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Original

Study of the effects of vinpocetine on indicators of acid-alkaline state followıng the ischemic brain damage

Estudo dos efeitos da vimpocetına em indicadores de estado ácido-alcalino após dano cerebral isquêmico

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ABSTRACT

Vinpocetine is a multipurpose medicine with several pharmacological targets. It is known for its neuroprotective properties. Its mechanism of action in brain pathology is due to a selective inhibitor of phosphodiesterase type 1, inhibition of voltage-gated sodium channels, and a decrease in calcium influx into neurons. Vinpocetine combines high clinical efficacy and safety of use. Therefore it successfully competes in the pharmaceutical market with an ever-increasing number of new medicines. The purpose of the work was to experimentally study the effects of vinpocetine in cats at a dose of 5 mg/kg on the indicators of the acid-base state (ABS) of arterial and venous blood in the simulation of total cerebral ischemia. The effect of vinpocetine on acid-base status indicators should be considered as the most important aspect of its action, contributing to the neuroprotective effect. The paper discusses possible molecular targets and mechanisms for implementing the protective effect of vinpocetine in ischemia, considering its favorable effect on ABS. These new findings may point to increased use of vinpocetine in human cardiovascular diseases accompanied by ABS deterioration.

Keywords: vinpocetine, cerebral ischemia, reperfusion, acid-base state, carbon dioxide tension.

RESUMO

Vimpocetina é um medicamento multiuso com vários alvos farmacológicos, conhecido por suas propriedades neuroprotetoras. Seu mecanismo de ação na patologia cerebral envolve inibição seletiva da fosfodiesterase tipo 1, inibição dos canais de sódio dependentes de voltagem e diminuição do influxo de cálcio nos neurônios. A vimpocetina combina alta eficácia clínica e segurança de uso.

Portanto, compete com sucesso no mercado farmacêutico com um número cada vez maior de novos medicamentos. O objetivo do trabalho foi estudar experimentalmente os efeitos da vimpocetina na dose de 5 mg/kg sobre os indicadores do estado ácido-base (ABS) do sangue arterial e venoso na simulação de isquemia cerebral total em gatos. O efeito da vimpocetina nos indicadores do estado ácido-base deve ser considerado como o aspecto mais importante de sua ação, contribuindo para o efeito neuroprotetor. O artigo discute possíveis alvos moleculares e mecanismos para implementar o efeito protetor da vimpocetina na isquemia, considerando seu efeito favorável no ABS. Essas novas descobertas podem apontar para o aumento do uso de vimpocetina em doenças cardiovasculares humanas acompanhadas de deterioração do ABS.

Palavras-chave: vimpocetina, isquemia cerebral, reperfusão, estado ácido-base, tensão de dióxido de carbono.

INTRODUCTION

Ischemic stroke is characterized by high morbidity and mortality and seriously affects patients' quality of life (1). Timely restoration of blood supply and oxygen supply to ischemic brain tissue is essential for the survival of patients with ischemic penumbra (2). Thrombolytic therapy is the best treatment option for ischemic stroke (3). However, reperfusion exacerbates damage and provokes dysfunction through a cascade of events, such as calcium overload, excitotoxicity, oxidative stress, inflammatory responses, and apoptosis, collectively referred to as "ischemia-reperfusion injury" (4).

The search for effective medicines for treating ischemic brain damage is an urgent task of modern science. The prospects for using taurine (5,6), resveratrol (7), and glycine (8) as neuroprotectors are shown. In the same way, Mn(III)tetrakis(1-methyl-4-pyridyl)porphyrin pentachloride (9), melatonin (7), hydroxymethylethylpyridine succinate, nicotinoyl gamma-aminobutyric acid, nimodipine, amlodipine besylate and S-amlodipine nicotinate (10), apovincaminic acid derivative (11), glutamic acid (12), magnesium sulfate (13), as well as herbal remedies - *Rhodiola rosea* (14), *Astragalus membranous* (7) and preparations of animal origin - cortexin, cerebrolysin, actovegin (15) and other compounds. Despite the search for new neuroprotective agents, vinpocetine is also the subject of numerous experimental and clinical studies, due not only to the high efficiency of this tool but the safety of its use (16,17).

