Introduction to Peptide Therapy

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Goals/Objectives:

- To understand how immune dysfunction and inflammation contribute to age-related diseases and how peptide therapy can address many abnormalities, underlying chronic illness and age-related illness.

- Be able to identify which patients and conditions would likely benefit from peptide therapy.

- To understand new treatment options for immune dysfunction, chronic illness, TBI, ADHD, autism and aging.
Peptide Therapy

- Short chain of amino acids
- Generally < 50-70 AA (> 50-70 becomes a protein)
- Natural, bioidentical or altered (synthetic)
- Seemingly simple peptides are found to regulate most every known process and system in the body in a tissue-specific manner
- While hormone therapy and optimization has been a mainstay of anti-aging medicine, it is being understood that regulatory peptides are the master controls of many functions of the body, including hormone production
Peptides

- Peptides are naturally occurring, bioregulatory chemicals in the body that act as master controls of many functions, including hormone production, cell signaling, and cell to cell communication.

- To date, >7000 naturally occurring peptides identified in our bodies.
Currently, peptides are available that are shown to safely and effectively improve and modulate specific parts of hormone production, immune function, the sleep cycle, the production of inflammatory mediators, DNA replication, cell division and renewal, cancer cell destruction and apoptosis, libido and sexual arousal, tissue healing and specific biological functioning of the brain, skin, eyes and urinary and reproductive systems.
Hormones work on nuclear receptors with resultant gene activation and protein synthesis.

Peptides are non-genomic that act on membrane receptors to activate an intracellular signaling cascade.

Peptide signaling molecules have more of a rapid response with less side-effects when compared to hormones.

Peptides have more precise tissue-selective effects, while hormones have less precise broader effects.
Peptide Classes

- Thymosins (immune modulators)
- Pineal hormones
- Nootropics
- Growth Hormone Secretagogues (GHSs)
- Melanocyte Stimulating Hormone (MSH) analogues
- Myostatin Inhibitors
- Others
Aspects of Aging

- Immune decline and dysfunction (immunosenescence)\(^\text{66}\)
- Increased inflammation and oxidative damage
- Multi-hormonal decline
- Reduced neurologic functioning and connectivity
- Decreased energy production
- Decreased protein synthesis\(^\text{66}\)
- Decreased detoxification
- Tissue and organ atrophy\(^\text{66}\)
Immunosenescence is multifactorial.

- Decreased telomere length in immune cells
  - For T and B cells, the ability to undergo extensive cell division and clonal expansion is crucial for effective immune function.

- Thymic involution
  - Results in TH1-TH2 shift
    - Increased risk of opportunistic and intracellular infections, autoimmunity, inflammation, and risk of cancer
    - Chronic illness becomes a vicious cycle of immune dysfunction

Immune Dysfunction (TH1-TH2 Shift)

Studies show that immune dysfunction is associated with a wide-variety of common chronic illnesses, including:

- Emotional stress;\(^2,72,76\)
- Depression;\(^5,6\)
- Dieting
- Insulin resistance, obesity, and diabetes
- Aging\(^1\)
- Chronic fatigue syndrome/fibromyalgia\(^3,4,78,79\)
- Autoimmune disease\(^80\)
- Cancer
- Chronic pain & pain meds
- Heavy metals toxin and plastics\(^73\)
- Chronic infections, including Lyme, viruses, candida and many parasites (infections make TH1 more susceptible to stress and glucocorticoid suppression)\(^9,70,75\)
- Oxidative stress: Glutathione depletion consistently results in TH1-TH2 shift
- GMOs
- Glucose, tobacco, alcohol
- Dysbiosis
- Food allergies or sensitivities\(^74\)
- Hormones (estrogens stimulate TH2; progesterone and testosterone TH1)
- Zinc and other mineral deficiencies\(^77\)
Cycle of Dysfunction with Chronic Illness

Component One
- Sleep Disorder
- GI Disorders
- Nutritional Deficiencies

Component Two
- Pituitary and Hypothalamic Dysfunction
- Hormone Deficiencies

Component Three
- Mitochondrial Dysfunction

Component Four
- Immune Dysfunction
- Autoimmunity
- Primary Infection or Reactivation of Latent Infection
- Coagulation Defect
- Environmental Toxins
- Neurotoxins

Component Six: Your maintenance plan

Holtorf, K. Cycle of Dysfunction of CFS/FM 2003
Immune Dysregulation (TH1-TH2)
TH1-TH2 Shift in HIV Determines Progression of Illness

