Growth hormone and prostate

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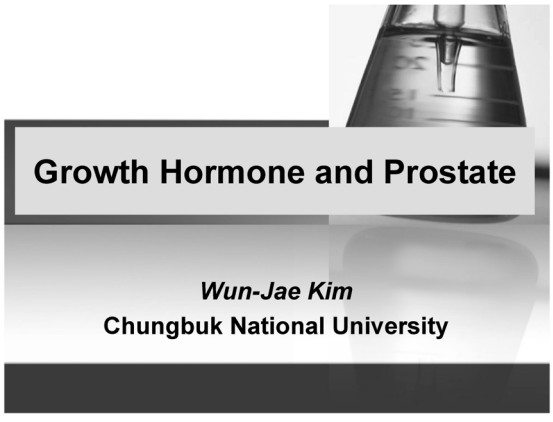
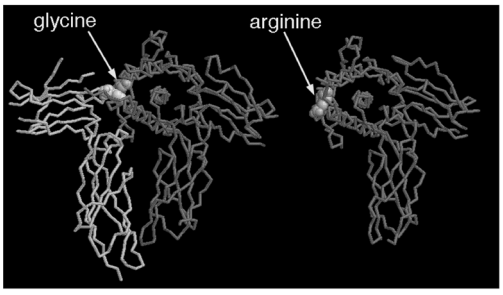
충북의대
김 원 재



Growth Hormone

- **Growth hormone (*somatotropin*):**
- **190 amino acids that is synthesized and secreted by cells called *somatotrophs* in the anterior pituitary.**

Growth Hormone



Growth Hormone

- **From GH-secreting somatotrope cells**
  - anterior pituitary gland
  - Determined by Pit-1 nuclear transcription factor. (Cell-specific)
- **Gene**
  - Chromosome 17q22
  - hGH-N
  - hGH-V : syncytiotrophoblast cells

Control of GH Secretion

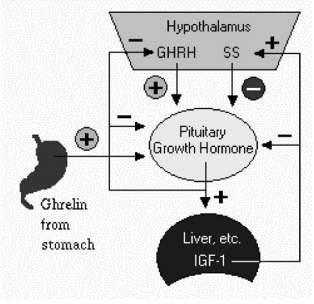
- GHRH
  - **44 amino acid hypothalamic peptide**
  - **Stimulates GH secretion and release**
- Ghrelin, GHRP
  - **Stimulate GHRH**
  - **Directly stimulate GH release**
- Somatostatin
  - **Somatotropin-release inhibiting factor (SRIF)**
  - **Hypothalamus (cf. CNS, GI tract, pancreas)**
  - **Inhibits GH secretion**
- Estrogen, glucocorticoid
- IGF-1: peripheral target hormone for GH

Control of GH Secretion

- **GHRH:** hypothalamic peptide stimulates both the synthesis and secretion of GH

  Somatostatin: produced by several tissues, including hypothalamus.
  - inhibits GH release in response to GHRH and to other stimulatory factors such as low blood glucose concentration.
- **Ghrelin:** secreted from the stomach. Ghrelin binds to receptors on somatotrophs and potently stimulates secretion of GH.
- **IGF-1:** High blood levels of IGF-1 lead to decreased secretion of GH not only by directly suppressing the somatotroph, but by stimulating release of somatostatin from the hypothalamus.

Control of GH Secretion



Surface Receptor on Somatotrope

- **GHRH receptor**
  - G protein coupled receptor (GPCR)
  - Signals through the intracellular c-AMP pathways
  - Activation
    - **Somatotrope cell proliferation**
    - **Hormone production**
    - **Dwarfism: inactivating mutation of GHRH receptor**
- **Ghrelin receptor**
  - In hypothalamus and pituitary
- **Somatostatin receptor (SSTR1 to SSTR5)**
  - SSTR2 & SSTR5: Suppress GH and TSH

