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EFFECTS OF 5-HT AGONIST ELETRIPTAN ON PASSIVE AVOIDANCE AND LOCOMOTOR ACTIVITY

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ABSTRACT

Purpose: Serotonin (5-HT) as neurotransmitter controls the appetite, sleep, learning and memory, endocrine regulation and depression. Eletriptan is a second-generation triptan and potent 5-HT agonist. **Methods**: Male Wistar rats were treated with: 1st group saline; 2nd and 3rd group eletriptan 0.1mg/kg and 0.5 mg/kg respectively. Step-through and step-down passive avoidance tests were used 2 days learning, short and long memory retention sessions. Criterion of up to 3 min staying in light compartment for step-through and up to 60 seconds on the platform for step-down was observed. Locomotor activity was measured as horizontal and vertical movements in activity cage for 5 minutes. The statistic evaluation was done by ANOVA. **Results:** On step-through test the low dose group showed significant decrease on 2nd day of learning session and on memory retention test compared to the controls. On step-down test rats with eletriptan in both doses significantly decreased the latency time. Rats treated with eletriptan in both doses increased significantly vertical activity and slightly the horizontal. **Conclusion**: Our data permit the suggestion that 5-HT agonist eletriptan influenced the learning and long memory retention in step-through and in step-down passive avoidance. Eletriptan stimulates predominant the vertical locomotor activity.

Key words: adaptogen, triptan, rats, serotonin neurotransmitter, cognitive effects

INTRODUCTION

Like most neurotransmitters, serotonin possesses a simple structure. However, the pharmacological consequences are more complex and diverse. Serotonin is involved in numerous functions in the human body including the control of appetite, sleep, memory and learning, temperature regulation, mood, behavior, cardiovascular function, muscle contraction, endocrine regulation, and depression. Low levels of serotonin may be associated with several disorders, namely increase in aggressive and angry behaviors, clinical depression, Parkinson's disease, obsessive-compulsive disorder, eating disorders, migraine, irritable bowel syndrome, tinnitus and bipolar disease. These effects are mediated via different serotonin (5-HT) receptors. (1)

Triptans are potent serotonin (5-HT) 1B/1D receptor agonists used to abort and treat migraine headaches. Although the triptans share pharmacodynamic characteristics at 5-$HT_{1B/1D}$ receptors, they differ pharmacokinetically. Generally, the triptans are metabolized by phase I monoamine oxidases (MAOs) and by various cytochrome P450 enzymes. However, each triptan has a unique metabolic profile. (2) These drugs selectively increase vessel resistance in a.carotis and in this way counteract its vasodilation, which is believed to be crucial for the pathology of migraine- paroxysmal dysfunction characterized with visual disturbances with aura connected with or followed by one-sided headache, nausea and vomiting.

Eletriptan is a new generation triptan, with high affinity 5-HT1B/1D receptors. It is used in the therapy migraine and cluster headache. This medicine is characterized with better efficacy and faster onset of its action than other drugs

from the same pharmacological group. Eletriptan has a 4-8-fold higher affinity than sumatriptan and other triptans. (3)

AIM

The aim of the current research was to evaluate the influence of eletriptan over the behavior of the rats with an accent on their memory functions after multiple applications.

MATERIALS AND METHODS

In this study, 24 male Wistar rats with 150-200 g body weight were used, divided in 3 groups (n=8). The rats were kept under standard laboratory conditions in an 08:00-20:00 h light/dark cycle and were provided with food and water ad libitum.The animals was treated intraperitoneally respectively **(Table 1):**

Table 1. *Experimental design*

First group (control)	Saline 0.1ml/100g
Second group	Eletriptan 0.1mg/kg
Third group	Eletriptan 0.5mg/kg

The following behavioral tests were used: step-through and step-down passive avoidance tests and locomotor activity.

1. The step-through passive avoidance test was performed in an automatic set-up of two compartment cage (Ugo Basile). Each rat is placed in to the light chamber. Learning and retention sessions consisted of three trails (door delay 7 sec., followed by electrical stimulation for 9 sec. at the intensity of 0.4mA). The latency of reactions (the animal remaining in the light chamber for more than 180sec.) was used as criterion for learning and retention.

2. The step-down passive avoidance test was performed in a set-up of single compartment cage with a plastic platform (Ugo Basile). Each rat is placed gently on the platform. Learning and retention sessions consisted of two trials (electrical stimulation duration of 10 sec. with intensity of 0.4 mA). The latency of reactions (the rat remaining in the platform for more than 60sec.) was accepted as the criterion for learning and retention.

In both tests, short memory retention was evaluated 24 hours after a two-day learning session. Memory retention (long memory) was evaluated on 9^{th} day from the first day of learning for step-down test and on 11^{th} day from the first day of learning for step-through test.

3. Locomotor activity test was performed in an automatic activity cage with UV detection for horizontal and vertical movements measurement. Each rat had single test for 5 min. The numbers of horizontal and vertical movements in units were recorded automatically.

