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ORIGINAL STUDIES

The effect of paliperidone treatment and exercise on the memory and learning ability in experimental depression

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Abstract

Background. Depression is a mental disorder characterized by pervasive low mood and loss of pleasure or interest in usual activities, which induces cognitive, especially memory and learning dysfunctions.

Aims. We aimed to study neurobehavioral changes in depressed animals, based on the effects of paliperidone and exercise on the motor memory and learning ability.

Methods. The research was conducted in 4 groups of animals, divided as follows: group I – control animals, group II – animals with reserpine-induced depression, group III – animals with reserpine-induced depression and paliperidone administration, group IV – animals with reserpine-induced depression, paliperidone administration and exercise.

Results. Long-term paliperidone treatment alone and associated with exercise has favorable effects on the learning ability of depressed animals at T_{30} compared to controls and compared to values at T_{14}. Paliperidone treatment associated or not with exercise has an unfavorable influence on the memory ability of depressed animals at T_{14} and T_{30}.

Conclusions. Exercise has favorable effects on the learning ability of depressed animals treated with an atypical antipsychotic.

Key words: depression, reserpine, paliperidone, Morris test, exercise.

Introduction

Depression is a mental disorder characterized by pervasive low mood and loss of pleasure or interest in usual activities, which induces cognitive, especially memory and learning dysfunctions.

A series of preclinical and clinical studies have suggested the favorable effect of co-treatment with atypical antipsychotics and antidepressants in drug-resistant depression.

Our previous research on reserpine-induced experimental depression in rats evidenced a decrease in the locomotor activity of sedentary animals based on the open field test. The use of paliperidone – an atypical antipsychotic – in sedentary depressed animals also induced a decrease in locomotor activity. Exercise in depressed animals treated with paliperidone has favorable effects on locomotor activity (Manea et al., 2019).

Objectives

We aimed to study neurobehavioral changes in depressed animals, based on the effects of paliperidone and exercise on the motor memory and learning ability.

Hypothesis

The use of atypical antipsychotics to enhance pharmacological treatment in depression and the favorable effect of exercise in the kinesiotherapeutic treatment of depression led us to study the effect of pharmacological (paliperidone) and physical co-treatment on the motor memory and learning ability in experimental depression.

Material and methods

The studies were conducted in the Experimental Research Laboratory of the Physiology Department of "Iuliu Haţieganu" University of Medicine and Pharmacy

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Cluj-Napoca, with the approval of the Bioethics Committee and the Sanitary Veterinary Authority Cluj-Napoca regarding the protection of animals used for experimental and scientific purposes.

Research protocol

a) Period and place of the research

The studies were performed on white male Wistar rats, aged 4 months, with a weight of 200-250 g, from the animal facility of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca. Throughout the duration of the research, 1 October - 30 November 2018, the animals were kept under adequate *vivarium* conditions: temperature, humidity, lighting, feeding and hydration. At the end of the experiment, the animals were euthanized with ketamine. The duration of the experiment was 30 days.

b) Subjects and groups

The animals were assigned to four groups (G) (n = 10 animals/group), as follows:

- G I – control animals, which were administered 5 ml/kg body weight/24 h physiological serum for 14 days
- G II – animals with depression induced by reserpine (DIR), 1 mg/kg body weight/24 h, administered intraperitoneally for 14 days
- G III - animals with DIR and paliperidone, 0.5 mg/kg body weight/24 h, administered intraperitoneally for 14 days, after induction of depression
- G IV – animals with DIR, paliperidone administration and exercise training by the swimming test, for 14 days

c) Tests applied

The research calendar, by objectives, days and tests applied, included:

- induction of depression T_0-T_{14} by reserpine (the preparation used was Reserpinum, Sigma) (Arora & Chopra, 2013; Ruiz et al., 2018)
- control of depression T_{11} based on the tail suspension test, for antidepressant activity - TST (Steru et al., 1985)
- treatment program T_{15}-T_{30} with paliperidone administration (the preparation used was Invega^R, Janssen-Cilag SpA, Italy)
- treatment program T_{15}-T_{30} with paliperidone and exercise by the swimming test, according to Nayanatara et al., 2005, one hour daily
- The Morris Water Maze Test (MWM) (1981) was used for spatial learning and memory based on water navigation. The learning and control values, expressed in seconds, indicate the learning and memory ability. The time points analyzed were days 0-T_0, 14-T_{14} and 30-T_{30}.

d) Statistical processing

Statistical analysis was performed with StatsDirect v.2.7.2 software. The results were graphically represented using Excel application (Microsoft Office 2010).

