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Time-Restricted Eating — A Powerful Way to Prevent Dementia

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STORY AT-A-GLANCE

- Time-restricted eating is a powerful approach that facilitates weight loss and helps reduce your risk of chronic diseases like Type 2 diabetes, heart disease, cancer and neurodegenerative diseases
- Among the many benefits of time-restricted eating is the upregulation of autophagy and mitophagy — natural cleansing processes necessary for optimal cellular renewal and function
- Research strongly suggests caloric restriction and time-restricted eating help combat Alzheimer's through these autophagy pathways
- The pathology hallmarks of Alzheimer's include amyloid beta plaques and tau tangles. Other pathological events frequently seen in Alzheimer's patients include synaptic deficits, mitochondrial dysfunction, oxidative stress and neuroinflammation
- Many of these are the result of insufficient autophagy, and one of the simplest ways to upregulate autophagy is by implementing time-restricted eating

Research overwhelmingly supports the notion that ditching the "three square meals a day" approach in favor of time-restricted eating (also referred to as intermittent fasting) can do wonders for your health, as your body simply cannot function optimally when there's a continuous supply of calories coming in.

The cycling of feasting (feeding) and famine (fasting) mimics the eating habits of our ancestors and restores your body to a more natural state that allows a whole host of biochemical benefits to occur.

It's a powerful approach that not only facilitates weight loss, but also helps reduce your risk of chronic diseases like Type 2 diabetes, heart disease, cancer and Alzheimer's.

While there are many variations, time-restricted eating typically involves not eating for at least 14 consecutive hours a day. However, not eating for 16 to 20 hours is likely closer to a metabolic ideal. This means you eat all of your meals for the day within a four- to eight-hour window.

Among the many benefits of time-restricted eating is the upregulation of autophagy and mitophagy — natural cleansing processes necessary for optimal cellular renewal and function. In a January 2020 review paper,[1] researchers explain how caloric restriction helps combat Alzheimer's specifically, through these autophagy pathways.

Preventing Alzheimer's Through Time-Restricted Eating

As explained in "The Effects of Caloric Restriction and Its Mimetics in Alzheimer's Disease Through Autophagy Pathways,"[2] two of the pathology hallmarks of Alzheimer's are amyloid beta plaques and neurofibrillary tangles formed by aggregates of tau protein.

"The aberrant accumulation of these misfolded and aggregated proteins results in neurotoxicity, and AD is therefore recognized as a proteinopathy," the paper states. Other pathological events frequently seen in the brains of Alzheimer's patients include:[3]

- Synaptic deficits and axonal degeneration
- Mitochondrial dysfunction
- Abnormal metal homeostasis
- Oxidative stress

- Neuroinflammation

Many of these occur as a result of "insufficient elimination of neurotoxic proteins or damaged intracellular organelles," the paper notes. In other words, they occur when there's insufficient **autophagy** occurring in your body. The good news is you can upregulate autophagy, and one of the simplest ways is by implementing **time-restricted eating**. As explained in this review:[4]

> *"Autophagy is a catabolic mechanism that ensures the removal of misfolded or aggregated proteins and maintains the turnover of cytoplasmic components.*
>
> *Under conditions of starvation or energy deficiency, phagophores are synthesized de novo in the cytoplasm from newly synthesized lipids or from intracellular organelles with membrane structures, such as the endoplasmic reticulum.*
>
> *Phagophores elongate and curve to form double-membrane autophagosomes, which then encapsulate cytosolic materials, misfolded proteins, or long-lived proteins.*
>
> *After fusion with lysosomes, any cargo is degraded by lysosomal enzymes. The autophagic process provides a strategy for clearing misfolded or aggregated proteins in proteinopathic disorders. Failure of autophagy leads to the accumulation of aggregates, which results in neurotoxicity and disease progression."*

Autophagy Dysfunction in Neurodegenerative Disorders

Autophagy dysfunction has been identified in several neurodegenerative and neuropsychiatric disorders and diseases, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS), Huntington's disease, ischemic stroke, schizophrenia and even drug addiction.[5]

Hence, it is believed that autophagy activation has an important role to play in the prevention and treatment of these conditions. Importantly though, using autophagy stimulators such as drugs, gene therapy or supplements can have undesirable side effects in some people, and may not be ideal.

Time-restricted eating, or calorie restriction, the authors note, is a safer and likely more effective strategy for most. So, just how does calorie restriction or intermittent fasting induce autophagy?

There are several mechanisms at play, but two important ones are activation of monophosphate-activated protein kinase (AMPK) and inhibition of the mammalian target of rapamycin (mTOR) pathway.[6] Calorie restriction also helps ameliorate Alzheimer's and other degenerative conditions by lowering inflammation and improving insulin sensitivity, mitochondrial function and oxidative stress.

The Benefits of AMPK Activation

AMPK is an enzyme essential for maintaining energy balance. It consists of three proteins (called sub-units) that together create a functional enzyme. AMPK is expressed in various tissues, including the brain, liver, skeletal muscle and fat cells, and is essential for activating autophagy.

