A Grouped Knowledge Presentation

"Bringing science to you!"

Disclosure

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

Equipment: N/A
Speakers Bureau: **NA**
Stock Shareholder: **NA**
Grant/Research Support: **NA**
Consultant: **NA**

Status of FDA devices used for the material being presented: N/A
Status of off label use of devices, drugs or other materials that constitute the subject of this presentation: N/A

Interventional Endocrinology:

Mark L. Gordon, M.D.

2020 Update on Growth Hormone

Program Lecture Goals

1. Learn about the pervasive nature of human Growth Hormone in the body.
2. Learn about the benefits of GH in cell function and repair.
3. Learn how to legally prescribe GH based upon the different challenge tests.
4. Learn about GH-secretagogues as an alternative to rhGH.

Program Content

1. **Introduction – Why replace Growth Hormone?**
2. **Neuroendocrinology**
3. **Actions of GH and IGF-1**
4. **Laboratory Diagnosis of Deficiency**
5. **GH activation of IGF-1**
6. **Cancer and GH/IGF-1 – The P53 Connection**
7. **Evaluation and Treatment - Protocols**
8. **Secretagogue Technology**

A case to think about

Case #1 – What needs to be done?			
9am draw	Results	Median	½ Life
Growth Hormone	14.20	~ 5.0 ng/ml	20 min
IGF-1	467	> 200 ng/ml	8-10 min
IGFBP-3	7200	> 4000 ng/ml	20-24 hrs

We'll address at the end of presentation.
Thank you ☺

The obvious question is:

So, Why Replenish GH?

The
Growth Hormone
Dilemma

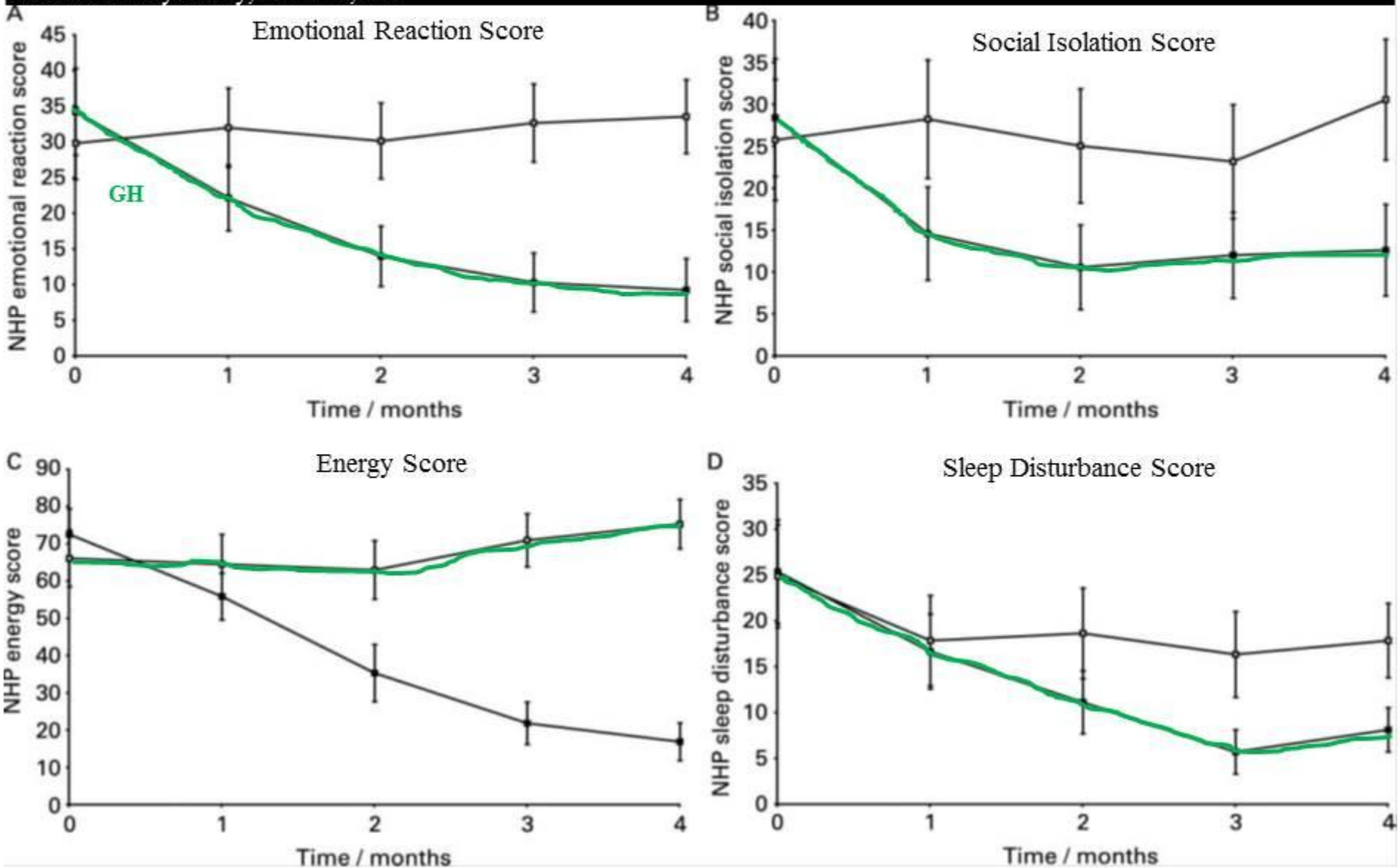
Neuropsychiatry

Psychiatric and neuropsychological changes in growth hormone-deficient patients after traumatic brain injury in response to growth hormone therapy. J Endocrinol Investigation. 2010 Dec;33(11):770-5. Maric NP, Doknic M, Pavlovic D, Pekic S, Stojanovic M, Jasovic-Gasic M, Popovic V

- GH-deficient TBI patients are depressed and have cognitive impairment.
- **GH therapy induced reduction of depression, social dysfunction, and certain cognitive domains.**

Atypical depression in growth hormone deficient adults, and the beneficial effects of growth hormone (rhGH) treatment on depression and quality of life.

European Journal of Endocrinology (2004) 151 325–332 Tripti Mahajan, Anna Crown, Stuart Checkley, Anne Farmer and Stafford Lightman, Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Institute of Psychiatry, London, UK.



Cardiology

Growth hormone replacement reduces C-reactive protein and large-artery stiffness but does not alter endothelial function in patients with adult growth hormone deficiency. Clinical Endocrinology, 62 . pp. 473-479 **2005**. Roland W. et al. Division of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

- GH replacement may lead to differentially altered production of vasorelaxant agents from the endothelium of large and small arteries. (▲NO)
- **Reduction in vascular inflammation (IL-6▼,TNF-α▼) is associated with reduced vascular risk.**
- (Add Testosterone and you get reduced TH1 and increased TH2 parameters promoting a greater anti-inflammatory environment.

Effects of growth hormone administration on Homocysteine levels in men with GH deficiency: a randomized controlled trial.

Journal Clin Endocrinol Metab. **2001**; 86(4):1518-24 Sesmilo G; et al. Department of Laboratory Medicine, Children's Hospital and Harvard Medical School, Boston, 02114, USA.

- GH decreases Homocysteine compared with placebo thereby, reducing Endothelial Dysfunction (the other ED).
- Homocysteine has been found to produce more Endothelial Dysfunction than Cholesterol.
- **Endothelial Dysfunction Factors** (EDF): Trans-fatty Acids, Glucose, Uric Acid, Progestins, Homocysteine, smoking, and Hx of Septicemia.

Gastroenterology

Pulmonology

Immunology

Orthopedics

Effect of Growth Hormone Treatment on Fractures and Quality of Life in Postmenopausal Osteoporosis: A 10-Year Follow-Up Study.

Emily Krantz, Penelope Trimpou, and Kerstin Landin-Wilhelmsen Clinic for Internal Medicine (E.K.), Södra Älvsborgs Hospital, SE-501 82 Borås, Sweden; and Section for Endocrinology (P.T., K.L.-W.), Sahlgrenska University Hospital at Sahlgrenska Academy, University of Gothenburg, SE-413 45 Gothenburg, Sweden

- GH increased BMD and bone mineral content dose dependently in all regions.
- After 10 years the number of fractures decreased from 56% to 28% in patients evenly distributed between groups.
- **In controls, fractures increased from 8% to 32% .**

Effect of Growth Hormone on Vitamin D Metabolism

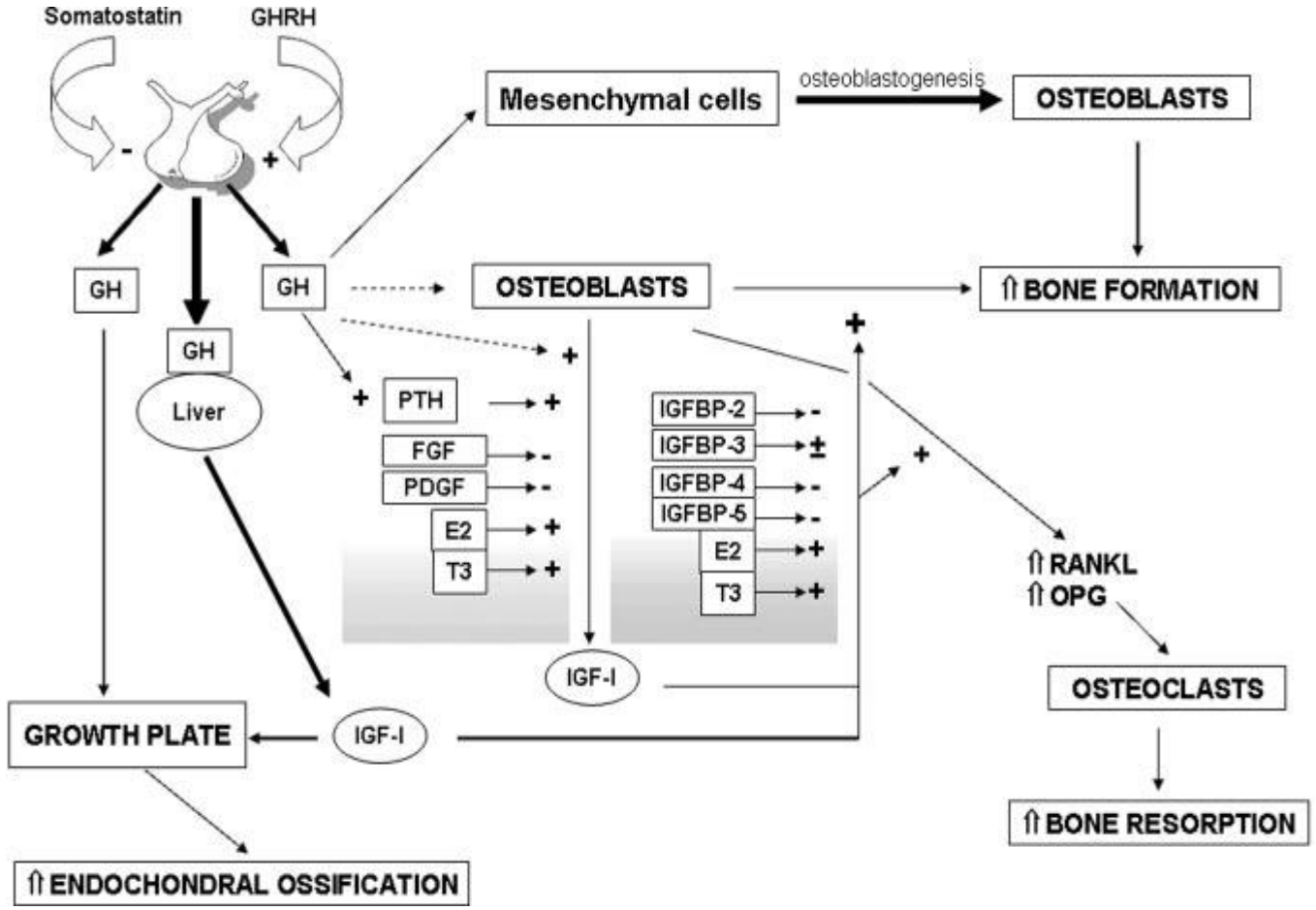
Nature 273, 246 - 247 (18 May **1978**); E. Spanos, D. Barrett*, I. Macintyre, J.Pike, E. Safilian. Endocrine Unit, Royal Postgraduate Medical School, Ducane Road, London W12, UK.

