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Review Article

Importance of L-Glutamate in the Stress of Animals

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2. Summary

L-glutamic acid (Glu-glutamate) is one of the major and strongest stimulatory neurotransmitters (along with aspartic acid, chinolic acid and glicyne) at the majority of excitatory synapses in the Central Nervous System (CNS), Sympathetic Nervous System (SNS) and peripheral tissues and organs of mammals and well as non-mammals. It mediates in the stress response through stimulation of the hypothalamo-pituitary-adrenal cortex (HPA) axis, thus increasing glucocorticoids, catecholamine and oxytocinsecretion certainly, which contributes to the biochemical and clinical behavioural stress responses.

Stress,accordingtoSelye,authorof this term and the creator of theory of stress [1,2],is a stereotypical, non-specific and complex physiological reaction of the organism to any load (thrust of impulses). It is a sum of biological reactions to the stimuli that pose a challenge or a threat (stress factors, aversive stimuli), which lead to the disturbances of body homeostasis. It is also defined as a dynamic adaptive relation between the requirements of the situation and the ability of the individual to adapt, characterised by lack of psychological and physical balance. There are different types of stress: positive (eustress)–positively mobilising the body, neutral (neustress)–neutral stimulus and adverse stress (distress). Adverse stress causes a disturbance in the activity and functions of the organism. It occurs when the strength of the stimulus affecting the organism exceeds its adaptive abilities or when the aversive stimulus is affecting the body for too long [3].

Stress reaction is caused by various factors. External–from different hypothalamic centres as well as somatic and autonomous afferent nerves (with a very important hypothalamic neurotransmitter- corticotrophin-releasing factor– CRF, playing a big role in stress, with one of its functions - activation of the anxious behaviour). Second group of factors are the internal ones – from the frontal via prefrontal cortex, responsible for proper recognition of the stressor. Additionally, important stressors are emotional (engaging hypothalamus, amygdale) and memory factors (activating hippocampus). Regardless of the nature of the adverse incentive, reaction of the organism is conducted via neural pathway, engaging limbic system in the response (hypothalamus, hippocampus, amygdale, regions of the prefrontal cortex), which forces on the sympathetic nervous system (through the release of the catecholamines) and the HPA axis (release of the glucocorticosteroids–cortisol or corticosterone) initiation of motoric, cognitive and behavioural responses related to defence („flightorfight") [4].

Stress is a basic reaction of the organism to a threat. In a stressful situation HPA axis is activated, resulting in the release of the corticotrophin-releasing factor (CRF), which in turn stimulates the release of the adrenocorticotropic hormone (ACTH) affecting the adrenal cortex. Ultimately, cortisol, commonly known as the stress hormone, is being released in the organism. It increases blood glucose (through intensification of the gluconeogenesis and glycogenolysis), accelerates decomposition of the fatty acids to ketone bodies, intensifies protein catabolism and increases blood pressure etc... In the studies conducted in sheep and rabbits [4, 5] the relationship between the stress factor effect – pain and the changes in cortisol and catecholamine blood levels have been proved [6, 7]. Studies show, that the longer exposure to the stress factor, the higher the level of glukokorticosteroids released from the adrenal cortex. Moreover, cortisol intensifies the effect of adrenaline and noradrenaline on the body – which are also involved in the reactions to adverse stimuli. Their release is a result

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of stimulation of the HPA axis (Figure 1)[3].

Along with the aspartic and quinolic acid, glutamate is one of the most important, the most common and the strongest excitatory neurotransmitters. It acts distinctively on specific glutamate receptors which are located in the CNS and PNS, as well as in the tissues and peripheral organs. The biggest concentration of the receptors for those excitotoxins within the CNS is found in the prefrontal cortex, striatum, hippocampus, rhinencephalon, cerebellum and the spinal cord [4]. Glutamate receptors are responsible for the excitatory transmission and are a complex element of the memory system, neural plasticity and other functions, thus having a primary role in the neurophysical processes. Glutamic acid is syntethised *de novo* in the glial cells or in the Glu-Gln glutaminase-mediated cycle. It increases the flow of ions into the cells. Glutamic receptors are inhibited by the chloride-independent membrane transport. Glu can be reabsorbed into the neurons in order to be used later. The excess of released glutamic acid is transformed by the adjacent astrocytes to the Gln, which in turn is being transported to the neurons where it is reconverted to Glu (**Figure 2**) [8].

In case of glutamatergic pathways the biggest role in pathophysiology of the disorders in the body are played by: descending cortico-basal pathway, descending cortico-striatal pathway, descending and ascending corticot-halamic pathways and the cortico-cortical pathways connecting pyramidal cells of the cerebral cortex [9,10]. Glutamic acid, affecting specific structures of the CNS, plays a main role in the maturation of the neurons, processes of learning and memory, neuroplasticity, transmission of nociceptive stimuli, analgesia, stress, autism and neurodegenerative diseases [11-13].

