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Ajinomoto's Excitotoxicity: A Bitter Taste

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ABSTRACT

Glutamic acid primarily serves as an important excitatory neurotransmitter in central nervous system and is an important excitatory amino acid (EAA). EAA represent major brain neurotransmitters and they are present in numerous neuronal systems and are involved in almost all aspects of normal and pathological brain activity. Changes in EAA transmission have been associated with the functional impairments characterizing major neurological disorders, including epilepsy, Alzheimer's disease, Parkinson's disease and schizophrenia etc. EAA also underlie the neuronal death associated with acute CNS insults, such as ischemia and post-traumatic lesions. The neurotoxicity of EAA, referred to as excitotoxicity, is presumably mediated primarily through an excess of EAA synaptic receptor stimulation. Excitotoxins are the substances which are capable of inducing excitotoxicity. They induce excitotoxicity through over stimulation of the ionotropic NMDA or AMPA/kainate receptor subtypes. They have been shown to produce an intense membrane depolarization and a massive increase in intracellular calcium leading to cell damage. Excitotoxins also promote cancer growth and metastasis. On expopsure to glutamate cancer cells become more mobile and that enhances metastasis, or spread. Our food stuffs and diet contains these excitotoxins in high amount as they are deliberately added to food items to enhance/alter taste. Glutamate is one such toxin added to foods usually as purified monosodium salt called monosodium glutamate or MSG. MSG is a potent excitotoxin which is the sodium salt of glutamic acid and due to its flavor enhancing properties it is used as a food additive in Asian cuisine and other diets making it a relevant aspect of the human diet worldwide. It increases the appetite by stimulating the appetite center but presently it has been debated for its safety and harmful effects. It affects almost every major organ in the body. In the present review resultant pathways associated with excitotoxicty of ajinomoto are deliberated with special reference to calcium signaling.

Keywords: Ajinomoto, excitotoxicity, glutamate.

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INTRODUCTION

A group of compounds called excitotoxins play a critical role in the development of several neurological disorders including migraines, seizures, infections, abnormal neural development, certain endocrine disorders, neuropsychiatric disorders, learning disorders in children, AIDS dementia, episodic violence, lyme borreliosis, hepatic encephalopathy, specific types of obesity and especially the neurodegenerative diseases, such as ALS, Parkinson's disease, Alzheimer's disease, Huntington's disease and olivopontocerebellar degeneration[1]. Unfortunately the top most body, the FDA refuses to recognize the immediate and long term danger to the public caused by the practice of allowing various excitotoxins to be added to the food supply, such as monosodium glutamate (MSG), hydrolyzed vegetable protein and aspartame etc. The amount of these neurotoxins added to our food has increased enormously since their first introduction. Since 1948 the amount of MSG added to foods has doubled every decade. By 1972, 262,000 metric tons were being added to foods and over 800 million pounds of aspartame have been consumed since it was first approved. Ironically, these food additives have nothing to do with preserving food or protecting its integrity. They only alter the taste of food and are used to enhance the taste of food so as to mask disagreeable taste and magnify desire. Excitotoxins are capable of inducing excitotoxicity, the term which was coined by Dr. John Olney in the year 1969 to describe the neuronal injury that results from presence of excess glutamate in brain[2]. Excitotoxins are usually acidic amino acids that react with specialized receptors in the brain in such a way as to lead to destruction of certain types of neurons. Glutamate is one of the more commonly known excitotoxins, but over seventy have thus far been identified.

Monosodium Glutamate

MSG is the sodium salt of glutamate. Glutamate is a normal neurotransmitter in the brain. In fact, it is the most commonly used neurotransmitter by the brain. Defenders of MSG say that how could a substance that is used normally by the brain cause harm? This is because, glutamate, as a neurotransmitter, exists in the extracellular fluid only in very, very small concentrations --- no more than 8 to 12uM. When the concentration of this transmitter rises above this level, the neurons begin to fire abnormally. At higher concentrations, the cells undergo this specialized process of delayed cell death, excitotoxicity. That is, they are excited to death. MSG ($C_5H_8NO_4Na$) contains 78% of glutamic acid, 22% of sodium and water.[3] The number of foods that contain MSG is astounding. It is present in chips, cold cuts, fresh produce that has been sprayed with pesticide, gelatin and in virtually every food served in every fast food restaurant.

