Hyperinflammation - a positive feedback loop leading to Alzheimer's?

Stressors increase NF-kB, reducing Nrf2, leading to hyperinflammation. NF-kB triggers mast cells, histamine excess increases NMDAR activity, which activates Retinoic Acid, which activates mast cells.

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Jun 13

This article combines the last two posts, looking closer at the link between histamine excess which can be common in Alzheimer's and is being seen in LongCovid. However, histamine excess is often unrecognized and lab tests can be inconclusive or false negatives.

Histamine excess is part of inflammatory reactions caused by many factors of modern life (NF-kB is part of the inflammatory pathways) and when the inflammation keeps escalating it may increase risk for misfolded protein accumulation leading to cell death. This occurs in the hippocampus in Alzheimer's patients as NMDA receptor over activity is also involved and both NMDA and H1 histamine receptors are more concentrated within the hippocampus. (H1-R, 2, viewable 3) (NMDAR - 17, viewable at 18)

Anti-inflammatory Nrf2 pathways would be protective against cell death in the case of excess misfolded proteins. (Subsection_Nrf2 function) Anything promoting NF-kB such as degranulation of mast cells would also be inhibiting Nrf2 as the two proteins share a circadian cycle protein. The histamine excess and increase in NMDA receptor activity can both affect mood in a manic, anxious, or irritable way depending on the person's mood.

Is delirium and histamine excess similar? A paper proposes that the idea needs more study and more effective non-pharmaceutical solutions.

> "***Histamine is arguably the most pleotropic neurotransmitter in the human brain, and this review provides a rationale, and proposes that this neuroactive amine plays a role in modulating the characteristic features of delirium.***" (53)

> "*In general, the most commonly described neurochemical changes associated with delirium include deficiencies in acetylcholine and/or melatonin, together with excess in glutamate and monoamines dopamine and noradrenalin, and bi-directional activity alterations (e.g., decreased or increased activity, depending on delirium presentation and trigger) in serotonin, γ-aminobutyric acid (GABA) and/or, importantly, histamine (Maldonado, 2013).*" (53)

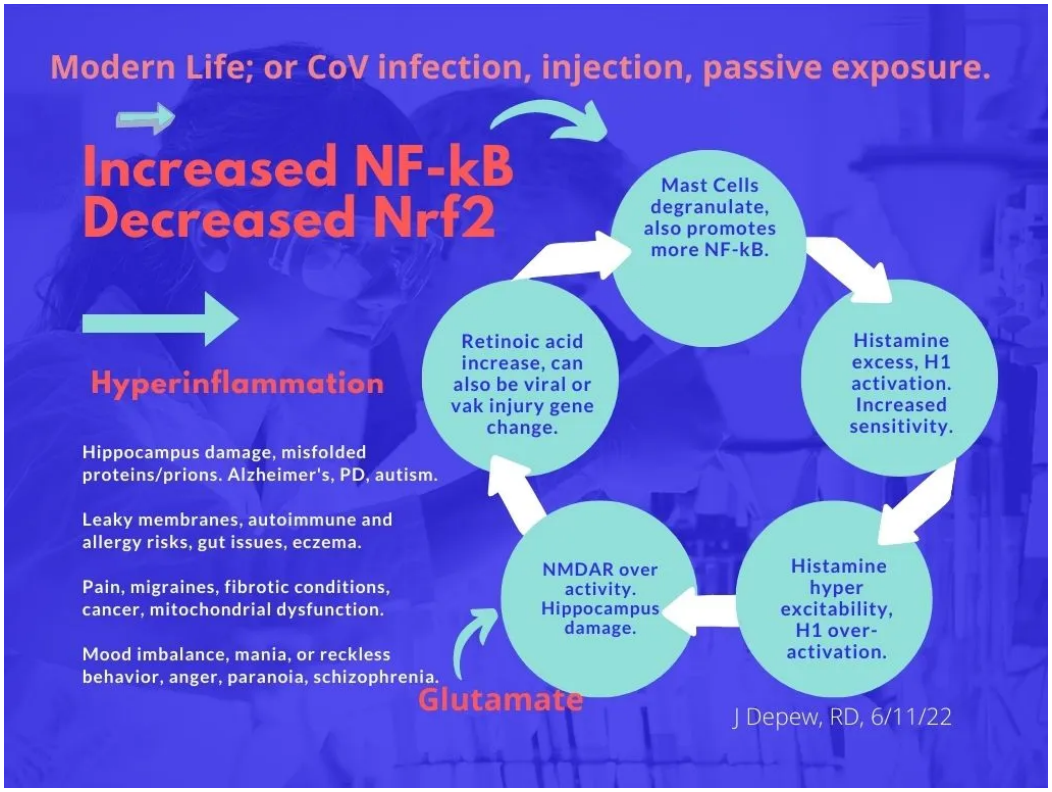
> "*The unknown nature of etiology for most types of delirium and the complete lack of placebo-controlled Randomized Controlled drug Trials, the lack of any FDA-approved drug treatment for delirium and the wide ranging nature of drugs with multiple chemical neurotransmitter pathways affected (variable across NHS Trust hospitals) used to treat it is clearly a major problem. Furthermore the lack of effective non-pharmacological approaches is also problematical (Wade et al., 2015, 2019; Richards-Belle et al., 2018) Without understanding more about the underlying nature of the pathways involved how can we hope to effectively and rationally treat it?*" (53)