Thymic peptides
- Thymosin Alpha 1 (TA1)
- Thymosin Beta 4 (Tβ4)
- Thymulin
- Thymogen

Nootropics
- Semax
- Selank
- Cerebrolysin

Pineal proteins
- Epithalon

Antimicrobial peptides
- LL-37

Others
- Follistatin
- BPC-157
High levels of type 2 cytokine-producing cells in chronic fatigue syndrome

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SUMMARY

The aetiology of chronic fatigue syndrome (CFS) is not known. However, it has been suggested that CFS may be associated with underlying immune activation resulting in a Th2-type response. We measured intracellular production of interferon (IFN)-γ and interleukin (IL)-2, type 1 cytokines), IL-4 (type 2) and IL-10 (regulatory) by both polyclonally stimulated and non-stimulated CD4 and CD8 lymphocytes from patients with CFS and control subjects by flow cytometry. After polyclonal activation, we found evidence of a significant bias towards Th2- and Tc2-type immune responses in CFS compared to controls. In contrast, levels of IFN-γ, IL-2 and IL-10-producing cells were similar in both study groups. Non-stimulated cultures revealed significantly higher levels of T cells producing IFN-γ or IL-4 in CFS patients. Concluding, we show evidence for an effector memory cell bias towards type 2 responsiveness in patients with CFS, as well as ongoing type 0 immune activation in unstimulated cultures of peripheral blood cells.

Keywords chronic fatigue syndrome cytokines immune activation Th1/Th2 cytokines

Evidence for T-helper 2 shift and association with illness parameters in chronic fatigue syndrome (CFS)

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Abstract

Few immunological markers have been consistently reported in CFS. However, a shift to a T-helper 2 (Th2) type immune response has been hypothesized for individuals with CFS. The current study investigated whether individuals with CFS who exhibited a stronger shift towards a Th2 type of immune response would also exhibit more severe symptoms, poorer neurocognitive functioning, and poorer physical and psychosocial functioning. The current investigation measured the percentage of Th1-like and Th2-like memory cells using cell surface flow cytometry in 114 individuals with CFS. The associations between the ratio of Th1 and Th2 memory cells and various illness parameters were then examined, including symptom severity, psychiatric functioning, neurocognitive functioning, salivary cortisol levels, and chronic pain symptoms. Results indicated that individuals who exhibited a more extreme shift towards a Th2 immune response also exhibited lower sleep and high levels of salivary cortisol. The implications of these findings are discussed.

Keywords chronic fatigue syndrome, T-helper 2 shift, immunology, salivary cortisol, cognitive functioning
Immune Modulating Therapies

- Increase TH1 and decrease TH2
- Boosting NK cell and lowering inflammatory cytokines
  - **Peptides (Thymosin alpha-1/BPC 157/Epithalon)**
  - LDN
  - IVIG (low dose or high dose - give 10-20 iu pitocin IV with each treatment if possible)
  - Ozone (MAH/Direct/High-dose/10-pass)
  - UVBI
  - LDA/LDI
  - Allergy elimination (gluten)
  - Antivirals (The deterioration in HIV is in direct correlation to the TH1/TH2 balance)
  - Antibiotics (do provoked WB, ECP and other immune markers whenever possible)
  - Transfer factors
  - Mushroom extracts
  - Isoprinosine
  - High dose B12
  - GcMAF/Leukine/Neupogen
  - Probiotics
  - Silver
  - Heparin
  - Antioxidants/Glutathione (low glutathione decreases TH1 and increases TH2)
  - Chelation (heavy metals stimulate TH2 and lower TH1)
  - Bee venom
  - Acupuncture
Fig. 1. Trend of thymic function through the course of the life. The thymulin titres of 93 subjects are plotted for each increment in age. Data are fitted to polynomial function using non-linear regression analysis (solid line; $r^2 = 0.8857$).
Thymus involution is influenced by age, obesity, caloric intake, genetics, inflammation, stress, pregnancy, toxins, hypothyroidism, low growth hormone, chronic infections, and zinc deficiency.

Progressive thymic dysfunction and immunosenescence naturally occur with aging and results in:

- Increased susceptibility to infections
- Inadequate immune response to vaccinations
- Increased propensity for autoimmune diseases
- Increased cancer risk
- Increased CV disease


According to the U.S. Center for Disease Control (CDC), approximately 80% of aged individuals are afflicted with at least one chronic disease as a result of a declination of thymic-related immune function.\(^7\)\(^3\)

- Obesity and calorie intake are strongly associated with thymic involution.

