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Original Article

Pharmacology Section

Relative Efficacy of Piracetam, Modafinil and Citicoline on Cognitive Function in an Animal Model

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ABSTRACT

Introduction: Nootropic drugs or cognitive enhancers are pharmacological agents that improve cognitive function and memory by various mechanisms. Drugs like piracetam, modafinil and citicoline have been used as nootropic agents.

Aim: To compare the relative efficacy of nootropics like piracetam, modafinil and citicoline on learning and memory in rats using the Morris water maze test.

Materials and Methods: A total of 30 Wistar rats were used for the study. The animals were divided into five groups (n=6). The groups I to V received gum acacia orally, scopolamine 2 mg/kg intraperitoneally, piracetam (52.5 mg/kg), modafinil (2.5 mg/kg), citicoline (25 mg/kg) respectively orally for twenty days. Learning and memory was evaluated using the Morris water maze test. The animals were trained in the Morris water maze on the last five days of dosing. Scopolamine 2 mg/kg was administered intraperitoneally to the above groups of animals (except Groups I and II) for induction of amnesia, 45 minutes before the behavioural test.

Results: Scopolamine induced marked impairment of memory evidenced by significant reduction ($p<0.01$) in the number of entries and time spent in the target quadrant when compared to the control group. There was significant ($p<0.05$) increase in the number of entries and time spent in target quadrant of the Morris water maze in the animals who were pretreated with piracetam, modafinil and citicoline, in comparison to the scopolamine treated group. Amongst the three nootropics, modafinil and citicoline showed significant ($p<0.05$) memory enhancement in comparison to piracetam.

Conclusion: Modafinil and citicoline can significantly reverse the memory impairment in scopolamine induced amnesia model in comparison to piracetam. However, further studies are warranted to confirm this result.

Keywords: Dementia, Memory, Morris water maze, Nootropics

INTRODUCTION

Learning and memory is a complex function of the brain, and several drugs have been shown to improve cognitive functioning. Learning is acquisition of new information and retention of the newly acquired information is described as memory. Nootropic drugs or cognitive enhancers are pharmacological agents that improve cognitive function and memory by various mechanisms [1]. The effectiveness of several of these drugs has been established and anecdotal evidences suggest that there are several more drugs that have nootropic like effect. Piracetam, modafinil and citicoline have been widely studied as cognition enhancers. Piracetam, a cyclic derivative of gamma-aminobutyric acid has been shown which facilitate learning and improve memory retention in various experimental procedures [2,3]. Modafinil is a drug used to promote wakefulness and has shown to improve working memory and attention span in various tests [4]. Citicoline, an over the counter drug used as a dietary supplement has shown to improve memory retention and also counteract neuronal degeneration [5]. Although, these drugs have been widely used as cognitive enhancers, there is a dearth of data comparing their effects. Hence, the aim of this study was to compare the cognition enhancing effect of piracetam, modafinil and citicoline on the Morris water maze.

MATERIALS AND METHODS

The present study was conducted at Department of Pharmacology, Kasturba Medical College, Manipal, Karnataka, India. Institutional animal ethics clearance was obtained before carrying out the experiment. A total of 30 animals were required for the study. Adult Wistar rats weighing 150-200 gm were used. The animals were provided with standard feed and water. The experiment was conducted using a Morris water maze.

Morris water maze [6,7] is a behavioural test to evaluate spatial learning and memory in experimental rodents, consisting of a circular tank (diameter 150 cm and height 45 cm), which was filled with water and maintained at 25°C. The water was made opaque by adding milk. The tank was divided into four equal quadrants (Q1, Q2, Q3, and Q4). A white platform (10 cm^2) was placed in Q4 quadrant (target quadrant) approximately 1 cm below the surface of water. The position of platform and clues were kept consistent throughout the training session. Each animal was subjected to four consecutive acquisition trials on each day with an interval of five minute, during which rats were trained to locate the hidden platform and allowed to remain there for 20 seconds. If the animal was unable to locate the hidden platform within 60 seconds, it was gently guided to the platform and allowed to remain there for 20 seconds. During each trial, the latencies of rats to locate the hidden platform were recorded and the latency was considered as an index of acquisition and learning. On the fifth day, the platform was removed and each rat was allowed to explore the pool for 60 seconds. The latency to enter and the total time spent in the target quadrant Q4 were noted as indices of retrieval [7]. Rats were divided into five groups (n=6). The animals were treated as mentioned in [Table/Fig-1].

