Рус. Eng.

PHARMACOLOGYCAL REVIEWS

UDC: 615.213

DOI: 10.18413/2500-235X -2016-2-3-86-94

Avdeeva N.V.[1]
Nikitina V.A.[2]
Kochkarova I.S.[3]
Litvinova A.S.[4]

THE POSSIBILITY OF ADMINISTRATION OF GLUTAMATE RECEPTORS ANTAGONISTS IN THE TREATMENT OF PARKINSON'S DISEASE

1) PhD of Medical Sciences, Assistant of the Department of pharmacology, Belgorod State National Research University 85 Pobedy St., Belgorod, 308015, Russia, e-mail: 7400468@mail.ru
2) 4 years student of medical and pediatric faculty of Medical University of NRU BelSU, 85 Pobedy St., Belgorod, 308015, Russia. e-mail: 999601@ bsu.edu.ru
3) Researcher at the Center of preclinical and clinical studies of the Belgorod State National Research University 85 Pobedy St., Belgorod, 308015, Russian Federation, e-mail: kochkarova@bsu.edu.ru
4) 6 years student of medical and pediatric faculty, Federal Autonomous Educational Institution of Higher Education Belgorod State University, 85, Pobedy St., Belgorod, 308015, Russia, e-mail: ann_netochka@mail.ru

ABSTRACT
Parkinson's disease is the slow-progressing chronic neurodegenerative disease. It caused by the progressive destruction and death of neurons that produce the neurotransmitter dopamine, primarily in the substantia nigra and also in other parts of the Central nervous system. Insufficient production of dopamine leads to the activating influence of the basal ganglia to the cerebral cortex. Guiding symptoms are muscle rigidity, hypokinesia, tremor, postural instability. Modern medicine has not yet found methods of curing disease, however, the existing methods of conservative and surgical treatment significantly improve the patient's quality of life and slow the progression of the disease. There is an assumption of the key role of glutamate receptors excessive activation in the pathogenesis of Parkinson's disease. It can be expected that glutamate receptors may be a new therapeutic target in the treatment of this pathology. The study of glutamate receptors blockers is an important task in the search for new pharmacological agents in the treatment of Parkinson's disease. Experiments on animal models suggest the change in the activity of these receptors can facilitate the primary motor symptoms of Parkinson's disease and also side effects caused by the levodopa replacement therapy. AMPA- NMDA receptors antagonists have shown the ability to reverse motor symptoms and levodopa-induced dyskinesia in preclinical models of Parkinson's disease. Metabotropic glutamate receptors antagonists are even more promising in the treatment of Parkinson's disease due to more "accurate" work in the synapse. These drugs also reduce motor deficits, as well as protecting the patient from neurodegeneration. Thus glutamate receptors are a promising target for the development of new pharmacological treatments of Parkinson's disease.
Key words: Parkinson's disease, glutamate receptors, basal ganglia, NMDA receptors, AMPA receptors, metabotropic glutamate receptors, levodopa-induced dyskinesia.

INTRODUCTION

First the Parkinson's disease (PD) was described by London physician James Parkinson in 1817 in "An Essay on the shaking palsy", therefore French neurologist Jean Charcot proposed to name the disease after Parkinson [1]. This disease is a slow-progressing chronic neurodegenerative disease, which affects about 3% of the population aged 55 years and older worldwide. Recently, in connection with the increase in life expectancy and improvement of diagnostic capabilities of medicine, there is PD some incidence rate. Guiding symptoms of PD are muscular rigidity, hypokinesia, tremor, postural instability, and sleep disturbance and cognitive defects [2]. Movement disorders, which are major clinical implications, are caused by a sharp fall in synthesis of dopamine in the

substantia nigra and striatum. Normally the amount of dopamine in these formations is hundreds times higher than the concentration in other brain structures, suggesting an important role of dopamine transmission in the activities extra pyramidal system. Loss of dopamine innervation of the neostriatum plays a crucial role in the control of motor activity [3]. Today dopamine replacement therapy is background at the unwrapped phase of PD. Because dopamine does not pass through the blood-brain barrier (BBB), its predecessor levodopa was synthesized. Levodopa passes through the BBB and metabolized in the brain under the action of dopamine decarboxylase to dopamine. Therapy of early disease begins with administration of dopamine receptor agonists [4]. Dopamine receptor agonists due to its chemical properties directly stimulate dopamine receptors, reproducing the effect of dopamine. Historically, they were first administrated to patients with PD as add-on therapy to levodopa, but later it was found that in the early disease of dopamine receptor agonists have comparable effect with levodopa. In most patients these drugs provide of motor symptomatic relief for several years. However, chronic exposure of these drugs leads to the emergence of motor fluctuations and drug-induced dyskinesia that militate against their long-term effectiveness [4, 5]. Adjuvant treatment to monoaminooxidase inhibitors, anticholinergic drug and COMT-inhibitors limited improves the effectiveness and acceptability of the treatment to levodopa. However, more effective therapy for unwrapped phase of motor symptoms of PD has not yet been found [4]. Besides, used at present pharmacological agents (mainly drugs containing levodopa) do not slow down the continued degeneration of dopaminergic neurons, which functional activity causes the conversion of levodopa into dopamine by action of dopamine decarboxylase and requires a gradual increase of the dose level to achieve the effect. This ultimately leads to acerbation of PD. Sameness of therapeutic agents for the treatment of PD largely associated with a deficit in knowledge on the cellular processes underlying the degeneration of dopaminergic neurons of the substantia nigra. The limitation of the pharmacological treatment of PD insists on the importance of non-dopaminergic therapeutic strategies for the treatment of the disease symptoms. Progress in the understanding of the anatomy and function of basal ganglia has given the opportunity to develop new strategies for treatment and slowing the progression of PD [3]. So the glutamate receptors have been proposed as promising therapeutic target for treatment of PD, since they transmit fast excitatory signals in fiber connection. Pharmacological manipulation of these receptors can change both normal and pathological neurotransmission that is observed in parkinsonian brain.

