Review article

Glutamate metabotropic receptors and its relationship with Amiotrophic Lateral Sclerosis (ALS)

Receptores metabotrópicos de glutamato e sua relação com a Esclerose Lateral Amiotrófica (ELA)

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS), a fatal neurodegenerative disease that affects upper and lower motor neurons, has as the most accepted pathophysiology the glutamate-mediated excitotoxicity. The present study aims to establish the relationship between this neurotransmitter and ALS, based on a literature review in the PubMed and Medline databases. Glutamate is the main neurotransmitter of the central nervous system (CNS) and the excitotoxicity generated by its accumulation in the synaptic clefts is considered one of the main mechanisms involved in the pathophysiology of ALS. People affected by ALS present a decrease in expression of certain metabotropic glutamate receptor (mGlu) groups in neurons and glial cells of these patients. mGlu has a prominent role in modulating glutamate excitotoxicity and are subdivided into three groups. Group 1 mGlu amplifies rapid excitatory synaptic transmissions, while groups 2 and 3 act as neuroprotective agents, since among other functions they inhibit glutamate release into the synaptic cleft. Finally, mGlu are considered therapeutic targets for the action of drugs that fight excitotoxicity and induce the production of neurotrophic factors, constituting an important action in the fight against ALS.

Keywords: Receptors Metabotropic Glutamate; Glutamate; Amyotrophic Lateral Sclerosis.

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Received on: 01/19/2021.

Approved on: 03/27/2021.

DOI: http://dx.doi.org/10.5935/2238-3182.20210024

RESUMO

A Esclerose Lateral Amiotrófica (ELA), uma doença neurodegenerativa fatal, que afeta neurônios motores superiores e inferiores, tem como fisiopatologia mais aceita a excitotoxicidade mediada por glutamato. O atual estudo tem como objetivo estabelecer a relação entre esse neurotransmissor e a ELA, a partir de uma revisão de literatura nas bases de dados Pubmed e Medline. O glutamato é o principal neurotransmissor do Sistema Nervoso Central (SNC) e a excitotoxicidade gerada pelo seu acúmulo nas fendas sinápticas é tida como um dos principais mecanismos envolvidos na fisiopatologia da ELA. Os indivíduos afetados pela ELA apresentam diminuição da expressão de determinados grupos de receptores metabotrópicos de glutamato (mGlu) nos neurônios e nas células da glia desses pacientes. Os mGlu possuem um papel de destaque na modulação da excitotoxicidade por glutamato e são subdivididos em três grupos. Os mGlus do grupo 1 amplificam as transmissões sinápticas excitatórias rápidas, e os dos grupos 2 e 3 atuam como neuroprotetores inibindo a liberação do glutamato na fenda sináptica. Os mGlus são, portanto, considerados alvos terapêuticos para a atuação de drogas que combatem a excitotoxicidade e induzem a produção de fatores neurotróficos, constituindo importante atuação no combate à ELA.

Palavras-chave: Receptores de Glutamato Metabotrópico; Glutamato; Esclerose Amiotrófica Lateral.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease, of late onset, characterized by the death of neurons in the motor cortex, brain stem and spinal cord, in other words, it affects both upper motor and lower motor neurons [1] leading to muscle wear, weakness and spasticity.[2]

Although the primary symptoms of ALS are associated with motor dysfunction, 50% of patients develop cognitive and / or behavioral impairment during the course of the disease and 13% have frontotemporal dementia.[2] This disease is fatal and usually, the patient does not live more than three years after the first symptoms appear. [3]

ALS affects between 2 and 3 every 100,000 individuals,[4] with approximately twice as much incidence in men as in women, with predominance in individuals over 45 years of age. [5]

Despite having a complex and still poorly understood etiology, it is known that genetic factors are responsible for only 5 to 10% of cases.[6,7] More than 30 genes associated with this pathology have been identified, being that 4 (C9ORF72, SOD1, TARDBP and FUS) responsible for about 70% of all cases of the familial forms.[2,5] SOD1 was the first ALS-related gene to be identified and corresponds to 20% of familial cases of the disease.[1]

One of the main factors responsible for the occurrence of ALS is glutamate-mediated excitotoxicity[1,3], which is found in high extracellular levels in the brain of patients with this disease.[8] This amino acid is the main excitatory neurotransmitter present in the central nervous system. During axonal depolarization, glutamate is released by presynaptic neurons and activates metabotropic glutamatergic receptors that are activated by the binding of neurotransmitters that induce a signaling pathway with consequent opening or closing of ion channels, indirectly. In addition, it activates receptors specific ionotropics that are transmembrane protein ion channels activated by ligands located on the postsynaptic neuronal membrane.[9]

