Peptides for Sleep, Improving Telomeres, Libido, Testosterone, and Memory

Edwin Lee, M.D., F.A.C.E.
Institute for Hormonal Balance
Orlando, FL

Dr. Edwin Lee
Disclosure

The following potential conflict of interest relationships are germane to my presentation.

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Status of off label use of devices, drugs or other materials that constitute the subject of this presentation: N/A
Peptides that will be discussed

- Epithalon
- Melanotan 1
- Bremelanotide PT 141
- DSIP
- CJC 1295
- Kisspeptin
- FGL
- Semax
Third eye

- Pineal Gland
- Small gland is located in the epithalamus
- Third eye refers to the gate that leads to spaces of higher consciousness
Pineal Gland - Third eye

- Pineal gland resembles like a pine cone
- Glandular tissue predominates in children and young adults
- Becomes fibrous and calcified with age
Pineal Gland - Third eye

- Photosensitive organ and an important timekeeper for the human body
- Produces melatonin
- Regulates daily body rhythms, day/night cycle, prevents jet lag
Pineal Gland - Third eye

The graph shows the secretion of melatonin [pg/mL] over different age groups from 5-10 years to over 70 years. The secretion peaks and troughs vary across these age groups, with the elderly group showing a flattened curve.
Pineal Gland - Third eye

- Involved in growth, puberty, fertility and aging
- Besides producing melatonin it produces epithalamin
- Discovered by researchers in Russia in the 1970’s

Epithalamin / Epithalon / Epitalon

• 4 amino acid

• Ala-Glu-Asp-Gly

• Approved for general use in the Soviet Union in 1990 and has been used in gerontology

• No adverse side effects according to Dr Khavinson
Epithalamin / Epithalon / Epitalon

- Epithalamin increases the life span of mice and rats
- Without the development of malignant tumors
- Anisimov VN¹, Khavinson VKh Ross Fiziol Zh Im I M Sechenova. 2001 Jan;87(1):125-36

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Epithalon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime Mean</td>
<td>289</td>
<td>328*</td>
</tr>
<tr>
<td>Lifetime Max</td>
<td>360</td>
<td>410*</td>
</tr>
</tbody>
</table>

¹Anisimov VN², Khavinson VKh Ross Fiziol Zh Im I M Sechenova. 2001 Jan;87(1):125-36
Epithalamin / Epithalon / Epitalon

- Epithalamin stimulates telomerase which in turn increases telomeres in our DNA
- Increase the telomeres by 33%

Epithalamin /Epithalon / Epitalon Study in elderly from 1992 to 2005

- Results of 15* year follow up study
- N = 79
- Age 60-69 with Stable CAD

- Group 1 received Epithalamin 6 courses over 3 years 1992 to 1995
- 10 mg in 2 ml saline IM every 3 days - 5 shots per course, (dose of 50 mg)
- 6 months intervals
- Total dose 300 mg
Epithalamin /Epithalon / Epitalon

3 year treatment Kaplan -Meier Survival Curve

Fig. 4. Cumulative survival curves of elderly coronary patients with rapidly aging CVS treated by different protocols. 1) basic therapy; 2) basic therapy + epithalamin. *p<0.05 compared to the parameters in the basic therapy group throughout the entire period of observation.


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<table>
<thead>
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<th>Control</th>
<th>Epithalamin</th>
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<tbody>
<tr>
<td>Cardiovascular Death</td>
<td>20/24 (83%)</td>
<td>6/13 (46.2%)</td>
</tr>
<tr>
<td>Survival</td>
<td>16/40 (40%)</td>
<td>26/39 (66.7%)</td>
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</tbody>
</table>
Epithalamin / Epithalon / Epitalon

- Epithalamin 6 courses over 3 years
- 10 mg in 2 ml saline IM every 3 days - 5 shots per course, (dose of 50 mg)
- 6 months intervals
- Total dose 300 mg

- Optional dosing
- Vial 2000 mcg/ml x 5 ml
- 1 mg (1 ml) sq a day x 50 days = 50 mg
- Repeat every 6 months to 1 year
Libido Booster
Libido Booster Peptide

- Men are easy
- Men only needs oxygen and a pulse
Libido Booster Peptide

- Women are a little more complicated
- Sincerity
- Reliability
- Commitment
- Integrity
Libido Booster Peptide

- Synthetic melanotropic peptides initiate erections in men with psychogenic erectile dysfunction
- Similar effects on libido are seen in women
Hypothalamic control of penile erection and sexual behavior
Pro hormone **Pro-opiomelanocortin**

Diagram:

- POMC
  - γ-MSH
  - ACTH
  - β-lipotropin
  - α-MSH
  - CLIP
  - γ-lipotropin
  - β-endorphin
  - β-MSH
Sexual Stimulation

- Only ACTH and α-MSH have shown the ability to generate sexual stimulation and penile erection in various animal species including rats, rabbits, cats, dogs and monkeys.

