatives, block CARs in a nonspecific manner, that is, disrupt CARs and ERs at approximately the same dose level [for review, see (6,12,15)]. This effect has been demonstrated in a number of widely different variations of the basic conditioned avoidance paradigm. However, the degree of separation between doses impairing the ability of animals to perform an avoidance response as opposed to doses that significantly disrupt ERs is not well established nor has the dose-effect correlation been analyzed extensively. In addition, only a few of the previous investigations studied systematically the effects of such a wide variety of drugs using the same conditioned behavior paradigm in animals (10,20). The present study, therefore, was performed to investigate the ability of nine psychotropic drugs to inhibit both avoidance and escape responses in rats and to quantitatively establish their relative specificity to suppress the avoidance response. This report also provides information on the minimal effective doses, effective dose range, time of onset and duration of action for each drug tested. The selected compounds belong to different chemical classes.

METHOD

Subjects

Twenty-nine male Wistar rats weighing between 200–300 g at the beginning of the experiment were used. They were kept in individual cages in a constant environment room (21 ± 1°C) under a 12 L : 12 D cycle (light on 7:00 a.m.) maintained by electric lighting. Food and water were provided ad lib except during the experimental sessions.

Apparatuses

Experiments were run in a standard one-lever operant conditioning chamber (LVE Model 1417, Lehigh Valley Electronics, Fogelsville, PA) housed in a ventilated, sound-attenuated

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enclosure. Electric shock was delivered to the grid floor, via a shock scrambler (LVE Model 131155), by a constant-current shock generator (LVE Model 1531). The warning signal was a pure tone of 4,000 cycles/s, with an intensity of 80 dB. The front wall contained a lever (LVE Model 1532) placed 3.5 cm above the grid floor and 2.0 cm from the left wall. A 24-ga pressure was required to activate the microswitch associated with the lever. The circuitry was such that the response was defined as the initial closure of the bar-activated microswitch. Arranged in this way, bar holding had no effect on the program. The avoidance schedule was programmed with a solid-state logic equipment and events were recorded with a Harvard cumulative recorder (Model C-3, Harvard Apparatus, South Natick, MA) and by electromechanical counters.

Procedure

Subjects were trained on a discrete conditioned avoidance-escape schedule in 200-min daily sessions until an avoidance performance of at least 80% had been maintained for three consecutive sessions. The schedule consisted of an 8-s warning buzzer followed immediately by a 5-s foot-shock (1.3 mA, delivered through the grid floor by a shock scrambler). Trials were presented at intervals varying from 20–60 s, the average interval being 40 s. This procedure allowed to present 30 trials during each 20-min segment of the session. Lever pressings made during the warning signal ended the conditioned stimulus and avoided the shock, scoring a conditioned response. If the avoidance response did not occur, the shock was delivered. Escape from the shock was contingent upon the subject's pressing the lever during the period of the aversive stimulus.

Subjects meeting the criterion received at least two additional 200-min sessions at weekly intervals before being submitted to the drugs. On successive weeks, a subject received a control run, then a series of randomly selected doses of a given drug, and finally a second control run. Most animals were exposed to two different drugs at all doses tested. Data obtained from subjects tested with a particular drug were rejected if the avoidance performance of the postdrug control run was lower than 80%. Compounds or the vehicle (0.2% methylcellulose water suspension) were administered intraperitoneally immediately before placing the subject in the test chamber. Drugs were given at doses high enough to obtain, when possible, various points of the dose–response effect for both behaviors. Five rats were used to study each dose level. All tests were performed between 9:00 a.m.–2:00 p.m.

The number of avoidance responses, escape responses, and times in which neither avoidance nor escape responses occurred were recorded for each 20-min segment of the 200-min session. To evaluate drug effects, the performance of each animal at a given dose was converted to the percentage of that animal's mean level of performance in the two control sessions that preceded and followed testing with that drug and expressed in terms of percentage loss of avoidance (the percentage of the 30 trials presented during each 20-min period in which the subject failed to make an avoidance response) or escape (the percentage of trials during each 20-min period during which both avoidance and escape responding were lost). The ED_{50} estimates were made by plotting on log-probability paper the above percentages; the approximate dose required to induce 50% of avoidance and escape loss was determined for each animal. For this evaluation, the maximal effect elicited by each drug on each measurement was always considered irrespective of the time of appearance. The significance of differences between these median effective doses was assessed by Student's *t*-test. The ratio of the ED_{50} inhibiting escape responding to the ED_{50} inhibiting avoidance behavior provided a quantitative measure of the degree of selectivity of the antiavoidance effect of each compound. For each group of experiments, dose–effect lines were computed by regression analysis. The Friedman two-way analysis of variance (ANOVA) was used to determine the significance of the dose–response relationship for the avoidance and escape data of the various drugs tested.