- The majority of people have pineal gland calcification by age 30.

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Thymic Peptides – Clinical Effects
(Thymosin alpha-1, thymosin beta-4, thymulin, thymogen)

- Improved tissue repair and healing \(^{35,36,37,41}\)
- Improved host defense to infection \(^{26,27,28,29,30}\)
- Reverse immunosuppression of chronic infection (Lyme) \(^{24,26,27,28,29,33,34,37}\)
- Increases antioxidant and glutathione production \(^{26,27,28,31,28,29,63,66}\)
- Boost NK function \(^{26,35}\)
- TH2-TH1 immune modulation (infections, cancer, herxheimer, autoimmune) \(^{26,27,28,30,31,33}\)
- Bind neuro/endotoxins \(^{111}\)
- Cardiac regeneration and protection post-MI, CHF, etc. \(^{39,65,98,99,100}\)
- Neurologic regeneration and protection post-stroke, TBI, Lyme, Alzheimer’s, neuropathy, Parkinson’s, etc. \(^{63,67,42}\)
- Stimulate stem cell activity and proliferation \(^{32,34,36,38,40,41,42}\)
- Increases longevity \(^{89,90,91}\)
- Almost non-existent side effects at 100-fold dose + excess \(^{103,104}\)
- Excellent safety profile with large therapeutic window (over 1000 fold) \(^{103,104}\)
TA1 Applications

- Approved in over 30 countries
- Cancer treatment/chemotherapy adjunct\(^{29,30,31,33}\)
- Treatment of Hepatitis B and C\(^{28,30}\)
- Treatment of AIDS\(^{28}\)
- Approved in USA as orphan drug
- Vaccine adjunct\(^{29}\)
TA1 Effects

TA1: Dual Mode of Action

Immunomodulatory

- ↑ T-cell production
- ↑ IL-2, IFN-γ
- ↓ IL-4, IL-10
- ↓ T-cell apoptosis

Antiviral

- ↑ MHC I
- ↓ Viral replication

VIRALLY INFECTED CELL

NK CELL

CD8+ T-CELL

CD4+ T-CELL

STEM CELL
TA1 Effects

**T Helper Cells**

TA1 increases Th1 subset

- **IL-2**
  - Control
  - ZDX
  - FN
  - ZDX + FN

- **IL-4**
  - Control
  - ZDX
  - IFN
  - ZDX + IFN

* p < 0.001 versus control
** p < 0.001 versus 5-FU

PBMCs from HCV patients

- CD4
  - Th1 (IL-2, IFNγ)
  - Th2 (IL-4, IL-10)


TA1 Effects

**Natural Killer Cells**

TA1 increases activity

- * p < 0.01
- ** p < 0.001

**Mean cytotoxicity**

- PBS:
  - 200:1
  - 100:1
  - 50:1

- ZDX:
  - 200:1
  - 100:1
  - 50:1

Immunorestorative Properties of TA1 in Lung Cancer Patients

- Double blind, randomized trial with 42 pts with localized, unresectable non-small cell lung cancer
- TA1 treatment given for up to 1 year following radiation therapy
- Statistically significant improvement in relapse-free survival (P=0.04) and overall survival (P=0.009) which correlated to T cell levels previously depleted by radiation

Antiaging properties of thymic protein

Bioidentical thymic protein was injected into mice starting at the age of 3.5 months prolonged mean life span by 28%, decreased rate of cancer 2.8 fold

Thymosin β4: multiple functions in protection, repair and regeneration of the mammalian heart

“Thymosin b4 (Tb4), has recently been described as a powerful regenerative agent with angiogenic, anti-inflammatory and cardioprotective effects on the heart and which specifically acts on its resident cardiac progenitor cells.”
These data indicate that TBeta4 treatment, improved functional recovery after encephalomyelitis, possibly, via reducing inflammatory infiltrates, and stimulating oligodendrogenesis.
These data indicate that Tβ4 likely acts on endothelial cells and Schwann cells to preserve and/or restore vascular function in the sciatic nerve which facilitates improvement of peripheral nerve function under diabetic neuropathy. Thus, Tβ4 has potential for the treatment of diabetic peripheral neuropathy.
**Thymosin β4 as a restorative/regenerative therapy for neurological injury and neurodegenerative diseases**

