Excitotoxins, Neurodegeneration and Neurodevelopment
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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 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 taste better. Aspartame is an artificial sweetener.

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. 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, 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 a specialized process of delayed cell death known as 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, 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 opthalmology 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 Opthalmology 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 statue. 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, including the hippocampus, circumventricular organs, locus cereulus, 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 indogenous. 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 born 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 summery 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.

Unfortunately, for the consumer, the corporate food processors not only continue 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.[10] 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.[11]

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.[12] 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 (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 as stated, based on present knowledge, is in the case of ALS. Also, the tomato plant contains several powerful antioxidants known to block glutamate toxicity.[13]

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.[14]

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.[15] 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).[16] 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.[17]

One interesting study found that persons affected by Alzheimer's disease also have widespread destruction of their retinal ganglion cells.[18] 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.

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 oxidation products.[19] For example, the brains of Alzheimer's disease patients have been found to contain high concentration of lipid peroxidation products and evidence of free radical accumulation and damage.[20, 21, 22]

In the case of Parkinson's disease, we know that one of the early changes is the loss of one of the primary antioxidant defense systems, glutathione, from the neurons of the striate system, and especially in the substantia nigra.[23] 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.[24] 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 because the catabolic 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. Of equal importance is the generation of the powerful peroxynitrite radical, which has been shown to produce serious injury to cellular proteins and DNA, both mitochondrial and nuclear.[25]

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).[26] It has also been shown that there is dramatic accumulation of aluminum within these granules.[27] 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.[28]

Another early finding in Parkinson's disease is the reduction in complex I enzymes within the mitochondria of this nucleus.[29] 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. As we shall see, when cellular energy is decreased, the toxic effect of excitatory amino acids increases dramatically.

In the case of ALS there is growing evidence that similar free radical damage, most likely triggered by toxic concentrations of excitotoxins, plays a major role in the disorder.[30] Several studies have demonstrated lipid peroxidation product accumulation within the spinal cords of ALS victims as well as iron accumulation.[31]

It is now known that glutamate acts on its receptor via a nitric oxide mechanism.[32] Overstimulation of the glutamate receptor can produce an accumulation of reactive nitrogen species, resulting in the generation of several species of dangerous free radicals, including peroxynitrite. There is growing evidence that, at least in part, this is how excess glutamate damages nerve cells.[33] In a multitude of studies, a close link has been demonstrated between excitotoxicity and free radical generation.[34-37]

Others have shown that certain free radical scavengers (antioxidants), have successfully blocked excitotoxic destruction of neurons. For example, vitamin E is known to completely block glutamate toxicity in vitro.[38] Whether it will be as efficient in vivo is not known. But, it is interesting in light of the recent observations that vitamin E combined with other antioxidant vitamins slows the course of Alzheimer's disease and has been suggested to reduce the rate of advance in a subgroup Parkinson's disease patients as well. In the DATATOP study of the effect of alpha-tocopherol alone, no reduction in disease progression was seen. The problem with this study was the low dose that was used and the fact that the DL-alpha-tocopherol used is known to have a much lower antioxidant potency than D-alpha-tocopherol. Stanley Fahn found that a combination of D-alpha-tocopherol and ascorbic acid in high doses reduced progression of the disease by 2.5 years.[39] Tocotrienol may have even greater benefits, especially when used in combination with other antioxidants. 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 antioxidants 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.[40]

Again, it should be realized that excessive glutamate stimulation triggers a chain of events that in turn sparks the generation of large numbers of free radical species, both as nitrogen and oxygen species. These free radicals have been shown to damage cellular proteins (protein carbonyl products) and DNA . The most immediate DNA damage is to the mitochondrial DNA, which controls protein expression within that particular cell and its progeny, producing rather profound changes in cellular energy production. It is suspected that at least some of the neurodegenerative diseases, Parkinson's disease in particular, are affected in this way.[41] Chronic free radical accumulation would result in an impaired functional reserve of antioxidant vitamins/minerals and enzymes, and thiol compounds necessary for neural protection. Chronic unrelieved stress, chronic infection, free radical generating metals and toxins, and impaired DNA repair enzymes all add to this damage.

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 h3O2 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 the exposure of tissues to free iron, especially in the presence of ascorbate. 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 of Parkinsonian brains.[42]

What has been shown in all these studies is a direct connection between excitotoxicity and free radical generation in a multitude of diseases and disorders such as seizures, strokes, brain trauma,viral infections, and neurodegenerative diseases. Interestingly, free radicals have also been shown to prevent glutamate uptake by astrocytes as well, which would significantly increase extracellular glutamate levels.[43] This creates a vicious cycle that will multiply any resulting damage and malfunctioning of neurophysiological systems, such as plasticity.