Delirium is probably not fun and can be dangerous to self or others. If the brain is in over-allergic mode - histamine hyperexcitability - that would be worth knowing. Because then it would be possible to do something to reduce the inflammatory signaling by avoiding allergens that lead to mast cell degranulation which releases histamine and promotes NF-kB; avoiding lifestyle inflammatory factors that promote NF-kB; and using histamine and NMDA receptor antagonists or modulating herbs or medications. Antagonists for the H3 histamine receptor may also be helpful. (53)

This article contains a potential mechanism of action for how histamine excess and NMDA receptor overactivity may combine in damaging the hippocampus in Alzheimer's dementia and other neurocognitive conditions. It also includes lifestyle and diet strategies that might help stop the escalating hyperinflammation of overactive mast cells, too much NF-kB and not enough Nrf2.

- First post, related background info: Nrf2 & NF-kB: 2 proteins to know.
- Second post - looks like spaghetti - Endoplasmic Reticulum… it got too long. I can't update it. The current version of it is in document form and has the full Reference List: Misfolded proteins, H1 and NMDA Receptors.
- See Table 1 for details about solutions for reducing the inflammation spiral, and Protocol Collation and Therapy Goals for more info & references.

Graphical Abstract: **Hyperinflammation - a positive feedback loop.**



Hyperinflammation, a positive feedback loop. Stress leads to NF-kB which inhibits Nrf2, which we need for cell and mitochondria maintenance.

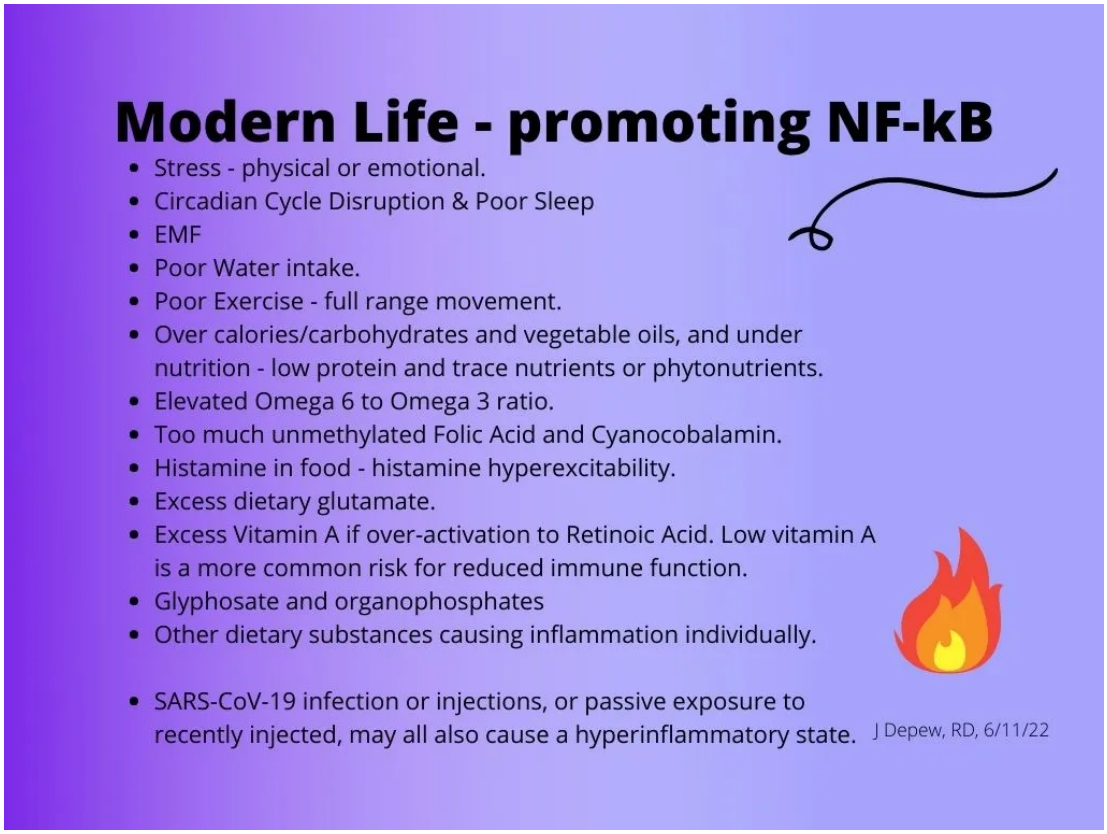
Hyperinflammation, a positive feedback loop.

