Pharmacology Biochemistry & Behavior, Vol 24 pp 187–191 1986 © Ankho International Inc Printed in the U S A 0091-3057/86 $3 00 + 00

Effects of Phencyclidine, N-Allyl-N-Normetazocine (SKF-10,047), and Verapamil on Performance in a Radial Maze

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McCANN, D J AND J C WINTER *Effects of phencyclidine, N-allyl-N-normetazocine (SKF-10 047) and verapamil on performance in a radial maze* PHARMACOL BIOCHEM BEHAV **24**(2) 187–191, 1986 —Two groups of eight rats were trained to obtain food pellets in an 8-arm radial maze Stable performance was assumed to be present when a criterion of 89% efficiency, i e , all arms entered within 9 arm entries was reached in 5 consecutive sessions The effects of phencyclidine (PCP) and N-allyl-N-normetazocine (SKF-10,047) were then evaluated in Group I The interaction between verapamil and PCP was examined in Group II Both PCP (6 mg/kg, IP, 15 min before testing) and SKF-10,047 (30 mg/kg, IP, 30 min) decreased efficiency but only PCP caused a concurrent increase in rate of arm entry Significant effects of PCP on rate and efficiency lasted for greater than 6 hours and less than 40 minutes, respectively Verapamil (20 mg/kg, IP, 30 minutes) was found to selectively potentiate the effect of PCP on efficiency This finding does not support the suggestion that verapamil may be useful in the treatment of PCP intoxication It is concluded that the radial maze may provide an interesting method for the study of PCP and other psychoactive drugs

Radial maze Phencyclidine N-allyl-N-normetazocine (SKF-10,047) Verapamil

THE radial maze was described less than a decade ago by Olton and Samuelson [34,38] Spatial memory was the term they used to describe the means by which rats solve the maze The initial studies of the radial maze as well as many subsequent investigations have generally supported two prevailing ideas regarding spatial memory These are that (a) environmental stimuli external to the maze are essential [35,37] and (b) the hippocampus is the crucial anatomic region [38,39]

Because acetylcholine (ACh) is generally believed to be of primary importance in the processes of memory, the effects of scopolamine and atropine in the radial maze have been well documented In general, it has been found that ACh-antagonists block both the acquisition [49,55] and performance [9, 16, 22, 33, 45, 55, 56] of the memory task Other drugs which have been studied in the radial maze are *d*-amphetamine [5, 8, 9, 16, 25], apomorphine [9], chloral hydrate [7], chlordiazepoxide [22], chlorpromazine [22], 3,4-diaminopyridine [12], diprenorphine [20], ethanol [14,15], haloperidol [6], leupeptin [48], methohexital [7], methysergide [6], morphine [4], naloxone [20], pentobarbital [16], pentoxifylline [13], phencyclidine [26], phenobarbital [40], phentolamine [6,22], physostigmine [9], piracetam [9], propranolol [6,22], serotonin [6], and delta-9-tetrahydrocannabinol [50,51]

In the only previous study of phencyclidine (PCP), Kesner *et al* [26] found that efficiency of responding by rats was reduced by the drug The purpose of the present investigation was to examine in greater detail the effects of PCP upon performance in the radial maze In addition, PCP was compared with N-allyl-N-normetazocine (SKF-10,047), a presumed agonist at opiate receptors of the sigma type [30] which has stimulus properties similar to those of PCP [46] Finally, the interaction of verapamil, a calcium antagonist previously reported to antagonize certain of the effects of PCP [1] was examined

METHOD

Animals

All subjects were male Fischer 344 rats obtained from Charles River Breeding Laboratories, Inc , Wilmington, MA They were housed in pairs under a natural light-dark cycle and had free access to water in the home cage Subjects were maintained at 75–80% of their expected free-feeding weight by limiting access to dry food to 2 hours per day

Apparatus

The radial maze consisted of a central hub, 34 cm in diame-

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ter, with eight 86 cm by 9 cm arms radiating from it The sides of each arm were 10 cm high at the center of the maze and sloped to a height of 6 cm at the end of the arms The maze was constructed entirely of aluminum with the exception of the food wells which were plastic cups 1 5 cm deep with a diameter of 2 cm The entire device was elevated 46 cm from the floor

