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EFFECTS OF SOME PSYCHOTROPIC AGENTS ON COGNITIVE FUNCTIONS IN RATS

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Abstract : The effects of some psychotropic agents were evaluated on cognitive function in rats. Acute administration of antipsychotic agents chlorpromazine, haloperidol or pimozide - all inhibited the active avoidance response as elicited by pole climbing test - the least effect being seen with pimozide. The antianxiety benzodiazepines, lorazepam and alprazolam, also attenuated active avoidance learning with the latter showing lesser effects. Maze task performance was differentially affected by these psychotropic drugs with maze traversing time being increased significantly after all drug treatments, except alprazolam.

Key words : psychotropic agents, active avoidance, maze task performance, cognitive function

INTRODUCTION

Psychotropic drugs are known to influence the learning/memory process by modulating central neurotransmitter systems (1). New drug development has led to the discovery of some psychotropic agents, which differ in some ways from their classical counterparts. For example, pimozide, a newer antipsychotic agent, is an atypical drug in that it is more specific for the mesolimbocortical DA system. Similarly, alprazolam is an atypical antianxiety agent, with additional antidepressant properties, and also different from the classical antianxiety benzodiazepines (2). The purpose of the present study was to evaluate the effects of some of these newer psychotropic agents on cognitive function using experimental models and to compare their effects with some of the more conventional agents.

METHODS

Subjects : Albino rats (150-200 gms) of either sex were housed in standard laboratory conditions (12 h light - 12 h dark schedule) with free access to food and water, and at a temperature of 22° ± 2°C. The rats were randomly assigned to different experimental groups with 10 animals per group (n=10).

Active conditioned avoidance response (3) : In this method, Cook's pole climbing apparatus (Techno) was used for inducing a stable baseline behaviour. The rats had to learn to jump on a pole to avoid footshock. A tone of 50 Hz was used as the conditioned stimulus and a footshock of 1. 0mA was the unconditioned stimuli. In the training procedure, the animal was initially allowed to adapt in the chamber for 1 min. This was followed, in succession, by conditioned and unconditioned stimuli, for a period of 15 sec each. The trial ended either after the

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animal responded by jumping on the pole or after 30 secs, whichever was earlier. An animal was given such trial everyday for 10 days. A trained animal either responded spontaneously or to buzzer without waiting for the shock. Retention of memory of painful stimuli established in the learning process was tested before and after drug treatment. It was quantified as the percentage of animals avoiding shock by jumping on to the pole. The data of the different treatment groups were compared for statistical significance.

Maze task : Assessment of memory was done using Hebbs-Williams maze (4). The apparatus consisted of three interconnected chambers A, B and C. Chamber B constituted the maze. Food deprived rats were placed in chamber A and challenged to learn and remember the location of C, after travelling through B. Their presence in chamber C was indicated by a pilot light. Chamber C contained the reward which was food for the hungry animal. The animals were trained for consecutive daily sessions, and the time required to traverse the maze was noted. They were considered trained when the maze completion time for 3 consecutive days were more or less constant. Learning index was then recorded for each animal before and after drug treatment. Effect on recall was assessed when drugs were administered intraperitoneally immediately after training.

Drugs : The drugs used were: chlorpromazine hydrochloride (Rhone Poulenc), pimozide and haloperidol (Jannsen), and alprazolam and lorazepam (Torrent). The drugs were dissolved in propylene glycol and freshly prepared drug solutions were injected intraperitoneally (ip) in a volume of 1 ml/kg, 2h prior to the experimental procedure. A vehicle treated group served as control. The drug doses were selected on the basis of previous literature and some of our earlier pilot studies, which showed that these dose levels, none of the drugs influenced motor activity (performance) by a significant extent.

Data analysis : The data was analysed using the Chi Square test with Yates modification and paired "t" test, wherever appropriate. A "P" value of atleast 0.05 was considered as the level of significance in all statistical tests.

RESULTS

Effect of drugs on the active avoidance response : The psychotropic agents used produced differential degrees of attenuation of the conditioned avoidance response (CAR). Chlorpromazine and haloperidol inhibited CAR in 90% of animals. Pimozide and lorazepam each did so in 70% and alprazolam in 50% animals ($P<0.05$, Fig. 1). Further, inhibition of CAR with haloperidol and particularly, pimozide were seen even after 24 hours of drug administration. In the vehicle treated group, 90% of rats jumped on to the pole within 5 sec (approx.) of the buzzer sound. Pretreatment with chlorpromazine, haloperidol, pimozide and lorazepam abolished the CAR, and rats waited for the shock to climb the pole. On the other hand, alprazolam pretreatment reversed this general trend and 50% of the animals climbed the pole even prior to the sound of buzzer.

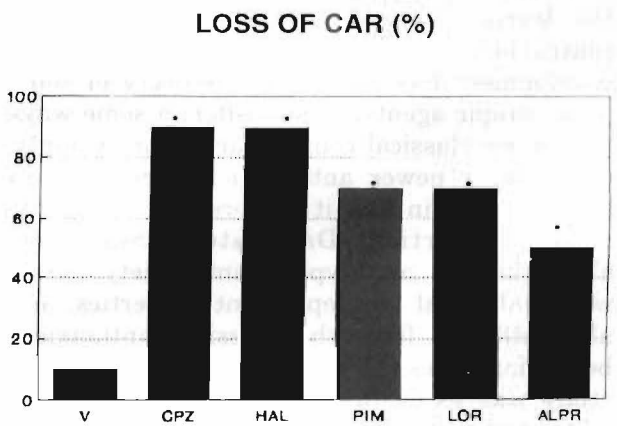

Fig. 1 : Effect of some psychotropic agents on conditioned avoidance response in rats (n=10, per group). V - Vehicle, CPZ - Chlorpromazine, HAL - Haloperidol, PIM - Pimozide, LOR - Lorazepam, ALPR - Alprazolam.

