THE EFFECTS OF THE PIRENPERONE AND KETANSERIN INJECTED INTO THE CA1 REGION ON SPATIAL DISCRIMINATION

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Abstract - In this study the effects of 5-HT$_{2A}$ receptor blockers in CA1 region of rat hippocampus on spatial learning were assessed in a T-maze, a spatial discrimination task. Rats were cannulated and bilateral injections of vehicle (saline) and 5-HT$_{2A}$ - selective antagonist, ketanserin (0.6, 1.2 or 2.4 μg / 0.5 μl) and pirenperone (0.1, 0.3, 1.2 or 2.4 μg / 0.5 μl) were injected through the cannulae 30 minutes before training each day. Results indicated that direct ketanserin and pirenperone injection did not affect spontaneous alternation. They also did not show a significant effect on trials to reach criterion and errors made by animals throughout spatial discrimination and reversal learning, but in the rats that received ketanserin produced dose dependent decrease in the latencies to enter the chosen arm in both learning and reversal stages. During extinction, no change was observed in the choice of the previously reinforced arm in both ketanserin and pirenperone groups. The slope of latency in highest dose of ketanserin (2.4 μg / 0.5μl) compared to the sham operated group but not in the pirenperone group.

These findings suggest that 5-HT$_{2A}$ receptors blockade (ketanserin, not pirenperone) in the CA1 region may decrease decision time and increase behavioural flexibility in T- maze.

Acta Medica Iranica 39 (4): 175-181; 2001

Key Words: Ketanserin, pirenperone, CA$_1$, T-maze, spatial discrimination, rat

INTRODUCTION

A great deal of research has been conducted concerning the role of serotonine (5-HT) on cognition. However, the literature regarding experimental evidence on the role of 5-HT in cognitive processes is rather controversial (1,2) and some of the reviews on the effects of serotonin on mnemonic function sugests that 5-HT exerts an inhibitory influence on learning and memory (3). Serotonergic neurotransmission involves the action of multiple 5-HT receptors types and subtypes 5-HT$_{1A}$, 5HT$_{1B/1D}$..., 5-HT$_{2A,2C}$ and 5-HT$_{3-7}$ (4). Previous pharmacological data provided some insight into the nature of the 5-HT receptors associated with learning and memory. These data may suggest that stimulation of 5-HT$_{1B/1D}$ receptors produces a decrease in learning, while blockade of 5-HT$_{2A/2C}$ receptors lead to an increase in learning (3,5,10,11). For example, ketanserin is a 5-HT$_2$ antagonist (6,7,8,9) and displays a high binding affinity for this receptor type (7,8). It is inactive at 5-HT$_1$ (7,8,12), 5-HT$_3$ and 5-HT$_4$ (12) binding sites, shows only moderate binding affinity for histamine H$_1$ and α_1- adernergic receptors, binds very weakly to dopamine receptor binding sites and is inactive in other known neurotransmitter receptor binding assay (7,8), produces an increase in consolidation of learning in the autoshaping task and spatial discrimination (10,11) and the effect of TFMPP (an agonist of 5-HT$_{1B}$) decrease the consolidation and this effect was reversed by (±) pindolol, ketanserin and ritanserin (10). Pirenperone also is clearly a potent antagonist which shows high specificity for the 5-HT$_2$ receptors in ligand binding and it has also a little effect on 5-HT$_1$ ligand binding and an affinity for the dopamine receptors (13,14). It could block the reduction in forced swimming test immobility (15), and some receptors show post training adminstration of serotonergic antagonists (ketanserin, pirenperone and mianserin) improve passive avoidance retention or adminstration of serotonergic receptor antagonists prior to retention test facilitated passive avoidance retrieval (16). The hippocampus has been traditionally linked to cognitive functions, particularly spatial memory (17,18,19,20,21). The serotonergic innervation of the hippocampus arises from 5-HT neurons of the median and dorsal raphe area (MR and DR) (18,22,23). The CA1 region of the hippocampus is rich in 5-HT receptors (24) and 5-HT containing terminals (25). The results of the researchers on the possible involvement of hippocampal 5-HT in the mediation of learning and memory provide evidence in support of its negative effect on one or more of hippocampal pathways involved in spatial information processing (18,26,27,28).

The present experiment was conducted to specifically examine the effect of $5\text{-}HT_{2A}$ receptor blockade in the CA1 region of rat hippocampus on spatial discrimination by pirenperone and ketanserin. A T-maze was used to test spontaneous alternation, spatial and reversal learning and extinction.

