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CURRENT RESEARCH ON PREVENTION STRATEGIES

ALZHEIMER'S PREVENTION

Research Roundup

ALZHEIMER'S PREVENTION

Alzheimer's Disease is the most common cause of dementia. Current research points to the cause of the neurodegeneration being a disproportionate inflammatory response resulting in the accumulation of amyloid beta plaque and tau protein tangles. Alongside the excessive inflammatory response is oxidative damage in the brain.[ref]

Prevention is the best strategy, and the initial damage in the brain starts one to two decades before symptoms are apparent. Current drug options for Alzheimer's can delay the progression of the disease, but they aren't a cure.

One copy of the APOE E4 allele increases Alzheimer's risk by more than 2-fold, but even without the APOE E4 allele, Alzheimer's prevention is still important. (You can check your APOE genotype on GeneticLifehacks.com if you want to know.)

Your overall health is important in Alzheimer's prevention; eating healthy foods, exercising regularly, keeping your brain active, and having good social connections all are basic strategies that everyone should incorporate.[ref] However, this is just the baseline, and we likely all know someone who met these health goals and still ended up with Alzheimer's disease.

This roundup of current research on Alzheimer's disease focuses on what is going on in the brain and prevention strategies for each pathway. The overarching picture is one of the specific reasons for increased neuroinflammation - from circadian disruption to plaque formation to an inability to cope with oxidative stress from your body's inflammatory response to pathogens that have reached the brain.

Topics covered in this report include:

1. Circadian Rhythm and Melatonin Production: Important for brain health and immune system modulation

2. Fibronectin, blood-brain barrier dysfunction, and preventing amyloid-beta plaque formation

3. Plasmalogens as a Key to Health Brain Aging: A key phospholipid that can counteract lipid oxidation in the brain

4. Oral Microbiome and Bacterial Translocation: Keeping bacteria out of the brain

5. Natural Supplements with Efficacy for Alzheimer's Disease

Prevention is the Key

CIRCADIAN RHYTHM AND MELATONIN:

Research shows a strong connection between circadian rhythm disruption, melatonin production, immune system regulation, and healthy brain aging.[ref][ref][ref][ref]

Your body's circadian rhythm is the 24-hour internal molecular clock that drives the timing of many cellular processes. Examples of our daily rhythms include sleeping, wakefulness, meal timing, changes in body temperature, the timing of producing digestive enzymes, the rise and fall of cortisol levels, and daily rhythms of blood pressure. Going deeper, about 40% of the genes that are active in a cell are impacted by circadian rhythm, and your immune response is strongly tied to your circadian clock.

The core circadian clock genes come in pairs - during the day, BMAL1 and CLOCK are telling your cells it is daytime, and at night, PER and CRY are telling cells that it is rest and rejuvenate time.

A key study in mice published in 2018 showed that BMAL1, a core circadian clock gene, is integral to the daily rhythm of amyloid-beta plaque. Disrupting BMAL1 expression in the brain causes an increased deposition of amyloid plaque and an increase in the expression of APOE.[ref] Building on that research, a 2020 study showed that BMAL1 regulates astrocyte activation in the brain. Disrupting BMAL1 increases neuroinflammation and accelerates Alzheimer's pathogenesis by altering the way astrocytes function.[ref] Astrocytes are the cells that help neurons function by clearing excess neurotransmitters and providing nutrients and growth factors. However, astrocytes are also responsible for the immune response and neuroinflammation.

Light during the day and darkness at night are foundational to our circadian rhythm. A new study shows that light at night from light pollution significantly increases the risk of Alzheimer's, especially at a younger age. The authors concluded: "nighttime light was more strongly associated with AD prevalence than alcohol abuse, chronic kidney disease, depression, heart failure, and obesity."[ref]

Sleeping in complete darkness increases melatonin levels at night. Melatonin production rises in the absence of light in the blue wavelengths. Recent animal studies clearly show

that melatonin is important in reducing amyloid beta levels. Melatonin also acts as an intracellular antioxidant to reduce neuroinflammation.[ref][ref]

Lifehacks for Circadian Rhythm and Melatonin:

1. Both quality and quantity are important in sleep. Chronic sleep disruption alters the expression of BMAL1 and directly increases symptoms of Alzheimer's.[ref]

2. Sleep in a dark room (no night lights, no streetlights coming through the window, no glowing power buttons).

3. Shut off your cellphones, tablets, and TV a couple of hours before bedtime. LED screens emit a lot of blue light which dysregulates circadian rhythm and decreases melatonin production. In addition, consider whether supplementing with time-release melatonin is right for you.

