Food Additive Excitotoxins and Degenerative Brain Disorders

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There are a growing number of clinicians and basic scientists who are convinced that 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)

An enormous amount of both clinical and experimental evidence has accumulated over the past decade supporting this basic premise.(2) Yet, the FDA still 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.* The amount of these neurotoxins added to our food has increased enormously since their first introduction. For example, since 1948 the amount of MSG added to foods has doubled every decade. By 1972, 262,000 metric tons were being added to foods. Over 800 million pounds of aspartame have been consumed in various products since it was first approved. Ironically, these food additives have nothing to do with preserving food or protecting its integrity. They are all used to alter the taste of food. MSG, hydrolyzed vegetable protein, and natural flavoring are used to enhance the taste of food so as to mask disagreeable taste and magnify desired taste. Aspartame is an artificial sweetener that goes by various brand names such as NutraSweet and Equal.

These toxins (excitotoxins) are not present in just a few foods, but rather in almost all processed foods. In many cases they are being added in disguised forms, such as natural flavoring, spices, yeast extract, textured protein, soy protein extract, etc. Experimentally, we know that when subtoxic levels of excitotoxins are given to animals in divided doses, they experience full toxicity, i.e., they are synergistic. Also, liquid forms of excitotoxins, as occurs in soups, gravies and diet soft drinks are more toxic than that added to solid foods. This is because they are more rapidly absorbed and reach higher blood levels.

So, what is an excitotoxin? These are substances, 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. 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 and aspartame use, usually say: 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.

It should also be appreciated that the effects of excitotoxin food additives generally are not dramatic. Some individuals may be especially sensitive and develop severe symptoms and even sudden death from cardiac irritability; but, in most instances, the effects are subtle and develop over a long period of time. While the food additives, MSG and aspartame, are probably not direct causes of the neurodegenerative diseases, such as Alzheimer's dementia, Parkinson's disease, or amyotrophic lateral sclerosis (ALS), they may well precipitate these disorders and certainly worsen their pathology as we shall see. It may be that many people with a propensity for developing one of these diseases would never develop a full blown disorder had it not been for their exposure to high levels of food borne excitotoxin additives. Some may have had a very mild form of the disease had it not been for the exposure. Likewise, food borne excitotoxins may be harmful to those suffering from strokes, head injury and HIV infection, and certainly should not be used in a hospital setting.

How Excitotoxins Were Discovered

In 1957, two ophthalmology residents, Lucas and Newhouse, were conducting an experiment on mice to study a particular eye disorder.(3) During the course of this experiment, they fed newborn mice 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.(4) 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.

Recent studies have shown that glutamate is the most important neurotransmitter in the hypothalamus.(5) 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 monosodium glutamate was much more widespread and included such areas as the hippocampus, circumventricular organs, locus ceruleus, amygdala-limbic system, subthalamus, and striatum.(6)

More recent molecular studies have disclosed the mechanism of this destruction in some detail.(7) Early on, it was observed that when neurons *in vitro* were exposed to glutamate and then washed clean, the cells appeared perfectly normal for approximately an hour, at which time they rapidly underwent cell death. It was discovered that when calcium was removed from the medium, the cells continued to survive. Subsequent studies have shown that glutamate, and other excitatory amino acids, attach to a specialized family of receptors (NMDA, kainate, AMPA and metabotrophic) which in turn, either directly or indirectly, opens the calcium channel on the neuron cell membrane, allowing calcium to flood into the cell. If unchecked, this calcium will trigger a cascade of reactions, including free radical generation, eicosanoid production, and lipid peroxidation, which will destroy the cell. **With this calcium triggered stimulation, the neuron becomes very excited, firing its impulses repetitively until the point of cell death, hence the name excitotoxin.** The activation of the calcium channel via the NMDA type receptors also involves other membrane receptors such as the zinc, magnesium, phencyclidine, and glycine receptors.

In many disorders connected to excitotoxicity, the source of the glutamate and aspartate is endogenous. We know that when brain cells are injured they release large amounts of glutamate from surrounding astrocytes, and this glutamate can further damage surrounding normal neuronal cells. This appears to be the case in strokes, seizures and brain trauma. But, food borne excitotoxins can add significantly to this accumulation of toxins.

The FDA's Response

In July 1995, the Federation of American Societies for Experimental Biology (FASEB) conducted a definitive study for the FDA on the question of safety of MSG.(8) The FDA wrote a very deceptive summary of the report in which they implied that, except possibly for asthma patients, MSG was found to be safe by the FASEB reviewers. But, in fact, that is not what the report said at all. I summarized, in detail, my criticism of this widely reported FDA deception in the revised paperback edition of my book, *Excitotoxins: The Taste That Kills*, by analyzing exactly what the report said, and failed to say.(9) For example, it never said that MSG did not aggravate neurodegenerative diseases. What they said was, there were no studies indicating such a link. Specifically, that no one has conducted any studies, positive or negative, to see if there is a link. A vital difference.

