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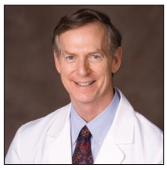
Review Article

The biochemical basis of neurodegenerative disease: The role of immunoexcitoxicity and ways to possibly attenuate it

Russell L. Blaylock

Department of Neurosurgery, Theoretical Neuroscience Research, LLC, Ridgeland, Mississippi, United States.

E-mail: *Russell L. Blaylock - blay6307@gmail.com



***Corresponding author:**
Russell L. Blaylock, M.D.
609 Old Natchez Trace Canton, MS.
Retired Neurosurgeon,
Department of Neurosurgery,
Theoretical Neuroscience Research, LLC, Ridgeland, Mississippi, United States.

blay6307@gmail.com

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ABSTRACT

There is growing evidence that inflammation secondary to immune activation is intimately connected to excitotoxicity. We now know that most peripheral tissues contain fully operational glutamate receptors. While most of the available research deals with excitotoxicity in central nervous system (CNS) tissues, this is no longer true. Even plant has been found to contain glutamate receptors. Most of the immune cells, including mask cells, contain glutamate receptors. The receptors are altered by inflammation, both chemokine and cytokines. A host of new diseases have been found that are caused by immunity to certain glutamate receptors, as we see with Rasmussen's encephalitis. In this paper, I try to explain this connection and possible ways to reduce or even stop the reaction.

Keywords: Autoimmunity, Flavonoids, Immunoexcitotoxicity, Neurodegeneration

INTRODUCTION

There is a definite rise in neurodegeneration in modern times, especially in the West. This entails the gradual or even rapid deterioration of the CNS and includes a rise in such neurodegenerative disease as Alzheimer's, Parkinson, prion, tautopathy disorders of the CNS, multiple sclerosis, and amyotrophic sclerosis (ALS), all of which started to increase over the last several decades.[50,68,96] There has been a spike in these disorders, especially among those injected with the COVID-19 so-called vaccine.[4] It is true that among certain individuals there is a genetic component, but for the majority of people it is age that is the most common association. There is evidence that people with "long COVID" will undergo progressive neurodegeneration and have an increase in Alzheimer's and progressive neurodegeneration. This is seen with the COVID-19 injection as well.

We have doomed many of our youth to develop one of these neurodegenerative diseases by the present state requirement for vaccines seen in most states. The number of injections has grown exponentially with the growth of the required vaccination injection handed down by government health authorities (Centers for Disease Control and Prevention).

There are other major contributing factors and these include: Poor health over a lifetime, many infections that are hard to clear (poor immunity) and resulting frailty, lack of exercise, numerous

vaccinations throughout life (particularly the COVID-19 injections), pollution, and geoengineering. Geoengineering is a government program (United Nations and some countries) to seed the atmosphere with nano-aluminum, which is inhaled into the lungs or nose and powerfully activates microglia within the CNS. The stated purpose is to prevent "global climate change."

Recently, there has been a concerted effort to understand the factors that lead to neurodegeneration and what can prevent neurodegeneration from happening. This includes the natural products.[8] Early in my studies, I felt like neurodegeneration was the result of several vitamin deficiencies. This has now been confirmed and many studies now point the way to its prevention.[8] They extended the studies and now have a better picture of what is causing neurodegeneration, or at least worsening it.

In this review, I want to briefly discuss the neurodegenerative diseases and concentrate on their prevention and possible treatment. Age has always been the number one risk factor associated with most degenerative diseases and there is a reason for this which I will discuss. There are certain cell types in the nervous system whose function we have only recently began to understand and they are intimately linked to the degenerative process. I will discuss this.

I have recently emphasized "immunoexcitotoxicity," which is the basis of neurodegeneration, which is an undeniable link between the immune system and excitotoxicity. I did not discover this link but rather gave it a name — immunoexcitotoxicity.[7,9]

THE NEURODEGENERATIVE DISEASES

For several reasons, neuron (brain cells) are dying as we get older and for some generally unknown reason, even among the youth. We now better understand this process but as with all science the pace is slow, the real thinkers are ignored or dismissed and as a result, real cures and useful process are very slow to be presented.[7] To many peoples' surprise, it is not the big medical centers or even the big names in researchers that lead the way. Science should teach us that it is the "outlier" who has many of the best ideas. That is, the person or persons who take a fresh look at a problem and refuse to just follow the crowd or the money often find the solution. We have seen this with numerous medical and scientific issues.[12] For instance the probiotics, the prebiotics, chronic fatigue syndrome, cancer causation and treatment, autism spectrum disorders (ASD) and many other scientific and medical issues. In each case, it was the people outside the system that brought the real innovation or supplied the important information.