Drugs

The drugs used were chlorpromazine HCl (CPZ), chlordiazepoxide HCl (CDP), morphine sulphate (MOR), haloperidol HCl (HAL), *d*-amphetamine HCl (AMPH), quipazine maleate (QPZ), sodium pentobarbital (PENT), imipramine HCl, (IMIP), and meprobamate (MPB). Compounds were suspended or solubilized in a 0.2% methylcellulose water suspension. The volume injected was always 0.2 ml/100 g body weight; except where noted, doses are expressed in terms of mM.

RESULTS

The psychoactive drugs tested showed a range of ability to disrupt avoidance and escape responding. Their time courses of inhibitory effects are presented in Fig. 1. CPZ, HAL, MOR, PENT, CDP, MPB, and AMPH produced a dose related inhibition of both avoidance and escape behaviors. The onset and duration of action were also dose related, but for most compounds a 200-min postinjection period was too short to adequately measure the duration of activity. However, for some compounds (PENT and MPB) a complete recovery in both responses was observed, even at higher doses, before the end of the session. It is apparent that compounds differed considerably in their onset and duration of action. The inhibitory effects of the two neuroleptics appeared more gradually and lasted over 200 min in contrast to the effect of PENT and IMIP, which displayed a rapid onset and short duration (140–160 min). It is also clear that maximal inhibitory activity of the drugs tested developed at different rates. For most compounds, peak activity was usually reached 40–80 min after drug administration, whereas the maximal inhibitory action of IMIP, PENT, and CDP occurred almost immediately after dosing (20 min).

Significant ($p < 0.05$) dose-related trends for inhibiting CARs and ERs were found for HAL, CPZ, MOR, PENT, CDP, MPB, and AMPH. IMIP also produced dose dependent inhibition of avoidance responding; however, the magnitude of the inhibitory effect on avoidance responding never exceeded 70% at maximal tolerated doses (0.178 mM/kg). This drug, at the doses tested (0.056–0.178 mM/kg), did not affect escape responding (Fig. 1). QPZ, a serotonergic agent (24), only affected CARs and ERs at toxic doses (not illustrated).

HAL was the most potent and effective drug in causing inhibition of avoidance and escape behaviors. The minimal effective dose to produce a detectable impairment of avoidance was in the order of 0.00031 mM/kg (0.12 mg/kg), whereas doses of 0.00178 mM/kg (0.67 mg/kg) were required to affect escape responding. In both conditions, attenuation was dose related and the peak effect of both curves occurred at the same time. CPZ, MOR, CDP, PENT, and MPB followed a similar pattern of action, although marked differences in the minimal doses to inhibit avoidance and escape responding were observed (Fig. 1).

The ED_{50} values to disrupt both avoidance and escape

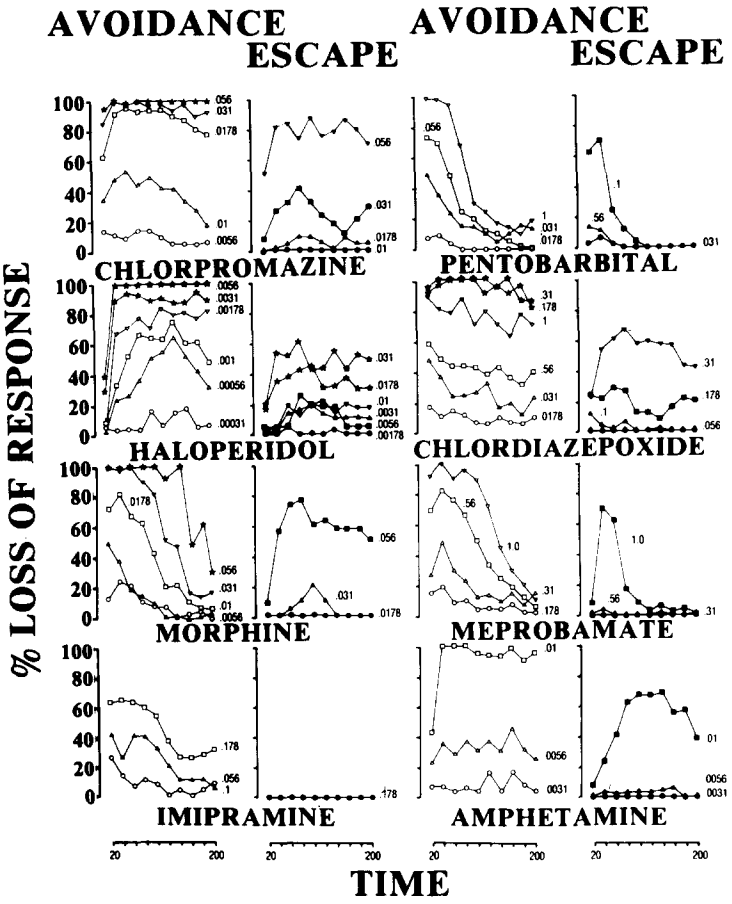

FIG. 1. Time course of avoidance and escape loss in rats after IP injection of various psychotropic compounds at the indicated dose levels. Doses of drugs are expressed in terms of mM/kg. Each point represents the mean of five animals. For clarity, in some cases doses disrupting conditioned avoidance responses but having no effect on escape reponses are not included. Abscissae, time after administration of drugs; ordinates, percentage loss of avoidance or escape in each 20-min period of the session (30 trials per each 20-min period). For each data point, the maximum variability (SD) was less than 15%.