GH Secretion

- **Pulsatile**
  - Greatest at night
  - Decline with age
  - Reduced in obese individuals
- **GH elevation**
  - Deep sleep, after exercise, physical stress, trauma, sepsis, estrogen replacement
- **Influenced by nutritional factors**
  - Suppressed by glucose
  - stimulated by malnutrition, fasting, high protein meal and L-arginine, dopamine, apomorphine, a-adrenergic …

GH Receptor

- 70-kDa
- **GHBP**
  - Soluble GH binding protein
  - A fragment of the receptor extra-cellular domain
  - Interact with GH in circulation
- **Liver**: greatest number of GH receptor

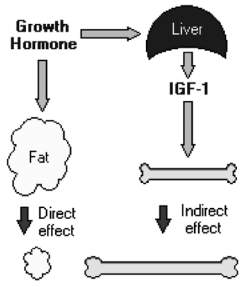
GH Intracellular Signaling

- **Receptor dimerization**
- **Signaling through JAK/STAT pathway**
- **Activated STAT**
  - Modulate expression of GH-regulated target genes

Physiologic Effects of GH

- **Direct effects** are the result of GH binding its receptor on target cells. Fat cells (adipocytes), for example, have growth hormone receptors, and GH stimulates them to break down triglyceride and suppresses their ability to take up and accumulate circulating lipids.
- **Indirect effects** are mediated primarily by a **IGF-1**, a hormone that is secreted from the liver and other tissues in response to GH. A majority of the growth promoting effects of GH is actually due to IGF-1 acting on its target cells.

Physiologic Effects of GH



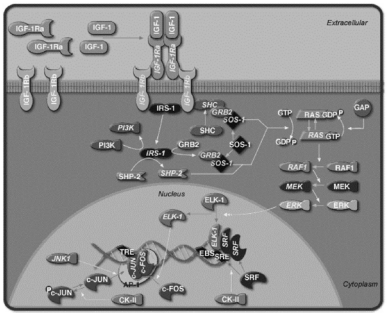
GH Actions

- **Induce protein synthesis & nitrogen retention**
- **Antagonizing insulin action**
  - Impaired glucose tolerance
- **Stimulates lipolysis**
  - Circulating fatty acid levels↑
  - Omental fat mass↓
  - Enhance lean body mass
- **Na, K, water retention, Inorganic phosphate↑**
- **Bone growth↑**
- **Stimulates epiphyseal prechondrocyte differentiation**

IGF-1

- **Insulin like growth factor – 1**
- **Potent growth and differentiation factor**
- **Indirect effect of GH**
- **Circulating IGF-I**
  - Mostly hepatic in origin
  - Log-linear relationship with GH
- **Peripheral tissue IGF-1**
  - Paracrine action
  - both dependent and independent of GH
- **GH administration**
  - Circulating IGF-1↑
  - Multiple tissues IGF-1 expression↑

IGF-I



IGF Binding Protein (IGFBP)

- **High affinity to IGF-I and II**
- **Regulate IGF bioactivity**
- **IGFBP3**
  - GH dependent
  - Major carrier protein for circulating IGF-I
- **IGFBP1-2**
  - Regulate local tissue IGF action
  - Do not bind circulating IGF-I

IGF-I and Prostate Cancer

- Hundreds of studies have identified IGF-1 as a key factor in the growth of prostate cancer.
- "High levels of IGF-1 play a key role in causing prostate cancer"
- "A diet without meat or dairy products could reduce the risk of prostate cancer"

(Allen NE et al. Br J Cancer. 2000)

GH and Prostate Cancer

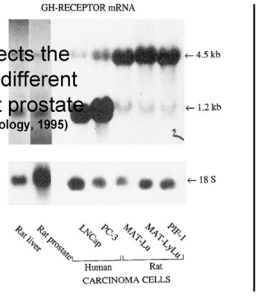
- **GH medications increase risks of colon, prostate and breast cancers.**
- **GH induces growth promoting and other effects by stimulating the liver to increase production of the natural IGF-1 whose blood levels normally decline with advancing age.**
- **Numerous scientific journals showing that elevated IGF-1 levels are strongly associated with major excess risks of colon, prostate, and breast cancers**