4. Exposure to morning sunlight also helps to keep your circadian rhythm on track. Go outside in the morning soon after you wake up for full sun exposure.

FIBRONECTIN, BLOOD-BRAIN BARRIER DYSFUNCTION, AND PREVENTING AMYLOID-BETA PLAQUE:

Recently, two large studies of the interaction of APOE E4 with other genetic variants have shed light on how changes in the blood vessels and the blood-brain barrier are important for the buildup of amyloid-beta plaques.[ref][ref]

In Alzheimer's, the buildup of amyloid-beta in the brain activates the immune system, causes inflammation, and eventually kills neurons.

The blood-brain barrier not only keeps bacteria and viruses out of the brain, but it also keeps out many molecules that normally circulate throughout the body. The brain is protected and prioritized, with certain molecules being kept in the brain and many molecules being filtered out.

In Alzheimer's, it's been known for a while that there is an increase in fibronectin in the blood-brain barrier.[ref] Fibronectin is best known for its role in forming blood clots, but it is also important in cell adhesion and the blood-brain barrier.

Individuals with the APOE E4 allele don't break down amyloid-beta quite as well as normal for clearance from the brain. Fibronectin interacts with and binds to many different particles, including amyloid-beta. The excess fibronectin in the BBB is believed to "negatively regulate amyloid beta clearance".[ref]

In addition, fibronectin changes in the BBB allow more fibrinogen into the brain. Fibrinogen is another clot-forming protein and decreasing fibrinogen helps to prevent Alzheimer's pathology (in animals).[ref]

Genetic variants that decrease fibronectin production have recently been identified as significantly decreasing the risk of Alzheimer's in people with APOE E4.

You can check your genes and learn more about fibronectin on Genetic Lifehacks.

Lifehacks for decreasing fibronectin and fibrinogen:

If you aren't one of the lucky few with the fibronectin gene variants, you could look at ways to naturally lower fibronectin levels.

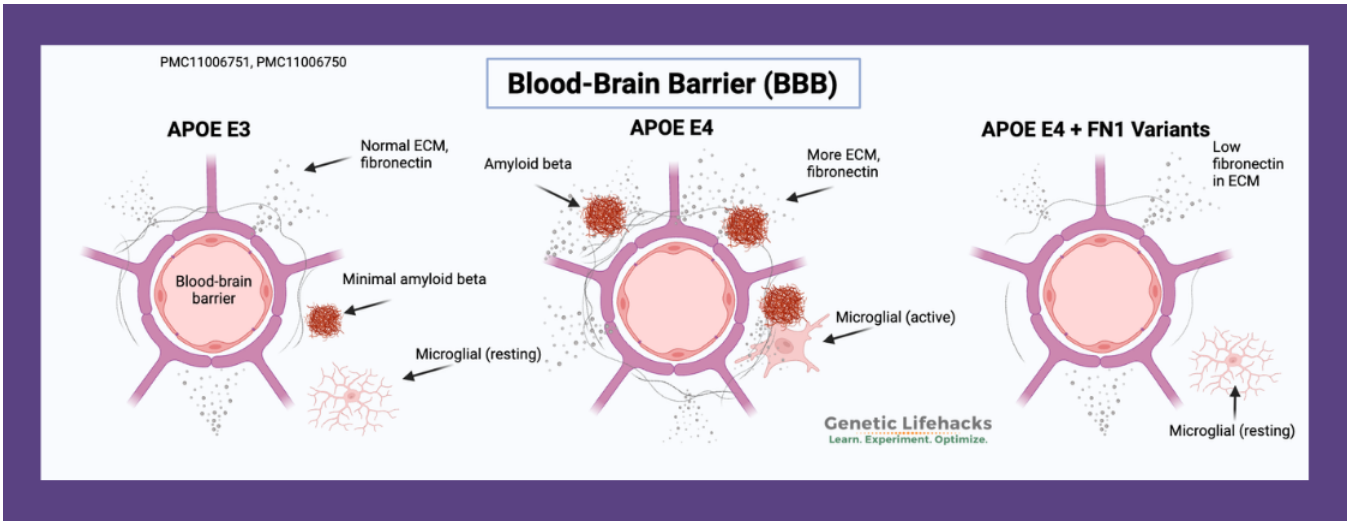
1. Reduce omega-6 oils: Studies show that omega-6 fatty acids increase fibronectin levels.[ref] "Vegetable oils" such as canola, corn, soybean, sunflower, and safflower oils are high in omega-6 fatty acids.

