

THE INFLUENCE OF SOME ANTIDEPRESSANT DRUGS ON SPATIAL MEMORY IN RATS

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Abstract

This study investigates the effects of antidepressant drugs paroxetine and venlafaxine on the spatial memory in rats. The experiment was carried out on old white Wistar rats (15 months) distributed into 3 groups of 7 animals each, treated orally for 1 month, as follows: Group I (Control): saline solution 0.3 mL/100 g weight; Group II (PRX): paroxetine 5 mg/Kg bw; Group III (VLX): venlafaxine 8 mg/Kg bw. The effects of these antidepressants on memory performance were assessed using the Y-maze test in a single session of eight minutes. Alternation was defined as a consecutive entry in three different arms of the device. The alternation percentage was calculated according the formula: $[\text{number of alternations} / (\text{total number of arm entries} - 2)] \times 100$. The data were analysed with SPSS 17 for Windows software, ANOVA method. In our experimental conditions the treatment with PRX and VLX resulted in a significant increase of the spontaneous alternation rate compared to control group in the Y-maze test. We can conclude that chronic administration of both antidepressant drugs paroxetine and venlafaxine was associated with the improvement of short-term spatial memory in old rats.

Rezumat

Acest studiu investighează efectele medicamentelor antidepressive paroxetin și venlafaxin asupra memoriei spațiale la șobolani. Experimentul a fost efectuat pe șobolani albi Wistar bătrâni (15 luni), repartizați în 3 loturi a câte 7 animale fiecare, tratați oral timp de o lună astfel: Lotul I (Martor): ser fiziologic 0.3 mL/100 g greutate; Lotul II (PRX): paroxetin 5 mg/kg corp; Lotul III (VLX): venlafaxin 8 mg/kg corp. Efectele acestor antidepressive asupra memoriei s-au explorat utilizând testul Y-maze, într-o singură sesiune de opt minute. Alternarea a fost definită ca intrarea consecutivă în trei brațe diferite ale dispozitivului. Procentul de alternare a fost calculat după formula: $[\text{numărul de alternări} / (\text{numărul total de brațe vizitate} - 2)] \times 100$. Datele au fost analizate cu ajutorul programului SPSS 17.0 pentru Windows și metoda ANOVA unifactorială. În condițiile noastre experimentale, tratamentul cu PRX și VLX a avut ca rezultat creșterea semnificativă a ratei de alternare spontană, comparativ cu lotul martor, la testul Y-maze. S-a pus în evidență faptul că administrarea cronică a ambelor medicamente antidepressive, paroxetină și venlafaxină, a determinat îmbunătățirea semnificativă a memoriei spațiale de scurtă durată, la șobolani bătrâni.

Keywords: paroxetine, venlafaxine, Y-maze test, memory, rats

Introduction

Antidepressants (tricyclic drugs, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors) are used, alone or in combination with other various drugs, for the treatment of major depressive disorders, eating disorders, for attention-deficit hyperactivity disorder, sleep disturbances, drug addiction and for a variety of conditions accompanied by pain [1, 10, 11, 17].

Antidepressants exhibit a number of pharmacological actions: they block the reuptake of

norepinephrine and serotonin, have direct and indirect actions on opioid receptors, inhibit histamine, cholinergic, 5-hydroxytryptamine and N-methyl-D-aspartate receptors, inhibit ion channel activity, and block adenosine uptake [8, 18]. Serotonin reuptake inhibitors have a great affinity for the serotonin reuptake carrier in the synaptic cleft in the central nervous system and much less affinity for the norepinephrine reuptake carrier, for the alpha- and beta-adrenergic, dopamine, histamine, serotonin and muscarinic receptors [5, 18]. The supposition that antidepressants are involved in the mediation of recognition memory is based on

some experimental reports revealing the modulation of memory consolidation by serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, but not by the tricyclic compounds [12].

To actually prove this hypothesis we investigated the effects of two antidepressants, the serotonin reuptake inhibitor paroxetine and serotonin-norepinephrine reuptake inhibitor venlafaxine on spatial memory performance in the Y-maze test, an experimental model for evaluating the eagerness of laboratory animals to explore new environment.

Paroxetine is a (3S,4R)-3-(1,3-benzodioxol-5-ylloxymethyl)-4-(4-fluorophenyl)piperidine derivative that acts as a selective serotonin reuptake inhibitor and the 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexan-1-ol compound, venlafaxine, is an antidepressant of the serotonin-norepinephrine reuptake inhibitor. Both of them are used in the treatment of different types of depression and anxiety disorders [5, 8, 18].

The aim of our study was the experimental investigation on the effects of paroxetine and venlafaxine on rat memory performances in the Y-maze test.

Materials and Methods

The experiment was carried out on old white Wistar rats (300–350 g, 15 months). The animals were housed in plastic cages in standardized laboratory conditions at $23 \pm 1^\circ\text{C}$ on a 12-hour dark cycle (light period, 07:00-19:00) with food and water *ad libitum*, except the period of the experiment. Before the test, the rats were placed on a raised wire mesh under a clear plastic box and allowed to acclimate to the testing room for 2 hours. Rats were distributed into 3 groups of 7 animals each and treated orally (using an eso-gastric device), for one month, as follows: Group I (Control): saline solution 0.3 mL/100 g weight; Group II (PRX): paroxetine 5 mg/Kg bw; Group III (VLX): venlafaxine 8 mg/Kg bw. Paroxetine and venlafaxine (Sigma Aldrich Chemical Co, Germany) solutions were extemporaneously prepared by dilution in saline.

We used a variant of classic maze, Y-maze test, which is a standardized experimental model that evaluates the cognitive ability and working memory in rodents by measuring the spontaneous exploratory behaviour [2, 3]. The apparatus consists of three equal white plastic arms tilted at an angle of 120° from each other and a central triangular platform. At the beginning of the experiment the animal was placed at the end of one arm of the maze and allowed to move freely in all three arms during a single session of eight minutes. The first 2 minutes were set for habituation and the remaining 6 minutes for the alternation between arms, recorded with photo beam breaks positioned at the

midpoint of each arm. A complete arm-entry was considered when the hind paws of the animal reached within the arm [7]. The following parameters were counted: latency of the first arm visit, number of arm visits, and percentage of time spent inside the arms, the number of the returns inside the same arm, the number of alternations. Alternation, thus reflecting the environment exploration ability, was defined as a consecutive entry inside three different arms of the device (a, b and c) in overlapping triplet sets (e.g. abcba bca = 4) [14]. The alternation percentage was calculated according to the formula: $[\text{number of alternations} / (\text{total number of arm entries} - 2)] \times 100$ [9].

A video camera was supplementary used during the session of experimentation, in order to monitor the animal behaviour without distressing it. The values were presented as $\pm$ SD and statistically processed using SPSS 17 for Windows and ANOVA method, followed by Neumann Keuls test as *post hoc*. P-values less than 0.05 were considered statistically significant comparing to those of the control group. The experimental protocol was implemented according to the recommendations of the University “Gr. T. Popa” Iasi Committee for Research and Ethical Issues, following the ethical standards of the European Community [19].

Results and Discussion

This behavioural model investigates if the rat can remember the arm it has just explored and would therefore enter one of the other arms of the device. The natural behaviour of animals consists of their choice of goal arm alternation. After multiple arm explorations the animal should show a tendency to enter a less recently visited arm [6].

Chronic treatment with paroxetine was associated with an increase of spontaneous alternation percentage ($43.86 \pm 3.29\%$) statistically significant ($p < 0.05$) compared to the control group ($35.14 \pm 3.13\%$) in the Y-maze test, suggesting its effects on short-term memory (Figure 1).

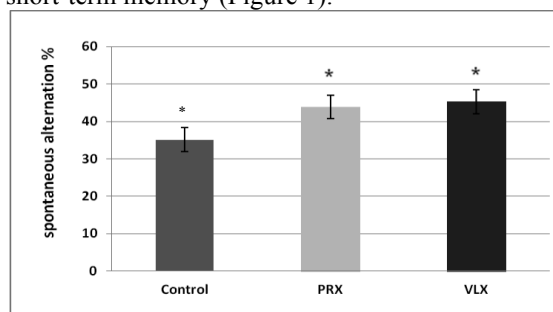


Figure 1.

Y-maze test - the effects of PRX and VLX on spontaneous alternation percentage. Values were expressed as mean $\pm$ SEM of spontaneous alternation percentage. * $p < 0.05$ vs. control

The old rats treated with VLX displayed significantly ($p < 0.05$) higher spontaneous alternation percentages (45.29 ± 3.25 %) than the control group (35.14 ± 3.13 %) in the same time interval during this experiment, action that could be correlated with a facilitation of extinction learning (Figure 1). The effects of VLX on the spontaneous alternation rate were more accentuated than those of PRX.

The counting of arm entries number is an important indicator of animal loco-motor activity. No significant differences were observed in the number of arm entries among the PRX group (17.29 ± 2.14 %), VLX group (17.14 ± 2.19 %) and control group (17.43 ± 1.81 %), (Figure 2). This observation suggests that oral administration of these antidepressants did not impair the normal spontaneous loco-motor activity in old rats.

