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TOXICITY OF MONOSODIUM GLUTAMATE

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Abstract

Monosodium glutamate, called in the European Union E621, is a food additive used for the purpose of a flavor enhancer, being responsible for the "Chinese restaurant syndrome". Due to its toxic effects on the whole organism, in recent decades a lot of research has been carried out on the consequences of its use in the food industry. Despite all the studies carried out, monosodium glutamate still raises many questions about the safety of its use. The current paper presents a brief review of the negative effects found so far.

Key words: monosodium glutamate, toxic effects, food additive, body, intoxication, oxidative stress

INTRODUCTION

Monoglutamate sodium has been consumed for millennia, especially by Asian peoples, being found in certain types of algae and *dashi fish.* In Japan, the aroma conferred by the addition of monoglutamate is called "umami", a term that defines savory dishes, as well as ripe tomatoes, juicy and heat-treated meats and some cheeses (Yamaguchi, Ninomiya, 2000).

The actual discovery and chemical isolation of this substance took place in 1908, by the Japanese chemist Ikeda Kikunae, of a species of seaweed called *Macrocystis pyrifera.* Initially, the purpose of the discovery of this substance was to constitute an inexpensive and easy-to-manufacture nutritional product. Sodium monoglutamate was thus patented in Japan in 1909 and since 1920 it has been widespread in the United States, Germany, France and the United Kingdom (Sand, 2005). The toxic effects of monosodium glutamate have been observed for several decades, questioning the safety of its use as a food additive. The main negative effects provoked by the consumption of monoglutamate are obesity, neurotoxic effects, consequences on the genitals and the well-known "Chinese restaurant syndrome". Numerous studies have stated that MSG causes panic attacks, asthma attacks in asthmatics, diarrhea and emesis (Airaodion, 2019).However, monoglutamate remains a food additive often used in human food.

ABSORPTION OF SODIUM MONOGLUTAMATE INTO THE BODY

Sodium monoglutamate is obtained by chemical synthesis by various processes: hydrolysis, autolysis, fermentation with acids and enzymes, bacteria, and subsequently processed as a fine white powder. It consists of 78% glutamate, 12.2% sodium and 9.6% water in the form of D-glutamic acid. Chemical synthesis also results in L-glutamic acid, pyroglutamic acid and other compounds (Ault, 2004). From natural food sources, the only metabolite resulting from the digestion of monoglutamate is L-glutamic acid, an amino acid with an important role in intermediate metabolism. It is found in a multitude of tissues, especially in muscle, nervous, renal and hepatic tissues. It has an important role in the metabolism of other amino acids and many proteins. In the brain, L-glutamic acid is produced exclusively from glucose and plays the role of a neurotransmitter, regulating processes such as synaptic and neuronal developmental activity, learning and memory processes.

However, the provenance of glutamic acid is relevant in these processes. The brain produces the necessary glutamic acid; the one resulting from digestion does not have the ability to cross the blood-brain barrier (Torii et al., 2013).

Following the consumption of proteins, they are hydrolyzed, in the stomach under the action of hydrochloric acid and pepsin and trypsin, and in the small intestine (specifically in the duodenum) under the action of pancreatic enzymes contained in intestinal juice (trypsinogen, elastase, chemotripsinogen and procarboxypeptidase), the protein molecules being thus fragmented (Kiela et al., 2016). Normally, the body eliminates excess glutamic acid, poisoning is prevented, by the degradation of the amino acid in urea (Munro, 1978). In the case of digestion of the chemically obtained MSG results in free glutamate, not bound by proteins; because of this the enzymatic decomposition will not occur. Glutamate will then be rapidly absorbed into the small intestine, and its blood level will increase sharply, thus resulting in the toxic effect.

"CHINESE RESTAURANT SYNDROME"

It has been found for over 40 years and involves the appearance of symptoms such as flushing of the face, general weakness, numbness of the posterior part of the neck, a sensation that can extend to the arms and sometimes even to the thorax. Subsequently, other symptoms were described: dizziness, flushing of the face, syncope, and facial pressure (Geha et al., 2000). MSG consumption has been associated with Chinese restaurant syndrome, but numerous studies dispute this fact (Zautcke et al., 1986, Freeman 2006). Other authors state that SRC could be

caused by too high a consumption of lipids and sodium, characteristic of Chinese gastronomy (Freeman, 2006).