The CNS is one of the most complex systems ever created in the universe. It has been studied by numerous experts in the field from every conceivable angle and still we are just beginning to understand its operation. Its development holds many secrets, many of which we will never understand. (A strong argument against the Technocrat who believes technology can solve all problems facing humans).

We understand that the CNS is created so that it can protect itself and that in nature, as well as the artificial environment; it uses this elaborate system to protect itself and carry on its minute to minute operation. It has its own immune system (which also uses the systemic immune system), it has a detoxification system, an anti-oxidant system, an energy system, and an anti-inflammatory system among other protective capabilities. All of these systems are very complex and we still understand only an incredible small amount that it can do to protect itself. It holds many secrets that are to be revealed slowly and only what God wants us to know.

Most neurodegenerative disease either begin with the onset of aging or there are several episodes of events that set the stage for later more rapid neurodegeneration later in life (multiple hit hypothesis).[16,22] In essence, in many cases it is what happens earlier in life that sets the stage for disease later in life. In essence, the first hit reduces the number of neurons in particular nuclei and the second hit or third kill the majority of neurons in that area. We see this with childhood vaccinations and many environmental toxins.[12] The most harmful effect occurs either during development (remember the brain has its greatest formation during the last trimester of pregnancy and the first 2 years of life and is complete at age 26 or 27) or it begins with aging.

This occurs with Parkinson's disease for instance. In this disease we can see that most of the cells in the substantia nigra (SN) (the main site of damage) can be lost early during development — say the mother is exposed to toxic pesticides or herbicides. No symptoms develop at this stage. As the child becomes an adult more of the cells are lost or become non-functional for various reasons. Once 80–90% of the cells die or are asleep, symptoms begin. Or at least that is what we thought. Many of these cells are just injured and not actually dead. They eventually will die if something is not done. The same is true for Alzheimer's disease.

For many neurodegenerative diseases, such as multiple sclerosis and ALS, we see that a great deal of destructive type events are occurring, such as excitotoxicity, inflammation, free radical production, poor defenses, and a lack of energy, etc. The rate of deterioration can very during the course of the disease. Sometimes it starts slow and speeds up rapidly as the critical cells become weaker. Sometimes, it is very slow and sometimes begins rapidly — with many factors at play. We are just beginning to understand these factors.

Basically neurons are grouped together with the neurons being linked and surrounded by astrocytes and microglia.

The purpose of the astrocyte basically is two-fold — to supply energy to the neuron and keep the glutamate (excitotoxin) level outside the neuron low. This is critical as a high glutamate can trigger excitotoxcity or death of the nearby neurons. Keeping the glutamate levels low in the extracellular space is the job of the microglia and astrocytes.

Both the astroglia (astrocyte) and the microglia utilize a group of transporters that move the excess glutamate into the two glia.[90] Some neurological disease, such as ALS, is thought to be due, at least in part, to a defective glutamate transport system.[86] This defect allows the glutamate to progressively rise outside the neuron where it does the harm. Normally, the glutamate is in a ratio of 1 to 10,000 outside to inside. Inside the cell, glutamate is safe—outside it is deadly. There is another situation where we see excitotoxcity with the glutamate outside the neuron being normal and that is with low energy generated by the cell.[53,67] The cell's energy is mostly produced by its mitochondria (some 95% of energy). In this case even physiological glutamate (normal) can cause excitotoxicity and destroy neurons. This is especially so with Alzheimer's disease where we see impaired mitochondria — low energy. It is also frequently seen with ASD where mitochondrial defects combined with multiple vaccinations is common. The vaccinations trigger immunoexcitotoxicity in these children — this has been well demonstrated.[10] It is known that inflammation is a powerful suppressor of mitochondrial energy production and increases free radical generation.