*P<0.05, compared to vehicle (Chi-Square test).

TABLE I : Effect of some psychotropic agents on maze task in rats.

Treatment (mg/kg,ip)	*Maze traversing time in secs (Mean ± SE)*		
	Before drug	*After drug*	*Increase*
Vehicle (2 ml)	36.2 ± 4.0	40.0 ± 6.2	3.8 ± 0.5
Chlorpromazine (2.5)	26.1 ± 2.9	47.0 ± 2.7*	20.9 ± 1.8*
Haloperidol (0.3)	43.6 ± 3.7	71.8 ± 12.6*	28.2 ± 3.7 *
Pimozide (0.1)	67.9 ± 9.5	123.0 ± 6.3*	55.1 ± 5.2*
Lorazepam (0.1)	11.7 ± 1.5	25.9 ± 2.3*	14.2 ± 1.5*
Alprazolam (0.02)	31.0 ± 2.7	35.2 ± 4.6	4.2 ± 0.5

n = 10 per group
*P<0.02 (compared to vehicle group)

Effect of drugs on maze task : These results are summarized in Table I. The psychotropic drugs tested showed differential degrees of increase in maze completion time. This percentage increase in time was maximum with lorazepam (121%) and least with alprazolam (13.5%). Pimozide showed an increase of about 81%, chlorpromazine 80% and haloperidol 65%. All these were significantly different (P<0.02) from controls except for alprazolam. Effect of pimozide on the learned cue was seen even after 24 h of drug administration.

At the doses used, no motor impairment was apparent on handling the animals. Further, no cataleptogenic effect was observed at these doses, except for a few animals with haloperidol treatment, when tested on a 10 cm horizontal bar for posture retention time. There was no apparent sedation/hypnosis as measured by the righting reflex time during/before experimental procedures after drug treatment.

DISCUSSION

Learning the memory involve machanisms like acquisition, storage, consolidation and recall. Active avoidance learning and maze task performance are reasonably good tests for cognitive function (5, 6). The data of the present experiments suggest that the drug induced changes could be interpreted as modification in the retrieval or recall phenomenon. The ability of the animal to identify the conditioning stimuli (buzzer) as precursor of the unconditioned stimulus (shock) involves recall of task and may implicate long term memory. The antipsychotic agents chlorpromazine, haloperidol and pimozide clearly influenced recall or retrieval, in that the animals waited for the unconditioned stimulus (shock) to climb the pole. Thus, these drugs presumably influenced the memory process. Amongst the neuroleptics studied, chlorpromazine and haloperidol had maximum effects, whereas pimozide had a lesser effect on the active avoidance response. Reports indicate that both suppression and stimulation of central dopaminergic (DA) activity can influence cognitive impairment and motor function (7). Our present results clearly show that interference in DA-ergic transmission interrupts the memory recall process, as seen in the experimental paradigms used in this study. The atypical neuroleptic, pimozide, which is relatively specific for A10 DA neurons and with minimal influence on the nigrostriatal DA system at low doses (8), showed lesser effects as compared to haloperidol or chlorpromazine (Fig. 1). Also, most animals with pimozide (which is also a preferential D_2 receptor blocker), and to lesser extent with haloperidol and chlorpromazine treatments, did not show any significant motor impairment. This also suggests that changes in motor function was not an inevitable correlate of the cognitive changes studied in the present experiments and that the mesolimbocortical DA system and the D_2 receptor was probably involved in this process. The effects seen with anxiolytics are interesting.

Lorazepam clearly abolished active avoidance learning in most rats and this is in agreement with the classical amnestic profile of the benzodiazepines. However, with the atypical drug alprazolam, much fewer animals showed loss of this phenomenon and this observation suggests a probable relative advantage with the use of this drug.

In the maze performance task, the involvement of a different cue, reinforcement or reward could have contributed to the nature of the drug effects. In this test, pimozide produced the maximum increase in the maze traversing time when compared to the controls and the response was also greater than that seen with other neuroleptics, viz., chlorpromazine and haloperidol. This further, suggests the involvement of the mesolimbocortical DA system in cognitive effects. With anxiolytics, lorazepam enhanced the performance time to the maximum extent (121% increase over control values). There was no appreciable change in maze completion time in the alprazolam treated animal group. This is in contrast to an earlier study which showed that this atypical BZD did modify learning and acquisition behavior (9). This is probably because of the fact that learning, acquisition and recall involve different neurobiological processes.

The present results suggest that specific DA-ergic systems may be involved in the modulation of the cognitive process. Interactions of ACh with DA in CNS are known (10) and totally ruling out the possibility of involvement of such interactions in learning and memory should be subject to further critical investigations. It is however, clear that psychotropic agents like pimozide and alprazolam have effects which are different from their more classical counterparts.

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