Natalia Valeryevna Pyatigorskaya et al /J. Pharm. Sci. & Res. Vol. 10(5), 2018, 1103-1106

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

New AMPA receptor positive modulators for rehabilitation of patients after cerebral accidents

Natalia Valeryevna Pyatigorskaya, Galina Eduardovna Brkich
The Sechenov First Moscow State Medical University,
119991, Russian Federation, Moscow, Trubetskaya Street, 8-2

Mstislav Igorevich Lavrov, Vladimir Aleksandrovich Palyulin
Lomonosov Moscow State University,
119991, Russian Federation, Moscow, Leninskie Gory, GSP-1

Zhanna Igorevna Aladysheva
The Sechenov First Moscow State Medical University,
119991, Russian Federation, Moscow, Trubetskaya Street, 8-2

Abstract

Stroke is an acute disorder of the cerebral circulation, characterized by a sudden appearance of focal neurological symptoms and/or cerebral symptoms, which persist for more than 24 hours or lead to death in a short period of time as a result of the cause of cerebrovascular origin.

The search strategy for new drugs for the therapy of cognitive impairment and rehabilitation of patients who underwent acute brain hypoxia due to ischemia or other brain damage involves the search for substances affecting synaptic plasticity and having ability to increase the production of neurotrophic factors.

A new class of AMPA receptor positive allosteric modulators (PAMs) based on the tricyclic derivatives of 3,7-diazabicyclo[3.3.1]nonane (bispidine) have been proposed using computer-aided molecular design techniques and further experimental studies. The innovative drug candidates with this scaffold provide the long-lasting activation of AMPA-receptors and production of neurotrophic factors, which allows the use of them for the therapy of cognitive impairments and for rehabilitation of patients who underwent acute cerebral hypoxia due to ischemia or other brain damage. The use of bispidine scaffold is very promising for the search, optimization and synthesis of compounds that potentially have a wide range of pharmacological effects.

The investigated drug candidate accelerates and enhances the rehabilitation activities, such as recovery of skills, working memory and attention.

Keywords: AMPA receptors, derivatives of 3,7-diazabicyclo[3.3.1]nonane, brain-derived neurotrophic factor, BDNF, NGF, positive allosteric modulator, PAM, rehabilitation of patients after brain damage.

INTRODUCTION

Stroke is an acute disorder of cerebral circulation, characterized by sudden appearance of focal neurological symptoms (sensory, motor, visual, speech, coordinative and other disorders) and/or cerebral disorders (headache, vomiting, alteration of consciousness, etc.), persisting for more than 24 hours or leading to death in a short time due to the cause of cerebrovascular origin. For the last 15 years stroke remains one of the leading causes of death in the world. According to statistics of the World Health Organization (2015), the global death rate from stroke was 6.24 million people, which exceeded the same indicator of 2000 (5.41 million) by 15.3% [1].

Only 10% of patients after a stroke recover almost completely, in 25% cases minor pathologies remain, and in 65% of patients the stroke leads to disability and the need for special care. The prognosis of the disease depends on the extent of the lesion and the recovery rate of oxygen supply. An extremely important factor in the success of therapy is the timely start of rehabilitation of the patient.

The main neurological symptoms of brain damage caused by acute hypoxia or trauma are motor disorders, speech and cognitive impairment. Cognitive impairment often occurs after a stroke and manifests in impairment of memory, attention, gnosis, praxis, decrease in intelligence. Memory impairments that develop after acute disorders of cerebral circulation, according to different authors, are observed in 23-70% of patients in the first 3 months after a stroke. The causes of pronounced cognitive impairment and even dementia can be: massive hemorrhages and extensive cerebral infarcts; multiple heart attacks; single, relatively small infarcts located in functionally significant areas (anteromedial divisions of the optic thalamus and adjacent areas, frontal lobes, parietal-temporal-occipital brain divisions, mediobasal divisions of the temporal lobe, pale globes).

Cognitive impairments revealed in connection with a stroke can occur in different periods: immediately after a stroke (acute cognitive impairment) and in a more delayed period (delayed post-stroke cognitive impairment); the latter are usually caused by concomitant neurodegenerative (often Alzheimer's) process, activated due to increasing ischemia and hypoxia. Post-stroke cognitive impairments worsen the prognosis, increase mortality and risk of recurrent stroke by 3 times, and also increase the severity of functional disorders after a stroke, significantly complicate rehabilitation.