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. 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. As stated, 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 would be expected to increase hypothalamic levels as well. One of the earliest and most consistent findings with exposure to MSG is damage to an area of the hypothalamus 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 other 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.[44] This would be the situation seen when individuals consume, on a daily basis, foods high in the excitotoxins - MSG, aspartame and L-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 continuous 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.[45] But, not only is the adjacent brain vulnerable, but the openings act as points of entry, eventually exposing the entire brain to potentially toxic levels of glutamate. Several clinicians have remarked that their MS patients 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.[46]

Recently, it has been shown that not only can free radicals open the blood-brain barrier, but excitotoxins can as well.[47] In fact, glutamate receptors have been demonstrated on the barrier itself.[49] 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, creating 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 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. 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.[50] 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 within the mitochondria of the substantia nigra.[51-52] 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 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.[53] I 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.[54] Acetyl L-carnitine enters the brain in higher 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 mitochrondial 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. We know, for example, approximately one third of Americans suffer from reactive hypoglycemia. That is, they respond to a meal composed of either simple sugars or carbohydrates (that are quickly broken down into simple sugars, i.e. 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 metabolize 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.[55]

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", a condition where the blood sugar is normal and the brain is hypoglycemic in isolation. 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.[55-57] 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.[58] 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.[59] 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.[60]

Another cause of isolated cerebral hypoglycemia is impaired transport of glucose into the brain across the blood-brain barrier. It is known that glucose enters the brain by way of a glucose transporter, and that in several conditions this transporter is impaired. This includes aging, arteriosclerosis, and Alzheimer's disease.[61-62] This is especially important in the diabetic since prolonged elevation of the blood sugar produces a down-regulation of the glucose transporter and a concomitant " brain hypoglycemia" that is exacerbated by repeated spells of peripheral hypoglycemia common to type I diabetics.

With aging, one sees several of these energy deficiency syndromes, such as mitochondrial injury, impaired cerebral blood flow, enzyme dysfunction, and impaired glucose transportation, develop simutaneously. This

greatly magnifies excitotoxicity, leading to accelerated free radical injury and a progressively rapid loss of cerebral function and profound changes in cellular energy production.[63] It is suspected that at least in some of the neurodegenerative diseases, Alzheimer's dementia and Parkinson's disease in particular, this series of events plays a major pathogenic role.[64] Chronic free radical accumulation would also result in an impaired functional reserve of antioxidant vitamins/minerals, antioxidant enzymes (SOD, catalase, and glutathione peroxidase), and thiol compounds necessary for neural protection. Chronic unrelieved stress, chronic infection, free radical generating metals and toxins, and impaired DNA repair enzymes all add to this damage.

It is estimated that the number of oxidative free radical injuries to DNA number about 10,000 a day in humans.[65] Under conditions of cellular stress this may reach several hundred thousand.Normally, these injuries are repaired by special DNA repair enzymes. It is known that as we age these repair enzymes decrease or become less efficient.[66] 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.[67-68] 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/ free radical 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.[69] 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.[70] There is growing evidence that protracted glutamate toxicity leads to a condition of receptor loss characteristic of neurodegeneration.[71] This receptor loss produces a state of disinhibition that magnifies excitotoxicity during the later stage of the neurodegenerative process.

Special Functions of Ascorbic Acid

The brain contains one of the highest concentrations of ascorbic acid in the body. Most are aware of ascorbic acid's function in connective tissue synthesis and as a free radical scavenger. But, ascorbic acid has other functions that make it rather unique.

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.[72] 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.

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.[73] 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.[74] It also attenuates the behavioral response of rats exposed to amphetamine, which is known to act through an excitatory mechanism.[75] 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 guineas pigs producing histopathological changes similar to ALS.[76]

It is known that as we age there is a decline in brain levels of ascorbate. When accompanied by a similar decrease in glutathione peroxidase, we see an accumulation of h302 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.[77]

In terms of its antioxidant activity, vitamin C and E interact in such a way as to restore each others 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 is consumed faster during oxidative stress than vitamin E. Once the vitamin C is totally consumed, vitamin E begins 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. This is because the free iron oxidizes the ascorbate to produce the free radical dehydroxyascorbate. 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, and are therefore at greater risk of widespread free radical injury.

