

MSG: Not Just Another Scare: Toxin Additives in Your Food and Drink

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There are a growing number of clinicians and basic scientists who are convinced that excitotoxins play a critical role in the development of several neurological disorders, including migraines, seizures, infections, abnormal neural development, certain endocrine disorders, specific types of obesity, and especially the neurodegenerative diseases; a group of diseases which includes: ALS, Parkinson's disease, Alzheimer's disease, Huntington's disease, and olivopontocerebellar degeneration.

An enormous amount of both clinical and experimental evidence has accumulated over the past decade supporting this basic premise. 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 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 that it tastes better. Aspartame is an artificial sweetener.

The public must be made aware that 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 (below toxic levels) of excitotoxins are given to animals, they experience full toxicity. 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 amino acids, that react with specialized receptors in the brain in such a way as to lead to destruction of certain types of brain cells. Glutamate is one of the more commonly known excitotoxins. MSG is the sodium salt of glutamate. This amino acid 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, is used by the brain only in very, very small concentrations - no more than 8 to 12ug. When the concentration of this transmitter rises above this level the neurons begin to fire abnormally. At higher concentrations, the cells undergo a specialized process of cell death.

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The brain has several elaborate mechanisms to prevent accumulation of MSG in the brain. First is the blood-brain barrier, a system that impedes glutamate entry into the area of the brain cells. But, this system was intended to protect the brain against occasional elevation of glutamate of a moderate degree, as would be found with un-processed food consumption. It was not designed to eliminate very high concentrations of glutamate and aspartate consumed daily, several times a day, as we see in modern society. Several experiments have demonstrated that under such conditions, glutamate can by-pass this barrier system and enter the brain in toxic concentrations. In fact, there is some evidence that it may actually be concentrated within the brain with prolonged exposures.

There are also several conditions under which the blood-brain barrier (BBB) is made incompetent. Before birth, the BBB is incompetent and will allow glutamate to enter the brain. It may be that for a considerable period after birth the barrier may also incompletely developed as well. Hypertension, diabetes, head trauma, brain tumors, strokes, certain drugs, Alzheimer's disease, vitamin and mineral deficiencies, severe hypoglycemia, heat stroke, electromagnetic radiation, ionizing radiation, multiple sclerosis, and certain infections can all cause the barrier to fail. In fact, as we age the barrier system becomes more porous, allowing excitotoxins in the blood to enter the brain. So there are numerous instances under which excitotoxin food additives can enter and damage the brain. Finally, recent experiments have shown that glutamate and aspartate (as in aspartame) can open the barrier itself. Another system used to protect the brain against environmental excitotoxins, is a system within the brain that binds the glutamate molecule (called the glutamate transporter) and transports it to a special storage cell (the astrocyte) within a fraction of a second after it is used as a neurotransmitter. This system can be overwhelmed by high intakes of MSG, aspartame and other food excitotoxins. It is also known that excitotoxins themselves can cause the generation of numerous amounts of free radicals and that during the process of lipid peroxidation (oxidation of membrane fats) a substance is produced called 4-hydroxynonenal. This chemical inhibits the glutamate transporter, thus allowing glutamate to accumulate in the brain.

Excitotoxins destroy neurons partly by stimulating the generation of large numbers of free radicals. Recently, it has been shown that this occurs not only within the brain, but also within other tissues and organs as well (liver and red blood cells). This could, from all available evidence, increase all sorts of degenerative diseases such as arthritis, coronary heart disease, and atherosclerosis, as well as induce cancer formation. Certainly, we would not want to do something that would significantly increase free radical production in the body. It is known that all of the neurodegenerative disease, such as Parkinson's disease, Alzheimer's disease, and ALS, are associated with free radical injury of the nervous system.

It should also be appreciated that the effects of excitotoxin food additives generally is 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 MSG and aspartame are probably not causes of the neurodegenerative diseases, such as Alzheimer's dementia, Parkinson's disease, or amyotrophic lateral sclerosis, they may well precipitate these disorders and certainly worsen their effects. 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

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food borne excitotoxin additives. Some may have had a very mild form of the disease had it not been for the exposure.

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. 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. 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. In other words it has not been looked at. A vital difference.

Unfortunately, for the consumer, the corporate food processors not only continue to add MSG to our foods but they have gone to great lengths to disguise these harmful additives. For example, they use such names as hydrolyzed vegetable protein, vegetable protein, hydrolyzed plant protein, caseinate, yeast extract, and natural flavoring. We know experimentally, as stated, when these excitotoxin taste enhancers are added together they become much more toxic. 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 food, that contain two, three or even four types of excitotoxins. We also know that excitotoxins in a liquid form 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 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.