- Vitamin D3 undergoes two hydroxylations; first in the liver, gut and perhaps other organs, to its major circulating form 25(OH)D3 and then in the kidney to $1,25(OH)_2D3$.
- The form $1,25(OH)_2D3$ is the most potent metabolite of Cholecalciferol and may be chiefly responsible for all the effects of the **vitamin/Hormone** on Calcium metabolism.
- Growth Hormone appears to influence the production of $1,25(OH)_2D3$ in the kidney. (Directly?)

Growth Hormone, Insulin-Like Growth Factors, and the Skeleton. Endocrine Reviews 29: 535–559, 2008.

Andrea Giustina, Gherardo Mazziotti, and Ernesto Canalis Department of Medical and Surgical Sciences (A.G., G.M.), Chair of Internal Medicine, University of Brescia, 25125 Brescia, Italy; Department of Research, Saint Francis Hospital and Medical Center (E.C.), Hartford, Connecticut 06105; and The University of Connecticut School of Medicine (E.C.), Farmington, Connecticut 06030

AGHD causes low bone turnover osteoporosis with high risk of vertebral and nonvertebral fractures, and the low bone mass can be partially reversed by GH replacement.



Endocrinology

The Effects Of Growth Hormone Replacement Therapy On Over Night Metabolic Fuels

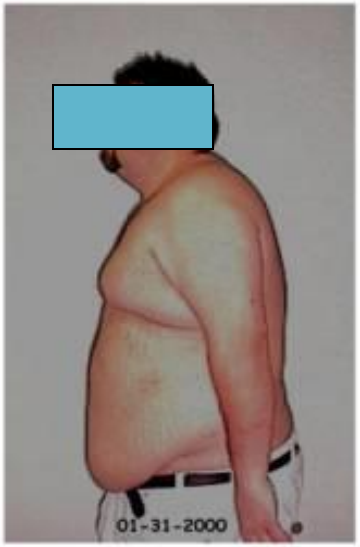
. Clin Endocrinol (Oxf) 2000 Jan;52(1):17-24. Kousta E Section of Endocrinology and Metabolic Medicine, Imperial College School of Medicine, St Mary's Hospital, London, UK.

- Growth Hormone replacement in hypopituitary adults increases fasting and overnight Non-Esterified Fatty Acid (NEFA*) concentrations, consistent with the known lipolytic effect of GH.
- **The appearance of NEFA represents the catabolism of stored body fat.**

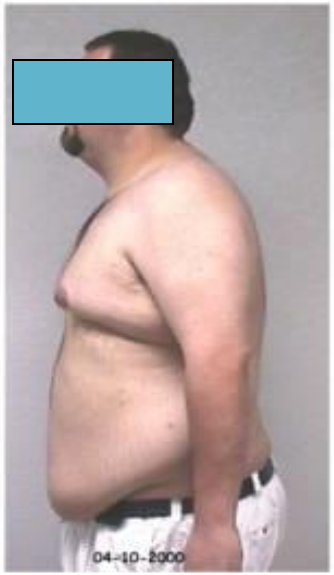
Metabolism of Fat

396 #

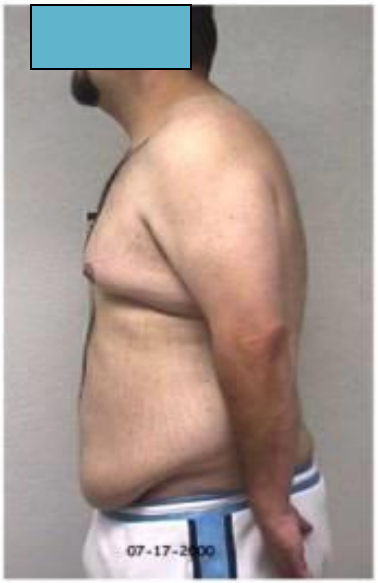
STARTING



3 months



6 months



229 #

9 months.

Body composition, physical exercise, growth hormone and obesity. Eat Weight Dird **2001** Sep;6(3 Suppl):28-37. Weltman A . Departments of Medicine and Human Services, University of Virginia, Charlottesville, VA 22903, USA.

- **GH secretion is blunted profoundly in individuals with *obesity* thereby blunting the natural production of the hormone..**
- Administration of GH to obese adults combined with dietary restriction and exercise appears to enhance favorable changes in body composition and decrease total body fat.

Therapeutic aspects of growth hormone and insulin-like growth factor-1 treatment on visceral fat and insulin sensitivity in adults. **Yuen K**, Dunger D, Division of Endocrinology, Oregon Health and Science University; Portland Oregon. Diabetes, Obesity and Metabolism; 9**, 2007,** 11-22. Blackwell Publishing.

- **Growth hormone exerts anti-insulin actions, whereas IGF-1 has insulin-like properties.**
- High Dose of GH has a major effects on lipolysis, promoting its anti-insulin effects, whereas IGF-1 acts as an insulin sensitizer that does not exert any direct effect on lipolysis or lipogenesis.
- Low Dose GH is able to improve patients with Metabolic Syndrome, as documented by increased values of “bioavailable” IGF-1, improved insulin sensitivity, and without induction of lipolysis.

Oncology

Insulin-like growth factor-I, its binding proteins, and growth hormone and breast cancer risk in The Nurses Health Study II.

Endocr Relat Cancer. 2006; 13(2):583-92. Schernhammer ES; Pollak MN; et al. Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115, USA.

- In a study of 300 women with Breast Cancer, circulating IGF-I, IGFBP-1, IGFBP-3, and Growth Hormone levels had **no** association with breast cancer risk in this cohort of premenopausal women.

Neurology

Insulin-like growth factor-I receptors and estrogen receptors interact in the promotion of neuronal survival and neuroprotection. Journal of Neurocytology 29, 425–437 (2000) GARCIA-SEGURA, et al. Instituto Cajal, Madrid, Spain

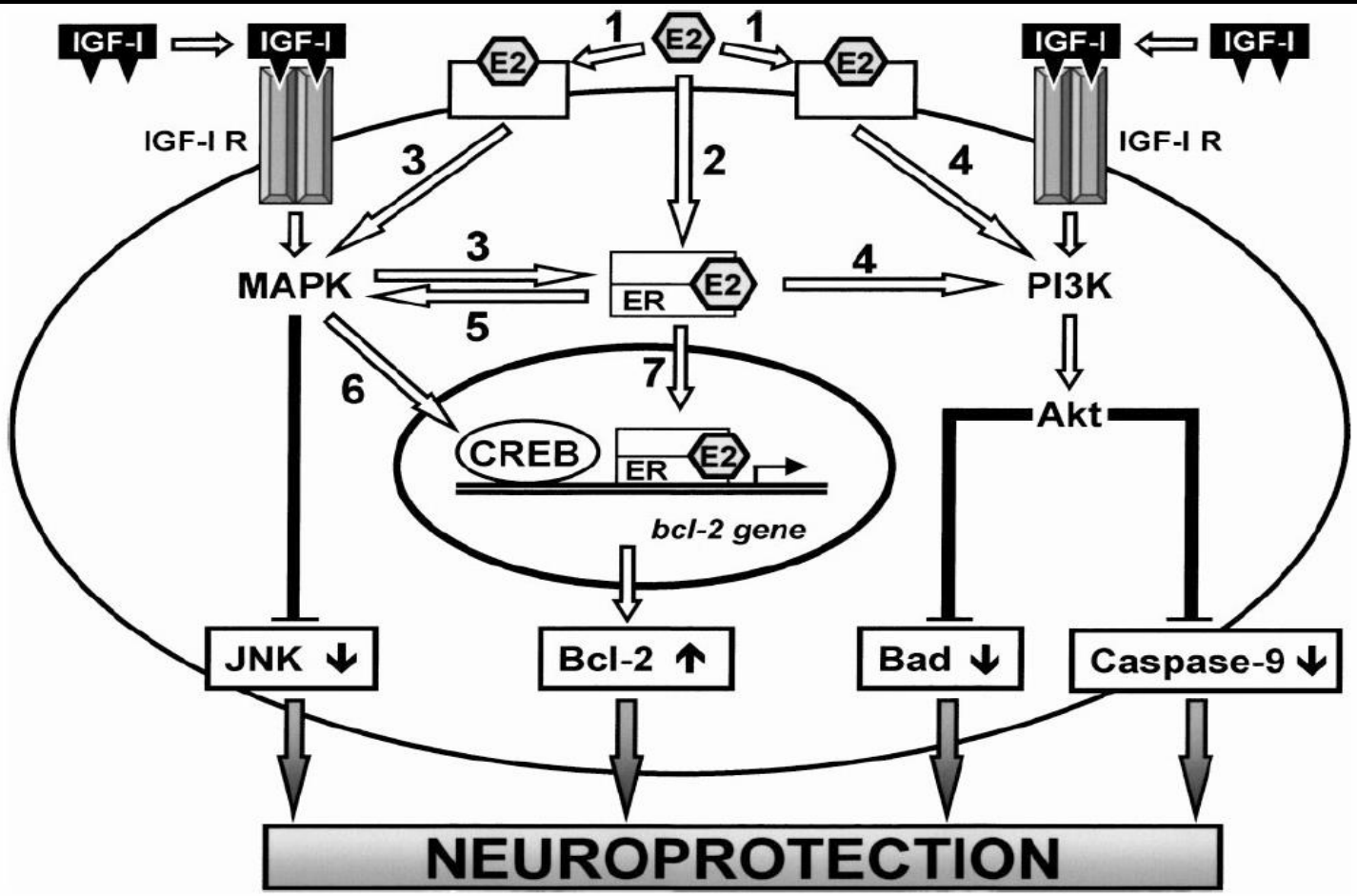


Fig. 4. Hypothetical sites of interaction of estrogen receptor and IGF-I receptor signaling on neuronal survival and neuroprotection. Estrogen may bind to membrane receptors (1) or to conventional receptors (2) and activate MAPK (3) and PI3K (4) and regulate JNK, Bad and caspase-9. Activation of IGF-I receptors may result in the activation of estrogen receptors via MAPK (5). The MAPK pathway may result in the activation of the transcription factor CREB (6) that may induce transcription of genes that are also targets of estrogen receptors (7), such as the *bcl-2* gene.

Insulin like growth factor I ameliorates demyelination induced by tumor necrosis factor-alpha in transgenic mice. J

Neuroscience Research. 2007 Mar;85(4):712-22. Ye P, Kollias G, D'Ercole AJ.Division of Endocrinology, Department of Pediatrics, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7039, USA. 2007

- Oligodendrocyte numbers in TNF-alpha/IGF-I was almost twice that in TNF-alpha only.
- IGF-I expression reduced (**1**) TNF-alpha-induced increases in apoptotic cell number, (**2**) active caspase-3 abundance, and (**3**) degradation of **M**yelin **B**asic **P**rotein (MBP).
- **These results indicate that IGF-I is capable of protecting myelin and oligodendrocytes from TNF-alpha-induced damage in vivo.**
  - **(Amyloid-β = TBI and Alzheimer's)**