2. Vitamin A: Animal studies show that vitamin A deficiency leads to higher serum fibronectin levels.[ref] Vitamin A in the retinol form is important in turning on or off gene transcription for a number of different genes, including several related to the extracellular matrix.[ref]

3. Berberine: A natural supplement derived from barberry, goldenseal, and Oregon grape, berberine has been shown in animal models of diabetes to downregulate fibronectin production.[ref]

4. Serrapeptase plus nattokinase: The natural proteolytic enzymes serrapeptase and nattokinase are able to break up fibrinogen. An animal model of Alzheimer's also showed that serrapeptase plus nattokinase was effective at reducing brain inflammation and reducing certain markers for Alzheimer's.[ref]

If you are taking a prescription medication, be sure to talk to your doctor or pharmacist about interactions with any supplements. Nattokinase, for example, may be counterindicated if you are already on an anticoagulant.



PLASMALOGENS AS A KEY TO HEALTH BRAIN AGING

Plasmalogens are a unique type of phospholipid and an essential component of cell membranes. In the brain, a specific subtype of plasmalogens, called ethanolamine plasmalogens, is abundant and important in preventing neurodegenerative diseases. [ref]

In addition to forming cell membranes, plasmalogens can act as a phospholipid antioxidant that counteracts oxidized lipids. Plasmalogens are thought to play a critical role in being able to neutralize ROS (reactive oxygen species) in the brain. In the presence of ROS, the plasmalogens are quickly degraded. Thus, plasmalogen levels may decrease quickly as they neutralize the oxidative stress.[ref][ref][ref]

In people with Alzheimer's disease, plasmalogen levels are very low. [ref] This seems to be even more of a problem with APOE E4. A study showed that people with APOE E4 (risky genotype) alleles have lower plasmalogen levels, while people with APOE E2 (protective genotype) have higher levels.[ref]

Clinical trials in Japan have shown supplemental plasmalogen to be effective at improving memory in people with Alzheimer's. It seems to be more effective if given in mild AD and in younger patients.[ref][ref]

See the Genetic Lifehacks article on Plasmalogens for more in-depth information.

Lifehacks for boosting plasmalogens in aging:

1. Diet: Foods high in plasmalogens include seafood, such as mussels, octopus, clams, oysters, squid, scallops, salmon, anchovies, and shrimp.[ref][ref]

2. Modified Keto: A ketogenic diet has been shown to improve plasmalogen levels in older adults, and a modified Mediterranean keto diet also showed promising results.[ref] A modified Mediterranean keto diet include seafood, lean meats, green leafy vegetables, nuts, and berries -- along with extra virgin olive oil.

3. Myoinositol: A couple of animal studies show that myoinositol increases brain ethanolamine plasmalogen levels. Cell studies also show that myoinositol likely increases ethanolamine plasmalogen levels.[ref][ref][ref] Myo-inositol is a sugar alcohol that is made in the brain and in the body. It is readily available as an inexpensive supplement.

4. Supplements: Plasmalogen supplements are available as well. Currently, the cost per serving is in the $3 to $6 range, with study participants using multiple servings per day to see benefits.[ref] This may be worth checking into if money is not an issue for you.

ORAL HEALTH AND BACTERIAL TRANSLOCATION:

Good oral health is also important in preventing Alzheimer's disease. The bacterial species *P. gingivalis* resides in the mouths of some people and causes gum inflammation. However, *P. gingivalis* and other oral species can sometimes get into the bloodstream, such as through bleeding gums, and then circulate.