Vinpocetine was synthesized over 50 years ago and registered under the commercial name Cavinton (Gedeon Richter) in 1978. The drug is a semi-synthetic derivative of the vincamine alkaloid from periwinkle plant (*Vinca minor* L. and *Vinca erecta* Rgl. et Schmalth), Apocynaceae. Vinpocetine is currently widely used in clinical practice in 47 countries around the world. Vinpocetine is widely used to treat various cerebrovascular disorders, cognitive dysfunction, memory impairment, tinnitus, macular degeneration, and glaucoma. In many countries, vinpocetine is widely available in nootropic nutritional supplements (18).

Recent studies have revealed new actions of vinpocetine in cardiovascular diseases, including atherosclerosis, obesity, neointimal hyperplasia, pathological cardiac remodeling, and ischemic stroke (19,20). Vinpocetine in chronic cerebral ischemia has an endothelium-protective effect, manifested in the partial restoration of endothelium-dependent vasodilation and inhibition of von Willebrand factor rejection during an arteriovenous occlusive test. Leveling of the neurological deficit with vinpocetine depends on the degree of recovery in a patient with endothelium-dependent vasodilation (21).

It is believed that the effectiveness of vinpocetine in the pathology of the central nervous system (CNS) is mediated by several mechanisms. The effect of vinpocetine on blood vessels is due to its effect on the metabolism of cyclic nucleotides in the smooth muscle cells

of the vascular wall by inhibiting Ca^{2+}/calmodulin-dependent type 1 phosphodiesterase (22). This effect leads to the prevalence of cAMP over cGMP, which contributes to the relaxation of cerebral vessels, reduces platelet aggregation and blood viscosity, and normalizes the deformability of erythrocytes. Vinpocetine selectively increases cerebral blood flow (20) and reduces cerebral vascular tone but has little effect on systemic circulation. A feature of the impact of vinpocetine on cerebral circulation is that it does not cause the phenomenon of "stealing"; on the contrary, it improves the blood supply to the affected area, and the blood flow in the intact area of the brain remains unchanged (23). It has been established that the anti-hypoxic effects of vinpocetine correlate with the protective effects observed in animal models of cerebral ischemia and with the therapeutic effects in patients with impaired cerebral blood flow (24).

Vinpocetine in patients with ischemic stroke (IS) has a protective effect on glial and astrocytic cells (25). It is known that astrocytes play an important role in maintaining brain function under physiological conditions and influencing the survival of neurons in pathological conditions, including ischemia-reperfusion and other brain lesions. It was found that during ischemic stroke, astrocytes can be activated, produce and release reactive oxygen species (ROS), pro-inflammatory cytokines and other factors that can adversely affect the survival of neurons in penumbra (26).

Ischemic and reperfusion brain injury can involve both astrocytes and microglia, which can produce inflammatory cytokines and other toxic mediators (4). It has been established that microglial TLR4/MyD88/NF-κB is one of the mechanisms of the neuroprotective action of vinpocetine in ischemic and reperfusion brain injuries (27). In addition, vinpocetine has a pronounced antioxidant, anti-inflammatory and anti-apoptotic effect. The antioxidant effect of the medicine is manifested due to a decrease in the activity of lipid peroxidation (LPO) in synaptosomes (28,29). Inhibition of voltage-dependent sodium channels while taking vinpocetine under experimental conditions leads to a slowdown in sodium accumulation in the cell, thereby reducing the toxic effect of oxidative stress during anoxia and damage during reperfusion (23). Under conditions of experimental ischemia, vinpocetine reduced the size of the focus of necrosis of the nervous tissue by 42% (30) by blocking NMDA receptors and reducing the entry of Ca^{2+} ions into the cell (31). In addition to the vascular and neuroprotective effect, vinpocetine affects the brain's neurotransmitter systems, enhancing the intracerebral metabolism of norepinephrine and serotonin (32). Improvements in psychomotor functions during the use of vinpocetine are associated with its effect on the level of dopamine and serotonin in the central nervous system. The restoration of cognitive functions and spatial memory is due to the inhibition of hippocampal and cortical PDE-1 with an increase in the cAMP/cGMP ratio, increased cholinergic neurotransmission and inhibition neuronal inflammatory mediators (23).