There are two clinico-pathogenetic forms of a stroke: ischemic and hemorrhagic stroke. Ischemic stroke (cerebral infarction) is caused by acute focal cerebral ischemia and leads to a cerebral infarction (ischemic necrosis zone). Hemorrhagic stroke (non-traumatic intracerebral hemorrhage) is caused by rupture of intracerebral vessel and penetration of blood into the brain parenchyma or rupture of arterial aneurysm with subarachnoid hemorrhage [2].

Ischemic stroke represents the largest proportion (70-85%) of all strokes and is the third most frequent cause of death and the first most frequent cause of disability among elderly people. Therefore, treatment of ischemic stroke is considered to be an actual problem of modern neurology [3].

In the event of a cerebrovascular accident, issues of early prevention and rehabilitation occupy an important place. The review by A.C. Kadykov and N.V. Shakhparonova (2014) is dedicated to the aspects of early rehabilitation of patients after stroke. Of particular interest is the problem of dementia and motor disorders, caused by stroke. The wide occurrence and significance of these disorders is confirmed by the results of various trials and neuropsychological tests [4].

Delayed post-stroke cognitive impairments are mediated by concurrent neurodegenerative process, which is activated in

response to increasing ischemia and hypoxia. During first 3 months of the early post-stroke period, a post-stroke cyst forms, and the range of motions and strength of the paretic extremities restores. In the next 3 months the recovery of lost motor skills continues. Speech restoration, mental and social re-adaptation require a longer period of time.

Neuroplasticity plays an important role in the process of post-stroke rehabilitation; it is characterized by the ability of different brain structures to change their structural and functional organization, to be involved in different forms of activity. Neuroplasticity is of paramount importance in acquiring new knowledge and skills, training, recovering after brain damage including as a consequence the cerebral circulation disorders [5]. T. Murphy et al. (2009) discuss the changes during stroke recovery in the plasticity of neurons and in motor ability [6].

Different medicamentous approaches to brain function restoration are used at different stages of rehabilitation.

Drugs, that reduce the need of neurons in oxygen associated with hypoxia and block excessive neuronal activity, are used during the acute stage of rehabilitation. Disaggregants/anticoagulants are used to prevent repeated episodes of hypoxia. Inhibitors of lysosomal enzymes and antioxidants are used for the protection of cell membranes. In addition, for the rehabilitation of patients after a stroke, drugs are used that facilitate penetration of glucose through the blood-brain barrier and increase its utilization by cells of various departments of the brain and spinal cord, as well as the drugs that improve the exchange of nucleic acids, synthesis of phospholipids and proteins in nerve cells.

Zakharov V. V. (2014) described pharmacological effects on the rate and degree of recovery of neurological functions after stroke. Pharmacological modulation of glutamatergic activity of the brain can favorably influence the course of the delayed post-stroke recovery period. Of particular interest is the creation of drugs capable of modulating functional activity of AMPA-receptors of glutamatergic mediator system and, thus, facilitating production of neurotrophic factors. At a later stage of rehabilitation, the challenge is to stimulate the growth and differentiation of new neurons and synapses. Glutamatergic system plays an important role in regulation of neuroplasticity and reparation processes. Synaptic transmission of excitatory neuronal discharges is impossible without glutamatergic neurotransmission [5].

Study by A. Clarkson et al. (2011) showed for the first time that an increase in the level of neurotrophic factor BDNF plays a role in restoration of motor apparatus after a stroke. Ampakine-induced stimulation of endogenous BDNF production was carried out on the model of ischemic stroke in *in vivo* tests, and combination of ampakine CX 1837 and exogenous BDNF was proposed for post-stroke rehabilitation [7].

The results of study by C. Maclellan et al. (2011) demonstrated that the level of BDNF should reach a threshold value before there is an improvement in motor function during post-stroke rehabilitation [8]. Review by Berretta A. et al. (2014) provides strong evidence that the neurotrophic factor BDNF plays a significant role both in the protection process and in the recovery process after a stroke [9].

The use of neuroprotective therapy for ischemic stroke has formed an ambiguous attitude. Although the model of artificial cerebral ischemia in experimental animal studies *in vivo* demonstrated the efficacy of multiple drugs, however, there is no evidence of their effectiveness in large placebo-controlled studies, and therefore they are not included in current international guidelines for the management of patients with ischemic stroke [3].

The ability of AMPA receptor positive allosteric modulators ("ampakines") was discovered to induce the expression of neurotrophic factors BDNF and NGF, which trigger the mechanisms responsible for the survival of existing neurons, as well as the growth and differentiation of new neurons and synapses, makes the development of new positive allosteric modulators (PAMs) of the AMPA receptor, based on the derivatives of 3,7-diazabicyclo[3.3.1]nonane, especially promising for the use in later stages of rehabilitation.