Michael Chopp & Zheng Gang Zhang

1Department of Neurology, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI, USA

Thymosin β4 (Tβ4) promotes CNS and peripheral nervous system (PNS) plasticity and neurovascular remodeling leading to neurological recovery in a range of neurological diseases. Treatment of neural injury and neurodegenerative disease 24 h or more post-injury and disease onset with Tβ4 enhances angiogenesis, neurogenesis, neurite and axonal outgrowth, and oligodendrogenesis, and thereby, significantly improves functional and behavioral outcomes. We propose that oligodendrogenesis is a common link by which Tβ4 promotes recovery after neural injury and neurodegenerative disease. The ability to target many diverse restorative processes via multiple molecular pathways that drive oligodendrogenesis and neurovascular remodeling may be mediated by the ability of Tβ4 to alter cellular expression of microRNAs (miRNAs). However, further investigations on the essential role of miRNAs in regulating protein expression and the remarkable exosomal intercellular communication network via exosomes will likely provide insight into mechanisms of action and means to amplify the therapeutic effects of Tβ4.

**Keywords:** microRNA, oligodendrocyte progenitor cells, thymosin beta 4, tissue plasminogen activator, traumatic brain injury

“Extended-release Tβ4 administration improves the retention, survival, and regenerative potency of transplanted MSCs after myocardial injury.”
BPC-157

- Pentadecapeptide BPC 157, composed of 15 amino acids, is a partial sequence of body protection compound (BPC) that is discovered in and isolated from human gastric juice
  - H-Gly-Glu-Pro-Pro-Pro-Gly-DL-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH
- Accelerates the healing of many different wounds, including tendon, gastrointestinal, ligaments, muscles, nervous system and other organs
- BPC 157 increases growth hormone receptors
- BPC 157 also promotes the outgrowth of tendon fibroblasts, cell survival under stress, and the migration of tendon fibroblasts
- This peptide is also shown to decrease pain in damaged areas
BPC-157

- Protects and prevents gastric ulcers
- Improves digestive function
- Protects and heals inflamed intestinal epithelium (leaky gut)
- Eosinophilic esophagitis
- It has also been shown to help in Inflammatory bowel disease
- Protects liver from toxic insults (alcohol, antibiotics, etc.) and promotes healing
- Traumatic brain injury\(^{27}\)
- May protect against acute and chronic toxic effects of alcohol symptoms of alcohol withdrawal
  - May antagonize 5HT2 receptor (high numbers of 5HT2 receptors found in depression and suicidal patients)

“Stable gastric pentadecapeptide BPC 157 is an anti-ulcer peptidergic agent, safe in inflammatory bowel disease clinical trials and wound healing, stable in human gastric juice and has no reported toxicity. Particularly, it has a prominent effect on alcohol-lesions (i.e., acute, chronic) and NSAIDs-lesions (interestingly, BPC 157 both prevents and reverses arthritis)... and acts as a free radical scavenger and exhibits neuroprotective properties.”

BPC -157

- Potential target conditions
  - Lyme disease/HIV (especially in conjunction with TA1)
  - Chronic viral or intracellular infections
  - CFS/Fibromyalgia
  - Autoimmune disease (asthma, lupus, etc)
  - Inflammatory conditions (markers: CRP, C4a, ESR, HTG FB)
  - CVD
  - Post surgical
  - Diabetes
  - Aging
  - Allergies
  - Chemical sensitivity
  - GI ulcers/inflammation
  - Inflammatory bowel disease
  - Leaky gut
  - H-pylori
  - Prevent/treat heart arrythmias

Epithalon/Epithalamin

- A four AA peptide isolated from Pineal gland
  - Ala-Glu-Asp-Gly

- Restores impaired, aged and damaged neurologic, immune and cardiovascular system, improves neuroendocrine and immune regulation and prevents multiple age-related diseases, such as HTN, memory loss, cancer, osteoarthritis and overall mortality and morbidity in humans and animals.

