THE NEW ARMENIAN MEDICAL JOURNAL
Volume16 (2022), Issue 4, p89-95

DOI: https://doi.org/10.56936/18290825-2022.16.4-89

INVESTIGATION OF CEREBROVASCULAR ACTIVITY OF NEW GABA-DERIVED SHORT PEPTIDES

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Received 26.05.2022; accepted for printing 18.08.2022

Abstract

Based on the important role of endogenous substances in the cerebral blood flow regulation, the cerebrovascular activity of new synthesized short peptides of γ-aminobutyric acid (GABA) and pyroglutamate has been investigated, considering the development of new drugs for the correction of cerebral circulation.

Taking into account the proven ability to increase cerebral blood flow of γ-aminobutyric acid and its endogenous metabolites, such as gamma butyrolactone, gamma hydroxybutyric acid, pyrrolidone, pyroglutamic acid, as well as synthetic analogues, such as picamilon, the influence of pyroglutamyl GABA, pyroglutamyl GABA ethyl ester, pyroglutamyl diGABA was observed on local brain blood flow in a state of impaired cerebral circulation.

The model of cerebral chronic hypoperfusion generated by right common carotid artery occlusion was used on rats weighing 180-240 g, under anesthesia with chloral hydrate (400 mg/kg). The investigated peptides were administered at a dose of 20 mg/kg, intraperitoneally. Cerebral blood flow changes were detected by laser Doppler flowmetry.

The conducted experiment revealed differences between the cerebrovascular activities of the studied short peptides. Thus, it was demonstrated that pyroglutamyl GABA exhibits a high ability to increase local cerebral blood flow, stimulating cerebral circulation by 65,2 %, compared with the value of hypoperfusion by right common carotid artery occlusion, after 40 minutes of injection. However, no essential changes in the studied indicator were recorded for pyroglutamyl GABA ethyl ester and pyroglutamyl diGABA.

The obtained data indicate that the prolongation of the short peptide chain leads to a decrease in cerebrovascular activity and opens up new perspectives for the development of pyroglutamyl GABA dipeptide as a promising agent for the correction of cerebral circulation.

Keywords: *pyroglutamyl GABA, pyroglutamyl GABA ethyl ester, pyroglutamyl diGABA, cerebral ischemia, cerebrovascular activity*

Introduction

Cerebrovascular accident or stroke is a neurologic symptom complex caused by cerebral ischemia or hemorrhage. Approximately 87% of strokes are ischemic infarctions. Stroke is the second leading cause of death and a major contributor to disability worldwide [*Kuriakose D, Xiao Z, 2020*].

Cite This Article as:

*Adamyan N.H., Shamilyan Q.M., Zhamharyan A.G., Topchyan H.V., Balasanyan M.G.(2022).*Investigation of cerebrovascular activity of new GABA-derived short peptides . The New Armenian Medical Journal, 16(4): 89-95, https://doi.org/10.56936/18290825-2022.16.4-89

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The effective stroke prevention strategies include modifying risk factors, thrombolysis, recovery of cognitive impairment and neuroprotection [*Kuriakose D, Xiao Z, 2020; Feigin V et al., 2021*].

During cerebral ischemia, reduced or blocked blood circulation deprives neurons of oxygen and glucose, which induces various destructive cellular reactions leading to neuronal death. The main cause of progressive neuronal death after an ischemic insult is neuronal overexcitation and aberrant activation of glutamate receptors and a massive accumulation of intracellular Ca2+ (excitotoxicity), resulting from γ-aminobutyric acid (GABA)/glutamate disbalance [*Bhat M et al., 2022*]. The GABA inhibitory role in counteracting glutamate-mediated excitotoxicity in stroke, as well as linking of a decreased GABA-ergic inhibition with increased neuronal plasticity has been proven [*Grigoras I, Stagg C, 2021*].