Important here: *P. gingivalis* has been found in the brains of deceased Alzheimer's patients. Research also shows that the oral microbiome differs in people with Alzheimer's compared to healthy people the same age. While a direct bacterial cause of Alzheimer's hasn't been established, decreasing overall inflammation through good oral hygiene may make a big difference to your brain.[ref]

A meta-analysis of 16 studies on the oral microbiome and the brain showed that the risk of Alzheimer's disease is up to 10-fold higher in people whose brains contain bacteria that are also found in the oral microbiome.[ref]

This also connects to the study on fibronectin and a leaky blood-brain barrier, which could allow bacteria to enter the brain in addition to fibrinogen. Oral bacteria in the brain will stimulate an immune system response from astrocytes, possibly leading to neuroinflammation and Alzheimer's plaque.[ref]

Lifehacks for your oral microbiome:

1. Stop bacteria from getting into the bloodstream: Good oral hygiene is important. If you feel like you're brushing, flossing, and doing everything right but still have inflammation in your gums, read through this Genetic Lifehacks article on gingivitis. Genetic variants in TNF-alpha and other inflammation-related genes cause excess inflammatory response and bleeding gums. Targeting your specific reason for excess inflammation may help reduce the bleeding gums.

2. Water-based flosser: A Water Pik or similar water flosser may be worth investing in. If flossing with regular dental floss causes your gums to bleed, then oral bacteria will enter your bloodstream regularly. Water flossers may be a good alternative if they don't cause bleeding for you.

3. Avoid antiseptic mouthwash? Antiseptic mouthwash may alter your oral microbiome and shift the balance to the wrong types of bacteria. Antiseptic mouthwash is linked to increases in blood pressure due to changes in the oral microbiome.[ref] While there is still more to learn here, the studies on the use of mouthwash and hospital mortality raise concerns as well.[ref]

Research shows that oral health may be important in Alzheimer's prevention

NATURAL SUPPLEMENTS WITH POTENTIAL BENEFITS:

There are several natural supplements that have been shown to have positive effects on Alzheimer's in both animal and human studies. I don't think any of these are individually more important than circadian rhythm, an intact blood-brain barrier, and the prevention of inflammation in the brain. Rather, these interact with the pathology of Alzheimer's in complementary ways.

BILE ACIDS & TUDCA:

Studies have found altered bile acid metabolites in Alzheimer's brains.[ref][ref] Certain bile acid metabolites are neuroprotective, while other bile acids are neurotoxic in the brain.[ref]

TUDCA is a supplement that provides neuroprotective bile acids. In a mouse model of hereditary Alzheimer's disease, six months of TUDCA supplementation prevented the Alzheimer's pathology that should have happened in these mice.[ref] Other studies show that TUDCA prevents cognitive impairment in animal models of Alzheimer's disease.[ref]

FOUR "COMBINED METABOLIC ACTIVATORS"

A recent phase II clinical trial using a combination of natural supplements showed significant improvements in cognitive scale scores for Alzheimer's patients. While this trial was in patients who already have Alzheimer's, I think the pathways targeted here are important for prevention. (Details on the trial in my Longevity Lifehacks article.)

The "combined metabolic activators" used in the clinical trial are compounds that are known to reduce oxidative stress and improve cellular energy in the brain. Each of these components individually has been looked at for neurodegenerative diseases and aging with somewhat positive results, but the combination of the four supplements showed actual positive results in humans with Alzheimer's. The CMA supplement contained12.35 g *L*-serine, 1 g nicotinamide riboside, 2.55 g N-acetyl-*L*-cysteine, and 3.73 g *L*-carnitine tartrate.[ref]

Note that the doses are much higher than normally taken for these supplements, and the goal of the study was to reverse or stop the damage that had already occurred in the brain. I'm not suggesting that high doses of these are needed at younger ages to prevent Alzheimer's, but each is worth looking into for overall brain health.

1) L-serine: Glycolytic pathway, plasticity

Serine is an amino acid that the body uses to create proteins. It is not considered an 'essential amino acid' to get from foods because the body can make it. Glycine can be converted into l-serine, and serine can be converted into glycine.