It's sometimes referred to as a "metabolic master switch" because it plays an important role in regulating metabolism.[7] It shifts energy toward cellular repair and maintenance, thus helping your body return to homeostasis (balance).

Low AMPK has been linked to insulin resistance, mitochondrial dysfunction, obesity, neurodegeneration and chronic inflammation. Activating AMPK produces many of the same benefits as exercise, dieting and weight loss,[8] all of which are known to benefit a range of chronic diseases and ill health.

AMPK is also an important neuroprotector,[9] thus making it particularly relevant in Alzheimer's prevention and treatment. In addition, AMPK stimulates cellular and

mitochondrial autophagy (mitophagy) and mitochondrial biogenesis, as well as five other critically important pathways:

- Insulin
- Leptin
- mTOR
- Insulin-like growth factor 1 (IGF-1)
- Proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α)

Benefits of mTOR Inhibition

MTOR is also an important pathway responsible for controlling autophagy. When you inhibit mTOR — which you can do through time-restricted eating — you activate autophagy. MTOR is basically a nutrient sensor. While insulin primarily senses your intake of carbohydrates, mTOR primarily senses protein.

That said, other nutrients can also activate or inhibit mTOR. Nutrients that activate mTOR include branched-chain amino acids, glutamine, methyl folate and vitamin B12.

Nutrients that inhibit mTOR include polyphenols like curcumin, fisetin, quercetin, resveratrol (found in wine) and epigallocatechin gallate (EGCG, found in green tea). Organic coffee and dark chocolate also contain high amounts of mTOR inhibiting polyphenols.

Why Cycling in and Out of Autophagy Is so Important

One of the reasons time-restricted eating works so well is because you're cycling through autophagy on a daily basis (opposed to only occasionally, were you to do longer fasts once a month or quarterly, for example). This cycling is really crucial. You don't want to inhibit mTOR and activate autophagy all the time. There needs to be a balance between breaking down and building back up.

If your glycogen levels get too low by fasting too long it will stimulate inflammation by causing your body to secrete more cortisol to compensate for the metabolic stress. Then your body will shift to breaking down fat which sounds great, but most of your stored fat is the polyunsaturated fat, linoleic acid (LA), and not saturated fat. When you start burning this fat you create even more inflammation and also oxidative breakdown products of LA (OxLAMs).

When you eat, your insulin goes up, mTOR is activated and autophagy is inhibited, thus allowing for cellular rebuilding and growth. Then, when you fast, insulin goes down, mTOR is inhibited and autophagy activated, thus allowing for the breakdown and elimination of dysfunctional cellular components. The next time you eat, the cycle of rebuilding begins anew, and so on.

When you're continuously eating, autophagy will be severely inhibited. As a result, damage continues to build up as damaged cells cannot be efficiently eliminated and regenerated. Many hormonal shifts also occur during fasting, including growth hormone.

Opinions about how long one should fast each day varies. As a general rule, the recommended range is between 12 and 18 hours of fasting each day. I'm of the opinion that 16 to 18 hours of fasting might be the sweet spot, as this allows your body to deplete the glycogen stores in your liver more and suppress mTOR and activate autophagy better.

Time-Restricted Feeding Improves Brain Function

As noted in "The Effects of Caloric Restriction and Its Mimetics in Alzheimer's Disease Through Autophagy Pathways," a number of animal studies have demonstrated that time-restricted eating helps prevent memory loss and improve cognition. The authors state, in part:[10]

> *"[Intermittent fasting] has been reported to optimize brain function and increase neuronal resistance to injury and disease … Behavioral improvements in AD*

mice that undergo IF might occur because of the effects of IF on balancing hippocampal excitability. In addition, IF prevents memory loss in ovariectomized rats infused with amyloid beta in hippocampal regions … short-term fasting (24 or 48 hours) was capable of enhancing neuronal autophagy in 5xFAD mice, which is a severe AD model …"

The Case for Eating Less, Period

Both animal and human studies also suggest people with a low calorie intake overall have a reduced risk for Alzheimer's compared to those eating a high-calorie diet.[11] In one animal study, animals whose diet was 30% lower in calories than normal restored memory performance after 10 months. High-calorie diets were also shown to result in autophagic failure in the hippocampus.[12]

Animal studies have further demonstrated that low-calorie diets reduce the amount of amyloid beta and tau in the brain, while high-calorie diets increase them.[13]

The beautiful characteristic of time-restricted eating is that it appears to replicate most of the metabolic benefits of calorie restriction without actually restricting calories. Additionally, because it is such a restricted eating window and a person's appetite is reduced, they typically wind up eating fewer calories anyway without any feeling of deprivation.

Siim Land does a great job on expanding on the differences between these two as they relate to longevity in the video at the top of the article. Even though the comparison is to longevity, the same pathways are also active in Alzheimer's, such as sirtuins, AMPK and NAD+.