1. NF-kB causes Mast cells to release histamine and other inflammatory chemicals.
    1. Solutions include promoting Nrf2, as activation of it will inhibit NF-kB.
    2. Reduce stressors that promote NF-kB - infection or chimeric spike; modern life - see Table 1.
    3. Reduce histamine in the diet and avoid any allergic triggers. Increase methyl folate and avoid formaldehyde too (also requires folate for breakdown.)
2. Histamine excess can cause leaky membranes and increased sensitivity to allergens or autoimmune risks from food proteins that are similar to ours.
    - Solutions include avoiding histamine containing or triggering foods; increase methyl folate and avoid unmethylated folic acid or cyanocobalamin in supplements or fortified foods.

3. Histamine over activity at the H1 receptor could add to NMDAR over activity by not allowing down regulation of the NMDA receptors by an unknown agonist of H1 histamine receptors.
    - Until someone discovers the mystery agonist which might help as a supplement/treatment, other phytonutrients that down regulate NMDAR or modulate the entry of calcium may be protective against hippocampus damage caused by NMDAR over activity.
4. NMDAR activity can activate vitamin A or carotenoids to Retinoic Acid.
    - Excess dietary glutamate is a frequent cause of excessive NMDAR activity. The solution is to avoid glutamate rich foods or seasonings.
5. Retinoic Acid causes Mast Cells to degranulate, releasing more histamine.
    - Epstein-Barr Virus is a known cause of a gene change in a liver enzyme that activated vitamin A or carotenoids to Retinoic Acid. Vaccine injury is theorized to also possibly be a cause of a similar change. For life then, too much mast cell activation and histamine excess might be an underlying health factor. The solution is to avoid foods or supplements rich in vitamin A and carotenoids, or retinoic acid medications.
    - See document: Retinoid Toxicity.

More detail about the positive feedback loop is included after the discussion of Table 1 farther along.

Table 1: **Modern life - promoting NF-kB**.



Is hyperinflammation a causal factor in Alzheimer's dementia? Is the misfolded protein accumulation a result of increased inflammatory white blood cell activity rather than the cause? Allergy or autoimmune damage within the brain?

The amount of amyloid in the brain is not always consistent with more severe symptoms. So, what is causing more severe Alzheimer's symptoms or damage? Histamine hyperexcitability itself can resemble schizophrenia or Alzheimer's so may it be causal of schizophrenia or Alzheimer's?

Hyperinflammation may be a positive feedback loop and hyperexcitability of histamine excess is a brain modulator out of control - positive feedback loop. Whatever thoughts or mood is present can escalate whether fear, anger, or grandiose mania. Histamine excess may also prevent down regulation of NMDARs by H1 histamine receptors that use a different agonist than histamine. Leading to more NMDAR activity. Dietary glutamate is also a common cause of excess NMDAR stimulation. Increased brain activity focused within the NMDAR rich hippocampus leads to over-excitement of brain cells and can lead to their death in the region. The NMDAR activity can stimulate more retinoic acid, which triggers mast cells, which degranulate and release inflammatory cytokines and histamine, which leads to more histamine hyperexcitability.

Too much hyperexcitability and the brain damage may lead to symptoms of Alzheimer's or may present as schizophrenia-like before the more severe forgetfulness of dementia occurs.

Background Alzheimer's dementia.

Alzheimer's has been thought to be due to buildup of amyloid-beta misfolded protein tangles, or problems with tau protein which helps stabilize microtubules - straight normally or arcing, not tangled. Over 200 experimental drugs targeting the amyloid protein tangles have not helped patient symptoms once reaching the clinical drug trial stage. Leaving the question - If the amyloid tangles are correlated with Alzheimer's but are not causal - then what is causal? What is causing amyloid-beta to buildup and hippocampus damage to occur in the brains of patients with Alzheimer's dementia?

Background schizophrenia.

Schizophrenia is more of a set of symptoms that can have several nutrient deficiencies or imbalance as a causal factor rather than 'one' condition with 'one' cause.

Toxoplasma gondii infection may be related to some cases. Low iodine/bromide excess, hypothyroidism may be involved; low vitamin D and/or vitamin D receptor gene alleles; low methyl folate and methyl B12, methylation gene alleles may be a factor; high dose niacin has been found to be a very helpful treatment; and a zinc deficiency and/or excess of copper in proportion to zinc may all be causal factors for worsening of schizophrenia-like symptoms. Lack of zinc during prenatal development may increase the child's later risk of schizophrenia. Lack of the CBD equivalent with excess of the THC equivalent endocannabinoid due to a gene difference, may also be an imbalance which CBD drops may help.

See post: The voices that people with schizophrenia are hearing may be their own. *High powered microphones were used to record patients with schizophrenia and it was found that they were hearing their own subvocal speech but not making the connection that it was their own thoughts.

Personal story with schizophrenia like symptoms caused by histamine excess, low zinc, vitamin D, and methyl B vitamins may have been additional factors:

Having had histamine hyperexcitability and having people tell me that I must have schizophrenia based on my behavior during the histamine meltdowns, I can share that

what it feels like is too much, way too much going on. So many thoughts are flying through at such a fast rate that remembering them doesn't occur, let alone, possibly identifying their source (as yourself). It can be a whirling, chaotic, scary, tornado of whatever shame or worry or fear that you might be thinking.