As a result of patent research, it was confirmed that the problem of creating innovative drugs with procognitive effect, containing substances of new class of AMPA receptor PAMs (ampakines) is an actual task and a subject of stable activity of inventors.

Currently there is a high level of activity in the field of development of pharmaceutical compositions, which combine ampakines and neuroleptics or narcotic analgesics, in order to potentiate the pharmacological activity of the latter, reduce therapeutic doses and alleviate the side effects caused by them, for example, inhibition of respiratory activity during the therapy with narcotic analgesics.

RESULTS AND DISCUSSION

Using molecular modeling techniques new positive AMPA receptor modulators, derivatives of 3,7-diazabicyclo[3.3.1]nonane based on a novel scaffold (Fig. 1) were designed [10].

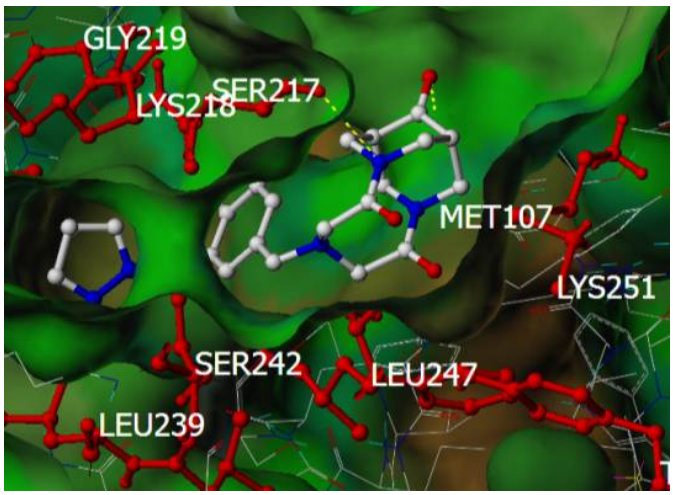

Fig. 1. New positive AMPA receptor modulators, derivatives of 3,7-diazabicyclo[3.3.1]nonane based on a novel scaffold.

3,7-Diazabicyclo[3.3.1]nonanes and their derivatives occupy a prominent place in modern scientific literature, and have wide application due to their unique chemical properties. Mazurov A. et al. (2013) carried out computer simulations for a large collection of compounds, containing the bicyclo[3.3.1]nonane framework, which are proposed as positive modulators of nicotinic acetylcholine receptors [11]. A number of researchers used the 3,7-diazabicyclo[3.3.1]nonane framework in the synthesis of antiviral agents by linking its derivatives with amino acids. This framework was chosen to provide the rigidity and high hydrophobicity of the molecule as well as a strict geometric orientation of amino acid residues [12], which made it possible to interact with the hydrophobic cavities of the viral shell proteins. Bispidines are also known as ligands for complex formation with the cations of Fe(II), Cu(II), etc. [13, 14]. The structure of many alkaloids (sparteine, lupanine, anagirine), which have a wide spectrum of pharmacological activity (spasmolytic, antiarrhythmic, psychotropic, analgesic), contains 3,7-diazabicyclo[3.3.1]nonane moiety. Derivatives of 3-azabicyclo[3.3.1]nonane exhibit antiviral, hypotensive, analgesic, spasmolytic, fungicidal, antibacterial activity. Many synthetic derivatives are also biologically active, which requires additional studies [15, 16, 17].

3,7-Diacyl-3,7-diazabicyclo[3.3.1]nonan-9-ones possess unique properties due to the rigidity of the framework, their geometric

parameters and strict orientation of the substituting groups at nitrogen atoms in parallel planes. The use of these structures is very promising for the search, optimization and synthesis of compounds that potentially have a wide range of pharmacological effects.

The computer-aided molecular design and optimization was performed for 205 new derivatives of 3,7-diazabicyclo[3.3.1]nonane, that potentially could have positive modulatory activity with respect to AMPA receptors, and the most promising of them were selected based on the results of modeling and synthesized. The selection criteria for tricyclic derivatives of 3,7-diazabicyclo[3.3.1]nonane were based on the docking data of structures, which have good predicted binding affinity to the modulator sites of AMPA receptor. It has been shown that tricyclic 3,7-diazabicyclo[3.3.1]nonane derivatives bind to AMPA receptors at the same binding sites as most other known AMPA receptor PAMs [1]. 3,7-Diazabicyclo[3.3.1]nonane derivatives potentiate AMPA receptors in *in vitro* experiments at record low picomolar concentrations [18].

