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Effects of Citalopram in Cognition and Memory in Experimental Animals

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Abstract: *Citalopram is an SSRI which enhances serotonin reuptake, a neurotransmitter involved closely in cognition and memory. With ever increasing cases of dementia and Alzeihmer's disease and lack of definitive treatment, research into other treatment options are necessary. This study aims to evaluate the cognition and memory enhancing effects of citalopram in experimental animals.*

Keywords:*Citalopram, cognition, memory, Morris water maze, 8 arm radial maze*

I. Introduction

Dementia is one of the main causes of dependence and disability at older ages. Dementia is a syndrome caused by a number of progressive illnesses that affects memory, thinking, behaviour and the ability to perform day to day activities. It mainly affects older people but 2 to 10% of all cases are estimated to start before the age of 65 years. After this, the prevalence doubles, with every five year increment in age. [1]

The cognitive impairment characterizing dementia may include memory loss, difficulty in understanding or using words, inability to carry out motor activities despite adequate motor function and failure to identify or recognize objects. [2] At present 44 million people are affected by dementia and this figure is expected to reach 135 million by 2050. [3]

Mounting evidence accumulated over the past few years indicates that the neurotransmitter serotonin plays a significant role in cognition. As a drug target, serotonin receptors have received notable attention due, in particular to the role of several serotonin-receptor subclasses in cognition and memory. [4]

Since the Selective Serotonin Reuptake Inhibitors (SSRIs) increase the serotonin levels hence theoretically these drugs should help in cognition and memory but there is no consensus regarding it, as various studies have found contradicting results.

Citalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) and used as an antidepressant. It allosterically inhibits the Norepinephrine Transporter (NET) by binding the receptor at a site other than the active binding site for serotonin. [5].

II. Methodology

The study was conducted in the Department of Pharmacology at Gauhati Medical College & Hospital after taking due approval from the Institutional Animal Ethics Committee. Citalopramhydrobromide and Scopolaminehydrobromide were obtained from Sigma Aldrich India, Bangalore. Piracetam was obtained from UCB India Pvt Ltd.Vapi, Gujarat.

The study was carried out in healthy, male swiss albino mice weighing 26 – 32 gm. The animals were procured from Animal House, Gauhati Medical College.

Mice chaw diet and water *ad libitum* during the experiment except the animals used for 8 Arm Radial Maze. Animals were maintained under controlled condition with 12 hour light and 12 hour dark cycles at a temperature of 24 ± 1^0 C and humidity of 55 ± 5 %. All the animals were acclimatized to laboratory condition for 7 days before conducting the experiment.

The animals were then divided into five groups each containing six animals. The groups were:

Group I: Normal Control Group: Received Normal Saline in the dose of 0.01 ml/gm/day intra peritoneally(i.p). Animals in this group received normal diet and water. No drugs or chemicals were administered to animals in this group.

Group II: Impaired Cognition And Memory Control: Received scopolaminehydrobromide 0.4 mg/kg, i.p to impair memory and cognition.

Group III: Impaired Cognition And Memory Standard: Received Piracetam 200 mg/kg i.pand scopolaminehydrobromide 0.4 mg/kgi.p.

Group IV: Cognition And Memory Enhancement Test Drug 1(Citalopram): Received Citalopram hydrobromide 10 mg/kg and scopolaminehydrobromide 0.4 mg/kg i.p.

Piracetam and citalopram were administered for a period of 14 days. During the training phase, from Day 11 to 14, scopolamine was administered in the groups II to IV after 45 minutes of administration of other drugs.

Training was started 30 minutes after injection of scopolamine/normal saline. On test days, i.e. 15th and 18th day, only normal saline was given 30 minutes prior to the retention test.

Themorris water mazeconsists of a circular pool filled with water, 122cm in diameter and 51cm deep with non-reflective interior surfaces (the interior was painted black). Water was filled upto 30cm. A platform (10 cm × 10 cm) was submerged 1 cm below the water surface in one of the quadrant. The experimental animals were given an acclimatization session two days before the training period started in the form of 30 sec swim around in the maze without the platform present.