Neuroendocrinology

- Regulation of Growth Hormone -

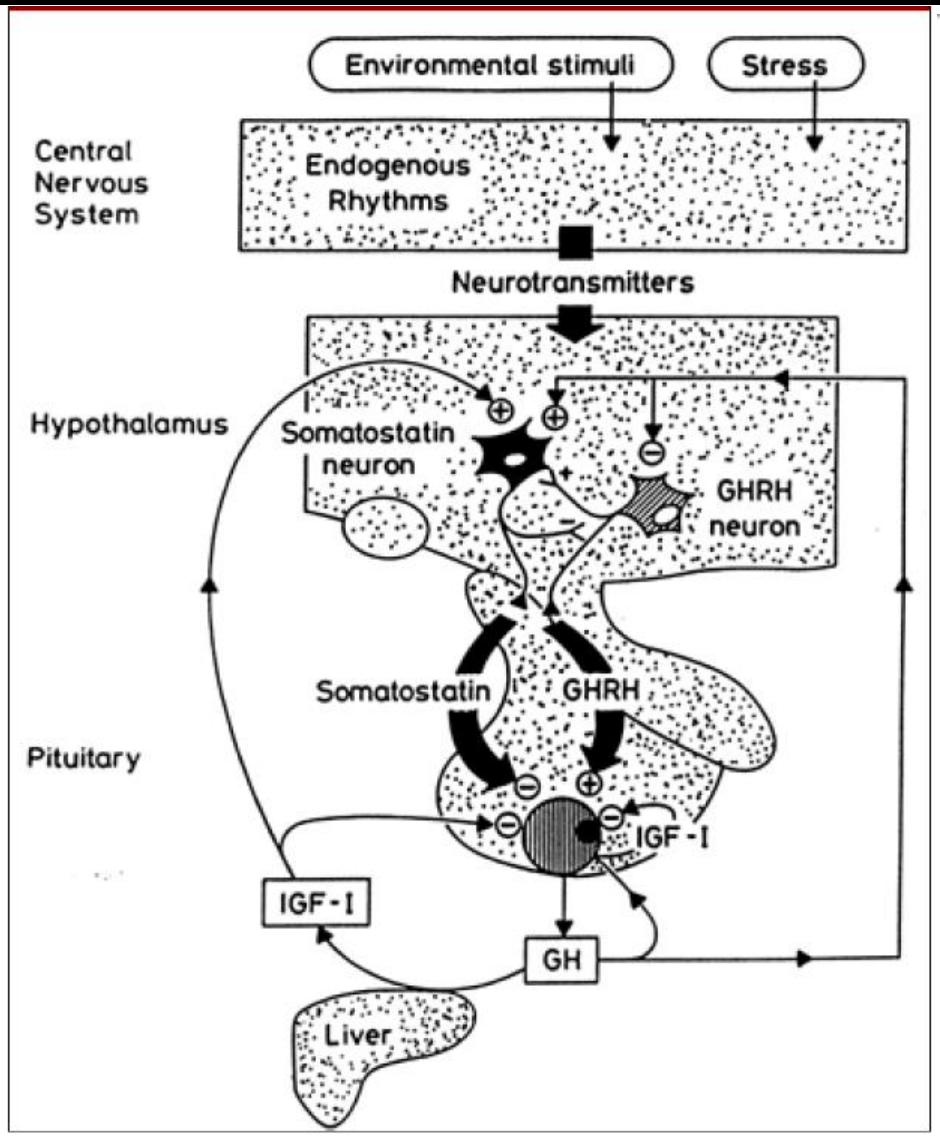
Central and Peripheral Control of GH

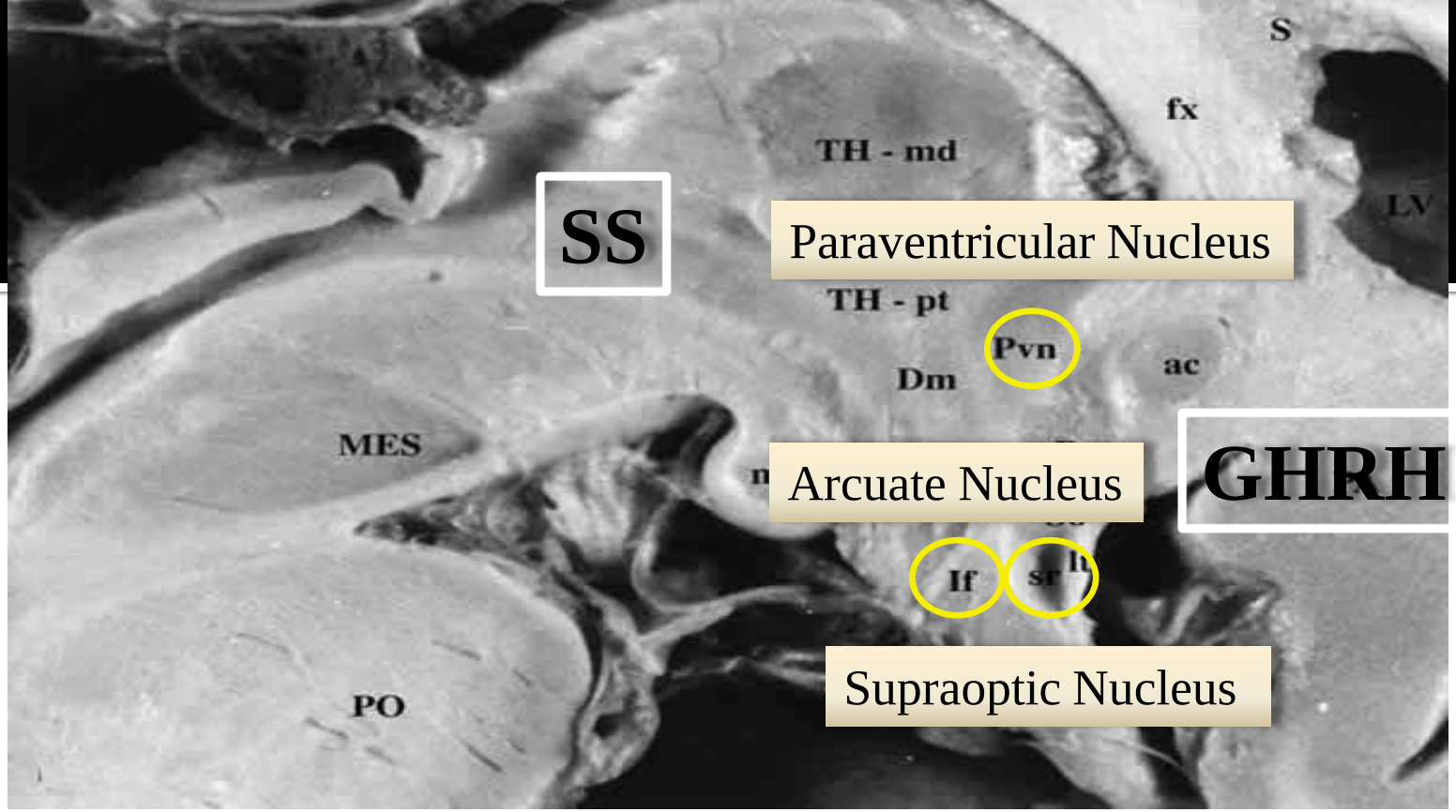
CENTRAL

1. GHRH
2. GHRHr
3. SCIF (SS)
4. Somatotropes
5. GH

PERIPHERAL

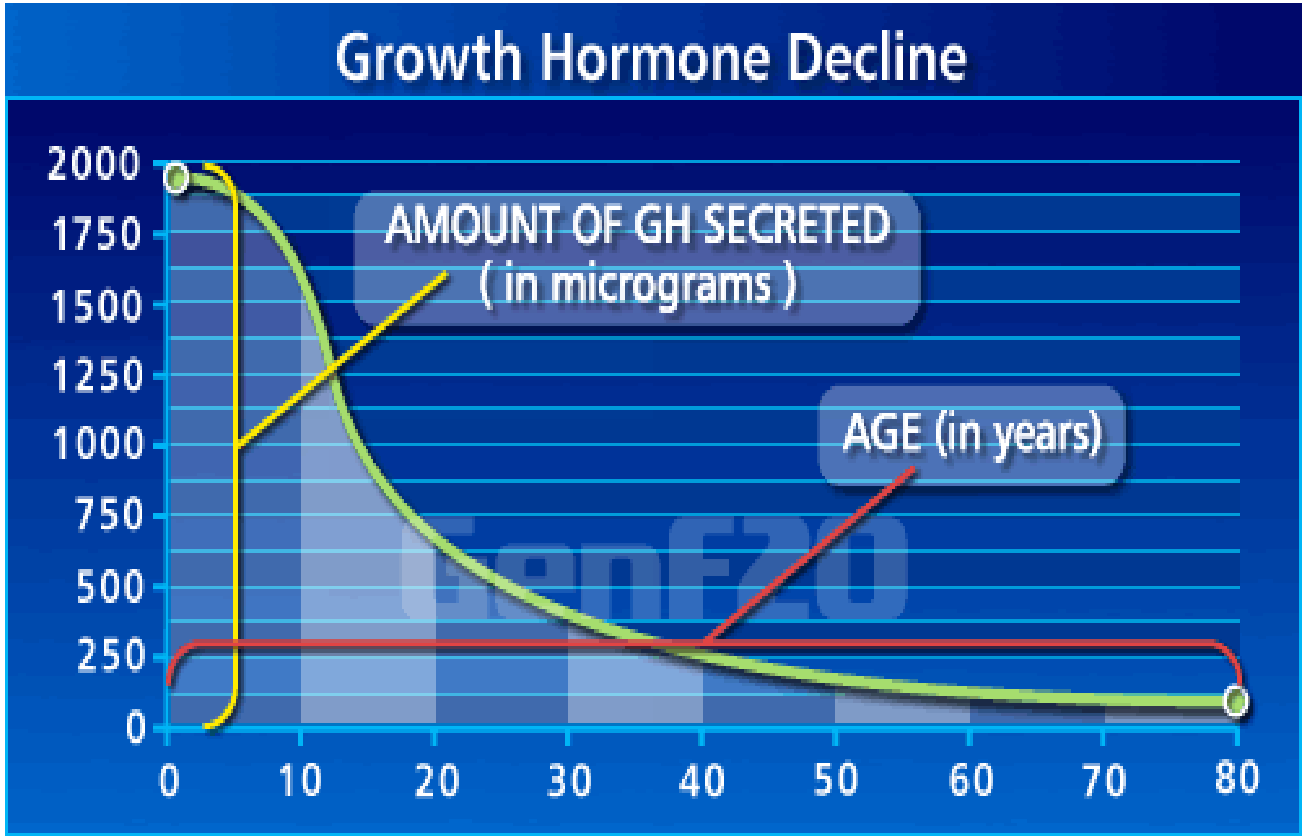
6. Liver
7. IGF-1, IGF-2
8. IGF BPs (1-6+)
9. ALS





Magnified view of fixed human brain in midsagittal orientation. **The third ventricle makes up the core of the hypothalamus** and extends into the pituitary stalk, creating the infundibular recess. Many of the major cell groups are located near the midline. These include the **preoptic nucleus** (Pop), **paraventricular nucleus** (Pvn), dorsomedial nucleus (Dm), ventromedial nucleus (Vm), **arcuate nucleus** (If), posterior hypothalamic nucleus (Po), and medial mammillary nucleus (mm). Ac = anterior commissure, fx = fornix, lt= lamina terminalis, ot = optic tract and chiasm, Lv = lateral ventricle, MB = midbrain, PN = pons, Sr = supraoptic recess, T = thalamus.

The GH Decline Curve.

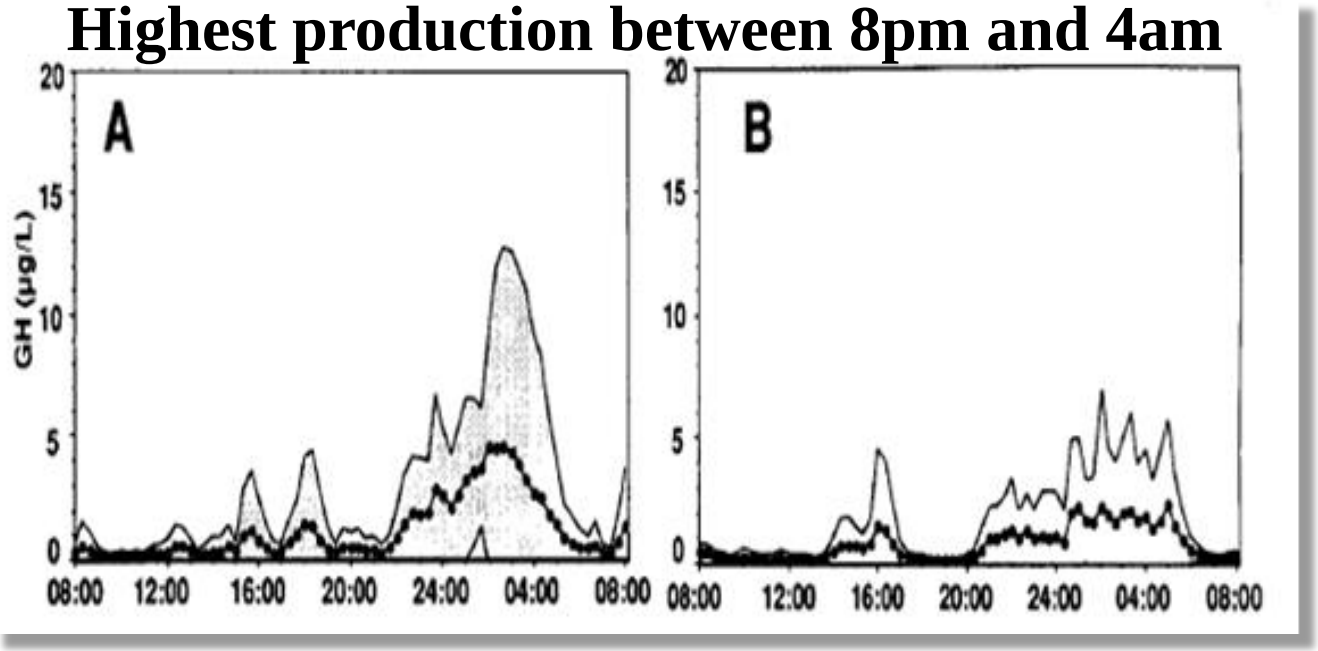


Approximately 14% decrease per decade after 20 years.