Physiological studies of the synthesized most promising tricyclic derivatives of 3,7-diazabicyclo[3.3.1]nonane in *in vivo* animal tests demonstrated the pronounced neuroprotective properties, significant improvement in memory and cognitive functions [19]. For most promising compounds Z-108, Z-109, Z-110 their influence on the processes of learning and memory formation was studied in mice on the model of amnesia caused by electric shock using the conditioned reflex of passive avoidance.

The tricyclic derivatives of 3,7-diazabicyclo[3.3.1]nonane are positive allosteric modulators of glutamate AMPA receptors [1]. Glutamate receptors are expressed on neuronal synapses and are activated by glutamic acid, the most common native neurotransmitter that transmits excitatory signals to nerve cells. AMPA PAMs either slow down the rate at which AMPA receptors lose sensitivity to prolonged glutamate exposure, or slow down the process of deactivating AMPA receptor after cessation of glutamate exposure [20].

The most important neurophysiological aspect of positive AMPA PAMs action is a so-called synaptic plasticity. One of its consequences is the effect of long-term potentiation, which is considered as one of the main mechanisms of neuronal memory. In addition, the basis of therapeutic potential of AMPA PAMs is their ability, due to depolarization of postsynaptic membrane, to significantly increase the expression of neurotrophic factors - NGF (nerve growth factor) and BDNF (brain-derived neurotrophic factor), which, in turn, is the most powerful mechanism of recovery of nerve cells [21].

Indications for the use of a positive modulator of AMPA receptors as a drug (but not an agonist and not an antagonist) will include acceleration and improvement of reconvalescence quality after cerebral accidents, since the acute phase and reconvalescence phase are facilitated by different pathogenic mechanisms. High safety and procognitive effect is expected for the innovative drug Z-109 under development, exceeding the first generation PAMs from other structural classes; oral administration is proposed in the dosage form of capsules or coated tablets.

Thus, modern treatment, including neuroprotective therapy for ischemic stroke, can reduce mortality and improve recovery of lost neurological functions [3]. The basis of therapeutic potential of PAMs from the group of tricyclic derivatives of 3,7-diazabicyclo[3.3.1]nonane is their ability, due to depolarization of the postsynaptic membrane, to significantly increase the expression of neurotrophic factors, NGF and BDNF, which, in turn, is a powerful mechanism of nerve cells recovery. Restoration of nerve cells, stimulation of their growth and differentiation constitute the main task of neuroprotective therapy at the late stages of post-stroke rehabilitation. Despite the significant achievements of modern medicine in understanding the pathogenesis of stroke and the expansion of treatment options, rehabilitation of patients after stroke requires an integrated approach and is a difficult task.

The search strategy for new drugs for the therapy of cognitive disorders and rehabilitation of patients, who underwent acute brain hypoxia due to ischemia or other brain damage, involves the search for substances that influence the synaptic plasticity, have ability to increase production of neurotrophic factors and, at the same time, have low toxicity and low effective dose.

CONCLUSION

Thus, discovery of the ability of AMPA receptor positive allosteric modulators to induce the expression of neurotrophic factors BDNF and NGF. Moreover, combinations of PAM with neuroleptics and narcotic analgesics are expected to be highly effective in mitigating the adverse effects of the latter (e.g., respiratory depression without suppressing analgesic effect of narcotic analgesics). The use of PAMs in emergency care for the patients with an overdose of narcotics or barbiturates with alcohol is very promising [22]. In experimental animal studies Chen Su et al. (2016) established the analgesic activity of ampakine CX 546. Authors discuss, from the pharmacological and pharmacokinetic point of view, the ability of ampakines to alleviate postoperative pain, improve mood and simultaneously stimulate respiratory rhythm [23]. Published results of studies confirm that PAMs promote neurogenesis in cell culture and is promising for the use in stem cell therapy [24].

As can be seen from the above, PAMs currently draw the interest of a large number of scientists; and the range of research areas is very diverse. The mechanism of pharmacological effects of ampakines is associated with their ability to influence neuroplasticity and to express neurotrophic factors through the modulation of AMPA receptors of glutamatergic mediator system.

REFERENCES

[1] World Health Organization. Global Health Observatory (GHO) data. Top 10 causes of death. Situation and trends. Date View April 17, 2018 http://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/

[2] Denisov I.N. [et al.], Diagnostics and tactics for stroke in general medical practice, including primary and secondary prevention: clinical guidelines. Approved at the IV All-Russian Congress of general practitioners (family physicians) of the Russian Federation. Kazan, 2013, pp. 33.

[3] Parfenov, V.A., Zakharov, V.V. and Gromova, D.O., Treatment of ischemic stroke. Application of choline alfoscerate: scientific review. Nervous diseases, 2013; 4: 34-40.

