



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.

Small-humanin-like peptides

Evidence Summary

SHLPs are mitochondrially derived peptides that enhance mitochondrial function and cell survival in response to stress. As endogenous peptides, they are likely safe, but safety as a therapeutic is unknown.

Neuroprotective Benefit: SHLP2 and SHLP3 may enhance cell survival by enhancing mitochondrial resistance to stressors, such as amyloid, and reducing mitochondrial-mediated apoptosis.

Aging and related health concerns: SHLPs may preserve mitochondrial function during aging, induce protective exercise-like metabolic adaptations, and improve glycemic control.

Safety: Safety data is lacking, but the endogenous SHLPs are associated with beneficial effects. There is a greater concern toward peptide administration-related reactions than effects from the peptides themselves.

Availability: Research use	Dose: Not established	Peptide sequence: See table below MW: Varied (from approximately 2400 to 4400 g/mol)
Half-life: Not established Estimated <30 minutes	BBB: Not established, penetrance potentially varied	
Clinical trials: None	Observational studies: SHLP2 levels, <350 pg/mL, were associated with prostate cancer risk	

What is it?

Small humanin-like peptides (SHLP) are mitochondrial derived peptides [1]. Six SHLP family members have been identified, thus far, and they range in length from 20 to 38 amino acids. Similar to humanin, the SHLPs stem from small open reading frames in the mitochondrially encoded 16S rRNA (MT-RNR2). SHLP1-6 have distinct and overlapping functions with humanin. In mice, the various SHLPs have been found in the liver, heart, kidney, spleen, muscle, brain, and prostate. SHLP1-6 differ in their expression pattern, and their ability to regulate cell viability and mitochondrial function.

Peptide	Amino Acids	Sequence
SHLP1	24	MCHWAGGASNTGDARGDVFGKQAG
SHLP2	26	MGVKFFTLSTRFFPSVQRAVPLWTNS
SHLP3	38	MLGYNFSSFPCGTISIAPGFNFYRLYFIWVNGLAKVWW
SHLP4	26	MLEVMFLVNRRGKICRVPFTFFNLSL
SHLP5	24	MYCSEVGFCEVAPTEIFNAGLVV
SHLP6	20	MLDQDIPMVQPLLKVRFLND

Neuroprotective Benefit: SHLP2 and SHLP3 may enhance cell survival by enhancing mitochondrial resistance to stressors, such as amyloid, and reducing mitochondrial-mediated apoptosis.

Types of evidence:

- 3 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia: None



Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Cytoprotection: SHLP2 & SHLP3 IMPROVE CELL SURVIVAL (Preclinical)

SHLP2 and SHLP3 have been shown to protect against oxidative stress-mediated mitochondrial dysfunction, and enhance cell survival, in preclinical models [1]. These SHLPs were similar to humanin, by protecting cells against the production of reactive oxygen species (ROS) in the context of serum starvation. SHLP2 and SHLP3 can enhance mitochondrial metabolism as evidenced by their ability to increase oxygen consumption rate and ATP levels. They can also modify mitochondrial function to protect against mitochondria-mediated apoptosis. Although the extracellular signaling pathways engaged by the various SHLPs vary, there is some overlap both with other mitochondrial derived peptides, such as humanin, and with each other. The promotion of cell survival by SHLP2 involves both the ERK and STAT3 pathways, but SHLP3 appears to only engage the ERK pathway.

Amyloid beta mediated toxicity: SHLP2 PROTECTS AGAINST A β IN CELL CULTURE

SHLP2 protected against lactate dehydrogenase leakage and reduced cytotoxicity in response to A β in mouse primary cortical neurons [1]. Although SHLP3 has been shown to be cytoprotective in other cell types, it was not protective against A β mediated toxicity in this assay. SHLP2 was also protective against A β -mediated cellular and mitochondrial toxicity in cultured retinal pigment epithelium cells. Treatment with SHLP2 increased cell viability by 21.95% following exposure to A β 42 [2].

