Scientific Research Publishing

Journal of Behavioral and Brain Science, 2019, 9, 13-25
http://www.scirp.org/journal/jbbs
ISSN Online: 2160-5874
ISSN Print: 2160-5866

Glutamate as a Neural Stress Factor in Humans and Animals

Bogdan Feliks Kania[1*], Katarzyna Ferdyn[1], Tomasz Wojnar[2], Grzegorz Lonc[2]

[1]Veterinary Institute, University Center for Veterinary Medicine, Jagiellonian University, Agricultural University in Cracow, Cracow, Poland
[2]Department of Anatomy and Pathomorphology, University Center for Veterinary Medicine, Jagiellonian University, Agricultural University in Cracow, Cracow, Poland
Email: *b.kania@ur.krakow.pl

How to cite this paper: Kania, B.F., Ferdyn, K., Wojnar, T. and Lonc, G. (2019) Glutamate as a Neural Stress Factor in Humans and Animals. *Journal of Behavioral and Brain Science*, **9**, 13-25.
https://doi.org/10.4236/jbbs.2019.92002

Received: December 27, 2018
Accepted: January 29, 2019
Published: February 1, 2019

Abstract

L-glutamic acid (glutamate-Glu) serves as one form with very strong stimulatory neurotransmitter (near aspartic, kainic, alpha-amino-3-hydroxy-5-methyl-4-izoxazole propionic acid (AMPA), chinolic and L-homocysteinic acid, glycine and D-serine) at the majority of neural excitatory synapse in the mammals and nonmammals central, sympathetic nervous system (CNS and SNS, respectively) and in different peripheral tissues and organ. It mediates interactions via stimulation an variety ionotropic N-methyl-D-Aspartate (NMDA), AMPA and kainate receptors (ligand gated calcium channels) and III groups of the metabotropic glutamate receptors ($mGluR_{1\text{-}8}$) family members (G-protein coupled receptors). It is good known different neuromodulation/interaction between Glu and norepinephrine (NE), dopamine (DA), gamma-amino-butyric acid (GABA), oxytocin/vasopressin (Oxy/AVP) and steroid receptors during stress in the central nervous system. In this review we describe the molecular structure of these glutamatergic receptors and discuss they neuropharmacology and clinical use probability of their antagonist, in stress particularly. On the other hand it was interesting if Glu can increase catecholamine (CA) release from motivational structures as stressoric factor in hypothalamo-pituitary adrenal axis (HPA) in the stress inducing processes. Our findings show that Glu more influences the brain's motivational structure, which may indicate its contribution to the stress response by direct modulating the amount of catecholamine released.

Keywords

Glutamate, Catecholamine, HPA Axis, Stressor, Neurotoxicity Disorders

1. Introduction

Glutamic acid, asparagines and glutamine (Gln) are formed from their precursor, aspartic acid (Asp). Glu is synthesized in the Krebs cycle from aspartic acid, a precursor of *α*-ketoglutarate. Glu, along with Asp, quinoline and L-homocysteine acid, is the most common stimulatory transmitter in the brain, peripheral nervous system, but also in all tissues and peripheral organs [1]. Glu is synthesized mainly in neurons as a stimulatory transmitter (next to Asp) causing an increase in the flow of positive ions (K^+, Na^+ and Ca^{2+}) into the cells. After binding to glutamatergic specific receptors it causes opening of ionic channels through which ions K^+, Na^+ and Ca^{2+} flow, increasing intracellular concentration of the latter from 1×10^{-7} even to 1×10^{-5}. Stimulation of these receptors ends with membrane transport system independent of Cl^-, which is used only for reabsorption of Glu and Asp by the presynaptic membrane. Glu can also be reabsorbed (reuptake) into neurons for later use [2]. Excess Glu released in synapses is converted to Gln (a compound devoid of excitotoxic properties) by adjacent astrocytes (Glial cells). Gln is safely transported de novo to neurons for reconversion to Glu. Excessive accumulation of Glu in astrocytes is the cause of excitotoxicity leading to inhibition of the possibility of further absorption of excess Glu. Glutamate stimulates specific receptors of N-Methyl-D-Aspartic acid (NMDAR) and metabotropic non-NMDAR receptors (mGluR) [3].

1.1. Roles of Glutamic Acid

Glu called glutamate—besides Asp acid and glycine—is the main neurotransmitter of CNS and SNS stimulation synapses of the nervous system and tissues and peripheral organs. It is used as a neurotransmitter by about 50% of brain neurons. It acts pre- and postsynaptically by stimulating glutamatergic receptors. These receptors are responsible for excitatory transmission and are important elements of complex memory systems, reading, neural plasticity and other basic functions for neurophysiology, including anxiety and stress processes. Five glutamatergic pathways are probably the most important in the pathophysiology of various disorders in the body. These are: descending cortico-brainstem pathway, descending cortico-striatal pathway, descending and ascending cortico-thalamic pathways and cortico-cortical pathways connecting the pyramidal cells of the cerebral cortex [4] [5].