responding are shown in Table 1. The order of potency (ED_{50} expressed in mM/kg in parentheses) of the drugs tested to suppress CAR was HAL (0.0005) > AMPH (0.0055) > CPZ (0.0081) > MOR (0.0110) > PENT (0.0327) > CDP (0.0402) > IMIP (0.0926) > MPB (0.2780). Note that HAL was 10 and 15 times more potent than AMPH and CPZ, respectively, the next two drugs in the list, and about 500 times more potent than MPB, the weakest member of the group. On the other hand, the order of potency (ED_{50} in mM/kg) to suppress escape responding was AMPH (0.0084) > HAL (0.0131) > CPZ (0.0303) > MOR (0.0441) > PENT (0.0808) > CDP (0.1742) > MPB (0.9380).

It is evident from Fig. 1 that doses of CPZ, HAL, MOR, IMIP, PENT, CDP, and MPB, producing significant (>40%) loss of avoidance, had no effect on escape responding. It is also clear that the highest dose of each drug, producing almost complete avoidance loss (>80%), caused only slight disruption of escape responding. The data in Table 1 indicate that HAL, CPZ, MOR, PENT, CDP, and MPB disrupt avoidance behavior at doses significantly lower than those required to affect escape responding. In contrast, AMPH significantly disrupted both behaviors at approximately the same dose level. This analysis could not be made for IMIP because this drug did not affect significantly escape responding; however, the two actions can clearly be distinguished in Fig. 1.

The degree of specificity for inhibiting avoidance behavior, given by the ratio ED_{50} escape failure/ED_{50} avoidance failure, is also shown in Table 1. The ratio volume of 26.20 for HAL was six times greater than that of CDP, the next drug in the list. The ratio values of CDP, MOR, CPZ, MPB, and PENT were not substantially different.

DISCUSSION

The present investigation confirms and extends the observations made by other authors indicating that CPZ, HAL, MOR, and IMIP disrupt CARs at lower doses than those needed to impair ERs. The results demonstrate also that, with appropriate doses, the action of PENT, MPB, and CDP on CARs is qualitatively similar to the former drugs. Their selectivity of action, estimated by the ED_{50} escape failure/ED_{50} avoidance failure, is about equal that of CPZ. Indeed, the selective blockade of CARs by CDP is slightly greater than that exerted by the phenothiazine derivative. Evidently, these

TABLE 1

AVOIDANCE AND ESCAPE BLOCKADE POTENCY AND LEVEL OF SELECTIVITY OF PSYCHOTROPICS TESTED

Drugs	A ED_{50} for Blocking CAR [mM/kg, IP (mg/kg)]		B ED_{50} for Blocking ER [mM/kg, IP (mg/kg)]		A vs. B (probability)	Ratio (B/A)
Haloperidol	0.0005	(0.2)	0.0131	(4.9)	<0.05	26.2
Chlordiazepoxide	0.0402	(12.1)	0.1742	(52.2)	<0.05	4.3
Morphine	0.0110	(8.4)	0.0441	(33.5)	<0.05	4.0
Chlorpromazine	0.0081	(2.9)	0.0303	(10.8)	<0.05	3.7
Meprobamate	0.2780	(60.6)	0.9380	(204.5)	<0.05	3.4
Pentobarbital	0.0327	(8.1)	0.0808	(20.0)	<0.05	2.5
Amphetamine	0.0055	(2.0)	0.0084	(3.1)	>0.05	1.5
Imipramine	0.0926	(26.0)	*		*	*
Quipazine	*		*		*	*

*Not obtainable.

findings do not agree with the old observation that barbiturates, benzodiazepines, and nonbarbiturate sedatives disrupt avoidance and escape behaviors at similar doses (7,10,20,21). Other authors have also failed to detect significant differences in the pattern of action between neuroleptics and anxiolytics in a similar paradigm (25).

Of the psychoactive drugs evaluated in the present study, HAL was the most selective for blocking CARs, followed, in order, by CDP, MOR, CPZ, MPB, and PENT. The ratio values of the latter drugs were not significantly different. Thus, the values of ED_{50} escape failure/ED_{50} avoidance failure ratio do not allow a distinction between CPZ and other types of CNS depressants.