PATHOPHYSIOLOGIC MECHANISMS OF PARKINSON'S DISEASE

Clinical symptoms of PD (akinesia, rigidity, tremor) are caused by a sharp fall in synthesis of dopamine in the substantia nigra and striatum. The synthesis of dopamine takes place in the nerve cell bodies of the nigrostriatal system. Here the mediator is formed in the form of small vesicles, which are transported by the axonal transport to the presynaptic membane. Under the influence of nervous impulse dopamine release in the synaptic cleft and impacting on the receptors of the postsynaptic membrane with an effect of its depolarization. It is assumed that about 80% of dopamine is absorbed in the presynaptic terminals on reuptake mechanism or are inactivated by COMT or monoamine oxidase type B (MAO-B). Such disorders of intrinsic cellular metabolism as a violation of mitochondrial respiration and energy failure of the neuron, the strengthening of free-radical oxidation with the formation of aggressive peroxides, excessive accumulation of free ions of Ca^{2+}, increased activity of glutamate excitotoxin are a key player in the factors contributing to degeneration and apoptosis of neurons.

L-glutamate is the major excitatory neurotransmitter in the brain of animals. Glutamate is found in all departments of a CNS, as it is not only a neurotransmitter but also a precursor of other amino acids. Bodies of glutamatergic neurons located in the cerebral cortex, olfactory bulbs, hippocampus, substantia nigra, cerebellum, retina. Glutamatergic synapses located in the tonsil of cerebellum, the striatum, granule neurons of the cerebellum. Glutamate is dispensable amino acid, it doesn't pass through the BBB, does not arrive to the brain through the blood. The synthesis is carried out in the brain, mainly intraneural. In addition to the main role of the excitatory neurotransmitter, glutamate can cause damage and death of dopaminergic neurons. This action of glutamate on neurons is designated by the term excitotoxicity [6].

Glutamate-mediated activity detected in almost all brain structures. The greatest number of binding sites is located in the cerebral cortex, hippocampus, striatum, mesencephalon and hypothalamus. Glutamate receptors are divided into ionotropic and metabotropic. There are several subtypes of glutamate receptors. Modern classification of ionotropic receptors based on their different sensitivity to the action of NMDA, AMPA, kainic acid and quisqualic acid. There are two groups of receptors: NMDA and non-NMDA (it is divided into AMPA and kainate).

Glutamate excitotoxicity is mediated by NMDA receptors. After glutamate occupancies these

receptors transport channels of neural membranes open and the access of glutamate to the neuron enables. Extensive binding of glutamate by NMDA receptors leads to increasing of current Ca^{2+} into the neuron through the channels of NMDA receptors. Due to the fact that the increasing of current Ca^{2+} is one of the leading mechanisms of the neuron death, it can be assumed that the mechanism of glutamate excitotoxicity in PD is associated with massive entrance of Ca^{2+} in dopaminergic neurons of the substantia nigra [7]. There is a hypothesis about the integral role of hyperactivation of the glutamatergic structures of Luys body in the pathogenesis of PD. Luys body performs the relateral tell of corticonigral glutamatergic influences [8]. The hypothesis postulates the importance of glutamate damage neurons of substantia nigra, starting from the pre-existing disease.

NMDA receptors consist of five subunits that are complexes of glycoprotein and lipids. The NMDA receptor is a receptor-ionophore complex, which includes 1) specific binding site of the mediator (L-glutamic acid); 2) regulatory or coactivatation specific binding site of glycine; 3) allosteric modulatory sites located on the membrane (polyamine) and ion channel (phencyclidine binding sites, divalent cation and voltage-gated Mg-binding site). Mg^{2+} ions selectively block the activity of receptors at high hyper polarization or depolarization. Glycine enhances the responses of NMDA receptor by increasing the opening frequency of the channel. In the absence of the glycine receptor is not activated by L-glutamate [6, 9]. It is known that NMDA receptors play an important role in learning and memory. Activation of glutamate receptors is considered a universal pathochemical process, causing damage to nerve cells in a variety of pathological states [4]. The neurotransmitter role of the glutamic acid lies in the ability to cause membrane depolarization of the neuron and therefore increase the conductivity of Ca^{2+} ions. Mediator function is in close connection with the exchange of Ca^{2+} that gives the opportunity to talk about the glutamate-calcium cascade. The glutamate action is manifested through the operation with specific neuroreceptors with protein structure and related in nature to cellular glycoproteins. Adverse of biochemical processes, observed in PD, triggers the glutamate-calcium cascade, leading to different changes in cellular metabolism caused primarily by activation of the membrane permeability and the m7ovement of Ca^{2+} inside the cell [9]. This phenomenon contributes to the adverse of fundamental cellular processes, uncoupling of oxidative phosphorylation, free radical formation, which in turn leads to increasing lipid peroxygenation, apoptosis and neuron death.