The average childhood and adult diet are filled with glutamate or glutamate derivatives in multiple forms. The worst is enzyme treated proteins, autolyzed yeast and soy protein products. One of the most common was monosodium glutamate (MSG). Food processers now use glutamate-containing products because MSG was outlawed by Congress for baby foods. Now they use alternated sources to evade the law and trick even knowledgeable people. (Hydrolyzed protein, soy protein, protein isolates, autolyzed yeast, and many others) Samuels led the charge against this practice.[88]

IMMUNOEXCITOTOXICITY: WHAT IS IT?

I coined the term "immunoexcitotoxicity" in an article on autism many years ago.[9] It had been described before that but not named.[29,64] We now know that immunity and excitotoxicity are intimately linked. They never seem to occur apart. Further, it seems that immunoexcitotoxicity is not limited to the CNS but can occur in many tissues and organs outside the CNS, for example the lungs and the gastrointestinal tract.[11]

Dr. John Olney coined the term excitotoxicity.[70]

We were good friends. I visited his lab many years ago and he provided me with one of the pictures in my book on excitotoxicity. Much has been learned about excitotoxicity since then.

Immunoexcitotoxicity simply means a connection between immune activation in the body and enhancement of excitotoxicity. This occurs principally by a number a systems at play. It has been demonstrated, for example, that the glutamate transporters are inhibited by reactive oxygen species (ROS) as well as activation of cell systems that make up the various glutamate (excitotoxic) receptors, basically called subunits.[98]

In the first instance ROS are known to paralyze the main glutamate transporter, GLT1 and GLAST.[98] As a result glutamate and other excitotoxins build up outside the neuron where the danger lies.

In most cases, the most destructive excitotoxic reaction occurs by opening a cell membrane calcium pore.[57,89] Calcium is the most common cell-signaling chemical and is responsible for a great deal of destructive reactions if not controlled.[82] As we age, cells have greater difficulty controlling calcium entry. Normally, the cell uses the mitochondria as a calcium sink. With excitotoxicity and inflammation we have an injury to mitochondria, thus impairing this protective system. Calcium is not only responsible for this cell injury but also promotes the progression of cancer.

In the immunoexcitotoxic reaction, ROS are massively generated and as a consequence the transporters are inactivated. The main cells for controlling extraneuronal glutamate are astrocytes and microglia. As the neurodegenerative process progresses, astrocytes undergo apoptosis, and necrosis, both of which release not only stored glutamate but also DNA products. These products activate receptors on the surface of the microglia that are excitotoxic.[94] Ionic mercury does this very efficiently, a major problem with previous childhood vaccines (ethylmercury, used in previously in vaccines is metabolized to ionic mercury in the CNS progressively destroying the astrocytes).[12]

Inflammatory cytokines generate a number of free radicals. A second reaction that has been recently recognized is the ability of some inflammatory cytokines (Interleukin-1 beta [IL-1ß] and tumor necrosis factor-alpha [TNF-alpha] to enhance particular excitotoxic subunits, for example the NR1 subunit of the NMDA receptor.[109] Lupus inflammation enhances anti-NR2 subunit activation, making the receptor more destructive.[40] A more common reaction associated with inflammation is the conversion of non-calcium permeable AMPA receptors to calcium permeable AMPA receptors.[39] This occurs in the endoplasmic reticulum, which stores these special receptors. Under inflammatory conditions, they are transferred to the neuron membrane and inserted into the synaptic plate.

Like NMDA receptors, they are calcium permeable and are responsible for enhanced excitotoxicity. The AMPA receptor

normally makes up the fast transmission system. With inflammation, anywhere, they become more destructive. Unlike NMDA receptors they are not controlled by magnesium.

The metabotropic receptors control the sensitivity of the main glutamate receptors, (NMDAR, AMPAR, and Kainate receptor). By enhancing the sensitivity of metabotropic receptor 1 (an activator), the inflammatory cytokines can enhance the sensitivity of the main receptors, especially NMDA receptors.[17] The metabotropic receptors operate through the G-protein system.