Histamine excess can lead to self-injury or violence against others as the out-of-control thinking is really irrational and quite difficult to control. I am glad to have survived it and discovered how just changing my diet helped me avoid the mood meltdowns. If you have a choice to not to have an out-of-control tornado in your mind, wouldn't you take it?

I have a number of metabolic gene differences (post: BHMT and post: gene alleles) that increase risk of methyl B deficiency, endocannabinoid, and likely zinc and B6. I had to modify a number of daily habits, add zinc and B6 supplements, and avoid medical marijuana strains that are very concentrated in THC but have no calming CBD or other non-euphoric cannabinoids. Low vitamin D and hypothyroidism may also have been factors. Adding high dose niacin has also helped. See post: Niacin & Early Treatment.

The diet changes are significant to avoid histamine, and would not be easy if a patient was being provided standard US food or really almost any standard meal plans. Change needs to occur with clinical research to show that the low histamine diet does help chronically ill patients on average, and then the menu itself would be changed for the average special-needs facility.

Current medications are not very helpful and patients with schizophrenia were likely to have better quality of life with the nutritional care strategies that were used a hundred years ago.

Putting a label on something and then saying the cause or cure are not known - but now you have a label - may seem reassuring, but really it is a nocebo. You have a PROBLEM, and it is not understood and cannot be helped. Or can it?

If we don't try to find a solution, then a problem cannot be helped.

Hyperinflammation anywhere leads to fibrotic scarring and cell death eventually if left unchecked - heart, liver, joints, nerves, all are at risk.

Hyperinflammation anywhere in the body can lead to fibrotic scarring and regions with dead cells if the inflammatory signaling remains excessive over time. Increased numbers of white blood cells were called to the area by inflammatory cytokines and proteins like NF-kB. Anything that promotes NF-kB like stress or infection is also inhibiting Nrf2 because they share a circadian cycle protein - both can't actively use it at the same time for chemical reactions. NF-kB would help fight an infection but lead to damage if chronically over active. Nrf2 is our DNA repair, immune function, and promoter of glutathione production and other antioxidants that we make for ourselves, and or our mitochondria.

What to do?

Change the modern lifestyle factors and remove individually inflammatory foods or other stressors from life.

All of the factors in Table 1 are listed below with more detail. They all can increase NF-kB or may lead to an increase - which also inhibits Nrf2. This puts us in a constantly inflamed state without the normal circadian cycle of nightly maintenance by the Nrf2 pathways.

- **Stress** - physical exertion from overwork, or strenuous exercise; an immune challenge from an infection or vaccination; or emotional stress - family or work issues, no autonomy, financial stress or housing, fear, worry, loneliness, lack of purpose, repetitive news messaging.
    - Stressors lead to oxidative stress and an increased need for B vitamins, vitamin C, D, and magnesium and other trace minerals.
    - Niacin/nicotinic acid plus mitochondrial cofactors, other Bs and minerals, can help promote NAD+ and protect against inflammation in a variety of ways.

> *"Since then, numerous studies have reinforced the view that NAD+ levels are key to neuronal function and survival. This includes the dependence on NMNAT2 and its NAD synthesis activity for axonal survival (Yan et al., 2010). Supplementing may help protect against Parkinson's Disease and Alzheimer's dementia and other neurologic conditions. NAD-boosting regimens prevent and in some cases can reverse neuronal*

> *degeneration associated with hearing loss, prion toxicity, retinal damage, traumatic brain injury (TBI), and peripheral neuropathy (Brown et al., 2014; Dutca et al., 2014; Hamity et al., 2017; Lin et al., 2016; Vaur et al., 2017; Yin et al., 2014; Zhou et al., 2015)* " (56)

    - Low nutrient levels can result quickly during acute or chronic stress. Supplementing with nutrient rich foods or supplements can help reduce damage caused by the oxidative stress and protect our mitochondria. Mitochondrial dysfunction is frequently an early sign of problems in chronic degenerative diseases. Promoting Nrf2 would help the body make more of our own antioxidants, repair DNA damage, and increase immune function.
    - Low nutrient levels can then also increase mental illness symptoms - depression, anxiety, paranoia and compulsive thinking, or irritability or rage. Mass Formation Psychosis or group think might be more likely when also magnesium deficient.

- **Circadian Cycle Disruption** - Any light at night disrupts melatonin production and likely other epigenetic changes that should be taking place in switching from daytime NF-kB pathways (and others) to night time Nrf2 pathways (and others).
    - Black out darkness during sleep or an eye cover.
    - Avoid bright lights and screen time in the three hours prior to sleep or wear blue light blocking glasses during those hours - may help insomnia.
    - Get full spectrum light or sunshine daily, in the morning ideally.
- **Poor Sleep** - causes reduced glymphatic flow in the brain which is needed to clean out toxins.
    - Follow the Circadian Cycle sleep tips and consider magnesium adequacy. Epsom salt soak (1-2 / week), 1/2 teaspoon of glycine or magnesium glycinate to provide 400 mg magnesium prior to bedtime may help.
    - Adequate zinc is needed for good sleep but may be taken at any time during the day, and high doses may be better tolerated with a meal.

