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Стаття надійшла 14.06.2024 р.

DOI 10.26724/2079-8334-2025-2-92-248-253
UDC 57:54:612.08

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BIOLOGICAL EFFECTS OF MONOSODIUM GLUTAMATE ON THE ORGANS OF THE NERVOUS SYSTEM

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In the body, monosodium glutamate is a mediator of the peripheral and central nervous systems. In both parts, it is related to metabolic and excitatory functions. Monosodium glutamate is widely used in the food industry as a flavor enhancer. Although food safety regulators generally recognize its safety for health, a number of studies have questioned its long-term safety. Taking into account all of the above, it can be assumed that monosodium glutamate, added to the diet in excessive amounts or with prolonged consumption, can cause behavioral, biochemical and morphological changes in structures such as the brain, hippocampus and cerebellum of adult mammals and lead to dysfunction in the central nervous system.

Key words: monosodium glutamate, food additives, central nervous system, brain.

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БІОЛОГІЧНІ ЕФЕКТИ ГЛУТАМАТУ НАТРІЮ НА ОРГАНИ НЕРВОВОЇ СИСТЕМИ

В організмі глутамат натрію є медіатором периферичної і центральної нервової системи. В обох частинах він має відношення до метаболічної та збудливої функції. Глутамат натрію широко використовується в харчовій промисловості в якості підсилювач смаку. Незважаючи на те, що регулюючі органи з безпеки харчових продуктів в цілому визнають його безпеку для здоров'я, низкою досліджень вона ставиться під сумнів з огляду на довгострокову перспективу. Беручи до уваги все вищесказане, можна припустити, що глутамат натрію, доданий до дієти в надмірній кількості або за тривалого споживання, може викликати поведінкові, біохімічні та морфологічні зміни в таких структурах, як головний мозок, гіпокамп і мозочок дорослих ссавців та призвести до дисфукції в центральної нервової системи.

Ключові слова: глутамат натрію, харчові добавки, центральна нервова система, головний мозок.

The study is a fragment of the research project "Structural reorganization of the organs of the immune, respiratory, nervous and excretory systems under the influence of various exogenous factors (monosodium glutamate, sodium nitrite, ethanol, methacrylate)", state registration No. 0121U108234.

In the body, glutamate can be considered as being present in two parts of the nervous system: the peripheral and the central; both are related to the metabolic and excitatory functions of the brain [5].

Despite their similar roles, it is generally accepted that the central and peripheral glutamate pools do not mix freely. Otherwise, this would pose a problem for regulating the levels of glutamate in the brain. The blood-brain barrier plays a crucial role in maintaining this separation, as it is capable of excluding most peripheral (plasma) glutamate, indicating that brain glutamate level is largely maintained by glutamate produced within the brain itself [18].

Under physiological conditions, this division of activity between the central and peripheral parts of the nervous system remains generally intact. However, in pathological states such as inflammation or hyperammonemia (which can result from various conditions, including liver failure), studies have shown activation of cerebral enzymes such as glutamate dehydrogenase, leading to an increase in extracellular glutamate concentration.

This suggests that, although the peripheral and central glutamate pools may appear distinct, their regulatory systems can interact with one another, and dysfunction in one may lead to a loss of regulatory capacity in the other. Moreover, the recognition of the link between excess brain glutamate and neuronal death raises important questions about the role of peripheral/central glutamate homeostasis interactions (through the brain-gut-liver axis) in the development of neurodegenerative diseases.

While the neurological changes resulting from hepatic encephalopathy are generally considered transient, reports of altered blood glutamate levels and/or liver enzyme activity in neurological disorders such as autism, schizophrenia, cognitive impairment and Alzheimer's disease [35, 43], and the suggestion that peripheral glutamate concentration positively correlates with central glutamate level [45] have sparked growing interest in the potential role of glutamate and glutamate homeostasis in nervous system disorders (particularly neurodegenerative diseases) and their relevance for the development of new therapeutic strategies. In this context, we discuss the evidence supporting the involvement of peripheral (plasma/liver) and central (brain) glutamate homeostasis in the pathogenesis of brain disorders, as well as the implications of these interactions for the development of novel treatment approaches.

