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.

Polyamine

Evidence Summary

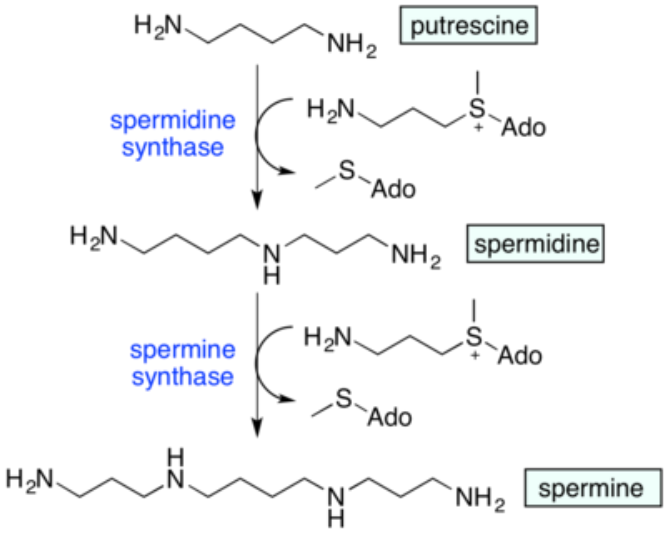
Polyamines are involved with health and disease, and increased intake might either help or harm. Spermidine has the most potential for anti-aging benefits.

Neuroprotective Benefit: Evidence for potential harm or benefit based on preclinical studies.

Aging and related health concerns: Poses potential increased cancer risk, but may have anti-aging and cardiovascular protective properties.

Safety: While dietary intake is safe, high-dose supplements have not been studied and are not available to average consumers. There are possible risks for promoting cancer progression.

What is it? Polyamines are small, positively-charged molecules that include spermine, spermidine, and putrescine. A 4th polyamine, agmatine, is synthesized by plants and some bacteria and can be metabolized into putrescine. Agmatine may function as a neurotransmitter in mammals but its physiological relevance in mammals is uncertain (Pegg 2010). The amino acid, arginine, can be used to synthesize putrescine.



Source: Wikipedia

Polyamines are highly conserved molecules that are integral to life. Polyamines can stabilize DNA conformation, protect DNA from various stressors, and help neuronal axons to regenerate after injury (Ramani 2014). Spermine can help to resolve inflammation while putrescine modulates immune T-cell activity. Polyamines can stabilize cellular membranes and play a role in many cellular functions like gene transcription, RNA translation, the formation of cell junctions, and apoptosis (Ramani 2014). The polyamine putrescine may help to control depression and anxiety (Fiori 2008) and depletion of putrescine by DFMO, a drug that depletes polyamines, caused anxiety-like behavior and memory impairment in rats (Gupta 2009) (see DFMO report).

Within the body, polyamines can come from internal synthesis, synthesis by the gut microbiome, or from dietary intake.

Neuroprotective Benefit: Evidence for potential harm or benefit based on preclinical studies.

Types of evidence:

- autopsy studies provide weak theoretical support for aging but not Alzheimer's disease
- extensive preclinical mouse studies on DFMO treatment to deplete polyamines
- Fruit fly studies suggesting benefit of spermidine supplementation

No information is available from clinical studies, either observational or randomized, regarding polyamine intake from supplements or an enriched diet.

Some studies indicate that Alzheimer's patients may have higher polyamine levels, suggesting that supplementation is unlikely to be beneficial in this population. Levels of polyamines were found to be high in the brain of Alzheimer's disease patients (Inoue 2013). Furthermore, putrescine, spermidine, and spermine levels in plasma were also found to be higher in mild cognitive impairment (MCI) patients who went on to develop Alzheimer's disease (Graham 2015).

It is not clear how polyamine levels are affected in the course of healthy aging, since results across studies have been inconsistent, possibly because the studies looked at different brain areas. In one study, putrescine and spermine levels in occipital cortex were unaffected by age while spermidine levels peaked at age 40 but then remained constant through old-age (Morrison 1995). Another study reported an age-dependent reduction in spermidine and spermine levels in the basal ganglia (Vivo 2001).