GH Receptor

- **GH receptors (GHR) were originally thought to be restricted to the liver, but GHR messenger RNA (mRNA) has recently been identified in a large number of tissues, including rat and human prostates.**

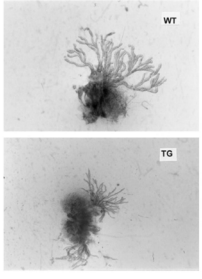
Lobie PE et al. Endocrinology, 1990
Reiter E et al. Mol Cell Endocrinol, 1992
Sobrier ML et al. FEBS Lett,1993

GH directly affects the function of the different lobes of the rat prostate
(Reiter E et al. Endocrinology, 1995)



Evidence that IGF-I and GH are required for prostate gland development

(RUAN W et al. Endocrinology,1999)



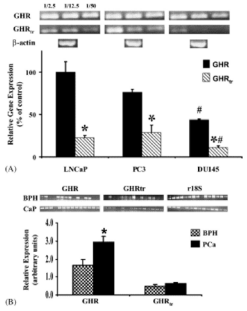
Photomicrographs of a representative dorsal prostate lobe from a 44-day-old wild-type mouse (*upper panel*) and one from a transgenic mouse expressing a mutant form of bovine GH that antagonizes the effect of endogenous mouse GH and causes dwarfism. The glands were placed in collagenase and the connective tissue removed so that the full glandular structure could be ascertained. The prostate architecture was impaired in the transgenic mouse with regard to size (0.6 cm2 *vs.* 0.17 cm2) and number of terminal duct tips (39 *vs.* 24).

Basal serum GH level and the Risk for CaP
: A Case-Control Study (Fuhrman B et al. The Prostate,2005)

- **Lower basal levels of GH are associated with increased CaP risk.**
- **The inverse correlation may be explained by the (-) feedback loop generated by IGF-1 produced by the tumor on GH secretion.**

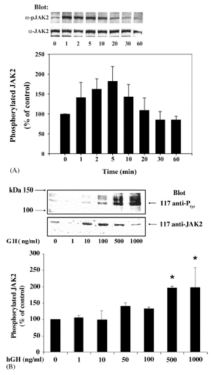
Expression of GHR mRNA isoforms

(Weiss-Messer E et al. Mol Cell Endocrinol, 2004)



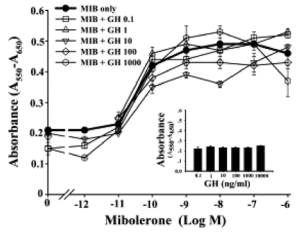
GH induces time-dependent tyrosyl phosphorylation of JAK2 in LNCaP cells

(Weiss-Messer E et al. Mol Cell Endocrinol, 2004)

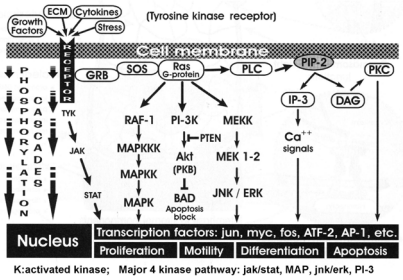


Lack of effects of GH alone or with androgen on LNCaP cell proliferation and PSA secretion

(Weiss-Messer E et al. Mol Cell Endocrinol, 2004)



Cell Signaling



K:activated kinase; Major 4 kinase pathway: jak/stat, MAP, jnk/erk, PI-3
PLC: phospholipase C; IP-3: inositol phosphate; DAG: diacylglycerol
PKC: protein kinase C, SOS: guanine nucleotide exchange factor

