Adult Onset Growth Hormone Deficiency

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Disclosure

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

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Growth Hormone

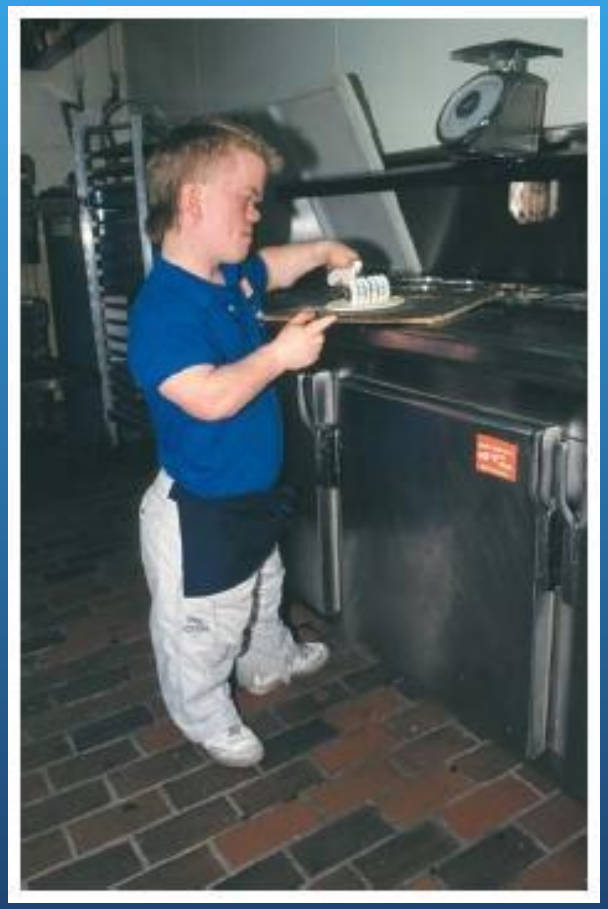
- Growth Hormone is a hormone that stimulates growth and cell reproduction. It is a 191- amino acid, singe chain protein hormone
  - Somatotropin = Growth Hormone
  - GH = Growth Hormone
  - Discovered by Dr. Li (Endocrinologist) in 1955
  - 1971 Dr. Li determined the structure of human growth hormone



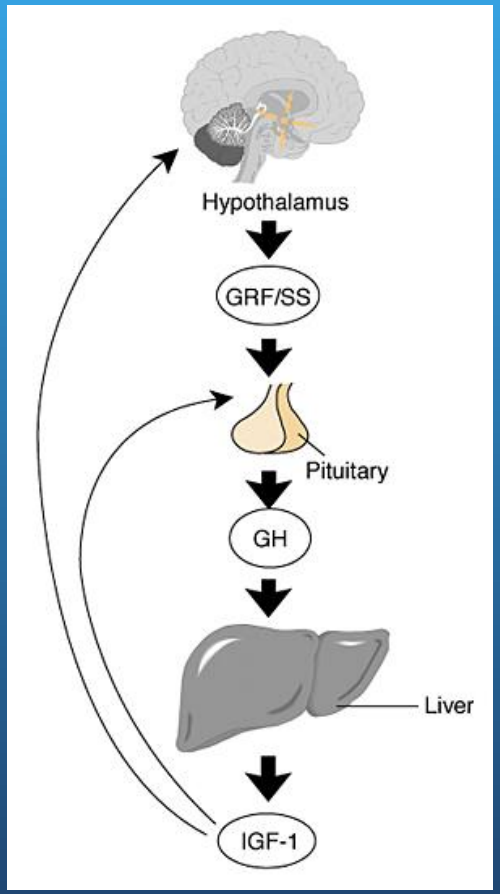
Growth Horome Deficiency



Growth Hormone Deficiency



Growth Hormone Axis

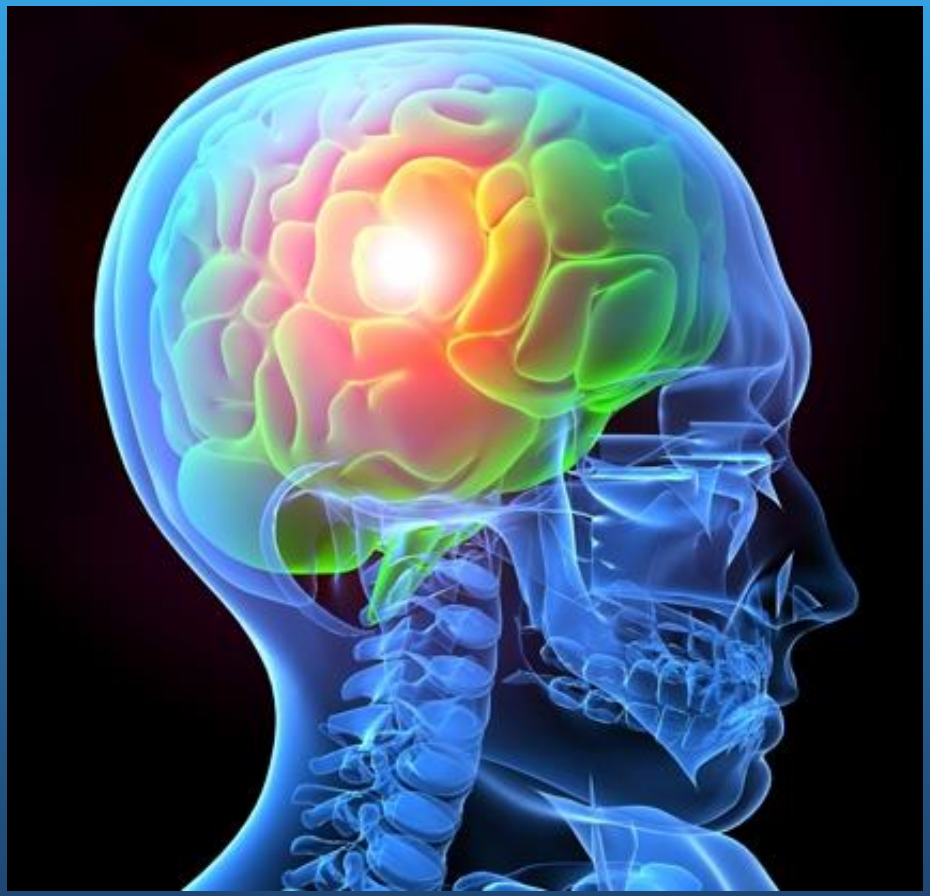


Stimulators and Inhibitors of GH

Stimulatory	Inhibitory
GHRH	Somatostatin “off switch”
Exercise	Lethargy
↑ Ghrelin	↓ Gherlin
↑ Amino Acids	↓ Amino Acids
↓ Blood glucose	↑ Blood glucose
↓ Fatty acids	↑ Fatty acids

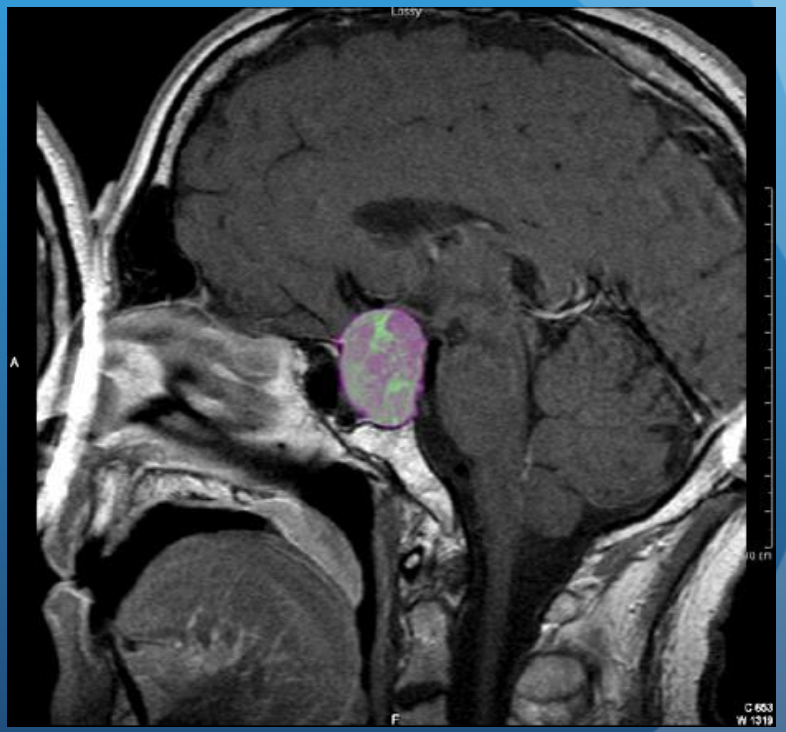


Growth Hormone Deficiency



Growth hormone deficiency

- Pituitary tumor or brain tumors
- Mutation of GHRH
- Prader Willi syndrome, Turner syndrome
- Chronic renal failure
- Radiation
- Sheehan syndrome



Growth Hormone Deficiency

- Ischemia or stroke
- Autoimmune inflammation-hypophysitis (rare)
- Traumatic Brain Injury



Growth Hormone Deficiency

- Small study of veterans who incurred mild TBI during combat
- 25% prevalence of Growth Hormone Deficiency with the glucagon stimulation test



Ioachimescu AG, et al. Pituitary. 2014 Sep 30.