BASAL GANGLIA AND PARKINSON'S DISEASE

All the movements performed by man, are controlled by the Central CNS, which includes the brain and spinal cord. It is very difficult organized system that meets virtually all that happens in the body. The role of higher nervous activity belongs to the cerebral cortex. Once man only to think about some intentional action, the cortex is already leading to readiness all the systems that are responsible for this action. One of such system is the so-called basal ganglia. The basal ganglia are an auxiliary motor system. It does not work independently, but in the close association with the cerebral cortex. The basal ganglia are involved in performing complex movements such as writing, drawing, walking, kicking the ball into the goal, lace shoes etc. It is responsible for driving speed and for the accuracy and quality of movements. Such movements are self-produced, so initially arising in the cerebral cortex. Hence, information on these movements comes into the basal ganglia that determine which muscles will be participate in them and how each of the muscles must be stressed that the movements were as precise and focused.

The basal ganglia consist of the nucleus caudatus and neostriatum, globus pallidus internus and externus, pars reticulate and pars compacta of substantia nigra and the Luys body. Neostriatum is the main part of the basal ganglia, which receives information from the cortex in accordance with somatotopic organization, and intralaminar nucleus of thalamus. The information comes from the basal ganglia, mainly through the globus pallidus internus and pars reticulate of the substantia nigra, passes through the thalamus (ventral intermediate nucleus and nucleus ventralis anterior), which are projected to the premotor cortex, the supplementary motor area and prefrontal cortex. The basal ganglia form several neuronal connections. There is striato-nigro-striatal connection, the end body of which is dopaminergic. This path degenerates in PD with the formation of cell inclusions Lewy bodies. There is also the connection between globus pallidus externus and Luys body, which is then projected in the globus pallidus internus and pars reticulate of the substantia nigra. This path is by nature excitatory and monitors the level of pulsation of the inhibitory neurons of the basal ganglia of thalamic areas. Despite the fact that the structure of the basal ganglia there is some degree of divergence and convergence relations, their projections form a parallel path, which in its most simplified form are classified on the motor way through the putamen, and non-motor way through the caudate nucleus.

The basal ganglia transmit their impulses with the help of special chemical compounds, called neurotransmitters. Their number and mechanism of action (exciting or inhibiting) determine how muscles will work. Dopamine is main inhibitory neurotransmitter which is secreted in the caudate nucleus and the putamen, therefore the destruction of dopaminergic neurons in the substantia nigra a patient with PD theoretically could lead to hyperactivity of the caudate nucleus and the putamen. It may be accompanied by the permanent presence of excitatory signals to the corticospinal motor control system. Excessive excitation of many or all muscles of the body leads to development of their rigidity. After the loss of inhibition in the feedback path, the excitement in some of this path might easily oscillate leading to tremor characteristic of PD.

More than 50-60% of dopaminergic nigrostriatal neurocytes die before clinical implications of PD (bradykinesia, increased muscle tone, resting tremor) begins. There is an assumption of the existence of multiple mechanisms by which brain cells may die [2]. One of the mechanisms is the pathological accumulation of the protein alpha-synuclein that is associated with ubiquitin in the damaged cells. This insoluble protein accumulates intracellular in neurons forming inclusions called Lewy bodies. Lewy bodies initial manifest in the olfactory bulb, medulla oblongata and the tegmentum of pons, and at this stage the disease is asymptomatic. During progression of the disease, Lewy bodies manifest in the substantia nigra, areas of the mesencephalon and basal forebrain, and in the last stage in the neocortex. These areas of the brain represent the main sites of the neurons degeneration in PD; however, Lewy bodies may not cause cell death, they can also carry a protective function. Other mechanisms of cell death include proteasome and lysosomal systems dysfunction and reduced mitochondrial activity. The accumulation of iron in the substantia nigra is usually registered in combination with protein inclusion. It may be associated with oxidative stress, protein aggregation and neuron death, but these mechanisms are understudied. The majority of patients have cognitive defects, affective disorders and autonomic disturbances, which can relate to the damage of the structures other than the nigrostriatal pathway.