GHR and GHBP

- **The full length human GHR and its soluble secreted form, GH binding protein (GHBP), - single gene.**
- **Alternatively spliced GHR: many isoforms expressed in a tissue and species specific manner.**
- **An exon 9-truncated isoform (GHRtr) may act as a dominant negative GHR and its expression is associated with increased GHBP shedding.**

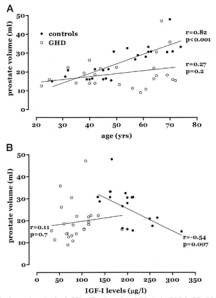
GHR and GHBP

- **GHR: activation of JAK and STAT**
- **GH, through dimerization of its receptor, activates predominantly JAK2 and STAT1, STAT3 and/or STAT5 (depending on cell type).**

- **MAPK, IRS-1/PI3K/Akt and pertussis toxin-sensitive G protein pathways activated by GH.**
- **GH stimulates p42/p44 MAPK in MCF-7 human mammary carcinoma cells, which in many ways resemble prostate carcinoma cells in general and LNCaP cells.**
  - **mitogenesis &/or cellular transformation in response to various stimuli**

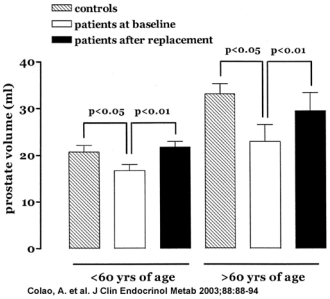
Effect of Growth Hormone (GH) and/or Testosterone Replacement on the Prostate in GH-Deficient Adult Patients

(Colao A et al.J Clin Endocrinol Metab,2003)



Colao, A. et al. J Clin Endocrinol Metab 2003;88:88-94

Prostate volume in controls, hypoandrogenemic, and euandrogenemic GHD patients subdivided in line with age



Colao, A. et al. J Clin Endocrinol Metab 2003;88:88-94

GHRH antagonists inhibit the proliferation of androgen-dependent and -independent CaP

(Letsch M et al. Proc Natl Acad Sci USA, 2003)

- **GHRH antagonists inhibit androgen-independent CaP.**
- **Combination with androgen deprivation inhibits androgen-sensitive tumors.**
- **Thus, the therapy with GHRH antagonist could be considered for the management of both androgen-dependent or -independent CaPs.**

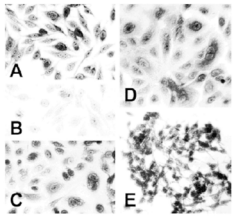
GH replacement does not increase serum PSA in hypo-pituitary men over 50 years

- **Design & Methods:**
  41 men aged over 50 years with adult onset hypopituitarism and GH deficiency. rhGH replacement were examined
  Median follow-up of 22 (range 2.5-32) months
  Serum PSA and IGF-I
- **Results:**
  Mean serum PSA remained unchanged during rhGH replacement, No correlation was found between the individual changes in serum IGF-I and changes in serum PSA.
- **Conclusions:**
  These data are reassuring thus far regarding the safety of GH replacement in relation to the prostate in this patient group.

Expression and action of the growth hormone releasing peptide ghrelin and its receptor in prostate cancer cell lines (Jeffery PL et al. J Endocrinol,2002)

- First to demonstrate the co-expression of the GHS-R and ghrelin in prostate cancer cells.
- Also the first study to provide evidence that a previously unrecognized autocrine/paracrine pathway involving ghrelin, that is capable of stimulating growth, exists in prostate cancer.

A potential autocrine pathway for GHRH and its receptor in human prostate cancer cell lines



A: ALVA41 cells expressing growth hormone releasing hormone (GHRH)-immunoreactivity. B: ALVA41 negative control cells not treated with GHRH antibody; (C) PC3, (D) DU145 and (E) LNCaP prostate cancer cells expressing cytoplasmic GHRH-immunoreactivity (brown). The non-immunoreactive nucleus is counterstained with haematoxylin (blue). Negative controls in the DU145, LNCaP and PC3 cell lines also failed to show GHRH-immunoreactivity (not shown).