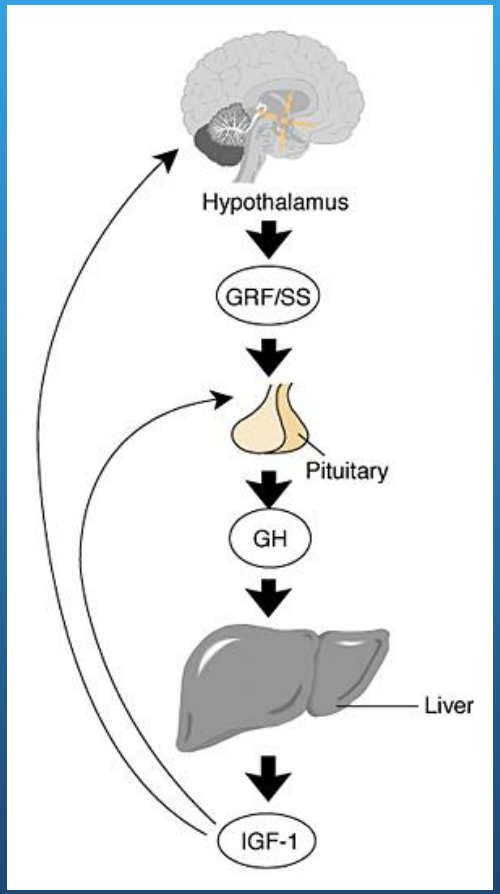
Traumatic Brain Injury

- In a meta analysis of 1015 TBI patients the most common pituitary hormone deficiencies
- Growth hormone and gonadotropin (FSH/LH) deficiencies
- Schneider HJ, et al. JAMA. 2007;298(12):1429-1438.

- 5 year Prospective study on 25 patients with TBI (64% mild and 36% with moderate to severe)
- 28% with GH deficiency
- 4% ACTH deficiency
- 4% Gonadotropin deficiency
- Taniverdi F, et al. J Neurotrauma. 2013;30(16):1426-1433



Growth Hormone Axis



IGF-1 (Insulin Growth Factor)

- IGF-1 is produced by the Liver.
- Stimulated by GH
- Approx 98% of IGF-1 binds to a binding protein
- 80% of IGF-1 binds to IGF- BP3



IGF-1

- Half life of 8 min when free
- Half life of 20 hours when bound to BP3



IGF-1 levels

Friedrich N, et al. Growth Hormone and IGF-1 Research 18(2008): 228-237

Age	Women IGF-1 ng/ml	Men IGF-1 ng/ml
20-24	175-260 (216)	188-257 (215)
30-34	139-195 (164)	137-199 (161)
40-44	110-163 (135)	113-172 (143)
50-54	108-167 (137)	110-160 (125)
60-64	94-139 (119)	93-134 (119)
70-74	73-119 (98)	82-125 (104)
Overall	110-182 (142)	114-187 (145)



Action of IGF-1

- Stimulates cell growth
- Inhibits programmed cell death
- Almost every cell in the human body is affected by IGF-1, especially cells in muscle, cartilage, bone, liver, kidney, nerves, skin and lungs.



- IGF-1 is the active hormone of GH

IGF Binding Proteins

- 6 IGF Binding Proteins
- Inhibit and Enhance IGF Actions
- IGF-1 + IGFBP-3 + Acid Labile Subunit = Ternary Complex
- Half-Life of Ternary Complex = 15 hours
- IGFBP-3 has independent actions and inhibits cancer



Adult Growth Hormone Deficiency

- Increase truncal and visceral fat
- Decrease lean mass
- Osteopenia
- Insulin resistance
- Increase mortality

- Van Bunderen CC. et al. *The Journal of Clinical Endocrinology & Metabolism*, Volume 96, Issue 10, 1 October 2011, Pages 3151–3159

- Increase athreosclerosis
- Decrease exercise capacity
- Decrease cardiac function
- Diminished quality of life

- Frohman LA, et al. *Ann Intern Med 2002 Aug 6;137(3):202-4*

Benefits of Growth Hormone



Growth Hormone & Cardiac Function

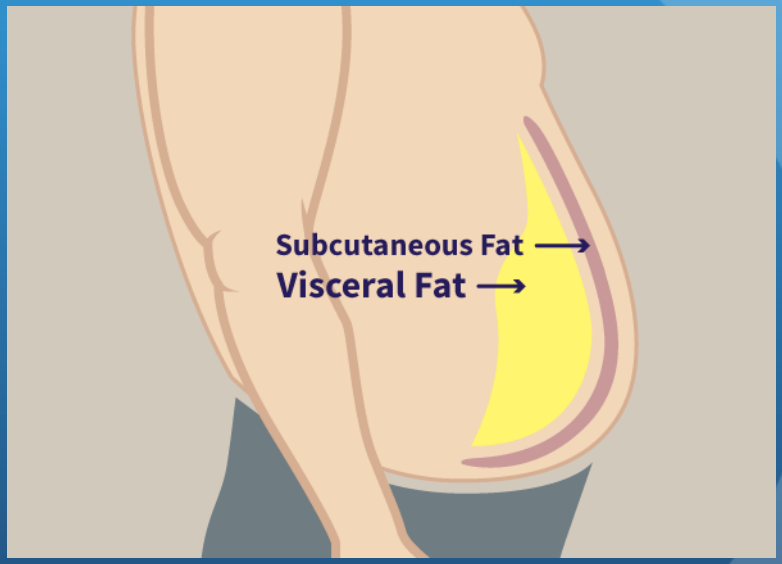
- 18 patients treated with GH x 2 years
- Mean dose of 0.5 mg per day
- Improved Ejection Fraction and Cardiac Function
  - Increased Left Ventricular Mass Index
- Reduced Metabolic Syndrome

- Follin C, et al J Clin Endocrinol Metab. 2006 May;91(5):1872-5



Growth Hormone and Fat

- Adipose Tissue is a major target for GH action
- GH inhibits adipocyte differentiation
- GH Rx reduces adipocyte size and enhances lipolysis



- Garten A, et al. **Endocrinology and Metabolism Clinics - Vol 41, Issue 2 (June 2012)**

Growth Hormone and Fat

- Double blind study in 254 HIV infected patients with excess Visceral Adipose Tissue (VAT)
- 4 mg daily versus 4 mg every other day
- 12 week study
- Group that got the 4 mg daily significantly reduced VAT (8.6%)
  - Kotler DP, et al. J Acquir Immune Defic Syndr. 2004 Mar 1;35(3):239-52.



Growth Hormone and Fat

- Double blind randomized placebo control 12 month study in postmenopausal women
- GH dose of 0.5 to 0.6 mg/day
- GH decrease CRP, IL-6 and Visceral Fat



- Franco C, et al. J Clin Endocrinol Metab. 2007 Jul;92(7):2644-7.

