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Effect of paliperidone treatment and exercise in experimental depression

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Abstract

Background. Depression is a mental disorder that has an important place among both psychiatric and non-psychiatric disorders.

Aims. We aimed to study, in an experimental model of depression induced in rats, the effects of an atypical antipsychotic associated with exercise on emotional and locomotor behavior.

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. Reserpine, used experimentally as a depression-inducing pharmacological agent, determines an increase in emotional behavior and a decrease in locomotor activity. Treatment with paliperidone (an atypical antipsychotic) in sedentary animals with experimental depression induces an increase in emotional behavior and a decrease in locomotor activity. Treatment with paliperidone in exercise-trained animals with experimental depression determines a moderate increase in emotional behavior and the maintenance of locomotor activity within normal limits.

Conclusions. Exercise has favorable effects on locomotor activity in depressed animals treated with an atypical antipsychotic.

Keywords: depression, reserpine, paliperidone, open field test, exercise

Introduction

Depression is considered to be a mental disorder that has an important place among both psychiatric and non-psychiatric disorders.

The World Health Organization estimates that depression affects about 121 million people and that by 2020 it will rank second in terms of prevalence, after cardiovascular diseases (***, 1998; Amato et al., 2081; West, 1992).

The disease may occur at any time of life, in children, adults and elderly. Prevalence is between 10-25% for women and 5-12% for men. The onset of major depressive disorder is in a 50% proportion between 20 and 50 years, with a mean onset of 40 years. Recent data report a decrease in the age of onset, even up to 20 years. After 50-65 years of age, the rate of depression is equal for the two sexes.

The most affected population groups are those that are socioprofessionally active (Prelipceanu, 2011).

Major depression is associated with a high percentage of mortality by suicide, 10-15% (Chapman & Perry, 2008).

Major depressive disorder is a common, chronic, recurrent, debilitating mental disorder, which leads to significant impairments of personal functional abilities.

Depression is a multicausal affective disorder, characterized by mood changes: sadness, discouragement, despair, inability to focus, sleep and appetite disorders, apathy, feelings of guilt, fatigue or low energy, weight changes, recurrent death and suicide ideas, psychomotor disorders. Major depressive disorder (MDD) – unipolar or bipolar depression – may have several forms: MDD with psychotic factors, melancholy, atypical depression, postpartum depression, treatment-resistant depression, depressive disorder with catatonic factors (Prelipceanu,

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2011; Chapman and Perry, 2008).

Antidepressants (AD) are drugs effective in the treatment of affective disorders and anxiety, which can improve or normalize altered mood in depression.

According to ICD-10, depressive disorders include: mild, moderate, severe depressive episode with/without psychotic symptoms; recurrent depressive disorder; depressive episode in bipolar affective disorder.

The action mechanism of AD is based on the involvement of the following neurotransmitter systems: noradrenergic, serotoninergic, dopaminergic and GABAergic.

The biochemical hypotheses regarding the etiopathogeny of depression are the hypothesis of monoamines (NA and 5-HT deficits) and the hypothesis of the imbalance between transmission pathways (hypo-NAergic and hyper-5-HTergic).

AD can be classified pharmacologically according to: the chronological criterion (first- and second-generation AD, which have similar efficacy, but different and unfavorable side effects); action on neurotransmitters (single-action AD and dual-action AD).

The therapeutic choice of a certain AD should meet the following criteria: safe administration, tolerance, rapidity of the effect, clinical experience, risk of side effects, comorbidities (Prelipceanu, 2011; Gheorghe, 2007).

Pharmacological treatment involves augmentation strategies, therapeutic combinations, therapeutic conversion and better results compared to monotherapy.

Augmentation strategies are aimed at improving the pharmacological effect and clinical efficiency of the administered AD, at avoiding psychic dependence and ensuring continuity.

Augmentation studies have assessed augmentation by: administration of lithium salts, thyroid hormones (triiodothyronine) or concomitant administration of buspirone, bupropion, pindolol; association of atypical antipsychotics: risperidone, olanzapine, clozapine; association with other types of AD such as: reboxetine, mirtazapine (Gheorghe, 2007).

The objectives of therapeutic combinations are an improvement of therapeutic efficacy, an acceleration of the antidepressant effect, the possibility of continuing the administration of the initial AD.

Therapeutic conversion is made by administering a pharmacological preparation, in case of no response to an initial AD. Conversion studies have evaluated: conversion of a tricyclic antidepressant (TAD) to another TAD; conversion of a TAD to a heterocyclic AD; conversion of a tricyclic or heterocyclic AD to a selective serotonin reuptake inhibitor (SSRI); conversion of a SSRI to a TAD (Gheorghe, 2007).

The aim of therapeutic conversion is to continue initial treatment with a single AD, to improve long-term therapeutic response, to ameliorate therapeutic adherence, to rapidly improve target symptoms.

Administration of mood regulating substances (lithium salts, carbamazepine, valproic acid salts) has a role in normalizing mood.

Non-pharmacological treatment is used in the case of patients with treatment-resistant depression, with partial or unsatisfactory response (therapeutic non-responders) (Prelipceanu, 2011; Gheorghe, 2007; Bruja, 2014; Goldberg, 2001; Micluția, 2010).

The non-pharmacological forms used are: cognitive-behavioral psychotherapy, in association with AD; repetitive transcranial magnetic stimulation, in association with an AD; vagus nerve stimulation; electroconvulsive therapy, in severe disorders with high risk of suicide; moderate exercise; antidepressant preparations used in traditional Eastern Asian medicine; light therapy, in depression with seasonal features.

Objectives

We aimed to study, in an experimental model of depression induced in rats, the effects of an atypical antipsychotic – paliperidone – associated with exercise on emotional and locomotor behavior.

Hypothesis

The use of atypical antipsychotics for the augmentation of pharmacological treatment in depression and the role of exercise in the improvement of depression led us to study the effects of an atypical antipsychotic and exercise in depressive disorder.

Material and methods

The studies were conducted in the Experimental Research Laboratory of the Physiology Department of "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, with the approval of the Committee of Bioethics 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.

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

- control of therapy - T_{30} by the open field test (OFT), according to Denenberg & Whimby, 1963, to test spontaneous emotional and locomotor behavior, hyperactivity, exploring behavior in an open space and induced anxiety.

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

a) Comparative statistical analysis for depressive behavior (Table I)

The statistical analysis of the tail suspension test (TST) values showed:

- considering the *4 studied groups of rats*

○ at time T_0 – no statistically significant differences between the groups ($p > 0.05$)

○ at times T_{14} and T_{30} – highly statistically significant differences between at least two of the groups ($p < 0.001$)

- considering the *3 studied time points*

○ in group I – no statistically significant differences between the studied time points ($p > 0.05$)

○ in groups II, III and IV – highly statistically significant differences between at least two of the time points ($p < 0.001$)

The statistical analysis of TST values evidenced the following for unpaired samples:

- at time T_0 – no statistically significant differences between the groups ($p > 0.05$)

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

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

The statistical analysis of TST values evidenced the following for paired samples:

Table I

Comparative analysis for TST values in the studied groups and statistical significance (values in seconds)

Time	Group	Mean ± SD	Statistical significance (p)							
T0	I	3 ± 0.8165		T0-T14-T30		I-II-III-IV		T0-T14	0.75
	II	2.7 ± 0.8233	I	0.6624	T0	0.2253	I	T0-T30	0.4609
	III	2.9 ± 0.9944	II	< 0.0001	T14	< 0.0001		T14-T30	0.6875
	IV	3.6 ± 0.9661	III	< 0.0001	T30	< 0.0001		T0-T14	0.002
T14	I	3.1 ± 0.7379	IV	< 0.0001			II	T0-T30	0.002
	II	12 ± 1.4907		T0	T14	T30		T14-T30	0.0027
	III	12.3 ± 1.3375	I-II	0.5894	< 0.0001	< 0.0001		T0-T14	< 0.0001
	IV	13.6 ± 1.9551	I-III	0.9542	< 0.0001	< 0.0001	III	T0-T30	0.002
T30	I	3.3 ± 0.8233	I-IV	0.2246	< 0.0001	< 0.0001		T14-T30	0.0488
	II	15.4 ± 1.7764	II-III	0.7048	0.6414	0.0007		T0-T14	< 0.0001
	III	8.9 ± 3.3483	II-IV	0.0526	0.0544	< 0.0001	IV	T0-T30	< 0.0001
	IV	10.4 ± 1.075	III-IV	0.1278	0.0997	0.0395		T14-T30	0.0003

Table II

Comparative analysis for open field test values and statistical significance (values in seconds)

Group	Score	Time	Mean ± SD	Statistical significance (p)							
				T_{14}-T_{30}	II	III	IV	T_{14}-T_{30}	II	III	IV
				Emotional score (ES)	0.0195	0.4679	0.0016	Locomotor score (LS)	< 0.0001	0.0273	0.002
I	ES	T_0	8.5 ± 1.1785		T_{14}-T_{30}	II-III-IV	0.1028		T_{14}-T_{30}	II-III-IV	< 0.0001
	LS		34.4 ± 4.0879				0.1349				< 0.0001
II	ES	T_{14}	11.8 ± 1.6193			I-II	0.0001			I-II	< 0.0001
		T_{30}	9.9 ± 0.8756			I-III	0.0009			I-III	< 0.0001
	LS	T_{14}	25.6 ± 1.7127		T_{14}	I-IV	< 0.0001		T_{14}	I-IV	0.0649
		T_{30}	18.2 ± 1.6193			II-III	0.0594			II-III	0.7457
III	ES	T_{14}	10.6 ± 0.9661			II-IV	0.6319			II-IV	< 0.0001
		T_{30}	10.3 ± 0.9487			III-IV	0.0652			III-IV	< 0.0001
	LS	T_{14}	25.2 ± 1.4757			I-II	0.0192			I-II	< 0.0001
		T_{30}	28.8 ± 2.8206			I-III	0.0033			I-III	0.0012
IV	ES	T_{14}	11.5 ± 1.0801		T_{30}	I-IV	0.3594		T_{30}	I-IV	0.9601
		T_{30}	9.1 ± 1.4491			II-III	0.4684			II-III	< 0.0001
	LS	T_{14}	30.9 ± 1.8529			II-IV	0.2435			II-IV	< 0.0001
		T_{30}	33.7 ± 2.0575			III-IV	0.0419			III-IV	0.0002

Legend: ES – emotional score, LS – locomotor score

- in group I – no statistically significant differences between the time points ($p > 0.05$)

- in group II – highly statistically significant differences between T_0-T_{14}, T_0-T_{30} and T_{14}-T_{30} ($p < 0.01$)

- in group III – highly statistically significant differences between T_0-T_{14} ($p < 0.001$), very statistically significant differences between T_0-T_{30} ($p < 0.01$) and statistically significant differences between T_{14}-T_{30} ($p < 0.05$)

- in group IV – highly statistically significant differences between T_0-T_{14}, T_0-T_{30} and T_{14}-T_{30} ($p < 0.001$).

b) Comparative statistical analysis for emotional and locomotor behavior (Table II)

The statistical analysis of open field test values – emotional score, considering *the groups of rats II, III and IV,* showed no statistically significant differences between the groups at time T_{14} or at time T_{30} ($p > 0.05$).

The statistical analysis of open field test values – locomotor score, considering *the groups of rats II, III and IV,* showed highly statistically significant differences between at least two of the groups both at time T_{14} and at time T_{30} ($p < 0.0001$).

The statistical analysis of open field test values for unpaired samples evidenced the following for:

- emotional score

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

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

- locomotor score

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

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

The statistical analysis of open field test values for paired samples (T_{14}-T_{30}) evidenced the following for:

- emotional score – statistically significant differences for group II ($p < 0.05$) and very statistically significant differences for group IV ($p < 0.01$)

- locomotor score – highly statistically significant differences for group II ($p < 0.001$), statistically significant differences for group III ($p < 0.05$) and very statistically significant differences for group IV ($p < 0.01$).

Discussions

Experimental depression model

Authors have studied depression in genetically selected animals and in models with depression induced surgically, pharmacologically and by acute and chronic stress procedures (Bruja, 2014; Puiu, 2014; Duman, 2010; Henn & Vollmayer, 2005; Willner, 1990).

Reserpine has been used as a depression-inducing pharmacological agent. Reserpine is the main alkaloid extracted from the root of the *Rauwolfia serpentina* plant, originating from India, Indonesia, Ceylon, Malaysia, Central Africa, Central and South America. It has a predominantly central tranquilizing, antidepressant action, as well as a peripheral action, by deregulating the metabolism of endogenous biogenic monoamines: noradrenaline, dopamine and serotonin. The tranquilizing effect occurs within 40-60 minutes of administration. Long-term administration has cumulative antipsychotic effects.

The use of reserpine in the form of various preparations (Raunervil^{+}, Rausedyl^{R}, Reserpin^{R}, Serpasil^{R}) for the treatment of essential hypertension is limited by the intense depressive state that it can induce. It is recommended only in psychoses accompanied by hypertension. This observation underlies the use of reserpine for experimental purposes, to induce depression (***, 2018).

Our results obtained in group G II, with reserpine administration, show the development of depressive behavior at time T_0 compared to controls (G I) on the TST test, and its significant increase at 14 days after administration (T_{14}) and at 30 days (T_{30}), compared to controls.

Emotional behavior evaluated by OFT increases significantly at 14 days compared to initial values. Locomotor behavior in the same test decreases significantly at 14 days and at 30 days compared to initial values.

Our results show that the pharmacological experimental model of reserpine-induced depression in G II is a valid model, in accordance with the findings of authors who used this model (Arora & Chopra, 2013; Ruiz et al., 2018). Depression induced in sedentary animals rapidly develops and lasts for a long time.

Administration of paliperidone, an atypical antipsychotic in experimental depression

Paliperidone is the active metabolite of risperidone, an atypical neuroleptic, which has a high affinity for D_2 and $5HT_2$ receptors that it inhibits. The preparation is indicated in schizophrenia, bipolar disorders and as a sleep inducer.

In group G III, with reserpine-induced depression and paliperidone treatment, the following were found:

- a significant increase in depression at T_{14} and T_{30} compared to G I and compared to initial values

- a significant increase in emotional behavior at T_{14} and T_{30} compared to initial values

- a significant decrease in locomotor behavior at T_{14} and T_{30} compared to initial values.

Co-treatment with reserpine and paliperidone in sedentary animals (G III) induces a significant decrease in depressive behavior at T_{30} compared to initial values and compared to T_{14}.

Paliperidone administration and exercise in experimental depression

The research performed on G IV shows:

- a significant increase in depressive behavior at T_{14} and T_{30} compared to G I and compared to initial values

- a significant increase in emotional behavior at T_{14} compared to initial values

- insignificant changes in locomotor behavior at T_{14} and T_{30} compared to initial values.

The antidepressant role of physical exercise has been demonstrated in various studies on human subjects (Matthews et al., 2011; Weber & Edwards, 2010; O'Connor, 2007; Krogh et al., 2009; McKercher et al., 2009; Blumenthal et al., 2007; Conn, 2010) and on animals with induced depression (He et al., 2012; Marais

et al., 2009; Sigwalt et al., 2011; Hendriksen et al., 2012; Dimatelis 2012; Russo-Neustadt et al., 2000; Dey et al., 1992; Soares et al., 2003).

The antidepressant mechanisms of exercise can be due to:

- an influence on the metabolism of serotonin and its precursors in the brain (He et al., 2012; Dey et al., 1992; Soares et al., 2003; Moon et al., 2012)
- an influence on the oxidant/antioxidant balance in the brain (Bruja, 2014) and to the protective antioxidant role of exercise (Arent et al., 2012)
- activation of neurotrophic factors in the hippocampus (Marais et al., 2009; Garza et al., 2004)
- changes in the functional level of proteins in the hippocampus under stress conditions (Yang et al., 2012; Dimatelis, 2012).

Compared to G III of sedentary animals, the results obtained for animals with depression, treated with paliperidone and exercise trained (G IV) show the following at 30 days:

- a significant increase in depressive behavior
- a significant decrease in emotional behavior
- a significant increase in locomotor behavior.

The results obtained in groups II, III and IV, compared to the control group (G I), evidence:

- a significant increase in depressive behavior at 14 and 30 days compared to initial values, with the greatest increases in G IV and compared to initial values
- a significant increase in emotional behavior at 14 days in groups II, III, IV and at 30 days in G III
- a significant decrease in locomotor activity at 14 days in groups II, III and at 30 days in G III.

Depending on the time of examination, the following were found for groups II, III and IV compared to initial values:

- the greatest significant increase in depression at 30 days in G II and at 14 days in groups III and IV
- a significant increase in depression in all groups at 14 days and at 30 days
- a significant increase in emotional behavior in groups II, III, IV at 14 days and in G III at 30 days
- a decrease in locomotor activity in all groups, with significant values at T_{14} and T_{30} in G II and G III, and a tendency to return to initial values in G IV.

Co-treatment with reserpine and paliperidone in exercise trained animals determined significantly decreased values of depressive behavior at T_{30} compared to sedentary animals, which supports the antidepressant role of exercise under these conditions.

Conclusions

1. The pharmacological experimental model of reserpine-induced depression is a valid model, the animals being characterized by an increase in emotional behavior and a decrease in locomotor activity.

2. Treatment with paliperidone – an atypical antipsychotic – in sedentary animals with reserpine-induced depression determines an increase in emotional behavior and a decrease in locomotor activity.

3. Treatment with paliperidone in exercise trained animals with experimental depression determines moderate increases in emotional behavior and the maintenance of locomotor activity within normal limits.

4. Exercise has favorable effects on locomotor activity in depressed animals treated with an atypical antipsychotic.

Conflicts of interest

There are no conflicts of interest.

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