In humans, vinpocetine is rapidly orally absorbed and undergoes extensive first-pass metabolism, during which most of the substance is hydrolyzed to its active metabolite, cis-apovinacamic acid. Neuroprotective effects of vinpocetine and its main metabolite, cis-apovinacamic acid, on NMDA-induced neurotoxicity in a rat entorhinal cortex lesion model (33).

Earlier, in the Pyatigorsk Medical and Pharmaceutical Institute laboratory, a study was made on the effect of vinpocetine and its derivatives on the exchange of oxygen and glucose in the simulation of acute cerebral ischemia in cats. It has been revealed that using vinpocetine leads to a decrease in postischemic hyperglycemia, activation of oxygen utilization in the brain, and suppression of postischemic metabolic lactic acidosis (34). Despite the great attention of scientists to vinpocetine, its effect on the processes of acid-base balance in the postischemic period is an unexplored aspect. At the same time, it is well known that CO_2 serves as one of the main regulators of cerebral blood flow (CBF) (35). This regulation is believed to occur through pCO_2-driven changes in cerebrospinal fluid (CSF) pH, with elevated and decreased pH causing direct re-

laxation and contraction of smooth muscle, respectively. However, there is evidence that pCO_2 acts independently of and/or in combination with changes in pH. This action may be due to the direct effect of cerebrospinal fluid pCO_2 on smooth muscle, as well as endothelium, nerves, and astrocytes. In connection with the special role of ABS indicators in regulating cerebral circulation, we studied the effect of vinpocetine on acid-base balance in the postischemic period.

Therefore, the purpose of this work was to study the effect of vinpocetine on blood ABS parameters in the post-ischemic period. The objectives of the work were to study changes in acid-base balance in animals that underwent acute cerebral ischemia followed by reperfusion without pharmacological correction (control group) and animals that received vinpocetine (experimental group), followed by an analysis of the effectiveness of the medicine and a discussion of possible mechanisms of its action from modern positions on the maintenance of ABS in CNS pathology.

METHOD

The experiments were carried out on cats weighing 3.0-3.5 kg under conditions of brain auto-hemoperfusion with a stable blood volume.

The study protocol was approved by the Independent Ethics Committee (IEC) of the Pyatigorsk Medical and Pharmaceutical Institute, a branch of the Volgograd State Medical University under code number 7, and all ethical issues on the use of animals were followed.

The animals were kept under vivarium conditions in a natural light regime on standard food with free access to water and food. The experiments were carried out following international ethical standards. Urethane (500 mg/kg) and chloralose (50 mg/kg) were used for anesthesia; blood coagulation was prevented by the administration of heparin (500 units/kg). Using an anesthetic in our experience allowed us to effectively suppress sensory, emotional, vegetative, and motor reactions in cats.

Cerebral ischemia was modeled by bilateral occlusion of the carotid arteries for 15 minutes against the background of systemic arterial hypotension up to 40 mmHg. (36). In blood micro-samples 15, 60. and 120 min after acute cerebral ischemia, pH and pCO_2 in arterial and venous blood were determined using a "Radelkis" micro-analyzer. Calculation of standard bicarbonate (SB), the sum of buffer bases (BB), and the shift (excess or deficit) of buffer bases (BE) was performed according to the Siggaard-Andersen nomogram. Arterial blood was taken from the common carotid artery; venous blood was taken from the sagittal sinus (37).