    - St. John's Wort prior to bed may help if waking up around 4:00 am is a frequent symptom. Waking in the early morning regularly may suggest low serotonin levels.
    - Have a cool room for sleep with extra blankets to add or remove as needed. We sleep better when our body is cooler, and our brain activity is slowed down. A gel ice pack wrapped in cloth and placed on the forehead while trying to go to sleep may help, similarly to how glycine can help with cooling the body down (it is a brain calming amino acid).
- **EMF** - turn off devices at night, reduce exposure during the day, ideally.
- **Poor Water intake** and/or excessive diuretic beverages with inadequate non-diuretic fluids. Leads to poor lymphatic and glymphatic drainage and risks from dehydration.
- **Poor Exercise** - full range body movement helps move fluid through the brain's glymphatic and body's lymphatic systems.
- **Over calories/carbohydrates and vegetable oils, and under nutrition** - too little quality protein and trace nutrients or phytonutrients.
    - Excess calories leads to poor autophagy - removal of cellular debris for reuse - misfolded proteins included or a cell with an overloaded Endoplasmic Reticulum that has been marked for apoptosis.
    - Excess carbohydrates leads to insulin resistance and inflamed fat cells that have a difficult time accepting more fat.
    - Low protein would make it more difficult for the body to remove misfolded proteins.
    - Excess omega 9 fatty acids in proportion to omega 3 leads to more Endoplasmic Reticulum stress, enlargement and increased accumulation of misfolded proteins.
- **Elevated Omega 6 to Omega 3 ratio** - promotes NF-kB.
    - More people than realized may need fish, krill, or algal sources of EPA and DHA omega 3 fatty acids as the average conversion rate from vegetarian sources like walnuts and flax seed oil is not very good.

- **Too much unmethylated Folic Acid and Cyanocobalamin** in supplements and fortified foods - may compete with methylated forms that are functional in a reaction. Whether they are inflammatory may depend on the person. A clinical trial with CoV patients found that B complex supplements and other nutrition support did help on average - folic acid and cyanocobalamin were used. (1)
- **Histamine in food** - can cause a range of symptoms from seasonal allergies to hyperexcitability.
    - Increased sensitivity may occur for people with methylation gene differences as folate is needed for breakdown of histamine.
    - Increased sensitivity may occur if there is a genetic difference in the DOA enzyme
    - Loratadine and other H1 antihistamines can help, and possibly H2 and H3 antagonists also. (53)
    - Flavonoids (60) such as quercetin, luteolin, and pomegranate catechins (61) may help reduce mast cell degranulation. Pomegranate may also help regrow hippocampal cells. (62)
        - Pomegranate prep, seeds and peel: G13. Pomegranate.
        - Also see this post about urolithin, a metabolite of pomegranate juice formed by healthy microbes in our intestines and which can then cross the blood brain barrier to reduce neuroinflammation in the brain: *Pomegranate, neuroinflammation, antimicrobial, metal chelator.*
- Other beneficial phytonutrient rich foods: G10. Nrf2 Promoting Foods.

> Regarding mast cells and pomegranate extract: "*Pomegranate extract (POMx) inhibits inflammation from activated human mast cells involved with connective tissue destruction and proteolytic activity associated with cartilage destruction, providing potential benefit for treating inflammatory diseases in which mast cells play an active role (Zafar et al. 2009).*" (61)

> Regarding flavonoids: "*The antihistaminic effect, histidine decarboxylase inhibition and mast cell stabilising effect of flavonoids may play an important role in the anti ulcer and anti*

> *secretory property of these compounds (Reimann et al, 1977; Fewtrell & Gomperts, 1977; Ramaswamy et al, 1979).*" (60)

- **Excess dietary glutamate** - or excess internal production - over activates NMDAR receptors. Eventually mitochondrial dysfunction leads to use of glutamate and glucose by fermentation which is less efficient but fewer nutrients and cofactors are needed. Cancer cells have mitochondria that feed on glutamate for energy.
- **Excess Vitamin A medications, foods, or carotenoid rich produce may be a problem if over-activation to Retinoic Acid is occurring in the liver**. This has been seen to happen after an Epstein-Barr viral infection and may be a factor for some vaccine injured (a theory developed prior to CoV injections). See: Retinoid Toxicity.
    - **Low vitamin A is a more common risk for reduced immune function**. Reviewing the Retinoid Toxicity symptom list or my questionnaire may be helpful as the effects can range throughout a variety of organ systems and also cause skin or mood symptoms. Low level problems may remain undiagnosed as anything specific or diagnoses for the various symptoms might be given - liver or kidney disease being more end stage if the problem continues.
    - The solution if excess Retinoic Acid is a problem, is to stop using meds with retinol (in many anti-aging skin products), and stop eating all rich sources of vitamin A, retinal, and carotenoids. This is harder than it sounds as that includes animal products and bright orange veggies and fruit (except citrus) and green leafy vegetables. Reducing excess active vitamin A would reduce the degranulation of mast cells by the Retinoic Acid. Less histamine would be released, and less histamine hyperexcitability or seasonal allergy symptoms would be experienced.
- **Glyphosate and organophosphates** increase the risk of misfolded proteins. Glyphosate may also have other effects on increasing hyperinflammation - positive feedback loop of increasing inflammation without normal modulating actions reducing some of the inflammatory activity.