Advances in recent decades in the prevention and recovery after stroke indicate the activation of GABA-egic signaling [*Feske S, 2021*]. New data indicate that pharmacological effects on this neurotransmitter system may be one of the simplest, but most effective means of preventing neuronal death caused by brain ischemia [*Schwartz-Bloom R, Sah R, 2001*]. Based on the significant role of GABA in cerebral blood flow regulation and neuroprotective processes, known as early as 1964 from the works of S.A. Mirzoyan and V.P. Hakobyan, and the discovery of the enzyme GABA-transaminase in cerebral vessels, which participates in GABA metabolism and cerebral blood flow regulation [*Rodríguez-Lozada J et al., 2018*], a number of compounds have been synthesized and studied that create promising opportunities to solve this problem.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

In this context, various GABA-ergic molecules have been tested in clinical trials, and some of them are already in use. These are both GABA natural analogues (γ – butyrolactone, γ - hydroxybutyric acid, pyrrolidone, pyroglutamic acid) [*Lun'shina E et al., 2002; Kapoor P et al., 2013; Tovar-Gudiño E et al., 2018*] and synthetic derivatives (picamilon, baclofen, pregabalin, vigabatrin) [*Varga V et al., 1988; Avula B et al., 2015*; *Sugimoto M et al., 2021*], and GABA-ergic modulators of various structures.

One of such preparations is picamilon (nicotinoyl-GABA). Picamilon is widely used as an agent exerting positive cerebrovascular, nootropic, and tranquilizing effects. Among the mechanisms underlying the realization of the effects of picamilon and its derivatives, two types can be distinguished: neuromediator and metabolic. A neuromediator mechanism is based, first of all, on the effect on the GABA-ergic system. In addition, picamilon suppresses the activity of Monoamine oxidase and acetylcholinesterase, activates the aerobic and anaerobic oxidation processes, increases the energy status of cerebral cells, and activates the antioxidant system. Picamilon is used as a cerebroprotector in some pathological and borderline states [*Denisenko O et al., 2014*].

Particular attention is given to the neutroprotector and cerebrovascular activity of a new drug composition GABA-mimetic pirrolidone and pyroglutamic acid. This drug is capable of improving the cerebral blood supply, limiting the zone of ischemic injury, preventing the increased level of lactate and lipid peroxidation products, modifying nitric oxide content, and restoring the psychoneurological status of experimental animals with ischemic brain injury models [*Mirzoian R, 2003*].

GABA derivative Baclofen (GABA-B receptor selective agonist) is approved by the Food and Drug Administration for the treatment of reversible spasticity, in particular, for the relief of flexor spasms, clonus, concomitant pain, common consequences of spinal cord lesions and multiple sclerosis. Intrathecal baclofen administration is approved for managing spasticity of cerebral origins [*Ghanavatian S, Derian A, 2022*]. Interestingly, recent data is revealing that baclofen can also play a role in neuroprotection after spinal cord injury [*de Sousa N et al., 2022*]. Clinically, baclofen is effective for the treatment of post-ischemic stroke symptoms, i.e., for the

relief of severe spasticity and associated pain. Sustained activation of GABA-B receptors with baclofen provides neuroprotection in *in vitro* and *in vivo* models of cerebral ischemia [*Hleihil M et al., 2021; Bhat M et al., 2022*].

Pregabalin is used to treat epilepsy and causes of neurogenic pain, such as fibromyalgia, diabetic neuropathy, and complex regional pain syndrome [*Lee J et al., 2021*]. It has a γ-aminobutyric acid-like structure, potently binds the CaVα2δ-1 subunit of voltage-gated calcium channels, reduces Ca2+ influx at the presynaptic nerve endings, and reduces the release of several neurotransmitters such as glutamate and noradrenaline. In cerebral ischemia, the main reason for cell death is the increase of excitatory amino acids. Anti-inflammatory and anti-apoptotic effects of pregabalin were previously shown by histopathological and biochemical methods, indicating that pregabalin might be a neuroprotective agent for the treatment of ischemia-reperfusion injury. The protective effect of gabapentin (another GABA analogue) against oxidative damage in mice by using GABA-ergic modulation was also shown. Hence, pregabalin may protect tissues from oxidative damage and neuronal damage by using GABA-ergic modulation [*Aşcı S et al., 2016*].

Vigabatrin is a second-generation antiepileptic drug, the therapeutic effect of which results from an increase in the level of γ-aminobutyric acid through the selective, irreversible inactivation of GABA transaminase (GABA-T). Despite the recognized efficacy of the drug, the use of Vigabatrin has been limited by reports of rare, but significant and characteristic of Vigabatrin, side effects. Vigabatrin is a well-tolerated drug; the most commonly reported adverse reactions are somnolence, sedation, irritability, and restlessness, but these are usually transient and dose-related. There is a need for more randomized, prospective and sufficiently extended trials which could definitively answer important questions about and reveal new pharmacological effects of Vigabatrin [*Golec W et al., 2021*].