In the case of ALS, amyotrophic lateral sclerosis, 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. 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 persons 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 high levels of glutamate.

It must be remembered that it is the glutamate molecule that is toxic in MSG (monosodium glutamate). 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, in the case of tomatoes, the plant contains several powerful antioxidants known to block glutamate toxicity.

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Hydrolyzed vegetable protein should not be confused with hydrolyzed vegetable oil. The oil does not contain appreciable concentration of glutamate, it is an oil. 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.**

A growing list of excitotoxins is 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. 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 (neural tube defects). It is thought that this is the protective mechanism of action 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.

Recent studies have shown that persons affected by Alzheimer's disease also have widespread destruction of their retinal ganglion cells. 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 makes one very suspicious. One could argue a common intrinsic etiology for central nervous system neuronal damage and retinal ganglion cell damage, but these findings are disconcerting enough to warrant further investigations.

The Free Radical Connection

It is interesting to note that many of the same neurological diseases associated with excitotoxic injury are also associated with accumulations of toxic free radicals and destructive lipid enzymes. For example, the brains of Alzheimer's disease patients have been found to contain high concentration of lipolytic enzymes, which seems to indicate accelerated membrane lipid peroxidation, again caused by free radical generation.

In the case of Parkinson's disease, we know that one of the early changes is the loss of glutathione from the neurons of the striate system, especially in a nucleus called the substantia nigra. It is this nucleus that is primarily affected in this disorder. Accompanying this, is an accumulation of free iron, which is one of the most powerful free radical generators known. One of the highest concentrations of iron in the body is within the globus pallidus and the substantia nigra. The neurons within the latter are especially vulnerable to oxidant stress

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because the oxidant metabolism of the transmitter-dopamine- can proceed to the creation of very powerful free radicals. That is, it can auto- oxidize to peroxide, which is normally detoxified by glutathione. As we have seen, glutathione loss in the substantia nigra is one of the earliest deficiencies seen in Parkinson's disease. In the presence of high concentrations of free iron, the peroxide is converted into the dangerous, and very powerful free radical, hydroxide. As the hydroxide radical diffuses throughout the cell, destruction of the lipid components of the cell takes place, a process called lipid peroxidation.

Using a laser microprobe mass analyzer, researchers have recently discovered that iron accumulation in Parkinson's disease is primarily localized in the neuromelanin granules (which gives the nucleus its black color). It has also been shown that there is dramatic accumulation of aluminum within these granules. Most likely, the aluminum displaces the bound iron, releasing highly reactive free iron. It is known that even low concentrations of aluminum salts can enhance iron-induced lipid peroxidation by almost an order of magnitude. Further, direct infusion of iron into the substantia nigra nucleus in rodents can induce a Parkinsonian syndrome, and a dose related decline in dopamine. Recent studies indicate that individuals having Parkinson's disease also have defective iron metabolism.

Another early finding in Parkinson's disease is the reduction in complex I enzymes within the mitochondria of this nucleus. It is well known that the complex I enzymes are particularly sensitive to free radical injury. These enzymes are critical to the production of cellular energy. When cellular energy is decreased, the toxic effect of excitatory amino acids increases dramatically, by as much as 200 fold. In fact, when energy production is very low, even normal concentrations of extracellular glutamate and aspartate can kill neurons.

One of the terribly debilitating effects of Parkinson's disease is a condition called "freezing up", a state where the muscles are literally frozen in place. There is recent evidence that this effect is due to the unopposed firing of a special nucleus in the brain (the subthalamic nucleus). Interestingly, this nucleus uses glutamate for its transmitter. Neuroscientists are exploring the use of glutamate blocking drugs to prevent this disorder.

And finally, there is growing evidence that similar free radical damage, most likely triggered by toxic concentrations of excitotoxins, causes ALS. Several studies have demonstrated lipid peroxidation product accumulation within the spinal cords of ALS victims. Iron accumulation has also been seen in the spinal cords of ALS victims.

Besides the well known reactive oxygen species, such as super oxide, hydroxyl ion, hydrogen peroxide, and singlet oxygen, there exist a whole spectrum of reactive nitrogen species derived from nitric oxide, the most important of which is peroxynitrate. These free radicals can attack proteins, membrane lipids and DNA, both nuclear and mitochondrial, which makes these radicals very dangerous.