Neurodevelopment:

Recent studies have shown that glutamate plays a vital role in the development of the nervous system, especially as regards neuronal survival, growth and differentiation, development of circuits and cytoarchitecture.[78] For example, it is known that deficiencies of glutamate in the brain during neurogenesis can result in maldevelopment of the visual cortices and may play a role in the development of schizophrenia.[79] Likewise, excess glutamate can cause neural pathways to produce improper connections, a process I call " miswiring of the brain". Excess glutamate during embryogenesis has been shown to reduce dendritic length and suppress axonal outgrowth in hippocampal neurons. It is interesting to note that glutamate can produce classic toxicity in the immature brain even before the glutamate receptors develop. High glutamate levels can also affect astroglial proliferation as well as neuronal differentiation. It appears to act via the phosphoinositide protein kinase C pathway.

It has been shown that during brain development there is an overgrowth of neuronal connections and cellularity, and that at this stage there is a peak in brain glutamate levels whose function it is to remove excess connections and neuronal overexpression. This has been referred to as " pruning". Importantly, glutamate excess during synaptogenesis and pathway development has been shown to cause abnormal connections in the hypothalamus that can lead to later endocrinopathies.[80]

In general, toxicological injury in the developing fetus carries the greatest risk during the first two trimesters. But, this is not so for the brain, which undergoes a spurt of growth that begins during the third trimester and continues at least two years after birth. Dendritic growth is maximal in the late fetal period to one year of age, but may continue at a slower pace for several more years. Neurotransmitter development also begins during the late fetal period but continues for as long as four years after birth. This means that alterations in dietary glutamate and aspartate are especially dangerous to the fetus during pregnancy and for several years after birth. The developing brain's succeptability to excitotoxicity varies , since each brain region has a distinct developmental profile. The type of excitotoxin also appears to matter. For example, kianate is non-toxic to the immature brain but extremely toxic to the mature brain. The glutamate agonist, NMDA, is especially toxic up to postnatal day seven while quisqualate and AMPA have peak toxicity from postnatal day seven through fourteen. L-cysteine is a powerful excitotoxin on the immature brain.

Myelination can also be affected by neurotoxins. In general, excitotoxic substances affect dendrites and neurons more than axons but axon demyelination has been demonstrated. During the myelination process, each fiber tract has its own spatiotemporal pattern of development, accompanied by significant biochemical changes, especially in lipid metabolism. More recent studies have shown an even more complicated pattern of CNS myelination than previously thought. This is of importance especially as regards the widespread use of aspartame, because of this triple toxin's effects on neuronal proteins and DNA. Of special concern is aspartame's methanol component and its breakdown product, formaldehyde.[81] Also, it is known that the aspartate moiety undergoes spontanous racemization in hot liquids to form D-aspartate, which has been associated with tau proteins in Alzheimer's disease.[82-83]

As you can see, the development of the brain is a very complex process that occurs in a spatial and temporal sequence that is carefully controlled by biochemical, structural, as well as neurophysiological events. Even subtle changes in these parameters can produce ultimate changes in brain function that may vary from subtle alteration in behavior and learning to autism, attention deficit disorder and violence dyscontrol.[84, 85, 86]

Experiments in which infant animals were exposed to MSG, have demonstrated significant neurobehavioral deficits.[87-88] Other studies have shown that when pregnant female animals were fed MSG their offspring demonstrated normal simple learning but showed significant deficits in complex learning, accompanied by profound reductions in several forebrain neurotransmitters.[89-90] In human this would mean that during infancy and early adolescence learning would appear normal, but with entry into a more advance education level, learning would be significantly impaired. In several ways, this animal model resembles ADD and ADHD in humans. Kubo and co-workers found that neonatal glutamate could severely injure hippocampal CA1 neurons and dendrites and, as a result, impair discriminative learning in rats.[91]

It is also important to note that neonatal exposure to MSG has been shown to cause significant alterations in neuroendocrine function that can be prolonged.[92-93] By acting on the hypothalamus and its connections to the remainder of the limbic connections, excitotoxins can profoundly affect behavior.

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 indogenous excitotoxin excess and neurological dysfunction and disease. Many of the arguments by the food processing industry has 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 stonger.[94] 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, micovascular 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 known 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.

I included the material about the special function of ascorbic acid because few are aware of the importance of adequate ascorbate levels for CNS function and neural protection against excitotoxicity. As we have seen, it 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.[95] 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.

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