The experiments were carried out on 2 groups of animals (6 animals in each group): the control group - animals that were injected with physiological saline and experimental groups - animals that were injected therapeutically (immediately after ischemia) with vinpocetine (5 mg/kg) in a volume of 0.5 mL/kg of body weight of the animal. The control group of animals was injected with an equivalent volume of the solvent (0.9% sodium chloride solution). Vinpocetine (Cavinton) solution manufactured by Gedeon richter (Hungary) was used in the experiments. Statistical processing of the results was carried out within the series according to the Student's t-test, between the series - according to the Wilcoxon-Mann-Whitney inversion test (38).

RESULTS AND DISCUSSION

Indicators of acid-base balance of laboratory animals before modeling cerebral ischemia corresponded to the physiological norm (Table 1). The resumption of blood flow in the ischemic brain in animals without pharmacological correction (control animals) led to a pronounced decrease in blood pH and pCO_2 (Table 2).

Table 1. Initial indicators of ABS in animals of the control and experimental groups

Animal group	Indicators	Initial data	
		Arterial blood	Venous blood
Control experiments	pH	7,42±0,01	7,37±0,01
	pCO_2 mmHg	34,4±3,7	45,3±4,9
	BB mmol/L	34,8±2,0	37,2±2,1
	BE mmol/L	-3,1±1,7	-2,4±1,7
	SB mmol/L	22,5±2,5	24,4±1,4
Vinpocetine	pH	7,41±0,01	7,35±0,01
	pCO_2 mmHg	36,0±3,7	52,8±6,2
	BB mmol/L	33,5±1,4	38,0±2,0
	BE mmol/L	-2,4±1,2	-2,5±1,4
	SB mmol/L	21,7±1,3	22,6±1,4

The observed active decrease in carbon dioxide in the blood is a compensatory factor aimed at reducing the "acidity" of the blood. It is also important to note that despite the compensatory decrease in pCO_2, the reserve capabilities of the body's buffer systems are exhausted. A sharp decline in blood pH (decompensated acidosis) occurs at 15 minutes of the reperfusion period (Table 2). In animals of the control group, the resumption of blood flow in the ischemic brain led to a pronounced decrease in blood pH, combined with a reduction in pCO_2 (Table 2). The increased removal of carbon dioxide from the blood in the post-ischemic period is a compensatory factor aimed at reducing the "acidity" of the blood. So, in the control series of experiments, immediately after the resumption of blood flow, there is a sharp decrease in the activity of the buffer systems of the body by more than 30% (Table 2). An even more pronounced drop is observed on the side of the carbonate buffer (by more than 40%). Since the decrease in carbonate buffer capacity in the reperfusion period occurs to a greater extent than in general, it can be concluded that hemoglobin plays a leading role in maintaining homeostasis under ischemia

Table 2. Changes in pH and pCO_2 in the postischemic period in control experiments and on the background of vinpocetine

Indicators	Animal group	15 min		60 min		120 min	
		A	B	A	B	A	B
pH	Control	-3,8± 0,14x	-4,1 ±0,01x	-4,0±0,42	-4,0±0,3	-4,1±0,42x	-4,2±0,28x
	Vinpocetine	-2,4 ±0,14x*	-2,3±0,14x*	-1,6±0,30*	-2,3±0,28x*	-1,1±0,14x*	-2,6±0,01*
pCO2	Control	-14,9 ±1,5x	-7,20 ±1,0x	-25,6±4,7x	-13,5±3,2x	-28,5±4,4x	-14,2±2,1x
	Vinpocetine	+1,6 ±1,6*	+22,7±2,9x*	-7,4±1,4x*	+3,9±1,8*	-9,6±2,5x*	+1,8±2,5*

x – P<0,05 compared to baseline. * - P<0,05 compared to control.