- Increases mean and maximal life span in humans and animals

- Inhibits spontaneous and induced carcinogenesis
Epithalon/Epithalammin

- Increases pineal synthesis of serotonin and melatonin
- Increases and restores telomere length $^{26,27}$
- Slows down aging of the reproductive system and restores estrous and fertility in old female rats. $^{58}$
- Increases T4 to T3 conversion $^{58}$
- Improves glucose tolerance and decreases insulin and triglyceride levels $^{58}$
- Activate gene expression and protein synthesis in specific target tissues $^{66}$
Aging is associated with decreasing cellular energy production (mitochondrial dysfunction), with resultant reduction in cellular metabolic activity.

Subsequent reduction in protein synthesis, age related tissue hypoplasia and atrophy of many tissues and organ systems, including thymus, pineal gland, and reproductive organs.
Effect of the Pineal Gland Preparation on Melatonin Level in Elderly People

<table>
<thead>
<tr>
<th></th>
<th>Melatonin level in blood at 3.00 a.m. (pg/ml)</th>
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<tbody>
<tr>
<td>Healthy people (20-40 y.o.)</td>
<td>63.4±9.2</td>
</tr>
<tr>
<td>Patients (60-74 y.o.), treated with polyvitamins</td>
<td>Initial level 32.4±6.8 *</td>
</tr>
<tr>
<td></td>
<td>After correction 28.1±5.9 *</td>
</tr>
<tr>
<td>Patients (60-74 y.o.), treated with preparation of the pineal gland</td>
<td>Initial level 24.2±5.1 *</td>
</tr>
<tr>
<td></td>
<td>After correction 59.0±12.6</td>
</tr>
</tbody>
</table>

* - p<0.05 as compared to healthy people index

Telomerase

- It is now known that age-associated healing and rejuvenation is limited secondary to critical shortening of telomeres in the course of cell division\(^\text{26}\).

- Human somatic cells have very low levels of telomerase activity that is required to elongate telomeres\(^\text{26}\).

- While malignant, sex, early embryonic and some stem cells have relatively higher amounts of telomerase.

- Epithalon induces the expression of telomerase, telomerase activity and elongation of in somatic telomeres\(^\text{26,27}\).
Overcoming of the Limit of Fibroblasts Division by Adding Epithalon

Increase in the number of cell divisions in the experiment by 42.5% as compared to the control.

Mean length of telomeres in G1 phase of the cellular cycle (conv. units) vs. Number of passages (cessation of cell division)

Control (intact “old” cells) vs. Epitalon (addition to the cell culture in the concentration of 0.05 μg/ml beginning from the 28th passage)

* - p < 0.05 as compared to the control

Increase in mean and maximum lifespan in animals consistently seen with both thymic and pineal gland peptides with direct correlation to increased cellular immunity with the subsequent reliable reduction in cancer in both animals and humans.
Effect of Peptide Bioregulators on the Lifespan of Mice

**NUMBER OF MICE, WHICH REACHED 2 YEARS OF AGE**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Vilon</th>
<th>Epitalon</th>
</tr>
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<tbody>
<tr>
<td>%</td>
<td>14</td>
<td>36</td>
<td>56</td>
</tr>
</tbody>
</table>

**LIFESPAN**

<table>
<thead>
<tr>
<th>Index</th>
<th>Control</th>
<th>Vilon</th>
<th>Epitalon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, days</td>
<td>685 ± 9</td>
<td>694 ± 13</td>
<td>721 ± 11 *</td>
</tr>
<tr>
<td>Maximum, days increase (%)</td>
<td>740</td>
<td>792</td>
<td>1053</td>
</tr>
</tbody>
</table>

* - p<0.05 as compared to the control

Epithalon

- 20 month long treatment of 0.5 mg per day epithalamin in female rats increased lifespan by 25%\(^{57}\)

- At age 16-18 months, 38% of control rats became menopausal or perimenopausal vs only 7% of treated rats

- No 16-18 month control rats were able to get pregnant after repeated mating compared to 25% of treatment group, with 5-9 healthy offspring each

Epithalon

- Female mice carrying the breast cancer gene HER-2/neu (genetically prone) received epithalon five times per week from 2\textsuperscript{nd} month of life until death\textsuperscript{34}

- The percent of mice that developed breast cancer was 3.7 fold higher in control group (73\% reduction in treatment group)

- Epithalon also decelerated the rate of aging of the reproductive system with only 8\% of aged mice having irregular menstrual cycles vs. 52\% of aged control mice

Randomized trial of 79 patients age 60-69 with severe CAD, with half receiving 6 courses of Epithalon (6 courses over 3 years of 10 mg q 3 days for 15 days with 6 months between courses). The patients were then monitored for another 10 years with no further Epithalon treatments.