Glu plays a key role in the maturation of neurons by regulating their migration and proliferation during nervous system development, learning and memory processes, neural plasticity, transmission of nociceptive stimuli, analgesia, stress, autism and neurodegenerative diseases [6].

Accumulated at too high concentrations in neurons has a neurotoxic and apoptotic effect leading to arthritic and neuro-degenerative changes in neurons [6]. It is therefore supposed to be the cause of many civilizational neurodegenerative diseases, such as epilepsy and diseases: Alzheimer's, Parkinson's, Huntington's [7] [8] and ischemic stroke, schizophrenia, depression or affective diseases

[3] [4] [5].

1.2. Synthesis of Glutamic Acid

Glu can be synthesized de novo in glial cells (astrocytes) with glucose in the Krebs cycle or in the Glu-Gln cycle with the participation of mitochondrial enzyme, glutamine. Glu is transported to the synaptic vesicles of the axonal endings by vesicular transporting proteins (VGLUT) and stored there (in a shallow and deep pool). As a result of depolarization of neuron released by exocytosis with Ca^{2+} and energy dissipation from adenosine-triphosphate (ATP) Glu penetrates into synaptic space, binding and stimulating its numerous specific receptors [9]. After the release, Glu is not broken down enzymatically, but is absorbed back from the synaptic gap to the adjacent glial cells by a transporter of excitatory amino acids transporter (EAAT). Then, with the help of the enzyme Gln synthase, it is transformed into Gln. This in turn is transported to the glial, where it is transformed into Glu by hydrolysis with the use of the glutaminase [10] [11].

The release of Glu into synaptic space is regulated by iNMDAR and mGluR (group II and III mGluR), but also by cholinergic, nicotinic and muscarinic receptors, adenosine, κ-opioid, $GABA_B$-ergic, cholecystokinine receptors (CCK-ergic) and neuropeptide Y receptors [1] (**Figure 1**). Glu released after depolarization of neuron endings saturates simultaneously and stimulates specific glutamatergic ion- and metabotropic receptors [12] [13].

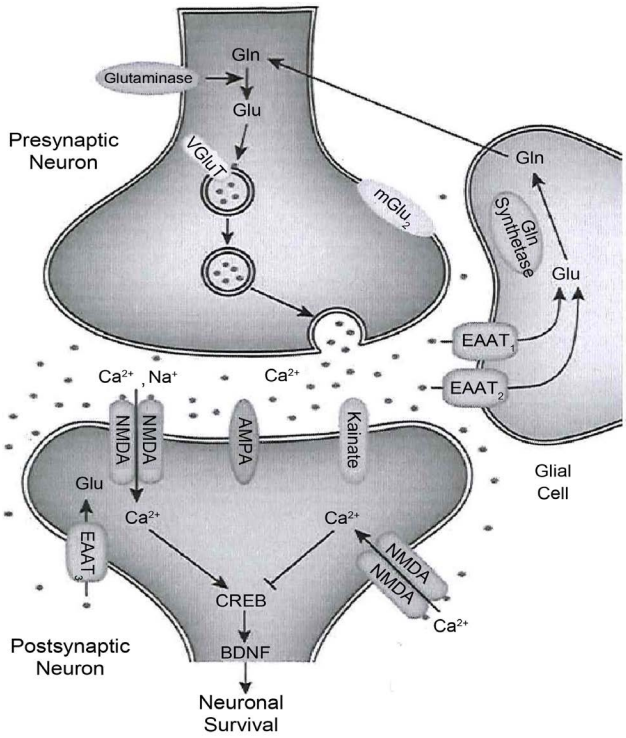

Figure 1. Glutamatergic synapse (acc. to [6]), (description of synapse functioning included in the text).

Glutamic acid acts in the body by stimulating iNMDAR, AMPAR and cainate receptors called N-methyl-D-aspartic and metabotrope (mGluR).

Groups belonging to III separate Arabic numerals 1 to 8: group I—$mGluR_1$, $mGluR_5$, group II—$mGluR_2$ and $mGluR_3$ and group III—$mGluR_4$ and $mGluR_{6\text{-}8}$ (**Figure 2**). Each receptor is composed of subunits [9].

Stimulation of mainly postsynaptic NMDA ion receptors, which are channels permeable for Ca^{2+}, K^+ and Na^+ ions, causes the opening of ion channels and the inflow of Ca^{2+} into the cell, which releases its functional potential. The inflow of Ca^{2+} into the cell causes activation of various intracellular enzymes, such as protein kinase A (PKA), MAPK family kinases or calmodulins. By activating transcription factors, they can change both the function and activity of glutamatergic receptors. These phenomena form the basis of synaptic plasticity, memory processes (synthesis of new synapses [8]) and are also responsible for the development of pathological processes such as stress, acute and chronic neurological diseases, psychiatric diseases or neuropathic pain [14] [15] [16].