The ischemic effect also leads to an increase in the deficiency of all the main components of the blood buffer system (Table 3).

It should also be noted that the BE index during the entire observation period in both arterial and venous blood had similar values. An increase in the deficiency of buffer bases in the postischemic period by more than 300% is associated with a significant increase in excess of "non-volatile" acids in arterial and venous

samples (Table 3). Thus, cerebral ischemia is accompanied by severe ABS disorders, which are of a decompensated metabolic nature. Significant ABS disorders in the brain are observed as early as 15 minutes of reperfusion and persist until the end of the experiment.

Therapeutic administration of vinpocetine effectively limits the development of an imbalance between the basic and acidic components of the blood, prevents a dynamic drop in blood pH (Table 2), stops hyperventilation and limits the depletion of the body's buffer systems (Table 3).

Table 3. Changes in blood ABS parameters (%) in the post-ischemic period in the control series of experiments and on the background of vinpocetine

Animal group	Indicators	15 min		60 min		120 min	
		A	B	A	B	A	B
Control	BB mmol/L	-34,1 ±4,4x	-32,6 ±3,8x	-36,6 ±4,8x	-30,4 ±3,6x	-38,6 ±4,9x	-36,9 ±4,4x
	BE mmol/L	+310,0 ±40,3x	+309,3 ±3,9x	+328,9 ±42,9x	+279,9 ±32,6x	+316 ±37,9x	+299,6 ±39,0x
	SB mmol/L	-40,9 ±5,3x	-44,5 ±5,6x	-41,8 ±5,0x	-38,5 ±5,1x	-40,3 ±5,2x	-41,8 ±4,6x
Vinpocetine	BB mmol/L	-30,2 ±12,4x	-17,1 ±4,1x*	-23,3 ±4,5x*	-15,9± 7,9x	-18,6 ±5,4x	-13,2 ±4,0x*
	BE mmol/L	+42,0 ±14,6x*	+85,7 ±26,4x*	+34,0 ±10,2x*	+85,7 ±18,9x*	+50,0 ±85,2*	+57,1 ±29,1*
	SB mmol/L	-36,4 ±8,7x	-26,3 ±4,9x*	-29,5 ±7,6x	-26,3 ±10,3x*	-25,0 ±7,9x	-18,4 ±6,9x*

ˣ – P<0,05 compared to baseline. * - P<0,05 compared to control.

The effectiveness of vinpocetine correction of ABS disorders in conditions of ischemic and reperfusion brain damage was ascertained already at the 15th minute of observation, when all the studied parameters in the venous sample favorably differed from those in the control (Tables 2 and 3).

The most pronounced differences in ABS parameters in experiments using vinpocetine relative to animals without treatment are noted by the 120th minute of reperfusion: the pH in the venous sample was 7.22±0.01, while in untreated animals did not exceed 7.06±0.02 (Table 2). No less significant differences in the blood flowing from the ischemic zone were also revealed when analyzing the indicators obtained by calculation (according to the Siggaard-Andersen nomogram): the lack of general buffer systems of the body was more than 20% less pronounced, the deficiency of the main blood components was more than 5 times, and the standard buffer - more than 2 times less than in the control series of experiments (Table 3). Similar changes were identified in arterial blood.

Thus, the therapeutic use of vinpocetine effectively limits the disturbance of acid-base balance and, thereby, prevents the development of decompensated metabolic acidosis.

Vinpocetine is a multifunctional drug that regulates many pathophysiological events associated with cardiovascular disease (20). It is widely used in stroke, cerebral atherosclerosis, and chronic cerebral ischemia. Various studies have confirmed its anti-inflammatory and antiplatelet effects on improving cerebral blood flow, brain metabolism, and cognitive function (39). It has been established that one of the mechanisms of its neuroprotective action in ischemia-reperfusion-induced injury is a decrease in the inflammatory response by inhibiting the expression of NF-κB and TNF-α (40). Vinpocetine improves neuronal plasticity and reduces the release of

inflammatory cytokines and chemokines from endothelial cells, vascular smooth muscle cells, macrophages, and microglia by inhibiting the NF-κB pathway (20). However, its protective mechanism during cerebral ischemia/reperfusion requires further study. In this work, we studied the effect of vinpocetine on ABS parameters during cerebral ischemia-reperfusion.