What we find is that there are many gaps in our knowledge concerning the toxicity of food additive excitotoxins. For example, virtually no long term studies have been done on the neuroendocrine effects of chronic excitotoxin additive feeding in humans. Likewise, there are no studies of regionally distributed brain levels of glutamate, aspartate and cysteine following chronic excitotoxin feeding. Most important, there are no studies of the effect of these excitotoxins on the physiology of the nervous system under conditions of low brain energy supply. In examining the research literature, virtually all studies of this problem, other than behavioral effects, are centered on microscopic pathologic changes and not functional alterations of either the neurons themselves or of the entire brain itself. This is of vital importance, since we know that neurons can have severely altered function without pathological change as seen on either light or electron microscopy. Several studies have been done that demonstrate significant alteration in brain neurochemistry with acute MSG exposure.(10,11)

The Corporate Response

Unfortunately, for the consumer, the corporate food processors not only continued to add MSG to our foods, but they have gone to great links to disguise these harmful additives. For example, they use such names as hydrolyzed vegetable protein, vegetable protein, textured protein, hydrolyzed plant protein, soy protein extract, caseinate, yeast extract, and natural flavoring. We know experimentally that when these excitotoxin taste enhancers are added together they become much more toxic than is seen individually.(12) In fact, excitotoxins in subtoxic concentrations can be fully toxic to specialized brain cells when used in combination. Frequently, I see processed foods on supermarket shelves, especially frozen or diet foods, that contain two, three or even four types of excitotoxins. We also know, as stated, that excitotoxins in liquid forms are much more toxic than solid forms because they are rapidly absorbed and attain high concentration in the blood. This means that many of the commercial soups, sauces, and gravies containing MSG are very dangerous to nervous system health, and should especially be avoided by those either having one of the above mentioned disorders, or who are at a high risk of developing one of them. They should also be avoided by cancer patients and those at high risk for cancer, because of the associated generation of free radicals and lipid peroxidation.(13)

In the case of ALS, we know that consumption of red meats and especially MSG itself, can significantly elevate blood glutamate, much higher than is seen in the normal population.(14) Similar studies, as far as I am aware, have not been conducted in patients with Alzheimer's disease or Parkinson's disease. But, as a general rule, I would certainly suggest that person's with either of these diseases avoid MSG containing foods as well as red meats, cheeses, and pureed tomatoes, all of which are known to have higher levels of glutamate.

It must be remembered that it is the glutamate molecule that is toxic in MSG. Glutamate is a naturally occurring amino acid found in varying concentrations in many foods. Defenders of MSG safety allude to this fact in their defense. But, it is free glutamate that is the culprit. Bound glutamate, found naturally in foods, is less dangerous because it is slowly broken down and

absorbed by the gut, so that it can be utilized by the tissues, especially muscle, before toxic concentrations can build up. Therefore, a whole tomato is safer than a pureed tomato. The only exception to this based on present knowledge, is in the case of ALS. Also, the tomato plant contains several powerful antioxidants known to block glutamate toxicity.(15)

Hydrolyzed vegetable protein is a common food additive and may contain at least two excitotoxins, glutamate and cysteic acid. Hydrolyzed vegetable protein is made by a chemical process that breaks down the vegetable's protein structure to purposefully free the glutamate, as well as aspartate, another excitotoxin. This brown powdery substance is used to enhance the flavor of foods, especially meat dishes, soups, and sauces. Despite the fact that some health food manufacturers have attempted to sell the idea that this flavor enhancer is "all natural" and "safe" because it is made from vegetables, it is not. It is the same substance added to processed foods. Experimentally, one can produce the same brain lesions using hydrolyzed vegetable protein as by using MSG or aspartate.(16)

A growing list of excitotoxins are being discovered, including several that are found naturally. For example, L-cysteine is a very powerful excitotoxin. Recently, it has been added to certain bread dough and is sold in health food stores as a supplement. Homocysteine, a metabolic derivative, is also an excitotoxin.(17) Interestingly, elevated blood levels of homocysteine has recently been shown to be a major, if not the major, indicator of cardiovascular disease and stroke. Equally interesting, is the finding that elevated levels have also been implicated in neurodevelopmental disorders, especially anencephaly and spinal dysraphism (i.e., neural tube defects).(18) It is thought that this is the protective mechanism of action associated with the use of the prenatal vitamins B12, B6, and folate when used in combination. It remains to be seen if the toxic effect is excitatory or by some other mechanism. If it is excitatory, then unborn infants would be endangered as well by glutamate, aspartate (part of the aspartame molecule), and the other excitotoxins. Recently, several studies have been done in which it was found that all Alzheimer's patients examined had elevated levels of homocysteine.(19)

One interesting study found that persons affected by Alzheimer's disease also have widespread destruction of their retinal ganglion cells.(20) Interestingly, this is the area found to be affected when Lucas and Newhouse first discovered the excitotoxicity of MSG. While this does not prove that dietary glutamate and other excitotoxins cause or aggravate Alzheimer's disease, it is powerful circumstantial evidence. When all of the information known concerning excitatory food additives is analyzed, it is hard to justify continued approval by the FDA for the widespread use of these food additives.