The most important receptor of the Glu-ergic system is the NMDAR receptor (GRIN—glutamate receptor, ionotropic). The name of the receptor comes from its selective agonist. The highest density of NMDAR occurs in motivational structures—hippocampus, basal nuclei, septum, hypothalamus, amygdala and prefrontal cortex of the brain. Apart from CNS, they are also located in ganglia of the vegetative system, spleen, adrenal glands and gastrointestinal tract.

In the polarized state, the receptor channel is blocked by Mg^{2+} ions, which, closing it, do not allow for its stimulation (potential-dependent blockade). The opening of the channel requires the presence of a 2-molecules receptor agonist—Glu and its coagonist—glycine or D-serine, which bind to the GluN1 subunit

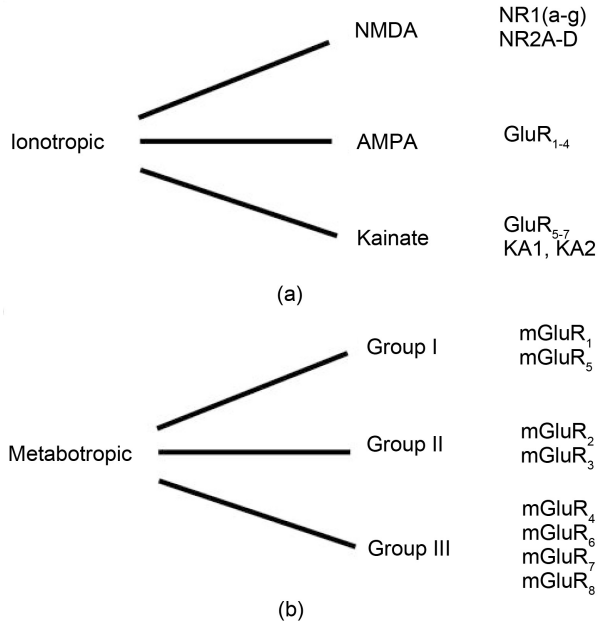

Figure 2. Breakdown of metabotropic glutamate receptors (modyf. by authors acc. to [2]).

in the place of GLY_B (one to each of the subunits, GluN1 and GluN2) and depolarization of the postsynaptic membrane in which the receptor is located; to displace the Mg^{2+} ions. Released to the synaptic gap Glu opens AMPA channels and causes initial depolarization of the membrane, thus lifting the magnesium blockade of the NMDA receptor. Under conditions of resting potential—and even in the presence of agonist and coagonist—the channel remains impermeable to ions. Only the removal of magnesium blockade, after initial depolarization of AMPA receptor by released Glu increases its permeability to Na^+, K^+ and Ca^{2+} ions. The blocking force of the ion channel depends on the subunit composition of the receptor. Thus, the combination of GluN1 and Glu2B makes the receptor a low affinity site for Mg^{2+} ions and the combination of GluN1 with GluN2A or GluN1 with GluN2C makes the receptor a strong magnesium blockade structure under conditions of membrane resting potential [17]. The receptor's ion channel can also block other substances on the basis of incompetent blockers (e.g. memantine, amantadine, ketamine) which can saturate their binding sites even in the presence of a specific receptor agonist. The blocking force of the canal depends, as always, on the membrane potential.

NMDAR is a tetramer consisting of pairs of subunits GluN1 and GluN2, rarely GluN3. Three basic families of NMDA receptor subunits have already been cloned: NR1, NR2 (NR2A-NR2D) and NR3 (NR3A and NR3B). The subunit NR1 is represented by one gene and the subunit NR2 by 4 genes: NR2A, NR2B, NR2C and NR2D [16]. Each of the subunits is composed of 4 transmembranous protein domains marked from M-1 to M-4 with lipophilic nature, N-end located on the outside of the cell and C-end located inside the cell. The M-2 domain forms a loop in the membrane and constitutes the wall of the ion channel. The end domains M-1, M-3 and M-4 located outside the membrane form bonds of agonist (in subunit NR2) and coagonist (in subunit NR1). M-2 domain is important for the permeability of the ionic channel for Ca^{2+} and blocking of this channel by Mg^{2+} and other substances [13] [18] [19]. AMPA receptors, like NMDAR, are tetrameric protein complexes forming the ion channel. In hippocampus neurons, for example, complexes composed of subunits $GluR_1$-$GluR_2$ and $GluR_2$-$GluR_3$ [20], dominate.

Cainate receptors are postsynaptic. Probably around CA1 of the hippocampus it may also occur as presynaptic. Quite a high density of cainate receptors was observed mainly in the neo cortex, cingulate cortex, caudate nucleus, hippocampus CA3, thalamus and hypothalamus, cerebellar granular cells and retina of the eye [20].