On the mechanistic side, polyamines could theoretically either harm or benefit at different stages of disease and aging. During health, polyamines play important roles in memory, synaptic function, DNA conformation, autophagy, and other pathways. Following injury, polyamine metabolism is induced via upregulation of the ornithine decarboxylase (ODC), which in turn can reduce arginine levels and has been speculated to cause immune suppression and Alzheimer's disease pathogenesis (Kan 2015).

- Harm: polyamines modulate NMDA receptor function in a manner regulated by beta-amyloid. Their depletion via DFMO was reported to protect against beta-amyloid toxicity in hippocampal primary cell culture (Gomes 2014).

- Harm: In animal models of traumatic brain injury or radiation, polyamine depletion via DFMO (an inhibitor of ODC) can protect against inflammatory responses. It may also protect against cognitive impairment, but the mechanism of action is unclear. Effects are seen on neurogenesis and activated microglia but these did not correlate with the effect seen on cognition (Allen 2014, Rosi 2012).

- Benefit: In fruit flies, aging brought both declining levels of polyamines and impaired cognition. Spermidine supplementation protected against age-related cognitive impairment, arguably through increased autophagy (Gupta 2013) and a shift in synaptic plasticity as monitored by the number of synaptic vesicles released (Gupta 2016).

Overall, polyamine regulation is likely involved with brain health and disease. However, high levels do not always seem to promote health and the complexities in the system have not been resolved. It also

remains unclear whether supplementation or enriched diets could effectively raise polyamine levels in the brain, given that the levels are tightly regulated by local synthesis and metabolism.

APOE4 interactions: No available evidence to-date

Aging and related health concerns: Poses potential increased cancer risk, but may have anti-aging and cardiovascular protective properties.

Types of evidence:

- 2 observational studies on age-related diseases, with either harm or benefit
- 1 observational study on natural levels in long-lived adults
- 1 mouse study and additional invertebrate studies on lifespan
- Indirect evidence for harm – polyamine depletion drugs under investigation for cancer

Evidence from humans is mixed and very limited, coming only from 2 studies on foods that contain many nutrients beyond polyamines. Above average dietary intake of polyamines was associated with a higher risk of colorectal adenoma in some high-risk patients (adjusted Odds ratio (OR): 1.39, 95% CI 1.06 to 1.83). The associations were strongest in younger participants, women, and those with the ODC GG genotype) (Vargas 2012). This study did not report on the association with individual polyamines but about 72% of the polyamine intake was from putrescine.

Meanwhile, high dietary intake of spermidine and/or spermine (but not putrescine) was reported to associate with a lower incidence of cardiovascular disease (CVD) (adjusted Hazard ratio (aHR) for incident CVD was 0.80, 95% CI 0.67 to 0.95). For death due to heart failure, the adjusted HR failed to reach significance but the trend was strong and reached significance for men (e.g. aHR for men was 0.42, 95% CI 0.42 to 0.68) (Eisenberg 2016). Within the body, polyamine levels have been reported to decline with age but the amount of spermine relative to other polyamines may be higher in long-lived adults (Pucciarelli 2012).

Spermidine specifically has been reported to have anti-aging properties, although the specificity is surprising given that it is synthesized from putrescine and metabolized into spermine. Only one study has looked at lifespan in mammals – it reported in mice that oral spermidine extended lifespan by roughly 10% without affecting body weight or composition (Eisenberg 2016). A beneficial effect was also seen with spermine but not putrescine. The effect extended into cardiac aging, with improved diastolic

function, reduced cardiac hypertrophy, and a modest reduction of age-related effects such as cardiomyocyte composition. The authors propose a mechanistic model whereby spermidine increases cardiac and renal autophagy and mitophagy, suppresses TNFα, and increases arginine bioavailability, thereby improving NO production and bioavailability (Eisenberg 2016). They had earlier reported that spermidine could promote longevity in invertebrates and cultured human cells, specifically via epigenetic deacetylation leading to increased autophagy and suppressed necrosis (Eisenberg 2009). In a mouse model of atherosclerosis, oral spermidine treatment (5 mM in water) reduced necrotic core formation and lipid accumulation but had no effect on plaque size and cellular composition (Michiels 2016). Other studies also argue that spermidine may have anti-aging properties (reviewed in Ingrams & Roth 2015, Minois 2011, & Minois 2014).