It is now known that glutamate acts on its receptor via a nitric oxide mechanism. Overstimulation of the glutamate receptor can result in accumulation of reactive nitrogen species, resulting in the concentration of several species of dangerous free radicals. There is growing evidence that, at least in part, this is how excess glutamate damages nerve cells. In a multitude of studies, a close link has been demonstrated between excitotoxicity and free radical

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generation. Others have shown that certain free radical scavengers (anti-oxidants), have successfully blocked excitotoxic destruction of neurons. For example, vitamin E is known to completely block glutamate toxicity in vitro (in culture). Whether it will be as efficient in vivo (in a living animal) is not known. But, it is interesting in light of the recent observations that vitamin E slows the course of Alzheimer's disease, as had already been demonstrated in the case of Parkinson's disease. There is some clinical evidence, including my own observations, that vitamin E also slows the course of ALS as well, especially in the form of D- Alpha-tocopherol. I would caution that anti-oxidants work best in combination and when use separately can have opposite, harmful, effects. That is, when antioxidants, such as ascorbic acid and alpha tocopherol, become oxidized themselves, such as in the case of dehydroascorbic acid, they no longer protect, but rather act as free radicals themselves. The same is true of alpha-tocopherol.

We know that there are four main endogenous sources of oxidants:

1. Those produced naturally from aerobic metabolism of glucose.
2. Those produced during phagocytic cell attack on bacteria, viruses, and parasites, especially with chronic infections.
3. Those produced during the degradation of fatty acids and other molecules that produce H₂O₂ as a by-product. (This is important in stress, which has been shown to significantly increase brain levels of free radicals.)
- And 4. Oxidants produced during the course of p450 degradation of natural toxins.

And, as we have seen, one of the major endogenous sources of free radicals is from exposure to free iron. Unfortunately, iron is one mineral heavily promoted by the health industry, and is frequently added to many foods, especially breads and pastas. Copper is also a powerful free radical generator and has been shown to be elevated within the substantia nigra nucleus of Parkinsonian brains.

When free radicals are generated, the first site of damage is to the cell membranes, since they are composed of polyunsaturated fatty acid molecules known to be highly susceptible to such attack. The process of membrane lipid oxidation is known as lipid peroxidation and is usually initiated by the hydroxal radical. We know that one's diet can significantly alter this susceptibility. For example, diets high in omega 3-polyunsaturated fatty acids (fish oils and flax seed oils) can increase the risk of lipid peroxidation experimentally. Contrawise, diets high in olive oil, a monounsaturated oil, significantly lowers lipid peroxidation risk. From the available research. The beneficial effects of omega 3-fatty acid oils in the case of strokes and heart attacks probably arises from the anticoagulant effect of these oils and possibly the inhibition of release of arachidonic acid from the cell membrane. But, olive oil has the same antithrombosis effect and anticancer effect but also significantly lowers lipid peroxidation.

The Blood-Brain Barrier

One of the MSG industry's chief arguments for the safety of their product is that glutamate in the blood cannot enter the brain because of the blood-brain barrier (BBB), a system of specialized capillary structures designed to exclude toxic substance from entering the brain.

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There are several criticisms of their defense. For example, it is known that the brain, even in the adult, has several areas that normally do not have a barrier system, called the circumventricular organs. These include the hypothalamus, the subfornical organ, organium vasculosum, area postrema, pineal gland, and the subcommisural organ. Of these, the most important is the hypothalamus, since it is the controlling center for all neuroendocrine regulation, sleep wake cycles, emotional control, caloric intake regulation, immune system regulation and regulation of the autonomic nervous system. Interestingly, it has recently been found that glutamate is the most important neurotransmitter in the hypothalamus. Therefore, careful regulation of blood levels of glutamate is very important, since high blood concentrations of glutamate can easily increase hypothalamic levels as well. One of the earliest and most consistent findings with exposure to MSG is damage to an area known as the arcuate nucleus. This small hypothalamic nucleus controls a multitude of neuroendocrine functions, as well as being intimately connected to several other hypothalamic nuclei. It has also been demonstrated that high concentrations of blood glutamate and aspartate (from foods) can enter the so-called "protected brain" by seeping through the unprotected areas, such as the hypothalamus or circumventricular organs.

Another interesting observation is that chronic elevations of blood glutamate can even seep through the normal blood-brain barrier when these high concentrations are maintained over a long period of time. This, naturally, would be the situation seen when individuals consume, on a daily basis, foods high in the excitotoxins - MSG, aspartame and cysteine. Most experiments cited by the defenders of MSG safety were conducted to test the efficiency of the BBB acutely. In nature, except in the case of metabolic dysfunction (Such as with ALS), glutamate and aspartate levels are not normally elevated on a daily basis. Sustained elevations of these excitotoxins are peculiar to the modern diet. (And in the ancient diets of the Orientals, but not in as high a concentration.)

An additional critical factor ignored by the defenders of excitotoxin food safety is the fact that many people in a large population have disorders known to alter the permeability of the blood-brain barrier. The list of condition associated with barrier disruption include: hypertension, diabetes, ministrokes, major strokes, head trauma, multiple sclerosis, brain tumors, chemotherapy, radiation treatments to the nervous system, collagen-vascular diseases (lupus), AIDS, brain infections, certain drugs, Alzheimer's disease, and as a consequence of natural aging. There may be many other conditions also associated with barrier disruption that are as yet not known.

