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Effects of Frovatriptan and Almotriptan on Locomotor Activity in Female Rats with Experimental Model of Migraine

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DEDICATED TO HUMANITY

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INTRODUCTION

Migraine headache is the third most prevalent medical disease in the world according to the Global Burden of Disease Study 2010 from WHO [1]. The headache is commonly unilateral, aggravated by routine physical activity, and can last a few hours to a few days, predominant in female. Migraine therapy has two goals: to terminate acute attacks; and to prevent the next attack from happening [2]. Current possibilities for acute treatment include: nonsteroidal anti-inflammatory drugs (NSAIDs), triptans and NSAID-triptan combinations, dihydroergotamine, non-opioid combination analgesics [3].

One of the targets for migraine treatment are the 5-$HT_{1B/1D}$ receptors. Triptans as 5-$HT_{1B/1D}$ receptor agonists are first-line therapeutic option for migraine attack. The triptans are potent vasoconstrictors as they induce intracranial vasoconstriction, inhibition of neurotransmitter release at peripheral and central trigeminal nociceptive terminals, via 5-$HT_{1B/1D}$ receptors [4].

Frovatriptan is a potent 5-$HT_{1B/1D}$ receptor agonist and has the highest 5-$HT1_B$ potency in the triptan class. In different clinical pharmacology studies, frovatriptan was shown to have a long terminal elimination half-life time about 26 hours [5].

Almotriptan is potent 5-$HT_{1B/1D}$ agonist and 5-HT_{1F} also. Almotriptan has the ability to inhibit the peripheral and central trigeminal activity associated with the release of neuropeptides [4]. In June 2009, almotriptan was the first approved triptan from the US Food and Drug Administration (FDA) to treat acute migraine in adolescents (12-17 years) [6].

Development of experimental model of migraine gives the possibility to reveal distinct differences in the pharmacodynamics of triptans and introduce an innovative and effective treatment strategies for migrane.

The **aim** of the experimental study was to assess the effects of frovatriptan and almotriptan on locomotor activity in female rats with nitroglycerin-induced migraine.

DESIGN OF THE EXPERIMENT

Experimental model of migraine

Each of the female rats was subcutaneously (s.c) injected with saline 0.1 ml/100 g and nitroglycerine (NTG) 10 mg/kg. 90 min after application of NTG the rats were treated with triptans.

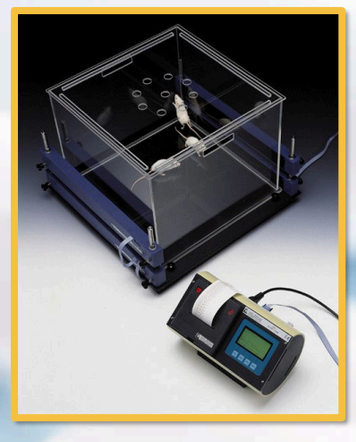
All groups were tested on “Activity cage” apparatus 40 min after injection of the triptans. The development of a clinically relevant migraine model is essential to improve the treatment methods and understanding migraine pathophysiology.

Female Wistar rats (n = 8) divided in 6 groups were treated subcutaneously (s.c) as follow:

- 1st control group with saline 0.1 ml/ 100 g;
- 2nd model group with nitroglycerin (NTG) 10 mg/kg and saline 0.1 ml/100 g;
- 3rd group with NTG and frovatriptan 2.5 mg/kg;
- 4th group with NTG and frovatriptan 5 mg/kg;
- 5th group with NTG and almotriptan 3 mg/kg;
- 6th group with NTG and almotriptan 6 mg/kg.

“Activity Cage” test

An automatic electronic apparatus ("Activity cage", Ugo Basile, Italy) was used to record horizontal and vertical activity in rodents. The motor activity of the animal was recorded by infrared photo sensors located on the walls and floor of the cell, which is automatically counted and printed in digital form. Each animal was placed in the center of the apparatus and left free to examine the field for 5 minutes once. Horizontal and vertical activity is reported in relative units.



STATISTICAL ANALYSIS

The statistic evaluation was done in SPSS (19.0). For each of the parameters, were calculated Mean and Standard Error (SEM). A Shapiro-Wilk test was performed to determine the level of distribution. Independent sample T-test and Mann-Whitney U test were performed depending on the level of distribution. In all assays, values of $p < 0.05$ were determined to be statistically significant.

