Inhibiting the GSK-3 Enzyme with Lithium Orotate May Slow Brain Aging and Dementia

Prevention Strategy to Slow Brain Aging and Dementia

One important prevention strategy to combat the issue of brain aging and dementia, especially the development of Alzheimer's disease, is to inhibit and reverse the structural changes and damages that occur in brains cells as part of normal aging.

Researchers have identified a number of these structural changes and defects. The major structural defects include:

- **Beta amyloid accumulation:** These neurotoxic plaques are protein clumps that damage the neuron and impede memory consolidation
- **Neurofibrillary tangles:** Neurons are clogged with neurofibrillary tangles which develop when tau proteins are dysfunctional
- **Tau protein dysfunction:** Neurons eventually die when tau proteins become dysfunctional and accumulate. Tau proteins provide structure to the microtubules of the neuron which creates a cellular skeleton for the neuron

Glycogen Synthase Kinase-3 Enzyme (GSK-3)

Glycogen Synthase Kinase-3 Enzyme (GSK-3) is an enzyme in the body that, when normally activated, is part of the system regulating glucose metabolism.

However, when GSK-3 is overly and excessively activated, it tends to damage cellular structures. Excessively activated GSK-3 can result in the following health issues in the body: 1 2 3

- **Accelerates aging in heart and muscle**

- **Accelerates aging in the skeletal system**
- **Accelerates aging in the stomach and liver**
- **Develops type II diabetes**
- **Develops Alzheimer's disease [4]**
- **Impairs autophagy which clears toxic debris inside cells**
- **Increases pro-inflammatory cytokines**

Glycogen Synthase Kinase-3 Enzyme (GSK-3) Contributes to Alzheimer's disease

The structural changes and defects that occur in the aging brain which develops into dementia and eventually Alzheimer's disease include accumulation of beta amyloid plaque and damaged tau proteins. Both of these results in neurofibrillary tangles which lead to neuron death.

Increased or aberrant over-expressive activity of the GSK-3 enzyme is a contributing factor in these structural changes.

Excessive GSK-3 damages (through the process of the hyperphosphorylation of tau proteins) tau proteins and is thought to directly promote amyloid beta production which leads to neurofibrillary tangles. [5]

As mentioned, GSK-3 normally regulates glucose/insulin metabolism. However, excessive GSK-3 may increase the development of Type II diabetes with glucose impairment and insulin resistance. It is clear that Type II diabetes increases accumulations of beta amyloid and damaged tau proteins. [6]

Because of this correlation, Alzheimer's disease is often called Type III diabetes.

This conclusion lead to the Alzheimer's strategy of inhibiting GSK-3 as a means to effectively lower blood glucose, while increasing insulin sensitivity. [7]

GSK-3 Inhibitors

Targeted inhibition of GSK-3 may have therapeutic effects with regards to mild cognitive impairment and dementia (including Alzheimer's disease). The identified GSK-3 inhibitors are of diverse chemotypes and mechanisms of action, which include inhibitors isolated from natural sources, cations (minerals), and synthetic small molecules.

The cation lithium was the first "natural" GSK-3 inhibitor discovered in 1996. [8]

Lithium

Lithium is a chemical element belonging to the alkali metal group. It is highly reactive and flammable. As a dietary mineral it is classified as a trace element and the available experimental evidence now appears to be sufficient to accept lithium as essential micronutrient. The suggested provisional Recommended Daily Allowance (RDA) for a 70 kg (154 lbs.) adult is 1,000 micrograms (mcg) per day.

