



Glutamate as the Central Transmitter in the Pathology of Diseases

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Abstract

This article will refer to the role of glutamic acid (glutamate, Glu) as a transmitter in a pathology of diseases. What kind of receptors are involved in this process, what is the path of transmitting pain? in the further part, there are described such disorders as: neuropathic pain, epilepsy, amyotrophic lateral sclerosis, mood disorders and the role that glutamate plays in them.

Keywords: Glutamate; Metabotropic and Ionotropic Glutamatergic Receptors; Neuropathic Pain; Epilepsy; Amyotrophic Lateral Sclerosis; Mood Disorders

Introduction

Glutamic acid (Glu) five-carbonic, dicarboxylic acid, endogenous amino acid of an acidic nature. Under physiological conditions, it occurs mainly in the form of an anion-glutamate, therefore both terms can be used interchangeably [1]. It is the major neurotransmitter that has an excitatory effect on the central nervous system (CNS) and autonomic nervous system (AUN). Additionally, and importantly, it forms the most extensive nervous conduction system, as it is used by as much as 35% to 40% of nervous synapses [2]. When its concentration is balanced with the amount of pre and postsynaptic inhibitory γ -aminobutyric acid (GABA), it ensures homeostasis and proper functioning of the nervous system [3]. The proper action of Glu is related to the following two types of receptors specific for it, with which it stereospecifically binds [4]. The actions related to the activity of glutamic acid are related to what are differently mentioned two types of receptors, using the stereospecific technique [5]:

a) Ionotropic (iGluR): 3 types of glutamatergic (Glu-ergic) ionotropic receptors (iGluRs) have been classified:

kainate receptor (KAR), α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartic acid

receptor (NMDAR) the most important, which is found in the highest concentration in the hippocampus. Through AMPAR and KARs, Glu stimulates the CNS intensively and quickly. In contrast, NMDARs serve a slow excitatory response that plays an important role in long-term synaptic potentiation (LTP) and neuroplasticity [1,5].

b) Metabotropic (mGluR) -After stimulation, mGluRs react slower than ionotropic receptors (tens of seconds) and are bound to G proteins. Metabotropic receptors are divided into 3 subgroups:

1. group I (mGluR₁ and mGluR₃) - Occurs with triphosphoinositol (IP₃) and Ca²⁺ ions
2. group II (mGluR₂ and mGluR₃)- Inhibits the activity of adenylate cyclase (AC), reducing the intracellular concentration of cAMP
3. group III (mGluR₄, mGluR₆, mGluR₇ and mGluR₈)- Inhibits the activity of adenylate cyclase, but has different preferences in relation to agonists than group II [4]. Knowing the basic information on the structure of Glu and its receptors, it is also necessary to mention its basal actions on animal organisms. Glu provides homeostasis in the CNS by interacting with the

inhibitory neurotransmitter GABA. Glu, by acting on NMDARs in GABA-containing neurons, increases the synthesis and release of GABA. This amino acid inhibits the activity of the remaining Glu-ergic nerve cells or other neurons [1,5]. Glu, as mentioned above, is a very important excitatory neurotransmitter in the CNS and AUN. It forms a permanent connection with mGluRs and iGluRs, through to which visual, sensory and auditory information reaches from the periphery to the cortex of the brain via Glu-ergic pathways [6]. Glutamic acid plays the most important role in learning and memory. This ability is dependent on the effect of Glu on synaptic plasticity through Glu binding receptors, which induce LTP. Recently, more and more studies focus on Glu and its receptors in various diseases such as neuropathic pain, epilepsy, amyotrophic lateral sclerosis, affective diseases, depression, intestinal pain, stress, neurodegenerative diseases, autism, etc. [5, 7, 8].

Pain Conduction Pathways

The painful stimulus is perceived by the receptors in the skin. The information is then sent to the spinal cord through the dorsal roots with afferent fibers. They form Glu-ergic synaptic connections with

neurons in the dorsal horns of the spinal cord [6]. Pain information is transformed there into an appropriate stimulus, which is sent via descending fibers to the effector of a given activity, thus protecting against the pain factor (usually it is a muscle that contracts under the influence of an impulse, which avoids further exposure of the pain stimulus). There are two types of pain-conducting fibers: C-type fibers are very thin and susceptible to damage. They do not have a myelin sheath, so the transmission of pain stimuli is very slow - 0.5–2 m/s. C-fibers, of which there are many, are combined into a “mesh”. Therefore, the field supported by C-fiber branches is usually extensive and the patient is only approximately able to locate this pain. C-fibers respond to mechanical, thermal and chemical stimuli (Figure 1). They transmit not only pain stimuli, but also stimuli causing pruritus [6-8].