There are other systems at play in excitotoxicity, such as the X_c system, which exchanges external cystine for internal glutamate.[14] The glutamate is expelled and is quickly and safely placed in the astrocyte or microglia. Inside the cell the cystine is utilized biochemically to make glutathione, a powerful cell protectant. If the glutamate transporters are paralyzed by ROS and/or inflammatory cytokines the externally exchanged glutamate remains and builds up in the extraneuronal space where it is destructive.

Recent research indicates that there are hemichannels that move glutamate out of the cell: in massive amounts and that inflammatory cytokines can activate these hemichannels worsening excitotoxicity.[97] Normally, in the CNS the cytokines are in very low concentrations. TNF-alpha and IL-6 at these concentrations are neuroprotective but at high concentration, as seen with infarction and trauma, make excitotoxicity worse. Repeated bouts of inflammation prime all immune cells, especially the macrophages and the microglia. On top of this we have inflammatory cytokines switching the calcium impermeable AMPA receptors into calcium-permeable, highly destructive AMPA receptors. As we have seen in the case of the autoimmune disease, multiple sclerosis, we have this switch occurring to the AMPA receptor in the oligodendroglia, responsible for myelin production.[95]

The glutamate transporters, some 5 in number, move the extracellular glutamate to the inside of the cell where it is safe.[55,87,91,94,105] Unfortunately, the transporters become inactivated in the face of inflammation — hence the term "immunoexcitotoxicity."

The second thing we learned is much about microglia in the CNS. These special immune cells are scattered all through the brain and spinal cord and are not evenly distributed, with the highest concentrations in the temporal lobes and a special nucleus — the SN. In fact, it is in the SN where Parkinson's disease has its greatest effect. It also has the highest concentration of microglia in the brain.[48,60]

Microglia are rapidly activated from any disturbance in the body, even minor surgery anywhere.[41,110]

Like all immune cells, they kill virus, bacteria and fungi. Sometimes, if chronically activated, they can kill neurons. When there is microglial activation, the astrocytes in the region are usually also activated. They too have glutamate transporters and contain larger stores of glutamate, which is released with inflammation.

Now we have two at least major cells, the astrocytes and microglia that release their glutamate with activation. This raises the glutamate level outside the neuron and the inflammation prevents the transporters from moving the excess glutamate inside the microglia and the astrocyte. This in turn causes the glutamate level outside the cells to rise rapidly — hence, immunoexitotoxicity. There are also other mechanisms that raise glutamate levels outside the neuron, such as the X_c antiporter and hemichannels.[49,74,97]

Recent studies have found that inflammation is the main starting event in all neurodegenerative diseases and even mood disorders (schizophrenia, anxiety, and depression).[3,19,84] Vaccines are the most common inflammatory event in the lives of many young people and a growing number of older people. Especially, people get a flu vaccine every year. Having a strong immune system means getting over infections fast or avoiding them.

As neurons begin to die in neurodegenerative diseases, they release their DNA (purines and pyrimidines) and microglia have receptors that activate them to these DNA chemicals. This aggravates the immunoexcitotoxicity which makes the degenerative progress faster.

There is another problem with inflammation as well as trauma to the head. This is called microglial priming. In this state the microglia becomes much more destructive.

MICROGLIAL PRIMING

When the microglia are activated they can assume a hyperactive state called "priming."[75]

Many immune cells will do that, especially macrophages. But here, in the nervous system, the primed microglia, when stimulated by anything, secrete higher levels of inflammatory cytokines (TNF-alpha, IL-1alpha and beta and IL-6.) as well as glutamate. Normally, in the brain the cytokines are in extremely low levels and at these low levels they actually protect and repair the neurons.[62,104]

When activated (by trauma or disease) primed microglia become extremely excitotoxic and inflammatory.[75] This happens with a stroke or head injury. In essence, primed microglia are much more destructive than normal. Ironically, as we age our microglia automatically become primed-that is why neurological degenerative disease are more common in this age group.[23,30] We discovered that in many conditions, priming of microglia and occurrence of priming had been present for very long periods. For example, it was shown that one man demonstrated microglia priming that lasted 17 years after a head trauma.[23]

Apparently this occurs after a stroke as well.[31] A number of stroke patients, some confined to a wheelchair, got up and walked 10 years after a stroke. According to Tobrnick *et al*., it is the persistent TNF-alpha that drives the prolonged inhibition of the partially damaged neurons.[100,101] In each case he injected Etanercept (A TNF-alpha – blocker) into the Batson's venous plexus around the spinal cord. Alzheimer's and Parkinson's patients have the same problem. (see video by Dr. Tobinick on YouTube).