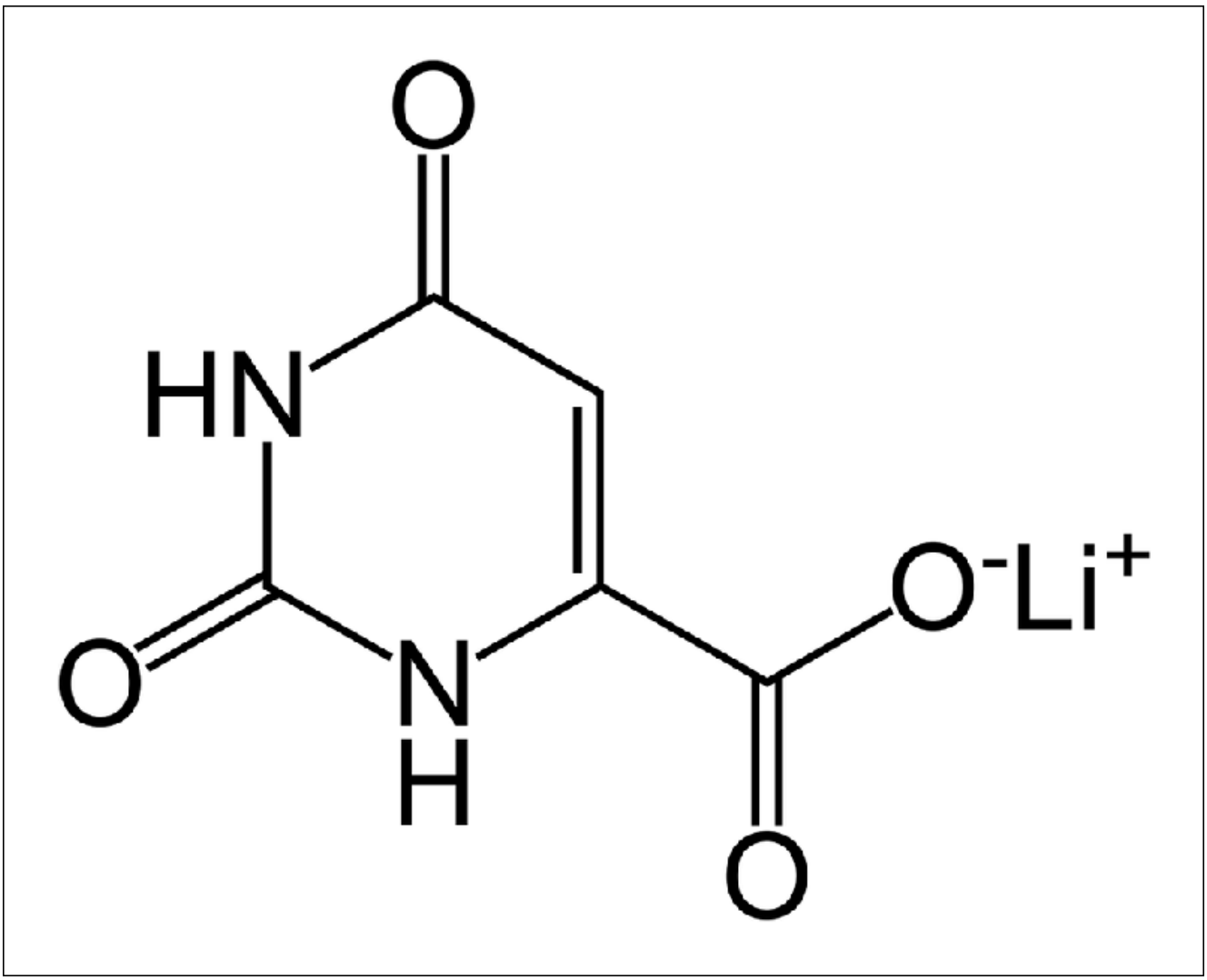

Figure 1: Lithium Orotate

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The lithium content in food varies by the region where the food is grown and varied growing techniques. Plant foods are richer in lithium than animal foods. The foods that have the largest concentration of lithium are the nightshade plants, including:

- **eggplants**
- **peppers**
- **potatoes**
- **tomatoes**

Other foods that contain lithium in trace amounts include:

- **apples**
- **bananas**

- **cabbage**
- **carrots**
- **cauliflower**
- **cinnamon**
- **cucumbers**
- **eggs**
- **lemons**
- **lentils**
- **milk**
- **mushrooms**
- **seafood**
- **seaweed**
- **seeds**
- **sugar cane**

Tap water (at least in the United States) is virtually devoid of any lithium, unless it is intentionally treated with lithium. Spring water, on the other hand, may contain trace amounts of lithium.

Because it may difficult to obtain the RDA of lithium daily from diet and water, the alternative is to supplement with a micro-dose lithium supplement (See Resources).

A study published in 2013 demonstrated that a microdose lithium amount of 300 mcg per day for 15 months stabilized cognitive impairment in patients with Alzheimer's disease. [9] The patients of the study showed no further cognitive decline during the study period while they supplemented with the microdose lithium.

The researchers concluded that the microdose lithium inhibited the phosphorylation of GSK-3. [10]

Lithium as GSK-3 Inhibitor

Lithium, which is a medication (as Lithium Carbonate) used for bipolar disorder, is a direct and indirect inhibitor of GSK-3.

The mechanism by which lithium inhibits GSK-3 is that lithium: [12]

- **Is a competitive inhibitor of GSK-3 with respect to magnesium**
- **Indirectly inhibits GSK-3 via enhanced serine phosphorylation and autoregulation**
- **Inhibits potassium deprivation**

In vitro, lithium has been shown to suppress tau phosphorylation, enhance tau–microtubule binding, and promote microtubule assembly. In vivo, lithium has been shown to reduce insoluble tau and ameliorate axonal transport deficiencies in transgenic Drosophila. [13]

Further studies have shown that lithium chloride significantly decreases amyloid-beta production in vivo through inhibition of GSK-3 activity. [14]

The form of lithium used in these studies is lithium chloride, which is only available by prescription. However, microdoses of a form of lithium that is not used in psychiatry has been shown to inhibit GSK-3. [15]

A study from 2015 examined a mouse model of Alzheimer's disease where the researchers supplied mice with microdoses of lithium carbonate in their drinking water. The mice that were treated with lithium retained the memory and cognitive performance of normal mice. [16] They also showed that the mice showed a decrease in amyloid-beta plaques in their brains.

Additional studies on lithium treatment for dementia demonstrates that lithium can:

- **block amyloid precursor protein (APP) deposits [17]**
- **reduce amyloid-beta secretion in cells and transgenic mice overexpressing APP [18]**
- **reduce tauopathy in transgenic mice overexpressing human mutant tau [19]**

Resources:

Lithium Orotate

Lithium Aspartate