The thin myelin Ad fibers differ significantly from the C fibers. They have much smaller receptor fields, which makes it much easier for the patient to identify the painful site (eg after a needle stick injury). Pain impulses are conducted to the spinal cord much faster than in the case of C fibers [6,7]. This allows for a quick “flight” reaction or preparation for “fight”.

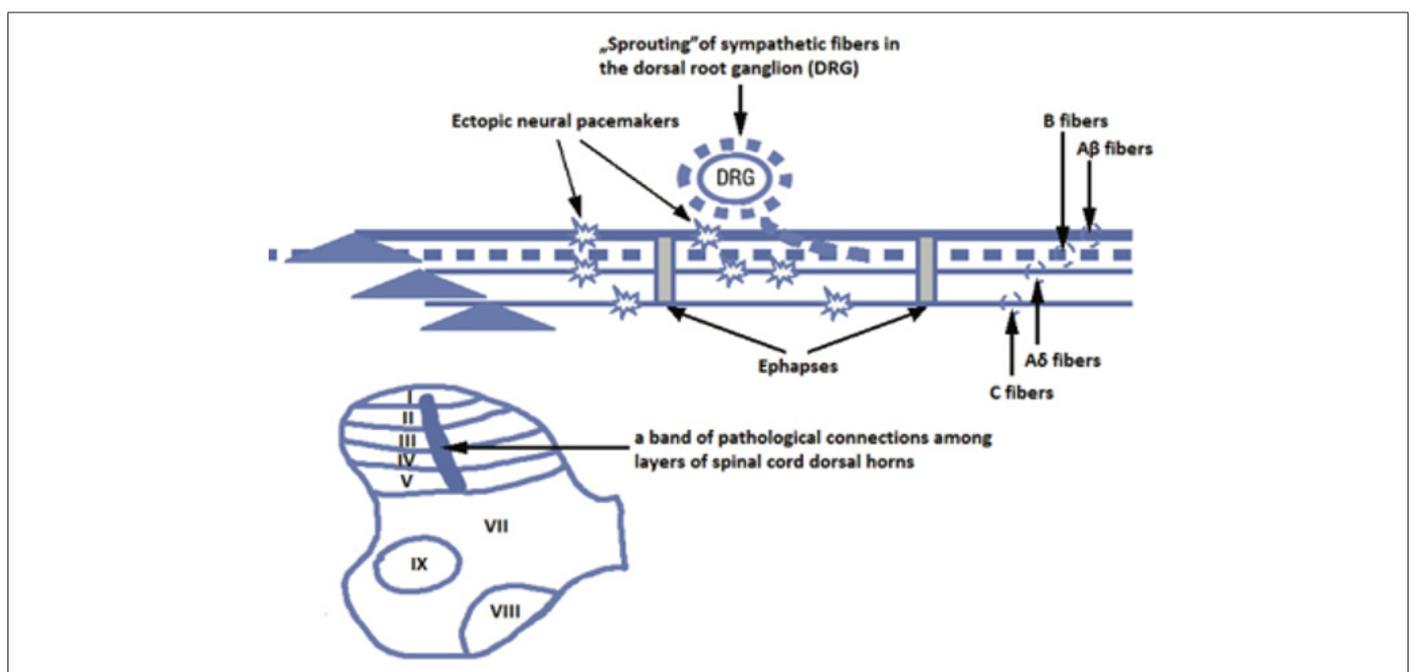


Figure 1: Diagram of the mechanism of pathological neuropathic pain (DRG-Dorsal Root Ganglion) [courtesy of Wordliczek et al. [8].

Glutamate and Neuropathic Pain

Depending on the type of pathomechanism, there are several types of pain [8-10]:

- a) Acute and chronic pain
- b) Receptor-nociceptive-somatic, visceral

- c) Non-receptor type, also called neuropathic pain, which is chronic pain.

Neuropathic pain is caused by damage to the CNS or AUN, which may be caused by metabolic disorders, infections or mechanical damage [8]. This type of pain is relatively little understood. The exact mechanism, the receptors that are most often involved, is being researched constantly to find the best treatment for patients.

