Antistress and antidepressant properties of dapoxetine and vortioxetine

Piotr Ratajczak[1]*, Krzysztof Kus[1], Małgorzata Zielińska-Przyjemska[2], Beata Skórczewska[1], Tomasz Zaprutko[1], Dorota Kopciuch[1], Anna Paczkowska[1] and Elżbieta Nowakowska[1]

[1] Department of Pharmacoeconomics and Social Pharmacy, Poznan University of Medical Sciences, Poznan, Poland,
[2] Department of Pharmaceutical Biochemistry, Poznan University of Medical Sciences, Poznan, Poland,
*Email: p_ratajczak@ump.edu.pl

The studies aimed to determine the antidepressant efficacy of single and chronic administration of dapoxetine alone and vortioxetine alone, as well as in the combination of these drugs. An additional objective of the study was to measure the effect of the active substances on the corticosterone level in chronically stressed animals. The study was conducted on male Wistar rats using non-stressed and stressed groups (chronic restraint stress). The experiment comprised both forced swimming test (immobility time test) and corticosterone level measurement using Corticosterone ELISA Kit. The obtained results confirm the antidepressant efficacy of used drugs upon both single and chronic administration and potential efficacy of these drugs administered in combination with stressed rats. Corticosterone level analysis, meanwhile, showed stress relieving properties of the study drugs, which reduced the animal stress hormone level, whether administered separately or in combination. Dapoxetine and vortioxetine have an antidepressant and stress relieving effect on rats subject to chronic stress both in monotherapy and in combined therapy. Because both study drugs are new additions on the market, further research is necessary to prevent interactions related, for instance, with uncontrolled use of two drugs with similar mechanisms of action but prescribed in different indications (dapoxetine is commonly used to treat premature ejaculation).

Key words: vortioxetine, dapoxetine, restraint stress, immobility time, corticosterone

INTRODUCTION

Mood disorders and depression are some of the most frequent causes of mental disability among communities worldwide (Nestler et al., 2002). The issue of depression, with its constant incidence growth, affects all of the world's countries; still, despite this high prevalence and severe consequence of the disease, research on pathogenesis and effective methods of treatment of depression (and other mental disorders) are much less advanced than those on other chronic complaints, such as diabetes. Numerous concepts in publications are frequently contradictory and fail to explain the symptoms observed in patients fully. A growing body of evidence nowadays suggests that pathogenesis of depression features multiple factors, including neurobiological, genetic, environmental (stress), and psychological (Hall and Reynolds-Iii, 2014).

The emergence of depression symptoms is believed to be associated with the deregulation of serotonin, noradrenaline, and dopamine levels in synaptic clefts. The appropriate concentration of these neurotransmitters in cortical and subcortical structures of the brain's limbic system is necessary for conditions maintenance of normal mental conditions (Kitaichi et al., 2010). Disturbed transmission within the frontal and temporal cortex and the amygdala also plays a significant role in depression's pathogenesis (Drevets et al., 2008).

The hypothalamic–pituitary–adrenal (HPA) axis dysfunction and the related chronic stress-induced hypercortisolemia play a significant role in the disease's pathomechanism. HPA axis adverse effect on the mood by the induced release of corticoliberin (hypothala-

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mus) and cascade release of corticotropin (pituitary gland), and then of cortisol (adrenal glands – the animal equivalent of the human stress hormone is corticosterone). Excessive exposure to stress increases the cortisol blood level and disturbs the HPA axis (in normal physiological conditions, high cortisol level would inhibit corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) secretion) (Herman et al., 2016). As a result of stress, the adrenal cortex becomes more sensitive to ACTH, leading to increased secretion of cortisol, which contributes to many central nervous system (CNS) disorders and further inhibition of neurogenesis. Increased cortisol level degenerates the limbic system's structures, specifically those of the hippocampus involved in memory processes. In addition to this, glucocorticosteroid (GR) receptors present in this structure, when stimulated, enhance the signal maintaining the stress response, causing further damage to various brain regions (Anacker et al., 2011).