All patients received standard basic therapy.

Over the subsequent 13 years, the CVS functional age was 16 years older compared to 7 years for the Epithalon group.

The CV morality of the treatment group was approximately half of control group 46% vs 83.3%, respectively.

The control group showed that there was a significant reduction in age-associated physical endurance by approximately 10%, while the Epithalon group improved during the test period by almost 10%.

Also, the Epithalon treated patients had a normalization of their circadian rhythm, increased melatonin production and improved carbohydrate and lipid metabolism.

Epithalon

“The obtained results demonstrate a high efficiency of epithalon therapy for prophylaxis of age-related pathology, including cancer, showing a new physiological way to slow down pathological processes and to extend human life spans”58

Peptide synergism

- The geroprotective effects of thymic and pineal (Epithalamin) peptides were investigated over a 6-8 years period in 266 elderly patients after being treated for the first two to three years of the study.

- **RESULTS:** “The obtained results convincingly showed the ability of the bioregulators to normalize the basic functions of the human organism, i.e. to improve the indices of cardiovascular, endocrine, immune and nervous systems, homeostasis and metabolism. Homeostasis restoration was accompanied by a 2.0-2.4-fold decrease in acute respiratory disease incidence, reduced incidence of the clinical manifestations of ischemic heart disease, hypertension disease, deforming osteoarthrosis and osteoporosis as compared to the control.”

- “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 and a 2.5-fold in the patients treated with Thymalin plus Epithalamin as compared to the control.”

- A separate group of patients was treated with the peptides annually for 6 years and their mortality rate decreased 4.1 times as compared to the controls.

Nootropics

- Semax
- Cerebrolysin
- Selank
Nootropics

- Neurotrophic action similar to that of nerve growth factors\textsuperscript{72-74}
- Peripheral and central nervous system stimulation
- Neuroprotective effects
- Shields neurons from neurotoxins, inflammation and injury
- Protects from stress and depression
- Improves memory (even in healthy adults)
- Neurological regeneration
  - TBI\textsuperscript{69}
  - Alzheimer's\textsuperscript{15,69-72}
  - Parkinson's'
  - Stroke\textsuperscript{69,73}
  - Toxin induced
- No significant side effects reported\textsuperscript{15,69,70,72,73}
Nootropics (Cerebrolysin)

- Double-blind, placebo-controlled trial
- Patients injected intravenously with 30 mL Cerebrolysin (97 pts) or placebo (94 pts) 5 days a week for 4 weeks.
- Evaluated effects on cognition and global function (via AD assessment scale)
- AD assessment score was significantly higher in the Cerebrolysin group (p=0.007)
- Authors conclude:
  - “Cere treatment was well tolerated and resulted in significant improvements in the global score two months after the end of active treatment.”

Nootropics (Cerebrolysin)

- Another double-blind, placebo-controlled study looking at efficacy of Cerebrolysin for AD

Authors conclude:

- “Notably, improvements were largely maintained in the Cere group until week 28, 3 months after the end of treatment...Cere treatment was well tolerated and led to significant improvement in cognition and global clinical impression. A sustained benefit was still evident 3 months after drug withdrawal.”

The heptapeptide Semax is a clinically used nootropic and neuroprotective drug [6]. It stimulates learning of animals [7] and increases the expression of BDNF and its high affinity trkB (tropomyosin kinase) receptors in the hippocampus [8].

In addition, it has been shown that chronic Semax injection under conditions of stress load exerts anxiolytic and antidepressant effects [9].
Semax can augment the effects of psychostimulants on central dopamine release and also stimulates central brain-derived neurotrophic factor (BDNF) synthesis. In addition, Semax could improve selective attention and modulate brain development and improve symptoms of ADHD.

Tsai SJ. Semax, an analogue of adrenocorticotropic (4-10), is a potential agent for the treatment of attention-deficit hyperactivity disorder and Rett syndrome. Med Hypo 2007;68(5):1146-6
Nootropics (SEMAX)

“Semax is one of the rare analogues of regulatory peptides which underwent all stages from fundamental investigations to practical usage. It has been demonstrated that this peptide is capable to stimulate operative memory and attention, to increase resistance to hypoxia and to improve brain circulation in experimental animals and human beings over prolonged period (20-24 h after intranasal administration in doses 0.015-0.050 mg/kg).”