Procedure

a Training At the start of a session, a 45 mg Noyes food pellet was placed in a well at the end of each arm and, on the first day only, a pellet was placed a short distance from the starting point to encourage exploration of the maze A session lasted until all eight food pellets were obtained or 10 minutes had elapsed An entry into an arm was scored whenever a rat had all four paws in an arm Performance during each session was scored by visual observation in terms of (a) efficiency of responding (8/number of arm entries before all eight arms were entered, expressed as a percentage) and (b) rate of responding (arm entries per minute until all eight arms were entered)

Two groups of subjects were trained Group I (N=8) was trained first and used to determine the dose-response functions for PCP and SKF-10,047 and the time course for PCP The interactions between verapamil and PCP were examined in Group II (N=8)

b Drug tests (1) Rats performed in the maze Monday through Friday The effects of vehicle or drug injection were determined on Wednesdays and Fridays All test sessions were 10 minutes in length even if all 8 food pellets were obtained earlier in the session Thus, Figs 1–3 give response rates for an entire 10-minute session Tests were conducted only if efficiency on the immediately preceding day was at least 89% PCP and SKF-10,047 were administered 15 min and 30 min, respectively, before testing (2) The time course of the effects of PCP was determined by interposing delays between injection and testing which ranged from 15 min to 24 hours (3) The interaction between verapamil and PCP was examined by injecting verapamil 30 min before testing, i e , 15 min before the injection of PCP or saline

Drugs

Phencyclidine HCl and N-allyl-N-normetazocine HCl (SKF-10,047) were provided by the National Institute on Drug Abuse, Rockville, MD Verapamil HCl was obtained from Searle Research and Development Division of G D Searle and Co , Skokie, IL All drugs were dissolved in saline and injected IP in a constant volume of 1 ml/kg of body weight

Statistics

Values for efficiency and rate of responding were compared with control data by means of individual applications of Wilcoxon's signed ranks test for paired data Differences were considered to be significant if they would be expected to arise by random sampling alone with a probability less than 0 05

RESULTS

All rats became highly efficient in obtaining the eight food pellets available during each session Stable performance was assumed to be present when a criterion of 89% efficiency in five consecutive sessions was reached The mean number

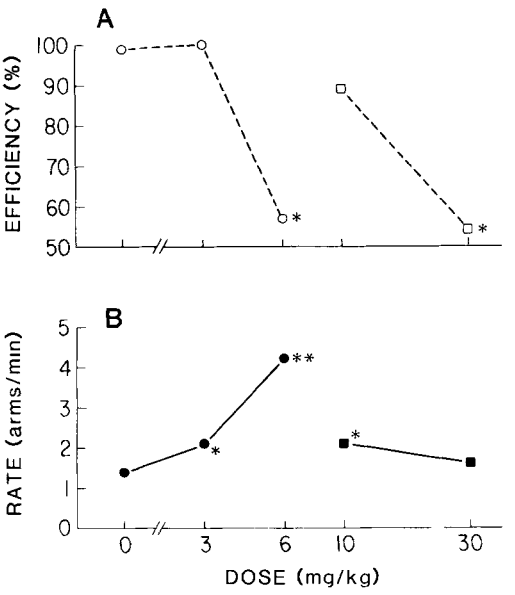

FIG 1 A and B Dose-response relationship for PCP (circles) and SKF-10,047 (squares) in an 8-arm radial maze Each point represents the mean of 1 determination in each of 8 subjects *Abscissa* Doses of drugs expressed on a log scale Drugs were administered IP 15 min before testing *Ordinates* A—efficiency, B—rate of responding $*p<0.05$, $**p<0.01$

of sessions to achieve that criterion (STC) was 15 for Group II Individual values were 11 for 4 rats, 14, 18, 20, and 21 Mean and individual values for STC were not calculated for Group I because of initial variations in the training conditions of the group Group II's mean rate of responding in obtaining the food pellets in the five sessions immediately preceding criterion performance was 4 7 arms per minute This rate is considerably higher than the control values shown in Figs 1–3 The apparent discrepancy is explained by the fact that training sessions were terminated after all 8 food pellets had been obtained, a procedure which greatly reduced time requirements for observation Untreated rats usually decrease their rate of exploration after each arm has been entered once This fact is reflected in the lower control rates for the 10-minute sessions presented in the figures