Keep in mind that the primed microglia not only increase inflammation but also excitotoxicity.[96,97] This observation seems to be forgotten in many papers written by immunologists. This double whammy kills the surrounding neurons or brain cells.

Much like amoeba, microglia have the ability to move around the brain and the spinal cord-driven by release of special attraction chemicals (chemokines from injured brain cells). Also be aware that glutamate activates microglia, especially when in high concentrations.[66]

What about nitric oxide? Well, it is a fad now and it is hard to dispel a fad. But, part of the excitotoxic reaction is the involvement of nitric oxide — a free radical component and energy inhibitor for cells — all cells.[37,90] Raising the nitic oxide level not only increases blood flow, it is part of the immunoexcitotoxic reaction. In essence, you can worsen the excitotoxic process by raising the level of nitric oxide.

Another intimate part of the immunoexcitotoxic reaction is the production of very destructive free radicals-especially the one called peroxynitrite. Nitric oxide forms an essential part of this radical. Nitric oxide also powerfully inhibits mitochondrial energy production so much for raising nitric oxide.[15]

When immunoexcitotoxicity occurs two connected events occur — inflammation and excitotoxicity. Both cause the generation of massive amounts of free radicals. Inhibiting free radicals inhibits both inflammation and excitotoxicity. There are many types of free radicals and many types of radical scavengers. These protective chemicals have different strengths and work in different parts of the cell. The flavonoids, such Nano-Curcumin, Hesperidin, and Nano-Quercetin both inhibit inflammation and immunoexcitotoxicity. They powerfully inhibit many free radicals including the very destructive peroxynitrite.[8,63]

OTHER CRITICAL VITAMINS

Riboflavin is essential for energy production in the mitochondria as is pyrodoxal 5-phosphate and thiamine.[81] The active form of the vitamin is riboflavin 5-phosphate, commonly called R-5-P. Riboflavin produces the flavin molecules used in energy production by the electron transport chain (ETC). It also has anti-oxidant power, anti-inflammatory effects and prevents excitotoxicity. It seems to play a major role in preventing Parkinson's disease.[56]

As an antioxidant riboflavin increases many of the antioxidant enzymes including glutathione and superoxide dismutase (SOD) which protect many cell components. This is especially important with the hereditary form of ALS, in which there is a low SOD activity. And it may increase activity of other antioxidant enzymes.[56] Studies in animals indicate that riboflavin is especially efficient in calming lipid peroxidation.[20,102] The brain is made of a very high levels of lipids as are most cell membranes and cell components. These are very vulnerable to oxidation in disease.

Normally reduced glutathione is not significantly affected by riboflavin activity, but with stress (as with alcohol) the glutathione level falls very rapidly.[56]

Riboflavin prevents lipid oxidation. Riboflavin is especially protective of the liver and kidneys. Riboflavin and R-5-P have been very effective in preventing migraine attacks.[56] In addition riboflavin is essential for turning oxidized glutathione into reduce glutathione, the effective antioxidant form.

Riboflavin has been shown to be very effective in mitochondrial deficiency disease in which complex I was impaired.[56] Riboflavin also increases complex II-iv. These are critical chemicals in the ETC used to generate energy. Incredibly, these affected people did not progress as long as they took riboflavin and in addition their ETC complex content increased.[61]

Riboflavin inhibited inflammation by inhibiting the cell's main inflammatory activator, NF_kB. Riboflavin suppresses TNF-alpha, cyclooxygenase, and increases IL-10 and anti-inflammatory cytokines.[61]

In addition, Vitamin D3 requires riboflavin. Riboflavin is utilized for generation of vitamin D3 and as a result can prevent a fall in this vitamin.[76]