Humanin has been shown to act as a chaperone to inhibit the misfolding and fibrilization of A β . While a similar role for SHLP toward neuronal A β has not yet been established, it appears likely due to the cytoprotective properties mentioned above, as well as its confirmed ability to inhibit the misfolding of other amyloids. Both humanin and SHLP were shown to inhibit the misfolding and seeding of islet amyloid polypeptide (IAPP) by binding misfolded, seeding-capable IAPP species [3].

APOE4 interactions: Unknown



Aging and related health concerns: SHLPs may preserve mitochondrial function during aging, induce protective exercise-like metabolic adaptations, and improve glycemic control.

Types of evidence:

- 1 biomarker study for SHLP2 levels in prostate cancer
- 1 exercise intervention study in men (n=10)
- Several laboratory studies

Aging: SHLP2 LEVELS DECREASE WITH AGE IN MICE

Circulating levels of SHLP2 were found to decrease with age in male and female mice [1]. A similar age-related decline is seen with levels of other mitochondrial derived peptides, such as humanin. Since these peptides are involved in enhancing and maintaining metabolic fitness, their decline may promote aging-related mitochondrial dysfunction.

Type 2 Diabetes: SHLP2 IMPROVES GLUCOSE CONTROL (Preclinical)

SHLP2 regulates insulin sensitivity, both peripherally and centrally, similar to humanin. SHLP2 enhances the ability of insulin to promote glucose uptake by peripheral tissues and decreases the production of glucose by the liver [1]. Intracerebral infusion of SHLP2 influences the hypothalamic response to insulin, suggesting that SHLP2 influences glucose tolerance via the same or very similar mechanism as humanin. SHLP2 may also protect islet cells from islet amyloid polypeptide-related stress, which is implicated in type 2 diabetes. SHLP2 exerts a chaperone-like activity, similar to humanin, that prevents amyloid misfolding and seeding [3].

Furthermore, in a male mouse model of diet-induced obesity, SHLP2 (2.5 mg/kg i.p. 2x/day for 3 days) significantly altered 77 plasma metabolites, with 16 increasing and 61 decreasing [4]. The effects largely overlapped with humanin treatment, with major pathway effects on glutathione metabolism, gamma-glutamyl-amino acid, sphingolipid metabolism, and acylcarnitine metabolism. These studies suggest that SHLP2 may exert metabolic-protective effects.

Exercise mimetic: SHLP6 INDUCED BY EXERCISE

SHLP6 was shown to be an exercise responsive peptide in healthy young men (n=10, age 24.5 ± 3.7 years) [5]. The effect was time dependent, as levels significantly increased with acute high intensity exercise, and then returned to baseline levels during the recovery period. The induction was similar to what was seen for humanin, however, the time course was slightly different. Since the effect did not



involve an increase in transcription, it is thought to involve an increase in the stability/decrease in degradation of the peptides. Although SHLP2 shares some cytoprotective properties with humanin, it was not responsive to acute exercise, suggesting that different SHLPs have different biological effects. It remains to be determined whether administration of SHLP6 could act as an exercise mimetic, by promoting the exercise-associated adaptations to mitochondria function/energy utilization, in the absence of exercise.

Age-related macular degeneration: SHLP2 IMPROVES MITOCHONDRIAL FUNCTION (Preclinical-cell culture)

In the ARPE-19 cell culture model of age-related macular degeneration, MT-RNR2 expression was decreased by 56%, and the levels of all five oxidative phosphorylation complex I-V protein subunits were decreased between 24 and 56% [2]. Treatment with SHLP2 increased levels of the oxidative phosphorylation complex protein subunits (I 350%, II 54%, III 32%, IV 221%, V 38%). SHLP2 also improved cell viability.