In addition to the binding site of agonists (Glu, Asp, glycine) in the glutamatergic complex of the NMDA receptor there are many sites of binding for substances conditioning or modulating the activity of this complex. These are: glycine binding site (GLY-B)—decisive for the opening of the ion channel; polyamine binding site—increases the frequency of opening of the ion channel and increases the affinity to glycine; fencyclidine binding site (PCP)—decisive for blocking the NMDAR ion channel; Mg^{2+} binding site—determines the blocking

of the ion channel; Zn^{2+} binding site—directly and indirectly inhibits activation of NMDAR; sensitive site to oxidative potential—through vitamin C, glutathione and free radicals; modulates oxidation and reduction reactions in the brain; site sensitive to pH changes—determines inhibition of NMDAR function; binding sites of araxin (spider venom)—non-competent NMDAR blockers; binding site of steroids—increases NMDAR function in the brain [21].

In order to activate NMDAR it is necessary—apart from the presence of Glu—to interact with glycine or closely related D-serine. Two enzymes are involved in the metabolism of D-serine: D-amino acid oxidase (DAO), which catalyzes the conversion of D-serine to hydroxypyruvate and its activator (D-amino acid oxidase activator—DAOA) [15] [22].

Under physiological conditions, NMDAR stimulation plays a key role in the course of neuroplasticity, memory and learning. The brain-derived neurotrophic factor (BDNF) is also important in these phenomena. Experiments have shown that in the background the phenomenon is associated with Val66Met polymorphism of the BDNF gene [23]. The activity of BDNF in this process is inhibited by glucocorticosteroids [24].

The stimulation of NMDAR is essential for neuronal excitotoxicity as a consequence of excessive activation of the receptor. This phenomenon occurs directly through increased agonist concentration and indirectly through Ca^{2+}. Excitotoxicity may also result in increased receptor sensitivity (e.g. decreased sensitivity to Mg^{2+}), impaired buffering or elimination of Ca^{2+} from the cell, increased sensitivity of intracellular enzymes to Ca^{2+}, energy deficiency resulting in partial depolarization of the receptor, as is the case in cerebral ischemia [14].

The second ionotropic glutamatergic receptor is the AMPA receptor (GRIA—glutamate receptor, ionotropic, AMPA). The name comes from the receptor agonist—*α*-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA). AMPA receptors are homomeric tetrameters that can be composed of different combinations of 2 or more subunits ($GluR_1$-$GluR_4$). The AMPA receptor is responsible for the flow of Na^+ and K^+ ions; if $GluR_2$ is missing, Ca^{2+} ions are also passed through. An additional source of AMPA receptor modulation is the binding site of Zn^{2+} ions. Zinc at low concentrations increases receptor activity, while at higher concentrations it inhibits it through direct blockage of the ion channel. The physiological role of AMPA receptors is not fully understood [13].

Ionotropic activity is also shown by cainate receptors, characterized by high affinity to cainic acid, from which they took their name (GRIK—glutamate receptor, ionotropic, kainate). The receptor is composed of 5 subunits, which were divided into 2 groups due to the degree of affinity. Three units: $GluR_5$-$GluR_7$ form a place of bond with a smaller one, while two: KA1 and KA2 with a higher affinity. Cainic acid acting on $GluR_5$, $GluR_6$ or $GluR_7$ causes activation characterized by rapid desensitization. Cainate receptor subunits are located primarily in the neocortex, rim cortex, caudate nucleus, hippocampus CA3, thalamus, hypothalamus and cerebellar granulosa cells [20].

Glutamatergic metabotrope receptors (mGluR), unlike ionotrope receptors (iNMDAR), are bound to the G protein and after stimulation initiate a cascade of release of secondary messengers, increasing the concentration of cAMP and phosphatidylinositol (IP_3) in the cell. The addition of Glu to the culture of nervous system cells triggers the activation of C phospholipase (PLC) and secondary IP_3. Metabotropic receptors react more slowly than ionotropic receptors (tens of seconds) because they are binding to G proteins. Agonists of this group of receptors cause slow depolarization of neuron by inhibiting the transmembraneous flow of K^+ ions.

Based on the similarity of amino acid sequences, comparable pharmacological profile and signal transduction mechanism, metabotrope receptors were divided into three subgroups (**Figure 2**):

- group I ($mGluR_1$ and $mGluR_5$ receptors)—associated with inositol-1,4,5-triphosphate (IP_3) and Ca^{2+}. It stimulates phospholipase C and this catalyzes hydrolysis of phosphatidylinositol-(4,5)-biphosphate (PIP_2) to 2 secondary messengers of inositolotriphosphate (IP_3) and diacylglycerol (DAG). This in turn activates protein kinase C and IP_3 binds to endoplasmic reticulum membrane receptors and releases Ca^{2+} [16] [25].
- group II ($mGluR_2$ and $mGluR_3$ receptors)—inhibits adenylate cyclase (AC) activity, reducing intracellular concentration of the first messenger—cAMP and inhibits excitability of neurons. $mGluR_2$ are mainly presynaptic receptors, as auto- or heteroreceptors. The $mGluR_3$ receptors, in turn, are located mainly postsynaptically [26].
- group III ($mGluR_4$, $mGluR_6$, $mGluR_7$ and $mGluR_8$ receptors)—inhibits adenylate cyclase activity, but has preferences different from group II receptors in relation to agonists.