During the training period, starting from day 11, the animal was placed in the desired start position in the maze, facing the tank wall. The mice were allowed 120 seconds to locate the submerged platform. Then, it was allowed to stay on the platform for 20 seconds. If it failed to find the platform within 120 seconds, it was gently guided onto the platform and allowed to remain there for 20 seconds. Each animal was subjected to four consecutive training trials on each day starting from Day 11 with an inter trial gap of 5 minutes. The drop location was changed for each trial during the training days and the target quadrant remained constant throughout the training period.

On the 15th day, 24 hrs after the last dose was administered, the platform was removed and each mouse was allowed to explore the pool for 120 seconds. The mean time spent by the animal in the target quadrant searching for the hidden platform, over 4 trials, was noted.

After a gap of two days, on the 18th day, again each mouse was allowed to explore the pool for 120 seconds to test for long term memory. The time spent in the training quadrant was noted.

Care was taken that the relative location of the water maze with respect to other objects in the laboratory serving, as prominent visual clues, were not disturbed during the total duration of the study. All the trials were completed between 09.00 and 17.00 hrs.

The **8- arm radial maze** is composed of a central octagonal platform 20 cm in diameter with eight arms (35cm × 5cm) extending from it. Each arm has a 5-mmdeep hole 1cm from the end, which was used as a food cup to avoid visibility of the food from the central platform. Doors were placed in each arm to separate the central platform from the arms. The maze was elevated 100 cm above the floor. The maze was made of wood and was placed in a room with various external cues in the form of a doorway, overhead light, overhead fan, poster in the walls that were visible to the mice while it was on the maze. Illumination was provided from above the maze in the form of a 6 watt bulb.

Mice were placed on the maze in pairs for 4 days before the start of the trial for acclimatization. Acclimatization was done in four days. Food rewards were placed at the end of only four arms of the radial arm maze before each test session. The same arms were baited for a particular mouse during each trial. The mice were then placed in the centre of the maze. The mice were allowed to explore the entered arm and to eat the food placed at the end of the arm. When the mice returned to the centre all arms were closed. After 10 seconds all arms were opened again and the mice was allowed to explore the maze again. The trial ended after 10 minutes or if all baits have been found. To prevent odour cues, the maze was wiped clean with spirit between animals. Each mouse was given 5 trials each day for 4 days. Five mazes were used and a particular mouse used the same maze daily. On the 15th and 17th day retention test was done. The following data was recorded:-

- Number of correct entries into baited arms.
- Number of entries into unbaited arms.
- Number of re-entries into baited arms.

In all cases, a visit was only counted when all four paws entered a particular arm.

The statistical analysis was carried out using Graph pad prism 5.01 software. Data were expressed as mean ± SEM. Results were analyzed by one way analysis of variance (ANOVA), followed by Tukey's multiple comparison test.p value < 0.05 was considered as statistically significant.

