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Review Article

Mechanism of neuroprotective effect of mGluR4 agonists

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Abstract

Introduction: This review of literature is to demonstrate a role of group III metabotropic glutamate receptors in maintaining the level of extracellular glutamate in ischemic stroke and neurodegenerative diseases.

Metabotropic glutamate receptors: mGluRs are classified into three groups. It is suggested that the activation of mGluR4 may have a neuroprotective effect.

Role of excitotoxicity in the development and severity of various brain diseases: An increase in the concentration of intracellular Ca^{2+} is the result of excessive accumulation of glutamate in the extracellular space. And a death of nerve cells occurs after a sequence of biochemical reactions, which was called excitotoxicity. It is followed by an imbalance between glutamatergic excitation and GABA-ergic inhibition. As a result of untimely activation of the inhibitory mechanisms, the accumulation of extracellular glutamate, and consequently the death of neurons, continues, which leads to more severe manifestations of the cerebral ischemia.

Role of modulation of mGluRs activity in neuroprotection: The literature describes a large number of studies proving that inhibition of hyperactive glutamatergic transmission has a neuroprotective effect. The most likely mechanisms of neuroprotection are inhibition of glutamate production in the substantia nigra, which in turn protects against glutamate-mediated excitotoxicity, and the reduction of the inflammatory effects.

Anti-inflammatory effect of mGluR4 agonists in the mechanism of neuroprotective action: The astroglial component may contribute to the protective action of mGluR4 modulators, since astrocytes and microglia have mGluR4.

Conclusion: mGluR4 agonists have the neuroprotective and anti-inflammatory effects.

Keywords

Parkinson's disease, neuroprotective effect, mGluR4 agonists, excitotoxicity, neurodegenerative diseases.

Introduction

In neurological diseases, the main mechanism of neuronal death is excitotoxicity along with apoptosis, necrosis and autophagy (Arkhipov et al. 2013). Excitotoxicity is a common link in the mechanisms of ischemia and many neurodegenerative and inflammatory diseases. Excitotoxicity occurs as a result of hyperactivation of ionotropic glutamate receptors, which leads to a disruption of the ion channels permeability. The accumulation of intracellular Ca^{2+} triggers

a pathway, which activate a number of enzymes that damage neurons. The influence on the excitotoxicity mechanisms is the main line of a search for neuroprotective agents for the treatment of such diseases as epilepsy, ischemic stroke, Parkinson's disease, etc. (Domin et al. 2016). The purpose of this article is to demonstrate the role of mGluRs in maintaining the level of extracellular glutamate in excitotoxicity or cerebral ischemia (Moyanova et al. 2011).

Metabotropic glutamate receptors

The main excitatory transmitter of the central nervous system is glutamate, which is able to modulate synaptic activity through ionotropic and metabotropic receptors. Metabotropic receptors can be located on both pre- and postsynaptic membranes. Metabotropic glutamate receptors (MGlur) are involved in many physiological and pathological processes, making them a promising target for the development of new therapeutic agents (Nicoletti et al. 2011).

Metabotropic receptors transmit a signal through G-proteins, which in turn lead to the opening or closing of the ion channels of the cell. MgluRs are classified into 3 groups (I-III). Group I mGluRs (mGlu1 and mGlu5) are usually located on the postsynaptic membrane and are linked to phospholipase C via G-protein, and their activation leads to hydrolysis of phosphoinositide and intracellular accumulation of Ca^{2+}. Group II (mGlu2 and mGlu3) and group III receptors (mGlu4, mGlu6, mGlu7 and mGlu8) are linked to the adenyl cyclase by negative feedback, and their activation inhibits the producing of cAMP (cyclic adenosine monophosphate) (Avdeeva et al. 2018, Johnson et al. 2009).

Group III mGlur receptors are predominantly located on the presynaptic terminals of glutamatergic and GABA-ergic neurons, participating in the regulation of synaptic transmission (Ferraguti et al. 2008, Selvam et al. 2018). The activation of mGlu receptors located on glutamatergic neurons causes a decrease in glutamate secretion, thereby inhibiting excitatory glutamatergic transmission (Schoepp 2001). Therefore, it is suggested that the activation of these receptors may have a neuroprotective effect.