“Semax significantly improves memory and attention in healthy men under extreme conditions of activities. Moreover at present semax is successfully used in treatment of patients with different diseases of CNS.

In the majority of cases the peptide exhibited positive effects and in no case it produced negative side actions or complications connected with its administration.”

Nootropics (Selank)

“The data obtained indicate that the individual administration of Selank was the most effective in reducing elevated levels of anxiety, induced by the administration of a course of test substances, whereas the combination of diazepam with Selank was the most effective in reducing anxiety in unpredictable chronic mild stress conditions.”


The optimizing action of the synthetic peptide Selank on a conditioned active avoidance reflex in rats.

Kozlovskii II1, Danchev ND.

Abstract
The actions of the synthetic heptapeptide preparation Selank on learning and memory processes in rats with initially low levels of learning ability were compared with those in normal rats, using a method based on acquisition of a conditioned active avoidance reflex, with repeated administration of peptide 15 min before the start of training sessions for four days. The effects of Selank (300 microg/kg) were compared with the effects of the nootrope piracetam (400 mg/kg). These experiments showed that Selank significantly activated the learning process in rats with initially poor learning ability, with effects apparent after first dose on training day 1. The effect progressively increased on repeated administration of Selank: the total number of correct solutions increased and the number of errors decreased (p<0.05). The maximum optimizing activity of Selank on learning in normal rats was seen on day 3 of repeated administration and training, i.e., after formation of the initial consolidation phase. The dynamic features of the development of the activating action of Selank and piracetam were described. Comparison of the results obtained here with data on the anti-anxiety actions of Selank suggested potential for its use in optimizing mnemonic functions in conditions of elevated emotional tension.
"It was established that Selank can enhance memory storage processes. Nootrope activity of the Selank is probably caused by its obvious effect on the level of serotonin and its metabolite in the brain."

[Experimental optimization of learning and memory processes by selank].

[Article in Russian]
Semenova TP, Kozlovskiǐ II, Zakhareva NM, Kozlovskaià MM.

Abstract
The effect of selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro), which is a synthetic derivative of the endogenous tetrapeptide tuftsin (stable with respect to tissue peptidases), on the learning and memory processes and metabolism of serotonin (5-HT) have been experimentally studied on Wistar rats. The animals were trained with food reward in 30 trials per day. Selank (300 microg/kg) or saline were injected after the 10th trial. Elaboration of conditioned reflex with food reward was continued 30 min later. Retention was tested 24 h, 7 and 30 days after treatment. A single injection of selank activated the metabolism of 5-HT in the hypothalamus and caudal brain stem for 30 min to 2 h. It was established that selank induces an increase in memory trace stability during 30 days. These findings provide direct evidence that selank, when injected during consolidation phase, can enhance memory storage processes. Nootrope activity of the selank is probably caused by its obvious effect on the level of serotonin and its metabolite in the brain.
## Peptide Usage Overview