Neurophysiologically patients with PD have an increase in the activity of neurons of the globus pallidus internus, which send excitation pulse to the Luys body as a result of loss inhibitory dopaminergic effects on neostriatum. The increase of the deceleration pulse from the globus pallidus internus (and, possibly, the pars reticulate of the substantia nigra) to nucleus ventralis anterior and ventral intermediate nucleus of thalamus leads to a decrease in the activation, patients find it difficult to start movement, because they have violation of activation of the supplementary motor area, while explaining the rigidity and tremor more difficult. In the early disease the condition of patients may improve on the top of administered therapy by the antiparkinsonian drugs.

Despite extensive studies, the cellular mechanisms underlying the degeneration of dopaminergic neurons of the mesencephalon in PD are understudied. Studies on genetic and toxic animal models suggest the possibility that oxidative stress, mitochondrial dysfunction, aberrant processing of proteins by the ubiquitin-proteosome proteolytic system, inflammation and activation of apoptosis play a role in the death of dopaminergic cells [10, 11].

Simplified model of the basal ganglia motor system provides an understanding of how indirectly degeneration of dopaminergic neurons of the substantia nigra is compensated by modulating synaptic transmission at other synapses within the basal ganglia, can provide opportunities for non-dopaminergic therapeutic strategies. The striatum is the primary input to the basal ganglia. It receives excitation from multiple areas of the cerebral cortex, including primary motor cortex and other motor areas.

TEST MODEL OF THE PARKINSON'S SYNDROME

A problem for experimental studies of the pathogenesis of PD is the inability of biological sampling from patients with this disorder, so there is practically no possibility of observing processes in living human cells in PD. There are well-known model of Parkinson's disease in vivo (in living organisms) and in vitro ("in vitro"). Closest to the processes of human cells are models of pathology in vivo on animals, but when they are used there are difficulties with results reproducibility, difficulty of the content of pure lines of animals and justify the use of models in vivo before the Ethics Committee.

At the same time, in recent years use the models in vitro are increasing. Thus, cell culture is a universal method for the study "physiological" and pathological processes elucidate of the signal transfer mechanism, gene regulation, cell proliferation and the mechanisms of their death. These models do not rule out in vivo models, but it is a good supplement to them, allowing you to study the physiological processes and mechanisms of pathogenesis of diseases, to understand the signal transfer mechanism, gene regulation, cell proliferation and death.

It is not revealed to PD occurred naturally in other animal species than humans, although animal models

which show some manifestations of the disease are used in research. There are genetic models that are based on unique gene mutations observed in nepotism PD. However, they are not able to recapitulate aspects of human disease, such as degeneration of dopaminergic neurons, and appeared to be more useful for the study of heredity of PD and not for the evaluation of new therapeutic strategies [12]. Animal models of PD are a means of assessing the ability of new drugs to reduce or stop the motor symptoms and to slow progression of neurodegeneration associated with this condition. Evaluation of new therapeutic target for the symptomatic treatment of PD often depends on the pharmacological and toxic models of PD in mice, rats and primates that are best suited to recreate the motor symptoms of the disease [13]. Pharmacological models are used to explore the therapeutic potential of the compounds, oriented on glutamate receptors, as they are convenient and economical. Pharmacological agents that induce the symptoms of PD include neuroplegics such as the mixed D1\D2 dopamine receptor antagonist haloperidol, which causes muscular rigidity, akinesia and catalepsy. One more thing is reserpine, which causes profound akinesia in rodents [13]. Since there is a lack of standardization of these models by different researchers, it is possible that this pharmacological model will produce different results due to different methodologies. Therefore it is very important to give attention to the methods for the interpretation and comparison of the results of these models. In addition, it is important to keep in mind that parkinsonism which is induced by pharmacological agents in rodents are reversible and do not reproduce the morphological markers of disease, and therefore cannot simulate all aspects of the disease caused by the degeneration of dopaminergic neurons of the substantia nigra. Toxic models of PD are useful for studying therapeutic strategies to treat motor symptoms and neuroprotection and to study the mechanisms of the disease. The appearance of Parkinson's disease symptoms in a group of drug addicts in the 1980-ies who consumed a contaminated consignment of the synthetic opiate MPTP (dopaminergic neurotoxin 1-methyl-4-phenyl-tetrahydropyridine), led to the fact that MPTP was perceived as the agent that causes a parkinson's syndrome in primates, mice, and humans. MPTP is used to study the cellular mechanisms underlying the cell death of dopaminergic system. MPTP can be administrated systematically, but it needs to be converted in the brain into an active metabolite 1-Methyl-4-phenylpyridinium ion (MPP+) by monoamine oxidase. MPP+ is selectively transported into dopaminergic nerve termination with help from the dopamine transporter and causing neurodegeneration by disrupting of mitochondrial function. In primates, MPTP administration closely replicates the behavioral problems of PD, and it is considered the best model for studying the antiparkinsonian effectiveness of new drugs for the treatment of humans. Other models on the basis of toxins include the insecticide rotenone, the herbicide paraquat and the fungicide maneb. Models based on toxins are most commonly used on primates. Transgenic rodent models that replicate various aspects of PD have also been studied [16]. The use of the neurotoxin 6-hydroxydopamine (6-OHDA) produces a model of Parkinson's disease in rats by targeting and destroying dopaminergic neurons in the nigrostriatal pathway with administration in the substantia nigra. 6-OHDA causes unilateral lesion of motor behavior of rats, and new therapeutic agents can be evaluated for treatment of these effects. Despite the fact that is no animal model is not able to perfectly replicate human disease, these models can be tools to assess the therapeutic potential of new targets and agents.

