Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

L-Serine

Evidence Summary

Evidence for benefits of L-serine on brain health and age-related conditions is weak. As a naturally-occurring amino acid it is likely safe, though studies suggest it may fuel cancer cell proliferation.

Neuroprotective Benefit: L-serine is required for synthesis of sphingolipids and preclinical studies suggest it may inhibit neuroinflammation; however, brain levels of L-serine in humans do not appear to be associated with dementia or cognitive dysfunction.

Aging and related health concerns: The Ogimi village known for longevity has high L-serine content in their diet, though there are other features to their diet that may contribute to longevity. Several human cancers rely on serine for proliferation.

Safety: L-serine is a naturally-occurring amino acid and is likely safe in moderation; studies in clinical populations have suggested it is generally well-tolerated, though some gastrointestinal side effects have been reported.

What is it? L-serine is an amino acid synthesized from other amino acids such as glycine or threonine and is involved in the biosynthesis of purines, pyrimidines, and other amino acids (PubChem; DrugBank). Serine is necessary for the production of sphingolipids via the synthesis of sphingosine, and serine is a head-group for phospholipids such as phosphatidylserine, which is a component of the cell membrane of neurons [1]. Although it is classified as a nutritionally non-essential amino acid because it can be produced in the body (e.g., by astrocytes in the brain), an external supply (from diet) is essential in maintaining necessary levels. L-serine has been used as a natural moisturizing agent in some cosmetics and skin care products. In the clinic, it is being tested in patients with Alzheimer's (NCT03062449), ALS, and hereditary sensory autonomic neuropathy type 1 (NCT01733407).

Neuroprotective Benefit: L-serine is required for synthesis of sphingolipids and preclinical studies suggest it may inhibit neuroinflammation; however, brain levels of L-serine in humans do not appear to be associated with dementia or cognitive dysfunction.

Types of evidence:

- 1 phase 1 study in ALS patients examining the effects of L-serine treatment on blood and CSF levels
- 4 observational studies of L-serine levels in CSF and/or blood
- 1 review on Okinawan diet and L-serine content
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?: Unavailable.

Human research to suggest benefits to patients with dementia: Unavailable. There is a phase II clinical trial underway that is testing the effects of L-serine in early-stage Alzheimer's disease (NCT03062449).

There have been several studies examining cerebral spinal fluid (CSF) and serum levels of L-serine in people with Alzheimer's, but no clear differences with controls have been found, nor correlations with cognitive functions. A study in 2016 showed that L-serine levels in CSF were not significantly different between Alzheimer's patients, people with other dementias, and elderly controls; they also found no correlations between CSF L-serine levels and cognitive functions as measured by MMSE scores [2]. An older study actually reported slightly higher serum levels of L-serine in Alzheimer's patients compared to controls, though this difference was not statistically significant (p=0.083) [3]. This study also failed to

demonstrate a correlation between MMSE scores with serum L-serine (or D-serine) levels. Postmortem studies have also shown that L-serine (and D-serine) concentrations in the brain were comparable between Alzheimer's disease patients and normal controls [4; 5]. Means ± standard errors of mean (SEMs) for L-serine concentrations of postmortem wet tissue were 666 ± 222 nmol/g for control brains and 750 ± 150 nmol/g for Alzheimer's patient brains [5].

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
L-serine crosses the blood-brain-barrier. A phase I study in 20 ALS patients reported that increasing L-serine doses (from 0.5 to 15.0 g, twice daily) resulted in increasing concentrations of L-serine in the CSF (and blood) [6]. Transport of L-serine across the blood-brain-barrier occurs via the sodium-dependent system A and the sodium-independent alanine, serine, and cysteine preferring system [7; 8].

L-serine is essential for the synthesis of sphingolipids and phosphatidylserine in some types of neurons [1]. L-serine is also essential for these neurons to undergo neuritogenesis. A biochemical analysis has shown that L-serine is synthesized from glucose and released by astrocytes but not by neurons, which is the major reason why this amino acid is an essential amino acid for neurons. Biosynthesis of membrane lipids, such as sphingolipids, phosphatidylserine, and phosphatidylethanolamine, in neurons is completely dependent on the contribution of astrocytes. Synthesis of endogenous L-serine and neuronal sphingolipids is essential for brain development.

Another way in which L-serine may affect brain function is via D-serine. L-serine can be converted to D-serine by the serine racemase enzyme [9] and D-serine acts as a co-agonist of glutamate NMDA receptors, which mediate synaptic plasticity, synaptogenesis, excitotoxicity, memory acquisition, and learning [10]. For more details, see the D-serine report from August 2017.