MATERIALS AND METHODS

Subjects

Male albino rats (200-250 g) 3-months old were obtained from breeding colony of the Pasteur Institute of Iran. Rats were housed five per cage in large cages before surgery and individually in small cages after surgery and maintained on a standard 12h-l2h light-dark cycle with lights on at 07.00. Rats were maintained at room temperature of 25 ± 2°C and food and water were made available.

Surgery

Approximately 7 days prior to initiation of the behavioural experiments, the rats were anesthetized with sodium pentobarbital (50 mg/kg I.P.) and were implanted with a stainless steel thin-wall cannulae (21 gauge) bilaterally into the CA1 region of the hippocampus (AP -3.80 mm from bregma; ML : ± 2.2 mm from midline; DV: -2.4 mm below the duramater according to the atlas paxinos and Watson (29). The tooth bar was at -3.3 mm. The cannulae and two anchoring screws were fixed to the skull with dental cement.

Drugs

Ketanserin, purchased from Sigma Chemical Co. and pirenperone from Research Biochemical International were dissolved in 0.9% isotonic saline.

Microinjection procedure

Before injection, the animal was restrained by hands, the cannulae stylets were removed and replaced with the injection needle (27- gauge) connected with a short piece of polyethylen tubing to a hamilton syringe. The needle was inserted 0.5 mm below the tip of the cannulae. 0.5 μl of saline or different doses of ketanserin (0.6, 1.2 or 24 μg / 0.5 μl) or pirenperone (0.1, 0.3, 1.2 or 24 μg / 0.5 μl) were injected during 1 minute. A total volume of 0.5 μl was injected into each side.

Behavioral assessment

One week after surgery, the animals were deprived of food to 85% of body weight and maintained at this level throughout behavioural testing.

Apparatus

The apparatus used consisted of a wooden T- maze with 15 cm height and start and goal boxes 16.5 cm x 16.5 cm; the length of the stem was 50 cm leading to L - shaped arms. The first part of each arm was 36 cm long and the second part which lead to the goal box had 30 cm length. Guillotine doors separated the start box from the stem and the goal boxes from the arms.

Training procedure

The protocol for this test was similar to that of Anneft's (30). Briefly, preliminary training took place on day 1 to 3. On days 4 and 5 (spontaneous alternation), food was available in both goal boxes on every trial. Each rat was confined to the start box for 10 seconds before being allowed to choose one of the goal boxes, where it was confined for a further 20 seconds. Eleven consecutive trials were given per day and the choice of right or left goal box, and also the latency between leaving the start box and entering the chosen arm were recorded. On days 6 to 8 (spatial discrimination and reversal), only one of the goal boxes was rewarded and the rats had to learn the correct one. Trials continued until the criterion of 5 cosecutive correct responses had been achieved. The choice of arm and latency between leaving the start box and entering the chosen arm were recorded on every trial. Immediately after reaching criterion, the contingenecies were reversed so that the previously unreinforced goal box was incorrect. Training continued until the new response was learnt, again to the criterion of 5 consecutive correct responses.

On day 9 (extinction), after spatial discrimination had been completed to 5 consecutive correct responses, an extinction stage was introduced. The food pellets were removed from T- maze and goal box choices; and the latencies were recorded over a further 10 trials.

Histology

At the end of each experiment, the animals were deeply anesthetized with ether and sacrificed by decapitation and the brains were removed. For histological examination of cannulae and needle placement in the CA_1 region, 100 μm thick sections were taken, mounted on slides, stained with cresyl violet and the cannulae tracks examined for each rat. Animals were accepted for data analysis only if both needle placements were located within the CA_1 region. There were several animals whose cannulae tip were not located at the correct position and their data were not included in analysis regarding their memory performance.