    - **PFAS** (67) and other modern toxins in foods and medications such as **bromide and fluoride** also can cause problems. Low iodine in comparison to the halides: bromide, fluoride and perchlorates, can lead to autoimmune hypothyroidism or other low thyroid and endocrine symptoms.
- **Other dietary substances** that may cause inflammation in excess or for more sensitive people - oxalates, lectins, TRP channel activators, or anything someone developed an allergy or autoimmune sensitivity too.

Those are some of the things that we need to improve if we hope to reduce the inflammatory effects of modern life, which can lead to misfolded proteins and neurodegenerative conditions.

Dietary influences and solutions:

Excess dietary glutamate and calcium can be risk factors for chronic degenerative conditions and inflammation, along with low magnesium, copper, inositol, (1), B6, and methyl folate. Adequate glycine is helpful while glyphosate residue can increase misfolded protein risks. Mitochondrial support nutrients and cofactors are needed, CoQ10, ALA, NAC or whey powder for cysteine. Also, magnesium, manganese, copper, and other trace minerals in balance help mitochondria and receptor and gene functions. Trace minerals may stabilize other chemicals, as they tend to have an electrical charge as ions.

Solutions for misfolded proteins also include allosteric modulators to help stabilize or modulate receptor function. Phytonutrient based solutions for histamine excess and/or NMDAR antagonists can help reduce over activity. Liposomal curcumin would be a bioavailable form of an NMDAR antagonist, and Vitamin D Receptor agonist with a reduced risk of hypercalcemia. It also may help reduce misfolded protein risk by promoting Heat Shock Proteins (55) which tag misfolded proteins for removal.

Lifestyle factors are important for reducing the promotion of inflammatory NF-kB and instead promoting anti-inflammatory Nrf2 - water, sunshine, exercise, sleep with black-out curtain level dark or eye cover and avoid EMF

Fibrinolytics to help break down fibrotic build-up before it is excessive may be helpful in inflammatory conditions and may be critical in CoV care. It has been found that our white blood cells break down the chimeric spike into seven prion-like domains but our plasmin can not break them down further like other amyloid proteins. (28, 29) Serrapeptase, a silkworm fiber enzyme, may be helpful or others: nattokinase, bromelain, or lumbrokinase.

See Table 1 for more details and Protocol Collation and Therapy Goals for other details and references.

SARS-CoV-19 chimeric spike and the injection version cause hyperinflammation.

SARS-CoV-19 infection or injections, or passive exposure to recently injected, may all also cause a hyperinflammatory state. The injections, mRNA in particular, seem even more severe as the mRNA sequence and chimeric spike were modified and is harder for the body to break down. In order to "*treat*" CoV, we need to improve as much of the above list of modern life problems that promote NF-kB — and also work on the special needs caused by inflammatory chimeric spike effects or CoV injection adjuvants. Polyethylene glycol and graphene oxide can have negative health effects and increase inflammation or allergy like reactions.

Believing that early treatment or preventive treatment can help - may also help it to help. The stressors of fear and isolation alone can lead to symptoms of edema, congestion, pain and fatigue - mimicking "*Covid-19*". And the repetitive messaging of fear or risk, may increase the chance of their occurring due to a nocebo effect. Think positive thoughts or listen to them and a positive placebo healing effect may be more likely.

Severe Covid-19 is largely out of control inflammation due to excess promotion of NF-kB and inflammatory cytokines by the chimeric spike. Increased NF-kB leads to reduced Nrf2 - which we need to repair DNA and also to remove an overload of misfolded proteins safely.

Low Nrf2 would increase cell death from misloaded protein overload, Endoplasmic reticulum (ER) stress.

Prion disease is generally deadly and fairly rapidly progressive. The misfolded prion can cause normal ones to misfold also so the body would rather kill a cell that is overloaded with misfolded proteins, safely by apoptosis (when Nrf2 is available), than let them collect and burst into the extracellular fluid. (Subsection_Nrf2 function)

Endoplasmic reticulum stress can be due to a gene allele that produces a misfolded protein - in Cov mRNA injected people, their cells are being told to make chimeric spike which contains prion-like domains once broken down partially by white blood cells.

Genetic changes that cause a misfolded protein to be transcribed regularly can be a cause of accumulation, seen in a patient with autism. (27) Misfolded protein accumulation begins in the Endoplasmic Reticulum (ER), where proteins are made and identified as wrong only after they are made. The problem occurs when too many problem proteins collect to be removed, the overload leads to ER stress. When the ER is too overloaded, coupling with mitochondria leads to apoptosis of the cell. (1) Low Nrf2 would make the death of the cell more likely. Misfolded proteins can cause misfolding of other proteins leading to larger tangles outside of the cell. Subsection: Endoplasmic Reticulum & misfolded proteins.

Mitochondrial dysfunction - fermentation of glutamate for energy.