Statistical evaluation: The values obtained were expressed as mean ± S.E.M. The comparison between groups was made by Student's test analysis of variance (ANOVA) in the Excel and Instant computer programs. A value of $P<0.05$ was considered as a significant difference.

RESULTS

1. Effects of eletriptan on Step-through passive avoidance test.

In the step-through passive avoidance test, control rats significantly prolonged ($P<0.05$) the latency of reaction on 2^{nd} day of learning, short and long memory tests compared to the 1^{st} day control group. The group treated with eletriptan 0.1mg/kg significantly decreased the latency of reaction ($P<0.05$) on 2^{st} day of learning session and on long memory retention test, compared to the same day controls. Rats treated with eletriptan 0.5mg/kg significantly decreased ($P<0.05$) the latency time on long memory retention test, compared to the respective day controls. **(Figure 1)**

2. Effects of eletriptan on Step-down passive avoidance test.

In the step-down passive avoidance test, control rats significantly prolonged ($P<0.05$) the latency of reaction on 2^{nd} day of learning, short and long memory tests compared with the 1^{st} day control group.

The group treated with eletriptan 0.1mg/kg significantly decreased the latency of reaction ($P<0.05$) during learning session, short and long

memory tests compared with the same day controls.

Rats treated with eletriptan 0.5mg/kg significantly decreased (P<0.05) the latency of reaction on learning session, short and long memory retention test. **(Figure 2)**