Food additives such as monosodium glutamate are widely used in the food industry as flavor enhancers. Although food safety regulatory agencies generally recognize it as safe for health [10, 44, 52, 59], a number of studies have questioned this in light of long-term effects [17, 23, 50, 57, 58]. A comprehensive review of the potential risks reported and those that may arise from chronic exposure to food additives allows for a critical assessment of the relevance of these findings [47].

On the other hand, the analysis of the existing publications shows that many of the reported adverse health effects of the additives have little relevance to chronic exposure in humans and are of limited informative value, as they are based on excessive dosages that do not correspond to levels typically consumed in food [58].

Several studies examine the effects of these substances on the nervous system, covering mechanisms such as oxidative stress, neuroinflammation and disruptions in neurotransmitter systems [1, 23, 51, 55]. However, for the most part, the food additives are studied individually, and their effects are not considered in relation to one another.

In this way, monosodium glutamate demonstrates the highest neurotoxicity [3], administarion of which has also been linked to cardiotoxicity, hepatotoxicity, low-grade inflammation, metabolic disorders, precancerous changes and behavioral alterations. Additionally, reports have indicated associations between monosodium glutamate consumption and tumorigenesis, increased oxidative stress and apoptosis in thymocytes, as well as genotoxic effects in lymphocytes [58].

The purpose of the study was to determine the effect of excessive intake of monosodium glutamate on the organs of the nervous system.

Monosodium glutamate (MSG), added to many processed foods, is a widely used flavor enhancer (known as umami), derived from L-glutamic acid, a natural amino acid, found in a variety of foods, with estimated average daily intake by humans of about 0.3-1.0 g in industrially developed European countries [2].

Studies on the effects of monosodium glutamate on food intake show that its addition enhances the flavor qualities of food and improves feelings of satiety, partly due to a sensory-specific mechanism. The macronutrient composition is a key regulator of monosodium glutamate impact on satiety and energy intake, as protein-rich foods fortified with monosodium glutamate, but not carbohydrate-rich foods, increase the sensation of fullness. An individual's nutritional status is also important, as those with lower nutritional/protein status tend to prefer higher concentrations of monosodium glutamate. Magerowski G. et al. explored the neurocognitive mechanisms underlying this effect. Their most striking observation was that adding monosodium glutamate to soups increased activity in brain regions associated with successful self-control during dietary decision-making in a group of healthy women, suggesting that glutamate may play a significant role in cognitive executive processes that regulate eating behavior and food choices [36].

Thus, in the body, glutamate can be considered as existing in two pools: peripheral and central, and both of which are involved in its metabolic and excitatory roles in the brain [45].

The excitatory effect of glutamate on nerve cells was first reported nearly six decades ago [19, 34]. Since that discovery, its role in brain metabolism as an excitatory neurotransmitter (within normal levels) and as an excitotoxin (in excess) has been extensively studied [30, 40, 60]. Currently, it is known that in the central nervous system of vertebrates (where up to 40% of synapses are glutamatergic), glutamate is not only the primary excitatory neurotransmitter but also an intermediate precursor of γ-aminobutyric acid (the main inhibitory neurotransmitter in the brain) [60]. In the brain, glutamate is one of the most abundant free amino acids and, similar to its peripheral effects, it is also at the crossroads of many metabolic pathways [37].

This calls into question the safety of monosodium glutamate based on dose, frequency and duration of exposure, as excessive consumption may trigger adverse health effects [54]. It has been reported that daily consumption of monosodium glutamate at high doses (2000–4000 mg/kg body weight) is toxic to both humans and experimental animals [13]. Although a dose of 100 mg/kg body weight is considered low, with continuous consumption, it can have significant toxic effects and may be harmful to health [32].

It is the abnormal accumulation of glutamate that can cause excitatory neurotoxic effects, potentially leading to damage to the central nervous system (CNS) [31].