PRINCIPLES OF THERAPY OF PARKINSON'S DISEASE

Despite the stage of the disease, the modern approach to the treatment of PD involves two main strategies such as the search for agents that can slow, delay or stop its progression (called neuroprotection) and the creation of new, more effective drugs for symptomatic treatment. The latter at the present time is recognized the primary. Principles of drug therapy of Parkinson's disease largely base on the concept of dopaminergic deficit, and also on modern concepts about the functioning of the dopaminergic synapse and the pathogenesis of neurodegenerative diseases. In accordance with these principles therapy of PD involves the use of drugs that increase the synthesis of dopamine in the brain; stimulate the release of dopamine from presynaptic terminals and inhibit its reuptake of presynaptic elements; inhibit the degradation (catabolism) of dopamine; stimulate the postsynaptic dopamine receptors; prevent of progressive neuronal death and slow the progression of the disease. The complex treatment of Parkinson's disease should include antioxidants (for example, natural vitamin E, not synthetic), exercise therapy. Because the disease is understudied, scientists still carry on polemics about possibility to slow the inevitable progression of the disease upon the existence of symptoms of PD.

Levodopa (precursor of dopamine) is a stereoisomer of dihydroxyphenylalanine (DOPA), which, as opposed to the dopamine, penetrates well into CNS. Under the action of the enzyme DOPA-decarboxylase levodopa is transformed into dopamine, thereby increasing its level in neostriatum.

The symptoms of Parkinson's disease disappear within a short period of time. Levodopa is effective only constant concentration control in the body. With disease progression, and a decrease in the number of cells of the neurons of the substantia nigra, its effectiveness is sharply reduced. 97-99% levodopa transforms into dopamine in peripheral tissues, causing many side effects of the drug. With the aim of reducing its number, levodopa is used in combination with inhibitors of DOPA decarboxylase (carbidopa, benserazide) that doesn't pass through the CNS. This combination metabolism of levodopa can occur only in the brain. The use of combinations of levodopa and carbidopa ("Nakom", "Sinemet") increases the likelihood of side effects from the CNS, such as dyskinesia (80% of cases), anxiety, depression, delusions, hallucinations.

MAO inhibitors (Selegiline, Rasagiline) metabolize dopamine, increasing its level in neostriatum. The use of these drugs with levodopa can reduce the dose of the latter.

Tolcapone, entacapone are COMT inhibitors, an enzyme that is responsible for the distribution of dopamine in the neurons. The administration of the combined precursor of dopamine leads to compensatory activation of this enzyme. The treatment efficiency is lowered. Tolcapone and entacapone inhibit COMT, allowing reducing the dose of levodopa.

Dopamine receptor agonists are bromocriptine (partial agonist of the dopamine receptors (D2)), lisuride (a derivative of ergot alkaloids), pergolide (dopamine receptors agonist (D1 and D2)).

Drug that inhibits excitation of neostriatum neurons by acetylcholine is trihexyphenidyl (Cyclodol) which is a muscarinic antagonist. Its effectiveness in PD is weaker than levodopa. It well eliminates tremor and muscular rigidity, but does not affect bradykinesia. It is used in composition of complex therapy.

Glutamate receptors antagonists (NMDA) are a relatively new group of drugs. Glutamate is exitotoxic transmitter in relation to pathways. Its action on NMDA receptors induces the movement of Ca^{2+} inside the cell, which leads to a sharp increase of stimulation and subsequent neuronal death in PD. Drugs that block glutamate receptors (amantadine, symmetrel) reduce toxic effects caused by stimulation of NMDA receptors.

Operative treatment of PD, which is aimed at reducing the activity of the Luys body, and deep brain stimulation, has been very effective [14, 15]. Deep brain stimulation (Luys body or the globus pallidus internus) significantly reduces motor symptoms (tremor, bradykinesia, rigidity), however, the exact mechanism by which this effect is achieved remains unclear. Unfortunately, surgery cannot be called widely available due to their relatively high cost and a large number of contraindications for their conduct. The fact that the lesion of the Luys body and globus pallidus with deep brain stimulation improves the symptoms of Parkinson's disease, suggests that pharmacological drugs which are able to reduce the activity of the Luys body can provide significant relief of motor symptoms.

OVERVIEW OF TESTS OF DIFFERENT TYPES OF GLUTAMATE RECEPTORS ANTAGONISTS

In the last 20 years there have been many studies showing that glutamate receptors antagonists can be used as drugs for the treatment of Parkinson's disease, as in combinations with levodopa and independently. The following is the main conclusions and assumptions obtained during the testing of these drugs.