When the barrier is dysfunctional due to one of these conditions, brain levels of glutamate and aspartate reflect blood levels. That is, foods containing high concentrations of these excitotoxins will increase brain concentrations to toxic levels as well. Take for example, multiple sclerosis. We know that when a person with MS has an exacerbation of symptoms, the blood-brain barrier near the lesions breaks down, leaving the surrounding brain vulnerable to excitotoxin entry from the blood, i.e. the diet. But, not only is the adjacent brain vulnerable, but the openings act as a points of entry, eventually exposing the entire brain to potentially toxic levels of glutamate. Several clinicians have remarked on seeing MS patients who were made worse following exposure to dietary excitotoxins. I have seen this myself.

It is logical to assume that patients with the other neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and ALS will be made worse on diets high in excitotoxins. Barrier disruption has been demonstrated in the case of Alzheimer's disease.

Recently, it has been shown that not only can free radicals open the blood-brain barrier, but excitotoxins can as well. In fact, glutamate receptors have been demonstrated on the barrier itself. In a carefully designed experiment, researchers produced opening of the blood-brain barrier using injected iron as a free radical generator. When a powerful free radical scavenger (U-74006F) was used in this model, opening of the barrier was significantly blocked. But, the glutamate blocker MK-801 acted even more effectively to protect the barrier. The authors of this study concluded that glutamate appears to be an important regulator of brain capillary transport and stability, and that overstimulation of NMDA (glutamate) receptors on the blood-brain barrier appears to play an important role in breakdown of the barrier system. What this also means is that high levels of dietary glutamate or aspartate may very well disrupt the normal blood-brain barrier, thus allowing more glutamate to enter the brain, sort of a vicious cycle.

Relation to Cellular Energy Production

Excitotoxin damage is heavily dependent on the energy state of the cell. Cells with a normal energy generation systems that are efficiently producing adequate amounts of cellular energy, are very resistant to such toxicity. When cells are energy deficient, no matter the cause - hypoxia, starvation, metabolic poisons, hypoglycemia - they become infinitely more susceptible to excitotoxic injury or death. In fact, even normal concentrations of glutamate are toxic to energy deficient cells.

It is known that in many of the neurodegenerative disorders, neuron energy deficiency often precedes the clinical onset of the disease by years, if not decades. This has been demonstrated in the case of Huntington disease and Alzheimer's disease using the PET scanner, which measures brain metabolism. In the case of Parkinson's disease, several groups have demonstrated that one of the early deficits of the disorder is an impaired energy production by the complex I group of enzymes from the mitochondria of the substantia nigra. (Part of the Electron Transport System.) Interestingly, it is known that the complex I system is very sensitive to free radical damage.

Recently, it has been shown that when striatal neurons (Those involved in Parkinson's and Huntington's diseases.) are exposed to microinjected excitotoxins there is a dramatic, and rapid fall in energy production by these neurons. CoEnzyme Q10 has been shown, in this model, to restore energy production but not to prevent cellular death. But when combined with niacinamide, both cellular energy production and neuron protection is seen. I would recommend for those with neurodegenerative disorders, a combination of CoQ10, acetyl-L carnitine, niacinamide, riboflavin, methylcobalamin, and thiamine.

One of the newer revelation of modern molecular biology, is the discovery of mitochondrial diseases, of which cellular energy deficiency is a hallmark. In many of these disorders, significant clinical improvement has been seen following a similar regimen of vitamins combined with CoQ10 and L-carnitine. Acetyl L-carnitine enters the brain in higher

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concentrations and also increases brain acetylcholine, necessary for normal memory function. While these particular substances have been found to significantly boost brain energy function they are not alone in this important property. Phosphotidyl serine, Ginkgo Biloba, vitamin B12, folate, magnesium, Vitamin K and several others are also being shown to be important.

While mitochondrial dysfunction is important in explaining why some are more vulnerable to excitotoxin damage than others, it does not explain injury in those with normal cellular metabolism. There are several conditions under which energy metabolism is impaired. For example, approximately one third of Americans suffer from what is known as reactive hypoglycemia. That is, they respond to a meal composed of either simple sugars or carbohydrates that are quickly broken down into simple sugars (a high glycemic index.) by secreting excessive amounts of insulin. This causes a dramatic lowering of the blood sugar.