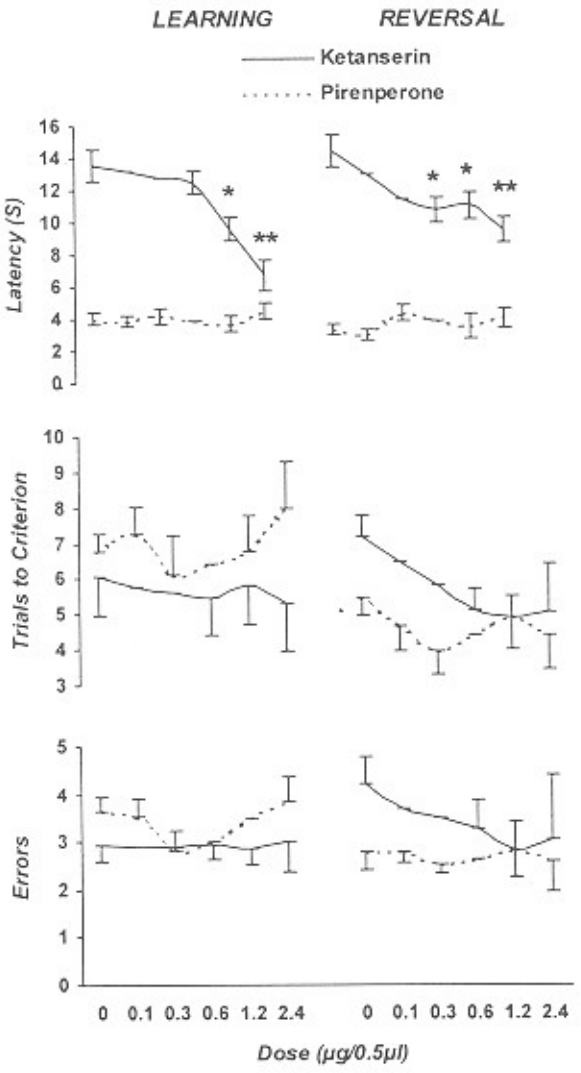


Fig. 1. Effect of different doses of ketanserin and pirenperone (injected into the CA_1 region) on spatial learning and reversal of rat performance in T-maze, over days 6-8.

A: Mean latency(ies) from leaving the start box to entering the chosen arm.

B: Mean number of trials to reach criterion.

C: Mean number of errors while reaching criterion.

(Ketanserin, n = 5 for each dose-Pirenperone, n = 7 for control, 0.3 and 2.4 μg/0.5 μl; n = 6 for 0.1 and 1.2 μg/0.5μl). Each point represents the mean + SEM. * P < 0.05, ** P < 0.01

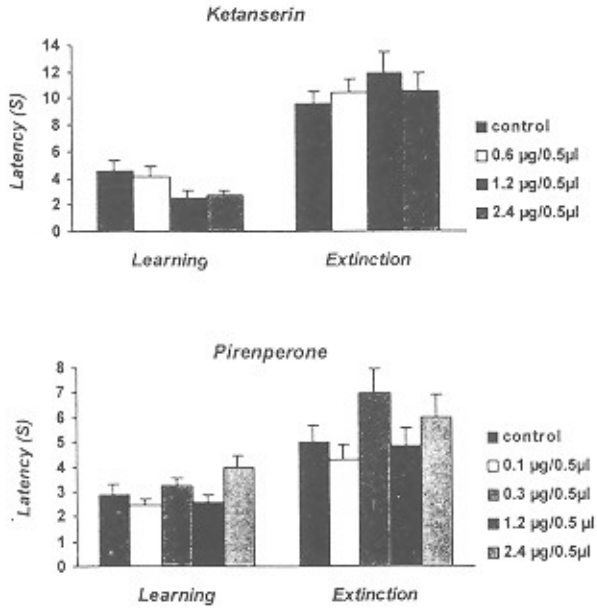


Fig. 2. Effect of ketanserin and pirenperone on mean latency(s) from leaving the start box to entering the chosen arm in learning and extinction phases (9th day).

Each bar represents the mean + SEM

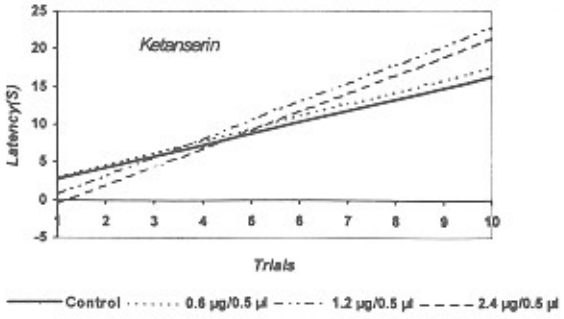
Statistics

All data were initially subjected to an analysis of variance (ANOVA) followed, where appropriate, by subsidiary, post-hoc, pair-wise comparisons using the Newman - Keuls procedure. The difference was considered significant at the level of $p<0.05$. A parallelism test followed by t- test was used to compare the slopes.

RESULTS

Spontaneous alternation

There were no significant differences in the percentage of alternate choices among the four ketanserin groups ($F_{3,16}$ = 2.18, n.s.) and in five pirenperone groups ($F_{4,28}$ = 1.277, n.s.). Latencies between leaving the start box and entering the chosen arm were not affected by intrahippocampal infection of ketanserin ($F_{3,16}$ = 0.47, n.s.) and pirenperone groups ($F_{2,28}$ = 0.5101, n.s.).