INFLUENCE OF SODIUM MONOGLUTAMATE IN OBESITY IN HUMANS AND LABORATORY ANIMALS

On the basis of recent studies, two theories have been developed according to which the consumption of MSG was associated with obesity: by increasing the palatability of food, the consumer having a tendency to overeat (Shi et al., 2010), or by the action of MSG on the hypothalamus, the energy balance of the body being unbalanced, the body developing the predisposition to store energy in adipose tissue (Insawand et al., etc., 2012).

This theory is based on the idea that MSG disrupts the hormonal action of the hypothalamus, in particular the activity of leptin (considered the main anti-obesity hormone, serving in the regulation of nutrition and in the energy balance of the body) (He et al. 2011, Hermanussen and Tresguerres 2003, Ahima and Flier, 2000).

Due to a form of obesity, with glucose tolerance and insulin resistance, occurring in newborn mice to which MSG was administered, interest has increased in cases of obesity occurring in people who consume foods rich in sodium monoglutamate.

Thus have been developed several premises about how it acts on metabolism. Induced MSG obesity was tested using 19-week-old rats, who underwent treatment with subcutaneous injections of 2 mg/g of MSG on postnatal days 2-4 and subcutaneous injections of 4 mg/g on postnatal days 6, 8 and 10. Following the treatment of MSG increased the expression of mRNA of interleukin-6 (it is a multifunctional cytokine, initially identified as a differentiating factor of B cells involved in the maturation of cells responsible for the production of antibodies, but it was also demonstrated to possess a wide range of additional activities, including action on blood vessels, neurons and T cells) (Bruce N. Cronstein, M. D., 2007), resistin and leptin in visceral adipose tissue and increased the amount of insulin, with effects on glucose tolerance (Roman-Ramos et al. 2011). Given that obesity in rats subject to the diet with MSG could be due to resistance to leptin (Dolnikoff et al. 2001), in terms of obesity in humans, one of the causes may be the amplification of foods with a high caloric value, in which the presence of MSG potentiates the taste (Bannai et al. 2013, Yeomans et al. 2008).

In accordance with the hypothesis under consideration, there is a significant increase in hunger and appetite for soup, even when it no longer contains MSG, this observation being made after the study of a sample, in which individuals were previously fed in four series with soup containing MSG (Yeomans et al., 2008).

The opposite results that include subjective assessments of the

feeling of hunger were observed in adults, who for six days were given an amount of MSG (2g/ day). However, this additive did not alter hunger and the feeling of saturation, but significantly increased gastric distention over a period of 2 hours after eating.

The use of MSG was also correlated with the increase in the level of some circulating amino acids (leucine, isoleucine, valine, lysine, cysteine, alanine, tyrosine and tryptophan), by comparison with the control group. However, between the control group, who were given feed with the addition of natrium chloride, and the batch to which they were given administered food with the addition of MSG, no differences in postprandial glucose and insulin were recorded (Boutry et al. 2011).

OXIDATIVE STRESS

Oxidative stress is caused by excessive production or continuous elimination of free radicals from cells, most of which are reactive oxygen species (ROS), but also nitrogen and sulfur (Sharma, 2015). They are byproducts of metabolism, being reactive chemical species that contain a single unparalleled electron on the external layer of the electronic shell.

Their effect consists in the oxidation of nucleic acids, proteins and lipids, in such a way that they cause alteration of the cellular structure, causing numerous diseases, many forms of cancer, cardiovascular diseases, arthritis and others. Free radicals are formed as a result of intra- and intercellular enzymatic reactions, an important source of intracellular free radicals being the ATP-forming reaction in the mitochondria and metabolism of cytochrome P450.

External sources of free radicals are some metal ions, chlorinated compounds, xenobiotics or exposure to UV or X-rays (Blessy et al., 2011). In a study conducted in 2012, Okwudiri and his collaborators demonstrated, using a batch of 24 Wistar rats, that the administration of 4g/kg body weight of MSG produced oxidative stress.