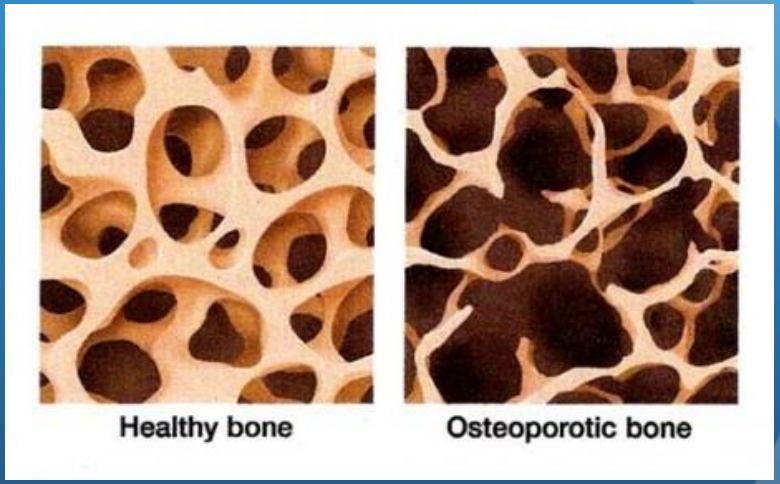
Growth Hormone Insulin Resistance

- Some studies shows that it improves IR (insulin resistance)
  - Follin C, J Clin Endocrinol Metab. 2006 May;91(5):1872-5.
  - Nam SY, et al. Int J Obes Relat Metab Disord. 2001 Aug;25(8):1101-7.
  - Thankamony A, et al. J Clin Endocrinol Metab. 2016 Jan;101(1):131-42
- Other studies shows that it can increase insulin resistance
  - Sanchez-Ortiga R, Clin Endocrinol (Oxf). 2012 Jul;77(1):86-93
  - Souza FM, et al, Arq Bras Endocrinol Metabol. 2011 Nov;55(8):559-65.



15 years of rhGH on bones

- 230 adults with adult GHD
- 15 years of treatment improved BMD in lumbar spine and stabilization of the femoral neck
- No increase in fracture



- Appelman-Dijkstra NM, Clin Endocrinol (Oxf). 2014 Nov;81(5):727-35

Growth Hormone Fibromyalgia

- Largest study and longest placebo controlled trial
- 120 patients x 18 months
- GH 0.006 mg/kg/day
- GH has been shown to reduce pain
  - Cuatrecasas G, et al. Pain. 2012 Jul;153(7):1382-9.



Growth Hormone Exercise Capacity

- Randomized single blind controlled study in 56 patients with CHF (II-IV)
- 28 patients
  - treated w/ GH 0.012 mg/kg every other day
- Improves Exercise Capacity
  - Improves Left Ventricular Function
  - Improves Quality of life
    - Cittadine A, et al. J Clin Endocrinol Metab. 2009 Sep;94(9):3329-36



Growth Hormone & Atherosclerosis

- 5 year study prospective controlled on GH treatment on atherosclerosis
  - N = 44
  - 26 in the treatment group
  - Avg dose is 6 mcg/kg/day
- Significant improvement in Atherosclerosis
  - Improved Intima-Media Thickness
    - Colao A, et al. J Clin Endocrinol Metab. 2008 Sep;93(9):3416-24.



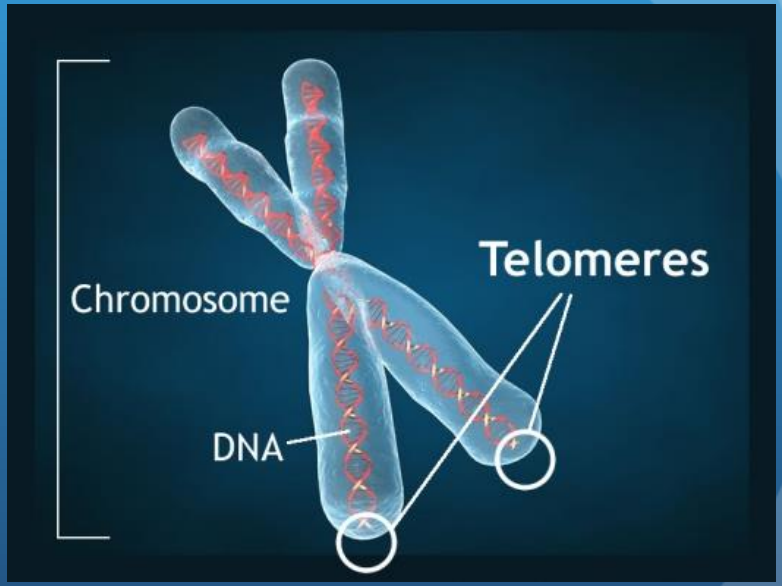
Growth Hormone & Immune System

- GH helps with the development T cells
- IGF-1 improves survival in Sepsis in mice
  - Prevents TNF- induced Kupffer cell death
  - Lowers TNF, IL-6 and improves hepatic bacterial clearance
  - Improves survival in mice with sepsis 12 hours later with IGF-1 Tx
    - Ashare A, et al. Am J Respir Crit Care Med. 2008 Jul 15;178(2):149-57.



Growth Hormone & Telomeres

- Currently no studies on HGH on improving on telomere lengths
- In a 2744 elderly men study showed that the men with the highest IGF-1 had the longest telomere lengths and the group with the lowest IGF-1 had the shortest telomere lengths.
  - J Clin Endocrinol Metab, 2009 Dec;94(12):5078-84.



Diagnosis for adult onset GH deficiency

- Screening test with IGF-1 and IGF BP3
- Insulin Tolerance Test
  - Gold Tolerance Test
  - Considered to be “dangerous”
- Glucagon Stimulation Test
- Later an MRI to rule out a pituitary tumor



There is one exception to testing

- If you have 3 or more pituitary hormone deficiency and a low IGF-1 then you do not need to do a stimulation test

  - Low ACTH with low cortisol
  - Low TSH with low T4 and low T3
  - Low LH with low testosterone
  - Low ADH with Diabetes Insipidus
    - Hartman ML, J Clin Endocrinol Metab. 2002 Feb;87(2):477-85.



Insulin Tolerance Test

- Fasting Test (Nothing eaten for 12 hrs)
- Baseline glucose and Growth Hormone
- An IV with Normal Saline at a rate to keep the vein open
- Insulin not a mixed 70/30 or a long acting insulin is given
- Fast acting Insulin is given at 0.1 to 0.5 units per kg intravenous push. Not SQ injection. Dose varies in insulin sensitivity



Insulin Tolerance Test

- Monitor finger stick glucose readings every 5 to 10 minutes
- If the finger stick glucose is less than 50 mg/dl and the patient is symptomatic then draw another glucose and GH
- Symptoms are hunger, dizziness, shakiness, sweating, tachycardia,



Insulin Tolerance Test

- A health care provider must be present during the entire test
- Have an Amp of Dextrose 50 grams next to the patient in case of an emergency (like a seizure)
- Patient to drink a soda with real sugar and also to eat candy and a sandwich to get the glucose above 90 mg/dl.



Insulin Tolerance Test

- Contraindicated
  - History of seizures
  - History of ischemic heart disease
- If the glucose is less than 40 mg/dl (serum levels will be lower) and the GH is less than 5 ng/mL then this test is positive for Growth hormone deficiency
- less than 3 ng/mL indicates severe Growth hormone deficiency



- Glynn N and Agha A International Journal of Endocrinology, vol. 2012, Article ID 972617, 7 pages, 2012.

