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.

Epithalamin/Epithalon

Evidence Summary

No human studies regarding effects on cognition or neuroprotection; however, some clinical evidence suggests it may decrease human mortality. Limited evidence suggests epithalamin is likely safe for long-term use.

Neuroprotective Benefit: Have not been tested in humans for prevention of cognitive decline, but preclinical studies suggest they may have anti-oxidant activity in the brain and increase melatonin levels.

Aging and related health concerns: Several Russian clinical trials suggest epithalamin may decrease mortality in older adults with cardiovascular disease, but these results have not been independently confirmed. Both epithalamin and epithalon may increase lifespan in flies, mice and rats.

Safety: Two 3-year epithalamin treatment trials (one with a 12-year follow-up) reported no severe adverse events in older adults and preclinical studies support a favorable safety profile, but a well-conducted Phase1 safety study and independent validation is needed to confirm safety.

What is it? Epithalamin (sometimes spelled "epithalamine") is a crude polypeptide extract of bovine pineal glands while epithalon (also spelled "epitalon") is a tetrapeptide isolate (Ala-Glu-Asp-Gly) from epithalamin that can also be made synthetically.

Because epithalamin contains a mixture of polypeptides it is difficult to determine which effects are due solely to epithalon. This also means that the contents likely vary between preparations of epithalamin extracts. Similarly, impurities in the synthetic preparation of epithalon may explain some observed discrepancies between *in vitro* and *in vivo* results (discussed below).

It is critical to note that every preclinical and clinical study discussed here has been conducted by Dr. Khavinson's group in Russia with no independent confirmation of their results. It should also be noted that at least half of the approximately 110 published articles on epithalamin and epithalon are in Russian and are not available in English translations, and thus were not included in this analysis

Neuroprotective Benefit: Have not been tested in humans for prevention of cognitive decline, but preclinical studies suggest they may have anti-oxidant activity in the brain and increase melatonin levels.

Types of evidence:

- 1 clinical trial
- Several preclinical studies

There is no evidence from preclinical animal or clinical human studies to suggest that either epithalamin or epithalon is neuroprotective. Neither substance has ever been tested in humans or animals for dementia prevention or treatment. However, several proposed mechanisms of action have bearing on brain health.

Epithalamin stimulates melatonin production in elderly adults with pineal gland dysfunction (Korkushko et al, 2004) as well as old rats (Anisimov et al, 1992). There is conflicting preclinical evidence as to whether the synthetic epithalon has similar actions. Epithalon failed to stimulate melatonin production in rats (Djeridane et al, 2003) but was reported to increase melatonin levels in older primates (Khavinson et al, 2001: abstract only, paper not available). The reasons for this discrepancy are not clear, but may be due to contaminants in the synthetic tetra-peptide preparation or differences in the test animals.

Epithalon may have several mechanisms of action distinct from possibly stimulating melatonin production. Lower levels of DNA damage were observed in senescence-accelerated mice (SAMP-1) treated with epithalon, an effect not observed with melatonin treatment (Rosenfeld et al, 2002). This may be attributable to eptihalon's antioxidant capacity. Several studies suggest that it may cross the blood-brain barrier, where it may stimulate cortical neurons (Sibarov et al, 2007) and increase levels of phosphor-CREB (Khavinson et al, 2012), a DNA-binding protein important in learning and memory. However, none of the available reports directly measured epithalon levels in the brain after administration.

Both epithalamin and epithalon show antioxidant activity and may improve organismal (flies and rats) antioxidant defense systems (Anisimov et al, 1997; Khavinson et al, 2000a; Kozina et al, 2007).

APOE4 interactions: There is no evidence to suggest that either epithalamin or epithalon affects *APOE4* carriers differently than non-carriers.

Aging, mortality and related health concerns: Several Russian clinical trials suggest epithalamin t may decrease mortality in older adults with cardiovascular disease, but these results have not been independently confirmed. Both epithalamin and epithalon may increase lifespan in flies, mice and rats.