Neuropathic pain is paroxysmal, violent. There may be sensory disturbances, such as: paraesthesia, dysaesthesia, hyperalgesia, hyperpathy, allodynia and vegetative disorders [7-10]. It is very important that neuropathic pain causes not only functional but also morphological disorders, thus leading to the so-called neuroplastic changes. At the cellular level, there is a sensitization of neurons in the posterior horns of the spinal cord, which leads to a reduction in the pain threshold, increased response to less intense stimuli and increased spontaneous activity of neurons, which leads to the death of neurons in the posterior horns of the spinal cord [8,11]. Neuropathic pain significantly changes the number of neurons. Microglia and astrocytes proliferate and neurons break down [12].

Due to the relatively poorly understood mechanisms responsible for neuropathic pain, the methods of treatment in this area are still very limited. However, more and more research is emerging on the role of Glu and its receptors (especially the mGluR₅) in the pathology of non-receptor pain [7,8]. As mentioned above, Glu-ergic junctions are formed in the spinal cord dorsal horn (SCDH). It is also in this part of the core that mGluR₅ metabotropic receptors are intensively expressed. SCDH plays a very important role in the plasticity of the brain, which is mediated indirectly by Glu and pain processes [7]. It is known that in animals, the physiological response to stimulation of mGluR₅ receptors in the spinal cord is a pain response. On the other hand, the blockade of the same receptors causes, among others analgesia. Additionally, an increase in Glu concentration is found during pain behavior in animals [7]. Due to the relatively poorly understood mechanisms responsible for neuropathic pain, the methods of treatment in this area are still very limited. However, more and more research is emerging on the role of Glu and its receptors (especially the metabotropic mGluR₅ receptor) in the pathology of non-receptor pain. As mentioned above, Glu-ergic junctions are formed in the dorsal horns of the spinal cord (SCDH). It is also in this part of the core that mGluR₅ metabotropic receptors are intensively expressed. SCDH plays a very important role in the plasticity of the brain, which is mediated indirectly by Glu and pain processes [13]. It is known that in animals, the physiological response to stimulation of mGluR₅ receptors in the spinal cord is a pain response. On the other hand, the blockade of the same receptors causes, among others analgesia. Additionally, an increase in Glu concentration is found during pain behavior in animals [8]. Despite the knowledge of the specific role of mGluR₅ in neuropathic pain, the exact course of this process is still unknown, be it via surface receptors or via intracellular pathways. Nevertheless, on the basis of the research performed, the following fact can be stated blocking mGluR₅ receptors in the spinal cord inhibits neuropathic pain reactions. In contrast, blockade of surface mGluR₅ shows little effect. Diminishing the intracellular Glu concentration by blocking its transporter EAAT-3 mimics the actions of the intracellular

antagonist mGluR₅. This indicates a direct relationship between the intracellular GPCR and the expression of in vivo behavior [7, 11]. The studies performed in this subject lead to the conclusion that it is intracellular mGluR₅ that participate in the pathophysiology of neuropathic pain (due to the significantly increased concentration of nuclear mGluR₅ in the neurons of the dorsal spinal horns in animals suffering from neuropathic pain) [8]. This holds the promise for a targeted therapy to block mGluR receptors to relieve neuropathic pain.

Glutamate and Epilepsy

The term epileptogenesis is associated with the development of symptomatic (acquired) epilepsy due to the formation of structural and biochemical changes in the brain. The period of epileptogenesis development begins with the occurrence of an injury causing brain damage and ends with the appearance of the first spontaneous epileptic seizures [14]. Taken together, substantial evidence shows that glutamate plays a pivotal role in normal neuronal signaling. Moreover, excess glutamate release associated with recurrent seizures and observed in chronic epilepsy leads to long-term alterations in normal neuronal signaling and network connectivity [15]. Again, it should be emphasized that the Glu-ergic system is the most important stimulant system, acting in all nervous systems of the body and leading to its plasticity [14]. It is assumed that disorders in its area lead to epilepsy. Moreover, current theories indicate that epilepsy is caused mainly by influencing iGluR receptors. mGluR receptors also play a role, but it is smaller than in the case of NMDA, AMPA or kainate receptors [16].