Glucagon Stimulation test

- Contraindicated
  - Diabetes
  - Pheochromocytoma or insulinoma (may provoke an attack)
  - History of unstable coronary artery disease
- Fasting from Midnight
- IV is inserted for IV access
- Glucagon 1 mg IM injection
  - 1.5 mg IM if patient weighs over 90 kg



Glucagon Stimulation Test

Yuen KC et al. Endocr Pract. 2016 Oct;22(10):1235-1244

- Serum Glucose and GH
  - Time zero,30, 60, 90, 120, 150 and 180 min
  - Blood glucose typically rises at 90 min then it falls
  - GH peaks b/w 120 and 180 minutes
- GH Deficiency is GH levels fail to rise above 3 ng/ml
- In 2016 AACE has suggested that a lower GH cut-point of 1 µg/L for overweight/obese patients and in those with glucose intolerance



Human Growth Hormone (HGH)

- Start low and titrate upwards
- Always use HGH at bedtime
- Start at 0.1 mg SQ qhs
- Average dose is 0.3 mg to 0.5 mg SQ at bedtime
- Occasionally - 1 mg SQ at bedtime



Side Effects w/ Growth Hormone

- Side effects may be
  - Swelling
  - Carpal Tunnel Syndrome
  - Paresthesia
  - Joint Pains
    - Usually improves by reducing the dose



Growth Hormone & Cancer

- Does GH cause Cancer?
  - No increase in cancer
  - Children and adults treated with GH has revealed no increase in observed cancer risk (Leukemia and Colon Cancer)
    - Endocrinology 2006, 64 (2): 115-121 P.J. Jenkins



Growth Hormone & Cancer

- 25 year retrospective study
  - (1985- 2009)
- Mortality rate from Cancer was not elevated in patients receiving GH

- Van Bunderen CC, et al. J Clin Endocrinol Metab. 2011 Oct;96(10):3151-9



Long term safety of GH (2018)

Stockholm K, et al. Clin Endocrinol (Oxf). 2018 Apr;88(4):515-528

- 28 year review of safety data from the manufacturers' Growth Hormone registries
- Data from 1988- 2016
- There was no increased risk of mortality in children or adults treated with GH
- There was no evidence of an increased risk of stroke, new malignancy, leukemia, non leukemic extra cranial tumors or recurrence of intracranial malignancy in patients without risk factors (history of radiation Rx)

GH Therapeutic Use

- GH has been used to slow or reverse some of the debilities of aging
  - Effects of aging diminished muscle strength and bone mass, reduced energy, reduced resilience
- In the US it is approved for adult onset GH deficiency
  - Proper diagnosis with a stimulation test is required
  - Unfortunate it is not approved for patients with GH insufficiency
    - physicians have lost their medical license & have went to jail for prescribing HGH without the proper testing





IGF-1 Therapy (Mecasermin/ Increlex)

- IGF-1 used in Laron syndrome
  - Mutation in the GH receptor
  - IGF-1 deficiency
  - Severe short stature
  - Reserved for Children or adults with Growth hormone resistance
  - Improves Insulin Sensitivity
    - Backeljauw P, et al. J Pediatr Endocrinol Metab. 2010 Jan-Feb;23(1-2):3-16.



IGF-1 with IGF BP3

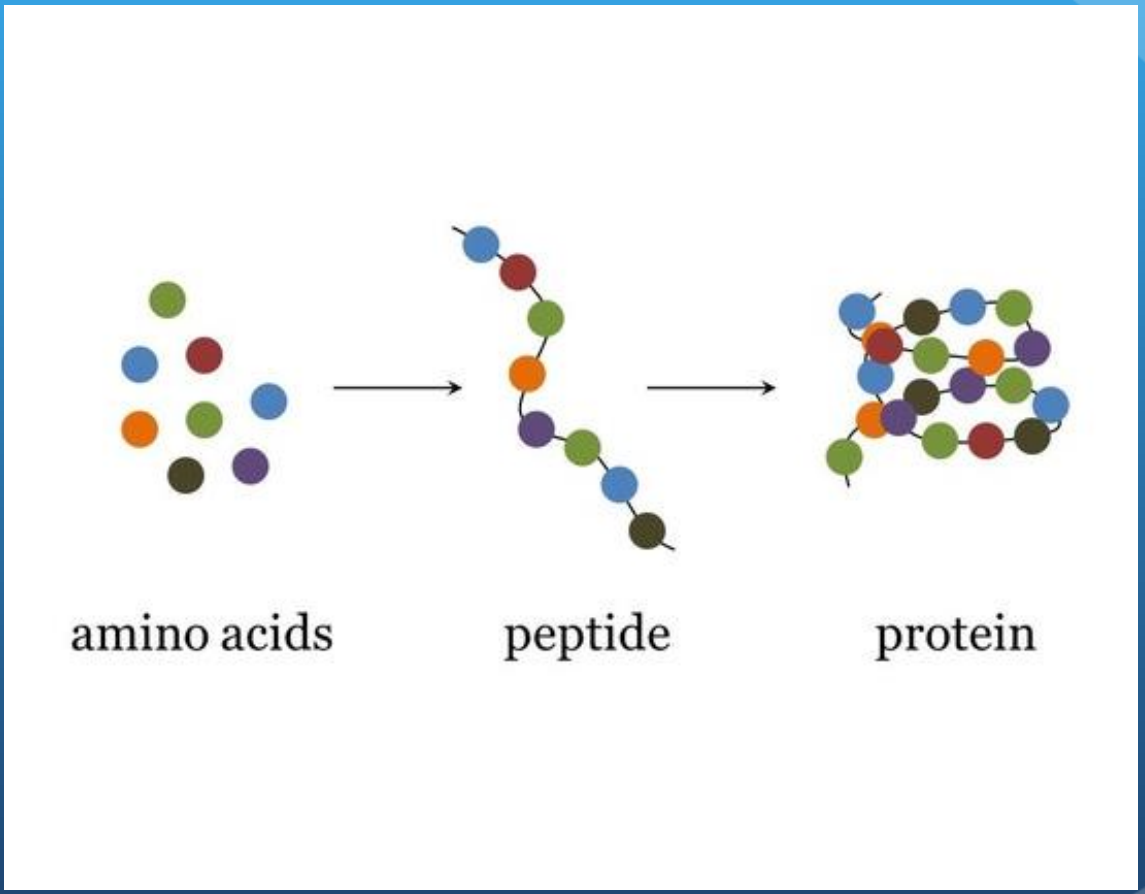
- Mecasermin rinfabate (Iplex)
  - IGF-1 with IGF Binding Protein 3
  - To prolong the half life of IGF-1
  - Less side effect of hypoglycemia
  - IGF BP-3 has independent actions and inhibits cancer
  - IGF BP3 inhibits tumor angiogenesis by decreasing VEGF
    - Ingermann AR, et al. J Biol Chem. 2010 Sep 24;285(39):30233-46.

IGF-1 with IGF BP3

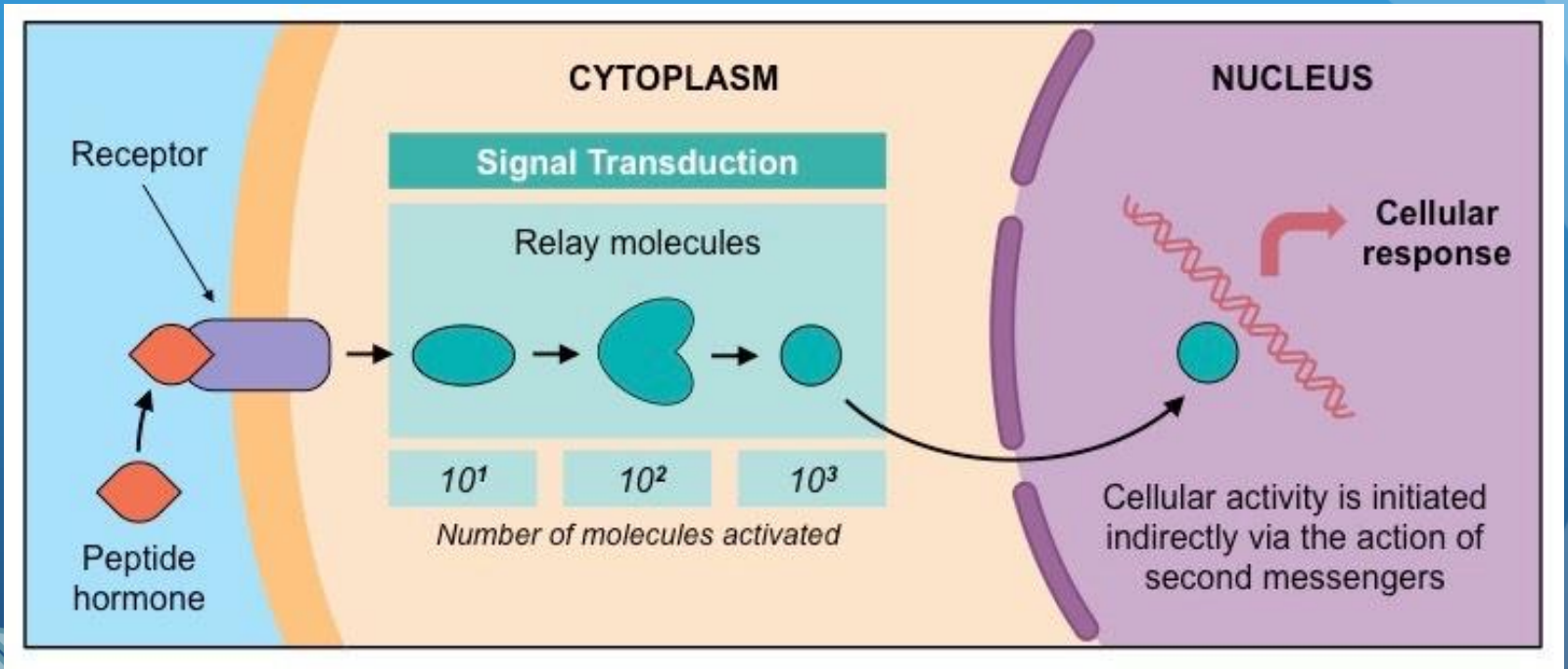
- Mecasermin rinfabate (Iplex)
  - Indicated for Children with severe primary IGF-1 deficiency
  - Trials looking at Muscular dystrophy, HIV associated adipose redistribution syndrome, retinopathy of prematurity
  - Unfortunately the trial looking at Iplex with Lou Gehrig's disease (ALS) did not help
- Sorenson EJ et al. Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. Neurology. 2008 Nov 25;71(22):1770-5