Taking into account the above, the cerebrovascular activity of new synthesized short peptides of γ-aminobutyric acid and pyroglutamate (pGlu) was investigated: pyroglutamyl GABA (pGlu-GABA), pyroglutamyl GABA ethyl ester (pGlu-GABA ethyl ester) and pyroglutamyl diGABA (pGlu-GABA-GABA) [*Adamyan N et al., 2020; Adamyan N et al., 2022*].

Material and methods

The cerebrovascular activity of peptides was studied on inbred white male rats weighing 180-240 *g* (n=18). To minimize circadian influences on the animal response, the experiments were performed between 09^{00} and 14^{00} *hours* at the laboratory room temperature of 22±1°C. Food and water were available *ad libitum*. Animals were kept in standard laboratory vivarium conditions in accordance with the Public Health Service Guide for the Care and Use of Laboratory Animals and approved by the Yerevan State Medical University Ethics Committee [*National Research Council, 2011*].

A model of chronic cerebral hypoperfusion was generated by right common carotid artery occlusion (RCCAO) in rats. Changes in the superficial cerebral blood flow were determined using a laser Doppler flowmetery apparatus Transonic System Inc. (USA) BLF-21 (with an N-type needle , combined with Hugo Sachs Elektronik (Japan) MC-641.).

The cerebral blood flow value was recorded at each time point, before occlusion (baseline), after the occlusion (maximum decrease in value), and after administration of the tested peptides, for 70 *minutes*. The cerebral blood flow values were expressed as a percentage of the baseline value, and the differences from RCCAO data were also calculated.

All procedures were performed under chloral hydrate anesthesia (400 *mg/kg*).

The animals were placed in a supine position and fixed to the surgical table. Through a small incision approximately 2-3 *cm* in the neck midline, the right common carotid artery was isolated from the vagal nerve and connective tissue by blunt dissection. Then the right common carotid artery was ligated with a silk suture. For the measurement of the surface cerebral blood flow, the operated rats were fixed on a stereotaxic apparatus in a sternal position, and their scalp was cut to expose the skull. A skull trepanation was performed, the area

of interest in the frontal cortex was set as a small oval with a 5 x 3 *mm* diameter, at 2 *mm* posterior and 3 *mm* lateral to the bregma. The detector (the probe with a diameter of 0.8 *mm*) was then placed from the oval window on the brain tissue and fixed perpendicularly to the cortical surface. Cerebral blood flow was expressed as arbitrary tissue perfusion units and continuously recorded before, during, and after RCCAO. For analysis, each experimental model's cerebral blood flow was compared with the preoperation baseline (%).

The experimental animals were divided into 3 groups:

I group (n=6) – injected pGlu-GABA,

II group (n=6) – injected pGlu-GABA ethyl ester,

III group (n=6) – injected pGlu-GABA-GABA.

Peptides were freshly dissolved in normal saline and injected intraperitoneally at a volume of 0.2 *mL*/100 *g* body weight of rats in a dose of 20 *mg/kg*.

Molecular docking was used for the interaction of pGlu-GABA (ligand) with GABA-T (protein) fragments. For docking purposes, the three-dimensional structure of 4-Aminobutyrate-Aminotransferase (Protein Data Bank code: 1OHV) was obtained from the Research Collaboratory for Structural Bioinformatics protein databank [*Jones G et al., 1997*]. The protein structure was prepared using the protein preparation wizard and optimized by removing the water molecules and hetero atoms. Ligands that were already present within the receptor in bound form were removed for the docking protocol. P-Glu-GABA, as a ligand, was prepared and docked for this study in flexible docking mode, and atoms located within a range of 10.0 Å from the amino acid residues were included in the active site. All the conformations generated were minimized prior to the docking study. Molecular docking studies were performed using the Genetic Optimization for Ligand Docking program 2020 version. According to the ChemPLP scoring function the lowest energy docked conformation for each of the docking cases was selected as the binding mode. Ligand geometry was minimized using the AM1 Hamiltonian as implemented in the program Gaussian 09[45] and used as MOL2 files. Best cluster poses and top ranked scores were saved and visually analyzed by Pymol [*PyMOL Molecular Graphics System, 2010*].