<table>
<thead>
<tr>
<th>Class</th>
<th>Pain</th>
<th>Immunity</th>
<th>Inflammation</th>
<th>Libido</th>
<th>Anti-aging</th>
<th>Weight Loss</th>
<th>Cognitive</th>
<th>Antioxidant</th>
<th>Sleep</th>
<th>Dose (µg)</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH FRAG T76-191</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>100-300</td>
<td>Healing, body fat, rejuvenation</td>
</tr>
<tr>
<td>Semax</td>
<td>Nootropic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>300-1000</td>
<td>Cognitive dysfunction, memory, stroke, dementia, depression, TBI, ADHD</td>
</tr>
<tr>
<td>Cerebrolysint</td>
<td>Nootropic</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>300-1000</td>
<td>Cognitive dysfunction, memory, stroke, dementia, depression, TBI, ADHD</td>
</tr>
<tr>
<td>Selank</td>
<td>Nootropic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>250-1500</td>
<td>Cognitive dysfunction, memory, stroke, dementia, depression, TBI, ADHD, anxiety, depression</td>
</tr>
<tr>
<td>CJC 1295 + Ipegorelin</td>
<td>GHRH/GHRP</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>100/200/500/500</td>
<td>Growth hormone stimulation</td>
</tr>
<tr>
<td>Follastatin</td>
<td>Myostatin Blocker</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>100-200mcg/2x/week</td>
<td>Weight loss, muscle building</td>
</tr>
<tr>
<td>Melanoten II</td>
<td>MSH Analog</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>300 mcg q1-3 weeks</td>
<td>Tanning, weight loss, libido</td>
</tr>
<tr>
<td>PT141/Bremelanotide</td>
<td>MSH Analog</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1-2 mg q1-3 days pm</td>
<td>Libido, weight loss, tanning</td>
</tr>
<tr>
<td>Thymosin Alpha 1</td>
<td>TH1 Stimulation</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>100-1000</td>
<td>Immune boosting for chronic infection, cancer</td>
</tr>
<tr>
<td>Thymulin</td>
<td>TH1-TH2 Balance</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>500-1000</td>
<td>Immune modulation, cancer, rejuvenation, neuroregeneration, muscle pain</td>
</tr>
<tr>
<td>Thymosin Beta 4</td>
<td>TH1-TH2 Balance</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>300-1000</td>
<td>Immune modulation, cancer, rejuvenation, neuroregeneration, muscle pain</td>
</tr>
<tr>
<td>BCP 157</td>
<td>Reduce TH2 (Inflammation)</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>100 mcg q1-3 weeks</td>
<td>Systemic or GI inflammation, healing, rejuvenation</td>
</tr>
<tr>
<td>DISP</td>
<td>Sleep Peptide</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>500-1000</td>
<td>Immunity, cancer, sleep, anti-aging, telomere lengthening, DNA repair</td>
</tr>
<tr>
<td>Epithalon</td>
<td>Pineal Gland Peptide</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>300-1000</td>
<td>Anti-biofilm, chronic infections, Lyme, anti-bacterial, anti-viral, anti-parasitic</td>
</tr>
<tr>
<td>LL-37</td>
<td>Anti-Microbial Peptide</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>200-1000</td>
<td>Muscle pain, muscle building</td>
</tr>
<tr>
<td>MGF</td>
<td>Saropenic IGF-1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>200-500</td>
<td>Muscle pain, muscle building</td>
</tr>
</tbody>
</table>

**Dosing** is based on the medical literature and what we have found safe and effective. Holter/Medical Group dosing given for SC delivery (other options potentially available).
**Dosing** are suggested guidelines; clinical and laboratory assessment is required.
**Dosing** is for reference and are to be used in conjunction with the patient's health care provider.
**Dosing** are suggested 5 days on 2 days off and 4 weeks on and 1 week off.

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**Conditions**
- Healing, body fat, rejuvenation
- Cognitive dysfunction, memory, stroke, dementia, depression, TBI, ADHD
- Cognitive dysfunction, memory, stroke, dementia, depression, TBI, ADHD, anxiety, depression
- Growth hormone stimulation
- Weight loss, muscle building
- Tanning, weight loss, libido
- Libido, weight loss, tanning
- Immune boosting for chronic infection, cancer
- Immune modulation, cancer, rejuvenation, neuroregeneration, muscle pain
- Systemic or GI inflammation, healing, rejuvenation.
## Peptide Suggestions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Go to Peptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS/FM/ME/Lyme/Chronic Infection</td>
<td>Thymosin Alpha-1, Thymosin Beta 4, Semax, Selank, LL-37, Thymulin, BPC 157</td>
</tr>
<tr>
<td>Cognitive Dysfunction/Neuro Damage</td>
<td>Semax, Selank, Cerebrolysin, Epithalon and Thymosin Beta 4</td>
</tr>
<tr>
<td>Aging/Preventive Medicine</td>
<td>Epithalon, Thymosin Beta 4, Thymulin, BPC 157, Semax, Selank</td>
</tr>
<tr>
<td>Sleep</td>
<td>Epithalon, DISP</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>Follistatin, GH FRAG 176-191</td>
</tr>
<tr>
<td>Libido/ED</td>
<td>PT-141, Melanotan, Semax</td>
</tr>
<tr>
<td>Anxiety/Depression</td>
<td>Semax, Cerebrolysin, Selank, DISP</td>
</tr>
</tbody>
</table>
Conclusions

Summary:

- Peptides are demonstrating to be a highly effective therapy for a wide-range of diseases and aging with little risk of side-effects.
- Peptide therapy can address underlying dysfunction of the immune system and cellular dysfunction.
- Effective for prevention and treatment for a wide-range of chronic and acute illnesses.
- Synergistic effects of umbilical cord stem cells and peptides can be very effective and may be replacing standard medications and therapies for chronic illness.
Thank You

Questions?

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617-630-2882


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