Results

The statistical analysis of the *Morris test values* (Table I, Fig. 1) showed the following:

- taking into consideration the *3 groups of rats* studied in the learning period
  - at time T_{14} – very statistically significant differences between at least two of the groups ($p < 0.01$)
  - at time T_{30} – highly statistically significant differences between at least two of the groups ($p < 0.001$)
- taking into consideration the *3 groups of rats* studied in the control period
  - at times T_{14} and T_{30} – highly statistically significant differences between at least two of the groups ($p < 0.001$)

The statistical analysis of the Morris test values in the learning period showed the following for *unpaired samples:*

- at time T_{14} – highly statistically significant differences between groups I-II, I-III and I-IV ($p < 0.001$), very statistically significant differences between groups II-III ($p < 0.01$) and statistically significant differences between groups III-IV ($p < 0.05$)
- at time T_{30} – highly statistically significant differences between groups I-II, I-III, I-IV, II-III, II-IV and III-IV ($p < 0.001$)

The statistical analysis of the Morris test values in the control period showed the following for *unpaired samples:*

- at time T_{14} - highly statistically significant differences between groups I-II, I-III, I-IV, II-III and II-IV ($p < 0.001$)
- at time T_{30} - highly statistically significant differences between groups I-II, I-III, I-IV, II-IV and III-IV ($p < 0.001$) and very statistically significant differences between groups II-III ($p < 0.01$)

The statistical analysis of the Morris test values showed for *paired samples between T_{14}-T_{30}* – in the learning period, highly statistically significant differences for groups III and IV ($p < 0.001$), and in the control period, highly statistically significant differences for groups III and IV ($p < 0.001$) and statistically significant differences for group II ($p < 0.01$).

The statistical analysis of the Morris test values showed the following for *paired samples between the learning period and the control period:*

- for group I – highly statistically significant differences ($p < 0.001$)
- for group II – very statistically significant differences ($p < 0.01$) at times T_{14} and T_{30}
- for groups III and IV – highly statistically significant differneces ($p < 0.001$) at times T_{14} and T_{30}

Discussions

The MWM test was used by many authors, who found in experimental depressed rat models an activation and an improvement of the learning ability and cognitive skills after treatment with/administration of:

- antidepressants such as Dormicum, Valdoxan and Cipralex (Puiu, 2014);
- mesoporous hydroxyapatite olanzapine (Shyong et al., 2017);
- non-steroidal anti-inflammatory drugs (Perveen et al., 2018);
- banana fruit pulp and peel extract (Samad et al., 2017);
- n-3 polyunsaturated fatty acid (Pérez et al., 2018);
- helicid (Li et al., 2019);
- liraglutide and sitagliptin (Kamble et al., 2016).

Other experimental studies showed the unfavorable effect of some agents on the cognitive functions tested by MWM in depression:

- blue light filtered white light (Meng et al., 2018);
- the lithium-pilocarpine model (Vrinda et al., 2017;

Table I

Comparative analysis of the Morris test values in the studied groups and statistical significance.

Time		Group	Mean	SE	Median	SD	Min	Max
Learning	T0	I	262.56	3.439	262.33	10.875	242.92	281.83
	T14	II	372.63	2.326	371.75	7.356	361.25	383.92
		III	387.58	3.578	387.96	11.315	375.08	408.08
		IV	375.43	2.513	377.79	7.948	359.58	384.00
	T30	II	376.27	3.376	376.88	10.676	352.83	388.58
		III	297.83	2.779	299.42	8.789	285.83	312.50
		IV	317.73	2.170	317.13	6.861	303.33	328.33
CTRL	T0	I	85.43	2.384	88.00	7.539	74.00	98.33
	T14	II	22.90	0.965	22.33	3.051	20.33	31.00
		III	12.97	0.612	12.67	1.934	10.67	17.33
		IV	13.60	0.499	13.33	1.578	11.33	16.00
	T30	II	15.07	0.730	14.33	2.308	12.67	21.00
		III	18.13	0.362	18.17	1.146	16.00	19.67
		IV	21.97	0.308	21.83	0.974	20.33	23.67