Misfolded protein degenerative conditions* also seem to include mitochondrial dysfunction along with histamine excess leading to or correlated with NMDAR receptor overactivity. Mitochondrial dysfunction is also seen in cancer cells. Mitochondria are needed to cause the safe removal of cells that are overloaded with misfolded proteins by apoptosis, so mitochondrial dysfunction would leave a damaged cell adding misfolded protein to the surrounding tissue, increasing misfolding exponentially within the region, or a dysfunctional senescent cell (37) might be the result.

*Mitochondrial degenerative conditions may include Alzheimer's dementia, Parkinson's Disease, ALS (Lou Gehrig's Disease), and possibly Multiple Sclerosis (MS) in addition to prion diseases. Some cancers also may lead to misfolded proteins. (1, 49) Misfolded proteins are also seen in autism and can be genetic in nature - an allele is transcribing a misfolding protein instead of a normal one. (27)

Mitochondria are needed to cause the safe removal of cells that are overloaded with misfolded proteins by apoptosis, so mitochondrial dysfunction would leave a damaged cell adding misfolded protein to the surrounding tissue, increasing misfolding

exponentially within the region, or a dysfunctional senescent cell (37) might be the result.

When hyperinflammation is allowed to escalate without check, then more and more cells are damaged, or go into a senescent, not quite dead, but no longer functional, state.

Once the whole house is on fire, the flames may not be able to be extinguished. Earlier provision of extra nutrients, protein, and immunomodulating phytonutrients can help put out tiny fires while they are still tiny.

CoV chimeric spike and the injection adjuvants also can cause hyperinflammation and lead to prion-like misfolding and fibrotic build up.

The damage from CoV infection involves hyperinflammation, however the injection version of the chimeric spike is even worse for causing hyperinflammation and specific cell receptor malfunction in addition to lodging in ACE2 receptors and disrupting their function. It also has multiple prion-like domains which are exposed when our white blood cells break down the spike into smaller pieces. (28, 29)

The chimeric spike protein is broken down into seven prion-like domains by our white blood cells, and the prion-like sections seem resistant to our normal plasmin method for further digestion and removal. (28, 29) The prion-like spike sections are leading to fibrotic build-up as they can trigger other cellular proteins to misfold also, in a chain reaction, like a line of dominoes falling once the first is knocked over.

Fibrosis/misfolded proteins, sHSPs, and our microtubules - axon support.

Fibrotic - fiber like, but a tangled plate of spaghetti instead of microtubules that are more like straight, powerful antennae like scaffolding supporting our intra or extracellular fluid and guiding chemicals and stabilizing our electrical fields. Microtubules also may support axons for our nerves. Multiple sclerosis may have similar underlying issues as conditions more typically thought of as misfolded protein conditions. (CoQ10, a mitochondrial cofactor is important for MS care.)

Heat shock proteins are a stress response and are chaperone proteins that help prevent misfolded protein tangles. (48) For a kitchen visual - raw egg is protein in a watery environment - add heat and the water partially evaporates and the heat causes the proteins to change form - denature - gentle heat leads to a softer texture, excess heat leads to a rubbery texture - the proteins changed form and can not be uncooked.

Chaperone proteins help stabilize and prevent misfolding during the heat or other stress - the insulator sleeve around a cold drink in the summer.

Adequate protein is necessary to have adequate chaperone proteins and other important proteins such as PERK, AFT6, and GRP78 that help prevent misfolded proteins in the Endoplasmic Reticulum. (Subsection_ER)

> "*Amino acid deprivation seems to limit the heat shock factor (HSF1) activity, which plays an important role in the synthesis of HSPs. Cells cultured with either leucine, lysine or glutamine deprivation show reduced HSF1, as well as HSPs mRNA levels. Thus, it is suggested that amino acid deprivation can compromise the defense capacity of the organism, since it may lead to the reduction of HSP synthesis [33].*" (47)

Certain phytonutrients or their food sources may help protect against misfolded proteins by promoting Heat Shock Proteins.

> "*This chapter briefly describes recent findings in the effects of phytochemicals on oxidative stress-involved ischemia/reperfusion injury, obesity, and liver diseases through regulation of heat shock proteins. These phytochemicals include* ***caffeic acid phenethyl ester from bee glue, synthetic oleanane triterpenoid CDDO-Im, curcumin from Indian spice turmeric, resveratrol from red grapes, naringin found in grapefruit, epigallocatechin-3-gallate from green tea, anthocyanins from pomegranate, and flavonoids****.*" (55)

Is prion disease airborne? CoV infection or passive exposure to injected people is airborne and can spread in body fluids.

Airborne? Classic prion disease CJD or Mad Cow Disease were thought to only spread by eating tissue with the misfolded prions or exposure directly to the prions, however exosome spread might be a possible airborne risk. Airborne spread may be an even greater risk from people who recently received CoV mRNA injections (the first two months post injection seems to have the greatest risk for causing passive symptoms in others). Animal research was successful at injecting one animal and having other non-injected animals in the same living area also produce the desired antigen - it was called passive vaccination by way of exosomes containing the injected genetic material being passed from the injected animals to the non-injected ones. See: Exosomes.