The animals were treated with the above mentioned drugs for a period of twenty days. Scopalamine 2 mg/kg was administered intraperitoneally [8], 45 minutes prior to the experiment to the rats belonging to groups II, III, IV and V. Group I underwent the Morris water maze test without being treated with scopolamine and served as positive control group. Rats equivalent doses in mg/kg body

Group	Drug
I	2 mL 2% gum acacia (Positive control)
II	2 mL 2% gum acacia + 2 mg/kg scopolamine i.p. (Negative control)
III	52.5 mg/kg piracetam orally + 2 mg/kg scopolamine i.p.
IV	2.5 mg/kg modafinil orally + 2 mg/kg scopolamine i.p.
V	2.5 mg/kg citicoline orally + 2 mg/kg scopolamine i.p.

[Table/Fig-1]: Drug treatment in various groups.

weight of clinical doses were calculated as mg/kg body weight as described by Paget GE and Barnes JM [9].

STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 16.0. One way Analysis of Variance (ANOVA) was used to compare the differences between the means of different groups. It was followed by Tukey's post-hoc test to compare the means of each treatment group with the other.

RESULTS

In the present study, scopolamine induced marked impairment of memory evidenced by significant reduction ($p<0.01$) in the number of entries and time spent in the target quadrant when compared to the control group [Table/Fig-2]. Pretreatment with piracetam, modafinil and citicoline, significantly improved ($p<0.05$) the number of entries and time spent in target quadrant in comparison to the scopolamine treated group. This suggests that the animals had learnt the position of the platform and impairment of learning by scopolamine was reversed, by treatment with piracetam, modafinil and citicoline. Amongst the three nootropics, modafinil and citicoline showed significant ($p<0.05$) increase in the time spent in the quadrant in comparison to the animals treated with piracetam.

Group	Drug	Number of entries in target quadrant (Mean±SE)	Time (seconds) spent in target quadrant (Mean±SE)
I	Positive control	5.58±0.35[a]	15.51±1.26[a]
II	Negative control	1.54±0.20*	7.03±0.40**
III	Piracetam	6.83±0.45[a]	14.92±0.71[a]
IV	Modafinil	7.04±0.39[a*]	19.14±16.7[a†]
V	Citicoline	7.46±0.43[a**]	21.93±1.24[a**†]

[Table/Fig-2]: Comparison of different groups on the Morris water maze.
ANOVA $p<0.05$, post-hoc Tukey's test [a] <0.05 vs group II; * <0.05, ** <0.01 vs group I; † <0.05 vs group III

DISCUSSION

All the major cognitive enhancers have a unique and novel mechanism of action. Piracetam, a widely used nootropic, though its exact mechanism is not known, is postulated to act as positive allosteric modulator of AMPA receptors and appear to modulate cholinergic systems [10]. Piracetam also affects the membrane fluidity which is compromised during aging [11]. Various studies have demonstrated the beneficial effect of piracetam on learning and memory [12,13]. Modafinil currently been used for Attention Deficit Hyperkinetic Disorder (ADHD), narcolepsy and hypersomnia has been shown to have neuroprotective and nootropic effect. The reduction in brain cellular oxidation and increase in cortical creatinine have been the proposed mechanisms [14]. Modafinil is majorly being used off-label by on-duty physicians, students and academic professionals with the aim of enhancing their cognitive abilities [15]. Citicoline (cytidine 5′-diphosphocholine, CDP-choline), due to its membrane stabilising, free radical scavenging actions and by playing an important role in phospholipid synthesis and neuronal repair, has been proposed for use in improving cognitive impairment, especially of vascular origin like stroke, brain injuries, vascular dementia etc. In addition, it has also shown to stimulate the release of neurotransmitters like dopamine [16]. However, most of the neuroprotective actions of citicoline have been noticed on long term administration of the drug [17].

Albeit there have been various studies comparing the efficacy of cholinesterase inhibitors like rivastigmine or donepezil with NMDA antagonist like memantine [18-20]. There is a clear dearth of information comparing the relatively newer cognitive enhancers like modafinil, piracetam or citicoline. In the present study, all the three drugs could reverse the memory impairment induced by scopalamine, however, modafinil and citicoline significantly reversed the memory impairment in scopolamine induced amnesia model in comparison to piracetam.

LIMITATION

The study however is not bereft of limitations. One of the major limitations is the duration of the study. Since, cognitive enhancers are chronically administered, the long term safety and efficacy of these drugs becomes a major determinant in the long term use of newer agents like piracetam, modafinil and citicoline [21]. Therefore, further studies are required in this aspect.

CONCLUSION

Modafinil, citicoline and piracetam significantly improved cognition tested using Morris water maze model in scopolamine induced amnesia models in rats. However, the significant improvement in learning and memory as witnessed in the modafinil and citicoline groups as compared to the piracetam group has to be probed further before validating the above results.

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