Alpha Melanocyte stimulating hormone (MSH)

- Alpha MSH is identical to the first 13 amino acids of ACTH
- ACTH has MSH like activity
- However - MSH has no ACTH activity
Melanotan derivatives of alpha MSH

- Both Melanotan 1 and Melanotan 2 are analogs of alpha melanocyte stimulating hormone (MSH)
- Melanotan 1 promotes tanning
- Melanotan 1 is 26 x more potent than $\alpha$-MSH

Melanotan 1

- Suggested dosing
  - 500 mcg SQ at bedtime for 2 weeks every night then after 2 weeks reduce it to 2 times a week to maintain your tan

- May help with weight loss

- Side effect nausea and dark spots on the skin will appear darker

- Potential risk of Melanotan in stimulating dysplastic naevi or possibly malignant melanoma

Melanotan 1

- Other names Afamelanotide

- Melanotan 1 as subcutaneous implant 16 mg combined UV-B phototherapy as a repigmentation therapy in vitiligo for 4 months

- Statistically significant superior and faster repigmentation compared to UV-B monotherapy

Melanotan 2 and Bremelanotide

- Melanotan 2 (7 AA)
- Bremelanotide PT 141 is a derivative of melanotan 2
- PT-141 is a potent initiator of erection with minimal side effects

- Of the 5 melanocortin receptor subtypes, only the MC3 and MC4 have been identified in CNS regions associated with activation of penile erection
- Bremelanotide PT 141 has a strong binding to MC receptors 1, 3 and 4

Libido Booster Peptide - Bremelanotide PT 141

- Bremelanotide is a peptide that activates the endogenous pathways involved in sexual response
- Centrally mediated, fast acting
- Binds to melanocortin receptor subtypes MC3 and MC4
Libido Booster Peptide- Bremelanotide PT 141

- Study of failure of Sildenafil with PT 141
- Randomized Double Blind Placebo controlled study
- N = 342 married men

- 10 mg bremelanotide as an intranasal spray 45 minutes to 2 hours prior to sexual stimulation
- use at least 16 doses/attempts

Libido Booster Peptide-Bremelanotide PT 141

- Patients in the bremelanotide group reported significantly greater intercourse satisfaction than those in placebo group ($p = 0.03$)

- Minor side effects of nausea, flushing and headaches

Libido Booster Peptide - Bremelanotide PT 141

- Study in Premenopausal women with sexual arousal disorder with bremelanotide PT 141
  - 18 women

- Intranasal dose of 20 mg bremelanotide
- More women reported moderate or high sexual desire following bremelanotide treatment vs. placebo (P = 0.0114)
Bremelanotide PT 141 Dosing

- Many different protocols
- PT 141 - 1000 mcg/ml
- 2 ml vial
- Suggested dosing 1 mg sq prn
- Variable response
- Libido can increase after 2-6 hours injections
- Recommend trying it 12 hour before the event
- Careful mixing it with PDE 5 inhibitor- 12 hour erections can occur
Bremelanotide PT 141 - Future Female Viagra

- June 2018
- FDA accepted a new drug application of bremelanotide for female sexual dysfunction with a review date for March 2019
- 30 clinical trials with over 2500 patients
- Autoinjector
  - www.thepharmaletter.com/article/amg-pharma-closes-deal-for-north-america-rights-to-rekynda
Another benefit of CJC 1295 is its ability to promote slow wave sleep. Slow wave sleep is responsible for the highest level of muscle growth and memory retention.