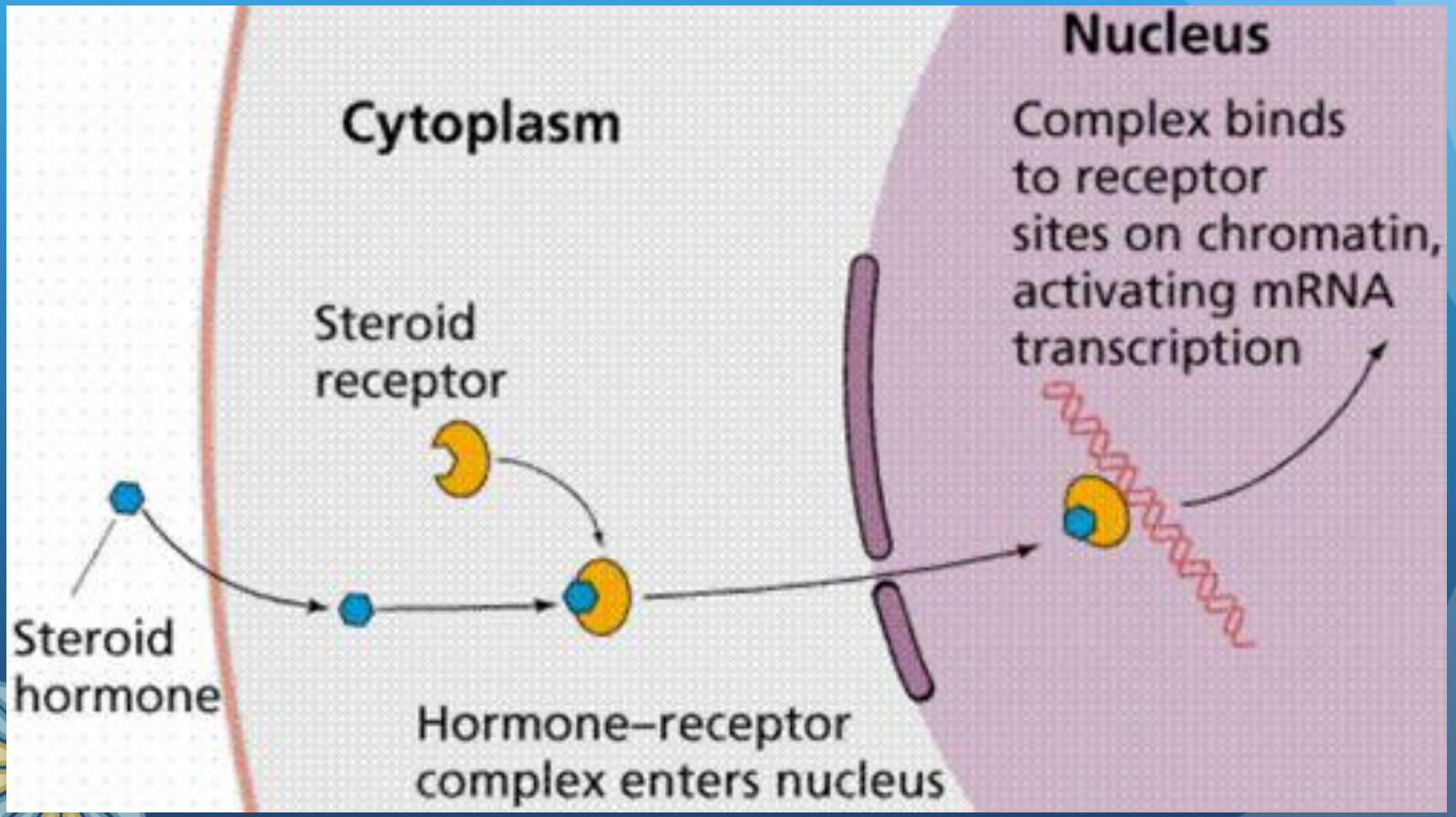
Peptides



Peptide Action



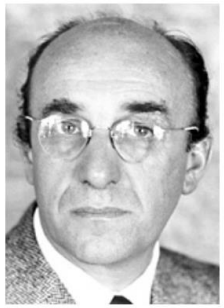
Steroid hormone action



Growth Hormone Releasing Hormone is a peptide

- GHRH is a 44 amino acid peptide hormone produced in the arcuate nucleus of the hypothalamus
- GHRH was first described by the Nobel Laureates, R. Guilleman and A. Shalley in the 1970's

The Nobel Prize in Physiology or Medicine 1977



Roger Guillemin
Prize share: 1/4



Andrew V. Schally
Prize share: 1/4



Rosalyn Yalow
Prize share: 1/2

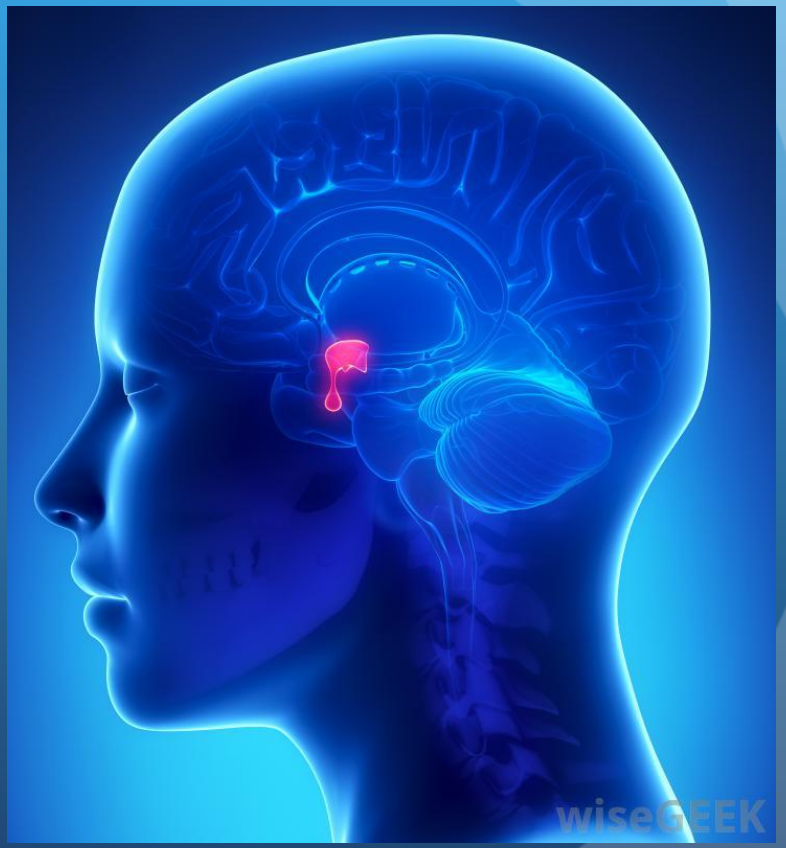
Use of rHGH vs GHRH

- rHGH is only one form of Growth Hormone, the 22 Kdalton.
- rHGH does not reproduce the normal pulsatile pattern of GH
- Growth hormone releasing hormone will release of 5 isoforms of Growth Hormone
- GHRH helps reproduce the normal pulsatile pattern of GH release