Jelly, Pastry, Candy, Biscuit, Fruity, Bread, Chocolate, Juice, Cerelac, Jam, Burgerburger, french-fries, pizza, cold drinks, noodles, chocolate etc contain MSG. The most alarming fact is the food industry increases the amount of MSG put in our food every year[4]. Glutamic acid is a non-essential amino acid, i.e., the body can produce its own glutamic acid, and does not depend upon getting glutamic acid from ingested food. Food manufacturing and chemical plants produce glutamic acid commercially. However glutamic acid, produced outside the body (for use in food, drugs, dietary supplements, cosmetics, fertilizers, personal care products, etc), can cause brain lesions, neuroendocrine disorders, learning disabilities, neurodegenerative diseases and many adverse reactions in humans and animals[5,6]. In 1957, two ophthalmology residents, Lucas and Newhouse, were conducting an experiment on mice to study a particular eye disorder[7]. During the course of this experiment, they fed newborn mice with MSG and discovered that all demonstrated widespread destruction of the inner nerve layer of the retina. Similar destruction was also seen in adult mice but not as severe as the newborns. The results of their experiment was published in the Archives of Ophthalmology and soon forgotten. For ten years prior to this report, large amounts of MSG were being added not only to adult foods but also to baby foods in doses equal to those of the experimental animals. Then in 1969, Dr. John Olney, a neuroscientist and neuropathologist working out of the Department of Psychiatry at Washington University in St. Louis, repeated Lucas and Newhouse's experiment.[8] His lab assistant noticed that the newborn of MSG exposed mice were grossly obese and short in stature. Further examination also demonstrated hypoplastic organs, including pituitary, thyroid, adrenal as well as reproductive dysfunction. Physiologically, they demonstrated multiple endocrine deficiencies, including TSH, growth hormone, LH, FSH, and ACTH. When Dr. Olney examined the animal's brain, he discovered discrete lesions of the arcuate nucleus as well as less severe destruction of other hypothalamic nuclei. In hypothalamus too, glutamate is the most important neurotransmitter [9] and since this early observation, monosodium glutamate and other excitatory substances have become the standard tool in studying the function of the hypothalamus. Later studies indicated that the damage by MSG was much more widespread and included such areas as the hippocampus, circumventricular organs, locus ceruleus, amygdala-limbic system, subthalamus, and striatum.[10]

MSG Toxicity

The infamous MSG was the first excitotoxin to be unleashed on the public. Easier said than done, if you eat anything out of a packet, can or bottle. And reading labels is not a guarantee of safety, because the US government permits manufacturers to omit this unpopular additive from

their labels unless the product contains 100% MSG and, of course, most countries import a great deal of manufactured food from the US. Further, any manufactured food you buy which lists many ingredients will almost certainly contain MSG, even though it is not itself listed. For example, a soup can which lists tomatoes as one of the ingredients does not have to disclose what is in those tomatoes. They could contain something to which you are allergic, and you would find out the hard way. Hidden sources of MSG (adapted from Dr Blaylock's book, Excitotoxins The Taste That Kills) are Plant Protein Extract, Monosodium Glutamate, Hydrolyzed Vegetable, Protein, Hydrolyzed Plant Protein, Calcium and Sodium Caseinate, Yeast Extract, Textured Protein, Autolyzed Yeast, Hydrolyzed Oat Flour etc. Early Findings of MSG toxicity include Flushing, Sweating, Headache/migraine, Low blood pressure, Flu-like achiness & malaise, Facial pressure and/or pain, Numbness to face or mouth, Dizziness/Light headedness, Chest Pain, Loss of balance (ataxia), Confusion/Disorientation, Heart Palpitations, Shortness of breath, Slurred speech etc. Later Findings include Asthma, Urticaria/Hives, Runny nose, Angioedema (swelling of-face, throat, tongue), Frequent night waking, Agitation/rage reactions, Seizures, Tremors, impaired memory &learning, Anxiety/panic attacks, Hyperactivity, Depression and Behavioral problems. Currently Under Investigation are dementia, Obesity, Vision: retinopathy,, cataracts, & visual, processing problems, Polycystic ovaries, Diabetes, Sex hormone imbalance, Infertility, Cancers, White matter lesions etc. Furthermore, monosodium glutamate (MSG) crosses placental barrier and distribute to embryonic tissues. Maternal intragastric (ig) administration of excessive MSG at a latestage of pregnancy resulted in a series of behavioral disturbance and histopathological brain lesions in the filial mice[11,12]. MSG unfortunately got a respectable place in our menu and it change our perception of the drink or food's flavor, creating a delicious and savory affect. Most people believe that it is used as preservatives, however, aside from actually leading us to enjoy and subsequently crave the product, the toxins have no other purpose. A major comfort food in India is the so-called "Chinese". Be it from a trendy upscale Chinese restaurant or from a street side food peddler selling it for a few rupees, Chinese food in India has a special taste to it. But many people find it impossible to replicate such taste and deliciousness when they cook at their homes. The secret ingredient that gives this special taste is Monosodium Glutamate (MSG), also known as Ajinomoto. Well, this is really not a secret ingredient in Chinese food in India, but the dangers associated with MSG may be unknown to many people. Remember, MSG is not usually added to any Indian dishes but is generously used in the Indianized Chinese food. Indian food itself uses a wide variety of spices that naturally add flavor to them and have no use for a chemical taste enhancer. The irony of it all is that cooks in