Role of excitotoxicity in the development and severity of various brain diseases

In the first hours and minutes after the onset of brain ischemia, a focus of necrosis is formed, which is based on the reactions of the glutamate-calcium cascade or excitotoxicity. The development of the glutamate-calcium cascade is triggered by the release of glutamate from the ischemic neurons into the intercellular space (Olney 1994).

The initial stage is characterized by a disruption of ion transport, resulting in intracellular accumulation of Ca^{2+}, which after a sequence of biochemical reactions leads to necrotic death of neurons. It is known that the principal way of Ca^{2+} entry into the cell is agonist-activated calcium channels, which are controlled by glutamate-activated receptors (NMDA receptors) (Hopkins et al. 2009).

The concentration of intracellular Ca^{2+} and glutamate in the extracellular space continues to increase. It is known that serum proteins migrate to the brain tissue as a result of the Ca^{2+} accumulation. The presence of albumin in conditions of increased glutamate release significantly increases the ischemic zone, as it potentiates excitotoxicity by keeping agonist-activated calcium channels of NMDA receptors open for a long time (Linde et al. 1996).

In the final stage, irreversible processes occur (first of all, free radical reaction, lipid peroxidation, excessive production of nitric oxide, eicosanoids, platelet-activating factor, etc.), leading to necrotic cell death (Olney 1994).

T.P.Obrenovitch et al. in their studies showed that the maximum concentration of glutamate in the extracellular space is reached as early as the first hours of ischemia, whereas the concentration of GABA increases only by the end of the first day of the pathology development. In the normal condition, the mechanisms of glutamate-ergic excitation and GABA-ergic inhibition are in balance, and the imbalance between the excitatory and inhibitory systems prevents the timely activation of protective inhibitory mechanisms of the brain. It is noteworthy that the glutamate level is higher in more severe cerebral ischemia compared to moderately severe ischemia. At the same time, GABA concentrations were higher in patients with moderate ischemia than in severe ones (Wahl et al. 1994). These data make it possible to suggest that regular administration of drugs that potentiate GABA-ergic inhibition, such as agonists of group III metabotropic receptors will lead to a milder disease progression in the event of a stroke.

Thus, not only excitotoxicity takes part in the development of acute cerebral ischemia, but also the imbalance between the inhibitory and excitatory mechanisms, shifted towards insufficient inhibition. This is confirmed by numerous studies on animals, in which acute cerebral ischemia was simulated (Voronkov and Pozdnyakov 2018).

Role of mGluR modulation in neuroprotection

The literature describes a large number of studies proving that inhibition of hyperactive glutamatergic transmission has a neuroprotective effect. With regard to the neuroprotective action of antagonists of ionotropic glutamate receptors (iGluRs) in the central nervous system, the results of clinical trials were unsuccessful due to the side effects, such as ataxia, sedation, psychotic effects and memory impairment (Ikonomidou and Turski 2002), due to which they have been widely administered in the clinical practice. Therefore, modulation of glutamatergic transmission may be a more promising neuroprotective strategy than direct receptor antagonism (Lea and Faden 2003, Rovira et al. 2016).

Experimental studies have shown the presence of the neuroprotective effect of group III mGluRs agonists. Neuroprotective efficacy of drugs affecting mGluR4 was also assumed in treating Parkinson's disease, autism and cerebellar ataxia (Power and Empson 2014). In haloperidol and reserpine models of parkinsonism the administration of mGluR4 agonists resulted in a decrease in the symptoms and signs (Niswender and Conn 2010). This study also showed that the activation of mGluR4 may ultimately prevent continuing neurodegeneration in Parkinson's disease.

MGluR4 receptor-mediated neuroprotection may be based on various mechanisms. The two most likely mechanisms are: inhibition of glutamate production in the substantia nigra, which in turn protects against glutamate-mediated excitotoxicity, and the reduction of the inflammatory effects.