It is known that cerebral ischemia leads to a deficiency of metabolic substrates and oxygen and then to metabolic acidosis. Limited oxygen availability promotes anaerobic glycolysis, which reduces pyruvate to lactate while producing a proton, which causes lactic acidosis (41). In turn, tissue pH decreases after the onset of cerebral ischemia. In addition, pCO2 in tissues increases 3–4 times, contributing to tissue acidosis. The spatial and temporal kinetics of metabolic acidosis dynamically changes as ischemia progresses. It is traditionally believed that acute acidosis in the nervous tissue leads to the formation of free radicals, disruption of mitochondrial respiration, disruption of protein synthesis, disruption of cellular Ca^{2+}-buffering, disruption of intracellular signal transduction pathways, and induction of DNA fragmentation (42). It has been shown that tissue acidosis in cell culture activates cytokine receptors and inflammatory pathways involved in delayed neuronal damage after hypoxia (2). We have previously demonstrated that vinpocetine can limit lactic acidosis in animals in the post-ischemic period (36), which should be considered as one of the mechanisms of its neuroprotective action in ischemic stroke. It is known that the death of neurons in acidosis is associated with specific pH-sensitive ion channels and exchangers and is caused by the accumulation of Ca^{2+} or the formation of cytotoxic edema.

Activation of acid-sensitive ion channel 1a (ASIC1a) is observed with a decrease in extracellular pH. Neuronal ASIC1s under conditions of acidosis promotes an uncontrolled influx of Ca^{2+}, which leads to intracellular overload of Ca^{2+} to initiate ischemic cell death. In addition, NMDA receptor signaling enhances ASIC1a-mediated Ca^{2+} current during ischemia because Ca^{2+}/calmodulin-dependent protein kinase II phosphorylates ASIC1a due to NMDA receptor activation. Further, in acidosis, ASIC1a is involved in programmed necrosis by recruiting the RIPK1 receptor (serine/threonine receptor-interacting protein kinase 1) (2). Taking into account the relationship between the development of acidosis and the activation of NMDA receptors, as well as the fact that Nyakas C, et al. found that vinpocetine causes a decrease in excitotoxicity by blocking NMDA receptors (33), it can be concluded that limitations of acid-base balance with vinpocetine and the presence of an antiglutamatergic effect should be considered as the most important mechanism of the protective effect on the damaged brain under conditions of ischemia-reperfusion.

Numerous studies have established that changes in the cerebrovascular acid-base balance of pCO_2, pH, HCO_3^- directly affect cerebral blood flow (34). The severity of changes in carbon dioxide tension (pCO_2), bicarbonate (HCO_3) and pH cause acid-base compensatory changes and cerebrovascular reactions (due to the rapid kinetics of the exchange between arterial blood, extracellular fluid and intracellular brain tissue). The “pH” index is recognized as the proximal compartment that alters the regulation of CBF by vascular smooth muscle cells. Recent studies indicate that the regulation of cerebral blood flow is affected by the severity of metabolic/respiratory disorders, including the degree of acid-base compensation (partial or complete); and secondly, the regulation of cerebral blood flow is independent of arterial pH and that diffusion of CO_2 across the blood-brain barrier is an integral part of the change in perivascular extracellular pH. In general, by realizing the integrative relationship between CBF, pCO_2, HCO_3^- and pH, experimental studies can provide insight into the improvement of cerebral blood flow regulation in clinical practice in the treatment of systemic acid-base disorders (43). Analyzing the favorable effect of vinpocetine on the tone of cerebral vessels during ischemia-reperfusion, it is necessary to consider its ability to limit ABS disorders, incl. and the ability to increase the concentration of carbon dioxide in the blood. Cerebral blood flow (CBF) is strictly regulated by changes in