Glutamic acid, as an excitatory neurotransmitter, also plays a major role in the aggressive reactions to stress. According to the research conducted in rats, in which the agonist of the glutamate receptors and antagonist of the $GABA_A$ receptors have been injected, in the animals which had previously been exposed to the aggressive experiences, an increase in aggressive behaviour has been observed, contrary to the animals, which did not experience aggressive situations in the past [6]. That proves the role of glutamic acid in the processes of learning and memory as well as its role, along with the GABAergic system, in the maintenance of homeostasis of the brain and the whole organism [14].

L-glutamate, under the physiological circumstances, depolarises presynaptic terminals of the various neurons, which results in the release of appropriate transmitters. It has been observed however, that the stressful situations cause irreversible changes in synaptic plasticity. It applies to metaplasticity of the glutamate synapses, bi-directional changes in endocannabinoid signalling and bi-directional changes in the strength of the GABAergic synapses [13]. Any dysfunctions in the glutamatergic system, regulated by relatively small GABAergic system, lead in turn to many neurodegenerative diseases such as: autism, schizophrenia, Parkinson's, Alzheimer's and Huntington diseases, epilepsy or cerebral ischemia [12]. As mentioned above, glutamic acid can intercede in aggressive reactions, pain as well as development of the neurotoxicity observed in ischemic brain damage. For in the experiments conducted in animals, with the use of specific antagonist of the glutamate receptor Inamdar, prevention of the nerve cells has been proved [7].

As the main and most commonly widespread excitatory neurotransmitter, glutamic acid plays a role in the processes of learning and memory, neuroplasticity, transmission of nociceptive stimuli, analgesia, autism and neurodegenerative diseases such as Parkinson's, Alheimer's, Huntongton, brain ischemia or epilepsy. L-glutamate is also involved in aggressive reactions and has a direct impact on the level or released catecholamines in stressful situations (**Figure 3**) [7].

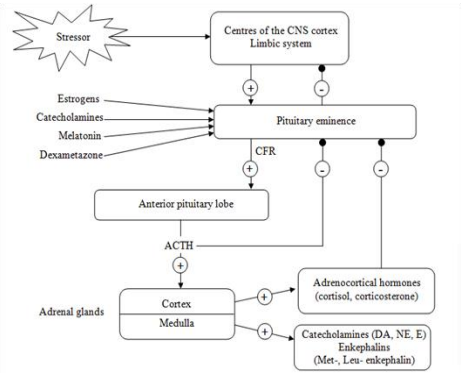

Figure 1: Flow chart of the neurohormonal reactions as a result of exposure to stress factors and the feedback loop of the HPA axis [acc. to 3].

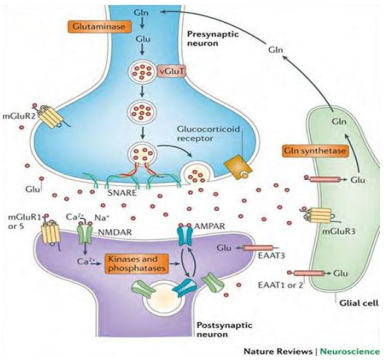

Figure 2: Glutamate synapse (Popoli et al., 2012).

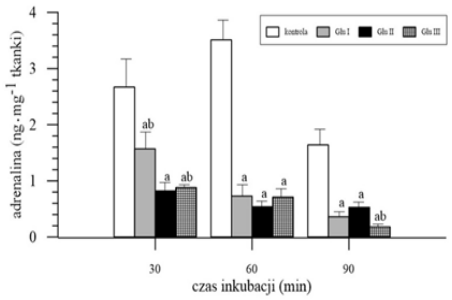

Figure 3: Changes in the concentration of epinephrine released from rabbit hypothalamus homogenates before and after 90 min period of incubation in the presence of added L-Glu in a concentration of 5 μM (GluI), 50 μM (GluII) or 200 μM (GluIII) (n=12), a – significant differences, (P < 0,05-0,01) compared to the values in the clinical control group; b – significant differences, (P < 0,05-0,01) between the applied doses of Glu [acc. to 7].

Glutamate plays a role of the mediator in the processes of stress and pain, which has an impact on the effector cells dependent on the presence of specific to the neurotransmitter receptors: glutamate, iNMDAR and mGluR receptors. This relates, in particular, to the stimulation of metabotropic receptors mGluR[1,2,4,5]. Stimulation of this type of receptors can simultaneously facilitate blocking the release of Glu from the presynaptic receptors, with interim continuous depolarisation of the presynaptic terminals, and it also increases the release of neurotransmitters from the adrenergic, serotoninergic, GABAergic and oxytocin fibers [14].

Particularly high concentration of the Glu- and OXY-ergic receptors have been found in the motivation centres of the CNS (hypothalamus, hippocampus, amygdale, cortex prefrontalis) and adrenal glands, which are the last link in, the most important in stress, HPA axis [11, 16].

In stressful situations the expression of the OXY- and GABA-ergic receptors increases as well, which indicates the importance of these processes in the stressful situations [16].

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