Types of evidence:

- Two clinical trials (one of which the paper is not available)
- Several preclinical *in vitro* and *in vivo* studies

One clinical trial treated 266 elderly adults with epithalamin (unknown dose/scheduling) for 2-3 years and observed them for the subsequent 4-5 years. The abstract states that treatment "normalize[d] the basic functions of the human organism, i.e. to improve[d] the indices of cardiovascular, endocrine, immune and nervous systems, homeostasis and metabolism." Unfortunately, the paper describing this trial is not available in English (Khavinson et al, 2003a).

A second placebo-controlled trial treated 70 older adults (~65 years old) with "accelerated aging" due to cardiovascular disease with epithalamin every 6 months for 3 years and followed them for another 9 years (Korkushko et al, 2006). Treatment consisted of 5 intramuscular injections of 10 mg epithalamin or saline with 3-day intervals. Over 12 years, the treatment group experienced a 28% decreased mortality rate and 2-fold lower rate of cardiovascular disease-specific mortality. A 3-year (15-year total)

follow-up study reported that epithalamin treatment "prevented age-associated impairment of physical endurance, normalized circadian rhythm of melatonin production and carbohydrate and lipid metabolism" (Korkushko et al, 2011). These results have not been validated by an independent trial.

Epithalamin and epithalon reportedly increase lifespan in flies, mice and rats (Anisimov et al, 1992; Anisimov et al, 1997; Anisimov et al, 1998; Khavinson et al, 2000b; Anisimov et al, 2003; Vinogradova et al, 2007; Vinogradova et al, 2008). However, none of these results has been replicated by a lab independent of Dr. Khavinson's group.

Several relevant potential mechanisms of action for epithalon have been described in *in vitro* human cell culture experiments. Epithalon treatment of human fetal fibroblasts increased telomere length (Khavinson et al, 2003b), while treatment of cultured leukocytes resulted in chromatin remodeling events, suggesting possible epigenetic actions (Khavinson et al, 2003c; Lezhava et al, 2006). Treatment of fetal fibroblasts resulted in cell proliferation beyond their Hayflick limit, suggesting epithalon may also have anti-senescence activity (Khavinson et al, 2004). But there are no publications independently replicating these results outside of Dr. Khavinson's group.

Lastly, epithalon may have utility in cancer prevention. Several preclinical studies in rats and cancer-prone mice suggest epithalon treatment decreased tumor formation rates (Anisimov et al, 2002; Kossoy et al, 2006; Vinogradova et al, 2007; Vinogradova et al, 2008).

Safety: Two 3-year epithalamin treatment trials (one with a 12-year follow-up) reported no severe adverse events in older adult, and preclinical studies support a favorable safety profile, but a well-conducted Phase1 safety study and independent validation is needed to confirm safety.

Without data from a well-conducted phase I safety trial or extensive epidemiological data, it is quite difficult to determine the safety of epithalamin or epithalon treatment. Since epithalamin is a crude polypeptide extract from a bovine gland, its overall safety is still questionable and is likely to be highly dependent on the manufacturing process. Similarly, since epithalon is either isolated or made synthetically, any impurities could pose a safety risk.

Dosing and Sources: Clinical studies on epithalon have not been conducted. However, epithalamin is approved in Russia for treatment of menopause-related symptoms, anovulatory infertility and hormone-dependent tumors (Anisimov et al, 1998). It is not approved for any medical uses outside of Russia. Reviewed clinical trials used different dosing, delivery and scheduling. Most rounds of treatment were

followed by a 4-6 month pause in treatment before resuming. Common doses and schedules were intranasal delivery (10-30 mg/day for 20-30 days) and intramuscular injection (5-10 mg/day for 10-20 days). Some animal experiments used subcutaneous injections but there was no available human data on this route of delivery.

Future research: The results discussed here would benefit greatly from independent replication and validation.

PubMed Search terms:

Epithalamin or epithalamine or epitalon or epithalon + following terms with and without filters for "clinical trial", "meta-analysis", and "review"

- Alzheimer's disease
- Neurodegeneration
- Dementia
- Cancer
- Cardiovascular
- Cognition
- Cognitive decline
- Aging
- Longevity
- Lifespan
- Telomere
- Telomerase
- Diabetes
- Lipids
- Cholesterol
- Hypertension
- Blood Pressue
- Toxicology
- Safety

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.