- a) **NMDA Receptors:** Play a key role in the process of epileptogenesis. There is an increase in the sensitivity and density of these receptors in specific areas of the brain, especially in the hippocampus, where their number increased by up to 100% in epileptic patients [17].
- b) **AMPA Receptors:** Are composed of four subunits with different combinations of homologous GluR₁₋₄ (or GluRA-D) peptides. In animal models of epilepsy, it has been shown that during the epileptogenesis process, AMPARs with a deficiency of the GluR₂ subunit appear, which leads to an increase in the permeability of these receptors for Ca²⁺ ions. This process is neurotoxic and leads to apoptosis, i.e. programmed cell death (in this case of nervous cells) [18].
- c) **mGluR Receptors:** It has been shown that changes in the activity of mGluR₁ receptors may play a special role in epileptogenesis, the activation of which prolongs the duration of the epilepsy and seizure potentials in the hippocampal region. The mechanism is very simple here, because stimulation of mGluR receptors leads to the release of Glu, which stimulates nervous cells (neurons) [14].

d) It is assumed that, especially in the initial stage of epilepsy, the synthesis of mGluR group I receptors is intensified and then decreased during the course of the disease. This can lead to an imbalance between neurotransmitters and the advantage of excitatory over inhibitory transmitters [19]. In patients with drug resistant partial epilepsy, an increase in mGluR₅ expression and density has been shown on dendrites and neuronal bodies in large parts of the hippocampus. This leads to theories that it is the change in the expression of these receptors that can lead to persistent hyperactivity in this area of the brain in people suffering from epilepsy.

Glutamate and Amyotrophic Lateral Sclerosis

Excessive stimulation of glutamate receptors causes excitotoxicity, a phenomenon implicated in both acute and chronic neurodegenerative diseases [e.g., ischemia, Huntington's disease, and amyotrophic lateral sclerosis (ALS)]. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease in which motor neurons are damaged. The pathogenesis of ALS is probably multifactorial, complex and not fully understood. It may involve such mechanisms as: oxidative stress, Glu acid toxicity, mitochondrial dysfunction, endoplasmic reticulum stress, protein aggregation, cytoskeleton dysfunction, axonal transport disorders, glial cell involvement, neuroinflammation, lactic acid dyscrasias or genetic factors [16,20-23]. In ALS, the balance between the processes of producing and removing excess Glu is disturbed [20]. Due to too high a concentration of Glu, an excessive release of Ca²⁺ occurs, which - as mentioned above - in excess causes the development of apoptosis of neurons. In the course of examinations of patients with ALS, an increased concentration of Glu acid and a reduction in the concentration of the Glu transporter have been demonstrated in an animal experimental model [21-23]. In other cases, a reduction in the concentration of Glu has been observed in many regions of the CNS in the tissues of people who died from ALS. In studies carried out in a transgenic mouse model, altered expression of the Glu AMPAR subunit, decreased expression and activity of the Glu EAAT2 transporter, and disturbed regulation of GluRs in astrocytes were found. It has been suggested that the permeability of AMPARs to Ca²⁺ ions in the anterior horns of the spinal cord may be impaired due to abnormalities within the GluR₂ subunit of the Glu AMPAR [21,23].

Glutamate and Affective Disorders

Affective disorders are a group of endogenous disorders in which mood, emotion and activity disorders occur periodically. These disorders can manifest themselves in the presence of depressive, hypomanic and manic syndromes as well as mixed

states. Again, this is a group of diseases whose exact mechanism, cause, is still under careful research. Due to the large influence of the Glu-ergic system on the nervous system, answers are sought in this area [24]. The results of some of the experiments carried out are presented below. Based on biochemical studies on an animal model of depression (learned helplessness), a reduction in the activity of both the excitatory amino acid transporter and the vesicular Glu transporter was demonstrated [25]. The obtained results may indicate that in this model of depression there may be an increased concentration of Glu [26]. In patients with affective disorders, a significant increase in the concentration of Glu in body fluids and tissues has been found. A positive correlation was also found between the increased concentration of Glu in the blood serum and in the cerebrospinal fluid in people showing symptoms of depression. Moreover, postmortem studies have shown increased levels of Glu in the prefrontal cortex in patients with both unipolar and bipolar affective disease [16]. Another type of research carried out was genetic-molecular research. Six genes were found that are associated with affective disorders. This group includes two genes, GRM3 and GRM4, related to the mGluR receptor subunits of the Glu-ergic system [24].

Conclusion

Research on the role of Glu in the nervous system and its diseases is carried out very intensively. The functions of this transmitter in living organisms are so extensive and diverse that subsequent studies provide more and more recent information that allows a better understanding of the mechanisms and dependencies that occur. It also gives high hopes for more effective therapies for diseases that have been problematic in practice so far.

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