III. Results

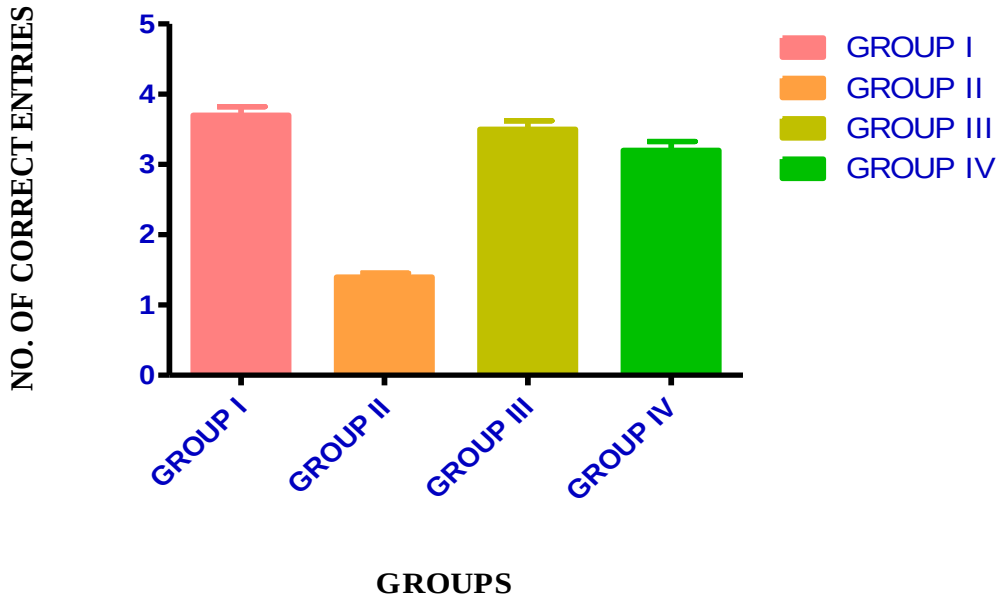
Table 1: Effect of citalopram in escape latency and time spent in target quadrant in mice (mean ± SEM) (in seconds)

GROUPS	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18
GROUP I NORMAL CONTROL	**111.073±1.438**	**101.250±0.667**	**71.145±1.384**	**54.058± 1.447**	**64.557± 1.220**	**61.328± 1.114**
GROUP II COGNITION CONTROL	**112.975± 1.700**	**111.008±1.338[a]**	**104.762±1.669[a]**	**101.995± 1.211[a]**	**34.098± 0.899[a]**	**30.792± 0.872[a]**
GROUP III COGNITION STANDARD	**107.663± 1.839**	**103.750± 0.973[b]**	**74.082± 0.988[b]**	**56.432± 1.211[b]**	**63.998± 0.797[b]**	**59.907± 1.877[b]**
GROUP IV	**109.167±**	**105.333±**	**77.500±**	**60.792±**	**60.000±**	**56.583±**

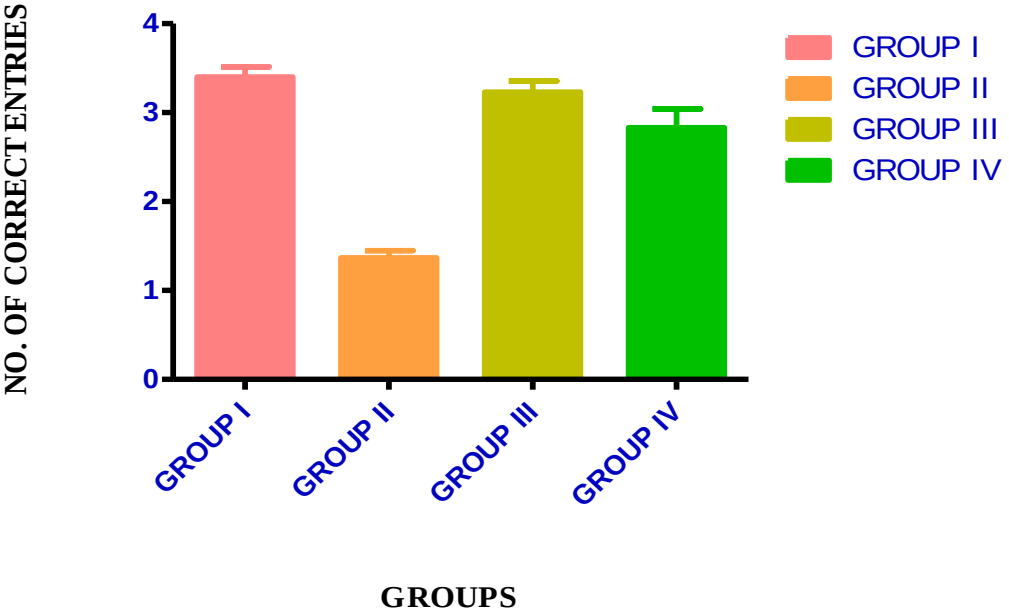
CITALOPRAM	**2.258**	**1.246**[b]	**1.514**[ab]	**1.823**[ab]	**1.065**[ab]	**1.145**[ab]

Values are expressed as Mean ± SEM (n=6);
One Way ANOVA followed by Tukey's multiple comparison test was done.
[a]p<0.05 when compared to the Normal control group.
[b]p<0.05 when compared to the Cognition control group.