The Cyclical Pulses of GH

Young production of GH and Older Production

Highest production between 8pm and 4am



The number of pulses and the amplitude of hormone production decreases as we get older.

Stimulators of GH secretion include:

- ✓ GHRH from the Arcuate nucleus
- ✓ Ghrelin
- ✓ Sleep (Melatonin)
- ✓ Dopamine (D2 Receptor)
- ✓ High Impact Aerobic Exercise (decrease Glucose)
- ✓ Hypoglycemia (decreased Glucose)
- ✓ Dietary protein (Ornithine, Pyroglutamine, Alpha-Ketoglutarate)
- ✓ Estradiol (E2) – Blocked with Aromatase
- ✓ DHEA-s (increases production by 20%)
- ✓ Vitamin D3
- ✓ Arginine (via suppression of SRIF)
- ✓ **Secretagogues** (Multiple points of stimulation)

Inhibitors of GH secretion include:

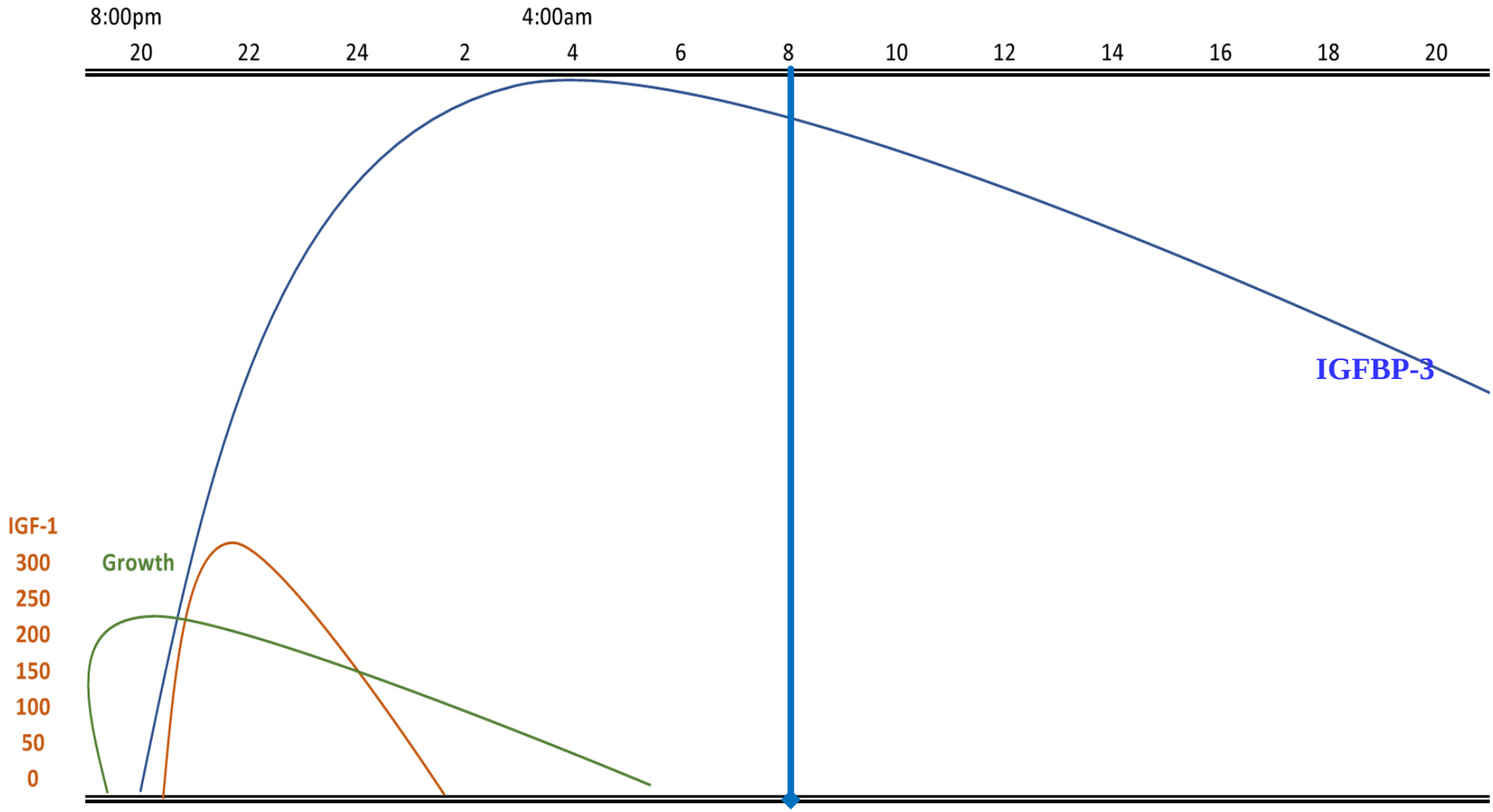
- ✓ Somatostatin from the **periventricular nucleus**
- ✓ Circulating GH and IGF-1
- ✓ Dietary Carbohydrate
- ✓ Dietary Fats
- ✓ Glucocorticoids
- ✓ Obesity
- ✓ Sedentary lifestyle
- ✓ Medication (Tamoxiphen)
- ✓ Anastrozole

Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: Link to brain reductions in acetylcholine. **Journal of Alzheimer's Disease 8:3; 2005 Pg247-268. E Rivera1, et al, Departments of Pathology and Medicine, Rhode Island Hospital and Brown Medical School, Providence, RI, USA**

- Reduced glucose utilization and energy metabolism occur early in the course of Alzheimer's Disease (AD) and correlate with progressive impaired cognition.
- **Glucose utilization and energy metabolism are regulated by insulin and IGF-I**.
- AD leads to a reduction in the main active product generated by Growth Hormone – IGF-1. Thereby, adding to the process of deterioration.
- Therefore, the judicial use of GH replacement to increase IGF-1 would have beneficial effects.

Radioimmunoassay of Growth Hormone-Dependent Insulin-Like Growth Factor Binding Protein in Human Plasma. *J Clin Invest*, **1986**, 78(6):1504-12.

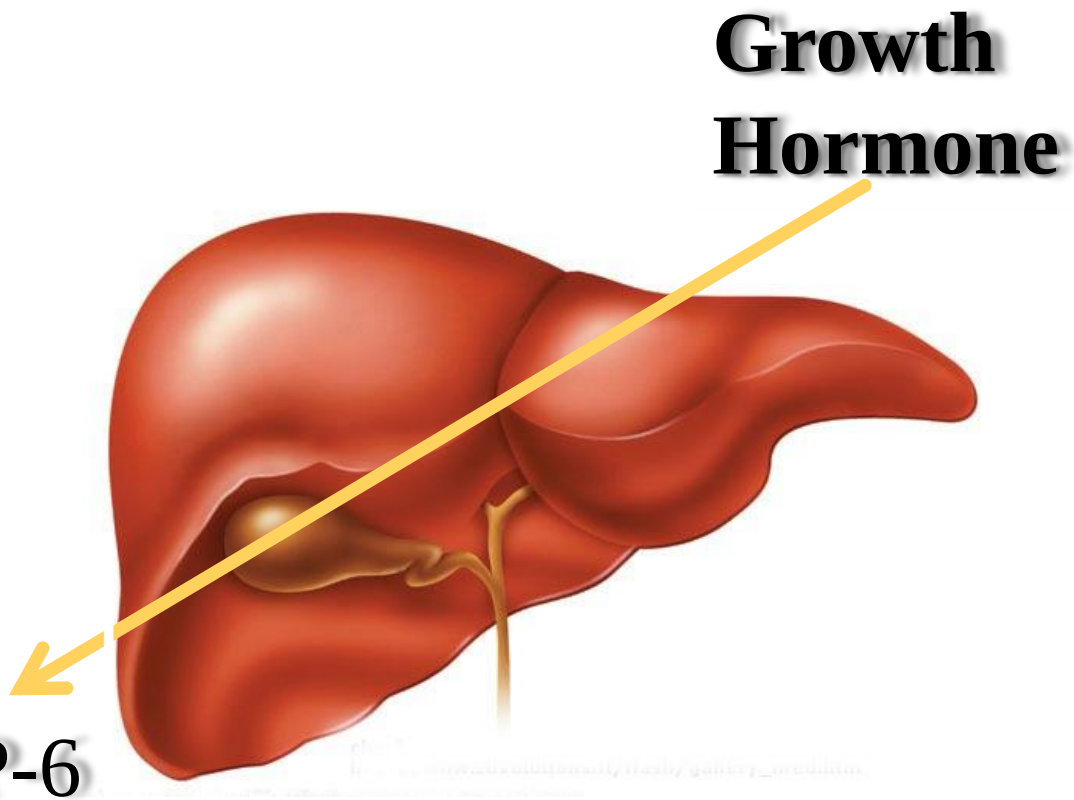
Baxter RC and Martin JL,



Radioimmunoassay of Growth Hormone-Dependent Insulin-Like Growth Factor Binding Protein in Human Plasma. *J Clin Invest*, **1986**, 78(6):1504-12. Baxter RC and Martin JL,

- A principal function of IGFBP-3 is to extend the half-life of the **IGFs from 8 minutes** to hours.
- The serum level of IGFBP-3 appears to be a constant over 24 hours and the protein was found to be GH dependent, which makes the detection of IGFBP-3 very useful in the evaluation of GH secretion.
- **A single BP-3 measurement correlates significantly with the logarithm of the integrated spontaneous GH secretions.**

Growth Hormone Triggers production of:



A. IGF-I and IGF-II
B. IGFPB-1 → IGFBP-6
C. Acid Labile Subunit

A: IGF-I

- IGF-1 is a primary mediator of the effects of GH being produced in the liver under the influence of GH.
- IGF-1 stimulates systemic body growth, and has growth-promoting effects on almost every cell in the body, especially **skeletal muscle, cartilage, bone, liver, kidney, nerves, skin, hematopoietic cell, and lungs**.
- IGF-1 can also regulate cell growth and development, especially in nerve cells, as well as cellular DNA synthesis.
- **Enhances 40-60 subunit of the Ribosome for transcriptional processes. Failed transcription leads to elevation in Homocysteine**.

Peripheral Infusion of IGF-I Selectively Induces Neurogenesis in the Adult Rat Hippocampus

Maria A. I. Åberg,1 N. David Åberg,1 Helena Hedba¨ cker,1 Jan Oscarsson, and Peter S. Eriksson1*Institute of Clinical Neuroscience, Sahlgrenska University Hospital, and Department of Physiology and Pharmacology, University, Sweden*

- Results showed that peripheral infusion of IGF-I increases progenitor cell proliferation and selectively **induces neurogenesis** in the progeny of adult neural progenitor cells.
- This corresponds to a **78% ± 17%** *increase* in the number of new neurons in IGF-I-treated animals compared with control.

** New TBI protocol for increase in Neurons.

A: IGF-II

- The major role of IGF-2 is as a growth promoting hormone **during gestation although;**
- IGF2 promotes granulosa cell proliferation during the follicular phase of the menstrual cycle, acting alongside FSH.
- After ovulation has occurred, IGF-2 promotes progesterone secretion during the luteal phase of the menstrual cycle together with LH.
- IGF2 acts as a co-hormone together with both FSH and LH.
- A study at the Mount Sinai School of Medicine found that IGF-II may be linked to memory and could potentially be used to treat Alzheimer's Disease.