Vortioxetine (VOR) is a new antidepressant used in severe forms of the disease, launched on the market in 2013. Its mechanism of action is multifunctional, depending on the location, it stimulates the serotonin receptor directly or inhibits serotonin reuptake (Pae et al., 2015). VOR is, on the one hand, an agonist of 5-HT_{1A} and 5-HT_{1B} receptors and, on the other, an antagonist of 5-HT_{1D}, 5-HT_3, and 5-HT_7 serotonin receptors, as well as a serotonin transporter inhibitor (SERT) (D'Agostino et al., 2015). In compare dapoxetine (DAP) is used as a strong and selective serotonin reuptake inhibitor in the treatment of premature ejaculation (PE) in men. Pathophysiology of premature ejaculation is related to a reduced serotoninergic transmission and reduced sensitivity of the 5-HT_{2C} receptor and or hypersensitivity of the 5-HT_{1A} receptor (Jhanjee et al., 2011). The drug increases the level of serotonin available in synaptic clefts, which then binds to the receptors mentioned above, thus delaying the ejaculation (Jhanjee et al., 2011). Analysis of animal models of PE led to the conclusion that DAP inhibited the ejaculation reflex acting on the supraspinal in the lateral paragigantocellular nucleus (LPGi). The released serotonin stimulates, among others, 5-HT_{2C} and 5-HT_{1A} receptors on descending serotonergic pathways leading from the LPGi to the Onuf's nucleus, resulting in delayed ejaculation (Yells et al., 1992). Moreover, owing to its good pharmacokinetic parameters, short biological half-life ($T_{1/2}$=17.8 h) and rapid onset of action, the drug can be used on an *ad hoc* basis (Hellstrom, 2009). Use of DAP in PE treatment also consolidated targeted therapies of brain regions responsible for sexual behavior, thalamus and hypothalamus, as proven in the experiment by Clement et al. (Clément et al., 2012).

Our studies aimed to examine an antidepressant efficacy of DAP, VOR, and the combination of those drugs as well as the level of corticosterone release after drug administration in the stressed rats.

METHODS

Animals and treatments

48 male Wistar rats were housed in cages (size 31 × 30 × 15 cm) in a light (lights on 07:00–19:00 h), temperature- and humidity-controlled animal facility. All procedures related to the use of rats in these experiments were conducted with due respect to ethical principles regarding experiments on animals (Directive 2010/63/EU), especially in case of sample size (n=6), which is consistent with the 3R principle (replacement, reduction, refinement). The study protocol was approved by the Local Ethics Committee for Research on Animals in Poznan (5/2018 – 23 February 2018).

The experiments were performed on male rats at the age of 3 months (90 days). The duration of the experiment was 30 days (14 days of stress procedure (1-14), 14 days of drug administration and forced swimming test (15-29), and 1 day (30) of decapitation procedure and blood collection). Forced swimming test took place at 15, 22, 29 days of the experiment (1×, 7×, and 14×). The animals were divided into two groups: 24 non-stressed rats (NS) and 24 restraint stressed rats (RS). Groups were further divided on: vehicle - saline group (0.9% sodium chloride) (control group 6 rats), VOR (2.5 mg/kg i.p.) group (VOR 6 rats), DAP (3 mg/kg i.p.) group (DAP 6 rats), VOR (2.5 mg/kg i.p.) + DAP (3 mg/kg i.p.) group (VD 6 rats).

On the day of the forced swimming test, all substances were injected 30 min before the test (at 1, 7, and 14 days of administration).

Animal model of depression

24 adult male Wistar rats belonging to the restraint stress group (RS) were subjected to regular stress (placing them for 2 h in metal restraint tubes) during the 14 days of a previously described protocol (Wood et al., 2003). NS rats (n=24) were left undisturbed in their home cages.

Forced swimming test

The experiment was conducted in accordance with a previously described methodology (Porsolt et al., 1978). The rats were placed individually in cylinders made of glass, of specific dimensions (height – 40 cm and diameter – 18 cm) and filled with water at 25±1°C up to the height of 17cm from the vessel bottom. The test was per-

formed with artificial lighting, at the peak of the administered drugs' effect. The rats were observed on cameras for 5 min, and their active swimming time was measured using SMART v3.0 software. Immobility time was identified as movements in the camera's field of view at or below the threshold of 13.10 cm^3/s (this volume corresponds to approximately 10% of rat body surface). The animal's immobility time was measured with a 2 s delay. One day before the Porsolt test, the rats were pretested by being put into the cylinders with water for 15 min. Both after the pre-test and three iterations of the test itself, the animals were left to dry in a room with a temperature of 30°C.

Corticosterone analysis

Next day (30 day of the experiment) after last forced swimming test protocol all of the rats (24 NS and 24 RS rats) were sacrificed by decapitation, and trunk blood was collected to establish corticosterone level in each group of animals (treated by vehicle or VOR, DAP, VOR+DAP). Blood was collected immediately to plastic tubes containing 10% ethylenediaminetetraacetate (EDTA). Due to the sensitivity of the Corticosterone ELISA kit, the rats did not receive any anesthetic substances that could falsify the test result. The blood was spun at 3000 rpm (4°C, 10 min), and the plasma placed in a fresh tube and frozen. Plasma samples were stored at –80°C until use. Plasma levels of corticosterone were determined using Corticosterone ELISA Kit (ENZO Life Science). Assays were performed according to the protocols provided by the manufacturer.

Statistical analysis

The data are shown as the mean values ± SEM. The data distribution pattern was not normal (unlike Gaussian function). Statistical analysis for the forced swimming test was carried out using the nonparametric Kruskal-Wallis test for unpaired data and MANOVA Friedman multivariate analysis of variance test for paired data. Statistical analysis for the corticosterone analysis was carried out using the nonparametric Kruskal-Wallis test. Statistical significance difference between the groups was tested using Dunn's *post-hoc* test and Dunnett's *post-hoc* test.

RESULTS

Effect of DAP, VOR treatment on immobility time analyzed in the Porsolt test on NS and RS rats

In multivariate analysis of variance (MANOVA) of immobility time statistical significance for VOR (H=4.6),

DAP (H=7.2) and VD (H=4.9) 14 days of treatment in NS group as well VOR (H=5.8), DAP (H=3.9) and VD (H=7.3) 14 days of treatment in RS group has been shown. Moreover, statistically analysis based on Kruskal-Wallis test has shown statistically significance for unpaired data from 1 (H=2.6), 7 (H=1.8) and 14 (H=3.7) days of treatment (VOR or DAP or VD) in NS group as well as 1 (H=4.0), 7 (H=5.7) and 14 (H=6.1) days of treatment (VOR or DAP or VD) for RS group.

Comparison of NS *vs.* RS control groups shows a statistically significantly higher immobility time in the Porsolt test for rats in the RS group than in the NS group (p<0.05 *vs.* NS control) (Figs 1-3) on day 1, 7, and 14 of the test, proving the depression-like effect of chronic stress.

A single administration of DAP (3 mg/kg i.p.) failed to cause a statistically significant difference between the immobility time of animals in NS groups *vs.* the control. In the non-stressed group, a statistically significant relationship (Fig. 3) was observed only upon chronic administration (14 days) of VOR (p<0.05 *vs.* NS control). In the RS group, on the other hand, single and chronic administration (1, 7, and 14 days) of VOR and DAP resulted in a statistically significant reduction of immobility time of rats compared to the control group (p<0.05 *vs.* RS control) (Figs 1-3). Results obtained suggests an antidepressant effect of the administered drugs in NS and RS group.

For VOR and DAP (VD) combined treatment, a statistically significant difference between immobility time of animals *vs.* control group was found only in the restraint-stressed group of rats (p<0.05 *vs.* RS control) (Figs 2-3). The result suggests that the combination of these drugs had an antidepressant effect observed following chronic administration for 7 and 14 days. No such effect was found in the NS group. Moreover statistically significant decrease of immobility time was observed in NS VOR *vs.* NS VD (p<0.05 *vs.* NS control) as well as RS VOR and RS DAP *vs.* RS VD (p<0.05 *vs.* RS control) after 14 days of treatment which proves that the combination of drugs reduce their therapeutic effectiveness (Fig. 3).

Effect of DAP and VOR treatment on plasma corticosterone level in NS and RS rats

Comparison of NS and RS control groups shows a statistically significantly higher corticosterone level (CORT) in rats in the RS group than in the NS group (p<0.05 *vs.* NS control) (Table I), proving the depression-like effect of chronic stress.

A statistically significant decrease of corticosterone level occurred in the NS group compared to the control group (p<0.05 *vs.* NS control) in rats receiving VOR (2.5 mg/kg i.p.), DAP (3 mg/kg i.p.), and the com-
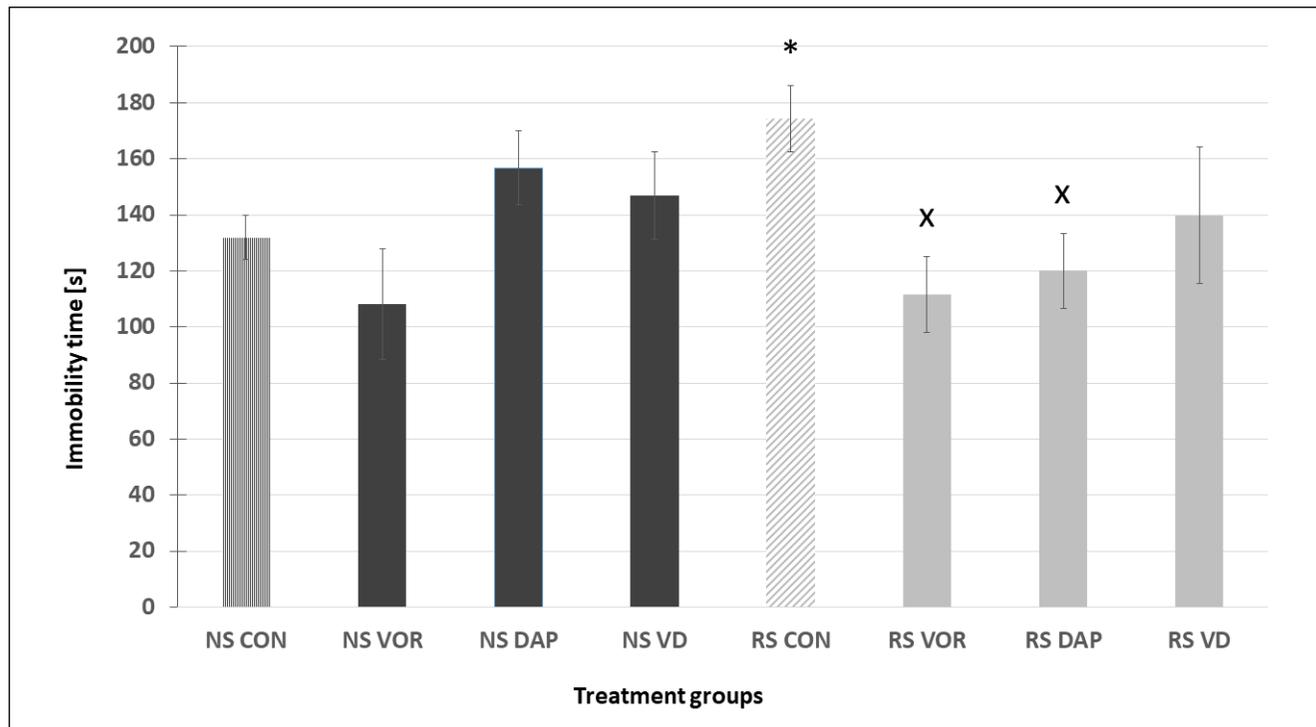
Fig. 1. Effect of dapoxetine and vortioxetine treatment on immobility time analyzed in the Porsolt test on non-stressed and restraint stressed rats (1×). * Statistically significant difference p<0.05 *vs.* NS control; ˣ Statistically significant difference p<0.05 *vs.* RS control n=6. NS – non-stressed; RS – restraint stressed; VOR – vortioxetine; DAP – dapoxetine; VD – vortioxetine + dapoxetine; CON – control.
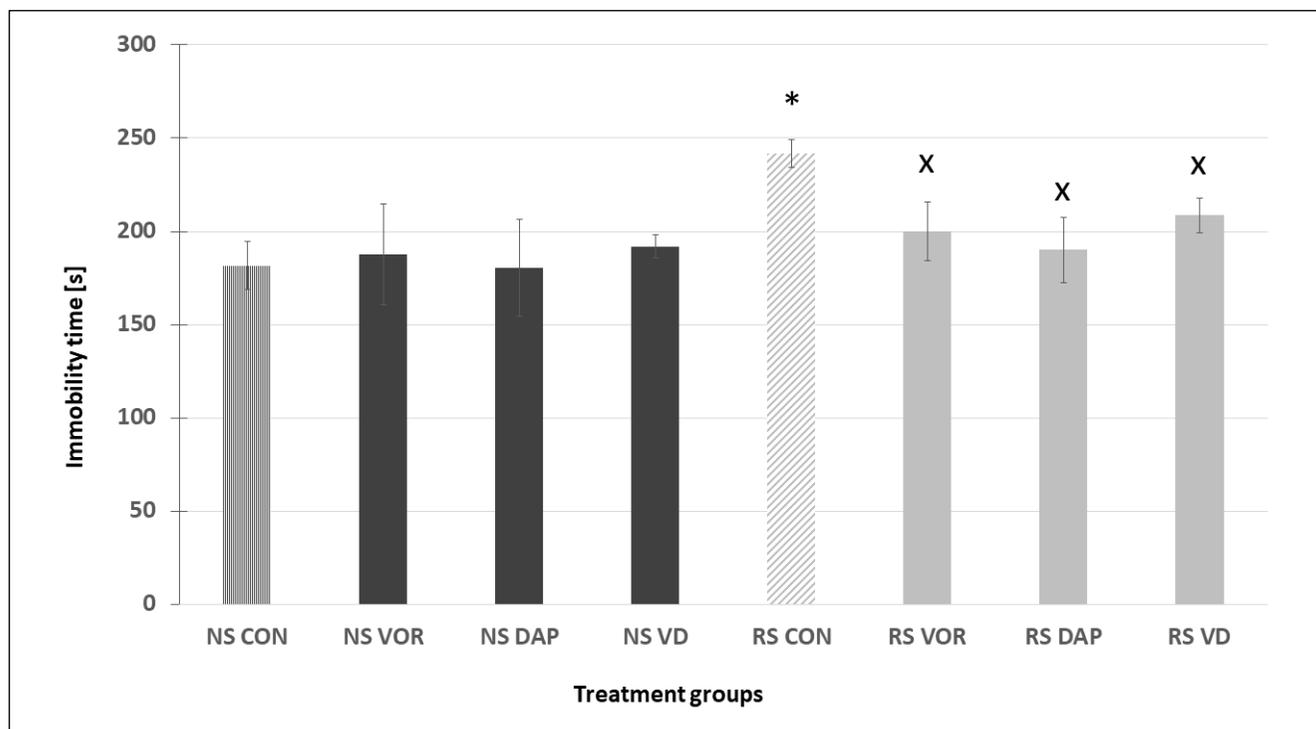
Fig. 2. Effect of dapoxetine and vortioxetine treatment on immobility time analyzed in the Porsolt test on non-stressed and restraint stressed rats (7×). * Statistically significant difference p<0.05 *vs.* NS control; ˣ Statistically significant difference p<0.05 *vs.* RS control n=6. NS – non-stressed; RS – restraint stressed; VOR – vortioxetine; DAP – dapoxetine; VD – vortioxetine + dapoxetine; CON – control.
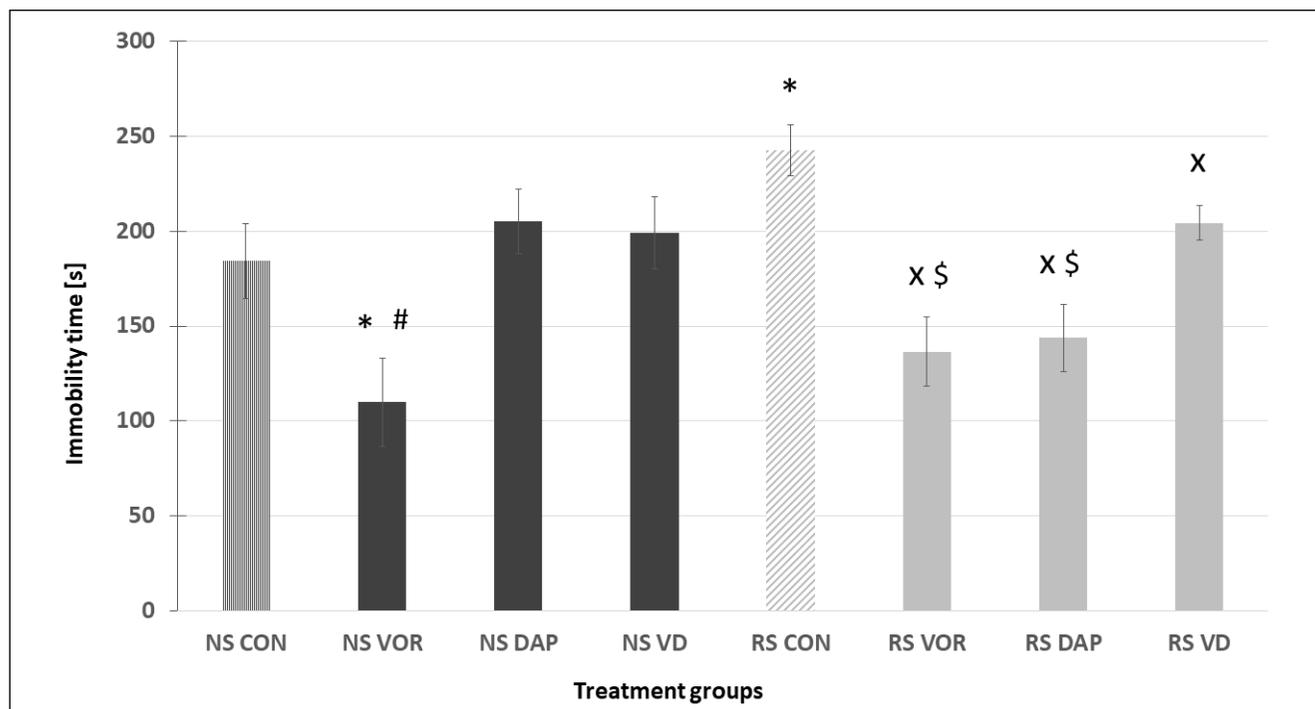
Fig. 3. Effect of dapoxetine and vortioxetine treatment on immobility time analyzed in the Porsolt test on non-stressed and restraint stressed rats (14×). * Statistically significant difference p<0.05 *vs.* NS control; [X] Statistically significant difference p<0.05 *vs.* RS control n=6; # Statistically significant difference p<0.05 *vs.* NS VD; [$] Statistically significant difference p<0.05 *vs.* RS VD n=6. NS – non-stressed; RS – restraint stressed; VOR – vortioxetine; DAP – dapoxetine; VD – vortioxetine + dapoxetine; CON – control.

Table I. Effect of dapoxetine and vortioxetine treatment on plasma corticosterone level in non-stressed and restraint stressed rats.

Group	Corticosterone [ng/ml]
NON-STRESSED (NS)	
Control	180.67±13.18
VOR 2.5 mg/kg i.p. 30 min before the test	**143.67±8.43*#**
DAP 3 mg/kg i.p. 30 min before the test	**102.33±4.34*#**
VOR 2.5 mg/kg i.p. DAP 3 mg/kg i.p. 30 min before the test	**119.94±5.91***
RESTRAINT STRESS (RS)	
Control	**332.5±10.67***
VOR 2.5 mg/kg i.p. 30 min before the test	283.61±17.81[X$]
DAP 3 mg/kg i.p. 30 min before the test	216.00±9.16[X]
VOR 2.5 mg/kg i.p. DAP 3 mg/kg i.p. 30 min before the test	190.89±12.97[X]
Kruskal Wallis H [7,47]	11.7

n=6; * Statistically significant difference p<0.05 *vs.* NS control; [X] Statistically significant difference p<0.05 *vs.* RS control; # Statistically significant difference p<0.05 *vs.* NS VOR+DAP; $ Statistically significant difference p<0.05 *vs.* RS VOR+DAP.

bination thereof (Table I) which could possibly show a stress-relieving effect of the study drugs. In addition to this, a statistically significant increase of corticosterone level was found in the NS group of rats receiving VOR and a statistically significant decrease of corticosterone level in the group of rats receiving DAP compared to the group receiving a combination of these drugs (p<0.05 *vs.* NS VOR+DAP).

In the RS group, meanwhile, a statistically significant decrease of corticosterone level was found compared to the control group (p<0.05 *vs.* RS control) in rats receiving VOR, DAP, and combination thereof (Table I) which also confirms the stress-relieving effect of these drugs. In the RS group, a statistically significant increase of CORT level was found in rats receiving VOR compared to the animals receiving a combination of these drugs (p<0.05 *vs.* RS VOR+DAP).

DISCUSSION

In our studies, animals in the RS control group had both an increased corticosterone level (Tab. I) and an increased immobility time analyzed in the Porsolt test (Figs 1-3) *vs.* the NS control group. Our results corroborate with results of the paper by Vega-Rivera et al.