China rarely use MSG as an ingredient while cooking! Monosodium Glutamate is a flavor enhancer invented by the Japanese scientist Professor Kidunae Ikeda and patented in the year 1909 by his company, Ajinomoto. This chemical is stabilized with salt and water to manufacture the MSG available in markets today. It has the same chemical property as the glutamic acid naturally produced in the human stomach. It is also similar to the glutamate formed when protein containing glutamic acid is broken down by cooking, fermentation or ripening. But the similarities between the commercial chemical MSG and the naturally forming glutamic acid seem to end there.

Excitotoxic Cascade

Glutamate is essential for learning and for both short-term and long-term memory. It is also the precursor to the inhibitory neurotransmitter, GABA. GABA is a calming neurotransmitter, and is essential for speech. GABA neurons damp the propagation of sounds so that a distinction can be made between the onset of a sound and background noise. (GABA is often used to help restore speech in individuals who have suffered strokes.) Problems occur if the normal process of regulation of glutamate malfunctions and if toxic levels of this excitatory neurotransmitter build up in the synaptic junctions. Glutamate, although it is the principal excitatory neurotransmitter. Cerebral glutamate is derived solely from endogenous sources; mainly from alpha ketoglutarate, which is a product of the Krebs cycle (citric acid cycle, TCA [tricarboxylic acid] cycle). Glutamate, like other neurosecretory substances, is initially synthesized by the endoplasmic reticulum and then transported to the Golgi apparatus for additional processing. Emerging from the opposite surface of the Golgi apparatus and wrapped inside a vesicular (bilipid) membrane, glutamate is then transported down the axon via a complex system of microtubules. Antegrade motion down the axon on the microtubules is mediated by molecules called motor kinesin, whereas cytoplasmic dynein generates retrograde motion. Mitochondria also accompany these transport molecules, providing the required energy. Upon reaching the axonal tip the vesicle with the enclosed glutamate merges with the presynaptic membrane by the process called exocytosis to release the glutamate into the synaptic space between neurons. The vesicular membrane is then recycled and transported back up the neuronal axon in a retrograde fashion via the microtubular network. The synaptic glutamate is finally freed to interact with specific receptor sites on the postsynaptic membrane of the adjacent neuron to initiate an important cascade of molecular events within that neuron[13]. The neuronal glutamate considered here acts as a neurotransmitter, which is the method of communication between neurons. This interaction between neurons may be either excitatory or inhibitory. The major excitatory amino acid

neurotransmitters areglutamate and aspartate, while GABA (Gamma-aminobutyric acid), glycine (amino acetic acid), and taurine are inhibitory[13].