The TSTQ in the citalopram group was significantly higher when the cognition control group was taken as control column, on both Day 15 and 18.



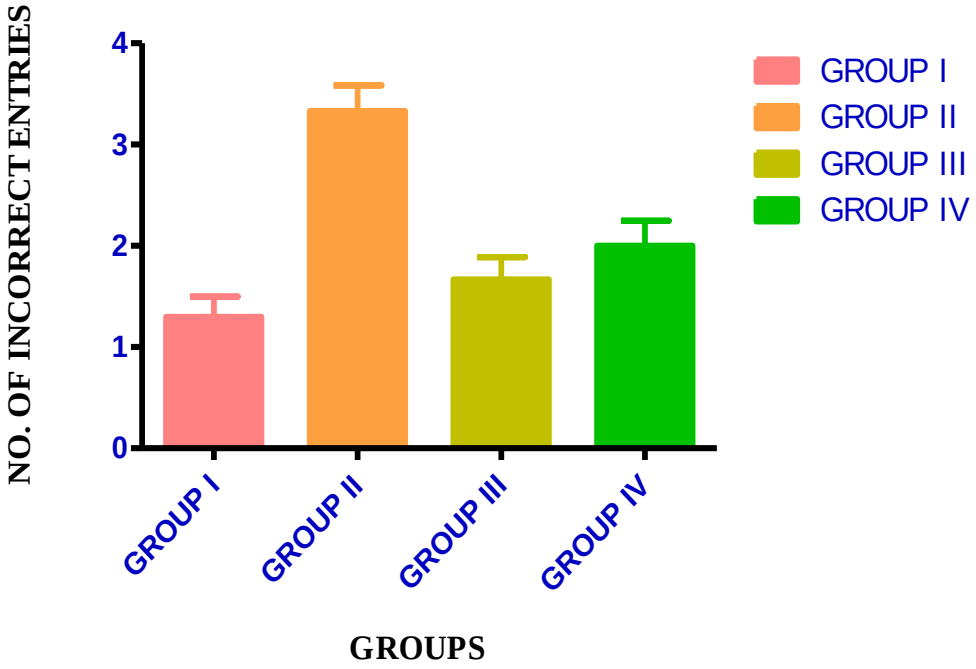
Graph 1 Number of correct entries on day 15



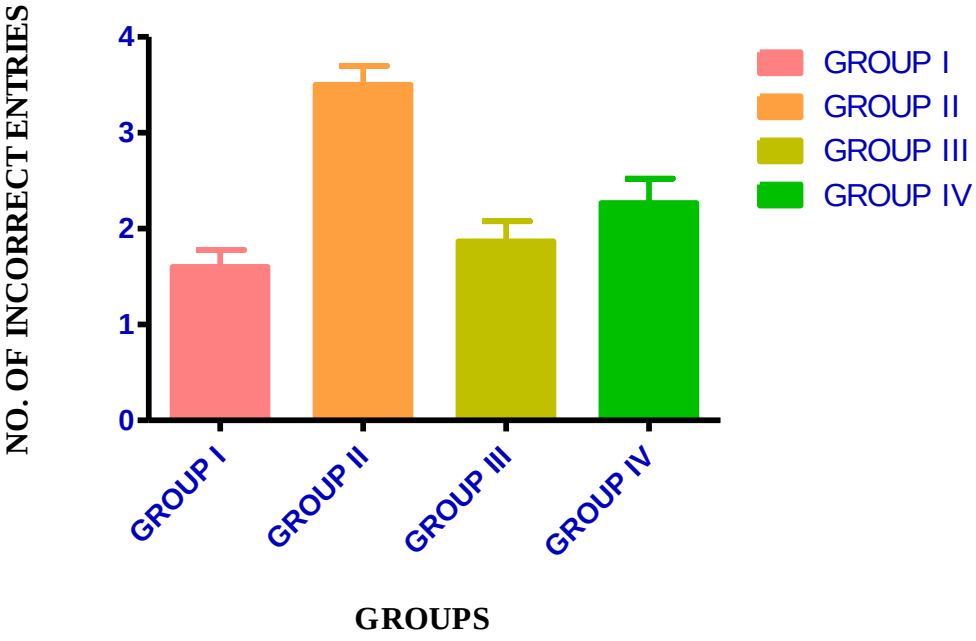
Graph 2 Number of correct entries on day 18