The stimulating effect of agonists on group I mGluR receptors causes desensitization associated with the intensification of phosphatidylinositol (PI) hydrolysis. It has been shown that PKC activation induces phosphorylation of the receptor, which plays a significant role in the process of desensitization development. Phosphorylation by PKC of group II and III receptors inhibits their ability of synaptic modulation of glutamatergic transmission. Moreover, activation of PKC also interferes with the ability of group II receptors to inhibit calcium channels.

Experimental studies have shown that activation of $mGluR_{2/3}$ receptors increases the expression of BDNF in the brain [20]. Metabotropic receptors together with NMDA receptors participate in the process of synaptic plasticity formation (learning, remembering) in the hippocampus CA1 region [15] [27]. These receptors modulate the ion channel activity for Ca^{2+} and K^+, thus regulating the synaptic activity of neurons, influencing the release of Glu as well as other neurotransmitters [17].

Group I receptors as mainly postsynaptic are located on the surface of neurons and dendritic spines mainly in brain structures. $mGluR_1$ is found in the ce-

rebellum, olfactory bulbs, CA3 area and dentate gyrus of hippocampus, thalamus and black brain substance. $mGluR_5$ is found in the cerebellum, CA1 and CA3 area of the hippocampus, basal nuclei, amygdala and striatum [7].

Stimulation of group II and II receptors causes both a decrease in cAMP concentration and inhibition of neuronal excitability.

1.3. Role of the Glutamatergic System in the Body

The glutamatergic system plays an important role both in the regulation of stress axes and neuroplasticity of the brain, and together with the pre- and postsynaptically inhibitory GABA-ergic system it performs the function of maintaining homeostasis in the brain. As it has already been indicated, dysfunctions of the glutamatergic system lead to many diseases such as schizophrenia, autism and diseases: Alzheimer's, Hungtington's, Parkinson's and epilepsy or in cerebral ischemia [28]. In recent years, there has been much evidence of changes in the function of many components of the glutamatergic system in affective diseases and the importance of glutamatergic mechanisms in the action of antidepressants and normotymic drugs or in the therapy of alcohol dependence syndrome [20]. The possibility of therapeutic use of agents (agonists or antagonists) directly modifying the glutamatergic system function in diseases has also been demonstrated [29].

2. Glutamate as a Neurotransmitter in Stress Signaling

Stress is the sum of biological reactions to challenging or threatening stimuli or perceptions (stressors) leading to homeostasis disorders. Stress can be positive (eustress) that mobilizes the body's vital forces. It can be neutral (neustress) as a stimulus for one neutral organism, although it can be positive for other individuals. Stress over a limited period of time helps to overcome hazards and maintain necessary functions by stimulating actions resulting in positive changes for survival [30]. Lack of ability to react to stress leads to the development of disorders of the body and diseases of important life-threatening systems (e.g. cardiac death).

Harmful stress due to the exhaustion of the initiating pathological changes (distress) is a disturbance of functions and/or functions which occur if the compensatory reactions are not adequate or unsuitable for the damaging factor (noxa) or if the stressors have operated for too long, and then they can lead to the development of functional disorders or diseases [31].

A stress reaction can be caused by various real-life factors: external (sensing, feeling) from the frontal cortex via the prefrontal cortex and internal (quantified) from different hypothalamic somatic and autonomous afferent nerve centres, emotional (amygdala) and memory (hippocampus). Regardless of the cause of the stressor's action, the body's reaction is conducted through nerve pathways involving not only the limbic system, but also, indirectly, the bluish fourth place lying in the side wall of the ventricle, connected with the hypothalamus, accord-

ing to the scheme: (locus coeruleus (LC) → coherent nervous system → adrenal spinal cord → catecholamine → hypothalamus → HPA → cortisol → higher CNS functions (motor, cognitive and behavioral responses).

First of all, the scale of the potential threat is analyzed. Higher cognitive fields of the prefrontal cortex are affected via its numerous large connections with amygdala and LC, which enhances anxiety and post-traumatical stress. The stimulus that triggers innate fear is gradually weakened (extinguished) [30].

On the other hand, there are autonomous and neuroendocrine reactions appropriate for the strength of the stressor. The former are related to the involvement of the limbic system (hippocampus, amygdala, thalamus, hypothalamus, locus coeruleus and nucleus of the solitary tract) [15].