The study was conducted using as indicators the enzymatic activity of superoxid dismutase, glutathione S-transferase, catalase and lipid peroxidase. After administering the treatment for 10 days, the individuals were slaughtered, and their kidneys were taken. The study found that the activity of superoxidismuase and catalase decreased considerably.

These enzymes are responsible for neutralizing ROS; their low concentrations indicate that they have been partially inactivated by ROS. Glutathione exhibits antioxidant action by directly binding free radicals or stabilizing cell membranes. Thus, the level of glutathione S-transferase increases in direct proportion to the concentration of free radicals. In the control group, the level of this enzyme showed standard values, but in rats administered MSG the enzyme level increased significantly.

Lipid peroxidase is another enzyme whose value increases directly proportionally in relation to ROS levels; and in this case, the value of lipid peroxidase increased significantly from that of the control group. It was also found that the blood concentration of glucose increased in relation to the administration of MSG. Hyperglycemia causes self-oxidation of glucose, altering its metabolism and leading to oxidative stress.

EFFECTS OF ESG ON THE REPRODUCTIVE TRACT

In a study conducted in 1993 in male mice it was found that following the administration of 2 mg/g body on days 2, 4, 6,8 and 10 of life, the number of primary spermatozoa cells on day 75 of life increased compared to the control group. The administration of double doses led to a decrease in the volume of the pituitary glands and testicles, reducing the level of testosterone in male rats (Miskowiak et al. 1993). In another study, Wistar-called females were given 0.04 mg/kg body weight alternating with 0.08 mg/kg body weight daily; it was found the occurrence of cellular hypertrophy of the follicular sheath and alteration of basal membrane cells in the ovaries (Eweka, Om'iniabohs 2011).

NEUROTOXIC EFFECTS

Glutamate is an excitatory neurotransmitter of the central nervous system of mammals (CNS), having a major importance in physiological and pathological processes (Mattson 2008). Glutamate receptors are divided into three types of ionotropic receptors and three groups of metabotropic receptors (Meldrum 2000).

They are distributed throughout the central nervous system, including the hippocampus and hypothalamus, where they are designed to regulate several important functions (Collison et al., 2012). MSG acts as a biochemical messenger, which used in high doses causes neuronal necrosis in arched hypothalamic nuclei in newborn rats (Pelaez et al. 1999).

In other news, the action of MSG is not only localized at the hypothalamus level. MSG (4 mg/g, subcutaneously, on postnatal days 1, 3, 5 and 7) led to changes in the prefrontal cerebral cortex, including a smaller number of neurons, short and less branched dendrites (Gonzalez-Burgos et al., 2001) and decreased cortical cell numbers compared to rats in the control group (Rivera-Cervantes et al. 2004).

In addition, numerous studies have shown that newborns undergoing treatment with MSG showed the death of neurons and the decrease in the number of photoreceptor and glial cells (Blanks et al. 1981, Reif-Lehrer et al. 1975, Hyndman and Adler 1981). Although the toxic effects of MSG on the CNS are previously mentioned in animal studies, interpretation problems arise in terms of results on humans. MSG injection subcutaneous or intraperitoneal in rats can create difficulties when it comes to comparing it with the intake of MSG

administered orally. No pathological changes were recorded in the hypothalamic nuclei in rat females and their conception products, nor in mice discontinued from the intake of MSG in food (14.0, 42.8 or 42.0 g / kg) (Takasaki 1978).

This can be interpreted on the basis of the results of the swine study, in which it was demonstrated that less than 5% of the glutamate ingested was absorbed in the intestinal into the portal blood (Reeds et al., 1996).

However, conflicting results from various areas of the brain were found in albinotic male rats fed a lower dose of MSG (3 g/kg/day) homogenized in the feed for 14 days. Histological examination of the cerebral cortex attests to degenerative changes surrounded by inflammatory cells in the granular layer (Hashem et al., 2012). The inconsistency of the above results requires further research to elucidate the mechanism of action of MSG in the CNS after absorption in humans.

CONCLUSIONS

Sodium monoglutamate remains one of the most widely used food additives, especially in eastern Asia. Even though numerous studies have been conducted that demonstrate its toxic effects on laboratory animals, these results are difficult to extrapolate on the human species. The subject remains a controversial one, which requires further research.

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