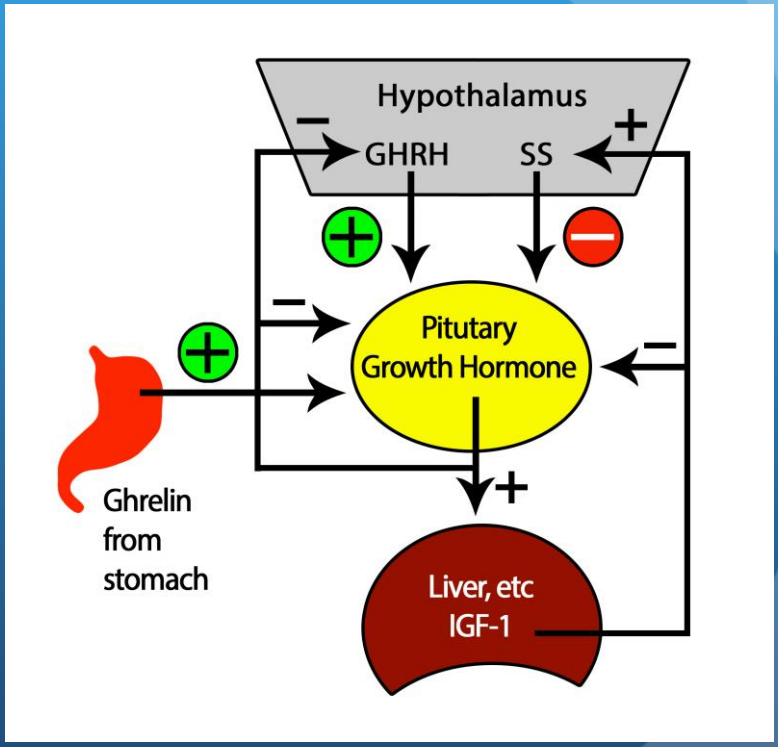
rHGH vs GHRH

- GHRH/ GHRP is more physiologic compared to rHGH
- One needs a working pituitary gland for GHRH/ GHRP to work



Growth Hormone Releasing Hormone

- GHRH is a 44 amino acid peptide hormone
- The first part 1-29 is the active part of the hormone to stimulate Growth Hormone
- Degraded by DPP4 enzyme



Sermorelin (Modified GHRH)

- Sermorelin is a synthetic version of the 1-29 amino acid of GHRH
- In 1991 Sermorelin was FDA approved for injection use to diagnosis and treatment of GH deficiency in children



- 16 children with short stature were treated with GHRH 1-29 for 9 months
- A significant improvement in height velocity was observed in the children
- SubQ 30 µg/kg per day

- Prakash, Amitabh, and Karen L. Goa. "Sermorelin." *BioDrugs* 12.2 (1999): 139-157.

Sermorelin (Modified GHRH)

- Is no longer commercially available
- Available through a compound pharmacy
- A dosage of 0.2 - 0.3 mcg of sermorelin once daily at bedtime by subQ injection

- Side effects of less than 1% include:

  Injection site reaction, headache, flushing, dysphagia, dizziness, somnolence and urticaria



Modified GHRH

- In the USA, the GHRH of choice has been Sermorelin
- In Australia the GHRH of choice is CJC 1295
- Another name for CJC 1295 is ModGRF129



CJC- 1295 (modified GHRH)

- Is a modified GHRH 1-29
- CJC 1295 has four amino acid substitutions in GHRH(1-29) to enhance activity and render it resistant to degradation by proteolytic enzymes

- Thorner, M. O. (2008), The Discovery of Growth Hormone-Releasing Hormone[1]: An Update. Journal of Neuroendocrinology, 20: 653–654.



- CJC 1295 has a half life of 30 minutes
- CJC 1295 with DAC (Drug affinity complex) half life is 6 days
- Sermorelin has a half life of 10-minutes

- Esposito, P., et al. "PEGylation of growth hormone-releasing hormone (GRF) analogues." *Advanced drug delivery reviews* 55.10 (2003): 1279-1291.

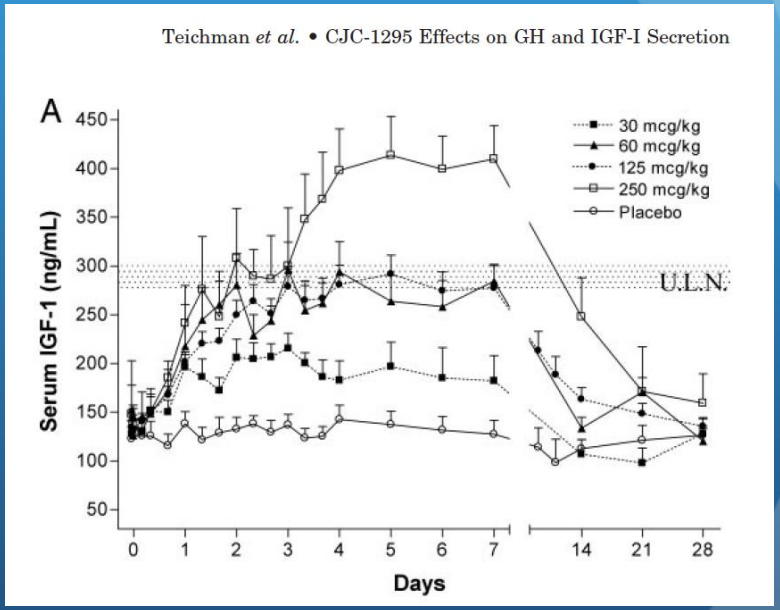
CJC- 1295 (modified GHRH)

- CJC 1295 can be compounded in two forms (DAC and non-DAC).
- Drug affinity complex (DAC) prevents enzymatic degradation thus increasing the half-life.
- Using CJC 1295-NON-DAC daily (between 6-8pm) provides a more effective GH spike at 1:00am.



CJC- 1295 (modified GHRH)

- Study looking at doses from 30 to 250 mcg/kg
- 24 healthy adults
- IGF-I levels increased within 8 hrs injection
- No serious adverse reactions were reported



- Teichman S, et al. The Journal of Clinical Endocrinology & Metabolism 91(3):799–805

CJC- 1295 (modified GHRH)

- 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.