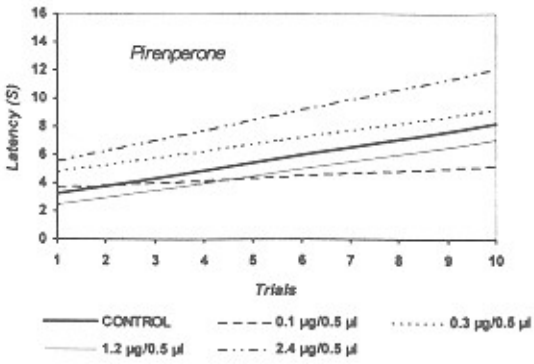


Fig. 3. Effect of different doses of ketanserin and pirenperone on increasing the mean latency(s) from leaving the start box to entering the chosen arm in extinction phase (9th day).
(Ketanserin, n = 5 for each dose-Pirenperone, n = 7 for control, 0.3 and 2.4 µg/0.5 µl; n = 6 for 0.1 and 1.2 µg/0.5 µl)

Spatial discrimination and reversal

There were no significant differences in trials to reach criterion among the groups in learning and reversal stages in ketanserin groups (ketanserin learning: $F_{3,16}$ = 0.080, n.s. ; reversal: $F_{4,28}$ = 0.5845, n.s.) and pirenperone groups (learning: $F_{4,28}$ = 0.503, n.s.; reversal: $F_{4,28}$ = 0.5845, n. s.). The number of errors of the ketanserin and pirenperone groups while acheiving criterion were not significantly different in the learning and reversal stages in ketanserin groups (learning: $F_{3,16}$ = 0.02, n.s. reversal: $F_{3,16}$ = 2.15, n.s.) and pirenperone groups (learning: $F_{4,28}$ = 0.7057, n.s. ; reversal: $F_{4,28}$ = 0.09729, n.s.). However, there were no significant differences in the latencies to enter the chosen arm in the pirenperone groups on both learning and reversal trials (learning: $F_{4,28}$ = 0.46, n.s.; reversal: $F_{4,28}$= 1.102, n.s.) but there were significant decreases in the ketanserin groups (learning: $F_{3,16}$= 11.56, p< 0.01; reversal: $F_{3,16}$ = 5.34, p< 0.01) (Fig 1).

Extinction

Over the 10 extinction trials, there were no significant differences in the percentage of previously reinforced arm choices among the ketanserin ($F_{3,16}$= 0.49, n.s.) and pirenperone groups ($F_{4,28}$ = 0.4042, n.s.).

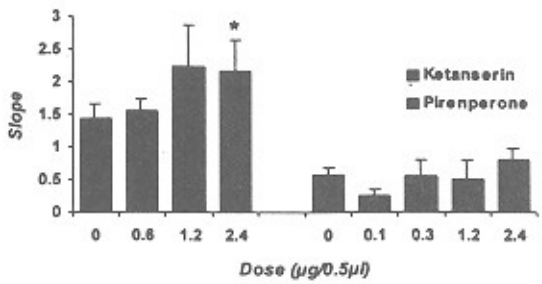


Fig. 4. Effect of different doses of ketanserin and pirenperone on slope of time increasing lines in extinction phase (9th day).
* P < 0.05. Each bar represents the mean + SEM

The latencies of both ketanserin and pirenperone groups to reach the chosen arm from the start box were not significantly different in learning (ketanserin: $F_{3,16}$ = 2.27, n.s. ; pirenperone: $F_{4,28}$= 2.323, n.s.) and extinction stages (ketanserin: $F_{3,16}$ = 0.51, n.s.; pirenperone: $F_{4,28}$ =1.828, n.s.) (Fig.2). On the extinction trials, there were no significant differences in the latencies of the ketanserin and pirenperone groups from leaving the start box to enter the chosen arm (Fig. 2), but the increase in slope of latency was higher in ketanserin groups and there was a significant difference between the group which had received 2.4 µg/0.5 µl ketanserin and the sham operated group (t= 2.266, 96 d.f., P< 0.05) but not in pirenperone groups (Fig.3 and 4).

DISCUSSION

The results in the present investigation indicated that ketanserin and pirenperone injected into the CA1 region of rat hippocampus had no significant effect on spontaneous alternation. Ketanserin but not pirenperone could reduce the latencies to enter the chosen arm throughout spatial discrimination and its reversal. At the extinction stage, ketanserin affected increasingly the slope of latency and caused it to be significantly higher in the group which had received the highest dose of ketanserin (2.4 μg/ 0.5 μl) compared to the sham operated group but there were no significant changes in slope of latency in pirenperone groups.

Some researchers have suggested that activation of 5-HT_{2A} receptor may be involved in impairment of memory in mice (31) and may play an inhibitory role in memory consolidation (5). Furthermore, it has been demonstrated that adminstration of ketanserin, one of the most selective antagonists of 5-HT_{2A} receptor subtype or other 5-HT_2 antagonists, can enhance the memory of a previously learned inhibitory avoidance response in mice (32,33,34,35), attenuate hypoxia-induced (5) or age- related (36) passive avoidance retention deficits in rats, improve cognitive performance in squirrel monkeys (37), and enhance protective effect of other agents against amnesia (38). Pirenperone, cianserin and ritanserin significantly reduced the number of errors expected to occur 24h after the 5 min of ischemia in a three-panel runway task (39). These studies provide strong support for the notion that blockade of the 5-HT2 receptors can enhance memory retrieval and protect against an experimentally induced amnesia and prevent) of working memory following transient forebrain ischemia (39).

The results of a number of studies show the negative influence of 5-HT on the processing of spatial information within the hippocampus. An inverse correlation has been observed between serotonergic content in the hippocampus and retention of conditioned reflexes in rats (27). It has also been reported that intrahippocampal 5-HT injection immediately after training impaired retention of a Y-maze brightness discrimination task in rats, while infusion of mianserin, a 5-HT_2 receptor antagonist, enhanced it (28). Ketanserin and pirenperone were found to be ineffective in a step-through passive avoidance test in the male rats (40) and also in rat elevated plus- maze (41). In addition, it has been indicated that intrahippocampal implantation of neonatal serotonergic nerve grafts impaired performance of rats on a complex spatial learning task (42), whereas, neurotoxin-induced depletion of 5-HT in hippocampus enhanced it (26). It has been reported that rats trained in the stone 14-unit T-maze, a complex, positively reinforced, spatial discrimination task learned significantly faster and made significantly fewer errors throughout training following selective neurotoxic (5,7DHT) deafferentation of the 5-HT in spatial learning within the hippocampus, and the different effects on spatial discrimination which 5-HT_2 receptor antagonists generally produce (18). The effect of serotonin on long - term potentiation (LTP) has been assessed in a number of in-vitro studies, and most of the reports have suggested that 5-HT inhibits induction of LTP in the CA1 region (43) and commissural synapses of rat hippocampus (44). In the CA1 region, it has been demonstrated that 5-HT_2 receptor blockade significantly enhances hippocampal LTP (45). The result of this study indicated that ketanserin and pirenperone injected into the CA1 region did not affect spontaneous alternation, since no difference was seen in the percentage of alternate choices and latency to choose an arm on days 4 and 5. There was also no significant effect on the number of trials to reach criterion and errors made by animals while achieving criterion in learning spatial discrimination task and its reversal. Ketanserin but not pirenperone reduce the latencies to enter the chosen arm in both learning and reversal stages dose-dependently. Thus rats receiving ketanserin were able to choose their way on each trial faster than sham operated group. On the other hand their decision time decreased following ketanserin injection. Since ketanserin did not affect the latencies on day 4 and 5, it could be concluded that latency decrease on days 6-8 was due to ketanserin effect on spatial discrimination and reversal but pirenperone had no effect on latency, error and trial to criterion in learning and its reversal spatial discrimination task on days 6-8. Over the 10 extinction trials, ketanserin caused the slope of latency increase to be higher in the ketanserin received group but pirenperone did not change it. At the extinction stage, when food reward is ommitted, the rats reduce the pace at which they run the maze, i.e. in the absence of reinforcer, they do not choose an arm with the same pace as before and the latency to enter the chosen arm increases. However, the increase in slope of latency was higher in the ketanserin received groups and there was a significant difference between the group which had received 2.4 μg/0.5 μl ketanserin and the sham operated group. Since Annett et al (30) have attributed this parameter to behavioural flexibility, it can be concluded that ketanserin could probably increase behavioural flexibility. Taken together, it seems that 5-HT_{2A} receptor blockade in the CAl region of rat hippocampus may decrease decision time and increase behavioural flexibility in T- maze and it seems that ketanserin is more effective than pirenperone. However, the effect of intrahippocampal injection of ketanserin and pirenperone on spatial discrimination should be

assessed using other types of learning and memory tasks, and additional studies are warranted in order to determine the exact role of 5-HT_{2A} receptors in this region in spatial learning and memory.

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