(2014), where the authors have suggested that animals exposed to stress had a higher CORT level and longer immobility time in the Porsolt test.

In our study, no antidepressant effect of DAP on NS rats was observed. The drug administered to RS, on the other hand, had an antidepressant effect both upon single and chronic treatment. DAP's antidepressant effect may be related to its strong affinity to 5-HT transporter. DAP acts by inhibiting SERT, which leads to increased serotonin levels in synaptic clefts and mitigated symptoms of depression (Kendirci et al., 2007). The fact that DAP only had an antidepressant effect on the RS group is likely to be related to the significantly lower 5-HT level in this group of rats (Yang et al., 2008). Rats exposed to chronic stress were found to have a lower activity of serotoninergic neurons and a reduced sensitivity of 5-HT_{1A} autoreceptor (Bambico et al., 2009). In addition to this, a lower concentration of 5-HT was observed in the dorsal nuclei of animals subject to mild chronic stress (Yang et al., 2008) and the hippocampi of rats separated from their mothers in their early life stages. Moreover, the antidepressant effect found in the RS group is confirmed by the results of a study by Farhan et al. (2016). The authors suggested that chronic administration of DAP to rats reduced behavior disorders resulting from exposure to chronic stress. As for VOR use, it was found to have an antidepressant effect both upon single and chronic administration to RS animals and upon chronic administration to NS animals. Our results corroborate with results of the study by Bang-Andersen et al. (2011), who proved VOR administered subcutaneously to rats at the doses of 2.5, 5, and 10 mg/kg to have an antidepressant effect (especially through $5HT_{1B}$, $5\text{-HT}_{3,}$ and 5-HT_7 receptors). Moreover, results obtained by Pehrson et al. (2013) claim that VOR compared to escitalopram increased extracellular levels of 5-HT, NA and DA in the prefrontal cortex and the hippocampus, as well as in nucleus accumbens, as confirmed by the multimodal mechanism of action of the drug. Also, Betry et al. (2015) point out that VOR, through its partial agonism to 5-HT_3 receptor prevents the harmful effect of stress-inducing factors on transmission of signals in synaptic clefts of the hippocampus and accelerates the proliferation of this structure's cells. Our study corroborates with the above study results proving the antidepressant effect in the RS group.

The paper also tested the antidepressant efficacy of combined therapy (VOR + DAP) to NS and RS rats. No antidepressant effect was found in the NS group either upon single or chronic administration, while in the RS group, immobility time was reduced upon chronic administration of the drugs. Moreover, it was found that prolonged combined administration of VOR and DAP in non-stressed, as well as restraint, stressed groups showed decreased effectiveness in comparison to alone use of both drugs. Absence of antidepressant activity in the NS group, as well as decreased effectiveness of combined use of drugs in comparison to drugs used alone, could be related to the interaction of the drugs in SERT inhibition, on the one hand, and the other, it may be related to neurotransmission processes occurring in the case of an increased 5-HT supply in synaptic clefts. Particular attention should be paid to 5-HT_{1A} autoreceptor which, with the increased availability of serotonin resulting from SERT blockade by DAP and VOR, and being directly stimulated by VOR (which is an agonist to this receptor), induces 5-HT reuptake process leading to reduced efficacy of drugs administered in combination (Jhanjee et al., 2011). Garcia-Garcia et al. (2014) confirm the role of 5-HT_{1A} receptors in the pathogenesis of depressive disorders. The authors described two subtypes of 5-HT_{1A}, presynaptic autoreceptors and postsynaptic heteroreceptors. Autoreceptors are responsible for the regulation of 5-HT levels in the synaptic cleft by reuptake of this neurotransmitter. Heteroreceptors are situated in brain regions involved in mood regulation, in the prefrontal cortex, the hippocampus, and the amygdala. In addition to this, authors (Garcia-Garcia et al., 2014) point out that symptoms of depression may be related to the increased number of autoreceptors and the simultaneously reduced number of heteroreceptors which can be translated into the results of our study, activation of autoreceptors by DAP and VOR could have caused a reduction of the number of heteroreceptors and, thus, reduce the antidepressant effect observed upon chronic administration of VOR. Also, Frank (2008) confirms that excessive stimulation of 5-HT_{1A} autoreceptors may reduce the activity of the serotoninergic system and induce a lower mood. Similar results are presented in the study by Pineda et al. (2010). The authors note that the excessive increase of 5-HT level in the synaptic cleft increases the number of 5-HT_{1A} receptors leading to the autoinhibition of serotonin release and, consequently, induces mood disorders. The paper also corroborates this hypothesis by Stockmeier et al. (1998), which proved an increased number of these receptors in the midbrain of suicide victims. As for the RS group, the observed antidepressant effect of combined administration of DAP+VOR may be related to the potentialized impact of these two drugs. VOR and DAP share the mechanism of action consisting of the ability to inhibit SERT and, thus, increase the 5-HT level in the synaptic cleft (Kendirci et al., 2007). This leads to the increased availability of serotonin to 5-HT_{1A} heteroreceptors and induces an antidepressant effect (Garcia-Garcia et al., 2014). It is an important fact that in the RS group animals, as