Excitotoxic Receptors

The excitatory effects of glutamate are exerted via the activation of three major types of ionotropic receptors and several classes of metabotropic receptors linked to G-proteins. The major ionotropic receptors activated by glutamate are commonly referred to as the N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5- methylisoxazole-4-propionate (AMPA) and kainic acid (KA) receptors. These ionotropic receptors are ligand-gated ion channels permeable to various cations[14]. NMDA receptors are Ca^{2+} favoring glutamate-gated ion channels that are expressed in most central neurons and were initially held responsible for neuronal injury, owing to their high Ca^{2+} permeability and conductance properties[15]. Continuous activation of large numbers of NMDA receptors (especially the NR1/NR2B-subtype) leads to increases in intracellular calcium loads and catabolic enzyme activities, which can trigger a cascade of events eventually leading to apoptosis or necrosis[16]. These downstream effects include mitochondrial membrane depolarization, caspase activation, production of toxic oxygen and nitrogen free radicals and cellular toxicity[17,18]. AMPA type glutamate receptors have also been implicated in excitotoxicity because assemblies of these receptors are highly permeable to Ca^{2+} and possibly contribute to the delayed neuronal cell death processes induced by Ca^{2+} overload. The Ca^{2+} permeability of the AMPA receptor is determined by the presence or absence of the GluR2 subunit in the receptor complex. Low expression of GluR2 permits the construction of AMPA receptors with high Ca^{2+} permeability and contributes to neuronal degeneration in ischemia. Surprisingly, decreasing GluR2 levels or selective blockage ofCa^{2+} -permeable AMPA receptors was also shown to protect against neurodegeneration[19]. Excitotoxicity has been implicated as the mechanism of neuronal damage resulting from acute insults such as stroke, epilepsy and trauma as well as during the progression of adult-onset neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease and Huntington's disease[20]. Accurate control of glutamatergic neurotransmission is of paramount importance, due to its involvement in both excitotoxic cell death and neural signaling[21]. Excitotoxicity is therefore a mechanism promoting cell death through the hyper activation of glutamatergic receptors or its analogues. This hyperactivation leads to excess calcium (Ca^{2+}) inflow to the cell, where this ion is sequestered inside mitochondria, leading to metabolic dysfunction, the generation of free radicals, the activation of proteases, phospholipases, endonucleases, nitric oxide synthase, and the inhibition of protein synthesis[22].

Calcium Homeostasis

For calcium homeostasis to be lost, regulatory mechanisms for this ion, including the calcium pump, the sodium/calcium (Na^+ /Ca^{2+}) exchanger and calcium buffering proteins, must first be overflowed. Once these systems saturate, excess calcium accumulates inside the mitochondrial matrix. This accumulation depolarizes the mitochondrial membrane by two different mechanisms: first, the increased concentration of positive ions in the mitochondrial matrix decreases the chemoosmotic potential across the membrane(leading in turn to reduced rates of adenosine triphosphate (ATP) synthesis), and second, the activation of mitochondrial transition pores (a mechanism normally used to shunt calcium back to the cytosol), which can lead to irreversible membrane depolarization if calcium unbalance is prolonged[23]. High calcium concentrations in the mitochondrial matrix also promote the generation of free radicals, which promote the peroxidation of membrane lipids, the synthesis of nitric oxide and the activation of enzymes involved in the catabolism of proteins, phospholipids and nucleic acids. In addition, nitric oxide can act as a retrograde messenger, further contributing to the excitotoxic effect of glutamate by enhancing its release from presynaptic terminals[24]. Glutamate excitotoxic calcium overload can be appreciated from the perspective of the normal mechanisms of neuronal calcium homeostasis. Intracellular cytosolic free calcium is maintained at very low concentrations (micromolar) relative to free extracellular calcium. Plasma membrane calcium transporters regulate this cytosolic free calcium concentration. Membrane transporters in general have been classified as antiporters, symporters, and ATP-coupled active transporters. These transporters are membrane protein compounds that are coupled to energy sources and change the distribution of substrate ions or molecules across a membrane. Antiporters and symporters are called secondary transporters because they use the energy from an existing ion gradient to drive the passage of another ion or molecule in the same (symporter) or opposite (antiporter) direction across a membrane as the energizing ion. Movement through the neuronal membrane is achieved by a change in the conformation of the protein-substrate complex. Complexing with two or more substrates is required to initiate conformational transitions in antiporters (opposite direction coupling) and symporters (same direction coupling). The primary transporters (ATP-coupled active transporter) couple a chemical reaction to theprotein conformational transitions that supply themetabolic energy required to generate concentration gradients of substrate ions across the membrane. Calcium is controlled by the antiporter and plasma-membrane calcium pump. The antiporter, which has a low affinity but high transport capacity for calcium, moves calcium out of the neuron by a sodium–calcium exchange mechanism. The sodium gradient across the