Calorie Restriction Mimetics

"The Effects of Caloric Restriction and Its Mimetics in Alzheimer's Disease Through Autophagy Pathways" also addresses the use of calorie restriction mimetics, compounds that mimic the effects of calorie restriction. The most thoroughly studied

and well-recognized mimetic is resveratrol, a polyphenol found in grape skins and certain berries, including blueberries and cranberries. According to the authors:[14]

> *"Several studies have revealed the potential efficacy of resveratrol supplementation for the prevention and treatment of AD. For example, treatment with resveratrol prevents neurotoxicity in cultured cells exposed to amyloid beta.*
>
> *In addition, in a rodent model of AD, resveratrol alleviated memory deficits, maintained the integrity of the blood-brain-barrier, ameliorated the plaque burden, in habited tau pathology, and suppressed microglial activation …*
>
> *The anti-amyloidogenic and neuroprotective effects of resveratrol in AD appear to be strongly associated with enhanced autophagic activity. Resveratrol activates SIRT1-dependent autophagy, which contributes to an attenuation of the neurotoxicity caused by amyloid beta. Moreover, resveratrol represses mTOR signaling and induces autophagy by activating the AMPK signaling pathway."*

Other Alzheimer's Prevention Guidelines

Aside from time-restricted eating, there are many other strategies that will help prevent (and in some cases, treat) Alzheimer's. Here's a rundown of what I believe are some of the most important:

Avoid trans fat and industrially processed vegetable oils — While diets high in healthy fats and antioxidants can go a long way toward warding off dementia, diets high in trans fats and processed omega-6 oils will promote it.

Research[15] published in the October 2019 issue of Neurology found a strong link between trans fat consumption and incidence of dementia and its various subtypes, including Alzheimer's. The worst dietary culprits were pastries, margarine, candy, caramels, croissants, nondairy creamers, ice cream and rice crackers.[16] Similarly, the

oxidized omega-6 fat found in processed vegetable oils can cause significant harm to your brain when consumed in excess.

Avoid sugar and refined fructose — Ideally, you'll want to keep your sugar levels to a minimum and your total fructose below 25 grams per day, or as low as 15 grams per day if you have insulin resistance or any related disorders.

Increase consumption of healthy fats, including marine-based omega-3 — Beneficial health-promoting fats that your brain needs for optimal function include coconut oil, organic butter from raw milk, ghee, grass fed raw butter, olives, organic virgin olive oil, nuts like pecans and macadamia, free-range eggs, wild Alaskan salmon and avocado.

Also make sure you're getting enough animal-based omega-3 fats from small fatty fish such as anchovies and sardines, or take a phospholipid-based supplement such as krill oil. High intake of the omega-3 fats EPA and DHA help prevent cell damage caused by Alzheimer's disease, thereby slowing down its progression, and lowering your risk of developing the disorder.

Avoid gluten and casein (primarily wheat and pasteurized dairy, but not dairy fat, such as butter) — Research shows your blood-brain barrier is negatively affected by gluten.[17] Gluten also makes your gut more permeable, which allows proteins to get into your bloodstream, where they don't belong. That then sensitizes your immune system and promotes inflammation and autoimmunity, both of which play a role in the development of Alzheimer's.

Optimize your gut flora by regularly eating fermented foods or taking a high potency and high quality probiotic supplement.

Improve your magnesium level — Magnesium threonate appears promising for supporting cognition and may be superior to other forms.

Optimize your vitamin D levels with safe sun exposure — Researchers believe

optimal vitamin D levels may enhance the amount of important chemicals in your brain and protect brain cells by increasing the effectiveness of the glial cells in nursing damaged neurons back to health.

Vitamin D may also exert some of its beneficial effects on Alzheimer's through its anti-inflammatory and immune-boosting properties. Sufficient vitamin D is imperative for proper functioning of your immune system to combat inflammation that is also associated with Alzheimer's.

Avoid and eliminate mercury from your body — Dental amalgam fillings, which are 50% mercury by weight, are one of the major sources of heavy metal toxicity. However, you should be healthy before having them removed. Once you have adjusted to following the diet described in my optimized **nutrition plan**, you can follow the **mercury detox protocol** and then find a biological dentist to have your amalgams removed.

Also avoid flu vaccinations as most contain mercury, aka thimerosal, a well-known neurotoxic and immunotoxic agent.

Avoid and eliminate aluminum from your body — Sources of aluminum include antiperspirants, nonstick cookware and vaccine adjuvants.

Exercise regularly — It's been suggested that exercise can trigger a change in the way the amyloid precursor protein is metabolized,[18] thus slowing down the onset and progression of Alzheimer's. Exercise also increases levels of the protein PGC-1alpha. Research has shown that people with Alzheimer's have less PGC-1alpha in their brains and cells that contain more of the protein produce less of the toxic amyloid protein associated with Alzheimer's.

Avoid anticholinergics and statin drugs — Drugs that block acetylcholine, a nervous system neurotransmitter, have been shown to increase your risk of dementia. These drugs include certain nighttime pain relievers, antihistamines, sleep aids, certain

antidepressants, medications to control incontinence, and certain narcotic pain relievers.

Statin drugs are also problematic as they suppress the synthesis of cholesterol, deplete your brain of coenzyme Q10 and neurotransmitter precursors, and prevent adequate delivery of essential fatty acids and fat-soluble antioxidants to your brain by inhibiting the production of the indispensable carrier biomolecule known as low-density lipoprotein.

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