During the retention teston **Day 15 and 18**, there was a statistically significant increase (p <0.05) in the number of correct entries in the citalopram group when the cognition control group was taken as control

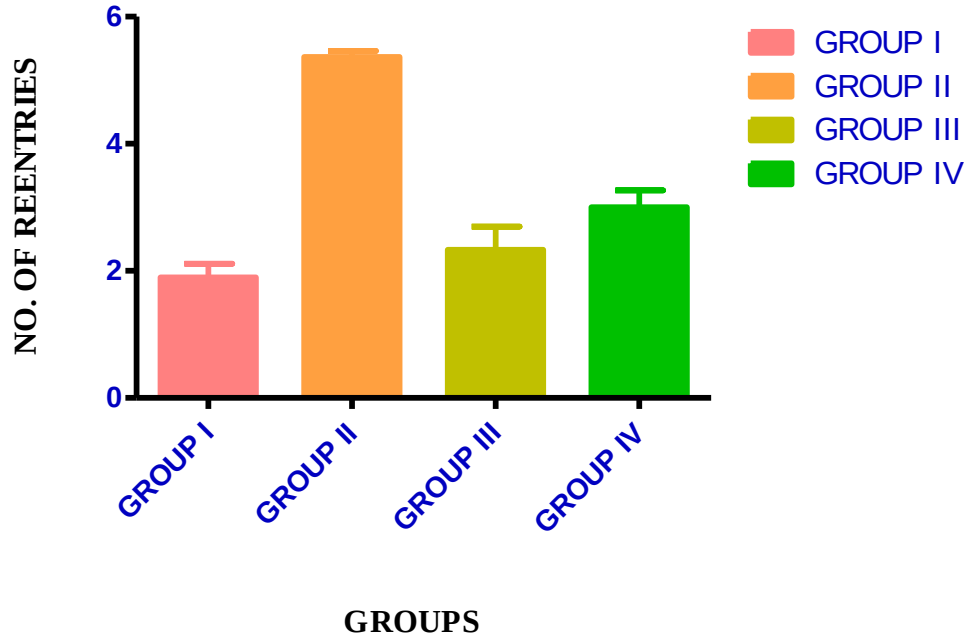
column. The number of correct entries in the citalopram group was however less than the standard drug, piracetam group but the difference was insignificant.