In the experiments were used pGlu-GABA, pGlu-GABA ethyl ester, pGlu-GABA-GABA, which were synthesized and structurally confirmed by MRI analysis in the scientific research laboratory "AZAD Pharmaceuticals LLC" (Yerevan, Armenia).

Statistical analysis of the study results was performed using Microsoft Excel 2010 and SPSS version 20.0. The results are presented as the mean and standard error (mean ± SE, %). Comparison between different groups was done by one-way ANOVA followed by Bonferroni's test to compare differences between the groups at the pre-determined time intervals. P-value less than 0.05 ($p<0.05$) was considered statistically significant.

Results and discussion

According to the obtained data, after the right common carotid artery occlusion, the local cerebral blood flow value decreased. Within 20 *minutes*, the value changes stabilized and the registered cerebral blood flow became lower compared to the baseline value by an average of 36.3%, amounting to 63.7% of the baseline level.

In the described condition, pGlu-GABA, as well as the other peptides, were administered at a dose of 20 *mg/kg*. The mentioned dose of peptides was based on the results of our previous investigations of antinociceptive activity, which indicates that their pharmacological activity is more pronounced at a dose of 20 *mg/kg*.

As evident from the results, intraperitoneal injection of pGlu-GABA at a dose of 20 *mg/kg* was accompanied by an elevation of cerebral blood flow, starting from the 10th *minute* of administration until the 70th *minute* of the experiment (Table,). The enhancement of the local cerebral blood flow reached its maximum value at the 40th *minute* of registration, amounting to 65.2%, compared with the RCCAO value (Fig.1).

During the monitoring of local cerebral blood flow values after administration of pGlu-GABA ethyl ester and pGlu-diGABA, it was statistically reliably demonstrated that there were no significant changes in the same model of cerebral hypoperfusion (Table).

Table.

Influence of pGlu-GABA, pGlu-GABA ethyl ester, pGlu-diGABA on local cerebral blood flow after right common carotid artery occlusion

Time		The blood flow value (%)		
Before occlusion		100.0		
After the occlusion		63.7±2.63*		
After drug injection		pGlu-GABA (n=6)	pGlu-GABA ethyl ester (n=6)	pGlu-diGABA (n=6)
Time after drug injection (*min*)	10	75.8 ±3.4*#	58.5±2.9*	59.9±4.0*
	20	81.0±5.2*#	57.0±2.7*#	59.9±4.2*
	30	89.9±6.9#	61.3±3.8*	56.7±3.0*#
	40	105.2±18.8#	58.7±3.6*	57.8±2.2*
	50	104.4±17.8#	56.2±3.2*#	56.9±2.3*#
	60	97.8±20.8#	53.0±2.2*#	54.1±2.2*#
	70	90.0±14.3#	53.3±1.4*#	55.5±2.9*#

Notes: *The data are presented as Mean ± Standard Error, % – compared with baseline; * – p<0.05, compared with baseline, # – p<0.05, compared with right common carotid artery occlusion pGlu-GABA – pyroglutamyl GABA, pGlu-GABA ethyl ester – pyroglutamyl GABA ethyl ester, pGlu-diGABA – pGlu-GABA-GABA*

Thus, the conducted experiments revealed that among the investigated short peptides, only the pGlu-GABA dipeptide exhibits cerebrovascular activity.

The results of the above-described in vivo experiments were confirmed by molecular docking analysis. For this purpose, the possible interaction of pGlu-GABA dipeptide with the GABA-T protein fragments was elucidated. GABA-T was chosen as a target for investigation of the molecular mechanisms of action of pGlu-GABA, as this enzyme participates in the metabolic degradation of GABA to succinate semialdehyde. It is obvious that agents, which inhibit the activity of GABA-T, contribute to increasing the endogenous level of GABA and thus reveal GABA-ergic action.

The molecular docking study results indicate that pGlu-GABA binds to the active site of the enzyme and forms interactions with the glutamate and arginine aminoacid residues and has a high docking score (Fig. 2). Moreover, pGlu-GABA binds with the salt bridge between these two aminoacid residues, which can lead to GABA-T inhibition. According to the literature data, this interaction is very crucial as the mentioned salt bridge plays an important role in GABA-T activity. These results suggest that one of the possible GABA-ergic action mechanisms of the presented new synthesized short peptide pGlu-GABA could be the GABA-T inhibition with subsequent enhancement of GABA levels in brain tissue.