CJC 1295 with Ipamorelin

- CJC 1295 non DAC with Ipamorelin
- Both are formulated at 2000 mcg/ml
- Start at 100 mcg or 0.05 ml or 5 units with an insulin syringe SQ at bedtime from Monday to Friday
- Side effect flushing for 5-10 minutes
- Can titrate to 200 mcg or 0.1 ml or 10 units SQ at bedtime Monday to Friday
- Take 2 days off per week to prevent “burn out”
Delta Wave - Deep Restorative Sleep

Brain wave frequencies relating to sleep

**Beta**
- While you are reading this, you are in Beta, this is the normal waking state (14-30 cps), cps = cycles per second

**Alpha**
- You are in Alpha when listening to music, watching TV or meditating. This is the normal resting state (8-13 cps)

**Theta**
- You are in Theta when you are in a pre-sleep semi-awake. This is the hypnoidal state (4-8 cps)

**Delta**
- Delta high quality regenerative sleep. This is the deep sleep state (0.5-4 cps)

*Dr Edwin Lee*
Delta Sleep Induced Peptide

- Delta sleep-inducing peptide was first discovered in 1974 by the Swiss scientist who isolated it from the cerebral venous blood of rabbits in an induced state of sleep.

Delta Sleep Induced Peptide (DSIP)

- 9 Amino Acid Peptide
- It has been found in both free and bound forms in the hypothalamus, limbic system and pituitary
- However the Gene for DSIP and where it is made is still unknown
Delta Sleep Induced Peptide (DSIP) in chronic insomniacs

- DSIP appears to help promote sleep in humans

- Study of 6 chronic insomniacs were given IV DSIP 25 nmoles/kg improved sleep quality

Delta Sleep Induced Peptide (DSIP) in Narcolepsy

- Repeated injections of DSIP was given to a 35-year-old male narcoleptic which reduced the frequency of sleep attacks.

- Schneider-Helmert D. *Eur Neurol.* 1984;23(5):353-7
Delta Sleep Induced Peptide (DSIP) on LH

- In rat studies DSIP has been shown to increase LH

- DSIP-may activate the hypothalamic neural circuitry responsible for stimulation of LH release reported to occur during sleep.

Delta Sleep Induced Peptide

- To prevent tachyphylaxis it is best to give the hypothalamus a break.
  - 1-2 nights a week
  - 100 mcg to 800 mcg Subcutaneous at bedtime
Puberty begins with a Kiss

- Kisspeptin is a neuroendocrine peptide than stimulates the release of Gonadotropin Releasing Hormone (GnRH) and is involved in the start of puberty.
Kisspeptin

Lee JH et al., Journal of the National Cancer Institute. 88 (23): 1731-7

- Kisspeptin is a peptide that is encoded by the KISS1 gene
- Originally identified as a human metastasis suppressor gene for melanoma and breast cancer metastasis
- KISS1 gene was discovered in Hershey, Pennsylvania in 1966
Kisspeptin- Released from KNDy


- Kisspeptin is released together with two other hormones, neurokinin B and dynorphin.

- Consequently, the nerve cells making kisspeptin, dynorphin and neurokinin B are popularly referred to as KNDy.
Kisspeptin increases LH and FSH

- Kisspeptin interacts with the KISS1 receptor or the GPR54 receptor
- Kisspeptin stimulates the release of GnRH and thus increases LH and FSH

KiSSpeptin

- Stimulates GnRH
- LH/FSH
- Gonadotropins
- Gonads
  > Sexual development
  > Gametogenesis

I’m Gonna rock n Roll all night and get Puberty every day!

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Kisspeptin initiates Puberty

$1 + 1 = 3$
1 + 1 = 3
If you don't use a condom
## Kisspeptin levels w/ hypogonadism

Masato Kotani et al. Endocrine Journal 2014, 61 (11), 1137-1140

<table>
<thead>
<tr>
<th>Condition</th>
<th>fmol/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls (7 men)</td>
<td>12</td>
</tr>
<tr>
<td>Kallman’s syndrome</td>
<td>43</td>
</tr>
<tr>
<td>Azoospermia (elevated FSH and LH)</td>
<td>41</td>
</tr>
<tr>
<td>Hypergonadotrophic hypogonadism</td>
<td>323</td>
</tr>
<tr>
<td>Hypogonadotrophic hypogonadism</td>
<td>6</td>
</tr>
</tbody>
</table>
Kisspeptin 54 increases testosterone

- Double blind placebo controlled crossover study
- N = 6
- 90 minute infusion 4 pmol/kg x min

- LH increased from 4.2 to 10.8
- Testosterone increased from 625 ng/dl to 718 ng/dl (p < 0.001)

Response to Kisspeptin -54 is preserved in 60 year old men (Older men)

- 5 men 60 years old compared to 5 men 29 years old
- 3 hour intravenous infusion kisspeptin-54 0.1, 0.3, 1.0 nmol/kg/h
- Dose dependent
- LH and FSH response to Kisspeptin was preserved
- Testosterone increased with Kisspeptin but less compared to younger men (age of 29)