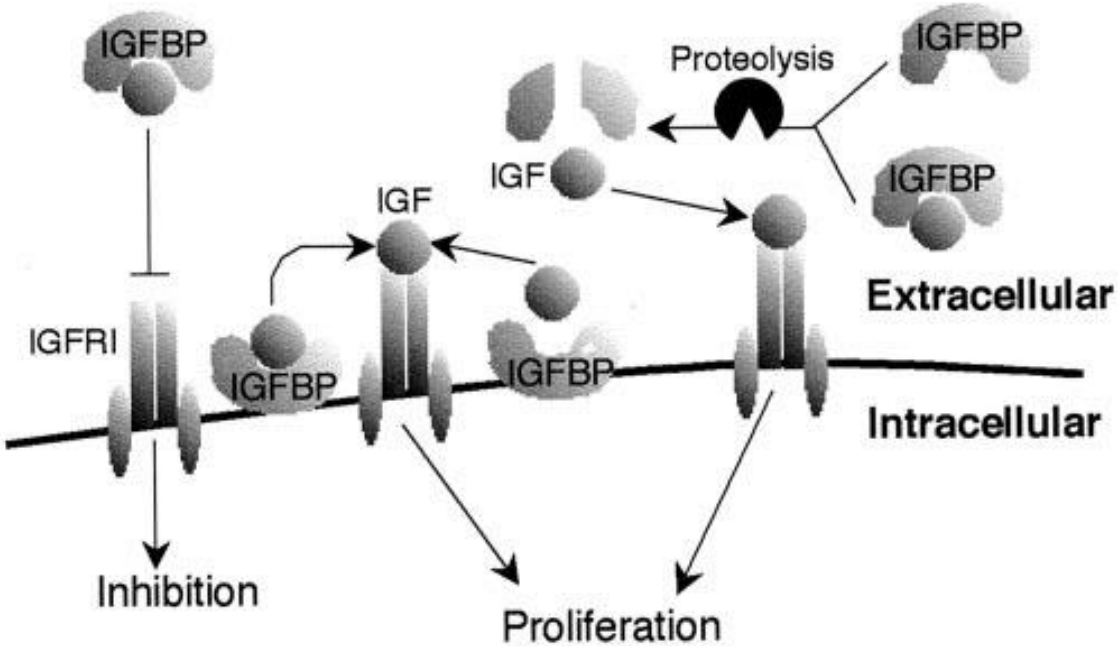
Insulin-like growth factor II (IGF II) in human brain: Regional distribution of-IGF II and of higher molecular mass forms (somatomedins)

Proc. Nati. Acad. Sci. Vol. 82, pp. 2153-2157, April 1985

- Twenty-four distinct areas of human brain were analyzed for the presence of IGFs.
- In cerebrospinal fluid, only IGF-II, but no significant amounts of IGF-I, could be found.
- The highest amounts of IGF-II occurs in the Anterior Pituitary which is up to 100 times more than in most other brain regions analyzed.
- **The results are interpreted as evidence for the presence of IGF-II synthesized locally in human brain.**

Cellular Actions of the Insulin-Like Growth Factor Binding Proteins.

Endocrine Reviews 23(6):824–854. 2002, Sue M. Firth and Robert C. Baxter, Kolling Institute of Medical Research, University of Sydney, Royal North Shore Hospital, St. Leonards, New South Wales 2065, Australia.



IGFBPs

- In addition to their roles in IGF transport, the six IGF-binding proteins regulate cell activity in various ways.
- By sequestering IGFs away from the type I IGF receptor, they may inhibit mitogenesis, differentiation, survival, and other IGF-stimulated events.

B: IGFBP-1 to IGFBP-6

(lecture available)

	Primary Functions
BP-1	Low circulating levels of IGFBP-1 are associated with well-known risk factors of **cardiovascular disease**.
BP-2	IGFBP-2 preventing **adipogenesis** and improved **insulin sensitivity**.
BP-3	IGFBP-3 has strong **anti-cancer** benefits in the nucleus.
BP-4	IGFBP-4 has strong Colon Cancer, **apoptotic affects**.
BP-5	IGFBP-5 levels decrease with age. Several lines of evidence indicate that it is a key component of **the IGF-system in bone**. Thus, it is the predominant IGFBP form stored in bone, where it is bound with high affinity to hydroxyapatite and extracellular matrix proteins.
BP-6	Predominantly found in serum and cerebrospinal fluid IGFBP-6 is unique among IGFBPs in that it has a higher affinity to IGF-II to IGF-I. IGF-II and other hormones have been shown to regulate the IGFBP-6 levels. **Brain – neuroprotection and genesis**.

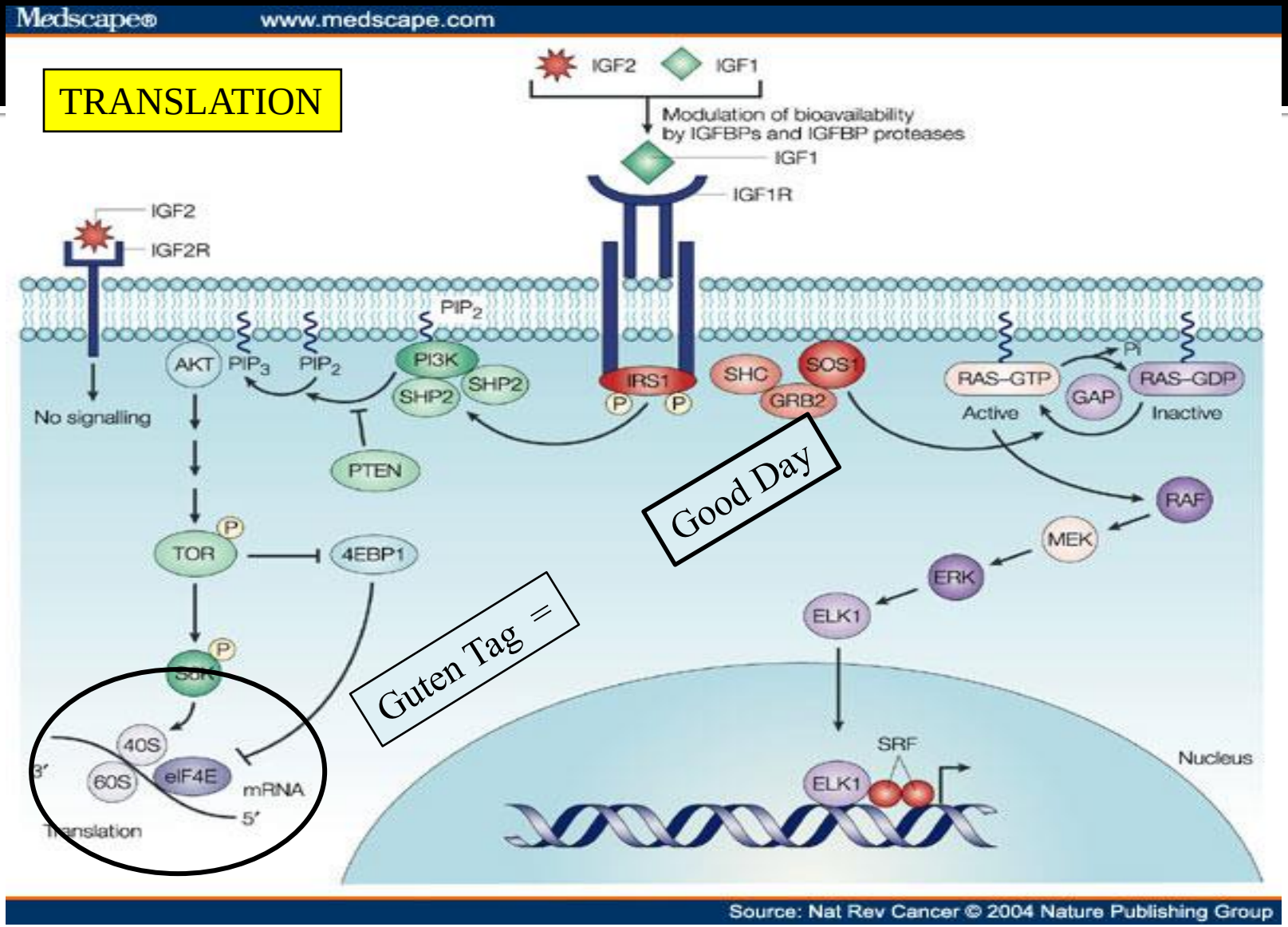
The acid-labile subunit (ALS) of the 150 kDa IGF-binding protein complex: an important but forgotten component of the circulating IGF system.

Journal of Endocrinology (2001) 170, 63–70. Y R Boisclair, R P Rhoads, I Ueki, J Wang and G T Ooi Department of Animal Science, Cornell University, Ithaca, New York 14853, USA Prince Henry's Institute of Medical Research, Clayton, Victoria 3168, Australia

- IGFs are found in **binary complexes** with members of a family of IGF-binding proteins (IGFBPs-1 to -6) in all biological fluids.
- In addition, in postnatal serum, most IGFs are sequestered into **ternary complexes** consisting of one molecule each of **IGF, IGFBP-3 or IGFBP-5, and acid-labile subunit (ALS).**
- Despite evidence that ALS plays an important role in the biology of circulating IGFs, it has received only limited attention relative to the other components of the IGF system.

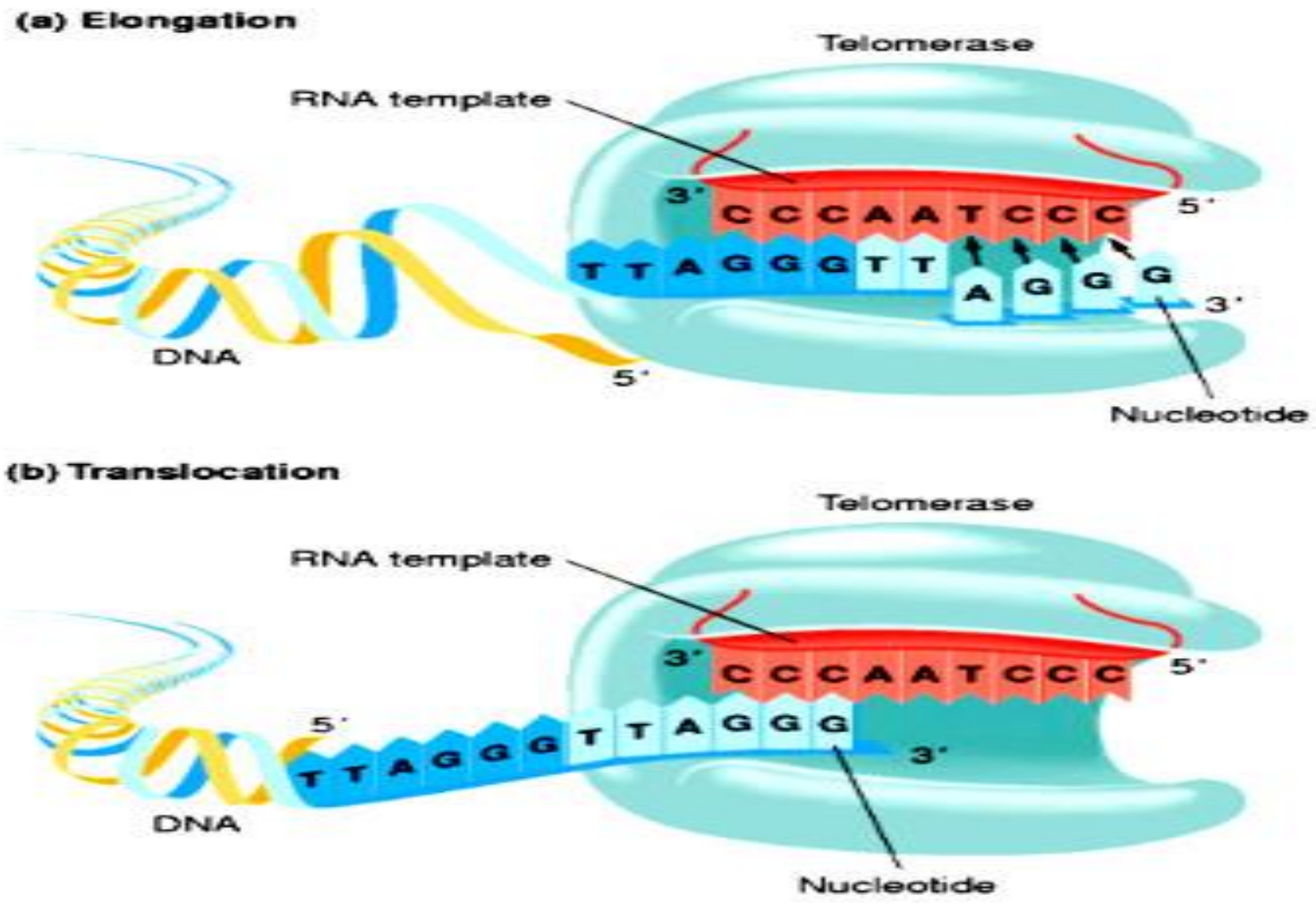
❖ IGF-1 (**8min**), IGF1+BP3 (**20-24hrs**), IGF-1+BP3+ALS (**200hrs**)

IGF-I and IGF-II Signaling



Direct activation of telomerase by Growth Hormone via phosphatidylinositol 3-kinase

Journal of Endocrinology (2005) 185, 421–428. L Gómez-García, F M Sánchez, M T Vallejo-Cremades, I A Gómez de Segura and E De Miguel del Campo Research Unit, La Paz University Hospital, Madrid, Spain.