Functional dysfunction (disregulation) of the HPA axis is a pathological feature of some mood, stress and anxiety disorders that lead to increased synthesis and release of CRH. Preclinical studies have shown that Glu as a stimulating amino acid plays a very important role in the regulation of the HPA axis [17]. The stimulation of projective glutamatergic fibers reaching limbic structures such as amygdala and brainstem structures such as the nucleus of the solitary tract testifies to the involvement of these structures in the stress reaction. Laboratory and clinical suggestions indicate that NMDAR antagonists act as antidepressants and that their prolonged use together with antidepressants has a significant effect on the function of the NMDA receptor. Clinical studies with glutamatergic receptor antagonists in patients with anxiety and mood disorders prove that they have mood-enhancing properties [3].

Stress causes immediate involvement of many different neural and neuroendocrine systems depending on the type of stressoric factor. Recent studies included synapses on neuroendocrine cells of the hypothalamic ventricular nucleus (PVN). They showed that stressful experiments leave irreversible traces that change the plasticity of these synapses. These stress-induced adaptations include the unique metaplasticity of glutamatergic synapses, bi-directional changes in endocannabinoid signaling and bi-directional changes in the strength of GABA-ergic synapses [32].

Stress is an indispensable attribute of all living beings. When the stress factor intensity exceeds the body's adaptability and the factor(s) persists longer, the body activates the alarm system. It manifests itself both by making the hypothalamo-pituitary-cortico-adrenal axis (HPA) as a result of which CRH → ACTH → cortisol (corticosterone and cortisol in rabbits or corticosterone in rodents) is released, and by stimulation of the sympathetic-medullo-adrenal system which results in the release of excitatory transmitters (E, NE, and/or DA) and in adrenergic structures of the CNS to release DA and NE [29].

As previously stated, amino acids: glutamic acid, aspartic acid, glycine and D-serine belong to the group of stimulant transmitters in the CNS and SNS. As a result of the stimulus acting as a stressoric factor, the release of stimulating amino acids, especially Glu in structures directly involved in the reception and

awareness of the stimulus effect, takes place. Especially in neurons of the hypothalamic PVN from which CRH is released. Glu released in CNS structures may also release central glucocorticoids and by depolarizing presynaptic endings it also releases a number of other neurotransmitters/neuromodulators (NE, DA, GABA, 5-HT, Oxy/AVP) of the brain and spinal cord, especially in motivational structures (hypothalamus, amygdala, hippocampus, prefrontal cortex) [32].

Under physiological conditions Glu depolarizes presynaptic endings of various neurons and releases appropriate synaptic transmitters from them. If it is synthesized or supplied to the body in excess, it is converted to Gln and stored in astrocytes. Released in excess, it causes rapid depolarization of neurons and thus increased release of stimulant transmitters (CA, glucocorticoids), which can initially protect the body from its damaging effect (noxa). The fact that Asp is an important agonist of the HPA axis is evidenced by the fact that the NMDAR antagonist MK-801 used before him prevented the increase in plasma concentration of both ACTH and corticosteroid in stress caused by the retrovirus, as a stressor [12]. Also the Glu release inhibitor and mGluR antagonists inhibited cellular breakdown caused by retrovirus infection as a stressoric factor in Kaposi cancer [12].

In conclusion, glutamic acid is one of the strongest neurotransmitters in stimulating structures of branched neurons forming 85% synapses, 20% are smooth, inhibitory, GABAergic neurons, forming only 15% of synapses. Thus, glutamatergic neurons and their synapses together with GABAergic neurons and their synapses modulate all central functions and determine the maintenance of homeostasis of the organism. Glu shows its activity via stimulation of many different types of ionotropic and metabotropic receptors. Under stressful conditions, the whole glutamatergic system is modulated by a relatively small GABA-ergic inhibitory system, modulated by a much smaller number of pathways releasing various other relays, including monoaminergic (DA, NE, E, 5-HT) and OXY/AVP and steroid [30]. However, it is mainly the glutamate/GABA-ergic interaction that maintains homeostasis and adaptation to stress. Disorder in HPA axis functions is a pathological feature of some stressful situations, mood disorders or anxiety. It causes synthesis and release of CRF. The number of data proving that Glu, a stimulating amino acid, plays an important role in the regulation of the HPA axis is increasing. Stimulation of glutamatergic projective fibers leading to limbic structures such as the amygdala and brainstem structures such as the solitary nucleus is involved in stress responses. This is confirmed by laboratory and clinical data, as NMDAR antagonists are used as antidepressants and that their chronic use significantly affects the function of NMDAR. Glu antagonists have already been used in patients with post-stress disorders, mood disorders and/or anxiety with good clinical outcome. HPA axis modulators, 5-HT drugs and Glu antagonists (especially the $mGluR_7$ receptor) may increase the number of neurotropic factors in the most important brain structures allowing regulation of stress, anxiety and affective diseases [4] [5] [6].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Meldrum, B.S. (2000) Glutamate as a Neurotransmitter in the Brain: Review of Physiology and Pathology. *Journal of Nutrition*, **130**, 1007S-1015S. https://doi.org/10.1093/jn/130.4.1007S

[2] Vyclicky, V., Korinek, M., Smejkalova, T., Balik, A., Krausova, B., Kaniakova, M., Lichnerova, K., Cerny, J., Krusek, J., Dittert, I., Horak, M. and Vyklicky, L. (2014) Structure, Function, and Pharmacology of NMDA Receptor Channels. *Physiological Research*, **63**, S191-S203.