Kisspeptin -10 increases Testosterone

- Kisspeptin-10 is the minimal kisspeptin sequence with full intrinsic bioactivity
- Infusion of kisspeptin-10 at 4 μg/kg · h for 22.5 hours
- Elicited an increase in LH from 5 to 21
- Increase in Testosterone from 478 ng/dl to 692 ng/dl (p < 0.001)
- Also increased LH pulse frequency
Kisspeptin- 10 in Type 2 Diabetics

- 5 men with low testosterone and with type 2 diabetes were compared to 7 healthy men
  - Age is 33.6 years old
  - BMI of 40.6
- Intravenous infusion of kisspeptin-10 (4 mcg/kg/h) was administered for 11 hours
  - Increase in LH from 3.9 to 20.7 IU/l
  - Increase in Testosterone from 245 to 329 ng/dl

Response to Kisspeptin for idiopathic hypogonadotrophic hypogonadism (IHH)

- LH response to iv boluses of kisspeptin (0.24-2.4 nmol/kg)
- In the future, Kisspeptin may be used to access and to treat hypogonadotrophic hypogonadism

Peptide FGL (15 amino acids)

- FGL is a Synthetic peptide derived from neural cell adhesion molecule.
- Developed in 2004
- FG Loop peptide
- FGL can cross the blood brain barrier
FGL reduces inflammation

• FGL reduces neuroinflammation

• FGL prevent age-related structural changes in synapses
FGL enhance memory

- FGL has been shown to enhance memory or protect neurons in:
  - Chronic stress
  - Depression
  - Ischemia
  - Traumatic Brain Injury
Peptide FGL potential treatment for Alzheimer’s disease

- Peptide Abeta 25-35 induces Alzheimer’s disease in rats

- FGL given subcutaneous was able to prevent or, if already manifest, strongly reduce all investigated signs of Abeta25-35-induced neuropathology and cognitive impairment.

- After FGL treatment, showing fewer amyloid plaques and better memory.
FGL mechanism

- FGL that binds to the Fibroblast Growth Factor Receptor 1 (FGFR-1), has been shown to have a beneficial impact on normal memory functioning

- FGL treatment stimulates activity-dependent delivery of glutamate receptors to synapses, leading to a long-term enhancement of synaptic transmission in hippocampal neurons.
FGL Phase 1 study

- 8-day, open-label, phase I study, 24 healthy male volunteers
- received single intranasal doses of FGL₇ (25, 100 and 200mg) ascending dose
- All three doses were well tolerated

FGL Phase 2 study

- Dec 2011
- A biotech company in Europe was awarded 6 million Euros to do a phase 2a study with FGL in Alzheimer’s
  - www.investegate.co.uk/article.aspx?id=201112080700475661T
Semax (7 amino acid analog to ACTH 4-10)
Semax (analogue of ACTH (4-10))

- Discovered and research in Russia (unfortunately a lot of studies are all in Russian without an abstract)
- 7 Amino acid
- Has no hormonal activity

Semax (analogue of ACTH (4-10))

- Study in rat brains occluding the middle cerebral artery
- Shown to increase brain-derived neurotrophic factor (BDNF), NGF (Nerve growth factor) TrkB (tyrosine kinase receptor type 2)
- Neurotrophic tyrosine kinase receptor type 2 (TrkB), which has the highest affinity for brain-derived neurotrophic factor (BDNF) and is involved in neuronal plasticity
Semax is nootropic

• 1997 a paper published
15 years experience

• Semax significantly
improves memory and
attention in healthy men
under extreme
conditions of activities

• intranasal administration
doses 0.015-0.050 mg/kg

Semax in stroke

- Study of 30 patients with acute ischemic stroke
- Semax improved in the recovery of stroke clinically and by EEG
- 12 mg for moderate stroke
- 18 mg for severe stroke
- Tx course--5 and 10 days

Semax is neuroprotective

- Study on neurons with glutamate toxicity
- Semax improved neuronal survival by on average 30%

Semax is neuroprotective

- Heavy Metals are involved in several neurodegenerative disorders
- Semax has a high affinity for copper and may be a chelating agent
- Semax reduced copper induced cytotoxicity

Semax

- Semax has a poor oral deliverly
- Can be delivered by Subcutaneous or intranasal

Suggested dosing
- 750 mcg per nasal spray in each nostril once a day. (total dose of 1500 mcg)
Peptides that was discussed

- Epithalon
- Melanotan 1
- Bremelanotide PT 141
- DSIP
- CJC 1295
- Kisspeptin
- FGL
- Semax