The Ubiquitous Growth Hormone

- A recent Genentech survey found over **450 GH actions** in **84 cell types**. These actions are mediated through the GH receptor, which was the first of the Class 1 Cytokine Receptors identified.
- GH exerts actions including regulation of immune function, bone turnover, muscle mass, extracellular fluid volume and **cytochrome P450** expression.

Growth Hormone

- ▲ Amino Acid Uptake
- ▲ Vascular Basement Membrane Thickness repair.
- ▲ **Hippocampus Stimulation**
- ▲ **Neuronal Growth and Repair**
- ▲ Stabilize Microtubule Tau Protein.
- ▲ **Lipolytic** (NEFA)
- ▲ Insulin Resistance
- ▲ Hyperglycemia.
- ▲ Cartilage formation.
- ▲ Cyp 450 kinetics
- ▲ **T4 to T3 conversion**.
- ▲ Telomerase increase.
- ▼ Homocysteine reduction
- ▲ Vitamin D sensitivity.
- ▲ Gluconeogenesis
- ▲ Vit D conversion in the Kidney

IGF-1

- ▲ Insulin-like effects (1/10th)
- ▲ Enhance NO production
- ▼ C-reactive Protein
- ▲ Hypoglycemic effect.
- ▲ Enhanced Transcription of protein.
- ▲ Muscle Protein Synthesis.
- ▲ Cortical Bone
- ▲ γ Interferon from WBC.
- ▲ Direct effect on bone like PTH.
- ▲ Regenerate Tau Protein microtubules
- ▲ Neuroregeneration
- ▲ Hippocampal up-regulation
- ▲ Enhancement of Cognition.
- ▲ Neural glucose uptake.

Laboratory Diagnosis of Adult Growth Hormone Deficiency (AGHD)

Table used with permission from the book:

TBI – A clinical approach to diagnosis and treatment.

Laboratory Evaluation of (GH)-(IGF-1) Axis				
Serum Results	GH	IGF-1	BP-3	Comments
Optimal levels	▼M	M	M	No treatment indicated.
Optimal	▼M	M	▼	No treatment indicated. Check Liver if risks.
Evaluation needed	▼M	▼	▼	Ultrasound of liver. Steroid Abuse? Drugs?
Questionable	M	▼	M	Rapid Clearance. Check for IGF-1 antibodies
Laron's Syndrome	▲	▼	▼	GH Insensitivity. Give IGF-1.
Central Dysregulation	▼	▼	▼	Perform Glucagon Stimulant Test. TBI History
Positive	▼	▼	M	Perform GST. Quercetin?
Positive	▼	M	▼	Perform GST.
Questionable	▼	M	M	Rapid clearance. Check for GH antibodies.

Table 6.2: Assessment of the Growth Hormone System. The median (**M**), less than median (▼) and above the median (▲) are shown in this table to direct whether there is the need to treat. These results do not take into account supplementation with any growth factors or known products that alter the natural production of one or more of these results. d/or IGFBP-3 consider an ultrasound for liver and review any medication or supplements that might be affecting the livers ability to generate these hormones.

The Diagnosis of **Partial** GH Deficiency in Adults with a Putative Insult to the Hypothalamo-Pituitary Axis.

Robert D Murray, Martin Bidlingmaier, Christian J Strasburger, and Stephen M Shalet.Department of Endocrinology, Christie Hospital1, Manchester, UK; St James's University Hospital, Leeds, UK; Medizinische Klinik-Innenstadt, Ludwig-Maximilians Universitat, D-80336, Munich, Germany; Charite Universitatsmedizin, D-10117, Berlin, Germany.

- The diagnosis of GHI in an individual is extremely difficult as the patients rarely exhibit additional pituitary hormone deficits and levels of GH-dependent proteins are normal in the majority.
- Diagnosis relies heavily on GH stimulation tests and requires two tests in all patients to define GHI; obesity when present is potentially a major confounder.

ITT – The Gold Standard

(worthless)

1. ITT – The Gold Standard (worthless).
2. IGF-1 serum testing (poor).
3. IGFBP-3 is logarithmic to GH (good).
4. 24 Hr Urine Growth Hormone (good).
5. Acid Labile Sub-unit (good).
6. Clonidine Challenge (children)
7. Arginine – GHRH (over-drive)
8. Glucagon Challenge Test (fair)

Is growth hormone stimulation testing in children still appropriate?

Growth Hormone IGF Res 2004 Jun;14(3):185-94. Gandrud L. Wilson D. Division of Pediatric Endocrinology and Diabetes, Stanford University Medical Center, S-302, Stanford University, Stanford, CA 94305, USA.

- The diagnosis of growth hormone deficiency has relied on measurement of GH concentrations following stimulation, with a non-physiologic provocative agent.
- **Due to the pitfalls associated with GH stimulation tests, specifically, the lack of reliability and accuracy of these tests, and their inability to predict who will benefit from GH therapy**.

"**We recommend that GH stimulation tests no longer routinely be used for the diagnosis of Growth Hormone Deficiency."**

Insulin Challenge Test

- In an **ITT**, insulin is administered intravenously to produce a plasma glucose level of less than 40 mg/dL (2.2 mmol/L); serum (or blood) glucose
- Serum GH levels are measured at times 0, 15, 30, 60, 90, and 120 minutes after administering insulin.
- GHD is diagnosed when the growth hormone level is less than 5.1 mcg/L.
- The ITT Test is contraindicated in patients with a history of TBI, seizures, or CVD and in anyone who wants to live.

Pharmacological testing for the diagnosis of growth hormone deficiency.

Growth Horm IGF Res. 1998; 8 Suppl A:1-8)Carel JC; Coste J; Gendrel C; Chaussain JL. Service d'Endocrinologie PÃdiatrique et INSERM U342, Hospital Saint Vincent de Paul, Paris, France.

- Evaluation of GH secretion using the GHST remains current practice, although the reliability of this "Gold Standard" test has been questioned.
- **In an analysis of 6,373 GHSTs which led to GH therapy in 3,233 children; re-evaluated of 208 young adults who were treated with GH for childhood onset GHD.**
- **We conclude that the current use of GHSTs as well as the criteria for idiopathic childhood GHD should be questioned.**

Growth Hormone Assay Standardization: An Important Clinical Advance. Michael C. Sheppard, Clinical Endocrinology, **2007;**66(2):157-161\

- Adult GH deficiency is recognized as a clinical syndrome associated with increased morbidity; its diagnosis is often problematic.
- **The logical test for GHD would be the measurement of serum GH in relation to IGF-1**. However, the pulsatile secretion of GH renders assessment of random serum GH concentrations worthless for diagnosis of GHD.
- Approximately 1/3 of patients with AGHD diagnosed by GH stimulation tests have normal IGF-1 levels.

❖ **24-hr Urine GH??**

Commercial assays available for insulin-like growth factor I and their use in diagnosing growth hormone deficiency

Hormone Research. **2001**; 55 Suppl 2:73-9. **Clemmons DR**. Division of Endocrinology, University of North Carolina, Chapel Hill, NC, USA.

- Presently, IGF-I measurement is currently the best indirect method available for screening and monitoring patients with GH Deficiency.

Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency

. J Clinic Endocrinology Metabolism 2002; 87(5):2067-79. Biller BM; Hartman ML. et al, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.

- Although, the serum IGF-I level provides less diagnostic discrimination than all five GH stimulation tests, a value of IGF1 below 77.2 mg/liter was 95% specific for GH deficiency.

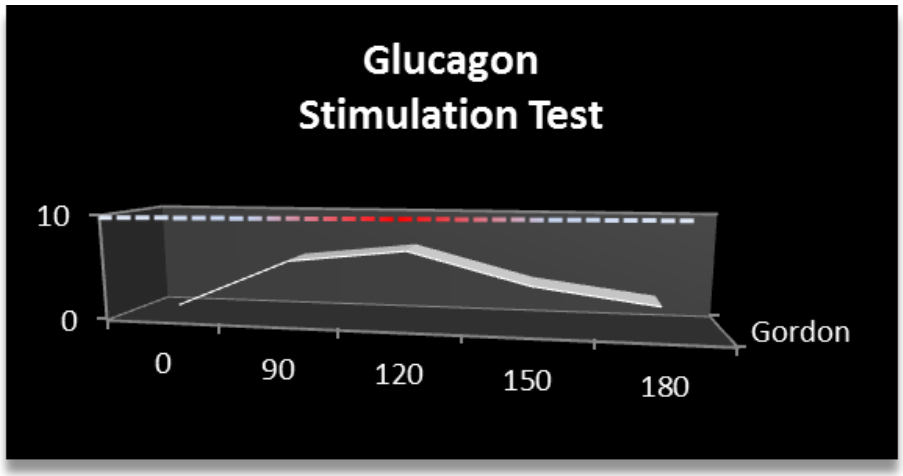
Assessment of GH status in adults with GH deficiency using serum growth hormone, serum insulin-like growth factor-I and urinary growth hormone excretion.

Clin Endocrinol (Oxf). 1995; 42(4):425-30. Bates AS; Evans AJ; Jones P; Clayton RN. Department of Postgraduate Medicine, University of Keele, Stoke-on-Trent, UK.

- A diagnosis of adult GH deficiency can be reliably made without the need for an insulin stress test by using a combination of:
- **low urinary GH excretion (uGH)**
- **subnormal IGF-I levels,** and
- **clinical assessment** with regard to the number of other pituitary axes affected.

Glucagon Stimulation Test

1: Fasting State.
2: Initial Blood Test GH (Cortisol).
3: SubQ **1mg** Glucagon < 90Kg or **1.5mg** >90 Kg.
4: Samples @ 90, 120, ~~150~~, 180 and ~~210~~ min.
5: **Subnormal GH response** < 9mU/L (< 3 ug/L).
6: Subnormal Cortisol response < 500-580 nmol/L.