A recent animal study showed two reasons why l-serine could be so important in Alzheimer's. First, the glycolytic pathway is impaired in the Alzheimer's brain. Not only does this decrease energy in the brain, but it also decreases serine biosynthesis. Second, serine is a co-agonist for NMDA receptors, which is important in synaptic plasticity. Importantly, the study showed that supplementing with l-serine could prevent Alzheimer's behaviors and deficits.[ref] Other studies also explain that l-serine is formed exclusively in glial cells, which are the brain cells that support neurons. In patients with Alzheimer's disease, serine metabolism is significantly altered in the brain. Moreover, restoring serine levels may prevent damage from altered brain energy in aging.[ref]

2) Nicotinamide riboside: Mitochondrial energy production

Nicotinamide riboside (NR) is a form of vitamin B3 that can directly impact NAD+ levels, which naturally decline with aging. NAD+ is essential for cellular energy production in the mitochondria and is also important in DNA repair and mitochondrial health. Research shows that NAD+ levels are reduced in the brains of animal models of Alzheimer's, and restoring NAD+ levels reduces neuroinflammation.[ref] A pilot study in people with mild cognitive impairment showed that 10 weeks of nicotinamide riboside (NR) at 1g/day was safe and associated with positive functional changes in the brain and frailty measures. However, cognitive test results weren't significantly different in the MCI group at 10 weeks. [ref]

3) N-acetylcysteine (NAC): Reducing oxidative stress in the brain

N-acetylcysteine (NAC) is a precursor of l-cysteine. The cysteine in NAC can be used by cells to create glutathione, which is an intracellular antioxidant that stops neuronal damage due to oxidative stress. Oxidative stress in the brain is linked to increased

amyloid-beta secretion and lipid peroxidation (this is why plasmalogens are important). In animal studies, NAC supplementation increases glutathione in the brain and improves learning and memory. In Alzheimer's brain culture studies, NAC has been shown to be protective against amyloid-beta plaque formation and against cell death in the neurons. [ref]

4) *L*-carnitine: Brain energy

Carnitine helps support mitochondrial energy by transporting long-chain fatty acids into the mitochondria. Circling back to the altered cell metabolism and glycolytic pathway in Alzheimer's, l-carnitine has been shown to mitigate cell damage caused by glycolysis-inhibiting drugs.[ref] A 2023 study showed that low l-carnitine levels were found in Alzheimer's patients and in early Alzheimer's progression.[ref]

METHYLENE BLUE

Methylene blue (Methylthioninium chloride) has been used in pharmacology for over a century. It is a fascinating compound that was first synthesized as a blue dye.

Mitochondrial dysfunction is believed to play a role in the pathogenesis of Alzheimer's disease. Methylene blue can reduce the production of free radicals in the mitochondria in the brain, and animal studies show good results for methylene blue and Alzheimer's.

A couple of phase III clinical trials in Alzheimer's patients used high doses of methylene blue and showed no benefits - except for in the control groups, which were given low doses of 4 -8mg/day. [ref][ref][ref]Multiple animal studies show *preventative* effects of methylene blue for Alzheimer's, but there hasn't been a human randomized, placebo-controlled clinical trial on it yet.[ref][ref]

More is not always better. With methylene blue, the dose matters quite a bit. At higher doses, methylene blue can take away electrons in the electron transport chain — slightly reducing energy production in the mitochondria.[ref] Talk with your doctor if you have questions on whether low-dose methylene blue is a good option for you.

CONCLUSION

Alzheimer's prevention strategies need to start long before the memory problems begin. Circadian rhythm optimization helps keep the brain in top condition and inflammation under control. Plasmalogens are important for combating oxidative stress when it occurs, and low fibronectin keeps amyloid-beta plaque from forming. Good oral health may help to keep bacteria from reaching the bloodstream and the brain. Supplements can help give the brain the energy it needs and provide the building blocks for antioxidants.

All of these strategies together may be needed to move the needle in preventing neurodegeneration. More research is needed on this topic, but in the meantime, you can make your own prevention plan today using what is currently known.

My Prevention Plan: