

Epitalon - A Peptide's Potential in Prolonging Life and Preventing Age-related Diseases

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History

Epitalon, or Epithalon, is a 4-amino acid peptide with the sequence Alanine-Glutamate-Aspartate- Glycine, which was first described as a possible metabolically active compound isolated from bovine pineal gland extract the early 2000's by a group of researchers in St. Petersburg, Russia.¹ This pineal gland extract is sometimes referred to as epithalamin. The effects of epithalamin have been known far longer, dating back as far as 1955.² The pineal gland is located in the brain, known for the secretion of melatonin and the regulation of the day/night cycle in humans and other vertebrates.

Early experiments in the USSR have shown that epithalamin has a life-prolonging effect on old animals. For a long time, it was not clear which constituent of epithalamin was responsible for this phenomenon. Eventually

however, it was discovered that this constituent was epitalon.

Preclinical Studies

Effects on lifespan

Especially interesting is the reported ability of epitalon to increase the length of the telomers, protective DNA sequences at the ends of chromosomes, which prevent the loss of DNA in each replication cycle of the cell. Telomer length is a important factor for biological age, as the breakdown of telomers is observed when individuals age. It was shown in a cell culture of human fibroblast, epitalon was able to increase telomer length by inducing the enzyme telomerase. This observation could be responsible for the observation that epitalon has a life-prolonging effect in many studies.³ Due to the telomere limitations, human cells

have a specific limited of divisions, after which the cells become inactive due to shortened telomers. The addition of epitalon to a culture of human cells helped to increase the maximum divisions possible by 30%. This property of epitalon could potentially help to slow down the aging process in humans or even to revert this process to a certain extent.⁴

A study performed on rats showed that epitalon and epithalamin both also possess antioxidative properties. This was determined by the increased expression of antioxidant enzymes like superoxide dismutase and ceruloplasmin. This increased production of such enzymes may contribute to a deceleration of aging mechanisms in a variety of tissues. Antioxidant effects were also seen in in vitro experiments.⁵

The mean life span of rats

exposed to constant illumination is decreased due to the disruption of the natural circadian rhythm. Epitalon (0.1 µg daily 5 times a week from the age of 4 months) did not change the life span of rats living under conditions of standard day/night regimen, while in rats exposed to constant light it promoted prolongation of the maximum life span. This shows epitalon is involved on the regulation of the day/night cycle. Epitalon exhibited virtually no effect on the development of spontaneous tumors in rats exposed to standard illumination, but significantly inhibited their development in rats exposed to natural light.⁶

Stress induced by unnatural lighting does also influence the hormone levels and reproductive cycle in female rats. Both epitalon and melatonin were effective in mitigating the negative influence of light stress in the reproductive cycle, especially in older animals.⁷ On another study, epitalon was shown to decrease the frequency chromosomal abnormalities and did not alter food consumption, body weight or mean life span of mice. It did however increase the maximum life span in some of the animals.⁸

A prolonged lifespan was also observed in the insect *Drosophila melanogaster*. Already at very low concentrations of epitalon (0.1×10⁻⁶ wt.%) it increased the lifetime of the flies by 11-16%. This indicated that the effect of epitalon is rather due to influencing gene expression in *Drosophila*, rather than due to direct effects of the peptide.⁹ The effect in *drosophila* also may be

related to its antioxidant properties.¹⁰

Genes & Chromosomes

Epitalon seems to be responsible for regulating a variety of genes. In mouse heart cells, epitalon altered the expression of 98 genes. If epitalon and vilon, another small peptide with potentially life-prolonging effects, were administered together, 144 genes were modulated. In some cases, gene expression was increased by over 6-fold.¹¹ Further observations of a direct effect on gene expression were made in other studies.¹² The incidence of chromosomal aberrations in mice was shown to be decreased by up to 30 % of mice treated with epitalon. The mice were monthly subcutaneously injected with epitalon (1 µg/mouse, 5 times a week) or with 0.1 ml physiological saline. Melatonin, on the other hand, had no effect on chromosomal aberrations.¹³

The effect of stabilizing DNA prompted researchers to investigate whether the increased stability of DNA had a positive effect on tumor formation. Mice with a genetically increased risk for cancer were injected with epitalon in a dose of 1 mg subcutaneously 5 times a week to from the 2nd month of life to death. Indeed, the peptide decreased the frequencies of malignant tumors and prolonged the average and maximum lifetimes of mice by 13.9%, respectively. Epitalon also decelerated the development of age-related disturbances in reproductive activity.¹⁴ Further

studies came to similar conclusions.¹⁵⁻¹⁷

Similarly, epitalon can not only stabilize the DNA of mice that have a natural susceptibility to cancer and new mutations, but it did also protect from the DNA altering effects of the common immuno-suppressive drug cyclophosphamide.¹⁸ This DNA stabilizing effect against carcinogenic substances was again shown in rats, which received 1,2-dimethylhydrazine to observe new formation of cancer with and without epitalon (5 x 1 µg per animal). In rats from the group treated with epitalon, tumors were smaller than in control animals. The incidence, as well the multiplicity of tumors were significantly decreased as well.^{19,20}

Ophthalmology

There are also reports indicating a positive effect of epitalon on the retina, the light sensitive structure of the eye, in rats. Epitalon (1.0 µg in 0.2 ml sterile physiological saline) was injected intraperitoneally in different generations of rats suffering from a hereditary degenerative disease of the retina. After 53 days, no electrical activity of the retina was observed in the control animals, while those injected with epitalon showed overall increased retinal activity, while some activity was retained as long as 83 days. This effect may be due to the DNA stabilizing and/or antioxidative effects of epitalon.^{21,22}

Studies in monkeys indicate epitalon is most effective in older individuals. If old rhesus monkeys received 10 µg epitalon in 1 ml

physiological saline intramuscularly, their melatonin production was restored to the levels of younger rhesus monkeys. This was also followed by a normalized day/night rhythm.²³

If applied orally, vilon and epitalon, improved transport characteristics of the small intestine in aged rats. Epitalon and vilon both enhanced passive glucose uptake, while glycine was better absorbed only under epitalon.²⁴ Effects on digestive enzymes were also investigated. Epitalon did partially restore the enzymatic activities of older rats back to those of younger individuals.²⁵

Other

Experiments on rats missing their pineal gland indicated that epitalon also serves as an immune system regulator, preventing the abnormal growth of immune cells in spleen tissue.²⁶ A study in older chickens and chickens without pineal gland reports shifts in the level of immune cells as well, but also in red blood cells. The peptide cortagene (Ala-Glu-Asp-Pro), which differs in only one amino acid from epitalon, did not induce the same effects.²⁷ In rats, epitalon induced a shift in types of blood cells, from lymphocytes from neutrophils, which corresponds to a different type of general immune system response.²⁸ Further evidence that epitalon has a stimulating effect on some types of immune cells was collected in mice.²⁹

Clinical Studies

In the course of aging both monkeys and people reveal decreased night and average daily level of melatonin in the blood plasma and reduced hormone circadian rhythm amplitude, which evidence the disorder of the pineal gland melatonin releasing function. Both epithalamin and epitalon recover night release of endogenous melatonin and lead to the normalization of the hormone circadian rhythm in the blood plasma.³⁰

A human clinical trial conducted on a sample of 162 retinitis pigmentosa patients found that epitalon produced a positive clinical effect in 90% of cases in the treated group. The patients were injected with 5 µg of epitalon close to the eyeball for 10 days. In most patients, the electrical activity of the retina, measured by Electroretinography, was improved.³¹

A further human clinical trial conducted on a sample of pulmonary tuberculosis patients, epitalon did not appear to correct pre-existing structural aberrations of chromosomes associated with telomere degradation, but did appear to exert a protective effect against the future development of additional chromosomal aberrations.³²