Vervets fed an environmental neurotoxin in their diet (BMAA-dosed fruit) for 140 days developed neurofibrillary tangles and β-amyloid deposits in the brain [11]. However, co-administration of L-serine with BMAA significantly reduced the density of neurofibrillary tangles. BMAA can be mistaken by cellular machinery for L-serine and be misincorporated into proteins, leading to protein misfolding, aggregation, and apoptosis [12]. BMAA exposure results in hyperphosphorylated tau, possibly by decreasing activity of protein phosphatase 2A through activation of the glutamate mGluR5 receptor [13]. In human neuronal cell culture, L-serine prevents misincorporation of BMAA as well as apoptosis [12]. It is unclear how L-serine affects neurofibrillary tangles or Aβ in Alzheimer's or dementias in the absence of such neurotoxins.

In a mouse model of traumatic brain injury (TBI), L-serine treatment (114, 342, or 1027 mg/kg, 3 hours after TBI and then twice daily, i.p.) led to neuroprotection of brain tissue through reducing inflammatory responses and improvement in recovery of neurological functions [14]. The treatment decreased the neurological deficit score, brain water content, lesion volume, and neuronal loss, while inhibiting caspase-3, reducing the levels of inflammatory markers (TNF-α, IL-1β and IL-6), and the numbers of activated astrocytes and microglia. L-serine induced the activation of glycine receptors, which alleviated neuronal excitotoxicity post-brain injury.

APOE4 interactions: It is unknown whether APOE4 carriers would respond to L-serine differently from non-carriers. A cell culture study has shown that neuronal activity increases L-serine release from astrocytes, which in turn enhances ApoE release from microglial cells [15]. It is unknown whether or how APOE genotypes affect this neuron-astrocyte-microglia network.

Aging and related health concerns: The Ogimi village known for longevity has high L-serine content in their diet, though there are other features to their diet that may contribute to longevity. Several human cancers rely on serine for proliferation.

Types of evidence:

- 1 analysis of L-serine content in Ogimi (Okinawa) diet
- Several laboratory studies

Lifespan: INCONCLUSIVE. Ogimi village within Okinawa has been called the "longevity village" because of its high number of centenarians. Ogimi diet is remarkably rich in amino acids including L-serine, with food items having a mean L-serine content of 542 mg/100g. L-serine content of the Ogimi diet in women over 70 years old (>8 g/day) was more than 3-fold higher than that of an average American dietary intake for women over 70 years old (2.5 g/day) [16]. The top 5 serine-rich foods in the Ogimi diet are tofu, pork, edamame, fuchiba (Japanese mugwort), and wakame (seaweed). While this study points out the high L-serine content in Ogimi diet, because it is observational in nature, it does not prove that it is responsible for the longer average lifespan. There are other features to the Ogimi diet that might contribute, such as high antioxidant levels, low calories, low glycemic index, and high levels of marine algae [17]. In fact, there are 13 species of marine algae in the top 25 most frequently consumed food items in Ogimi.

In a study in *C. elegans*, 18 out of 20 amino acids (all except phenylalanine and aspartate) extended lifespan, with serine and proline showing the largest effects [18]. Lifespan extension appeared to be related to altered mitochondrial tricarboxylic acid (TCA) cycle metabolism and respiratory substrate utilization resulting in the activation of the DAF-16/FOXO and SKN-1/Nrf2 stress response pathways. Amino acid-mediated lifespan extension was AAK-2/AMPK-dependent. Serine and histidine also stimulated transcriptional activity of the hypoxia-inducible factor-1 (HIF-1). In addition, serine and tryptophan partially blocked the high glucose-mediated reduction of lifespan. Although the results appear to suggest that select amino acids may be beneficial for lifespan extension, *C. elegans* worms were grown in a liquid medium including heat-killed *E. coli* with no added amino acids (unlike standard nematode growth media which contain amino acids). The only sources of amino acids were the dead bacteria and the individually supplemented amino acid. Thus it is not surprising that supplementation of the majority of amino acids prolonged lifespan. It is not possible to extrapolate findings from this study to impacts of amino acid supplementation in humans.

Cancer: INCONCLUSIVE/POTENTIAL HARM. Several human cancer types such as breast and colorectal cancers rely on serine for cell proliferation and survival [19; 20; 21]. It is proposed that serine is utilized to increase *de novo* nucleotide synthesis in highly proliferative cells. Indeed, analysis across hundreds of human cancer samples spanning 4 major cancer types confirmed that nucleotide synthesis pathways were universally upregulated in all cancer types compared to corresponding healthy tissues [19]. Serine is also used for the production of NADPH; regulation of redox status by serine may be critical to cell proliferation.

In a rodent model of breast cancer, protein levels of phosphoglycerate dehydrogenase, an enzyme that catalyzes the first step in the serine biosynthesis pathway, are significantly elevated [22]. Accordingly, suppression of this enzyme in cancer cell lines decreased cell proliferation.

