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Chapter

Association between Peripheral Blood Inflammatory Markers, Endothelial Dysfunction Markers, and Depression

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Abstract

The authors present an analysis of current research and their own data on the link between endothelial dysfunction (ED) and the severity of depression in middle-aged patients with cerebral microangiopathy. Levels of peripheral inflammatory and endothelial dysfunction markers were measured using the enzyme-linked immunosorbent assay (ELISA). The results of the comparative and correlation analyses showed a statistically significant correlation between the severity of depression and increased levels of inflammatory, as well as endothelial dysfunction

Keywords: inflammatory marker, endothelial dysfunction maker, depression, cerebral microangiopathy, Divaza

1. Introduction

Depression and cardiovascular diseases (CVD) are the leading problems of modern healthcare [1]. The global prevalence of depressive disorders ranges from 4.4 to 20%. About 350 million people suffer from depression [2, 3].

The World Health Organization (WHO) considers depression and atherosclerosis as the main causes of disability in CVD and predicts that by 2030, depression will be the leading one. The fact that a depressive disorder is more common in women and the elderly people (in whom CVD is often underestimated) determines the need for effective preventive measures in these risk groups [4, 5].

The multiple factors contributing to the strong association between depression and atherosclerosis are not well studied. Authors discuss various mechanisms of linkage between these diseases [6–12], i.e., the activation of neuroendocrine system [5].

Frequently, depression is considered an unfavorable prognostic factor for the CVD development [6–8]. Unhealthy lifestyle (physical inactivity, smoking), as well

as inflammation and metabolic syndrome, has been proposed to explain the relationship between depression and the development of atherosclerosis [9, 10, 12, 13].

In patients with depression, elevated levels of such markers of systemic inflammation as pro-inflammatory cytokines (tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6)), C-reactive protein (CRP), as well as reduced levels of interleukin-1 (IL-1) and interleukin-8 (IL-8) [14–17], lead to hyperactivation of the hypothalamic-pituitary-adrenal axis [18]. Also intestinal inflammation causes remote effect on the brain and depression. Unbalanced gut microbiota shifts tryptophan metabolism toward kynurenine pathway affecting gamma-aminobutyric acid (GABA), dopamine, and serotonin levels [19, 20]. Studies have shown that stimulation of the vagus nerve modulates the inflammatory response and relieves the depression symptoms [21, 22].

Many studies focus on the activation of inflammatory processes as a common pathogenetic pathway between CVD, cerebrovascular disorders, and depression. In this respect, there are two aspects of the role of pro-inflammatory mechanisms: the first reveals the causal relationship between depression and inflammation and/or endothelial dysfunction (ED); the second shows the connection between inflammation, ED, and atherosclerosis [5]. ED and/or elevated levels of peripheral markers of inflammation are found in atherosclerosis and cardiovascular events [23]. Patients at high risk of acute coronary syndrome can be identified based on the elevated levels of inflammatory markers [24]. These markers are associated with atherosclerosis and activation of the immune system. The immune system components can indirectly influence the progression of atherosclerotic vascular lesions.

Risk factors for CVD, which at the same time predispose to atherosclerosis, cause dysfunction of the vascular endothelium. The vascular endothelium, as a regulator of vascular homeostasis, is involved in different processes, such as keeping a balance between vasodilatation and vasoconstriction, inhibition and stimulation of smooth muscle cell proliferation and migration, thrombus formation, and fibrinolysis [25].

When imbalance occurs, ED develops, causing excessive vascular permeability, platelet aggregation, leukocyte adhesion, and production of cytokines. A failure in synthesis or a violation of the activity of nitric oxide (NO) (which is manifested by insufficient vasodilatation) also is considered as a potential mechanism by which endothelial dysfunction leads to atherosclerosis. The low systemic levels of NO have been postulated to be responsible for the increased risk of cardiovascular events observed in subjects with depression, as NO produces vasodilatation [26].

Among other cardiovascular risk factors, obesity increases morbidity and mortality from CVD. The relationship between depression and obesity is complex and includes behavioral, biological, and pathological associations [27]. The mechanisms leading to the development of obesity affect the vascular system and especially the endothelium function, mainly due to the pathological role of TNF-α in the generation of reactive oxygen species and reducing the availability of NO [28].