When the blood sugar falls, the body responds by releasing a burst of epinephrine from the adrenal glands, in an effort to raise the blood sugar. We feel this release as nervousness, palpitations of our heart, tremulousness, and profuse sweating. Occasionally, one can have a slower fall in the blood sugar that will not produce a reactive release of epinephrine, thereby producing few symptoms. This can be more dangerous, since we are unaware that our glucose reserve is falling until we develop obvious neurological symptoms, such as difficulty thinking and a sensation of lightheadedness.

The brain is one of the most glucose dependent organs known, since it has a limited ability to burn other substrates such as fats. There is some evidence that several of the neurodegenerative diseases are related to either excessive insulin release, as with Alzheimer's disease, or impaired glucose utilization, as we have seen in the case of Parkinson's disease and Huntington's disease.

It is my firm belief, based on clinical experience and physiological principles, that many of these diseases occur primarily in the face of either reactive hypoglycemia or "brain hypoglycemia". In at least two well conducted studies it was found that pure Alzheimer's dementia was rare in those with normal blood sugar profiles, and that in most cases Alzheimer's patients had low blood sugars, and high CSF (cerebrospinal fluid) insulin levels. In my own limited experience with Parkinson's and ALS patients I have found a disproportionately high number suffering from reactive hypoglycemia.

I found it interesting that several ALS patients have observed an association between their symptoms and gluten. That is, when they adhere to a gluten free diet they improve clinically. It may be that by avoiding gluten containing products, such as bread, crackers, cereal, pasta ,etc, they are also avoiding products that are high on the glycemic index, i.e. that produce reactive hypoglycemia. Also, all of these food items are high in free iron. Clinically, hypoglycemia will worsen the symptoms of most neurological disorders. We know that severe hypoglycemia can, in fact, mimic ALS both clinically and pathologically. It is also known that many of the symptoms of Alzheimer's disease resemble hypoglycemia, as if the brain is hypoglycemic in isolation.

In studies of animals exposed to repeated mild episodes of hypoxia (lack of brain oxygenation), it was found that such accumulated injuries can trigger biochemical changes that resemble those seen in Alzheimer's patients. One of the effects of hypoxia is a massive release of

glutamate into the space around the neuron. This results in rapid death of these sensitized cells. As we age, the blood supply to the brain is frequently impaired, either because of atherosclerosis or repeated syncopal episodes, leading to short periods of hypoxia. Hypoglycemia produces lesions very similar to hypoxia and via the same glutamate excitotoxic mechanism. In fact, recent studies of diabetics suffering from repeated episodes of hypoglycemia associated with over medication with insulin, demonstrate brain atrophy and dementia.

Again, it should be realized that excessive glutamate stimulation triggers a chain of events that in turn triggers the generation of large numbers of free radical species, both as nitrogen species and oxygen species. Once this occurs, especially with the accumulation of the hydroxyl ion, destruction of the lipid components of the membranes occurs, as lipid peroxidation. In addition, these free radicals damage proteins and DNA as well. The most immediate DNA damage is to the mitochondrial DNA, which controls protein expression within that particular cell and its progeny. It is suspected that at least some of the neurodegenerative diseases, Parkinson's disease in particular, are inherited in this way. But more importantly, it may be that accumulated damage to the mitochondrial DNA secondary to progressive free radical attack (somatic mitochondrial injury) is the cause of most of the neurodegenerative diseases that are not inherited. This would result from an impaired reserve of antioxidant vitamins/minerals and enzymes, increased cellular stress, chronic infection, free radical generating metals and toxins, and impaired DNA repair enzymes.

It is estimated that the number of oxidative free radical injuries to DNA number about 10,000 a day in humans. Normally, these injuries are repaired by special repair enzymes. It is known that as we age these repair enzymes decrease or become less efficient. Also, some individuals are born with deficient repair enzymes from birth as, for example, in the case of xeroderma pigmentosum. Recent studies of Alzheimer's patients also demonstrate a significant deficiency in DNA repair enzymes and high levels of lipid peroxidation products in the affected parts of the brain. It is also important to realize that the hippocampus of the brain, most severely damaged in Alzheimer's dementia, is one of the most vulnerable areas of the brain to low glucose supply as well as low oxygen supply. That also makes it very susceptible to glutamate toxicity.

Another interesting finding is that when cells are exposed to glutamate they develop certain inclusions (cellular debris) that not only resembles the characteristic neurofibrillary tangles of Alzheimer's dementia, but are immunologically identical as well. Similarly, when experimental animals are exposed to the chemical MPTP, they not only develop Parkinson's disorder, but the older animals develop the same inclusions (Lewy bodies) as see in human Parkinson's.