As for the hypothesis of inhibition of glutamate production, previously conducted *in vitro* studies showed that L-AP4, the agonist of group III metabotropic glutamate receptors, suppressed the glutamate-mediated excitation of dopaminergic neurons in the substantia nigra pars compacta, and the local intranigral administration of L-SOP reduced the release of glutamate in the substantia nigra pars compacta (Mercier and Lodge 2014). As a result, it was concluded that mGluR4 are a key subtype of metabotropic receptors responsible for inhibition of glutamatergic excitation in the substantia nigra (Valenti et al. 2005). In further studies, a putative neuroprotective effect of mGluR4 agonists, including inhibition of glutamate release in the substantia nigra, was studied. The administration of another positive allosteric modulator PHCCC ((7E)-7-hydroxyimino-N-phenyl-1,7 a-dihydrocyclopropa[b]chromene-1a-carboxamide) in the globus pallidus leads to the elimination of the MPTP-induced motor disorders. Thus, the neuroprotection in the MPTP-induced parkinsonism model is based on the mGluR4-mediated normalization of glutamatergic excitation in the substantia nigra or indirectly through the correction of the pallid subthalamic pathway and the subsequent inhibition of glutamatergic excitation in the substantia nigra pars compacta (Battaglia et al. 2006).

In most studies, group III mGluRs agonists were administered mainly before, simultaneously, or shortly after the disease onset. The study of neuroprotective effect of group III mGluRs agonist ACPT-I after its delayed administration (30 min-3 hours) showed its effect on kainite-induced excitotoxicity. The main conclusion of this study was that ACPT-I reduced kainite-induced neuronal damage *in vitro* and *in vivo*.

Anti-inflammatory effect of mGlur4 agonists neuroprotection

It is known that activated microglia participates in neurodegeneration of dopaminergic neurons in the substantia nigra by the release of pro-inflammatory cytokines and reactive oxygen species. Normally, neurons with astrocytes release factors that inhibit the microglia activity. A brain injury leads to the microglia activation and its attachment to neurons. Further, a cytoskeleton of the microglia cells is disrupted, and microglia acquires phagocytic activity. The activated microglia releases inflammatory cytokines, which increase the inflammatory response, as well as neurotoxins (TNF-α and others), which leads to damage of other neurons. Experimental animal models showed the importance of inflammatory processes associated with activation of microglia in the degeneration of nigrostriatal dopaminergic neurons (Kucheryanu et al. 2012).

The presence of mGluR4 on astrocytes and microglia increases the likelihood of the astroglial component contributing to the protective action of mGluR4 modulators (Taylor et al. 2003).

Inflammation plays a key role in the pathogenesis of many neurologic diseases, including Parkinson's disease (Schapira 2009, Tansey and Goldberg 2010). In 6-OHDA-induced parkinsonian syndrome in rats, microglia is activated, and the level of pro-inflammatory cytokines in the corpus striatum and substantia nigra pars compacta increases, after which the microglial cells group along the dopaminergic neurons and become phagocytic (Cicchetti et al. 2002). In experiments on mice, L-AP4 administration decreased pro-inflammatory cytokines production, which proves the role of mGluR4, including astroglial ones in the potential anti-inflammatory action (Besong et al. 2002). In another study, the administration of a positive allosteric modulator of mGluR4 – VU0155041 (cis-2-[[(3,5-Dichlorophenyl) amino]carbonyl] cyclohexanecarboxylic acid) significantly decreased the level of GFAP (glial fibrillary acidic protein – a predictor of the neuron cell death) and IBA-1 (ionized calcium-binding adaptor molecule 1) in mice with 6-OHDA-induced astroglial neurotoxicity, which also confirms this theory. Although these mechanisms have been just started to be studied, the obtained results support the assumption about the anti-inflammatory effect of mGluR4.

Conclusion

Metabotropic glutamate receptors are involved in the activation of intracellular metabolism and play an important role in the regulation of the Ca^{2+} entry into the cell caused by the activation of NMDA receptors in cerebral ischemic stroke, Parkinson's disease and inflammation.

MGluR4 agonists correct the imbalance between GABA-ergic inhibition and glutamate-ergic excitation, providing neuroprotective and anti-inflammatory effects. In this regard, drugs modulating mGluR4 are involved in the activation of intracellular metabolism and can be recommended for use in the treatment of Parkinson's disease, acute cerebral ischemia and inflammatory diseases (Bossi et al. 2018, Lester et al. 2010).

Conflict of interests

The authors state no conflict of interest concerning with the present submitted manuscript.

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