In mice, manipulation of diet to limit serine levels can inhibit tumor growth without impairing health [23]. However, it is currently unknown how L-serine intake (dietary or supplementation) impacts cancer risk or progression in humans.

Safety: L-serine is a naturally-occurring amino acid and is likely safe in moderation; studies in clinical populations have suggested it is generally well-tolerated, though some gastrointestinal side effects have been reported.

Types of evidence:

- 2 clinical trials
- A few preclinical studies

No clinical studies have tested the safety of L-serine supplementation in healthy adults. In a phase 1 safety trial in 20 ALS patients, L-serine treatment (0.5-15.0 g, twice daily) for 6 months was generally well-tolerated and appeared to be safe [6; 24]. Two patients withdrew from the trial due to gastrointestinal side effects (1 patient due to bloating after receiving 15 g twice daily for 4 months; the other patient due to nausea and loss of appetite after receiving 7.5 g twice daily for 1 month). No other adverse events were noted in the remaining study participants. No changes were observed in routine blood tests, including blood, urea, and creatine levels. Three patients died during the study, but the deaths were due to progression of ALS and not the study drug. L-serine in doses up to 15 g twice daily appeared to be safe in patients with ALS. Exploratory analysis of efficacy suggested that L-serine might slow disease progression, though this needs to be confirmed in a phase II trial, which is being planned. The other pilot clinical study in 14 patients with hereditary sensory autonomic neuropathy type 1 testing L-serine treatment (200 or 400 mg/kg/day) for 10 weeks did not discuss any adverse events [25]. Although the study was not designed to assess neurological outcome, some patients reported a subjective increase in sensation (e.g., a tingling feeling in the hands). Another subject described great improvement in skin robustness and in nail and hair growth, which is a good sign since this disease is often accompanied by very delicate skin and ulcerations.

In the same paper, they examined a mouse model of hereditary sensory autonomic neuropathy type 1 and found that a 10% L-serine-enriched diet reduces neurotoxic sphingolipids while improving motor and sensory performance as well as measures of male fertility [25]. In contrast, a 10% alanine-enriched diet increased neurotoxic sphingolipids and led to severe peripheral neuropathy.

Drug interactions: No information on L-serine is provided on drugs.com or WebMD.com.

Treato.com does not have a numeric rating for L-serine, but of the few reviews, 11 were positive and 8 were negative as of October 2017. Of a total of 533 posts about L-serine, 89 different concerns were raised including tiredness (11), anxiety (9), fatigue (9), exhaustion (8), and neurotoxicity (8).

Sources and dosing: L-serine is a naturally-occurring dietary amino acid. It is abundant in soy products, sweet potatoes, eggs, meat, and some edible seaweed. L-serine is considered as GRAS and is widely sold as a dietary supplement in capsule and powder forms. Neither Labdoor nor ConsumerLab have analyzed or ranked L-serine supplements. The dose used in an ongoing Alzheimer's trial is 15 grams, twice daily, in the form of gummies (NCT03062449). The gummies are produced in a GMP compliant facility in Knechtel, Chicago, IL, and each contains 1 g of L-serine, packaged in a foil packet containing 15 pieces.
Research underway: A randomized double-blind placebo-controlled phase II study testing the effects of L-serine in early-stage Alzheimer's disease is currently underway at the Dartmouth Hitchcock Medical Center (NCT03062449). The study involves treatment with L-serine (15 g, twice daily, in gummy form) for 9 months. The trial is currently recruiting participants and is scheduled to be completed in July 2018. A randomized double-blind placebo-controlled study testing the efficacy of L-serine in people with hereditary sensory neuropathy type 1 was recently completed (May 2017; NCT01733407), but the results have not been published yet. This disease is caused by mutations in the SPTLC1 gene encoding the enzyme serine palmitoyltransferase, which catalyzes the reaction of palmitoyl-CoA with serine to form sphinganine. Mutations in this gene result in reduced affinity for L-serine, leading to reactions of palmitoyl-CoA with alanine and glycine, which form neurotoxic sphingolipids. The rationale for this trial is to supplement L-serine so that the enzyme can correctly catalyze the reaction of palmitoyl-CoA with serine.

Search terms:
Pubmed, Google:

- + cognitive, + ApoE, + clinical trial, + meta-analysis, + lifespan, + diabetes, + neuropathy, + cardiovascular, + inflammation, + cancer, + atherosclerosis

Websites visited for L-serine:

- Clinicaltrials.gov
- Examine.com (0)
- Treato.com
- DrugAge (1)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Labdoor.com (0)

- ConsumerLab.com (0)

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