Eicosanoids and Excitotoxins

It is known that one of the destructive effects triggered by excitotoxins is the release of arachidonic acid from the cell membrane and the initiation of the eicosanoid reactions. Remember, glutamate primarily acts by opening the calcium pore, allowing calcium to pour into the cell's interior. Intracellular calcium in high concentrations initiates the enzymatic release of arachidonic acid from the cell membrane, where it is then attacked by two enzymes systems, the cyclooxygenase system and the lipooxygenase system. These in turn produce a series of

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compounds that can damage cell membranes, proteins and DNA, primarily by free radical production, but also directly by the "harmful eicosanoids."

Biochemically, we know that high glycemic carbohydrate diets, known to stimulate the excess release of insulin, can trigger the production of "harmful eicosanoids." We should also recognize that simple sugars are not the only substances that can trigger the release of insulin. One of the more powerful triggers includes certain amino acids, including leucine, alanine, and taurine. Glutamine, while not acting as an insulin trigger itself, markedly potentiates insulin release by leucine. This is why, except under certain situations, individual "free" amino acids should be avoided.

It is known that excitotoxins can also stimulate the release of these "harmful eicosanoids." So that in the situation of a hypoglycemic individual, they would be subjected to production of harmful eicosanoids directly by the high insulin levels, as well as by elevated glutamate levels. Importantly, both of these events significantly increase free radical production and hence, lipid peroxidation of cellular membranes. It should be remembered that diets high in arachidonic acid, such as egg yellows, organs meats, and liver, may be harmful to those subjected to excessive excitotoxin exposure.

And finally, in one carefully conducted experiment, it was shown that insulin significantly increases glutamate toxicity in cortical cell cultures and that this magnifying effect was not due to insulin's effect on glucose metabolism. That is, the effect was directly related to insulin interaction with cell membranes. Interestingly, insulin increased toxic sensitivity to other excitotoxins as well.

The Special Role of Flavanoids

Flavonoids are diphenylpropanoids found in all plant foods. They are known to be strong antioxidants and free radical scavengers. There are three major flavonols - quercetin, Kaempferol, and myricetin, and two major flavones - luteolin and apigenin. Seventy percent of the flavonoid intake in the average diet consist of quercetin, the main source of which is tea (49%), onions (29%), and apples (7%). Fortunately, flavonoids are heat stable, that is, they are not destroyed during cooking. Other important flavonoids include catechin, leucoanthocyanidins, anthocyanins, hesperedin and naringenin.

Most interest in the flavonoids stemmed from their ability to inhibit tumor initiation and growth. This was especially true of quercetin and naringenin, but also seen with hesperetin and the isoflavone, genistein. There appears to be a strong correlation between their anticarcinogenic potential and their ability to squelch free radicals. But, in the case of genistein and quercetin, it also has to do with their ability to inhibit tyrosine kinase and phosphoinositide phosphorylase, both necessary for mammary cancer and glioblastoma (a highly malignant brain tumor) growth and development.

As we have seen, there is a close correlation between insulin, excitotoxins, free radicals and eicosanoid production. Of particular interest, is the finding that most of the flavonoids, especially quercetin, are potent and selective inhibitors of delta-5-lipoxygenase enzyme which initiates the production of eicosanods. Flavones are also potent and selective inhibitors of the

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enzyme cyclooxygenase (COX) which is responsible for the production of thromboxane A₂, one of the "harmful eicosanoids". The COX-2 enzymes is associated only with excitatory type neurons in the brain and appears to play a major role in neurodegeneration.

One of the critical steps in the production of eicosanoids is the liberation of arachidonic acid from the cell membrane by phospholipase A₂. Flavonones such as naringenin (from grapefruits) and hesperetin (citrus fruits) produce a dose related inhibition of phospholipase A₂ (80% inhibition), thereby inhibiting the release of arachidonic acid. The non-steroidal anti-inflammatory drugs act similarly to block the production of inflammatory eicosanoids.

What makes all of this especially interesting is that recently, two major studies have found that not only can non-steroidal anti- inflammatories slow the course of Alzheimer's disease, but they may prevent it as well. But, these drugs can have significant side effects, such as GI bleeding, liver and kidney damage. In high doses, the flavonoids have shown a similar ability to reduce "harmful eicosanoid" production and should have the same beneficial effect on the neurodegenerative diseases without the side effects. Also, these compounds are powerful free radical scavengers and would be expected to reduce excitotoxicity as well.

But, there is another beneficial effect. There is experimental, as well as clinical evidence, that the flavonoids can reduce capillary leakage and strengthen the blood brain barrier. This has been shown to be true for rutin, hesperedin and some chalcones. Rutin and hesperedin have also been shown to strengthen capillary walls. In the form of hesperetin methyl chalcone, the hesperedin molecule is readily soluble in water, significantly increasing its absorbability. Black currents have the highest concentration of hesperetin of any fresh fruit, and in a puree form, is even more potent.

