

THE PHARMACOLOGICAL EFFECT OF VALPROIC ACID, LEVETIRACETAM, CARBAMAZEPINE AND THE COADMINISTRATION OF VALPROIC ACID – LEVETIRACETAM AND CARBAMAZEPINE – LEVETIRACETAM ON TACTILE SENSITIVITY, MOTOR ACTIVITY AND THE FORMATION OF CONDITIONED REFLEX IN RATS

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Abstract

The purpose of this study was to evaluate the motor behaviour, tactile pain sensitivity, and learning behaviour of animals treated with two classic anticonvulsants: carbamazepine and valproic acid, as well as their association with levetiracetam. The motor activity was determined with Activity Cage (Ugo Basile, Italy), the tactile sensitivity was assessed using two tests: von Frey and Dynamic Plantar Aesthesiometer (Ugo Basile, Italy), whereas the conditional reflex formation was determined with the Conditioned Place Preference (Ugo Basile, Italy). The horizontal and vertical motor activity of animals treated with valproic acid and carbamazepine presented a statistically significant drop at all times of the assay, while the combination of levetiracetam potentiated the motor depressant effect of the two active substances. Following the tactile sensitivity assessment, it was observed that the reduction of this parameter was maximal for the combination of carbamazepine/levetiracetam. The conditioning parameters were influenced differently by levetiracetam treatment, thus: the latency of the animals' migration into the room opposite the conditioning chamber increased significantly, as did the number of received full electric shocks. Further research will be conducted to define the pharmacological profile of levetiracetam in combination with other classic anticonvulsants.

Rezumat

Scopul cercetării a fost de a evalua comportamentul motor, sensibilitatea dureroasă tactilă și comportamentul de învățare al animalelor tratate cu două anticonvulsivante clasice: carbamazepina și acidul valproic, dar și cu asocierile dintre acestea și levetiracetam. Activitatea motorie s-a determinat cu aparatul Activity Cage (Ugo Basile, Italia), sensibilitatea tactilă s-a determinat cu ajutorul a două teste: Filamente von Frey și Dynamic Plantar Aesthesiometer (Ugo Basile, Italia), iar formarea reflexului condiționat s-a determinat cu aparatul Conditioned Place Preference (Ugo Basile, Italia). Activitatea motorie orizontală și verticală a animalelor tratate cu acid valproic și carbamazepină a scăzut semnificativ statistic la toate momentele determinărilor, iar asocierea levetiracetamului a potențat efectul deprimant motor al celor două substanțe active. În urma evaluării sensibilității tactile s-a observat că reducerea acestui parametru a fost maximă pentru asocierea carbamazepină/levetiracetam. Parametrii condiționării au fost influențați diferit de tratamentul cu levetiracetam, astfel: a crescut semnificativ latența de trecere a animalelor în încăperea opusă incintei de condiționare și numărul de șocuri electrice primite integral. Cercetări ulterioare vor fi conduse pentru definirea profilului farmacologic al levetiracetamului, în asociere cu alte anticonvulsivante clasice.

Keywords: antiepileptic, neuropathic pain, motor activity, conditioned reflexes

Introduction

Drugs can influence central nervous system functions such as psychical processes [17], tactile pain sensitivity [24] and motor activity [5].

Some antiepileptics also possess other pharmacological effects such as mood stabilizers or influencing neuropathic pain.

In clinical practice, the dose-efficacy (dose-toxicity) relationship can be monitored by measuring the plasma concentration. Although it is not routinely

determined in antiepileptic drugs as with other compounds (such as immunosuppressive compounds) [22], therapeutic monitoring is advisable in order to avoid toxicity and to quantify drug interactions due to effects of anticonvulsant drugs on microsomal mixed-function oxidases.

Taking into account that antiepileptic drugs possess complex mechanisms of action that can influence the above mentioned parameters, we investigated the way the co-administration of classic antiepileptic drugs (carbamazepine, valproic acid), with a modern one (levetiracetam) would influence them.

Valproic acid is an anticonvulsant drug with a complex mechanism of action: it increases central levels of γ -amino butyric acid thus enhancing its action [9, 11]; blocks the fast sodium channels in the inactive state, prolonging the refractory period of the nervous cells [21]; blocks T (thalamic) type calcium channels [11]; modulates conductivity in the voltage dependent potassium channels, although this is still subject to debate [9]; inhibits histone deacetylase 1 (HDAC1) and other histone deacetylases [10, 18]. The anticonvulsant mechanism of carbamazepine is not yet fully understood. Apparently it acts at the postsynaptic level by blocking the sodium channels, thus reducing the ability of the neurons to discharge high and repeated electrical potentials. The same reduction of the neuronal excitability is also obtained at the presynaptic level by blocking the voltage dependent sodium channels, thus lowering the neurotransmitter release in the synaptic slit [25].

Other types of mechanisms attributed to carbamazepine that can influence nervous activity are inhibition of histone deacetylases similarly to the way valproic acid acts [2], and the activation of glutamate transporters which play a role in the extracellular homeostasis of the glutamate [13].

Levetiracetam is the first representative of a new class of anticonvulsants that inhibits glycoprotein 2A in the SV2A synaptic vesicles [15]. On *in vitro* models of acute epilepsy, levetiracetam proved to be effective [20], and the molecular mechanisms show its involvement in modulating neuronal activity by blocking the N type or P/Q type voltage dependent calcium channels and by reducing calcium release from the intracellular deposits [19]. Other molecular mechanisms suggest the inhibition of the delayed rectifier potassium current [16]; the inhibition of $\text{Cl}^-/\text{HCO}_3^-$ exchange [14]; the modulation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [3] and the inhibition of the cholinergic transmission by blocking the voltage dependent calcium channels at the level of sympathetic nerve neurons [23].

Materials and Methods

Animals: Male Wistar rats (290.20 ± 68.76 g; $n = 54$) were provided by the "Carol Davila" University of

Medicine and Pharmacy rodent farm. The rats were given free access to food and water. A constant 21 - 24°C temperature and 45 - 60% humidity was maintained over the course of the experiment.

All experimental procedures were carried out in accordance with the Directive 2010/63/UE of 22nd September 2010, the Romanian law 43/2014 regarding the protection of animals used for experimental and other scientific purposes and approved by the Ethical Committee of the Faculty of Pharmacy Bucharest.

Experimental protocol: The animals were divided into 6 groups and treated daily at the same hour, for 26 days, as follows: Group M (the control group): distilled water - 0.5 mL/100 g bw, orally; Group V: valproic acid - 100 mg/kg bw, orally; Group C: carbamazepine - 100 mg/kg bw, orally; Group L: levetiracetam - 100 mg/kg bw, orally; Group V+L: valproic acid - 100 mg/kg bw + levetiracetam - 100 mg/kg bw, orally; Group C+L: carbamazepine - 100 mg/kg bw + levetiracetam - 100 mg/kg bw, orally

The horizontal (HMA) and vertical motor activity (VMA) were determined for 5 minutes using an Ugo Basile (Italy) Activity Cage in days D₀, D₁₂, D₂₅.

The tactile sensitivity was determined in days D₀, D₁₁, D₂₄ using 2 methods.

The von Frey manual filaments evaluate the tactile sensitivity by measuring the posterior paw retraction time. The filament set used for this purpose contained the following sizes: 4.17; 4.31; 4.56; 4.74; 4.93; 5.07; 5.18 and 5.46. A positive response was considered when the rat retracted its paw quickly. The 50% response threshold was determined as an expression of tactile sensitivity using the up and down Dixon method [7, 8] validated and applied by Chaplan *et al.* in 1994 [4].

Dynamic Plantar Aesthesiometer (Ugo Basile, Italy) evaluates the tactile sensitivity by applying a stimulus with increasing force from 0 to 40 g on the plantar surface of the posterior paw, for 10 seconds. The retraction of the paw, automatically stops the stimulus and the mechanical pressure that generated this response is registered. Each rat was tested 6 times (3 times for each posterior paw) with the same stimulus. The results are presented as the mean of 6 measurements.

The conditioned reflexes were measured with a Conditioned Place Preference Cage (Ugo Basile, Italy) in days D₀, D₁₄, D₂₆. The animals were placed in the conditioning chamber in order to accommodate to the testing ground. They received no stimuli for 10 minutes. After that the animals were subjected to a basal conditioning test (Table I), respecting the parameters below.

Table I

Conditioning parameters used in the test

Parameter	Value
Total number of learning intervals	30
Time between learning intervals	20 s
Time between auditory stimulus/electric shock = consolidation stimulus	0.0
Duration of auditory stimulus = conditioning stimulus	10 s
Duration of electric shock	5 s
Shock intensity	1 mA
Auditory stimulus intensity	70 Db
Frequency	670 Hz

The evolution of the following parameters was determined: Latency (LA) - the time between the initiation of the auditory stimulus and the animal's response (going to the other side of the cage); ST - the number of animal passes to the other half of the cage during the auditory stimulus; RE - the number of passes of the animal to the other half of the cage during the electrical stimulus; TR - total number of electric shocks received.

Statistical analysis: The normal distribution was determined by the use of D'Agostino & Pearson test. For group comparison, parametric tests: t-Student and ANOVA followed by Dunnett or Bonferroni post-tests (for normal distribution) and non-parametric

tests: Mann-Whitney or Wilcoxon (for abnormal distribution) were used.

Results and Discussion

Motor activity

The HMA, when compared to the baseline, decreased for all groups (Table II). This can be explained by the fact that animals introduced in the same testing environment, get accustomed to it, and therefore, the exploring activity is lower. The most significant decrease was observed for valproic acid, carbamazepine and the association groups. The levetiracetam group recorded the lowest decrease in HMA.

Table II

Horizontal motor activity (HMA) throughout the experiment

Group/parameter	Initial horizontal motor activity					
	M	V	C	L	V + L	C + L
M ± SD	385.3 ± 138.8	430 ± 88.16	429.6 ± 89.64	392.4 ± 54.84	371.6 ± 65.38	435.6 ± 71.88
ANOVA, p	ns, p > 0.05					
Effect (%) vs Control	-	+11.6	+11.5	+1.84	-3.55	+13.05
Post-test Dunnett vs Control	-	ns	ns	ns	ns	ns
Group/parameter	Horizontal motor activity in the 12 th day					
	M	V	C	L	V + L	C + L
M ± SD	300.4 ± 126.8	273.2 ± 102.8	207 ± 45.6	355.9 ± 83.66	209.2 ± 56.73	201.4 ± 69.38
ANOVA, p	** p < 0.01					
Effect (%) vs baseline	-22.03	-34.46	-51.82	-9.3	-43.7	-53.76
Post-test Dunnett vs baseline	ns	**	***	ns	***	***
Effect (%) vs Control	-	-12.43	-9.79	12.73	-21.67	-31.73
Post-test Dunnett vs Control	-	ns	ns	ns	ns	ns
Group/parameter	Horizontal motor activity in the 25 th day					
	M	V	C	L	V + L	C + L
M ± SD	228.4 ± 83.31	137 ± 65.13	134.9 ± 51.96	236 ± 59.81	97.9 ± 44.56	101.1 ± 28.82
ANOVA, p	*** p < 0.001					
Effect (%) vs baseline	-40.72	-68.14	-68.6	-39.86	-73.65	-76.79
Post-test Dunnett vs baseline	*	***	***	***	***	***
Effect (%) vs Control	-	-27.42	-27.88	0.86	-32.93	-36.07
Post-test Dunnett vs Control	-	**	**	ns	***	***

M – mean; SD – standard deviation; ns – p > 0.05; * – p ≤ 0.05; ** – p ≤ 0.01; *** – p ≤ 0.001

The HMA of all groups, except for the levetiracetam group, decreased statistically significant when compared with the control on the 12th and 25th days of the experiment. The highest reduction levels were observed for the groups treated with the combinations of antiepileptics (Table II).

The VMA of the animals treated with antiepileptics decreased in all moments of the experiment when compared to the baseline, while on the 25th day of the experiment, the VMA of the control had an oscillating trend. Analysing these, it can be observed that the VMA of the levetiracetam group did not

decrease in a statistically significant manner when compared with the baseline. The most obvious reduction of the motor activity was observed in the carbamazepine group. For the valproic acid group, the most evident reduction of the VMA was observed on the 25th day of the experiment.

When valproic acid or carbamazepine are associated with levetiracetam, a decrease of VMA can be observed. The highest level of this motor activity reduction after treatment with 2 antiepileptic drugs was observed on the 12th day of the experiment (Table III).

Table III

Vertical motor activity (VMA) throughout the experiment

Group/parameter	Initial vertical motor activity					
	M	V	C	L	V + L	C + L
M ± SD	51.33 ± 24.62	47.22 ± 13.38	48.44 ± 15.48	49.67 ± 18.18	54.44 ± 25.11	44.22 ± 16.66
ANOVA, p	ns, p > 0.05					
Effect (%) vs Control	-	-8.01	-5.63	-3.24	+6.06	-13.85
Post-test Dunnett vs Control	-	ns	ns	ns	ns	ns
Group/parameter	Vertical motor activity in the 12 th day					
	M	V	C	L	V + L	C + L
M ± SD	52.56 ± 25.37	34.33 ± 14.61	29.00 ± 9.76	42.33 ± 17.08	19.89 ± 13.32	19.33 ± 10.31
ANOVA, p	***, p < 0.001					
Effect (%) vs baseline	2.39	-27.3	-40.13	-14.78	-63.46	-56.29
Post-test Dunnett vs baseline	ns	ns	*	ns	**	***
Effect (%) vs Control	-	-29.69	-42.52	-21.99	-65.85	-58.68
Post-test Dunnett vs Control	-	ns	*	ns	***	***
Group/parameter	Vertical motor activity in the 25 th day					
	M	V	C	L	V + L	C + L
M ± SD	42.89 ± 31.85	22.67 ± 10.19	26.67 ± 12.89	32.44 ± 8.033	25.11 ± 16.08	17.11 ± 7.253
ANOVA, p	*, p < 0.05					
Effect (%) vs baseline	-16.44	-51.99	-44.94	-34.69	-53.87	-61.31
Post-test Dunnett vs baseline	ns	**	**	ns	*	***
Effect (%) vs Control	-	-35.55	-28.5	-37.43	-25.01	-44.87
Post-test Dunnett vs Control	-	ns	ns	ns	ns	**

M – mean; SD – standard deviation; ns – p > 0.05; * – p ≤ 0.05; ** – p ≤ 0.01; *** – p ≤ 0.001

The effect of the tested substances on motor activity can be explained by the following data documented by scientific literature. Levetiracetam influences the glutamate transmission by locking on a vesicular protein, thus inducing a reduction in glutamate release [15, 19, 20]. However, this substance does not influence the motor activity in a statistically significant manner. Valproic acid enhances the GABA neurotransmission by inhibiting GABA reuptake and biotransformation. It also blocks central sodium channels preventing the propagation of electrical impulses through neuronal synapses [9-11]. These mechanisms are directly involved in the sedative action and motor activity reduction. Carbamazepine reduces the nervous impulse propagation by blocking the sodium channels, but also the cerebral calcium channels. Another valid explanation for the inhibition effect of the CNS is the blocking of NMDA glutamate receptors. The complexity of its mechanism of action explains why carbamazepine induces the highest and most statistically significant reduction in motor activity [2, 13, 25].

Although levetiracetam seems to influence the motor activity differently than the tested classic anticonvulsants, the reduction levels of this parameter are significantly enhanced by associating valproic acid or carbamazepine

with levetiracetam, than administering them as monotherapy.

The possible explanations for this phenomenon are revealed below.

When associating carbamazepine with levetiracetam a synergism of action occurs at the glutamate transmission level where both substances act, in conjunction with the membrane stabilization effect of carbamazepine as a consequence of blocking the ionic voltage dependent channels.

When associating valproic acid with levetiracetam, the excitatory neurotransmitter (glutamate) deficit overlaps the hyperactivity of the inhibitory GABA neurotransmission.

Tactile sensitivity

For the von Frey filament sensitivity assessment, higher mean values for the 50% withdrawal threshold (vs baseline), for all treated groups, were observed, except valproic acid for which an increase in this parameter was recorded (Figure 1). The association of levetiracetam with valproic acid, antagonized its effect on tactile sensitivity. The decreased tactile sensitivity was maximal for the combination of carbamazepine/levetiracetam.

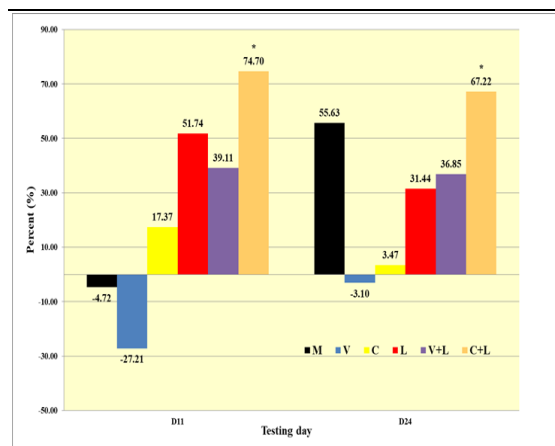


Figure 1.

Modification (%) of the response threshold vs baseline after applying von Frey filaments

The tactile sensitivity determined by the Dynamic Plantar Aesthesiometer was evaluated by recording the paw withdrawal time and maximum tolerated force for stimulus of 4 g/s (Figure 2 and 3). Valproic acid induced an increase in tactile sensitivity throughout the experiment, whereas for carbamazepine and levetiracetam groups, an increase in the response time (Figure 2) and maximum support force parameters (Figure 3) were observed.

Considering the association of valproic acid/levetiracetam, after 11 days of treatment, an increase in the response time and maximal force was observed, *versus* the groups treated with the two antiepileptics, separately. The combination of carbamazepine/levetiracetam induced a statistically significant decrease in the tactile sensitivity when compared with the baseline.

These results correlated with the data previously obtained, clearly showing a synergism of action for the association of carbamazepine/levetiracetam in reducing tactile sensitivity.

The results of this study showed that the combination of levetiracetam with valproic acid or carbamazepine induces a significant reduction in tactile sensitivity in both methods. Clinical research studies [6, 12] showed that the efficacy of levetiracetam is modest in reducing neuropathies, but non-clinical data have shown that high doses of levetiracetam (540 mg/kg bw) may reduce experimentally induced neuropathy [1]. Thus, hypotheses may be made for further experimental research to determine the efficacy of levetiracetam (in medium or small doses), combined with antiepileptics or other therapeutic classes (analgesics, antidepressants) to reduce neuropathic pain.

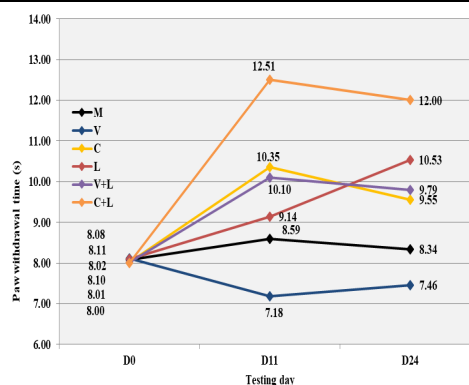


Figure 2.

The mean of paw withdrawal time for mechanical stimulation of 4 g/s.

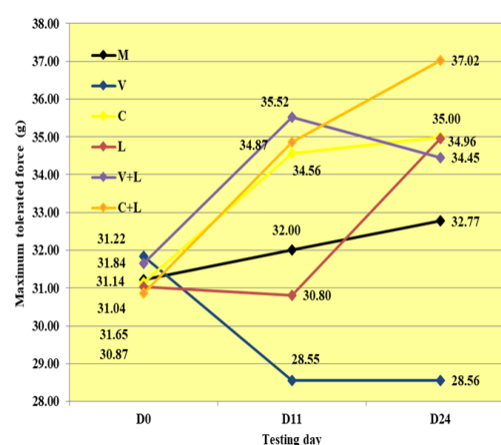


Figure 3.

The mean of the maximum tolerated force for mechanical stimulation of 4 g/s.

Conditional reflexes

The results of the study revealed that LA did not significantly change when compared with the baseline, except for the levetiracetam group for which a statistically significantly increase ($p = 0.0341$) was observed (Table IV).

ST did not change statistically significant for the control and valproic acid groups, but decreased significantly for the carbamazepine and the anticonvulsant associations groups (Table IV). The reduction of this parameter can be attributed to the sedative effect of valproic acid and carbamazepine. For the levetiracetam group, ST increased statistically significantly on the 26th day of the experiment, suggesting a learning behaviour because the auditory stimulus precedes the electrical stimulus.

RE did not change statistically significant when compared with the baseline in any of the tested groups (Table V). In general, for this parameter, there was a downward trend, except for the carbamazepine/levetiracetam group, for which there was a slight increase after 14 days of treatment.

Table IV

Variation of LA (the time between the initiation of the auditory stimulus and the animal's response) and ST (the number of animal passes to the other half of the cage during the auditory stimulus) throughout the experiment and the statistical significance

Parameter	LA			ST		
CONTROL GROUP						
Testing day	D ₀	D ₁₄	D ₂₆	D ₀	D ₁₄	D ₂₆
M ± SD	2482 ± 213.8	2456 ± 400.2	2417 ± 360.5	0.90 ± 0.74	1.33 ± 1.94	1.22 ± 1.20
ANOVA, p	ns, 0.08406			ns, 0.0910		
Effect (%) vs baseline		-10.47	-26.18		48.11	35.77
VALPROIC ACID GROUP						
M ± SD	2353 ± 165.2	2531 ± 236.5	2446 ± 370.4	-26.18	0.56 ± 1.01	0.75 ± 0.71
ANOVA, p	0.3639			0.7624		
Effect (%) vs baseline		7.56	3.95		-16.66	-38.26
CARBAMAZEPINE GROUP						
M ± SD	2479 ± 311.4	2501 ± 304.6	2413 ± 362.4	0.50 ± 0.97	0.78 ± 0.97	2.00 ± 1.31
ANOVA, p	ns, 0.8473			* 0.0194		
Effect (%) vs baseline		0.88	-2.66		55.56	300 * ^a
LEVETIRACETAM GROUP						
M ± SD	2348 ± 269.7	2616 ± 296.2	2629 ± 149.8	0.56 ± 1.01	0.11 ± 0.33	1.10 ± 0.99
ANOVA, p	* 0.0341			* 0.0500		
Effect (%) vs baseline		11.41	11.96 * ^a		-80.00	97.98 * ^a
VALPROIC ACID - LEVETIRACETAM GROUP						
M ± SD	2417 ± 242.8	2574 ± 235.9	2327 ± 309.6	0.40 ± 0.52	0.30 ± 0.67	2.88 ± 2.10
ANOVA, p	ns, 0.1453			*** 0.0002		
Effect (%) vs baseline		6.49	-3.72		-25	618.75 *** ^a
CARBAMAZEPINE - LEVETIRACETAM GROUP						
M ± SD	2623 ± 139.5	2573 ± 279.8	2559 ± 169.0	0.30 ± 0.67	0.30 ± 0.67	2.00 ± 1.53
ANOVA, p	ns, 0.7831			** 0.0021		
Effect (%) vs baseline		-1.90	-2.43		0	566.66 *** ^a

M – mean; SD – standard deviation; ns – $p > 0.05$; * – $p \leq 0.05$; ** – $p \leq 0.01$; *** – $p \leq 0.001$; ^a – according to post-test Dunnett

TR increased from baseline for the control, valproic acid and levetiracetam groups (Table V). The increases were statistically significant only for the levetiracetam treated group. This phenomenon suggests that animals did not acquire a learning behaviour after an intense stimulus. For carbamazepine and associations groups, decreases of the number of electric shocks received

($p > 0.05$) were observed. For the carbamazepine/levetiracetam group, on the 26th day of the experiment, there was an increase in the number of electric shocks received, suggesting that levetiracetam antagonizes the carbamazepine learning reflex induced by electrical stimulation.

Table V

Variation of RE (number of passes of animals to the other half of the cage during the electrical stimulus) and TR (total number of electric shocks received) throughout the experiment and the statistical significance

Parameter	RE			TR		
CONTROL						
Testing day	D ₀	D ₁₄	D ₂₆	D ₀	D ₁₄	D ₂₆
M ± SD	18.78 ± 4.82	15.13 ± 8.18	17.00 ± 8.12	10.80 ± 6.51	15.30 ± 9.96	11.20 ± 9.32
ANOVA/p	ns, 0.5878			ns, 0.4533		
Effect (%) vs baseline		-19.43	-9.00		41.66	3.7
VALPROIC ACID						
M ± SD	20.50 ± 6.10	17.11 ± 3.72	17.88 ± 5.11	8.50 ± 5.60	11.67 ± 4.47	9.25 ± 6.76
ANOVA/p	ns, 0.333			ns, 0.4619		
Effect (%) vs baseline		-16.53	-11.07		37.29	8.82
CARBAMAZEPINE						
M ± SD	19.00 ± 8.17	19.13 ± 6.88	18.00 ± 4.84	11.70 ± 9.14	9.125 ± 7.74	7.375 ± 6.32
ANOVA/p	ns, 0.9364			ns, 0.5176		
Effect (%) vs baseline		0.68	-5.26		-22.00	-36.96
LEVETIRACETAM						
M ± SD	20.90±6.86	14.10±8.16	16.00±4.94	8.00±7.23	15.40±8.83	18.90±4.38
ANOVA/p	ns, 0.0870			** 0.0060		
Effect (%) vs baseline		-32.53	-23.44		92.5 ^{*a}	136.25 ^{**a}

Parameter	RE			TR		
VALPROIC ACID - LEVETIRACETAM						
M ± SD	19.00±6.96	18.00±4.74	18.89±4.54	10.60±6.96	10.50±3.96	9.89±6.51
ANOVA/p	ns, 0.9154			ns, 0.9640		
Effect (%) vs baseline		-5.26	-0.57		-0.94	-6.70
CARBAMAZEPINE - LEVETIRACETAM						
M ± SD	15.00±6.8	18.50±6.91	11.13±4.88	15.50±4.536	13.88±7.568	18.30±3.592
ANOVA/p	ns, 0.0883			ns, 0.2273		
Effect (%) vs baseline		23.33	-26.00		-10.45	18.06

M – mean; SD – standard deviation; ns – $p > 0.05$; * – $p \leq 0.05$; ** – $p \leq 0.01$; *** – $p \leq 0.001$; ^a – according to post-test Dunnett

The results showed that the conditioning parameters are influenced differently by the treatment applied, as follows: the time between the initiation of the auditory stimulus and the animal's response (LA) increases statistically significantly only for levetiracetam; the number of animal passes to the other half of the cage during the auditory stimulus (ST) decreases for the carbamazepine and associations groups; the number of passes of the animal to the other half of the cage during the electrical stimulus (RE) showed statistically insignificant variations when compared with the baseline; the total number of electric shocks received (TR) significantly increased only for the levetiracetam group.

Conclusions

Classic antiepileptic drugs (valproic acid and carbamazepine) significantly reduced the horizontal and vertical motor activity of animals. The effect was more pronounced after the repeated administration. Levetiracetam did not significantly reduce the motor activity of the animals, but in combination with valproic acid or carbamazepine potentiated their motor activity reduction.

The combination of levetiracetam with valproic acid or carbamazepine resulted in a significant reduction in tactile sensitivity evaluated by von Frey filaments and Dynamic Plantar Aesthesiometer.

In the conditioning tests, the pharmacological profile of levetiracetam, influenced by the partially elucidated mechanisms of action was different from the classic antiepileptic profiles. The research has highlighted that the levetiracetam learning phenomenon is triggered by the auditory stimulus, and high-intensity stimuli (electric shock) decreases the learning response of this drug.

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