GH
and Cancer

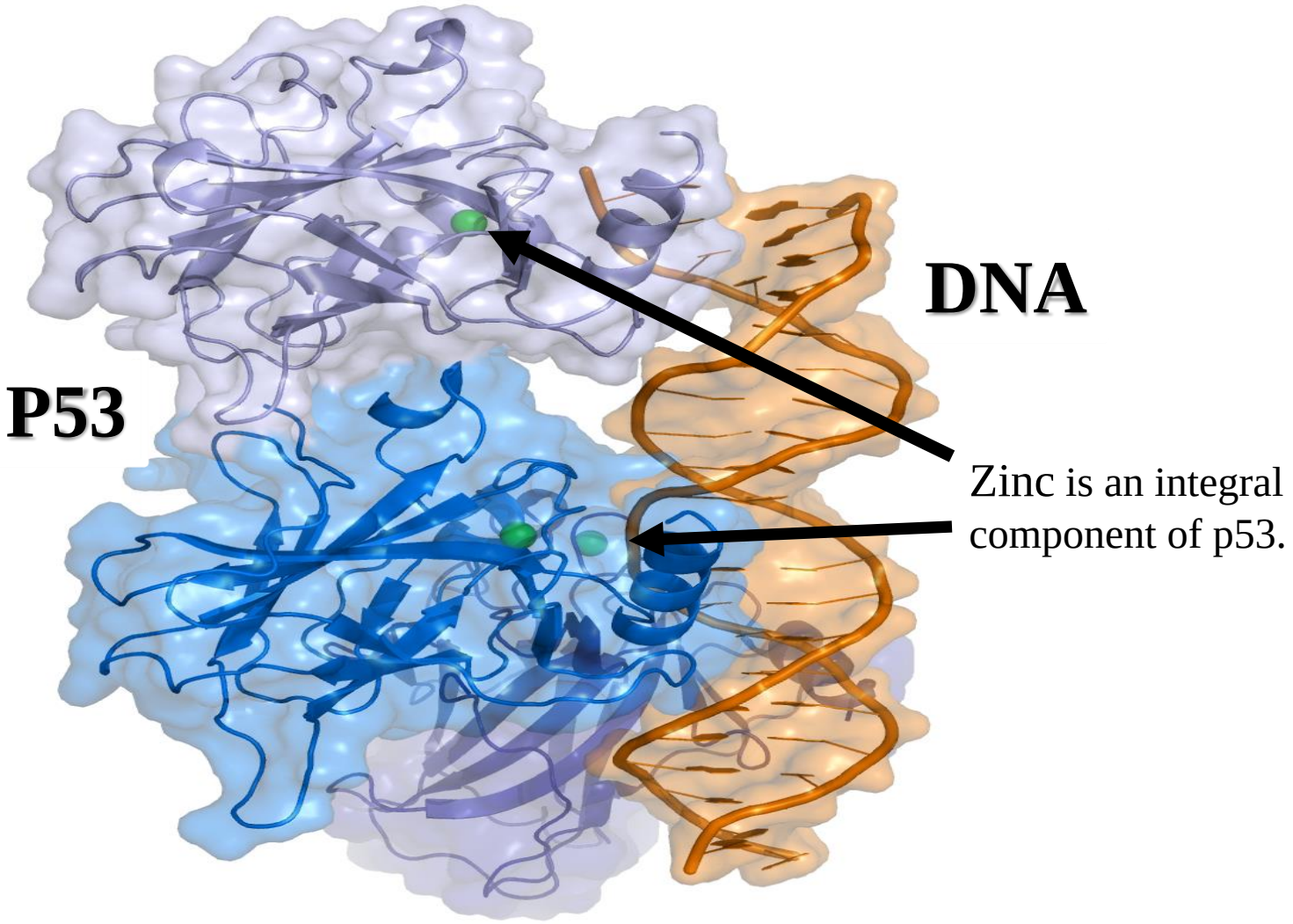
p53 and IGFBP-3: Apoptosis and Cancer Protection

Adda Grimberg
Division of Pediatric Endocrinology, The Children's Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, Pennsylvania, 19104. Received 28 April 2000

- **P53**, is perhaps the single most important human tumor suppressor, which is commonly mutated in human cancers.
- Normally genotoxic stress, and hypoxia activate p53, which, through DNA-specific transcription activation, triggers cell cycle arrest and apoptosis.

1. P53 is a resident of both the nucleus and the cytosol.
2. P53 exists in two states Phosphorylated and not.
3. When P53 is not Phosphorylated it can migrate into the cytosol where it is degradated.
4. When P53 is Phosphorylated it becomes trapped in the nucleus.
5. It is the rising levels of intranuclear P53 that precipitates Apoptosis.

Side Note



p53 and IGFBP-3: Apoptosis and Cancer Protection

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- One of the genes involved in the induction of **p53** was also identified as encoding for **IGFBP-3**.
- IGFBP-3 has been defined as the principal carrier of IGF-I in the circulation and the primary regulator of the amount of free IGF-I available to interact with the IGF-1 receptor.

It appears that BP-3 is juxtaposed to the P53 gene in that when P53 is encoded there is an increase in BP-3 production too.

p53 and IGFBP-3: Apoptosis and Cancer Protection

Adda Grimberg
Division of Pediatric Endocrinology, The Children's Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, Pennsylvania, 19104. Received 28 April 2000

- IGFBP-3 enhanced induction by p53 constitutes a new means of cross-talk between the p53 and the IGF axes, and suggests
- that ***the ultimate function of IGFBP-3 may be to serve a protective role against the potentially carcinogenic effects of GH and IGF-I*.**

Therefore;

- If GH causes the liver to produce both IGF-1 and IGFBP-3(amongst other products) and
- IGF-1 is pro-mitotic and
- IGFBP-3 is anti-mitotic and anti cancer
- Then the net effect of GH would be a better cancer negating effect and not a pro-cancer effect.

YOU think!

What Increases IGFBP-3 ?

- Growth Hormone
- P53 detecting aberrancy in the genetic material.
- Hypoxia
- Quercetin (anti cancer flavonoid)
- Retinoic Acid

Secretagogues

Specific receptors for synthetic **GH S**ecretagogues in the human brain and pituitary gland.

Journal of Endocrinology (**1998**) **157,** 99–106. G Muccioli, Et Al. Dept of Anatomy, Pharmacology and Forensic Medicine, Dept of Biomedical Sciences and Human Oncology, Dept of Internal Medicine, University of Turin, Turin, **Italy**, **Pharmacia and Upjohn**, Stockholm, **Sweden**, Europeptides, Argenteuil, **France**, and Faculty of Pharmacy, University of Montreal, Montreal, **Canada**.

- Research centers have identified specific receptors in the human brain and pituitary gland that are unique for synthetic-GH Secretagogues.
- These compounds are believed to be the synthetic counterpart of an endogenous GH secretagogue involved in the neuroendocrine control of GH secretion.

Endocrine and Non-Endocrine activities of growth hormone Secretagogues in humans

. Hormone Research. **1999**; 51 Suppl 3:9-15. Ghigo E; Arvat E; Broglio F; Giordano R; Gianotti L; Muccioli G; Papotti M; Graziani A; Bisi G; Deghenghi R; Camanni F Department of Internal Medicine, University of Turin, **Italy**.

- These secretagogues (s-GHS) have been found to possess **strong, dose-dependent and reproducible** GH releasing effects.

Peripheral estrogen receptor alpha selectively modulates the waveform of GH secretory bursts in healthy women. Veldhuis JD, Keenan DM, Bowers CY. Am J Physiol Regul Integr Comp Physiol. 2007 Oct;293(4):R1514-21. Epub 2007 Aug . Endocrine Research Unit, Mayo Medical and Graduate Schools, Clinical Translational Research Unit, Mayo Clinic, Rochester, MN 55905, USA.

- Estradiol drives GH secretion via estrogen receptors (ER-a) located in the hypothalamus and pituitary gland.

Estrogens regulate the hepatic effects of growth hormone, a hormonal interplay with multiple fates. Front. Endocrinol., 2013. Leandro Fernández-Pérez, Borja Guerra, Juan C. Díaz-Chico and A. Flores-Morales. Oncology-Molecular and Translational Endocrinology Group, Clinical Sciences Dept, Faculty of Health Sciences, Associate Unit of University of Las Palmas de Gran Canaria and Biomedical Institute "Alberto Sols"-CSIC, Las Palmas de Gran Canaria, Spain. Molecular Endocrinology Group, Novo Nordisk Center for Protein Research, University of Copenhagen, Copenhagen, Denmark

- Growth hormones influence on the livers production of IGF-1, BPs and ALS are influenced by the presence of Estrogens.
- **Estrogens and GH act on the liver to enhance growth through anabolic and metabolic pathway enhancements in both genders.**
- Failure to maintain optimal levels of Estrogens can affect the transcriptional induction of growth and repair mechanisms in the liver.

Homologous Down-Regulation of Growth Hormone-Releasing Hormone Receptor Messenger Ribonucleic Acid Levels

Endocrinology **138:** 1058–1065, 1997. G. Aleppo, et al, *Department of Medicine, Section of Endocrinology and Metabolism, University of Illinois at Chicago, Chicago, Illinois 60612*

- Repeated stimulation of pituitary cells in vitro with GHRH resulted in diminished responsiveness, a phenomenon referred to as ***Homologous Desensitization***.
- One component of GHRH-induced desensitization is a reduction in GHRH-binding sites, which is reflected by the decreased ability of GHRH to stimulate a rise in intracellular cAMP.

Neuroendocrine Control of Growth Hormone Secretion.

Physiological Reviews Vol. 79, No. 2, April 1999. E Muller, V Locatelli, and D Cocchi. Department of Pharmacology, Chemotherapy, and Toxicology, University of Milan, Milan; and Department of Biomedical and Biotechnology Sciences, University of Brescia, Brescia, Italy

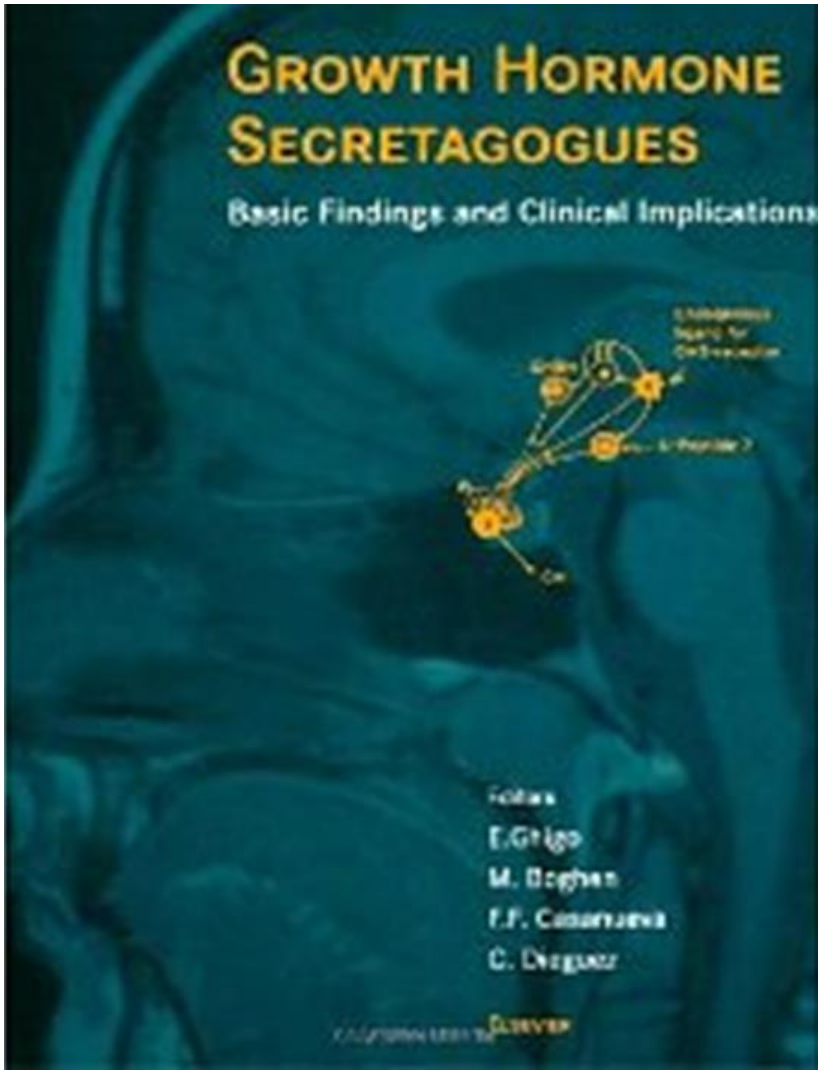
- Preliminary results, from a number of articles, indicate that there is a 40% decrease in intrinsic GH production when injectable GH is used for 2 days. Eventually 100% decrease.
- Therefore, the extrinsic GH being used must first correct this deficit before benefits are obtained.
- Use combination of Secretagogue with low dose GH to preserve endogenous GH production.- *MLG*

Optimizing GH Production

1. Correct DHEA and Testosterone.
2. Balance Estradiol and Progesterone.
3. Improve sleep to increase melatonin.
4. Add L-Arginine
5. Try natural Secretagogues.

