Original Article

Pharmacology

Cognition-Enhancing Effect of Oral Therapeutic Doses of Methylphenidate in Rats

1. Nausheen Alam 2.Rahila Najam

1. Asstt. Prof. of Pharmacology, Faculty of Pharmacy, Federal Urdu University, Karachi
2. Prof. of Pharmacology, Faculty of Pharmacy, University of Karachi.

ABSTRACT

Objective: To determine the effects of oral therapeutic doses of methylphenidate, on memory. It was thought that long term use of methylphenidate possibly may lead to tolerance in the ability of the drug elicit enhancement of learning and memory. A dose-dependent effect may therefore help to extend the therapeutic use of the drug for better clinical response.

Study Design: Experimental / Analytic study

Place and Duration of Study: This study was conducted in the Department of Pharmacology, Faculty of pharmacy, University of Karachi, Karachi for a period of period of 4 weeks.

Materials and Methods: Twenty-four male Albino Wister rats (weighing 180-220g) were randomly assigned to four groups, one control and 3 test groups. The experimental protocol was designed to administer methylphenidate orally two times daily for 4 weeks. Four groups were: (i) Saline (1.0 ml/kg/ day), (ii) Methylphenidate (2mg/kg/day) (iii) Methylphenidate (5mg/kg/day) (iv) Methylphenidate (8mg/kg/day) treated groups. Behavioral activity of rats i.e. performance of rats in passive avoidance test was monitored weekly. The experiment was performed in a balanced design to avoid the order effect.

Results: In the present study methylphenidate treated rats exhibited an increased in Passive Avoidance learning as there was increased in the latency time to reach the punished compartment as compared to control rats. This memory improvement effect of methylphenidate on PA was dose dependent in 1st week as the rats treated with 8 mg/kg/day took greater time to reach the dark box than 5mg/kg/day and 2mg/kg/day, but in 2nd, 3rd and 4th week it was seen that rats treated with fore mention doses took same time but greater than 1st week to enter the punishable compartment

Conclusion: It can be concluded that high dose produce greater cognitive effect in short term treatment than low and moderate doses, however in long-term treatment all the doses produce similar improvement in memory without tolerance in cognition

Key Words: methylphenidate, oral dose, cognition, passive avoidance test.

INTRODUCTION

Cognition enhancement has received much attention in recent scientific literatures due to our aging society and the increasing prevalence of Alzheimer's disease. However, the healthy young population also engages in drug use to enhance memory. Methylphenidate a medication effective to enhance attention[1,2,3], and cognition[4] in ADHD patients, as well as in healthy subjects[5,6,7,8].This has raised concern regarding the ethical and safety aspects of potential cognition-enhancing drugs[9,10,11]. These issues aside, it is important to know if the drug does actually have cognition-enhancing effect after long-term administration.

Methylphenidate blocks the dopamine transporter and the noradrenaline transporter[12,13,14,15], thus increasing the extracellular concentrations of these catecholamines. The attention-improving characteristic of methylphenidate has been attributed to the amplification of dopamine release in the central nervous system[16]. Dopamine (DA) modulates cognitive performance in part via its regulation of the prefrontal cortex through dopamine D1 and D2 receptors[17]. Methylphenidate (MPH) increase DA signaling in the brain and are used in the treatment of attention deficit hyperactivity disorder (ADHD) and other neuropsychiatric disorders to enhance attention and cognition[18,19,20,21].

Purpose of our study was to monitor the effects of oral therapeutic doses of methylphenidate, on memory function in rats. It was thought that long term use of methylphenidate possibly may lead to tolerance in the ability of the drug elicit enhancement of learning and memory. A dose-dependent effect may therefore help to extend the therapeutic use of the drug for better clinical response.

MATERIALS AND METHODS

2.1 Test systems used (Animals):

Locally bred Albino Wister rats (weighing 180-200g) were housed individually under 12 h light and dark cycles (light on at 06:00h) and controlled room temperature (24+2℃) with free access to tap water and cubes of standard rodent diet at least 7 days before the start of experiment so that they could become familiar to the environment. They were accustomed to various handling procedures to nullify stress effects. All experiments were performed according to the protocols approved by the local animal care committee.

2.2 Behavioral assessment

Passive Avoidance Test: Passive avoidance paradigm consists of two compartments as an illuminated 'safe' and a dark 'punishable' one. Both compartments were connected with a door that enable free crossing from one compartment to another. Both compartments had a grid floor. The diameter of rods was 5 mm with 0.5 cm distance between the rods.

In the training session, rat was placed in an illuminated box. Once the rats prompted by their instinct stepped its four paws into the dark compartment, rats received 1.5 mA foot shock through the grid floor to its paws for 5 seconds. After receiving the foot shock, it immediately came back to illuminated safe compartment. During the test period (24 hour later), rats were placed in the bright compartment again for a maximum of 5minutes. The step- through latency that indicates the time elapsed before the rat entered the dark compartment was recorded in the test session as described earlier [22]. Passive avoidance test of all drug treated and control animals were performed weekly in a balance design to avoid order effect.

2.3. Drugs: Methylphenidate HCl was obtained from local medical store and prepared in 0.9% NaCl (saline). Drug was administered in a volume of 1 ml/kg of body weight by per oral route twice a day to the treated animals and control animals were treated with saline (0.9%) at the dose of 1 ml/kg per oral twice a day.