It has also been shown that vitamin D3 is protective of the same cells primarily affected by Parkinson's.[56] Vitamin D3 has been shown to also inhibit microglial activation and increase the anti-inflammatory cytokine IL-10.[56]

Riboflavin has been shown to be essential for the formation of another critical vitamin, pyridoxal 5-phosphate, the active form of vitamin B6.[56] Vitamin B6 enhancement has been associated with a lower risk of Parkinson's in several studies.[64] Carbidopa, which bonds vitamin B6, increase the progression and death rate of Parkinson's patients. This Vitamin (B6) is essential for the formation of dopamine.[2,38]

Both vitamins are critical for formation of kynurenines, an inhibitor of glutamate toxicity by the most common receptors. People with chronic migraines and Parkinson's disease have very high levels of a stimulator of these glutamate receptors and a very low level of kyrurenines, the protector against excitotoxicity.[56]

Glutamate excitotoxicity damages mitochondrial function and the low energy increases the sensitivity of the excitotoxic receptors. Riboflavin inhibits neuronal glutamate release and glutamate excess and plays a major role in both Parkinson's and migraine as well as many other diseases, neurologic, and otherwise.[56]

What we see is that a deficient intake of Riboflavin not only affected the metabolism of other vitamins that are protectors of the CNS (Vitamin B6 and D3), but also reduces the risk of excitotoxicity which is a principle cause of Parkinson's disease as well as other diseases.

High dose pyridoxal is known to be toxic to nerves at a dose of 50 mg.[6,34] It has been shown to cause a peripheral neuropathy, while pyridoxal 5-phosphate at a similar level, even as high as 100 mg, is not toxic to nerves.

Deficiency of riboflavin in common in developing countries and has been shown to require a transporter to enter cells.[77] In the UK riboflavin deficiency is common. It is estimated that 54% of non-elderly have a deficiency in riboflavin absorption because of this problem.[77] About 10% to 15% of the world's population has a deficiency in this transporter and require a higher dose of riboflavin than normal.[65]

Riboflavin is also one of the B-vitamins needed to lower blood levels of homocysteine and its derivatives. Elevated blood homocysteine has been associated with increased heart attacks and other vascular diseases. Homocysteine, and especially its metabolic derivatives, are rather powerful excitotoxins and produce abundant free radicals.[28]

Riboflavin supplementation has been suspected to improve the motor and cognitive signs of multiple sclerosis.[67] This vitamin plays as essential role in myelin formation, the main site of attack of this disease as well as an antioxidant, anti-inflammatory and anti-excitotoxic.

There is growing evidence that virtually all autoimmune diseases are excitotoxic, even peripheral ones.[3,5,17,21,25-27,32,33,35,36,40,45,47,52,58,59,71,78-80,95-97,99,103,109]

I chose to feature multiple sclerosis as it has the greatest amount of study and convincing evidence indicated that the greatest damage is by excitotoxicity and accounts for the progressive neurodegeneration with a burnout of the immune reaction. The references above also include SLE and human immune cells, which contain glutamate and glutamate receptors as cited.

THIAMINE AND NEURODEGENERATIVE DISEASE

There is growing scientific and clinical evidence that that the vitamin thiamine and its derivativities drastically reduced neurodegeneration of all kinds.[13,44,69] This is especially true for Alzheimer's disease and Parkinson's disease. I would encourage all dealing with the symptoms of Parkinson's disease to watch the interview with Daphne Bryan, author of the book on using thiamine to overcome Parkinson's symptoms (Parkinson's and B1 Therapy). (https://mail.google.com/mail/u/0/#search/Emile/FMfcgzGrcjQDLcvshlzcRcMDGPmblHJM?compose=new&projector=1) She has also written a book on the subject.