Researchers assessed the protective effects of thymic (thymalin) and pineal (epithalamin) peptides in 266 elderly patients during 6–8 years. The bioregulators were applied for the first 2–3 years of observation. All agents were injected intramuscularly daily at

10 mg for 10 days (at 100 mg per course), two courses one year apart. A separate group included 10 women and 10 men treated with thymalin and epithalamin simultaneously at 10 mg each for 10 days annually for 6 years. The obtained results convincingly showed the ability of both epithalamin and thymalin to improve the indices of cardiovascular, endocrine, immune and nervous systems, homeostasis and metabolism. Such a significant improvement in the health state of the peptide-treated patients correlated with decreased mortality rate during observation: 2.0–2.1-fold in the thymalin-treated group; 1.6–1.8-fold in the epithalamin-treated group; 2.5-fold in the patients treated with thymalin plus epithalamin as compared to the control. A separate group of patients was treated with thymalin in combination with epithalamin annually for 6 years and their mortality rate decreased 4.1 times as compared to the control.³²

Another prospective cohort study on a sample of 79 coronary patients spanning in excess of 12 years found improved metrics of physical endurance, circadian rhythm, and carbohydrate and lipid metabolism in the treated group relative to the control group following 3 years of biannual epithalamin treatments, as well as a 50% lower rate of cardiovascular mortality, a 50% lower rate of cardiovascular failure and serious respiratory disease, and a 28% lower rate of overall mortality.³³

Over three years 39 coronary heart patients received, in



addition to basic therapy, regular courses of epithalamin. Long-term treatment with epithalamin (6 courses over 3 years) decelerated aging of the cardiovascular system, prevented age-associated impairment of physical endurance, normalized circadian rhythm of melatonin production and carbohydrate and lipid metabolism. The protocol of peptide treatment was as follows: 10 mg in 2 ml saline intramuscularly, every 3 days, 5 injections per course, with 6-month intervals between the courses. A significantly lower mortality in the group of patients treated with epithalamin in parallel with basic therapy also indicated a positive effect on life quality and life span.³³

A randomized clinical study of epithalamine spanning over 12 years was carried out in elderly patients with coronary heart disease and accelerated aging of the cardiovascular system. Long-term treatment with epithalamine decreased the degree of cardiovascular aging. After 12 years the number of elderly subjects dead in the group treated by epithalamine was 28% lower than in the control group, despite the same basic therapy. Cardiovascular mortality was 2-fold lower in patients treated by epithalamine; the incidence of cardiovascular failure and respiratory diseases was 2-fold lower in this group. Long-term treatment with epithalamine was associated with a positive effect on the long-term life prognosis in elderly subjects with accelerated aging.³⁴

Conclusion

Epitalon shows remarkably positive results in animal and human trials. There is good evidence that epitalon has the ability to prolong the lifespan. This seems to be due to epitalon's ability to regulate the genes for anti-oxidative enzymes and telomerase, as well as several other proteins. This leads to a stabilization of cell DNA and a higher ability of tissues to regenerate.

Epitalon cannot be administered orally as all studies use injection techniques. There is the option this peptide might be effectively absorbed in sublingual or intranasal applications, but there are no studies exploring this possibility. Effective doses for injection are in the range of 10 mg peptide per injection. Additionally, the biggest effects are expected to be seen in older individuals, leading to a "rejuvenation" of some metabolic processes. In younger individuals, it may lead to a slow down of the aging process.

A number of human clinical trials with epithalamin have been conducted on the around the year 2000, with very promising results. However, almost all studies on epitalon and epithalamin have been conducted by the St. Petersburg Institute of Bioregulation and Gerontology. Since then, no more clinical data on epitalon or epithalamin has been published. Hopefully, other groups of researchers will re-evaluate the data published so far and confirm the results.

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