On the basis of numerous studies it can be assumed antiparkinsonian effect of NMDA receptors antagonists, since NMDA receptors mediate glutamatergic excitation of neurons in the striatum and Luys body, which is shown in various animal models (rats treated with haloperidol, monkeys treated with MPTP) [7]. Receptor blockade may be competitive and noncompetitive antagonists. Competitive antagonists of NMDA receptors (SDZ 220-581) directly block glutamate recognition site of the NMDA-receptor. Noncompetitive antagonists of NMDA receptors (MK-801, dextrorphan, MSZ 2\579, CP-101606) connect the phencyclidine recognition site of the NMDA receptors. It is known that these antagonists and antagonists of the glycine site (MRZ 2\570, L-701324, (R)-HA-966)) revert catalepsy and muscular rigidity which are induced by blockade of dopamine receptors in rats. Numerous studies show that NMDA receptors antagonists such as MK-801 and MRZ 2\579, also revert akinesia and other motor disorders in rodents, whereas antagonists of the glycine site of the NMDA-receptors is not effective in this model. Assume that the antiparkinsonian effect of NMDA receptors antagonists consist in blockade of the activity of these receptors in the striatum and the output nuclei of the basal ganglia. Another possible mechanism by which this effect is achieved is the reduction in the release of acetylcholine from cholinergic neurons of the striatum. It is also interesting that some NMDA receptors antagonists can potentiate the effect of levodopa suppressing motor fluctuations and dyskinesia that was shown in models of rodents and primates, and consequently it can be most effective in

combination with levodopa therapy. There is a perception that global inhibition of NMDA receptors may lead to the development of serious side effects, such as psychosis, learning disability and disordered motor function. This assumption leaves in doubt the development prospect of NMDA receptors as new therapeutic target. Therefore testing of combinations of NMDA receptor specific subunits has renewed interest in this issue. NR2B is a subunit of NMDA receptor in a large number is found in the striatum and in nuclei of the basal ganglia, so it is assumed that agents that selectively affect NMDA receptors containing the NR2B subunit may have more specific impact on the function of the receptor in areas of the brain relevant to the pathophysiology of PD. Such agents have been developed and studied their antiparkinsonian effects in animal models. For example, traksoprodil (CP-101606) changes catalepsy caused by haloperidol in rats and reducing motor symptoms of Parkinson's disease in affected by MPTP monkeys. Another NMDA NR2B selective receptor antagonist ifenprodil also reduces motor symptoms of PD in affected by MPTP monkeys. In addition, these drugs improve the effectiveness of levodopa that speaks about the clinical benefits of combination treatment.

At present amantadine is only used as the NMDA receptors antagonist, which blocks the noncompetitive NMDA-receptors in therapeutically effective concentrations. Amantadine stimulates release of dopamine from presynaptic terminals, reduces the reuptake dopamine in the synapse, inhibits glutamatergic influence the frontal cortex on the striatum and has a distinct holinoblokirutm anticholinergic activity. As antagonist of glutamate receptors amantadine can implement its action at the level of the excitotoxic cascade [16, 17].

Although clinical benefit of amantadine monotherapy is questionable, double-blind, placebo-controlled study showed that amantadine reduces dyskinesia and motor fluctuations in patients treated by levodopa. These data suggest that further study NMDA receptors antagonists may be of utility to complex therapy with levodopa. Besides amantadine inhibits the development of dementia in patients with PD, suggesting another positive effect of the blockade of NMDA receptors. Another NMDA receptors antagonist remacemide was also studied in patients with PD, both as monotherapy and in complex with levodopa. However, despite its antiparkinsonian effect in rats and primates, it has not shown the desired effect on people, causing some doubts in the use of NMDA receptors antagonists in the symptomatic treatment of PD. Thus further clinical studies using more selective drugs are very promising [7].

AMPA receptors antagonists were also proposed as potential therapeutic agents; however, preclinical studies have shown that they do not possess antiparkinsonian activity in monotherapy. For example, systemic administration of NBQX and GYKI 52466 does not prevent catalepsy induced by haloperidol in rats. NBQX monotherapy has also not improved motor symptoms in rats induced by 6-OHDA and MPTP affected primates. In addition GYKI 52466 has no effect on akinesia in rats with monamine deficite, and does not intensify activities of levodopa in the same model. However, other studies have shown antiparkinsonian effect of AMPA receptors antagonists, independently and in combination with dopaminergic therapy. For example, NBQX has set up muscular rigidity (but not akinesia) induced by reserpine in rats, and motor deficite in MPTP affected primates. Also noted that NBQX improves the ability of levodopa to set up motor deficite in lesions of the substantia nigra in rats and primates. It is assumed that the different results of the studies were due to the fact different methods of induction of parkinsonism in animals (models with the use of neurotoxins has been more promising).