These statements are supported by the understanding that endogenous glutamate plays a role in both physiological and pathological processes. Glutamate performs various physiological functions: it is a primary substrate for energy production in enterocytes, an intermediary in protein metabolism, a precursor of important metabolites such as glutathione (GSH, a modulator of oxidative stress) and N-acetylglutamate (a regulator of metabolism), as well as the dominant excitatory neurotransmitter in the central nervous system, where it plays a crucial role in neuronal function [42]. It is transported into the bloodstream and ultimately raises the level of glutamate in the brain, causing functional impairments, particularly through oxidative stress. Significant alterations in neuronal redox homeostasis have been reported, including increased lipid peroxidation, elevated nitrite concentrations and decreased level of antioxidants [4, 46].

The findings show that monosodium glutamate increases striatal weight, elevates level of malondialdehyde (MDA) and significantly decreases the activity of catalase (CAT), superoxide dismutase (SOD), as well as glutathione (GSH) levels. Additionally, monosodium glutamate significantly impairs the activity of ATPases in the striatum and cerebellum, including Na^+/K^+-ATPase, Ca^{2+}/Mg^{2+}-ATPase, and total ATPase activities [4].

Morphological changes occur, such as alterations in the histology of hippocampal neurons or damage to neurons in the brain and cerebellum, accompanied by increased levels of cholinesterase in the brain and blood serum [9, 46].

Excessive neuronal excitation by glutamate is a well-known cause of excitotoxicity, a key factor in numerous neurodegenerative disorders. The excitotoxic effect of MSG on the brain leads to significant impairments in short-term memory, deficits in spatial learning and alterations in exploratory behavior [8, 29]. These excitotoxic effects of monosodium glutamate arise from glutamate's interaction with its receptors, promoting apoptosis and necrosis of neuronal cells [11].

An increased concentration of endogenous glutamate in the central nervous system activates NMDA, AMPA or mGluR1 receptors and can contribute to acute brain damage seen in conditions such as status epilepticus, cerebral ischemia or traumatic brain injury. It may also play a role in chronic neurodegeneration, similar to that observed in disorders like amyotrophic lateral sclerosis and Huntington's chorea [3, 7, 40].

Recent studies have shown that monosodium glutamate induces neurotoxicity through two pathways: it disrupts the oxidative stress balance within the antioxidant system and affects the cholinergic system, in which acetylcholinesterase (AChE) plays a significant role [11]. An important mechanism in the regulation of cell proliferation and apoptosis is the mitogen-activated protein kinase p38 (p38 MAPK) signaling pathway [24]. In neonatal rats, MSG-induced alterations in MAPK pathway expression levels led to apoptosis of neurons in the hippocampus [48]. In this study, the group that received monosodium glutamate showed elevated levels of NF-κB and p38 MAPK proteins. Increased extracellular glutamate concentration may activate the p38 MAPK signaling pathway, which is involved in various apoptotic processes [24].

On the other hand, the excess of cytokines in the brain significantly contributes to the development of neurotoxic and neurodegenerative diseases [56]. It has been demonstrated that elevated levels of inflammatory markers such as TNF-α and NF-κB induce tissue damage through an inflammatory mechanism associated with the activation of nuclear factor kappa B (NF-κB) [12].

The findings from several studies highlight the critical role of glucose and lipid metabolism in maintaining neuronal health and reveal the pathological consequences of monosodium glutamate in neurodegenerative diseases. Observations show that prolonged daily consumption of monosodium glutamate significantly increases blood glucose, cholesterol and blood pressure levels, while decreasing serum insulin levels [3, 14, 39]. Elevated glucose level is closely associated with increased oxidative stress and inflammation, which are recognized factors in neurodegenerative processes [20]. Hyperglycemia stimulates the generation of ROS through multiple pathways, including glucose auto-oxidation, activation of the polyol pathway, and excessive production of advanced glycation end products [25]. The accumulation of ROS overwhelms antioxidant defense systems, leading to oxidative damage of cellular macromolecules such as lipids, proteins, and DNA that is a hallmark characteristic of neurodegenerative

conditions like Alzheimer's disease [15]. Additionally, elevated glucose level activate inflammatory signaling pathways, leading to the release of pro-inflammatory cytokines [20]. Chronic inflammation induced by these cytokines contributes to neuronal dysfunction and cell death, further exacerbating neurodegenerative processes [16]. Similarly, high cholesterol levels disrupt neuronal membranes and increase amyloid-beta aggregation, while elevated triglyceride levels promote oxidative stress and systemic inflammation [38].