- Perras B, et al Psychoneuroendocrinology 1999 Oct;24(7):743-57

Growth Hormone Releasing Peptides- since 1984 (not GHRH)

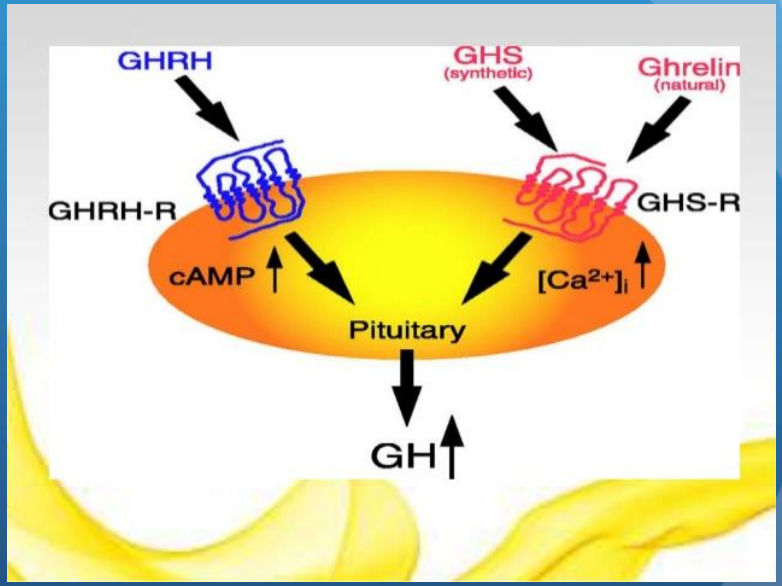
- **Growth Hormone Releasing Peptides (GHRP)** are a chemical class of Growth Hormone (GH) secretagogues that act on the hypothalamus and the pituitary to release GH
- Growth hormone releasing peptide-6 (GHRP 6) - hexapeptide (6 amino acids) was discovered in 1984
- GHRP 6 was the first GHRP discovered



- Johansen PB, et al. x e n o b i o t i c a , 1998, v o l . 28, n o . 11, 1083± 1092

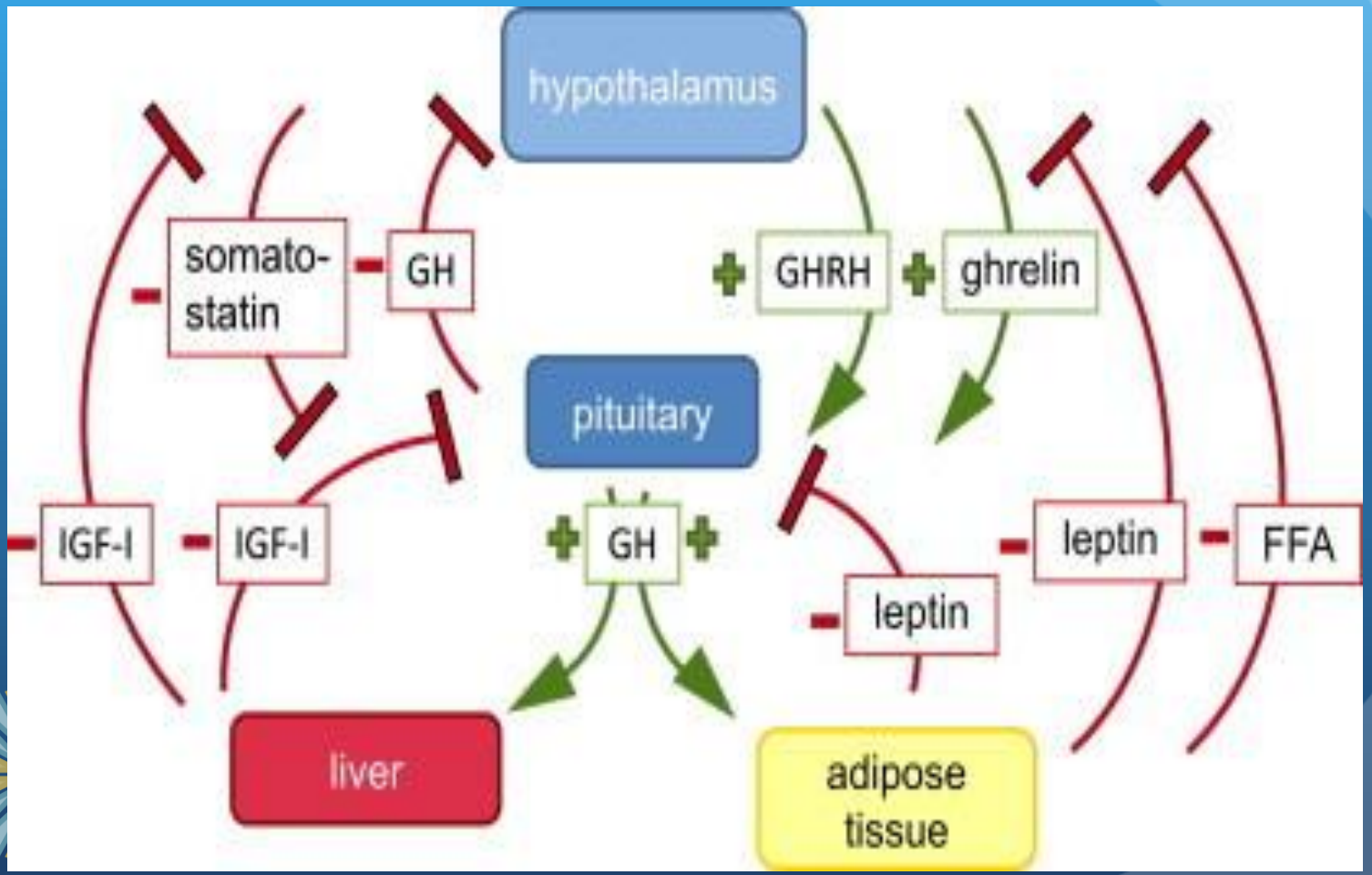
Growth Hormone Releasing Peptide –GHRP not GHRH

- GH-releasing peptides (GHRP), can induce GH release from the pituitary.
- GHRP acts differently than GHRH. GHRP acts on a different receptor called Ghrelin receptor.



Growth Hormone Axis -2

Endocrinology and Metabolism Clinics - Volume 41, Issue 2 (June 2012)



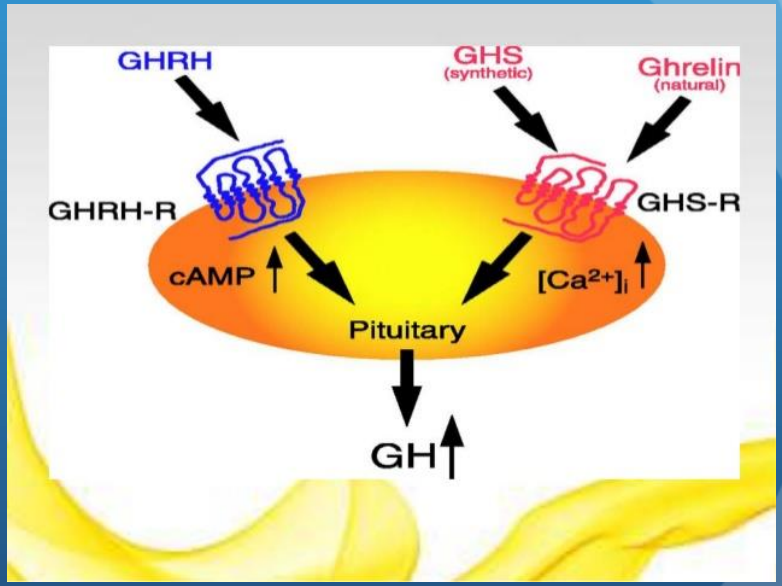
Different GHRP

- GHRP-1
- GHRP-2
- GHRP-4
- GHRP-5
- GHRP-6
- Alexamorelin
- Ipamorelin
- Hexarelin

- Thomas, Andreas, et al. *Analytical and bioanalytical chemistry* 401.2 (2011): 507-516.

Another type of GHRP- Ipamorelin

- Ipamorelin is a third generation of GHRP with 5 Amino acids
- Ipramorelin increases Growth Hormone via Ghrelin receptor
- Ipamorelin lowers somatostatin levels which Increases GH