Morphogenic and tumorigenic potentials of the mammary GH/GHR system (Garderen E et al. 2002. Mol Cell Endocrinol)

- A GH/GHR system seems to be present in human prostatic cancer as well, which represents another highly prevalent hormone-sensitive malignancy in humans.
- The role of the GH/GHR system in prostatic cancer needs further elucidation.

Effect of 2 Years of GH and IGF-1 suppression on prostate diseases in acromegalic patients

(Colao A et al. J Clin Endocrinol Metab,2000)

- **Hyperplasia, but not cancer, is frequent in acromegalic men, and that the GH-IGF axis and age are independently associated with the development of this process.**

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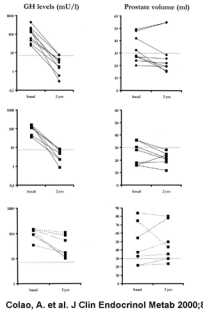
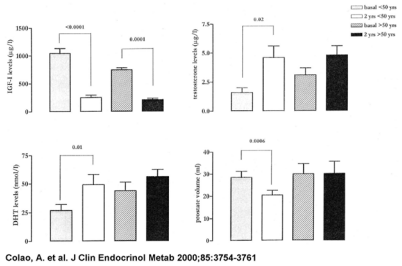


Colao, A. et al. J Clin Endocrinol Metab 2000;85:3754-3761



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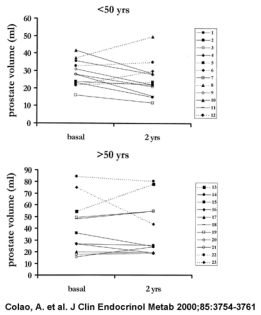
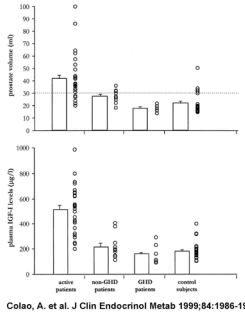


Colao, A. et al. J Clin Endocrinol Metab 2000;85:3754-3761

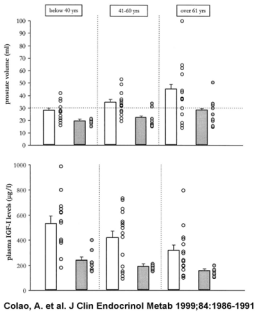
Effect of GH and IGF-1 on Prostate Disease: An Ultrasonic and Endocrine Study in Acromegaly, GH Deficiency, and Healthy Subject
(Colao A et al. J Clin Endocrinol Metab, 1999)

- **In conclusion**

  Chronic excess of GH and IGF-I causes prostate overgrowth but not prostate cancer.

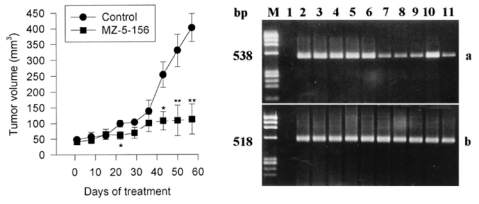


Colao, A. et al. J Clin Endocrinol Metab 1999;84:1986-1991



Colao, A. et al. J Clin Endocrinol Metab 1999;84:1986-1991

GHRH antagonist MZ-5-156 inhibits growth of DU-145 human androgen-independent prostate carcinoma in nude mice and suppresses the levels and mRNA expression of insulin-like growth factor II in tumors. (Lamharzi N et al. Proc Natl Acad Sci USA, 1998)



- **Inhibition of growth of DU-145 human androgen-independent prostate cancers in nude mice by the GH-RH antagonists may be mediated through a reduction in the levels and mRNA expression of IGF-II in tumors.**
- **These results reinforce the view that GH-RH antagonists could be used for the treatment of prostate cancers and other cancers that are influenced by IGFs.**