[3] Wolak, M. (2014) Investigation of Ionotropic Glutamate Receptors NMDA an AMPA in the Antidepressive Drugs Mechanism of Action (pol). Ph.D. Thesis, Collegium Medicum in Cracow, Cracow, 10-30.

[4] Permoda-Osip, A. and Rybakowski, J. (2011) The Role of Glutamatergic System in the Mechanism of Antidepressant and Mood-Stabilizing Action in Mood Disorders (pol). *Farmakoterapia w Psychiatrii i Neurologii*, **2**, 57-65.

[5] Peromoda-Osip, A. and Rybakowski, J. (2011) Glutamatergic Conception of Mood Disorders (pol). *Psychiatria Polska*, **45**, 875-888.

[6] Pittenger, C. and Duman, R.S. (2008) Stress, Depression, and Neuraplasticiity: A Convergence of Mechanisms. *Neuropsychopharmacology*, **33**, 88-109. https://doi.org/10.1038/sj.npp.1301574

[7] Pilc, A., Chaki, S., Nowak, G. and Witkin, J.M. (2008) Mood Disorders: Regulation by Metabotropic Glutamate Receptors. *Biochemical Pharmacology*, **75**, 997-1006. https://doi.org/10.1016/j.bcp.2007.09.021

[8] Hunt, D.L. and Castillo, P.E. (2012) Synaptic Plasticity of NMDA Receptors: Mechanisms and Functional Implications. *Current Opinion of Neurobiology*, **22**, 496-508. https://doi.org/10.1016/j.conb.2012.01.007

[9] Du, J., Gray, N.A., Falke, C.A., Chen, W., Yuan, P., Szabo, S.T., Einat, H. and Manji, H.K. (2004) Modulation of Synaptic Plasticity by Antimanic Agents: The Role of AMPA Glutamate Receptor Subunit 1 Synaptic Expression. *Journal of Neuroscience*, **24**, 6578-6589. https://doi.org/10.1523/JNEUROSCI.1258-04.2004

[10] Car, H. (2009) Współdziałanie pomiędzy glutaminianem a kwasem γ-Aminomasłowym w ośrodkowym układzie nerwowym. *Neuropsychiatria i Neuropsychologia*, **4**, 116-125.

[11] Schiffer, H.H. and Heinemann, S.F. (2007) Association of the Human Kainate Receptor *GluR7* Gene (*GRIK*3) with Recurrent Major Depressive Disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, **144B**, 20-26. https://doi.org/10.1002/ajmg.b.30374

[12] Espey, M.G. and Basile, A.S. (1999) Glutamate Augments Retrovirus Induced Immunodeficiency through Chronic Stimulation of the Hypothalamic-Pituitary-Adrenal Axis. *Journal of Immunology*, **162**, 4998-5002.

[13] Köles, L., Kato, E., Hanuska, A., Zádori, Z.S., Al-Khrasoni, M., Zelles, T., Rubini, P. and Illes, P. (2016) Modulation of Excitatory Neurotransmission by Neuronal/Glial Signaling Molecules: Interplay between Purinergic and Glutamatergic Systems. *Purinergic Signaling*, **12**, 1-24. https://doi.org/10.1007/s11302-015-9480-5

[14] Gass, J.T. and Olive, M.F. (2008) Glutamatergic Substrates of Drug Addiction and Alcoholism. *Biochemical Pharmacology*, **75**, 218-265. https://doi.org/10.1016/j.bcp.2007.06.039

[15] Linsambarth, S., Moraga-Amaro, R., Quintana-Donoso, D., Rojas, S. and Stehberg, J. (2017) The Amygdale and Anxiety. In: Ferry, B., Ed., *The Amygdale—Where Emotion Shape Perception*, *Learning and Memories*, Neuroscience InTech, 139-171.

[16] Zhang, Z., Li, Y., Zhao, Q., Huang, K., Wang, P. and Yang, P. (2009) First Evidence of Association between G72 and Bipolar Disorder in the Chinese Han Population. *Psychiatric Genetics*, **19**, 151-153.

[17] Dingledine, R., Borges, K., Bowie, D. and Traynelis, S.F. (1999) The Glutamate Receptor Ion Channels. *Pharmacological Review*, **51**, 7-61.