There is no potential conflict of interest

RESULTS

Female rats with migraine model only, did not show significant change in horizontal and vertical activities compared to control group with saline. While both groups with NTG model treated with frovatriptan 2.5 mg/kg and 5 mg/kg significantly ($P < 0.05$) increased the number of horizontal movements compared to the model group with NTG (Fig. 1).

The other parameter for vertical activity was significantly ($P < 0.05$) increased in the group treated with frovatriptan 2.5 mg/kg compared to the group with the NTG model (Fig. 2).

Fig. 1.

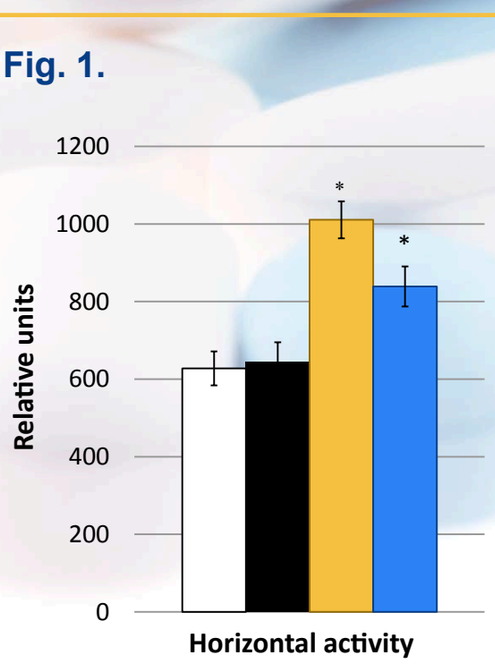
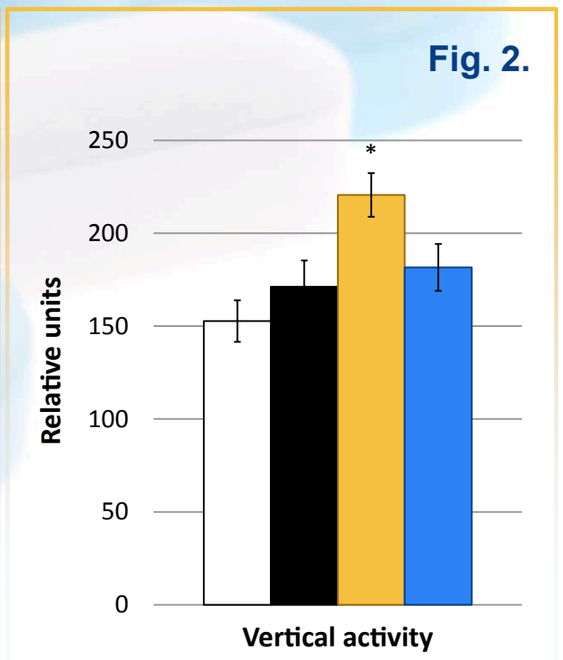


Fig. 2.



In the series of experiments conducted with female rats treated with almotriptan at doses of 3 mg/kg and 6 mg/kg, did not show significant differences in both the horizontal and vertical activity compared to the nitroglycerine treated group (Tab. 1).

Tab. 1.

Indicator	Control (saline) 0.1 ml/100 g	NTG 10 mg/kg	NTG 10 mg/kg + Almotriptan 3 mg/kg	NTG 10 mg/kg + Almotriptan 6 mg/kg
Horizontal activity	627,75 ± 43,75	644,75 ± 50,33	773,75 ± 49,55	503,12 ± 47,98
Vertical activity	152,75 ± 11,17	171,25 ± 14,11	220,37 ± 12,09	149,37 ± 13,62

CONCLUSION

The absence of changes in locomotor activity in the NTG model group is in line with the results from other studies [7]. In our experimental study the presence of significant changes in locomotor activity between the model group and frovatriptan treated groups suggests anti-migraine effects of triptans, trough suppression of the pain-related avoidance reaction. That permits us to propose that 5-$HT_{1B/1D}$ receptors in some subcortical areas – caudate putamen, n. accumbens, hypothalamus in mice and rats, participate also in the modulation of locomotor acivity. Moreover, frovatriptan possesses high agonistic activity to 5-$HT_{1B/1D}$ receptors. The lack of changes in spatial orientation in animals treated with almotriptan, could be due to lower affinity to 5-HT_{1B} receptors than frovatriptan, and higher to 5-HT_{1F} receptors.

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