Significantly more research is needed to further study the multiple associations between inflammation, markers of ED, and depression in patients with CVD [29]. Therefore, we have performed our own study aimed at identifying the relationship between the levels of peripheral inflammatory markers and markers of ED with the level of depression in patients with cerebral microangiopathy associated with arterial hypertension and cerebral atherosclerosis.

2. Materials and methods, results, discussion

The study included middle-aged (44–60 years old) outpatients of both sexes, with cerebral microangiopathy. The diagnosis was based on (1) the presence of a

vascular disease (arterial hypertension and/or cerebral atherosclerosis) and focal neurological symptoms in combination with cerebral symptoms (headache, dizziness, noise in the head, memory loss, etc.), (2) ultrasonic signs of cerebrovascular atherosclerosis according to duplex scanning of the main arteries of the head, and (3) signs of morphological changes in the brain according to neuroimaging data (subcortical and periventricular leucoaraiosis and/or focal changes of gray and white matter in the form of postischemic cysts and/or lacunary strokes and/or diffuse atrophic changes in the form of ventricular dilatation or subarachnoid spaces). Also all patients had depression (≥8 points on the Hospital Anxiety and Depression Scale (HADS)). Study participants were capable of communicating with the researcher, understanding and signing the informed consent form.

All patients received Divaza for 3 months. Divaza is a drug with endothelial protective as well as nootropic (neuroprotective, neurotrophic) activity and good safety profile [30–54].

Combination drug Divaza was developed based on previously discovered pharmacological effects of its active pharmaceutical ingredients—release-active antibodies to S100 (RAF of Abs to S100) and release-active antibodies to endothelial NO synthase (RAF of Abs to eNOS) (including their different technological versions). The important feature of RA forms of a substance is the ability to exert modifying effect on the original substance or its target [Symmetry, 2018]. Since this activity is released during technological processing of the original substance, it has been termed as the released activity and the produced drug as the released-active drug.

Preclinical studies have shown that Divaza successfully combines properties of the monocomponents [see ***Appendix 1****]. The overall therapeutic effect results in an enhanced ability of experimental animals to remember and reproduce the developed skills as well as overcome artificially induced anxiety and depression. Furthermore, therapeutic effect of Divaza on functional activity of endothelium has been confirmed by normalizing such integrative indicator of the physiological status as blood pressure: RAF of Abs to eNOS exerted hypotensive effect in animals with arterial hypertension and, at the same time, did not alter parameters of system hemodynamics in normotensive condition. Importantly, RAF of Abs to eNOS given to animals along with nitroglycerin, an exogenous NO-donor, resulted neither in a drug-drug interaction nor in excessive vasodilation (the drug did not enhance the nitroglycerin effect in normotensive animals).*

Noteworthy, Divaza, while exerting a normalizing psychotropic effect, did not cause sedation and/or muscle relaxation (unpublished data).

RAF of Abs to S100, RAF of Abs to eNOS, and combination drug Divaza did not exert any toxic effect as assessed by evaluation of single- and repeat-dose (chronic) toxicity, genotoxicity, reproductive and developmental toxicity, local tolerance, allergenic properties and immunotoxicity even when administered at doses more than 100 times exceeding the recommended human daily doses [31, 32].

During the study, patients were allowed to take concomitant drugs for correcting the main risk factors for CVD development (antihypertensive drugs, diuretics, antiplatelet drugs, anticoagulants, statins, and antidiabetic drugs).

An assessment of the dynamics of clinical and laboratory parameters was performed at baseline and after 3 months of therapy. Clinical examination of patients included collecting and analyzing complaints, anamnesis, anthropometric measurements of body weight and height to calculate body mass index (BMI), and thorough neurological examination, including neuropsychological testing and emotional status assessment using HADS.

Serum levels of peripheral markers of endothelial inflammation (CRP, monocyte chemoattractant protein-1 (MCP-1)) as well as biomarkers of ED (endothelin-1, eNOS, vascular endothelial growth factor (VEGF), S100B protein, von Willebrand

factor, fibrinogen) were determined by ELISA. The amount of circulating desquamated endothelial cells (CECs) was detected according to J. Hladovec with modifications.

ELISA reference values of biomarkers were CRP up to 1 mg/l, MCP-1 0.228–0.475 ng/ml, endothelin-1 0.3–0.5 ng/ml, eNOS y < 450 units VEGF 101–409 pg/ml, S100B protein 29–56.5 μg/l, CECs 2–4 cells/100 μl, von Willebrand factor < 4 cu, and fibrinogen 2–4 g/l.