The proposed molecular mechanisms involved in ALS neurodegeneration involve mitochondrial changes, formation of undegraded toxic protein aggregates, cytoskeleton breakdown, reduced production of neurotrophic factors by glial cells and excitotoxicity, whose action of glutamate on ionotropic receptors (iGlu) and metabotropics (mGlu) have a prominent role.[10,11]

The mGlu receptors are involved in the pathophysiology of several neurodegenerative diseases, being considered potential targets for the performance of drugs that combat excitotoxicity and induce the production of neurotrophic factors.[5]

The study aimed to analyze the contribution of metabotropic receptors of the excitatory neurotransmitter glutamate to ALS.

Methodology

A literature review was performed by using a bibliographic and transversal search from the databases: PubMed (National Center For Biotechnology Information) and MedLine.

The following descriptors were used to limit the selection of the articles: (glutamate) AND (amyotrophic lateral sclerosis). In addition, the search was reduced to articles published between 2000 and 2019, in which only full articles in English were included.

Finally, exclusions were made regarding the title and reading of abstracts, in order to select the articles that really support the research objectives. The selection process is described in Figure 1.

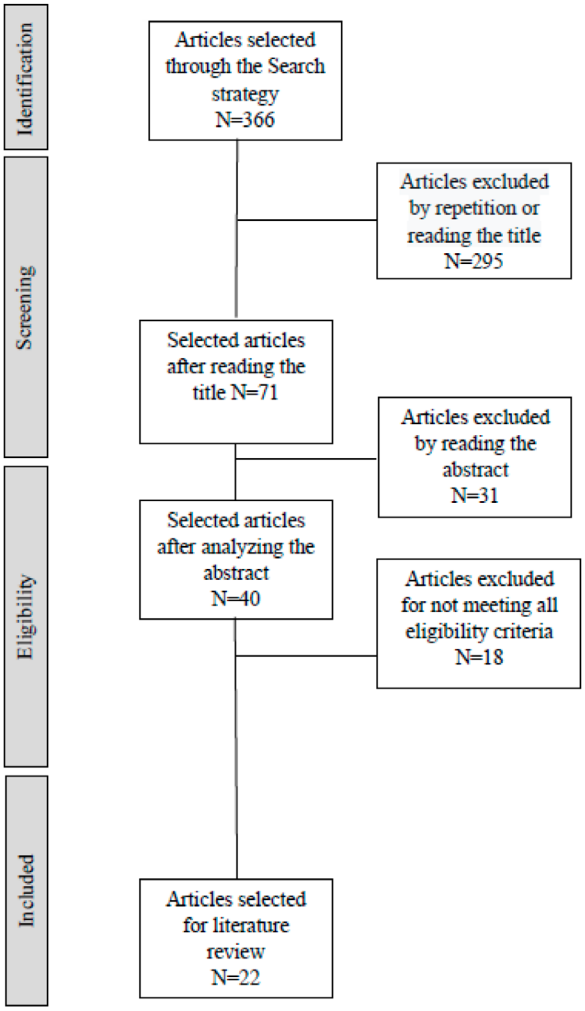

Figure 1. Article selection process.

Results and Discussion

glutamate is the most important excitatory neurotransmitter in the central nervous system (CNS) of mammals, involved in most brain functions. Whereas the extracellular accumulation is toxic, its ideal concentrations are maintained by glial cells and neurons.[12] This occurs through sodium-dependent glutamate (GLT) transporters which keep extracellular glutamate levels below the threshold for excitotoxicity.[5] There are five subtypes of these transporters, however, GLT 1, also known as the excitatory amino acid transporter 2 (EAAT 2), is the most important, as it is responsible for 90% of glutamate clearance by glial cells, in addition to having greater expression during adult life.[5] These transporters act on the translocation of glutamate across the membrane, requiring between 10 and 75 milliseconds to complete this process.[4]

The mGlu receptors are transmembrane proteins that modulate neuronal excitatory transmissions and induce the synthesis and release of neurotrophic factors in glial cells. These glutamatergic receptors are classified into 3 groups according to their sequence homology, signaling and pharmacology.[1] Group 1 mGlu is composed of mGlu 1 and mGlu 5, group 2 of mGlu 2 and mGlu 3 and group 3 of mGlu 4, mGlu 6, mGlu 7 and mGlu 8.[5]