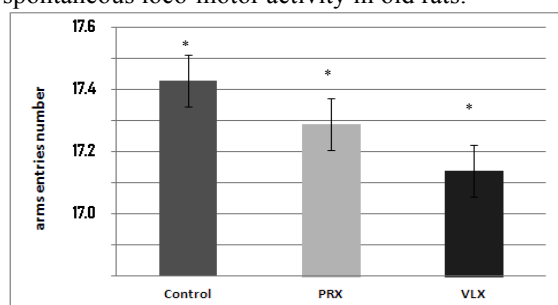


Figure 2.

Y-maze test - the effects of PRX and VLX on the number of arms entries. Values were expressed as mean ± SEM of the number of arms entries. * $p < 0.05$

Alternation is a parameter evaluating the animal environment exploratory capacity [6]. Oral administration of PRX (6.71 ± 1.80 %) for one month period determined an increase of the alternations number, statistically significant ($p < 0.05$) compared to the group treated with saline solution (5.43 ± 1.40 %) (Figure 3).

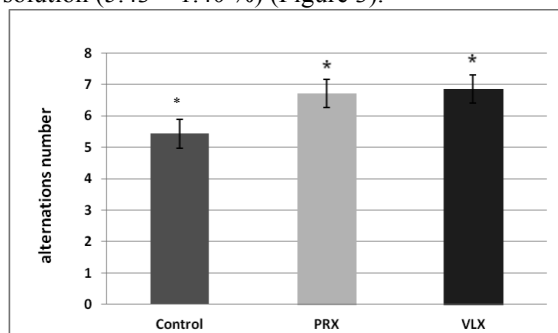


Figure 3.

Y-maze test - the effects of PRX and VLX on the number of alternations. Values were expressed as mean ± S.E.M of the number of alternations. * $p < 0.05$

The treatment with venlafaxine (6.86 ± 1.35 %) resulted in a significant increase of the alternations number ($p < 0.05$), compared to control group (5.43 ± 1.40 %); its effects were higher than those of paroxetine in the same time interval in Y-maze test (Figure 3). No significant changes were observed among the groups treated with PRX, VLX and saline solution either in the latency of the first arm visit or in the percent of time spent inside the arms (Table I).

Table I

Y-maze test - the effects of PRX and VLX on the latency of the first arm visit and on the percent of time spent inside the arms. Values were expressed as mean ± S.E.M of the number of alternations.

	Latency of the first arm visit (seconds)	Percent of time spent inside the arms (%)
Control	17.33 ± 1.21	32.17 ± 1.33
PRX	17.50 ± 1.38	31.83 ± 1.83
VLX	17.17 ± 1.60	32.33 ± 1.37

Literature data reports that antidepressant medication could influence the cognitive functions of laboratory animals; different experimental researches demonstrated that the memory performance was improved by the treatment with selective serotonin reuptake inhibitors and also with selective serotonin-norepinephrine reuptake inhibitors, but not by the administration of tricyclic antidepressants. However, scientific data are controversial, this topic being still under investigation [4, 12]. Opposite to this, other authors have proved that tricyclic antidepressants may induce favourable effects on the memory performance. Experimental researches revealed that the tricyclic antidepressant drug imipramine facilitates neurogenesis and improves cognitive and motor function in mice with traumatic brain injury [13]. Other potential pharmacological influences of antidepressant drugs on cognitive performances in laboratory animals have been reported. Fluoxetine and mirtazapine were effective in ameliorating depressive-like behaviour in the forced swimming test [15], and the new atypical antidepressant vortioxetine demonstrated an enhancement of episodic memory in the freezing behavioural model in rats [16].

In our experiment, Y-maze test was used to evaluate the cognitive function, loco-motor activity and learning ability of laboratory animals. Rats typically prefer to visit a new arm of the device rather than return to one that has been previously explored. During the period of experimentation an increase of the alternations number was observed after chronic administration of both paroxetine and venlafaxine. The effects of selective serotonin-norepinephrine reuptake inhibitor venlafaxine were more accentuated than the effects of selective

serotonin reuptake inhibitor paroxetine in this behavioural experimental model in old rats.

Old rats treated chronically with either paroxetine or venlafaxine were found to improve spatial memory acquisition, demonstrated by the significant increase of spontaneous alternation percentage in the Y-maze assay. The improvement of the learning performance and spatial memory was not influenced by the effects of these two antidepressant drugs on loco-motor activity, because the administration of them for one month was not associated with a facilitation of the exploratory capacity or with a significant modification of the arms entries compared to the control group.

Conclusions

The Y-maze experimental model, used to assess the willingness of rodents to explore new environments, showed an improvement of spatial memory in the rats treated chronically with antidepressant drugs, paroxetine and venlafaxine. This was indicated by an increase of spontaneous alternation percentage compared to control groups, suggesting significant effects on short-term memory performances. In our experimental conditions, venlafaxine proved to be more efficient in facilitating extinction learning than paroxetine in this behavioural model in old rats.

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