Figure 1, panel A shows the dose-related decrease in efficiency caused by PCP (circles) and SKF-10,047 (squares) in Group I Efficiencies following doses of 6 mg/kg of PCP and 30 mg/kg of SKF-10,047 were significantly different from their respective control values The decreased efficiency following the 6 mg/kg dose of PCP was accompanied by a significantly increased rate of responding (panel B) In contrast, the maximum increase in rate following SKF-10,047 was not correlated with the maximum effect on efficiency and it was of much smaller magnitude than that at 6 mg/kg of PCP Figure 2 illustrates the time course in Group I of the 6 mg/kg dose of PCP As expected, the effects on both efficiency and rate of responding diminish with time However, a significant effect on rate persists for a much longer period

In Fig 3 are seen the results of experiments in Group II

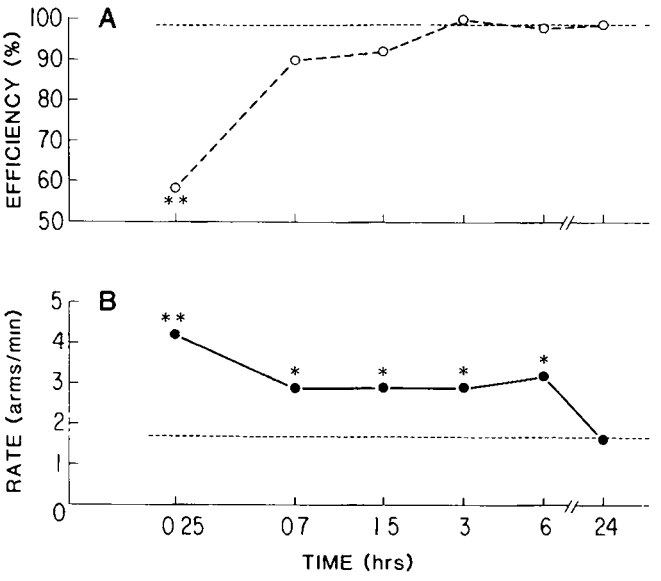

FIG 2 A and B Time course for the effects of a 6 mg/kg dose of PCP in an 8-arm radial maze Each point represents the mean of 1 determination in each of 8 subjects *Abscissa* Time in hours after administration of PCP expressed on a log scale Dotted lines indicate mean control values *Ordinates* A—efficiency, B—rate of responding *$p<0$ 05, **$p<0$ 01

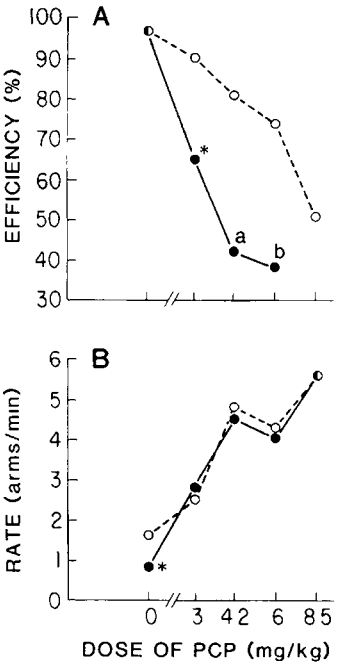

FIG 3 A and B Dose response relationship for PCP alone (15 min before testing, open circles) and in combination with verapamil HCl (20 mg/kg, 30 min before testing, closed circles) in an 8-arm radial maze Each point represents the mean of 1 determination in each of at least 4 subjects *Abscissa* Dose of PCP expressed on a log scale *Ordinates* A—efficiency, B—rate of responding *$p<0$ 05 [a]Five of eight rats did not complete the maze [b]Four of eight rats did not complete the maze