Un-natural Secretagogues

- GHRH (fragment)
- GHRP-2
- GHRP-6
- Hexarelin
- Ipamorelin
- MK-677
- SM-130,686
- Tabimorelin
- Capromorelin
- Secretropin



Homologous Down-Regulation of Growth Hormone-Releasing Hormone Receptor mRNA Levels*

Endocrinology **138:** 1058–1065, 1997

Grazia Aleppo, Stanley F. MOSKAL II, Paula A. De Grandis, Rhonda D. Kineman,Lawrence A. Frohman, *Department of Medicine, Section of Endocrinology and Metabolism, University of Illinois at Chicago, Chicago, Illinois 60612*

- Repeated stimulation of pituitary cell cultures with GH-releasing hormone results in diminished responsiveness, a phenomenon referred to as homologous desensitization.
- One component of GHRH-induced desensitization is a reduction in GHRH-binding sites, which is reflected by the decreased ability of GHRH to stimulate a rise in intracellular cAMP.

GHRH
Growth Hormone Releasing Hormone

- Is a 44-amino acid peptide hormone produced in the Arcuate Nucleus of the Hypothalamus.
- GHRH is released from neurosecretory nerve terminals of these arcuate neurons, and is carried by the hypothalamo-hypophyseal portal system to the anterior pituitary gland where it stimulates growth hormone (GH) secretion by stimulating the growth hormone-releasing hormone receptor.

SS

GHRH GHRH-r Somatotropes GH

Ghrelin

- Ghrelin is a potent stimulator of growth hormone secretion from the anterior pituitary gland.
- The ghrelin receptor is a G protein-coupled receptor, known as the growth hormone secretagogue receptor.
- Ghrelin binds to this receptor which is present in high density in the hypothalamus, pituitary as well as vagal afferent cell bodies and vagal afferent endings throughout the gastro-intestinal tract.

Ghrelin

Ghrelin Strongly Stimulates Growth Hormone (GH) Release in Humans

KAZUHIKO TAKAYA[1], HIROYUKI ARIYASU[1], NAOTETSU KANAMOTO[1], HIROSHI IWAKURA[1], AKIHIRO YOSHIMOTO[1], MASAKI HARADA[1], KIYOSHI MORI[1], YASATO KOMATSU[1], TAKESHI USUI[2], AKIRA SHIMATSU[2], YOSHIHIRO OGAWA[1], KIMINORI HOSODA[1], TAKASHI AKAMIZU[1], MASAYASU KOJIMA[3], KENJI KANGAWA[3], AND KAZUWA NAKAO[1]

[1]Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan, [2]Clinical Research Institute, Center for Endocrine and Metabolic Diseases, Kyoto National Hospital, Kyoto 612-8555, Japan, and [3]Department of Biochemistry, National Cardiovascular Center Research Institute, Osaka 565-8565, Japan

ABSTRACT Ghrelin is a recently identified endogenous ligand for the GH secretagogue receptor and is involved in a novel system for regulating GH release. However, little is known about its GH-releasing activity and other endocrine effects in humans. To address this issue, we studied the GH, ACTH, cortisol, PRL, LH, FSH, and TSH responses to synthetic human ghrelin. In four normal male adults (28-37 yr), iv ghrelin administration released GH in a dose-dependent manner and 0.2, 1.0, and 5.0 μg/kg ghrelin produced 43.3 ± 6.0, 81.5 ± 12.7, and 107.0 ± 10.7 ng/mL of the GH peak values at 30 min, respectively. ACTH, cortisol, and PRL levels were also elevated after ghrelin injection, while the lowest dose (0.2 μg/kg) resulted in only minimum peak values of these hormones (22.8 ± 3.0 pg/mL, 9.4 ± 1.9 μg/dL, and 4.6 ± 0.6 ng/mL, respectively). There were no significant changes in LH, FSH, or TSH levels. This is the first study showing evidence that ghrelin strongly stimulates GH release in humans.

Warning

- Some of the products listed are furnished for LABORATORY RESEARCH USE ONLY.
- The product may not be used as drugs, agricultural or pesticidal products, food additives or household chemicals.

GHRP-2 Peptide

- D-ALA-D-2-NAL-ALA-TRP-D-PHE-LYS-NH2
- GH-releasing peptides (GHRPs) are synthetic peptides that like GHRH act directly on pituitary somatotrophs to stimulate GH release. GHRP-2, an investigational drug, is one of the most potent members of the GHRP family. It has been shown to be effective in adults via the oral and intranasal as well as the iv route of administration.
- $530 for 100mg.

GHRP-6

- **Growth hormone releasing hexapeptide** (GHRP-6) is one of several synthetic met-enkephalin analogs that include unnatural D-amino acids, were developed for their growth hormone (GH) releasing activity and are called GH secretagogues.
- GH-releasing peptides (GHRPs) are synthetic peptides that like GHRH act directly on pituitary somatotrophs to stimulate GH release. Growth hormone (GH) release is stimulated by a variety of synthetic secretagogues, of which growth hormone-releasing hexapeptide (GHRP-6) has been most thoroughly studied; it is thought to have actions at both pituitary and hypothalamic site.
- These secretagogues are distinct from growth hormone releasing hormone (GHRH) in that they share no sequence relation and derive their function through action at a completely different receptor.

Hexarelin

- **His-2-Me-D-Trp-Ala-Trp-D-Phe-Lys-NH2**
- Hexarelin (HEX), a non-natural peptidyl GHS, which possesses strong GH-releasing activity but also significantly stimulates Prolactin (PRL), ACTH, and Cortisol secretion.

Growth hormone status during long-term hexarelin therapy.

J Clin Endocrinol Metab. 1998 May;83(5):1644-9. Rahim A, O'Neill PA, Shalet SM. Department of Endocrinology, Christie Hospital, Withington, Manchester, United Kingdom.

- Hexarelin, a powerful GH-releasing peptide, is capable of causing profound GH release in normal subjects after oral, intranasal, i.v., and s.c. administration.
- We have demonstrated that chronic Hexarelin therapy results in a partial and reversible attenuation of the GH response to Hexarelin.

- **Homologous Down-Regulation**

Sermorelin

- **Sermorelin**, sometimes called **GRF 1-29**, is a growth hormone releasing hormone analogue.
- It is a 29-amino acid polypeptide representing the 1-29 fragment from endogenous human growth hormone releasing hormone (GHRH), and is thought to be the shortest fully functional fragment of GHRH.

Secretropin

- This is a multifaceted secretagogue in having a composition that stimulates Growth Hormone production, release, and reduces SS production through:

1. Stimulation of Ghrelin production.
2. DR2 Receptors.
3. GHRH-r
4. Somatotropes.
5. GHR-s
6. Suppression of SS.

Prolactin: Structure, Function, and Regulation of Secretion

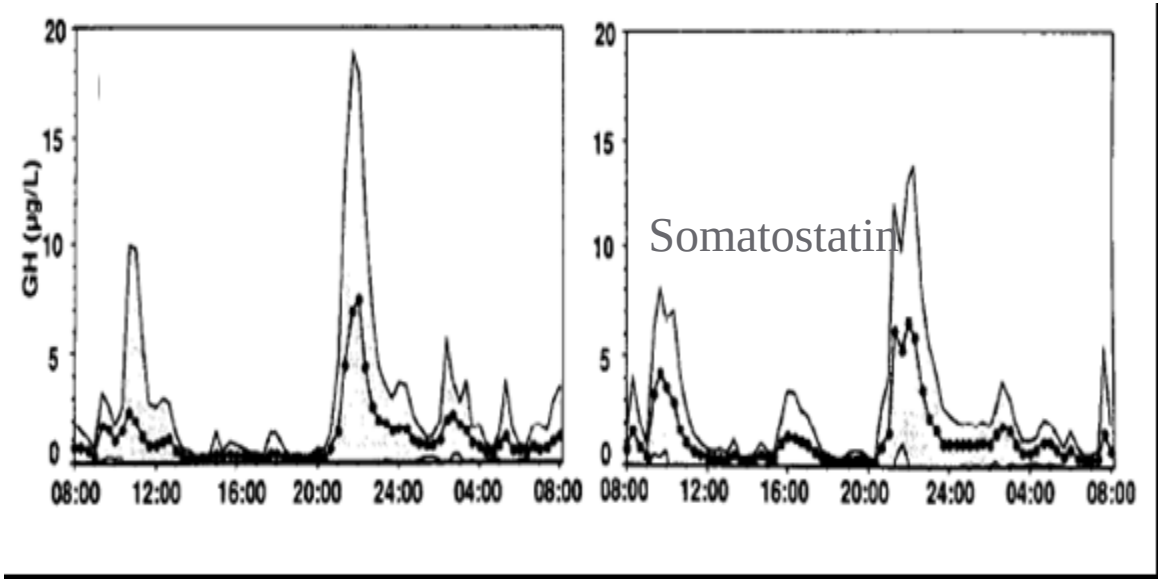
Marc E. Freeman, Bela KANYICSKA, Anna LERANT, AND Gyorgy Nagy. Department of Biological Science, Florida State University, Tallahassee, Florida; Department of Anatomy, The University of Mississippi Medical Center, Jackson, Mississippi; and Neuroendocrine Research Laboratory Department of Human Morphology, Semmelweis University School of Medicine, Budapest, Hungary. 2000

- Somatostatin not only inhibits GH, but the secretion of Prolactin, TSH, and ACTH as well.
- Therefore, treatment of a patient with anything that potentially raises the production of Somatostatin will affect these other hormones.

Arginine suppresses Somatostatin production
2 - 4 grams at bedtime.

Single channel approach

Low Dose GH Stimulation vs. High Dose Stimulation



Over stimulation of the AP leads to an elevation in the production of Somatostatin with a corresponding decrease in the release of GHRH leading to down regulation in the production of growth hormone.

Neuroendocrine Control of Growth Hormone Secretion.

PHYSIOLOGICAL REVIEWS Vol. 79, No. 2, April 1999. Eugenio E. Muller, Vittorio Locatelli, Daniela Cocchi, Department of Pharmacology, Chemotherapy, and Toxicology, University of Milan, Milan; and Department of Biomedical and Biotechnology Sciences, University of Brescia, Brescia, Italy

Somatostatin 's Impact on GH Production

- Preliminary results, from a number of articles, indicate that there is a 40% decrease in endogenous GH production when injectable rhGH (GH) is used for just 2 days.
- Eventually 100% decrease (30 days).
- Thereafter, the exogenous rhGH becomes the only source of the hormone.
- Recovery can take over a year (Millennium Study).

Novo Nordisk's Report on Secretagogues

DRUG DISCOVERY TODAY **1999** Nov;4(11):497-506 Ankersen Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Malov, Denmark.

- The discovery of a new class of compounds that stimulate the release of growth hormone (GH) in a manner distinctly different from growth hormone-releasing hormone (GHRH) is advancing the understanding of the mechanisms that control GH secretion.

Novo Nordisk's Report on Secretagogues

Growth hormone secretagogues: recent advances and applications. DRUG DISCOVERY TODAY **1999** Nov;4(11):497-506 Ankersen Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Malov, Denmark.

- These compounds, the GH secretagogues, act at both pituitary and hypothalamic levels, and even elicit effects in the CNS and peripheral systems.

Treatment: Why we fail.

- Treatment benefits are NOT predicated on the correction of ONE deficient or insufficient hormone.
- It is about correcting all deficiencies and insufficiencies simultaneously*.

*** SYNERGY -** The phenomenon in which the combined action of two(or more) drugs is greater than the sum of their effects individually.

Summary

- The ubiquitous benefits of GH, IGF-1 and BPs mandates a constant vigil to maintain their healthy levels.
- Psychological, Physiological and Physical health have been documented consistently to be affected by deficiency and sufficiency.
- Longevity fueled by quality of life can only be achieved when Growth Hormone is optimized.

Closing Statement

Attempt to maintain GH/IGF/BPs levels by natural means or with the use of a Secretagogue or a low dose regimen of GH supported with timely and appropriate monitoring.

The Millennium Office Assistant

An Expert-AI System for integrative hormonal analyses

Get a free trial license for the new Office Assistant.
Send your request to: support@mhcapp.com

www.TBIHelpNow.com/the-millennium-app

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