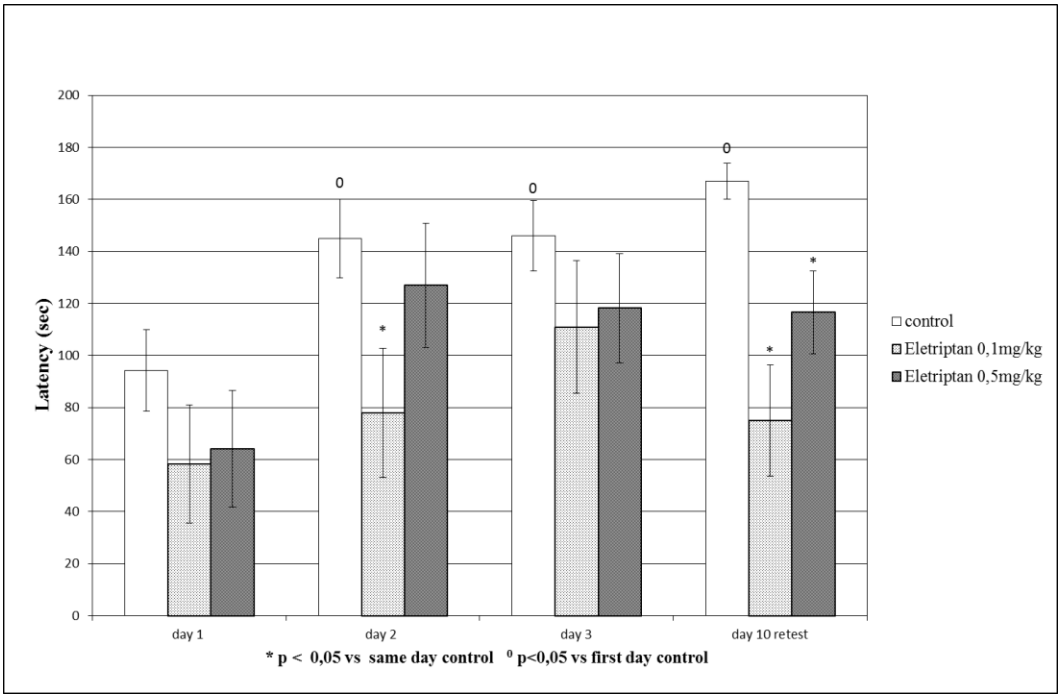

Figure 1. Effects of eletriptan on passive avoidance Step through test

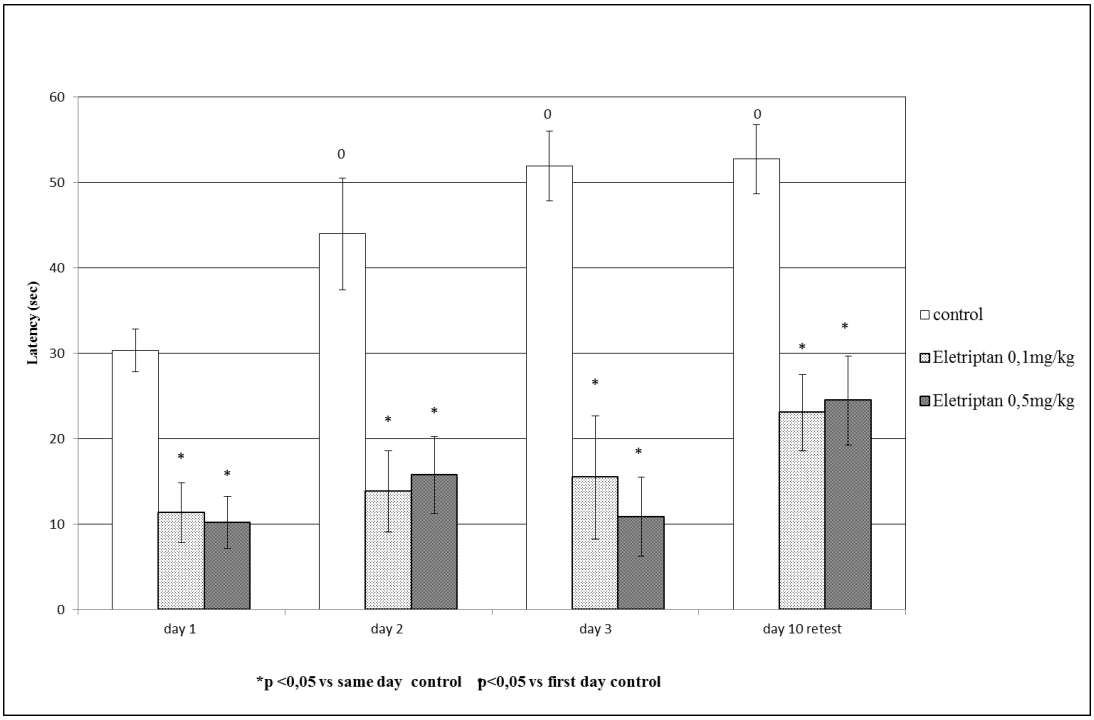

Figure 2. Effects of eletriptan on passive avoidance Step down test

3. Effects of eletriptan in activity cage test.

Controls showed decrease on the horizontal and vertical activity. Rats treated with eletriptan 0.1mg/kg or 0.5mg/kg significantly increased only the vertical activity ($P<0.05$) compared to the control. Both doses of eletriptan did not change the horizontal activity. **(Figure 3)**

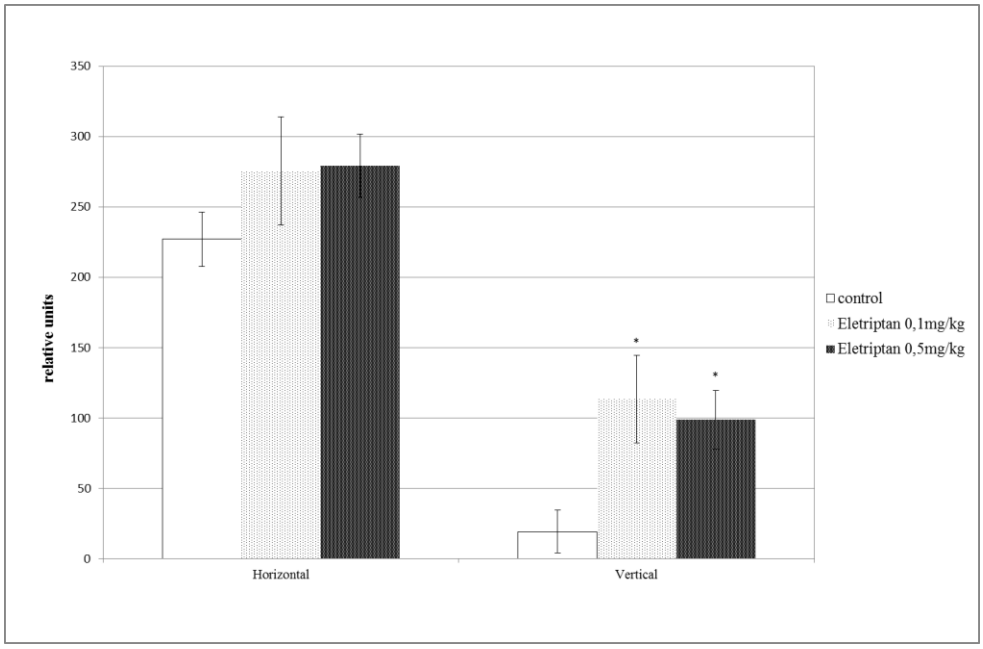

Figure 3. Effects of eletriptan in activity cage test

DISCUSSION

Our data permit the suggestion that 5-HT agonist eletriptan influenced the learning and long memory retention in step-through and in step-down passive avoidance. Eletriptan stimulates predominant the vertical locomotor activity. Having in mind its antimigraine effects due to it may be speculated that eletriptan shall improve the memory functioning as well improved cerebral blood flow. Our results are consistent with other similar studies in the scientific literature [4, 5] suggesting that the positive results of eletriptan on passive avoidance tests are due to its effect on the cognitive functions. In conclusion, the results from the present study demonstrate that studied drug eletriptan increase learning and memory in passive avoidance tests Step-through and Step-down and stimulate the locomotor activity and exploration.

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