Prostate cancer: SHLP2 LEVELS <350 pg/mL ASSOCIATED WITH INCREASED RISK

SHLP2 may serve as a biomarker for prostate cancer, however, the associations between circulating SHLP2 levels and prostate cancer were only significant in white men [6]. SHLP2 levels were significantly lower in white men with prostate cancer compared with white men controls (196 vs. 393-pg/mL, $p < 0.001$). SHLP2 levels were not significantly different between controls and cases for black men, which likely stems from the lower circulating levels of SHLP2 for black men relative to white men, on average (290 vs. 393-pg/mL, $p < 0.001$). However, SHLP2 levels 350-pg/mL was predictive of a lack of prostate cancer with an accuracy of $\geq 95\%$, in both races.

Safety: Safety data is lacking, but the endogenous SHLPs are associated with beneficial effects. There is a greater concern toward peptide administration-related reactions than effects from the peptides themselves.

Types of evidence:

- Several laboratory studies



The safety data for SHLPs is limited to a handful of cell culture and short-term animal model studies [1; 2; 4]. No major safety signals have been noted, but these studies were also not designed to evaluate safety.

As endogenous mitochondrial derived peptides, SHLPs are expected to be relatively safe, and the primary safety concerns stem from the projected methods of administration via injection or infusion.

Drug interactions: Interactions have not been evaluated, but they may interact, possibly in a synergistic manner, with other metabolic regulating therapies.

Sources and dosing:

SHLPs are available for research use from commercial suppliers, but are not yet available for human therapeutic use. Therapeutic dosing has not been established. Since the different SHLPs exert different effects throughout the body in tissue-specific and context specific ways, different SHLPs, or SHLP combinations, may be better suited to different aging-related conditions. In rodent studies, SHLPs were primarily administered via intraperitoneal injection [1; 4].

Research underway:

The biology of SHLPs continues to be studied in preclinical models, but no clinical trials are yet under way.

Search terms: SHLP

Pubmed, Google:

- Alzheimer's disease, neurodegeneration, cardiovascular, diabetes, aging, cancer, exercise, metabolism

References:

1. Cobb LJ, Lee C, Xiao J *et al.* (2016) Naturally occurring mitochondrial-derived peptides are age-dependent regulators of apoptosis, insulin sensitivity, and inflammatory markers. *Aging (Albany NY)* **8**, 796-809. <https://pubmed.ncbi.nlm.nih.gov/27070352>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4925829/>.
2. Nashine S, Cohen P, Nesburn AB *et al.* (2018) Characterizing the protective effects of SHLP2, a mitochondrial-derived peptide, in macular degeneration. *Sci Rep* **8**, 15175-15175. <https://pubmed.ncbi.nlm.nih.gov/30310092>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6182005/>.



3. Okada AK, Teranishi K, Lobo F *et al.* (2017) The Mitochondrial-Derived Peptides, HumaninS14G and Small Humanin-like Peptide 2, Exhibit Chaperone-like Activity. *Sci Rep* **7**, 7802-7802. <https://pubmed.ncbi.nlm.nih.gov/28798389>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5552803/>.
4. Mehta HH, Xiao J, Ramirez R *et al.* (2019) Metabolomic profile of diet-induced obesity mice in response to humanin and small humanin-like peptide 2 treatment. *Metabolomics* **15**, 88-88. <https://pubmed.ncbi.nlm.nih.gov/31172328>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6554247/>.
5. Woodhead JST, D'Souza RF, Hedges CP *et al.* (2020) High-intensity interval exercise increases humanin, a mitochondrial encoded peptide, in the plasma and muscle of men. *Journal of Applied Physiology* **128**, 1346-1354. <https://journals.physiology.org/doi/abs/10.1152/japplphysiol.00032.2020>.
6. Xiao J, Howard L, Wan J *et al.* (2017) Low circulating levels of the mitochondrial-peptide hormone SHLP2: novel biomarker for prostate cancer risk. *Oncotarget* **8**, 94900-94909. <https://pubmed.ncbi.nlm.nih.gov/29212276>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5706922/>.

Disclaimer: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the [Terms & Conditions](#).

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](#).