Statistical significance (p)							
Learning	T14	II-III-IV	0.0022	CTRL	T14	II-III-IV	< 0.0001
	T30		< 0.0001		T30		< 0.0001
	T14	I-II	< 0.0001		T14	I-II	< 0.0001
		I-III	< 0.0001			I-III	< 0.0001
		I-IV	< 0.0001			I-IV	< 0.0001
		II-III	0.0026			II-III	< 0.0001
		II-IV	0.4243			II-IV	< 0.0001
		III-IV	0.0124			III-IV	0.4327
	T30	I-II	< 0.0001		T30	I-II	< 0.0001
		I-III	< 0.0001			I-III	< 0.0001
		I-IV	< 0.0001			I-IV	< 0.0001
		II-III	< 0.0001			II-III	0.0016
		II-IV	< 0.0001			II-IV	< 0.0001
		III-IV	< 0.0001			III-IV	< 0.0001

T14-T30	Learning			CTRL		
	II	III	IV	II	III	IV
	0.4786	< 0.0001	< 0.0001	0.002	0.0002	< 0.0001

Learning-CTRL	T0	T14			T30		
	I	II	III	IV	II	III	IV
	< 0.0001	0.002	< 0.0001	< 0.0001	0.002	< 0.0001	< 0.0001

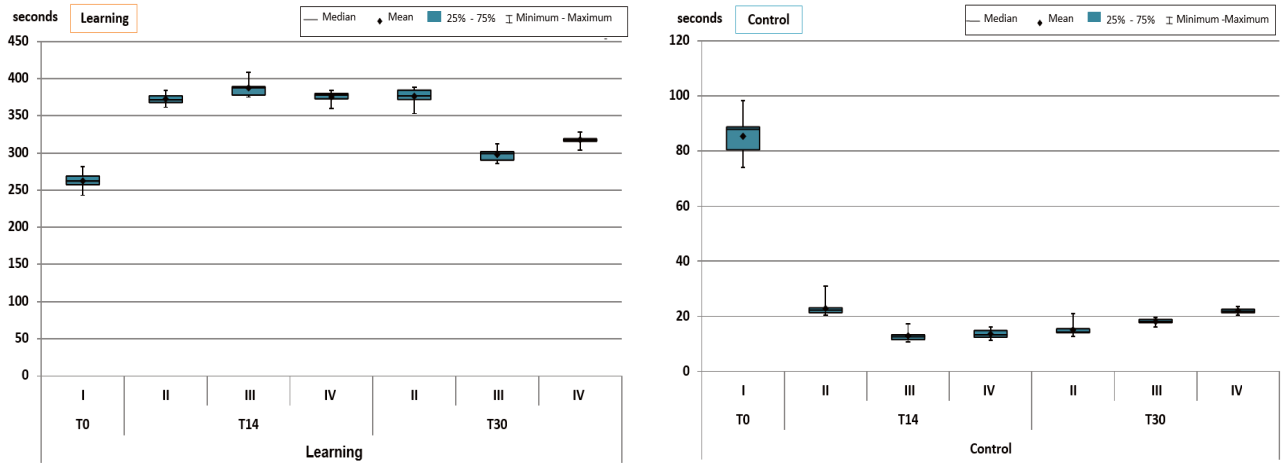

Fig. 1 – The Morris test in the studied groups.

Kalemenev et al., 2015);

- electroconvulsive shock (Chen et al., 2018; Ren et al., 2016).

Our learning assessment results indicate a significant decrease in the learning ability of all groups at T_{14} and a significant increase at T_{30} compared to control values and T_0.

Learning control for memory assessment indicates a significant decrease at T_{14} and T_{30} compared to initial values at T_0 and control values in all groups.

Conclusions

1. Long-duration paliperidone treatment alone and associated with exercise has favorable effects on the learning ability of depressed animals at T_{30} compared to controls and compared to values at T_{14}.

2. Paliperidone treatment associated or not with exercise has an unfavorable influence on the memory ability of depressed animals at T_{14} and T_{30}.

Conflicts of interest

There are no conflicts of interest.

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