which were designed to test the interaction between PCP and verapamil The dose-response relationship for PCP on efficiency (panel A, open circles) is shifted to the left in the presence of verapamil (panel A, closed circles) When combined with verapamil, the 3 mg/kg dose was significantly potentiated A comparable statistical statement cannot be made at doses of 4 2 and 6 mg/kg because too few of the rats completed the maze Failure to complete the maze was not due to decreased response rate On the contrary, the combination of verapamil and PCP produced ataxia to the point that the subjects repeatedly fell from the maze However, the data of Fig 3 leave little doubt of potentiation at those doses as well Data for the combination of 8 5 mg/kg of PCP and verapamil are not shown because only 1 of 8 subjects was able to complete the maze in the allotted 10 minutes In contrast with the potentiation by verapamil of PCP's effects on efficiency, there were no significant effects on rate of responding (panel B) By itself, verapamil caused a decrease in rate To avoid possible fatalities in trained animals, the effects of greater doses of verapamil on performance in the maze were not extensively evaluated However, in five trials subjects received verapamil at a dose of 30 mg/kg (IP, 30 minutes before testing) No subjects completed the maze during a 10-minute session The number of arm entries ranged from 1 to 7 with no reentries

DISCUSSION

The present results confirm the observation by Kesner *et al* [26] that PCP decreases the efficiency of rats in solving a radial maze The observed increases in rate of responding are consonant with many previous reports of PCP-induced increases in spontaneous motor activity (e g , [32]) However, effects on efficiency and on response rate appear to be dissociable in that (a) SKF-10,047 produces effects on efficiency without a rate increase and (b) PCP's effects on efficiency and rate appear to follow a somewhat different time course

There is both behavioral and biochemical evidence to support the suggestion that PCP and SKF-10,047 may decrease efficiency by a similar mechanism, the two drugs have similar stimulus properties [46], they produce cross-physical dependence and cross-tolerance [47], and they both appear capable of binding to muscarinic ACh [3, 18, 23, 28, 54] and sigma opiate [18, 41, 42, 58] receptors Because of the well documented ability of atropine and scopolamine to decrease efficiency of performance in a radial maze [9, 16, 22, 33, 45, 55, 56], the *in vitro* demonstrations that PCP can act as a muscarinic antagonist [3, 28, 29] are of obvious interest On the other hand both phencyclidine and SKF-10,047 show anticholinesterase activity *in vitro* [23, 28, 29] Vanderwolf and Leung [53] found that PCP and atropine differentially affected neuronal activity in the rat hippocampus, a brain area shown to be crucial for efficient performance in a radial maze [38,39] PCP (10 mg/kg, IP) eliminated atropine-resistant rhythmical slow activity (RSA) while actually increasing atropine-sensitive RSA The possible involvement of sigma opiate receptors is supported by their high concentration in rat hippocampal tissue [42, 44, 58] In addition, binding of PCP and SKF-10,047 to serotonin$_2$ [31] and opiate

receptors of the mu [27, 54, 57] and kappa [57] type have been reported Clearly PCP's effects on efficiency and rate of responding may be mediated by different receptor mechanisms

From these data alone no conclusions can be made with regard to what psychological functions are disrupted by PCP and SKF-10,047 The decreased efficiency may have resulted from a direct effect on the memory process or an effect on a nonassociative factor such as perception [36]

Because of evidence that verapamil both displaces PCP from its receptor sites [17, 18, 19, 43] and antagonizes PCP's contractile effects on isolated cerebral arteries [1] we examined verapamil in the radial maze with the expectation that it would antagonize the behavioral effects of PCP However, the data of Fig 3 clearly show potentiation by verapamil of PCP-induced decreases in efficiency Falling from the maze by rats treated with verapamil plus PCP likewise suggests potentiation This effect was unanticipated in that it never occurs in drug-free rats and only rarely at the highest doses of PCP alone Because "falling from the maze" seems a crude and undesirable end point, future experiments will employ a maze with higher side walls On the other hand, more explicit investigation of the verapamil plus PCP-induced increases in ataxia might prove fruitful

The observed potentiation may have resulted from verapamil's calcium antagonist properties or its ability to bind to alpha$_1$-adrenergic [24], serotonin$_2$ [52], muscarinic ACh [10, 11, 24], or "high affinity" [^{3}H]PCP receptors [17, 18, 19, 43] Presumably the latter type of receptor is identical to the sigma opiate receptor [18, 41, 42, 58] The likelihood that the potentiation is a consequence of changes in the disposition of PCP is diminished by the failure of verapamil to alter PCP's effects on response rate Whatever the mechanism involved, the observed potentiation does not support the proposal that verapamil be used in the treatment of PCP intoxication [1]

The present data suggest that the radial maze may provide an interesting alternative method for the study of PCP and other psychoactive agents

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