Preclinical studies of AMPA receptors antagonists in the treatment of levodopa-induced dyskinesias gave more encouraging results for the potential use of these drugs in the treatment of PD. Noncompetitive AMPA receptors antagonist LY300164 (Talampanel) improves motor symptoms and reduces levodopa-induced dyskinesia in MPTP affected monkeys. Competitive AMPA receptors antagonist – LY293558 in combination with levodopa reduces levodopa-induced dyskinesia in 6-OHDA rats. Interestingly, combined blockade by low (ineffective) doses of the AMPA and NMDA receptors antagonists reduces levodopa-induced dyskinesia in rats and primates, suggesting the possibility of using low doses of glutamate receptors antagonists to reduce dyskinesia [7].

Metabotropic glutamate receptors (mGluR), in contrast to the "fast" ionotropic, provide a slow response to glutamatergic signals, and also represent a therapeutic target for the treatment of PD. Metabotropic glutamate receptors consist of seven transmembrane domains connected to to G-proteins, which mediate most of the effects of these receptors activation. Itself receptors consist of two subunits one of which binds glutamate. Metabotropic glutamate receptors (mGluR) are divided into three groups (mGluRI , mGluRII and mGluRIII), although discovered eight genes that encode it (mGluRI

includes mGluR1 and -5, mGluRII is mGluR2 and -3, mGluRIII is mGluR4, -6, -7). Metabotropic glutamate receptors are activated by lower concentrations of glutamate than the main ionotropic AMPA receptors. A group of mGluRI are usually located on the postsynaptic membrane around the synaptic cleft. The effect of activation of these receptors opposes the effect of dopamine and directly stimulates the hyperactive nuclei in the Parkinsonian brain [18]. Furthermore, its activation potentiates currents of NMDA receptors in the striatum and Luys body. Antagonists of these receptors could have antiparkinsonian effect by reducing the excitation of hyperactive basal ganglia. In accordance with this hypothesis, several negative allosteric modulators of mGluR5 (MPTP and MTEP) have antiparkinsonian effect on animal models. Interestingly, combined treatment by MPEP and A_{2A} adenosine receptors antagonists causes a noticeable reduction of akinesia in 6-OHDA or reserpine affected rats. This suggests the effectiveness of symptomatic therapy of PD with the combination of mGluR5 antagonists and A_{2A} adenosine receptors antagonists. A similar effect is observed with the introduction of MPEP and MK-801 in 6-OHDA affected rats, which also indicates a possible antiparkinsonian effectiveness of simultaneous administration of NMDA receptors antagonists and mGluR5 antagonists. Systemic administration of MTEP to 6-OHDA affected rats reduces levodopa-induced dyskinesias in animals for a long time treated with levodopa. These data indicate that the possibility of mGluR5 antagonists may be useful for symptomatic treatment of PD in patients receiving long-term treatment by levodopa. Despite the positive result in the study of antiparkinsonian effect of mGluR5 antagonists, the mGluR1 antagonists (EMQMCM) failed to reduce levodopa-induced dyskinesia, in connection with which they cannot be a promising target for the treatment of motor symptoms of PD.

The data of electrophysiological studies show that the activation of mGluRII in the hypothalamic-nigral synapses reduces their excitation. In accordance with this intranigral or intracerebroventricular adminisrtation of the mGluRII antagonist (DCG-IV, LY379268) restores the reserpine-induced akinesia in rats. Another mGluRII antagonist (LY354740) reverses haloperidol-induced catalepsy and muscular rigidity in rats. However mGluRII do not affect the locomotor deficit caused by the reserpine to rats, which limits the therapeutic potential of this group to relief the motor symptoms of PD. Physiological studies on brain slice of rats showed that the selective mGluRIII agonist (L-AP4) reduces synaptic transmission striato-pallidal and the hypothalamic-nigral synapses. Also microdialysis studies have shown that L-AP4 and L-SOP reduce the release of GABA in the globus pallidus in rats. These data suggest that activation of mGluRIII can facilitate motor symptoms of PD, or by reducing the activity of the indirect pathway, or by reducing the activity of the nuclei in the hypothalamus. L-AP4 may be very effective in the treatment of PD symptoms, because it acts on the asymmetry of the forelegs 6-OHDA affected rats to the same extent as levodopa. Intrapallidal administration of L-SOP facilitates the reserpine-induced akinesia in rats, which confirms the hypothesis that the decrease in the activity of these synapses can have therapeutic efficacy.

Glutamate receptors may be promising targets for treatment of neurological and psychiatric complications associated with PD, such as anxiety, depression and cognitive defects. The mGluRII and mGluR5 antagonists have anxiolytic action in preclinical models of anxiety, suggesting the possibility of their use for the treatment of both motor and psychiatric symptoms of PD. Also mGluRIII, mGluR5 and mGluRII antagonists are effective in preclinical models of depression, suggesting that they may be targets for treatment of depression in patients with PD.

CONCLUSION

The main drugs in the treatment of PD are levodopa and its derivatives, as well as the phenothiazine type antipsychotics and anticholinergic drugs. Unfortunately, they have quite a large number of side effects, and over time, the dosage should be increased, otherwise its cease to be effective. This poses a lot of problems. The physician should determine the time of starting therapy and the group of drugs with which is more expedient to start the treatment to postpone the development of side effects at a later date. Until now, scientists and clinical physicians have failed to find ways of slowing down the pathological process, and the more it stops or prevent. Although PD is tried to cure, the experts can only partially eliminate the symptoms but not the cause itself. Today, all the efforts of scientists aim at finding drugs which are not only soften the symptoms of the disease, but also stop the degenerative processes responsible for its progression.