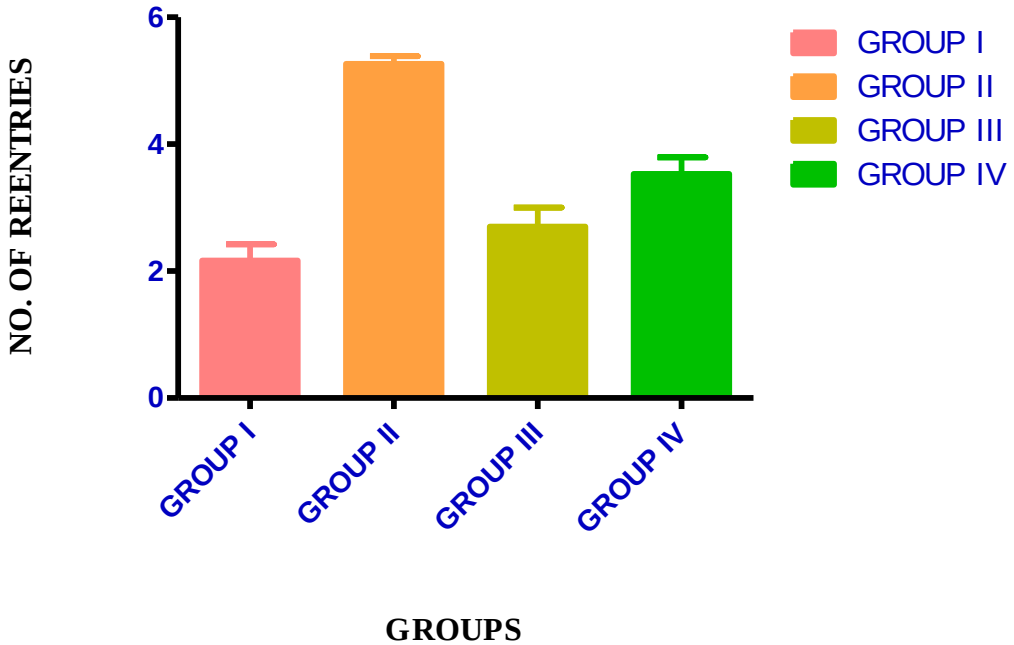
GRAPH 3 Number of incorrect entries on day 15



GRAPH 4 Number of incorrect entries on day 18



GRAPH 5 Number of reentries on day 15



GRAPH 6 Number of reentries on day 18

During the retention teston **Day 15 and 18**, there was a statistically significant decrease ($p < 0.05$) in the number of incorrect and reentries in the citalopram group when the cognition control group was taken as control column. The number of incorrect and reentries in the citalopram group was however more than the standard drug, piracetam group but the difference was insignificant.

IV. Discussion

Chronic diseases such as dementiacontribute a large share of disease burden in low- and middle income countries. [6] There is no definitive treatment of dementia; it is mainly symptomatic and palliative. The SSRI Citalopram, is a valuable tool to study the central serotonergic system in experimental neuropharmacology due to its selective effect on 5-HT uptake and also because this effect is not related to alterations of catecholamines.[7] [8]There is great variation in the doses used for citalopram in different animal studies. [9] [10] [11]In this study, the most commonly used dose, 10 mg/kg was taken, in corroboration to previous studies.[12] [13] Further studies are needed for understanding the detailed effects of different doses of citalopram in cognition.

The positive effects of citalopram in cognition evaluated here runs in line with a study where citalopram reversed both scopolamine and tetrahydrocannabinol (THC) induced impairment of spatial memory using an 8-Arm Radial Maze model. The results obtained from the study are consistent with the results of the present study. [14]

Similar results were replicated in studies where chronic intermittent cold stress (2 weeks) was used to impair learning and induce a cognitive deficit. It was seen that both acute and chronic treatment (3 weeks) with citalopram produces beneficial effects in chronic intermittent cold stress induced deficit in cognition and memory. [15] [16]

Further studies on chronic intermittent cold stress (5 weeks) induced cognitive deficit and impaired learning also produced similar results. Citalopram treatment in the last 3 weeks of the 5 week stress improved reversal learning in the stressed rats. [17]

In addition the present study correspond the results found in several clinical trials studying the effects of citalopram on cognition.

Citalopram was reported to improve memory and cognition in healthy volunteers [18]and in acute stroke patients. [19]

As suggested by the results of the present study, citalopramshowed significant improvement in the cognition of hospitalized, demented, non depressed patients [20] and also showed significant improvement in cognition parametersas compared to a placebo-treated subgroup. [21]

V. Conclusion

Dementia is a debilitating condition affecting the patients as well as their caregivers.Cognitive disturbances in dementia patients render them unable to perform day to day activities. Citalopram might offer help and better cognitive status in such patients. However, further elaborate studies are needed to evaluate its utility in such cases.

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