well as in other stress-based models (Wang et al., 2017), serotonin availability is lower; thus, administration of drugs affecting the serotoninergic system may induce pharmacological effect sooner and more evidently than in the non-stressed groups.

As mentioned above, stress is an important factor involved in the pathogenesis of depression. In stressful circumstances, the corticoliberin (CRH) secreted by the hypothalamus stimulates the pituitary to produce corticotropin, which, in turn, stimulates the adrenal glands to secrete cortisol (corticosterone CORT) (Herman et al., 2016). The conducted test of corticosterone level in stressed and non-stressed rats shows that the level of this hormone is significantly higher in the RS group compared to the NS group (Table I) which is consistent with the study conducted by Ayensu et al. (1995). The authors proved mild chronic stress to cause the said hormone's level increase in rats. Similar results were obtained in the study by Pitman et al. (1988), where rats exposed to restraint stress had higher plasma CORT levels. In our studies, CORT levels were seen to decrease upon administration of VOR, DAP, and in combination thereof in the NS and RS groups *vs.* their relevant control groups. Our results corroborate with the results of the study by Pepin et al. (1989). The authors note that antidepressant drugs can suppress excessive activation of the HPA axis by increasing mRNA level and, as a result, by inducing synthesis of receptors for glucocorticosteroids located in the amygdala or hypothalamus. Increased quantities of these receptors resulted in sensitization of the HPA axis to the excessive level of cortisol (corticosterone) and blocked the secretion of the hormone by way of negative feedback (Pepin et al., 1989). On the other hand, Hlavacova et al. (2018) believe that antagonist effect to 5-HT$_3$ receptor might be another mechanism of action responsible for CORT level reduction by vortioxetine. A similar conclusion was confirmed in the study by Kurhe and Mahesh (2015).

Please note that the obtained results of corticosterone level analysis show that VOR, with its better antidepressant profile than DAP or combination of the two drugs, reduced CORT level to a limited extent. DAP or combination of the drugs reduced the animal stress hormone level in our study to a much greater extent, both in the NS and in the RS group. Schüle et al. (2004) put forward the hypothesis that the increased CORT level may be due to NA reuptake inhibition. Increased NA levels in the synaptic cleft, in turn, activate the α$_1$ receptor, which results in CRH secretion and the subsequent CORT release (Schüle et al., 2004). This corresponds to the probable mechanism of action of VOR, suggesting modulation of noradrenaline neurotransmission (within NA transporter) observed following administration of the drug. Also, Fuller et al. (1996) note that activation of the 5-HT$_{1A}$ receptor occurring following VOR administration may also be directly correlated with the increased level of the animal stress hormone. In the study conducted for the purposes of this paper, it was also found that the combination of VOR+DAP reduced corticosterone to a greater extent than VOR administered alone both in the NS and in the RS group. This situation may be related to the potentialized effect of the two drugs in inducing biosynthesis of receptors for glucocorticosteroids and sensitizing the HPA axis to the increased corticosterone level (Pepin et al., 1989).

CONCLUSION

Exposure to stressful situations makes the body synthesize the stress hormone (cortisol or corticosterone), which in excess leads to CNS degeneration and neurogenesis inhibition. This results in damage to a structure playing a vital role in mood regulation. The study also confirmed the antidepressant efficacy of VOR, DAP, and combination of these drugs in the group of stressed animals. Because of the study drugs' mechanisms of action, special care should be taken when combining them in therapy as such combination if uncontrolled may lead to several dangerous drug interactions and, consequently, reduce their efficacy.

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