membrane drives this exchanger. The PMCA, on the other hand, has a high affinity but low transport capacity for calcium. This active pump transports one Ca for each ATP hydrolyzed. One distinguishing feature of the calcium pump is the enhanced activation of the pump by binding Ca/calmodulin, which results in a 20- to 30-fold increase in the affinity of the substrate Ca site. The mitochondrion and endoplasmic reticulum are also significant sources of calcium stores. An antiporter mechanism maintains high calcium concentrations in the mitochondria by moving free calcium from the cytosol to the mitochondria while an antiporter and an ATP-dependent active pump sequester the endoplasmic reticulum calcium. Glutamate receptor over stimulation increases intracellular calcium by directly opening ion channels and secondarily affecting calcium homeostatic mechanisms. As mentioned, the initial glutamate receptor opening of the sodium/calcium channels not only allows the influx of calcium but also causes membrane depolarization. The depolarization would in turn activate the voltage-dependent calcium channels, which would further increase the intracellular calcium levels. The decreased sodium gradient across the cell membrane caused by the glutamate receptor–coupled channels, however, would also reduce the ability of the sodium gradient–dependent antiporter to remove intracellular calcium. Superimposed disorders that decrease ATP production (ie, hypoxia, neurodegenerative disorders, etc) would adversely affect the activity of the ATP-dependent calcium transporters as well as the energy-dependent sodium potassium pump, which would then also affect the transmembrane sodium gradient and therefore the antiporter function[25]. The glutamate-induced elevated calcium levels proceed to over activate a number of enzymes, including protein kinase C, calcium/cadmodulin-dependent protein kinase II, phospholipases, proteases, phosphatases, nitric oxidesynthase, endonucleases, and ornithine decarboxylase. Some of these enzymes can also produce positive feedback loops to accelerate the down-ward spiral toward neuronal death. Activation of phospholipase A, for example, would generate platelet-activating factor and arachidonic acid and its metabolites. Platelet-activating factor directly contributes to the excitotoxic cascade by increasing glutamate release. Arachidonic acid inhibits reuptake of glutamate from the synaptic space, leading to further activation of glutamate receptors and more arachidonic acid formation. Increased arachidonic acid levels form oxygen free radicals, which activate phospholipase A, leading to more arachidonic acid formation. These enzymes and the generated feedback loops rapidly lead to neuronal self-digestion by protein breakdown, free radical formation, and lipid peroxidation. Another important activated enzyme is nitric oxide synthase, which forms nitric oxide. Nitric oxide performs a variety of normal biological functions but the excessively stimulated NMDA receptors will produce abnormally increased

levels of nitric oxide and superoxide ions. These substances may react and form peroxynitrite, which is extremely toxic, resulting in neuronal death. Nitric oxide can damage DNA as well as inhibit mitochondrial respiration, which in turn would create more free radicals and cause additional membrane depolarization. The nitric oxide–initiated neurotoxic cascades are important components of the mechanism of cell death in many neurodegenerative disorders, including Huntington disease[25-30].

CONCLUSION

MSG is one of the chemicals that have far reaching implications on human health including obesity, diabetes, cognitive deficits, proepileptic, retinal pathologies, genotoxicity, proasthamatic, besides having role in hormonal imbalance, renal and hepatic toxicity. Not only present generation but future generation because of its genotoxixc potential is threatened with its unstoppable and unfortunately popular use. Even then its continuous and prevalent use is hard to be understood. Health regulatory authorities are supposed to make people aware about the disastrous consequences associate with its use and health guidelines need to be strengthened regarding inclusion of these excitotoxins in the food stuffs.

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