The importance of these compounds again emphasizes the need for high intakes of fruits and vegetables in the diet, and may explain the low incidence of many of these disorders in strict vegetarians, since this would supply a high concentration of flavonoids, carotenoids, vitamins, minerals, and other antioxidants to the body. Normally, the flavonoids from fruits and vegetables are only incompletely absorbed, so that relatively high concentrations would be needed to attain the same therapeutic levels seen in these experiments. Juice Plus allows us to absorb high, therapeutic concentrations of these flavonoids by a process called cryodehydration. This process removes the water and sugar from fruits and vegetable but retains their flavonoids in a fully functional state. Also the process allows one to consume large amounts of fruits and vegetables that would be impossible with the whole plant.

Iron and Health

For decades we, especially women, have been told that we need extra iron for health -that it builds healthy blood. But, recent evidence indicates that iron and copper may be doing more harm than good in most cases. It has been well demonstrated that iron and copper are two of the most powerful generators of free radicals. This is because they catalyze the conversion of hydrogen peroxide into the very powerful and destructive hydroxyl radical. It is this radical that does so much damage to membrane lipids and DNA bases within the cell. It also plays a major role in the oxidation of LDL-cholesterol, leading to heart attacks and strokes.

Males begin to accumulate iron shortly after puberty and by middle age have 1000mg of stored iron in their bodies. Women, by contrast, because of menstruation, have only 300 mg of stored iron. But, after menopause they begin to rapidly accumulate iron so that by middle age they have about 1500 mg of stored iron. It is also known that the brain begins to accumulate iron with aging. Elevated iron levels are seen with all of the neurodegenerative diseases, such as Alzheimer's dementia, Parkinson's disease, and ALS. It is thought that this iron triggers free radical production within the areas of the brain destroyed by these diseases. For example, the part of the brain destroyed by Parkinson's disease, the substantia nigra, has very high levels of free iron.

Normally, the body goes to great trouble to make sure all iron and copper in the body is combined to a special protein for transport and storage. But, with several of these diseases, we see a loss of these transport and storage proteins. This is where flavonoids come into play. We know that many of the flavonoids (especially quercetin, rutin, hesperidin, and naringenin) are strong chelators of iron and copper. In fact, drinking iced tea with a meal can reduce iron absorption by as much as 87%. But, flavonoids in the diet will not make you iron deficient.

Phosphotidyl serine and Excitotoxicity

Recent clinical studies indicate that phosphotidyl serine can significantly improve the mental functioning of a significant number of Alzheimer's patients, especially during the early stages of the disease. We know that the brain normally contains a large concentration of phosphotidyl serine. Interestingly, this compound has a chemical structure similar to L-glutamate, the main excitatory neurotransmitter in the brain. Binding studies show that phosphotidyl serine competes with L-glutamate for the NMDA type glutamate receptor. What this means is that phosphotidyl serine is a very effective protectant against glutamate toxicity. Unfortunately, it is also very expensive.

The Many Functions of Ascorbic Acid

The brain contains one of the highest concentrations of ascorbic acid in the body. Most are aware of its function in connective tissue synthesis and as a free radical scavenger. But, ascorbic acid has other functions that make it rather unique. Ascorbic acid in solution is a powerful reducing agent where it undergoes rapid oxidation to form dehydroascorbic acid. Oxidation of this compound is accelerated by high pH, temperature and some transitional metals, such as iron and copper. The oxidized form of ascorbic acid can promote lipid peroxidation and protein damage. This is why it is vital that you take antioxidants together, since several, such as vitamin E (as D-alpha-tocopherol) and alpha-lipoic acid, act to regenerate the reduced form of the vitamin.

In man, we know that certain areas of the brain have very high concentrations of ascorbic acid, such as the nucleus accumbens and hippocampus. The lowest levels are seen in the substantia nigra. These levels seem to fluctuate with the electrical activity of the brain. Amphetamine acts to increase ascorbic acid concentration in the corpus striatum (basal ganglion area) and decrease it in the hippocampus, the memory imprint area of the brain. Ascorbic acid is known to play a vital role in dopamine production as well.

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One of the more interesting links has been between the secretion of the glutamate neurotransmitter by the brain and the release of ascorbic acid into the extracellular space. This release of ascorbate can also be induced by systemic administration of glutamate or aspartate, as would be seen in diets high in these excitotoxins. The other neurotransmitters do not have a similar effect on ascorbic acid release. This effect appears to be an exchange mechanism. That is, the ascorbic acid and glutamate exchange places. Theoretically, high concentration of ascorbic acid in the diet could inhibit glutamate release, lessening the risk of excitotoxic damage. Of equal importance is the free radical neutralizing effect of ascorbic acid.