Conclusion

In this brief discussion of a most complicated and evolving subject, I have had to omit several important pieces of the puzzle. For example, I have said little about the functional components of the receptor systems, the glutamate transporter and its relation to ALS and Alzheimer's dementia,

receptor decay with aging and disease, membrane effects of lipid peroxidation products, membrane fluidity, effects of chronic inflammation on the glutamate/free radical cycle, stress hormones and excitotoxicity, the role of insulin excess on the eicosanoid system, or the detailed physiology of the glutamatergic system. I have also only briefly alluded to the toxicity of aspartame and omitted its strong connection to brain tumor induction.

But, I have tried to show the reader that there is a strong connection between dietary and endogenous excitotoxin excess and neurological dysfunction and disease. Many of the arguments by the food processing industry have been shown to be false. For example, that dietary glutamate does not enter the brain because of exclusion by the blood-brain barrier, has been shown to be wrong, since glutamate can enter by way of the unprotected areas of the brain such as the circumventricular organs. Also, as we have seen, chronic elevations of blood glutamate can breech the intact blood-brain barrier. In addition, there are numerous conditions under which the barrier is made incompetent.

As our knowledge of the pathophysiology and biochemistry of the neurodegenerative diseases increases, the connection to excitotoxicity has become stronger.(21) This is especially so with the interrelationship between excitotoxicity and free radical generation and declining energy production with aging. Several factors of aging have been shown to magnify this process. For example, as the brain ages its iron content increases, making it more susceptible to free radical generation. Also, aging changes in the blood brain barrier, microvascular changes leading to impaired blood flow, free radical mitochondrial injury to energy generating enzymes, DNA adduct formation, alterations in glucose and glutamate transporters and free radical and lipid peroxidation induced alterations in the neuronal membranes all act to make the aging brain increasingly susceptible to excitotoxic injury.

Over a lifetime of free radical injury due to chronic stress, infections, trauma, impaired blood flow, hypoglycemia, hypoxia and poor antioxidant defenses secondary to poor nutritional intake, the nervous system is significantly weakened and made more susceptible to further excitotoxic injury. We know that a loss of neuronal energy generation is one of the early changes seen with the neurodegenerative diseases. This occurs long before clinical disease develops. But, even earlier is a loss of neuronal glutathione functional levels.

A word about ascorbic acid: Few are aware of the importance of adequate ascorbate levels for CNS function and neural protection against excitotoxicity. We are finding out that ascorbic acid plays a vital role in neurobehavioral regulation and the dopaminergic system as well, which may link ascorbate supplementation to improvements in schizophrenia.

Our knowledge of this process opens up new avenues for treatment as well as prevention of excitotoxic injury to the nervous system. For example, there are many nutritional ways to improve CNS antioxidant defenses and boost neuronal energy generation, as well as improve membrane fluidity and receptor integrity. By using selective glutamate blocking drugs or nutrients, one may be able to alter some of the more devastating effects of Parkinson's disease. For example, there is evidence that dopamine deficiency causes a disinhibition (overactivity) of the subthalamic nucleus and that this may result in excitotoxic injury to the substantia nigra.(22) By blocking the glutamatergic neurons in this nucleus, one may be able to reduce this damage.

There is also evidence that several nutrients can significantly reduce excitotoxicity. For example, combinations of coenzyme Q10 and niacinamide have been shown to protect against striatal excitotoxic lesions. Methylcobolamine, phosphotidylserine, picnogenol and acetyl-L-carnitine all protect against excitotoxicity as well.

Of particular concern is the toxic effects of these excitotoxic compounds on the developing brain. It is well recognized that the immature brain is four times more sensitive to the toxic effects of the excitatory amino acids as is the mature brain. This means that excitotoxic injury is of special concern from the fetal stage to adolescence. There is evidence that the placenta concentrates several of these toxic amino acids on the fetal side of the placenta. Consumption of aspartame and MSG containing products by pregnant women during this critical period of brain formation is of special concern and should be discouraged. Many of the effects, such as endocrine dysfunction and complex learning, are subtle and may not appear until the child is older. Other hypothalamic syndromes associated with early excitotoxic lesions include immune alterations and violence dyscontrol.

Over 100 million American now consume aspartame products and a greater number consume products containing one or more excitotoxins. There is sufficient medical literature documenting serious injury by these additives in the concentrations presently in our food supply to justify warning the public of these dangers. The case against aspartame is especially strong.

Footnote

*** See FDA position papers at http://www.fda.gov/opacom/backgrounders/msg.html and http://www.fda.gov/bbs/topics/ANSWERS/ANS00772.html.**

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