[4] Raimkulova H.B., Rehabilitation of patients with the consequences of ischemic cerebral stroke: literature review. Vestnik KazNMU, 2015; 2: 434-438.

[5] Zakharov, V.V., Glutamatergic Therapy in Rehabilitation Period after Ischemic Stroke. Effective pharmacotherapy, 2014; 42: 6-14.

[6] Murphy, T., Plasticity during stroke recovery: from synapse to behavior. Nat Rev Neurosci., 2009; 10(12): 861-872.

[7] Clarkson, A. [et al.], AMPA receptor-induced local brain-derived neurotrophic factor signaling mediates motor recovery after stroke. J Neurosci., 2011; 31(10): 3766-3775.

[8] Maclellan, C. [et al.], A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. Neurorehabil Neural Repair., 2011; 25(5): 477-483.

[9] Berretta, A., Tzeng, Y.-Ch. and Clarkson, A., Post-stroke recovery: the role of activity-dependent release of brain-derived neurotrophic factor: review. Expert reviews of Neurotherapeutics, 2014; 14(11): 1-10.

[10] Lavrov, M.I. [et al.], Novel bivalent positive allosteric modulator of AMPA-receptors. Reports of the Academy of Sciences, 2015; 464(5): 1-4.

[11] Mazurov, A.A. [et al.], Novel nicotinic acetylcholine receptor agonists containing carbonyl moiety as a hydrogen bond acceptor. Bioorg. Med. Chem. Lett., 2013; 23: 3927-3934.

[12] Haridas, V. [et al.], Bispidine-Amino Acid Conjugates Act as a Novel Scaffold for the Design of Antivirals That Block Japanese Encephalitis Virus Replication. PLOS Neglected Tropical diseases, 2013; 7(1): 1-11.

[13] Comba, P., Wadepohl, H. and Wiesner, S., Optimization of the efficiency of oxidation catalysts based on iron bispidine complexes. Eur. J. Inorg. Chem., 2011; 50: 2610-2615.

[14] Enomoto, T., Synthetic study toward ecteinascidin 743: concise construction of the diazabicyclo[3.3.1]nonane skeleton and assembly of the pentacyclic core. J. Org. Chem., 2010; 75: 4876-4879.

[15] Ivanova, E.V., Mono- and bicyclic anionic σ-adducts of 3,5-dinitropyridine derivatives in the synthesis of polyfunctional saturated heterocyclic compounds: dis. ... cand. chem. sciences: Tula, 2014, pp. 222.
[16] Ramachandran R. [et al.], Synthesis, stereochemistry and in vitro antimicrobial evaluation of novel 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-4-phenyl-2,3-dihydrothiazoles. Bioorganic & Medicinal Chemistry Letters, 2011; 21: 6301–6304.
[17] Xaiver, J.J.F., Synthesis and antibacterial, antifungal activities of some 2r,4c-diaryl-3-azabicyclo[3.3.1]nonan-9-one-4-aminobenzoylhydrazones. Med. Chem. Res., 2012; 21: 345–350.
[18] . Lavrov M. [et al.], New picomolar AMPA receptor modulators: design, synthesis and studies. Frontiers in medicinal chemistry: emerging targets, novel candidates and innovative strategies. Drugs of the future, 2009; 34: 4-6.
[19] Zefirov N. S., Palyulin V. A., Lavrov M. I. and Zapolsky M.E., Tricyclic derivatives of 3,7-diazabicyclo[3.3.1]nonanes, potentially possessing pharmacological activity, pharmaceutical compositions on their basis and method of administration: RF patent No. RU 2480470 C2.
[20] Ward, S., Bax, B. and Harries, M., Challenges for and current status of research into positive modulators of AMPA receptors: a review. British Journal of Pharmacology, 2010; 160: 181–190.
[21] Yanev, S. [et al.], Neurotrophic and metabotrophic potential of nerve growth factor and brain-derived neurotrophic factor: Linking cardiometabolic and neuropsychiatric diseases. World J Pharmacol., 2013; 2(4): 92-99.
[22] Ren J., Ding, X. and Greer, J. J., Respiratory depression in rats induced by alcohol and barbiturate and rescue by ampakine CX717. Journal of Applied Physiology, 2012; 113(7): 1004-1011.
[23] Su C. [et al.], AMPAkines Target the Nucleus Accumbens to Relieve Postoperative Pain. Anesthesiology, 2016; 125: 1030-1043.
[24] Schitine C. [et al.], Ampakine CX546 increases proliferation and neuronal differentiation in subventricular zone stem/progenitor cell cultures. Eur J Neurosci, 2012; 35(11): 1672-1683.