The study included a total of 262 patients between 44 and 60 years of age (mean age 54.2 ± 7) with cerebral microangiopathy and depression. Among patients there were 110 (42.1%) men (mean age 50.8 ± 6.3) and 152 (57.9%) women (mean age 57.4 ± 8.1). One hundred ninety-eight (75.6%) patients had grade 1 arterial hypertension, 64 (24.4%) had grade 2 arterial hypertension, 152 (58%) had type 2 diabetes mellitus, and 169 (64.5%) had obesity (BMI > 30 kg/m^2). The severity of depression on the HADS hospital scale was 12.84 ± 5.67 points.

The sociodemographic and clinical characteristics of patients are presented in **Table 1**.

The initial patient sample (n = 262) was divided into two groups: a group with clinically significant depression (≥11 points on the HADS scale) (n = 146) and a group with subclinically significant depression (8–10 points on the HADS scale) (n = 116). At the time of inclusion in the study, no statistically significant differences between groups by sociodemographic characteristics were identified.

A comparative analysis revealed that in the group of patients with clinically significant depression (n = 146), the CRP level was 6.11 mg/l, which was statistically different from the group of patients with subclinical depression (n = 116) where CRP was 2.03 mg/L ($p < 0.05$). The level of MCP-1 in the group of patients with clinically significant depression (n = 146) was 2.02 ng/ml, while in the group of patients with subclinical depression (n = 116), it was 0.66 ng/ml ($p < 0.05$).

After a correlation analysis, the presence of a statistically significant direct linear association between the severity of depression and the level of CRP (correlation coefficient r = 0.85, $p < 0.05$) as well as between the severity of depression and the level of MCP-1 (r = 0.8, $p < 0.05$) was shown.

It was revealed that elevated values of peripheral markers of endothelial inflammation are associated with clinically significant depression. The results are presented in **Table 2**. A reliable association was determined between inflammation and depression ($p < 0.001$), which remained significant after adjusting for risk factors for CVD.

Parameter	Main group (n=262)
Mean age, years:*	54,2±7
Sex, %	
Men	42,1
Women	57,9
BMI, %	
>30 kg/m^2	64,5
≤30 kg/m^2	35,5
Comorbidities, %	
Arterial hypertension I/II grade	75,6/24,4
Type 2 diabetes mellitus	58,0
The mean HADS score :*	12,84±5,67

*Note:*data shown as M±SD; BMI – Body Mass Index, HADS – Hospital Anxiety and Depression Scale*

Table 1.
Baseline clinical characteristics of patients.

After 12 weeks of treatment with Divaza, we observed a statistically significant change in the values of peripheral inflammatory markers toward the reference values: before treatment, the mean CRP value was 9.25 ± 3.5 mg/l, and after treatment it was 7.73 ± 3.12 mg/l ($p < 0.01$); before treatment the average value of MCP-1 was 2.81 ± 1.3 ng/ml, and after treatment it became 1.9 ± 1.2 ng/ml ($p < 0.01$).

Depending on the individual dynamics of peripheral inflammatory marker values, all patients (n = 262) were divided into two groups: with positive (n = 176) and with negative (n = 45) dynamics. The values of peripheral markers of endothelial inflammation in the groups before and after treatment are presented in **Table 3**.

Normalization of peripheral inflammatory and endothelial dysfunction markers led to psycho-emotional status improvement in patients (**Table 4**).

The results show that the reduction of inflammation was accompanied by a decrease in the severity of depressive symptoms, which, in turn, confirms the association between inflammation and depression.

Markers	OR*	95% CI	p	OR**	95% CI	p
CRP	4,17	1,18-14,7	0,001	1,5	1,3-1,8	0,001
MCP-1	4,67	1,99-10,97	0,001	1,67	0,63-2,86	0,001

*Note: # corrected for age, type 2 diabetes, obesity * excluding adjustment for age, diabetes mellitus, obesity; ** adjusted for age, diabetes mellitus, obesity; CRP – C-reactive Protein, MCP-1 – Monocyte Chemoattractant Protein 1; OR– Odds Ratio, CI – Confidence Interval*

Table 2.
Association between peripheral markers of endothelial inflammation and depression#.

Markers	Baseline		After Divaza treatment	
	Group with individual positive dynamics of endothelial inflammation marker values (n=176)	Group with individual negative dynamics of endothelial inflammation marker values (n=45)	Group with individual positive dynamics of endothelial inflammation marker values (n=176)	Group with individual negative dynamics of endothelial inflammation marker values (n=45)
CRP, mg/l	4,1±1,8	6,8±3,2	3,75±1,5*	5,2±2,7*
MCP-1, ng/ml	1,02±0,53	2,03±0,97	0,55±0,28*	1,5±0,63*

*Note:Data shown as M±SD;*p<0.05 between the groups before and after treatment, CRP – C-reactive Protein, MCP-1 – Monocyte Chemoattractant Protein 1*

Table 3.
Peripheral markers of endothelial inflammation level before and after treatment with Divaza.

The severity of depression before and after Divaza treatment

Baseline		After Divaza treatment	
Group with individual positive dynamics of endothelial inflammation marker values (n=176)	Group with individual negative dynamics of endothelial inflammation marker values (n=45)	Group with individual positive dynamics of endothelial inflammation marker values (n=176)	Group with individual negative dynamics of endothelial inflammation marker values (n=45)
13,7±6,8	12,85±6,3	8,12±4,1*	11,6±5,7

*Note:*p<0.05 between the groups before and after treatment*

Table 4.
The severity of depression before and after Divaza treatment.

To assess the possible involvement of other endothelial mediators in the development of depression in patients with cerebral microangiopathy, an integrative endothelial dysfunction index was calculated.

In factor analysis the most significant variables involved in the formation of the integrative endothelial dysfunction index were identified. The levels of laboratory markers of ED with evidence or possible role in the development of endothelial dysfunction, CRP, MCP-1, VEGF, fibrinogen, Willebrand factor, S100 protein, CECs, eNOS activity, and endothelin-1, were considered as variables.

CRP, MCP-1, endothelin-1, CECs, and fibrinogen levels statistically significantly formed one active factor—the integrative endothelial dysfunction index.

Using group of patients who had all laboratory values of ED within the reference range (n = 41), we defined an average value of the integrative endothelial dysfunction index equal to 1.32 ± 0.38 conv. units as the age norm.

Comparative analysis of the integrative endothelial dysfunction index values revealed its statistically significant increase in the group of patients with clinically significant depression (0.12 ± 0.04 conv. units) compared with the group of patients with subclinical depression (1.14 ± 0.3 conv. units) ($p < 0.05$).

A correlation analysis identified the presence of an inverse statistically significant correlation between the integrative endothelial dysfunction index and severity of depression ($r = -0.83$; $p < 0.05$).

When evaluating associations, we found that the integrative endothelial dysfunction index is associated with clinically significant depression (OR 1.36, 95% CI 1.23–1.45). The data are presented in **Table 5**.

The main hypothesis of this study was that in middle-aged patients with cerebral microangiopathy, the presence of depression is associated with modified levels of both peripheral inflammatory and endothelial dysfunction markers. To the best of our knowledge, patients with clinically significant depression were more likely to have elevated values of peripheral markers associated with endothelial inflammation and modified levels of ED markers compared with patients with subclinical depression ($p < 0.05$).

When studying the correlation between the severity of depression and elevated values of peripheral markers of inflammation, as well as altered levels of markers of ED, a significant correlation was found; furthermore there were no association with age, obesity, and diabetes mellitus ($p < 0.001$).

The concomitant administration of drugs aimed to correcting the main risk factors of CVD with Divaza helped to normalize the levels of peripheral inflammatory markers ($p < 0.05$), which was accompanied by the reduction of depressive symptoms in middle-aged patients with cerebral microangiopathy.

Integrative endothelial dysfunction index#					
OR*	**95% CI**	**p**	**OR ****	**95% CI**	**p**
1,91	1,55-2,36	0,001	1,36	1,23-1,45	0,001

Note: # adjusted for age, type 2 diabetes, obesity; * excluding adjustment for age, diabetes mellitus, obesity; ** adjusted for age, diabetes mellitus, obesity; CRP – C-reactive Protein, MCP-1 – Monocyte Chemoattractant Protein 1; OR– Odds Ratio, CI – Confidence Interval

Table 5.
Integrative endothelial dysfunction index#.

The study revealed the association between abnormal levels of peripheral markers of inflammation, markers of ED, and the severity of depression in middle-aged patients with cerebral microangiopathy accompanied by arterial hypertension and cerebral atherosclerosis. Drug therapy of endothelial dysfunction contributed to the normalization of the emotional status in these patients.

Inflammation can be considered as a causative agent of the development of depression, which is associated with the brain vascular network damage. Damage of the endothelium stimulates the release of pro-inflammatory cytokines, which play a leading role in the deposition of lipids in the arterial wall and proliferation and migration of smooth myocytes into the intima of the blood vessels, causing thrombus formation followed by occlusion of the blood vessels.

Previous studies showed that patients with severe types of depression had elevated levels of peripheral inflammatory markers compared with patients without depression [54]. In particular, a major depressive disorder is accompanied by the dysregulation of the immune system with activation of the factors participating in the inflammatory response [55]. An increase in the secretion of pro-inflammatory cytokines (IL-1β, IL-2, IL-6, Interferon-gamma, TNF-α, etc.) and CRP has been demonstrated [56]. Our results further indicate the dependence of the level of depression on the levels of inflammatory markers.

As a possible mechanism of the association between peripheral inflammatory markers and depression, the involvement of microglia, which is able to use pro-inflammatory cytokines as catalysts for tryptophan degradation, was considered. Alteration of tryptophan metabolism can cause depressive symptoms by reducing serotonin synthesis [57].

IL-6 is a potent stimulator of the hypothalamic-pituitary-adrenal axis and induces the release of other pro-inflammatory cytokines [58]. These observations led Leonard B.E. to the conclusion that depression is a disease of inflammation in response to chronic psychological stress. The author considered stress as a common denominator in the etiopathology of cerebrovascular diseases, cardiovascular diseases, and depression [59].

CRP is a protein of the acute phase of inflammation that is activated by pro-inflammatory cytokines (e.g., IL-6) [60]. CRP is usually studied in the context of vascular medicine; however, elevated CRP levels are a risk factor for atherosclerosis and cardiovascular diseases. Therefore, the relationship between CRP and cardiovascular diseases was beyond the scope of cardiology. In recent decades, CRP has become a central element for psychiatric research, especially in the area of depression. Depressed patients have been shown to exhibit significantly higher levels of CRP compared to patients in the control group [61].

Wium-Andersen et al. demonstrated an association between CRP levels and psychological stress in 73,131 Copenhagen residents. After adjusting for age, gender, smoking, physical activity, and chronic somatic diseases, it was noted that elevated levels of CRP correlated with depression [62].

The meta-analysis performed by Howren et al. summarizes data from studies on participants with elevated level of inflammatory markers (CRP, IL-1, IL-6) and depression, taking into account the BMI. Researchers concluded that there are associations between high CRP level and depression after adjusting for BMI [63]. This suggests that the relationship between CRP and depressive disorders does not depend on BMI. In our study, similar results were obtained: an association was found between the level of CRP and depression—OR 4.17 (95% CI 1.18–14.7, $p < 0.001$), which persisted after adjustment for age, obesity, and diabetes mellitus —OR 1.5 (95% CI 1.3–1.8, $p < 0.001$). These facts demonstrate the independent

character of the mutual effects between the activity of the inflammatory processes and the level of depression.

Despite this, many hypotheses have been proposed regarding the association of elevated CRP values with depression using various covariates that can affect these relationships: from BMI and general physical health to the type of depression, which makes it likely that there is a multifactorial and bi-directional relationship between depression and inflammation [64].

Frasure-Smith et al. demonstrated that the association between CRP level and depression is important for predicting future adverse cardiovascular events [65]. There is a lot of evidence in the scientific literature about significant and sustained elevations of CRP level in depressed patients, which may or may not normalize after remission of depression symptoms, indicating a continued possibility of adverse cardiovascular events even after recovery from depression [66].

In 2015, the results of Setiawan E. et al. were published, where authors concluded that depression causes inflammation. The researchers obtained the first nonexperimental evidence that besides neurons, glial cells, namely, microglia, play an important role in depressive disorders [67]. However, despite these findings, it is difficult to conclude that depressive disorders are a trigger of inflammation. It is possible that stress and other risk factors lead to depressive disorders that affect the activation of microglia and a change in its structure, in turn, increasing the level of depression, i.e., it may be a continuum. The data obtained in the present study on the reduction of the level of depression ($p < 0.05$) accompanied by a decrease in the inflammatory activity of the endothelium with the help of a therapy that does not have an antidepressant effect also suggest the two-sided associations between inflammation and depression.

ED is a vascular phenotype that predisposes to atheromatosis and atherosclerosis and, therefore, may be a predictor of cardiovascular events [68].

Endothelial dysfunction can lead to immunological changes, activation, adhesion of white blood cells, and aggregation of platelets in the vascular damage area. The attachment of monocytes and lymphocytes to endothelial cells is associated with the activation of cell adhesion molecules [69]. Chronic mild inflammation is known as a predictor of myocardial infarction and ischemic stroke. ED is a "critical intermediate phenotype" in the association between mild inflammation and CVD. ED can be considered as an "intermediate phenotype" in depression based on the presence of mild chronic inflammation in many patients with depressive symptoms [70]. Depression can be regarded as a chronic stressor that contributes to the development of ED due to the disruption of cell adhesion, platelet hypercoagulation. Depression is associated with higher levels of MCP-1, p-selectin, and others. Some researchers consider ED as a biomarker of arterial atheromatosis, which can be a sign of depression [71]. The present study has shown that there are strong associations between inflammatory markers and markers of proatherogenic activity (endothelin-1, CECs, and fibrinogen). Based on the values of CRP, MCP-1, endothelin-1, CECs, and fibrinogen, an integrative indicator of endothelial dysfunction had higher values in patients with clinically significant depression, compared with patients with subclinical depression ($p < 0.01$). An inverse statistically significant correlation was found between the integrative endothelial dysfunction index and severity of depression ($r = -0.83$; $p < 0.05$). Moreover, this association between the integrative endothelial dysfunction index and depression did not depend on age, type 2 diabetes mellitus, and obesity ($p < 0.001$)—the risk factors known to raise the incidence of CVD.

Do et al. focused on the association of individual symptoms of depression (a symptom of hopelessness that can turn into suicidality) with markers of ED.

The researchers concluded that negative psychosocial features which can affect cardiovascular diseases in part through their impact on the early stages of atherosclerosis, as well as specific psychosocial features such as hopelessness, may play a more significant role in this process than other depressive symptoms [72].

Thus, ED is a crucial factor in the bilateral relationship between depression, chronic inflammation, and cardiovascular diseases [73].

3. Conclusions

Despite growing evidence that underlines the bilateral relationship between depression and CVD and the fact that the mechanisms of their connection were partially identified (e.g., inflammation, ED), further research with a large sample size is required.

Novel pharmacological approaches based on discoveries related to the immune and neurotransmitter systems are in high demand.

The development and implementation of preventive measures and lifestyle correction, which can reduce the burden of cerebrovascular diseases and depression, are required as well.

Conflict of interest

The studies of the combination of released-active form of antibodies to S100 protein and released-active form of antibodies to endothelial NO synthase, mentioned in this review, were funded by a grant from OOO "NPF 'MATERIA MEDICA HOLDING'." Fateeva V.V., Nikulina K.V., Khacheva K.K., Khakimova G.R. and Epstein O.I. are employees and a founder of the OOO "NPF 'MATERIA MEDICA HOLDING'," respectively. Divaza is a preparation manufactured and marked by OOO "NPF 'MATERIA MEDICA HOLDING'." Patents on Divaza belong to Epstein O.I. Vorob'eva O.V. received an investigator grant from OOO "NPF 'MATERIA MEDICA HOLDING'" to conduct the clinical trials of Divaza, mentioned in this review.

Abbreviations

CVD	cardiovascular diseases
CRP	C-reactive protein
TNF-α	tumor necrosis factor alpha
IL	interleukin
GABA	gamma-aminobutyric acid
ED	endothelial dysfunction
HADS	hospital anxiety and depression scale
RA	release-activity
RAF of Abs to S100	release-active form of antibodies to S100B
RAF of Abs to eNOS	release-active form of antibodies to endothelial NO synthase
BMI	body mass index
ELISA	enzyme-linked immunosorbent assay
MCP-1	monocyte chemoattractant protein-1
CEC	circulating endothelial cells

Appendix

Drug	Studied activity	Test system	Results	Ref
Pharmacodynamics				
RAF of Abs to S100	Neuroprotective activity	Mouse neuroblastoma C-1300 cells deprived of glucose and O2	RAF of Abs to S100 added to the incubation medium accurately before or 20 h before the hypoxia induction increased the number of survived cells by 1.8- and 2.1-times, respectively	[33]
	Antidepressive activity	Adult outbred male albino rats	RAF of Abs to S100 increased the number of the wheel turns in Nomura forced swimming test by 1.8-2.2-times	[34, 35, 36]
			RAF of Abs to S100 decreased the duration of immobility in Porsolt forced swimming test by 1.6-times	[35]
	Anxiolytic activity	Adult outbred male albino rats	RAF of Abs to S100 increased the number of punished water intakes in Vogel conflict test by 1.4-3.2-times	[34, 36, 37, 38, 39]
			RAF of Abs to S100 increased the number of entries into open arms of EPM, the time spent in open arms and the number of leanings over the edge of the maze by 1.9-, 5.4- and 4.9-times, respectively	[34, 39]
			RAF of Abs to S100 increased the number of entries into the center of the open field up to 2.4±0.7 vs 0±0 in control group	[34, 39]
		Adult Rj:Wistar (Han) male rats	RAF of Abs to S100 increased the number of punished water intakes in Vogel conflict test by 1.5-times	[38]
RAF of Abs to eNOS	Endothelio-protective activity	Adult Wistar male rats with NO deficiency, induced by L-NAME	RAF of Abs to eNOS reduced arterial blood pressure (184.3±7.0 mm Hg vs 190.3±6.7 mm Hg in L-NAME-group) and the exhaustion of myocardial fractional flow reserve by 11%	[40]
		Adult Wistar male rats with NO deficiency, induced by L-NAME	RAF of Abs to eNOS improved microcirculation in the ischemic area, stimulated neoangiogenesis and promoted recruitment of additional capillaries into general circulation; RAF of Abs to eNOS improved the metabolism of endothelial capillaries and significantly	[41]

Drug	Studied activity	Test system	Results	Ref
			decreased the number of desquamated endotheliocytes that was the unique morphological criteria for endothelium damage degree	
		Adult Wistar male rats with hypoestrogen-induced NO deficiency	RAF of Abs to eNOS reduced arterial blood pressure (158.5±15.0 mm Hg vs 160.0±6.2 mm Hg in control group) and the exhaustion of myocardial fractional flow reserve by 26.9%	[40]
	Antidepressive activity	Adult outbred male rats	RAF of Abs to eNOS increased the number of punished water intakes in Vogel conflict test by 1.6-times	[42]
	Anxiolytic activity	Adult outbred male rats	RAF of Abs to eNOS increased the number of entries into open arms of EPM and time spent in open arms up to 1.50±0.71 and 34.4 8.50 s (vs 0±0 in control group for both parameters), respectively	[42]
	Influence on the cardiovascular system	Hypertensive adult ISIAH male rats	RAF of Abs to eNOS reduced arterial blood pressure by 5.7%	[43]
		Normotensive adult Wistar male rats	RAF of Abs to eNOS did not affect systemic hemodynamics, did not augment nitroglycerine effects	[44]
Divaza	Endothelio-protective activity	Thoracic aorta rings of adult male SHR rats	Divaza improved acetylcholine-induced relaxation of aorta vascular smooth muscle by 1.4-times	Un-published data
	Neuroprotective (antioxidant) activity	Adult outbred male rats with experimental acute hemic hypoxia	Divaza decreased the content of diene conjugates in the cerebral hemispheres by 9.7-27.8% in the heptane fraction and by 7.5-47.4% in isopropanol fraction. The accumulation of 2-thiobarbituric acid-reactive products was reduced by 20.1-27.5%	[45]
	Neurotropic activity (neurite outgrowth)	Brain cortex neurites of rat fetuses (gestational day 17) without any branching	Divaza increased the value of neurite outgrowth by 9.6%	Un-published data
	Anti-amnestic activity	Adult Wistar male rats with β-amyloid-induced amnesia	Divaza increased the latency of the entry into the dark compartment of CPAR experimental chamber by 3-times	[46]
	Antidepressive activity	Adult outbred male rats	Divaza increased the number of the wheel turns in Nomura	[47]

Drug	Studied activity	Test system	Results	Ref
			forced swimming test by 1.8-times	
	Anxiolytic activity	Adult outbred male rats	Divaza increased the number of punished water intakes in Vogel conflict test by 2.5-times	[47]
Mechanisms of action				
RAF of Abs to S100	Influence on Abs to S100 activity (ability to induce LTP)	Hippocampal slices (400 μm) of mature Wistar rats	Abs to S100 inhibited the induction of LPT, whereas RAF of Abs to S100 offset this inhibiting activity	[48]
	Influence on electrical properties of cell membranes	Isolated neurons of Helix pomatia	RAF of Abs to S100 suppressed generation of action potential in a dose-dependent manner and increased the maximal speed of its growth via changing the volt-ampere characteristics of the incoming current channels	[49]
	Involvement of GABAA-ergic system in the realization of RAF of Abs to S100 effects	Adult outbred male albino rats	Bicuculline and picrotoxin (GABAA-receptors antagonists) decreased the anxiolytic effect of RAF of Abs to S100 in Vogel conflict test by 1.8- and 1.6-times, respectively	[37]
	Involvement of GABAB-ergic system in the realization of RAF of Abs to S100 effects	Adult outbred male rats	Baclofen (GABAB-receptors agonist) decreased the anxiolytic effect of RAF of Abs to S100 in Vogel conflict test by 2.2-times, whereas phaclofen (GABAB-receptors antagonist) increased it by 1.4-times; both baclofen and phaclofen decreased antidepressive effect of RAF of Abs to S100 in Nomura's forced swimming test by 1.5- and 1.7-times, respectively	[50]
		CHO cells expressing human GABA receptors	RAF of Abs to S100 exerted antagonism at GABAB1A/B2-receptors inhibiting agonist-induced responses by 30.2% and also inhibited specific binding of ([3,4-3H]-cyclohexylmethyl)phosphinic acid ([3H]-CGP54626) to GABAB1A/B2-receptors by 25.8%	[51]
	Involvement of serotonergic system in the realization of RAF of Abs to S100 effects	Adult outbred male rats	Ketanserin (5-HT2 receptors antagonist) decreased both the anxiolytic effect of RAF of Abs to S100 in Vogel conflict test and antidepressive effect of RAF of Abs to S100 in Nomura forced swimming test by 1.9- and 2-times, respectively	[36]

Drug	Studied activity	Test system	Results	Ref
		CHO and CHO-K1 cells	RAF of Abs to S100 increased specific radioligands binding to 5-HT1F-, 5-HT2B-, 5-HT2Cedied- and 5-HT3-receptors by 142.0%, 131.9%, 149.3% and 120.7%, respectively; also RAF of Abs to S100 exerted antagonist effect at 5-HT1B-receptors inhibiting their functional activity by 23.2% and agonist effect at 5-HT1A-receptors enhancing their functional activity by 28.0%	[51]
	Involvement of dopaminergic system in the realization of RAF of Abs to S100 effects	CHO and CHO-K1 cells	RAF of Abs to S100 increased specific radioligand binding to D3-receptors by 126.3% and exerted antagonism at D3-receptors inhibiting their functional activity by 32.8%	[51]
	Involvement of glutamatergic system in the realization of RAF of Abs to S100 effects	Rat brain cortex neuronal cells	RAF of Abs to S100 decreased specific radioligand binding to NMDA-receptors by 39.1%	[52]
	Involvement of σ1-receptor in the realization of RAF of Abs to S100 effects	Human leukemic T-cell line (Jurkat); human breast cancer cell line (MCF-7)	RAF of Abs to S100 decreased specific radioligand binding to native and recombinant human σ1-receptors by 75.3% and 40.3%, respectively	[51]
RAF of Abs to eNOS	Effects on vascular endothelial function	Cavernous bodies of adult Wistar male rats	RAF of Abs to eNOS increased eNOS activity, the content of NO derivates and the content of cGMP by 2.4-, 1.3- and 4-times, respectively	[53]
Divaza	Involvement of σ1-receptor in the realization of Divaza effects	Segments of vas deferens of male albino Dunkin-Hartley guinea-pigs	Divaza increased the amplitude of tissue contraction induced by standard agonist by 2-times	[54]

Notes: ** - adapted from [73], CPAR - conditioned passive avoidance reflex, EPM - elevated plus maze, LPT - long-term potentiation.*

Appendix 1.
Experimental studies of pharmacological activity and mechanisms of action of RAF of Abs to S100, RAF of Abs to eNOS and combination drug Divaza.

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