[18] Jin, C. and Woodward, J.J. (2006) Effects of 8 Different NR1 Splice Variants on the Ethanol Inhibition of Recombinant NMDA Receptors. *Alcoholism*: *Clinical and Experimental Research*, **30**, 673-679.

[19] Walker, R.M., Christoforou, A., Thomson, P.A., McGhee, K.A., Maclean, A.M. and Mühleisen, T.W. (2010) Association Analysis of Neuregulin 1 Candidate Regions in Schizophrenia and Bipolar Disorder. *Neuroscience Letters*, **478**, 9-13. https://doi.org/10.1016/j.neulet.2010.04.056

[20] Łukasik, K., Piotrowska, K. and Pietrzak, B. (2010) The Role of Glutamatergic System in the Pathogenesis and Treatment of Alcohol Dependence (pol). *Postępy Higieny i Medycyny Doświadczalnej*, **64**, 534-543.

[21] Sanacora, G., Zarate, C.A., Krystal, J.H. and Manji, H.K. (2008) Targeting the Glutamatergic System to Develop Novel, Improved Therapeutics for Mood Disorders. *Nature Reviews Drug Discovery*, **7**, 426-437.

[22] Maeng, S. and Zarate, C.A. (2007) The Role of Glutamate in Mood Disorders: Results from the Ketamine in Major Depression Study and the Presumed Cellular Mechanism Underlying Its Antidepressant Effect. *Current Psychiatry Reports*, **9**, 467-474. https://doi.org/10.1007/s11920-007-0063-1

[23] Ninan, I., Bath, K.G., Dagar, K., Perez-Castro, R., Plummer, M.R. and Lees, F.S. (2010) The BDNF Val 66Met Polymorphism Impair NMDA Receptor-Dependent Synaptic Plasticity in the Hippocampus. *Journal of Neuroscience*, **30**, 8866-8870. https://doi.org/10.1523/JNEUROSCI.1405-10.2010

[24] Kawashima, H., Numakawa, F., Adachi, N., Mizuno, H. and Ninomiya, M. (2010) Glucocorticoid Attenuated Brain-Derived Neurotrophic Factor-Dependent Upregulation of Glutamate Receptor via the Suppression of microRNA-132 Expression. *Neuroscience*, **165**, 1301-1311.

[25] Murphy, S.N. and Miller, R.J. (1989) Two Distinct Quisqualate Receptors Regulate Ca^{2+} Homeostasis in Hippocampal Neurons *in Vitro*. *Molecular Pharmacology*, **35**, 671-680.

[26] Di Liberto, V., Bonomo, A., Frinchi, M., Belluardo, N. and Mudo, G. (2010) Group II Metabotropic Glutamate Receptor Activation by Agonist LY 379 268 Treatment Increases the Expression of Brain Derived Neurotrophic Factor in the Mouse Brain. *Neuroscience*, **165**, 863-873. https://doi.org/10.1016/j.neuroscience.2009.11.012

[27] Stefansson, H., Sigurdsson, E., Steinhorsdottir, V., Bjornsdottir, S., Sigmundsson, T. and Ghosh, S. (2002) Neuregulin 1 and Susceptibility to Schizophrenia. *American Journal of Human Genetic*, **71**, 877-892. https://doi.org/10.1086/342734

[28] Javitt, D.C., Schoepp, D., Kalivas, P.W., Volkow, N.D., Zarate, C., Merchant, K., Bear, M.F., Umbricht, D., Hajos, M., Potter, W.Z. and Lee, C.M. (2011) Translating

Glutamate: From Pathophysiology to Treatment. *Science Translational Medicine*, **28**, 102mr2.

[29] Obrenovitch, T.P. and Urenjak, J. (1997) Altered Glutamatergic Transmission in Neurological Disorders: From High Extracellular Glutamate to Excessive Synaptic Efficacy. *Progress in Neurobiology*, **51**, 39-87. https://doi.org/10.1016/S0301-0082(96)00049-4

[30] Mathew, S.J., Coplan, J.D., Shoepp, D.D., Smith, E.L., Rosenblum, L.A. and Gorman, J.M. (2001) Glutamate-Hypothalamic Pituitary-Adrenal Axis Interactions: Implications for Mood and Anxiety Disorders. *CNS Spectrums*, **6**, 555-556, 561-564. https://doi.org/10.1017/S1092852900002091

[31] Zhuo, M., Wu, G. and Wu, L.J. (2011) Neuronal and Microglial Mechanisms of Neuropathic Pain. *Molecular Brain*, **4**, 31-42. https://doi.org/10.1186/1756-6606-4-31

[32] Bains, J.S., Cusuling, J.I.W. and Inoue, W. (2015) Stress-Related Synaptic Plasticity in the Hypothalamus. *Nature Review of Neuroscience*, **16**, 377-388. https://doi.org/10.1038/nrn3881