There is now substantial evidence that ascorbic acid modulates the electrophysiological as well as behavioral functioning of the brain. It also attenuates the behavioral response of rats exposed to amphetamine, which is known to act through an excitatory mechanism. In part, this is due to the observed binding of ascorbic acid to the glutamate receptor. This could mean that ascorbic acid holds great potential in treating disease related to excitotoxic damage. Thus far, there are no studies relating ascorbate metabolism in neurodegenerative diseases. There is at least one report of ascorbic acid deficiency in guinea pigs producing histopathological changes similar to ALS.

It is known that as we age there is a decline in brain levels of ascorbic acid. When accompanied by a similar decrease in glutathione peroxidase, we see an accumulation of H₂O₂ and hence, elevated levels of free radicals and lipid peroxidation. In one study it was found that with age not only does the extracellular concentration of ascorbic acid decrease but the capacity of the brain ascorbic acid system to respond to oxidative stress is impaired as well.

In terms of its antioxidant activity, vitamin C and E interact in such a way as to restore each other's active antioxidant state. Vitamin C scavenges oxygen radicals in the aqueous phase and vitamin E in the lipid, chain breaking, phase. The addition of vitamin C suppresses the oxidative consumption of vitamin E almost totally, probably because in the living organism the vitamin C in the aqueous phase is adjacent to the lipid membrane layer containing the vitamin E.

When combined, the vitamin C was consumed faster during oxidative stress than the vitamin E. Once the vitamin C was totally consumed, the vitamin E began to be depleted at an accelerated rate. N-acetyl-L- cysteine and glutathione can reduce vitamin E consumption as well, but less effectively than vitamin C. The real danger is when vitamin C is combined with iron. Recent experiments have shown that such combinations can produce widespread destruction within the striate areas of the brain. This is because the free iron oxidizes the ascorbate to produce the powerful free radical hydroxyascorbate. Alpha-lipoic acid acts powerfully to keep the ascorbate and tocopherol in the reduced state (antioxidant state). As we age, we produce less of the transferrin transport protein that normally binds free iron. As a result, older individuals have higher levels of free iron within their tissues, including brain.

Conclusion

In this discussion, I tried to highlight some of the more pertinent of the recent findings related to excitotoxicity in general and neurodegenerative diseases specifically. In no way is this an all inclusive discussion of this topic. There are many areas I had to omit because of space, such as alpha-lipoic acid, an antioxidant that holds great promise in combatting many of these diseases.

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Also, I did not go into detail concerning the metabolic stimulants, the relationship between exercise and degenerative nervous system diseases, the protective effect of methycobalamin, and the various disorders related to excitotoxins.

I also purposely omitted discussions of magnesium to keep this paper short. It is my experience, that magnesium is one of the most important neuroprotectants known. I would encourage those who suffer from one of the excitotoxin related disorders to avoid, as much as possible, food borne excitotoxin additives and to utilize the substances discussed above. The fields of excitotoxin research, in combination with research on free radicals and eicosanoids, are growing very rapidly and new information arises daily. Great promise exist in the field of flavonoid research as regards many of these neurodegenerative diseases as well as in our efforts to prevent neurodegeneration itself.

A recent study has demonstrated that aspartame feeding to animals results in an accumulation of formaldehyde within the cells, with evidence of significant damage to cellular proteins and DNA. In fact, the formaldehyde accumulated with prolonged use of aspartame. With this damning evidence, one would have to be suicidal to continue the use of aspartame sweetened foods, drinks and medicines. The use of foods containing excitotoxin additives is especially harmful to the unborn and small children. By age 4 the brain is only 80% formed. By age 8, 90% and by age 16 it is fully formed, but still undergoing changes and rewiring (plasticity). We know that the excitotoxins have a devastating effect on formation of the brain (wiring of the brain) and that such exposure can cause the brain to be "miswired." This may explain the significant, almost explosive increase in ADD and ADHD. Glutamate feeding to pregnant animals produces a syndrome almost identical to ADD. It has also been shown that a single feeding of MSG after birth can increase free radicals in the offspring's brain that last until adolescence. Experimentally, we know that infants are 4X more sensitive to the toxicity of excitotoxins than are adults. And, of all the species studied, cats, dogs, primates, chickens, guinea pigs, and rats, humans are by far the most sensitive to glutamate toxicity. In fact, they are 5x more sensitive than rats and 20x more sensitive than non-human primates.

I have been impressed with the dramatic improvement in children with ADD and ADHD following abstention from excitotoxin use. It requires care monitoring of these children. Each time they are exposed to these substances, they literally go bonkers. It is ludicrous, with all we know about the destructive effects of excitotoxins, to allow our children and ourselves to continue on this destructive path.

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