In one study, treatment with arginine and a probiotic extended lifespan and reduced liver senescence in mice (Kibe 2014). It's not clear whether polyamines mediated this effect. The authors report that arginine treatment increased spermine and spermidine in the blood and increased putrescine in the gut but they do not report how dual treatment with arginine and the probiotic, which led to a stronger benefit, altered polyamine levels.

Despite the potential for anti-aging properties, high polyamine intake may potentially pose risk to people with cancer or specific diseases. Polyamines are enriched in cancerous tissue and their depletion via DFMO or other drugs continues to be investigated for cancer prevention and treatment (e.g. Kreul 2012, Jeter 2012, Goyal 2013). Epithelial cell tumors like colon cancer and skin cancer are known to have high polyamine levels (Ramani 2014) and the strongest clinical evidence for DFMO is in trials on those conditions. As mentioned above, high polyamine intake has been associated with increased risk of colorectal adenoma (Vargas 2012).

A user on Longecity reported reduced knee pain with 30 mg mixed in grapefruit juice, with two days of use. However, no further reports on knee pain by that user or others were reported over the following 3 years of the forum discussion, significantly calling into question the relevance of this ad-hoc claim.

Safety: While dietary intake is safe, high-dose supplements have not been studied and are not available to average consumers. There are possible risks for promoting cancer progression.

Types of evidence:

- Prevalence in common foods
- 2 observational studies of high-intake diets
- preclinical studies

Polyamines are a natural component of many foods. However, supplements are not available, possibly because of the unpleasant odor of concentrated sources. As described above, the human data for diets that contain high levels of polyamines are limited and mixed. One study reported a higher risk for colorectal adenoma while another study reported lower risk of cardiovascular disease, particularly with spermidine or spermine. These results match the predictions of basic research, which has suggested that polyamines and specifically spermidine may promote long-term health but foster cancer progression once the disease has initiated (see aging section). Chronic elevation of polyamine levels in the brain has been proposed to contribute to major depressive disorder (Limon 2016).

Dosing and Sources:

Levels of polyamines are influenced by dietary intake, gut microbiome, and local synthesis. One study in rats suggested that body tissue can retain around 10% of dietary putrescine, 40% of dietary spermidine, and 8% of dietary spermine (Ramani 2014, Linsalata 2014).

Polyamine supplements are not commercially available, possibly because of the expected unpleasant odors. Nevertheless, a diet enriched with specific polyamines is achievable through whole foods. Corn and green pea soup are rich with spermidine; select legumes and meats are rich with spermine; corn, grapefruit and oranges are rich with putrescene. Of the polyamines, spermidine may have the best properties for long-term health (see aging section) although it is not clear why spermidine rather than the related polyamines would have such effects.

Agmatine supplements, although commercially available, are not a reliable method to increase polyamine levels. Agmatine treatment may instead decrease spermidine and spermine levels via activity on related enzymes, SSAT & ODC (Ramani 2014).

Probiotics and prebiotics that alter the gut microbiome may affect polyamine synthesis. For example, it may be inhibited by Lactobacillus rhamnosus GG (Orlando 2016). On the other hand, spermidine levels

were increased in healthy adults by a yogurt that contained Bifidobacterium lactis LKM512 (Matsumoto 2004). "The LKM512 yogurt used was fermented with B. animalis subsp. lactis LKM512, L. delbrueckii subsp. bulgaricus LKM1759, and S. thermophilus LKM1742. The numbers of B. animalis subsp. lactis LKM512 and the two lactic acid bacteria were 5.2 × 107 and 4.7 × 108 CFU/g, respectively. The placebo consisted of yogurt fermented by both lactic acid bacterial strain LKM1759 and LKM1742. The amount of ingested LKM512 yogurt or placebo was 100 g/day/individual." (Matsumoto 2009).

The same scientists have reported in mice that the probiotic yogurt combined with arginine led to increased lifespan, reduced colonic senescence and inflammation, and protected from cognitive decline with age (Kibe 2014, Matsumoto 2011). The yogurt is not commercially available in the United States but probiotic pills and yogurts with Bifidobacterium lactis are available.

Future research: More research would be valuable on the effects of polyamines either in mammalian models or in observational human studies. Similarly, the probiotic approach has limited data available to-date.

Search terms:

Pubmed:

- polyamines or each name (putrescine or spermidine or spermine) with aging, lifespan, cognitive, Alzheimer's, apolipoprotein e.
- arginine, Alzheimer
- polyamine, pharmacokinetic