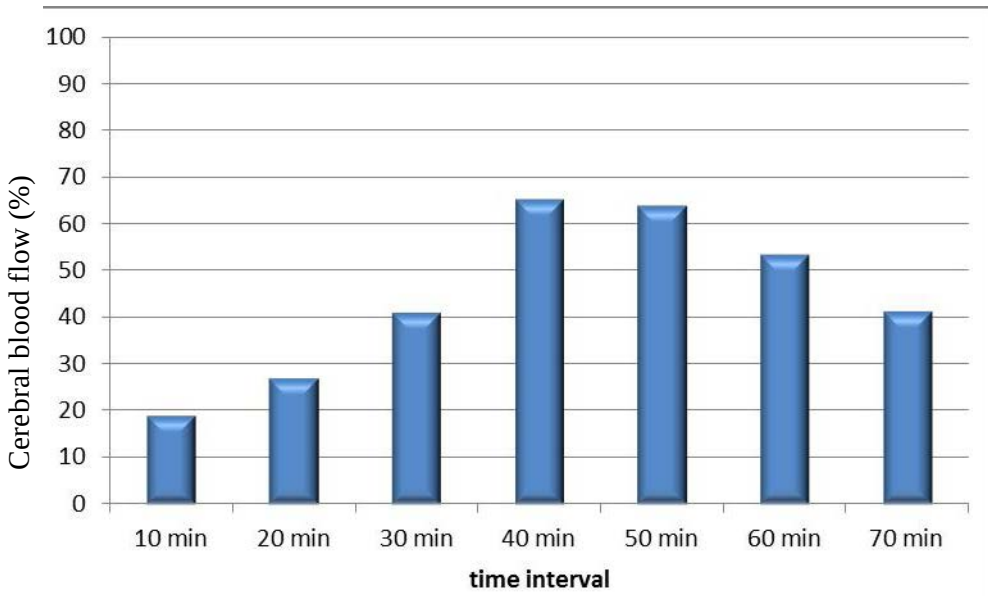

Figure 2. *Enhancement (%) of impaired by right common carotid artery occlusion cerebral blood flow after injection of pGlu-GABA, compared with occlusion.*
Notes: pGlu-GABA - pyroglutamyl GABA; time interval 10 min.

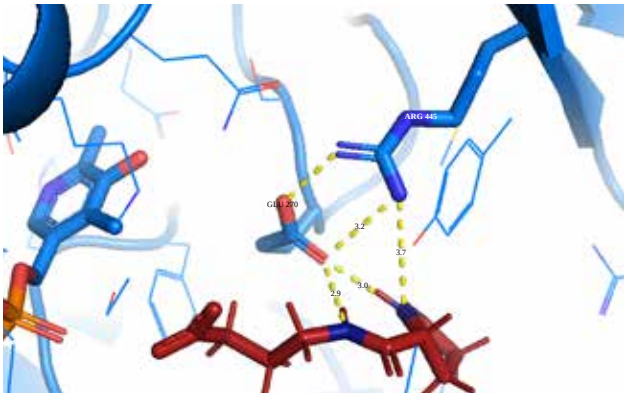

Figure 2. *Molecular docking of pGlu-GABA with GABA transaminase.*

Conclusion

The conducted experimental investigation discovered a new agent with cerebrovascular activity among GABA-containing short peptides. It was demonstrated that pGlu-GABA stimulates blood supply to the brain by increasing local cerebral blood flow in the brain cortex, which was manifested in a condition of impaired cerebral circulation caused by unilateral common carotid artery occlusion. In a state of hypoperfusion after the rats' treatment with an intraperitoneal injection of pGlu-GABA at a dose of 20 *mg/kg*, an increase in cerebral blood flow of about 65% was registered.

The analysis of the possible molecular action mechanism of pGlu-GABA by the molecular docking method allows us to suggest that one of the possible action mechanisms of the new synthesized short peptide pGlu-GABA could be GABA transaminase inhibition, followed by increased GABA levels in brain tissue.

The obtained data open up new perspectives for the development of new agents with cerebrovascular activity for the correction of impaired cerebral circulation, based on pGlu-GABA and its structural analogues.

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THE NEW ARMENIAN MEDICAL JOURNAL

Volume16 (2022). Issue 4

The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

Rector of YSMU

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Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "VARM" LLC
Director: Ruzanna Arakelyan
Armenia, 0018, Yerevan,
Tigran Mec 48, 43
Phone: (+374 91) 19 29 00,
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