2.4. Experimental protocol: Twenty-four male Albino Wister rats (weighing 180-220g) were randomly assigned to four groups, one control and 3 test groups, each containing six animals. The experimental protocol was designed to administer methylphenidate orally two times daily for 4 weeks.

Four groups were: (i) Saline (1.0 ml/kg/day), (ii) Methylphenidate (2mg/kg/day) (iii) Methylphenidate (5mg/kg/day) (iv) Methylphenidate (8mg/kg/day) treated groups.

Behavioral activity of rats i.e. performance of rats in passive avoidance test was monitored weekly. The experiment was performed in a balanced design to avoid the order effect.

2.5. Statistical analysis: Results are represented as mean ±S.D. Statistical analysis of passive avoidance test was performed by two-way analysis of variance (ANOVA) repeated measure design. Post hoc comparison of groups was performed by Newman-Keul test. Values of $p<0.05$ and $p<0.01$ were considered as significant.

RESULTS

Dose related effect of methylphenidate on performance of rats in passive avoidance test.

Fig. shows the effects of methylphenidate doses on the performance of rats in PA test. Two-way ANOVA repeated measure revealed a significant dose ($F=200.4$, $df=3,20$, $P<0.01$), week ($F=32.9$, $df=3,20$, $P<0.01$) effect and also a significant interaction between the two factors ($F=10.97$, $df=9,60$, $P<0.01$).

Post hoc comparison by Newman-keuls test showed that retention of Passive Avoidance was improved in test rats than in controls as low dose (2 mg/kg/day), moderate dose (5 mg/kg/day) and high dose (8mg/kg/day) of methylphenidate significantly ($P<0.01$) increased latency time in all 4 weeks compared to similar week saline treated rats and in 2nd ,3rd and 4th week from 1st week values.

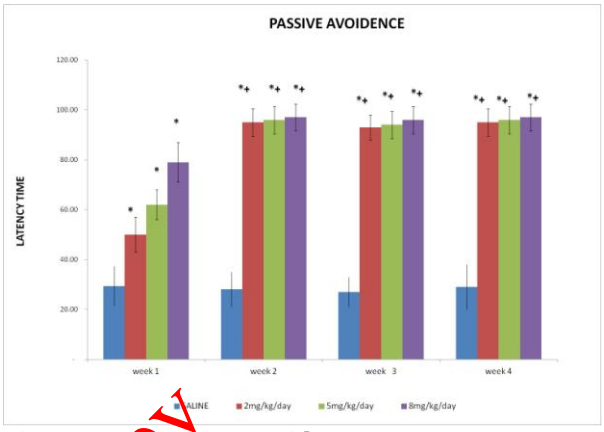

Figure No. 1: Passive Avoidance

DISCUSSION

Methylphenidate has been shown to potentiate the cognitive effect and is the main medication prescribed for attention deficit hyperactivity disorder[23] to improve memory[24] attention and concentration[25,26,27], yet there is increasing evidence that they do not promote learning[27], which can be due to tolerance to the cognitive effect of the drug.

In the current study we chose passive avoidance test to measure effects in memory function following methylphenidate administration at three different doses. Study showed methylphenidate treated rats exhibited an increased in Passive Avoidance learning as there was increased in the latency time to reach the punished compartment as compared to control rats. This memory improvement effect of methylphenidate on PA was dose dependent in 1st week as the rats treated with 8 mg/kg/day took greater time to reach the dark box than 5mg/kg/day dose and the rats treated with 5mg/kg/day day took greater time to reach the dark box than 2mg/kg/day dose, but in 2nd , 3rd and 4th week it was seen that rats treated with fore mention doses took same time to enter the dark punishable compartment which showed that high dose produce greater cognitive effect in short term treatment however in long-term treatment all the doses produce similar cognitive effect.

Central dopaminergic systems play a critical role in the regulation cognitive behavior. Memory improvement effect of methylphenidate in the present study is due to increased DA levels as there is an overwhelming evidence for a critical role of dopamine in

cognition[28,29]. Cognitive symptoms have been associated with dopamine disregulation in numerous diseases including schizophrenia[30], depression[31], drug addiction[32] and Parkinson disease[33]. Support for a role of dopamine in cognition also comes from studies of dopaminergic drug in normal subject[34]

Methylphenidate blocks the dopamine transporter[12,13,14,15] thus increasing the extracellular concentrations of these dopamine. The memory improvement effect of methylphenidate has been attributed to the amplification of dopamine release in the central nervous system[16]. Dopamine (DA) modulates cognitive performance in part via its regulation of the prefrontal cortex through dopamine D1 and D2 receptors[17]. Methylphenidate (MPH) increases DA signaling in the brain and is used in the treatment of attention deficit hyperactivity disorder (ADHD) and other neuropsychiatric disorders to enhance attention and cognition [18,19,20,21]

CONCLUSION

In summary this study provides the documentation of significant relationship between oral therapeutic doses of methylphenidate and cognation .Our results suggest that initially cognitive enhancing effect is dose dependent, but later on cognitive improvement response in low, moderate and high doses of methylphenidate became similar after long term use.

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Address for Corresponding Author:
Dr. Nausheen Alam,
Asstt. Prof. of Pharmacology,
Faculty of Pharmacy,
Federal Urdu University, Karachi