More detail about the Hyperinflammation positive feedback loop:

1. Degranulation of Mast Cells releases histamine and promotes NF-kB.

As we age many of our previous functions aren't working as well. Inflammation can cause mast cells to degranulate sending out histamine, cytokines and promoting NF-kB which leads to other inflammatory signaling. Inflammation within our lymphatic vessels can lead to increased white blood cells in the area which can increase fibrosis and cell damage in the area if it continues. Lymphatic function might also be reduced leading to more buildup of toxins in extracellular areas.

> "*We found that the reactivity of aged contracting lymphatic vessels to LPS-induced acute inflammation was abolished and that activated mast cells trigger NF-ϰB signaling in the mesentery through release of histamine. … We conclude that proper functioning of the mast cell/histamine/NF-ϰB axis is necessary for reactions of the lymphatic vessels to acute inflammatory stimuli as well as for interaction and trafficking of immune cells near and within the collecting lymphatics.*" (54)

*LPS - a bacterial endotoxin that CoV spike worsens the effects of.

2, 3, 4. H1-Rs & NMDARs; Hippocampus - center for daily memory formation, at risk from dietary glutamate or histamine excess.

The hippocampus is an early target in Alzheimer's because it has both more NMDA receptors (NMDARs) than average and more H1 histamine receptors.

An agonist of NMDAR receptors, dietary glutamate, is common in modern life and it can be made internally. Agonists are activators, too much activation of the NMDA receptor can lead to an influx of too much calcium into the brain cell leading to excitement. The glutamate foods or seasonings can lead to addictive overeating as they are stimulating to the brain - tasty and the exciting feeling may promote ovr-eating. Too much overactivity of a cell can lead to cell death. Subsection: Hippocampus has more NMDARs.

The hippocampus also has more H1 histamine receptors than average, so histamine excess from degranulated mast cells, triggered by NF-kB inflammatory signaling, would

also be leading to inhibition of hippocampal cells. Histamine is a brain modulator in normal levels, helping us to maintain an even midpoint between emotional extremes.

> "*In the cerebellum and hippocampus, abundant histamine H1 receptors are localized in the dendrites of pyramidal and Purkinje cells (Hill et al., 1997). Hippocampal activation of histamine H1 receptors induce the inhibition of firing and hyperpolarization in hippocampal neurons (Haas, 1981).*" (51, viewable 52)

The different types of histamine receptors have slightly different roles within the brain and body.

> *"Histamine driven H1 and H2 receptor-mediated actions are mostly excitatory, while H3 receptors act as inhibitory auto- and heteroreceptors..."* (53)

4. NMDARs; Prion misfolding can lead to increased NMDAR activity.

The accumulation of misfolded prion proteins also may increase NMDAR activity because their normal function includes down regulating the receptors. Subsection: Misfolded proteins & NMDAR down regulation.

3, 4. NMDAR and the H1 histamine receptor mystery modulator - down regulator.

NMDAR receptors are a link between Alzheimer's misfolded protein damage and histamine excess seen in Alzheimer's. The H1 histamine receptor can down regulate NMDAR activity but seems to use a different agonist than histamine to do so - a mystery to solve! An unknown to discover and name! Histamine excess would be activating H1 receptors in a way that could be symptomatic of seasonal allergies or worse histamine symptoms, while not providing the unknown agonist's down regulation of NMDARs.

Various NMDAR antagonists are known and some are used beneficially for Alzheimer's or other neurocognitive conditions. Subsection: Phytonutrients that are antagonists of NMDARs. Antihistamines have been found useful for Alzheimer's care and in Covid treatment. Histamine excess has been a common problem among people with LongCovid symptoms.

Allosteric modulators are among the types of chemicals that can act as modulators of NMDAR activity - increasing the channel being opened, while inhibiting the entry of calcium - allowing function without excess calcium intracellularly. Subsection: Allosteric Modulators.

Curcumin is a Vitamin D receptor agonist that reduces risk of calcium excess in comparison to taking vitamin D supplements. It may help reduce toxicity of amyloid and inhibit amyloid-beta fibril formation, results have been inconclusive. [The Essential Medicinal Chemistry of Curcumin, 34] Curcumin is also an NMDAR antagonist. (11, subsection: Phytonutrients-NMDAR antagonists). It is more bioavailable in liposomes, which may form in food preparations that contain phospholipids in a watery broth or beverage (Golden Milk). See Curcumin-bioavailability, within Phytonutrients, Molecular Docking - the synergy of soup - it may be really good food!

5.Mast cells are also degranulated by Retinoic acid.

See Retinoid Toxicity. An excess may be activated by the liver in response to a viral infection such as Epstein-Barr Virus and possibly traditional vaccination injury.

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Reference List

Full Reference List, linked within the subsections, is available in the document version: Misfolded Proteins, H1 and NMDA Receptors.

3 Comments

Write a comment...

Godwin The Huge Jun 16 ♥ Liked by Jennifer Depew, R.D.

Ty Jennifer and thank you for making this free to the public.

♡ 1 Reply Collapse •••

Skylover_once Jun 14 ♥ Liked by Jennifer Depew, R.D.

very informative, many thanks!

♡ 1 Reply Collapse •••

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