Group 1 metabotropic receptors are related to the hydrolysis of the phospholipid membrane, negatively modulate potassium channels and amplify rapid excitatory synaptic transmissions.[5] Under physiological conditions, the mGlu 1 and mGlu 5 receptors are found expressed in human spinal cord neurons.[13,14] The hyperactivation of group 1 mGlu receptors can culminate in the release of calcium from intracellular stocks, leading to an excessive increase of this ion in the intracellular environment.[1] Additionally, these receptors, since they contribute to glutamatergic excitotoxicity, are molecular targets for ALS therapy.[15]

Group 2 receptors inhibit the release of glutamate under conditions of excessive synaptic activation.[16] MGlu 3, also located in astrocytes,[17] increase the production of neurotrophic factors, reduce the release of presynaptic glutamate, increase the removal of glutamate from the synaptic cleft and increase the expression of glutamate transporters from glial cells.[5]

The group 3 mGlu receptors attenuating excitotoxicity and inhibit the release of glutamate, as well as gamma-aminobutyric acid (GABA) because they are located in the presynaptic terminals close to the active neurotransmitter release zone.[5]

One of the main factors responsible for the pathogenicity of ALS, which leads to the death of motor neurons, is glutamate-mediated excitotoxicity, which consists of neuronal damage resulting from excessive activation of glutamatergic receptors due to increased levels of glutamate in the synaptic cleft.[3] The evidence for glutamate-mediated excitotoxicity to ALS is based on the presence of high extracellular levels of this neurotransmitter in a high percentage of ALS patients, both sporadic and familiar, in the reduction of the expression of the glutamate transporter in affected areas of the CNS and in the observation that improvement in excitotoxicity is, so far, the only strategy clinically adopted to slow the progression of the disease in ALS.[1]

Glial cells have an important protective function in neurodegenerative diseases, as they operate by reducing extracellular glutamate levels, thus avoiding their excitotoxicity when their limit levels are reached or exceeded. Glutamate reuptake is reduced in the motor cortex and spinal cord of patients with ALS due to the functional reduction of excitatory amino acid transporters in these glial cells, suggesting a possible increase in glutamate excitotoxicity.[5]

In vivo studies of tomography images show that the SOD1-G93A gene stimulates the increase of expression of mGlu 5 receptors along with the inflammatory response in the brain, spinal cord and lungs of rats during disease progression.[18] Therefore, the increased expression of group 1 mGlu receptors can be considered a mechanism for modulating glial cell function in a context of glia-neuron communication during the process of motor neuron degeneration in ALS.[5]

Neuronal protection against oxygen, glucose and nitric oxide deprivation[19,20], the production of neurotrophic factors, increased glutamate absorption and protection against astrocyte degeneration are neuroprotective mechanisms of ALS related to mGlu 3 receptors, which belong to group 2 of mGlu receptors.[21]

Group 3 mGlu receptors are also considered to be potentially neuroprotective, as they have the ability to reduce the release of presynaptic glutamate.[17] In addition, in situ hybridization studies of the spinal cord of people with ALS have shown high levels of mGlu 4 receptor expression and low levels of mGlu 7 in most of these patients' neurons.[5] The activation of group 3 mGlu receptors by L-2-amino-4-phosphonobutyric (L-AP4), a nonspecific agonist, increased the cellular survival of motor neurons by 90% and attenuated kainate-induced degeneration.[22]

To date, no medication is available to effectively neutralize the progression of ALS. Only two drugs have been approved for therapy: riluzole, which modestly improves survival and quality of life, and, very recently, edaravone, which shows some efficacy only in patients in the early stage of the disease.[2]

Conclusion

The excitotoxicity associated with glutamate accumulation is related to the pathophysiology of several neurodegenerative diseases, including ALS. The mGlu receptors play an important role in the modulation of glutamatergic levels in the synaptic cleft, and those in group 1, composed of mGlu 1 and mGlu 5, contribute to this excitotoxicity. In contrast, those in group 2, composed of mGlu 2 and mGlu 3, inhibit the release of this neurotransmitter under conditions of excessive synaptic activation and increase the removal of glutamate in the synaptic cleft. Likewise, those in group 3, composed of mGlu 4, mGlu 6, mGlu 7 and mGlu 8, have a similar role in inhibiting excitotoxicity. Therefore, these metabotropic receptors are an important target for further studies aimed at improving the therapy for ALS.

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