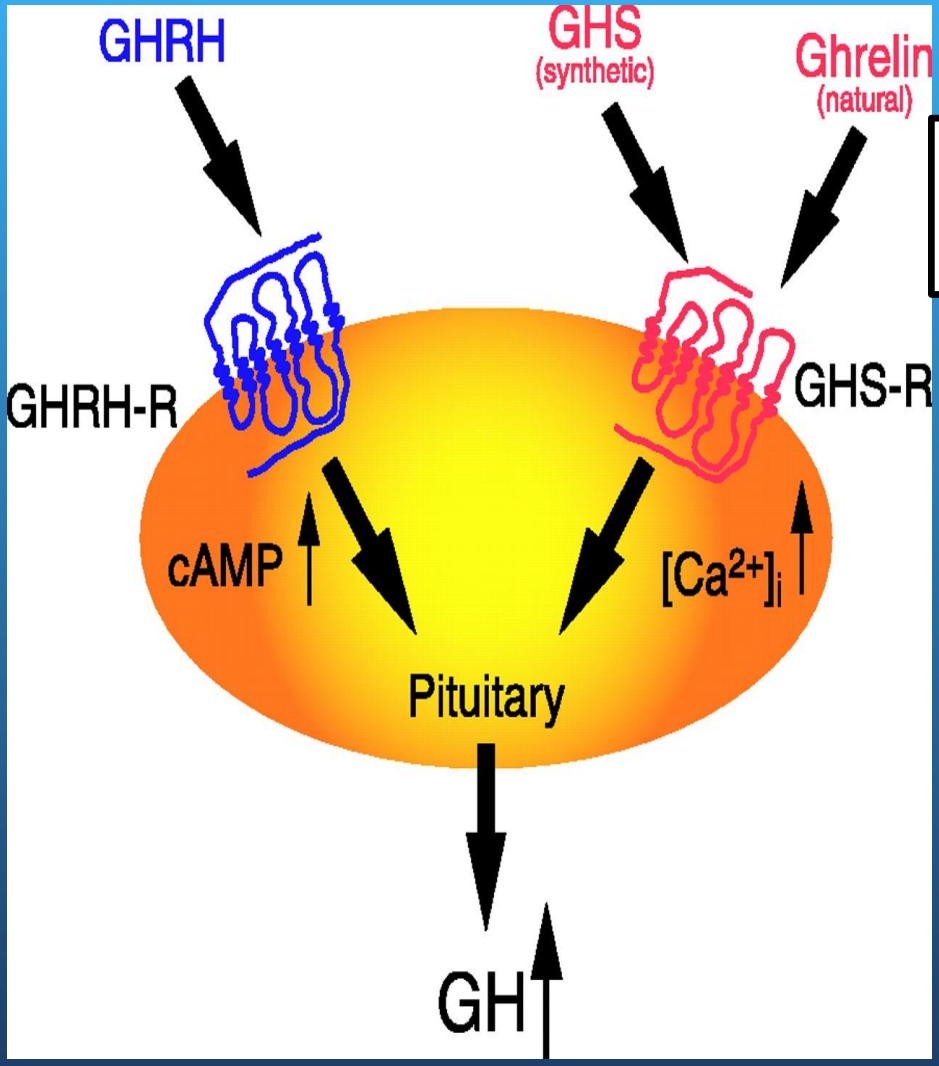
Another type of GHRP- Ipamorelin

- Ipamorelin was originally developed by Novo Nordisk
- Ipramorelin does not raise cortisol, prolactin or aldosterone
- .



PEPTIDES & THE PITUITARY

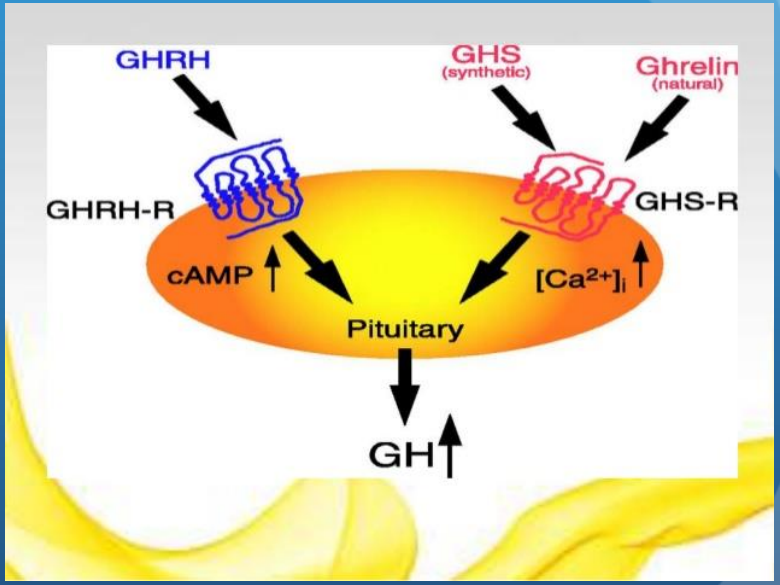
CJC-1295
TESOMORELIN
SERMORELIN
GRF-18



IPAMORELIN
HEXARELIN
GHRP6
GHRP2

CJC 1295 with Ipamorelin

- The action of CJC 1295 (modified GHRH) is potentiated by adding GHRP
- One of the most effective is Ipamorelin



CJC 1295 with Ipamorelin

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




HOT
STUFF

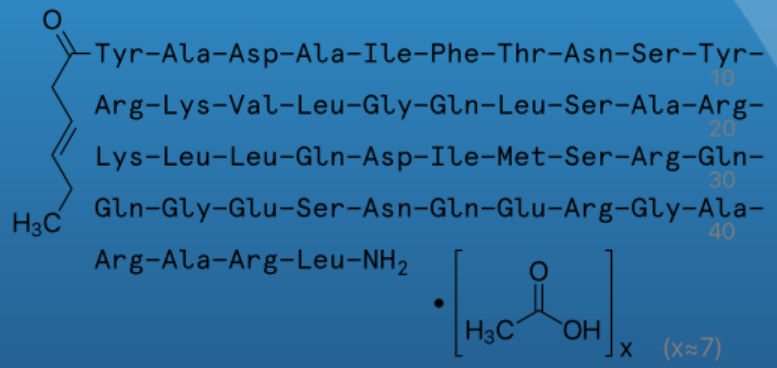
Tesamorelin- GHRH

- Tesamorelin, developed by the Canadian pharmaceutical company Theratechnologies
- Tesamorelin (brand name Egrifta)
- Stabilized against dipeptidyl peptidase IV (DPP4) degradation
- Half life of 30 minutes
- GHRH half life of 7 min



Tesamorelin- GHRH

- 44 amino acids of human GHRH with the addition of a *trans*-3-hexenoic acid group
- formerly known as TH9507



Tesamorelin- GHRH

- 2010 FDA approves Tesamorelin for HIV lipodystrophy



Tesamorelin- GHRH

- Harvard Study- in Healthy Men
- Tesamorelin 2 mg sc once daily for 2 wk
- Raises IGF-1 level by 182

	Base-line	2 week	4 week
IGF-1	148	329	161

- Takara L, et al. J Clin Endocrinol Metab, January 2011, 96(1):150–158



Tesamorelin- GHRH

- Reduces Triglycerides
- Reduces Visceral Adipose Tissue
- Reduces Carotid Intima Media Size
- Improves Cognition in people over 60 years

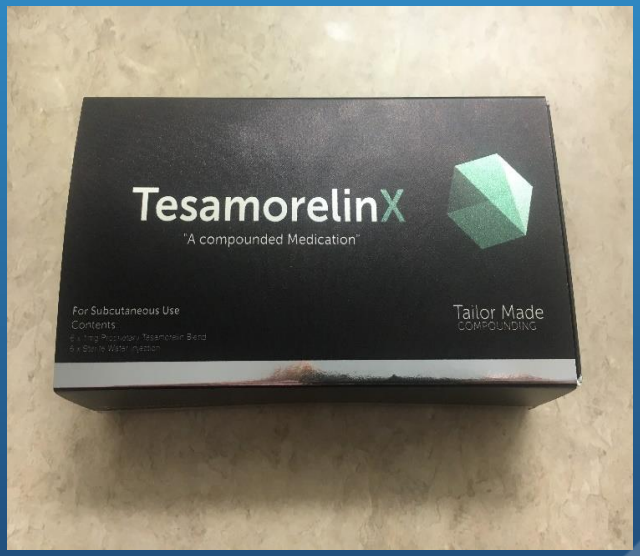


- Baker, L. D. et al. Arch. Neurol. doi:10.1001/archneurol.2012.1970

Tesamorelin - Dosing Protocol

- 1 mg injected at bedtime subcutaneously 5-6/7 days a week
- Compounded with Trehalose instead of Manitol





Growth Hormone Therapy

- Decreases truncal and visceral fat
- Increase lean mass
- Improves bone density
- Lowers Insulin resistance
- Decreases athreosclerosis
- Improves exercise capacity
- Increase cardiac function
- Improves quality of life.



- Frohman LA, et al. *Ann Intern Med 2002 Aug 6;137(3):202-4*


Thank
You