The brain is highly susceptible to oxidative damage due to its intense oxidative metabolic activity, high concentration of polyunsaturated fatty acids, abundance of redox-active transition metal ions, relatively low antioxidant capacity, and the fact that it is composed of neurons that are inherently non-replicating [11]. Recent studies indicate that increased levels of MDA and NO in the hippocampus are associated with decreased level of GSH and reduced activity of SOD and GPx [41].

Other studies have documented a decrease in ACh level in the synaptic cleft due to monosodium glutamate, leading to cellular degeneration and an increased concentration of cholinesterase in brain tissues [41]. The following authors confirmed that monosodium glutamate suppresses ACh and serotonin concentrations while increasing levels of GABA and AChE [3].

Other studies have shown that exposure to monosodium glutamate causes an increase in hippocampal TNF-α, IL-1β, and Aβ levels, along with a decrease in AKT. The primary mechanism may involve its ability to stimulate pro-inflammatory cytokine production, where these cytokines specifically bind to the promoter region of target genes regulated by NF-κB to initiate the inflammatory response [12]. The observed effects are explained by the induction of oxidative damage caused by monosodium glutamate [28].

In general, pathological effects depend on the level of endogenous glutamate and the susceptibility of specific brain regions [56].

The hippocampus has a higher density of glutamate receptors than other brain regions, making it one of the most vulnerable areas to excitotoxic damage [48]. It is known that excitatory amino acid transporters (EAATs), particularly EAAT2, regulate glutamate levels. Reduced expression of EAAT2 in the hippocampus leads to increased level of monosodium glutamate, resulting in neuronal damage and ultimately contributing to pain manifestations and anxiety-like behavior [31].

A number of studies have been conducted to investigate the potential toxic effects of monosodium glutamate on neurons in various regions of the hippocampus in prepubertal rats. Since monosodium glutamate caused a reduction in neuronal signaling molecules such as BDNF, NMDA receptors, and NPY in the CA1 and DG regions of the hippocampus in prepubertal rats compared to the control group, caution is warranted regarding monosodium glutamate consumption, as it may affect neurons involved in memory in these age groups [27]. Another *in vitro* study demonstrated that monosodium glutamate induces cytotoxicity in primary neuronal cultures [33]. The result of the subsequent study concluded that oral and subcutaneous administration of monosodium glutamate induced changes in the hippocampus, including decreased activity of cyclic AMP-activated protein kinase (AMPK) and increased levels of the apoptosis mediator Fas ligand [21, 36]. An upregulation of the pro-apoptotic protein Bax (Bcl-2-associated X protein) has also been reported [49].

In the cerebral cortex, the neurotoxic effects of monosodium glutamate are manifested by significantly elevated levels of malondialdehyde, nitric oxide, tumor necrosis factor-alpha, interleukin-1β, acetylcholinesterase, monoamine oxidase and caspase-3, alongside decreased levels of glutathione, catalase, superoxide dismutase, dopamine and serotonin. Additionally, monosodium glutamate induces histopathological changes in the cortical region, as confirmed by biochemical and immunohistochemical tests [22].

Regarding CNS function, increased aggression, possibly due to excessive activation of glutamatergic pathways, is associated with decreased levels of γ-aminobutyric acid (GABA), while reduced locomotor activity may result from free radical-induced dopaminergic neurodegeneration. Administration of monosodium glutamate has also been correlated with altered antioxidant defense homeostasis, secondary to the loss of neuronal membrane integrity and functionality, leading to increased nonspecific permeability to multiple ions and pathological changes in intracellular metabolic processes [6, 53].

Conclusion

Taking all of the above into account, it can be concluded that monosodium glutamate, when added to the diet in excessive amounts or consumed over a prolonged period, may cause behavioral, biochemical and morphological changes in structures such as the brain, hippocampus and cerebellum of adult mammals, ultimately leading to CNS dysfunction.

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Стаття надійшла 13.06.2024 р.