The study of glutamate receptors antagonists is an important task in the search for new pharmacological agents for the treatment of PD. Selectiveness of new agents is a key feature. Although the development of selective agents will

help to understand which subtypes of receptors mediate pro – or antiparkinsonian effects, it remains possible that the ideal treatment for PD will be directed at several subtypes of receptors.

ABBREVIATION LIST

6-OHDA – 6-hydroxydopamine
AMPA – alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
BBB – blood-brain barrier
CNS- central nervous system
COMT – catechol-O-methyltransferase
DOPA – dihydroxyphenylalanine
GABA – gamma-amino-butyric acid
MAO-B – monoamine oxidase type B
mGluR – Metabotropic glutamate receptors
MPP+ – 1-Methyl-4-phenylpyridinium ion
MPTP – 1-methyl-4-phenyl-tetrahydropyridine
MTEP – 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine
NMDA – N-methyl-D-aspartate
PD – Parkinson's Disease

REFERENCES

1. Lees A. J. Unresolved issues relating to the shaking palsy on the celebration of James Parkinson's 250th birthday. *Mov Disord.* Vol. 22, no. Suppl 17 (2007): S327—334. [PubMed] [Fulltext]
2. Obeso JA, Rodríguez-Oroz MC, Benitez-Temino B et al. «Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease». *Mov. Disord.* 23 (Suppl 3) (2008).: S548–59. [PubMed] [Fulltext]
3. Delong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. *Arch Neurol.* 64(1) (2007): 20-24. [PubMed] [Fulltext]
4. Chen JJ, Swope DM. Pharmacotherapy for Parkinson's disease. *Pharmacotherapy.* 27(12 Pt2) (2007): 161S-173S. [PubMed] [Fulltext]
5. Stacy M, Galbreath A. Optimizing long-term therapy for Parkinson disease: levodopa, dopamine agonists, and treatment-associated dyskinesia. *Clin Neuropharmacol*. 31 (1) (2008): 51-56. [PubMed] [Fulltext]
6. Olanow C.W., Stern M.B., Sethi K. The scientific and clinical basis for the treatment of Parkinson's disease. *Neurology.* V. 72, 21, Suppl. 4 (2009): 149. [PubMed] [Fulltext]
7. Kari A. Johnson, P. Jeffrey Conn, Collen M. Niswender «Glutamate receptors as therapeutic targets for Parkinson's disease». *CNS Neurol Disord Drug Targets*. 8 (6) (2009,Dec): 475-491. [PubMed] [Fulltext]
8. Karaban I.N. Use of Glutamate Receptor Blocker Amantadine in Neurology. *International neurological journal.* 2 (2012): S195-201. [eLIBRARY]
9. Blanpied T.A., Clarke R.J., Johnson J.W. Amantadine inhi-bits NMDA receptors by accelerating channel closure during channel block. *J. Neurosci.* 25 (2005): 3312-3322. [PubMed] [Fulltext]
10. Betarbet R, Sherer TB, Greenamyre JT. Ubiquitin-proteasome system and Parkinson's diseases. *Exp Neurol.* 191 Suppl 1 (2005):S17-S27. [PubMed] [Fulltext]
11. Pizedborski S. Pathogenesis of nigral cell death in Parkinson's disease. *Parkinsonism Relat Disord.* 11 (Suppl 1) (2005): S3-S7. [PubMed] [Fulltext]
12. Terzioglu M, Galter D. Parkinson's disease:genetic versus toxin-induced rodern models. *FEBS J.* 275(7) (2008): 1384-1391. [PubMed] [Fulltext]
13. Betarbet R, Sherer TB, Greenamyre JT. Animal models of Parkinson's diseases. *Biossays.* 24(4) (2002): 308-318. [PubMed] [Fulltext]
14. Walter BL, Vitek JL. Surgical treatment for Parkinson's disease. *Lancet Neurol.* 3(12) (2004): 719-728. [PubMed] [Fulltext]
15. Wichmann T, DeLong MR. Deep brain stimulation for neurologic and neuropsychiatric disorders. *Neuron.* 52(1) (2006): 197-204. [PubMed] [Fulltext]
16. Shapira A.H. Etiology and pathogenesis of Parkinson's disease. *Neurol. Clin.* V. 24 (2009): 583-603. [PubMed] [Fulltext]
17. Thomas A., Bonnani L., Gambi F. Pathological gambling in Parkinson's disease is reduced by amantadine. *Ann. Neurol.* V. 68 (2010): 400-404. [PubMed] [Fulltext]
18. Conn PJ, Battaglia G, Marino MJ, Nicoletti F. Metabotropic glutamate receptors in the basal ganglia motor circuit. *Nat Rev Neurosci.* 6(10) (2005): 787-798. [PubMed] [Fulltext]