There is a derivative of thiamine called benfotiamine that raises the blood thiamine higher and longer than supplementing with thiamine itself.[5,73] Studies have shown that it improves the cognitive ability of some impaired adult humans.[72]

As for Parkinson's disease, the dose of the thiamine varies greatly and a person would have do a little experimenting. Use the book to determine the dose and other related issues. There have been several studies showing the benefits of thiamine in Parkinson's disease.[18,42,54]

Thiamine, like other B-vitamins, requires a specific carrier for absorption from the intestines (duodenum). A number of older people have a problem absorbing thiamine and with aging it gets worse. Patients treated with L-dopa have a significantly higher spinal fluid level of thiamine than untreated patients. The cerebrospinal fluid (spinal fluid) is an excellent way to determine brain levels of many chemicals.[42]

There is a great deal of evidence for the involvement of thiamine deficiency in Parkinsonism. For example, researchers have found that thiamine injection within the affected area of the brain causes dopamine release from neurons — considerably higher.[107] Remember, it is this neurotransmitter that is deficient in Parkinson's patients. Likewise, thiamine deficiency can cause the brain's dopamine levels in that area (striatum) to fall.[92] Excess alcohol consumption is a major cause of thiamine deficiency. Patients with thiamine dementia were found to have a low thiamine level in the frontal cortex, the area responsible for this effect.[46]

Thiamine problems are also related to another very common and growing type of neurodegeneration — Alzheimer's disease. In a particularly comprehensive study, Ramamoorthy *et al*. examined the brains of humans, as well as animal models subject to thiamine deficiency.[83] As we see with the Alzheimer's brain there was a direct link with neuroinflammation, which is directly related to immunoexcitotoxicity.[108] In addition, they conclusively demonstrated that the main problem with the Alzheimer's brain is a difficulty with thiamine transport, which is directly linked to pro-inflammatory cytokines. Using high doses of thiamine bypassed the transporter and forced thiamine into the neurons by diffusion.

Thiamine, which controls a number of energy reactions, mainly enters cells, including neurons, by using specific cell

transporters whose job it is to move thiamine into the cell. It was found that both transporters were not only dependent for thiamine entry but were inhibited by inflammatory cytokines (TNF-alpha, IL-1β and IL-6). This explains, in part, the link between inflammation of the brain (and body) and neurodegeneration.

It should be appreciated that the inflammation also enhances the sensitivity of the destructive glutamate receptors considerably and inhibits glutamate uptake into astrocytes and microglia. Nitric oxide makes all this much worse.

A lack of thiamine also makes glucose, the main sugar for the brain, more toxic. Thiamine makes it less toxic. We know that a major part of this problem is a defect in the ability of the Alzheimer brain to generate energy. Thiamine plays a major role in generation of energy by making energy enzymes more sensitive.

Examination of Alzheimer's brains demonstrated that thiamine levels were consistently low in the affected areas. Thiamine also plays a major role in both beta amyloid deposition as well as hyperphosphorylated tau protein, both deposited in the Alzheimer brain.[108]

High dose thiamine and benfotamine are known to increase energy levels of people and to remove brain fog.[72] Inflammatory cytokines, as with the flu, are known to make one sleepy and tired.

They also found that the most powerful inhibitor of thiamine transport into brain cells was the pro-inflammatory cytokine IL-1β. In *addition,* they also found that a low thiamine levels altered over 700 genes, many of which are associated with degeneration. Many studies have confirmed much of this.[51]

Prevention of Alzheimer's may involve several approaches. Most important is high dose thiamine in compounds that maximize levels of thiamine for a prolonged period, such as benfotamine and dibezoylthiamine. Benfotamine is available now and is reasonable in price and both are extremely safe. I will continue to follow this research and write about it.

Nano-Gingko Biloba is well absorbed and has the anticoagulant effect of a single adult aspirin. It also has a compound that lowers one of the main inflammatory cytokine — TNF-alpha. It should not be taken with other anticoagulants. Nano-Curcumin and Nano-Quercetin, as well as many other flavonoids, also inhibit microglia and excitotoxicity (immunoextotoxicity). Together, they should be protective against neurodegenerative diseases.[8,93,106]

Both are iron chelators. As a result they should be taken 20 min before a meal and have your blood iron level tested once a month should you take it long term. Nano-Quercetin also will lower blood sugar and could cause problems for those with reactive hypoglycemia and who mix it with their blood sugar lowering medications.

Zinc has been shown to activate microglia and should not be taken unless you have been tested and found to be deficient.[43] Never take more than 50 mg a week. Luteolin is the most effective for brain stimulation for repair and was shown to remove some cases of brain fog as was apigenin.[1,24,85]

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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