The discrepancy between the present findings and those previously reported may involve various factors. The most important is perhaps related to the criterion used. In many studies, measurement of selective depression of avoidance behavior is based upon a dose that produces almost maximal loss of avoidance behavior and has little or no effect on escape responding (21,27). Data on the general shape of the escape curve are lacking for most compounds classified as selective and nonselective CAR inhibitors. The statement that some drugs decrease significantly CARs at doses that minimally attenuate ERs may be true, and even be useful for drug screening, but remains rather meaningless as long as the relative position of such doses within the dose-response curve for affecting escape behavior is not known, and therefore it cannot measure the magnitude of the specificity of action. In pharmacology, the selectivity of action is best defined by the degree of separation between dose-response curves along the *x*-axis. Such a measurement enables us to quantitatively establish the relative selectivity of a given action. Using this criterion, both neuroleptics and nonneuroleptics tested are selective inhibitors of avoidance behavior.

It is also reasonable to suggest that differences between these and previous findings might also be related to the experimental procedures. For example, in the present study the relative durations of the conditioned stimulus and unconditioned stimulus were relatively shorter (8 and 5 s, respectively) than those used in some of the previous investigations that studied the selectivity of action for these drugs (7,10,21). In addition, numerous previous studies indicate that the differential spread between suppression of avoidance and escape behavior can be varied considerably by adjusting the stimulation parameters (3,13,14,16). Hence, it would seem possible that the selective inhibition of CARs by nonneuroleptic drugs can be demonstrated only when the ER is provoked by a high-intensity shock, as occurred in the present study. Moreover, many of the previous analyses of the effect of drugs on avoidance-escape behavior, although using a similar schedule, were made using other techniques, for example, pole-climb (7) and one-way shuttle (5) avoidance responses. In conclusion, the disparity between these findings and those of other authors might be the result of a number of basic differences in experimental procedures.

Although most drugs tested selectively suppressed CARs, large differences in the minimum effective doses and potency were found. Their ED_{50} values are in reasonable agreement with values obtained by other authors using different conditioning techniques and levels of training (5,17,20,22,23,27). Further, they also differed in their capacity to induce maximal or near maximal avoidance loss. The intensity of the depressant effects of HAL, MOR, and MPB upon avoidance behavior, at doses not affecting or minimally affecting (< 10% at any point) ERs, was more pronounced than those observed with any of the other drugs tested. It seems that, under this criterion, these drugs are the only selective blockers of CARs. Of particular interest is the observation that, when the doses were high enough, the time-response curves for avoidance failure and escape failure ran a parallel course; the peak effect in both curves usually occurred at the same time.

The similarity in the pattern of action between neuroleptics and nonneuroleptics raises the question whether these drugs are acting by a similar mode of action. Early studies claimed that the selective inhibitory action of drugs on CARs was due to their ability to inhibit fear-motivated behavior (6,12). Present evidence indicates that the differential strengths of the avoidance and escape responses is the primary factor in the selectivity of drugs on CAR performance (3,14) and that drug-induced failures are due to deficits in the ability to initiate responses rather than a deficit in associative processes or suppression of emotional reactions (4,14). The finding that the ratio value for HAL was over seven times that for CPZ, whereas the butyrophenone is not more efficacious in reducing psychotic symptoms than CPZ, and the fact that, at equally effective clinical doses, HAL is much more likely to induce

extrapyramidal symptoms than CPZ (2) appear to add further support to this conclusion.

On the other hand, several studies have shown that the selective depletion or blockade of central dopaminergic neurotransmission produces a deficit in CARs (1) and that the effect of neuroleptics on this behavior is primarily dependent upon a direct dopamine receptor blockade (8,22). The similarity in the profile of drug effects noted in the present study suggests that the nonneuroleptic drugs tested may also affect CARs by disrupting dopamine transmission. Consistent with this view is the observation that IMIP, MOR, PENT, and CDP, acting through different mechanisms, can interfere with this neurotransmission (11,17,18,19,26,28). Alternatively, the tested drugs may also disrupt CARs via nondopaminergic mechanisms. The wide-ranging actions of psychoactive drugs on various neuronal pathways, such as the noradrenergic, cholinergic, histaminergic, serotonergic, and others, have to be considered. Indeed, it is quite unreasonable to think that any behavior affected or induced by these types of drugs is the result of a single mechanism. Because the drugs tested differed considerably in their onset and duration of action, and in potency, their overall ability to interfere with the normal functioning of the mechanisms governing this complex behavior might be implied. This consideration does not detract from the concept that dopamine-receptor blockade is a plausible explanation for the behavioral effects of neuroleptics, but it does imply that a broadening of the concept to cover other neural processes may increase our understanding of the effects of drugs, acting via mixed neuromechanisms, on complex behaviors.

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