arterial pCO_2 and arterial pO_2 (44). It has been experimentally shown that various vasoactive factors, including the release of norepinephrine, endothelin, adrenomedullin, C-natriuretic peptide (CNP), and nitric oxide (NO), may play a role in arterial blood gas-induced changes in CBF. Hypercapnia increases CBF and causes a net cerebral release of nitrite (a marker of NO). The release of cerebral CNP is also seen with changes in CO_2 (43).

It is known that CO_2 modulation of NO release from the endothelium, astrocytes, and neurons may represent additional pathways for the regulation of vascular contractility. Given the special role of pCO_2 in the regulation of vascular contractility through endothelial vasoactive factors, the need to preserve functional endothelium is of particular importance (34).

Analysis of the effect of vinpocetine on changes in pCO_2 in the postischemic period indicates the ability of this drug to limit postischemic hypocapnia. And hypercapnia, which was revealed in experiments with vinpocetine at 15 minutes of reperfusion in a venous sample, should be considered a positive moment, since an increase in the carbon dioxide content in the blood contributes not only to vasodilation but also reduces the rate of oxygen consumption by the brain due to a change in cerebral blood flow (45).

The obtained results of the study indicate that the therapeutic use of vinpocetine contributes to limiting the severity of AB disorders caused by acute cerebral ischemia. This aspect of the action of vinpocetine should be considered one of the valuable aspects of its neuroprotective action.

Vinpocetine has traditionally been considered an effective treatment for ischemic stroke. It is part of a combination of antihypertensive agents and contributes to the limitation of metabolic disorders in animals with comorbidity than combination therapy without vinpocetine (46). An analysis of the literature data and data of our own study indicates that vinpocetine can potentially be used to develop a promising drug for the treatment of ischemic stroke to limit the buildup of the acid-base state (25). It should also be noted that vinpocetine is of particular interest as a neuroprotective agent in patients with diabetes mellitus, a disease that is one of the risk factors for ischemic stroke (47). In addition, this disease is characterized by the development of oxidative stress (48; 49. 50), which can effectively limit vinpocetine (28; 29).

CONCLUSION

Vinpocetine has a long history of use in cerebrovascular disease, including ischemic stroke. In clinical studies, vinpocetine therapy in patients with ischemic stroke was associated with increased cerebral blood flow, improved glucose uptake and parenchymal oxygen utilization, better recovery of neurological function, less growth in infarct lesions, and improved cognitive skills (19).

Indicators "pCO_2" and "pH" can independently and simultaneously regulate the contractility of cerebral vessels. The regulation of vascular tone by pCO_2 can occur through endothelium-dependent mechanisms. Additional sites of action for pCO_2 as well as pH may include neurons and astrocytes (51). It is believed that the underlying regulatory mechanism(s) of pCO_2/pH also varies with vessel type, magnitude, and duration of exposure to altered pCO_2/pH (34).

Despite the long history of vinpocetine use in wide clinical practice (more than 30 years), interest in studying the mechanisms of its action among biochemists, molecular biologists, and clinicians does not fade away. Every year previously unknown properties of the drug are revealed, opening up new prospects for its use. The multiplicity of points of application of vinpocetine, combined with high clinical efficacy and safety of use, allows it to successfully compete with an ever-increasing number of new drugs on the pharmacological market for a long time (15). Its multi-prolonged actions, including vasodilator, antioxidant, anti-inflammatory, anti-thrombotic, and anti-remodelling, may work together to produce a synergistic therapeutic effect, thereby providing significant benefits in these multifactorial cerebrovascular and cardiovascular diseases (38).

Conflict of interest statement
The authors report no conflicts of interest.

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