

**Skinny****SCIENCE**®

**MEDICAL NEWS**

**EDUCATIONAL SERIES**

**L-ARGININE M2**®

**GROWTH HORMONE**  
**IGF & L-ARGININE**

**No. 22884**

**July 2008**

**This Series is published at**  
**[SkinnyScienceEDU.com](http://SkinnyScienceEDU.com)**

# GROWTH HORMONE

## IGF & L-ARGININE

Growth Hormone (GH) is a protein hormone released from the anterior pituitary gland under the control of the hypothalamus. GH is the *primary* anti-aging hormone in humans. In children, GH has growth-promoting effects on the body.

GH effects bone metabolism and promotes growth of long bone before growth plate closure, increases skin thickness, and decreases subcutaneous fat deposition in older persons.

GH stimulates the secretion of somatomedins from the liver, which are a family of insulin-like growth factor (IGF) hormones. These, along with GH and thyroid hormone, stimulate linear skeletal growth in children.

In adults, GH stimulates protein synthesis in muscle and the release of fatty acids from adipose tissue (anabolic effects), and inhibits uptake of glucose by muscle while stimulating uptake of amino acids. Amino acids are used in the synthesis of proteins, and the muscle shifts to using fatty acids as a source of energy.

GH secretion occurs in a pulsatile (short, concentrated secretion) and sporadic manner. Thus, a single test of the GH level is usually not accurate. Its biological activity is best measured by insulin like growth factor (IGF-1).

### GH & GENOMIC LOCUS

The Growth Hormone locus, a 66 kb region of DNA, is located in chromosome 17q22-q24 and consists of 5 homologous genes, which appear to have been duplicated from an ancestral GH-like gene. Because of their origin from an ancestral GH-like gene, all five genes in the GH genomic locus share 95% sequence identity including their promoters (105): proximal elements in the promoter bind Pit-1/GHF-1.

### GH & CHILDHOOD GROWTH

African-American girls have higher blood levels of the biologically active form of a potent growth hormone known as "free IGF-1" than their Caucasian peers.

These hormonal differences help explain why African-American girls grow faster and taller than their Caucasian counterparts. This genetic trait is also related to tendency towards weight gain in adulthood.

Trials conducted at the *USDA/ARS Children's Nutrition Research Center at Baylor College of Medicine* in Houston reported that free IGF-1 may be responsible for weight gain in African-Americans:

"This raises the question of whether high levels of free IGF-1 are accelerating growth in African-American children and whether these higher levels could be a factor in excessive weight gain if they persist once growth is complete," said Dr. William Wong, a Baylor professor of pediatrics.

This study was the first to report ethnic differences involving Insulin-like Growth Factor-1 (IGF-1) (*Journal of Pediatrics*).

The study involved 136 normal-weight, healthy African-American and Caucasian girls between the ages of 9 and 17, and was designed to gain insight into the reason African-American girls are more sexually mature, taller and heavier, with both more lean muscle mass and body fat than their Caucasian counterparts.

"In addition to the higher levels of free IGF-1, the African-American girls had corresponding lower blood levels of two specific binding proteins. These binding proteins tie up free IGF-1 in the bloodstream, making it inactive," states Dr. Wong.

According to Wong, the liver's production of one of these binding proteins is inhibited by insulin.

"These results suggest that insulin might be involved in how much free IGF-1 is in circulation," he said. This is significant because non-diabetic, healthy, normal-weight African-American children also have higher blood insulin levels.

Higher blood insulin levels predispose individuals to insulin-resistant Type 2 diabetes. However, even if diabetes does not develop, high insulin levels can contribute to the development of high cholesterol levels, weight problems and hypertension, which are all more prevalent among African Americans.

In humans, chronic elevation of insulin levels leads to type 2 diabetes and obesity. GH modulates insulin resistance, and low GH levels are consistent with weight gains, obesity, and insulin resistance. Acute exercise decreases insulin, thus providing a non-drug methodology for increasing lifespan and reduction of diabetes risks.

"If we can unravel the molecular and genetic mechanisms responsible for ethnic differences in free IGF-1 levels, we might also discover factors that predispose African Americans to high insulin levels and related weight and cardiovascular problems," Wong said.

*Journal of Pediatrics*, 1999; 135:296-300.

Copyright © Skinny Science EDU

## GROWTH HORMONE AXIS

GH acts both directly through its own receptor and indirectly through the induced production of Insulin-like Growth Factor I (IGF-I). The expression of the IGF-I gene is determined by the activity of its promoters and by transcription factors that stimulate or inhibit their activity. The most potent regulator of IGF-I expression in *postnatal* life is GH.

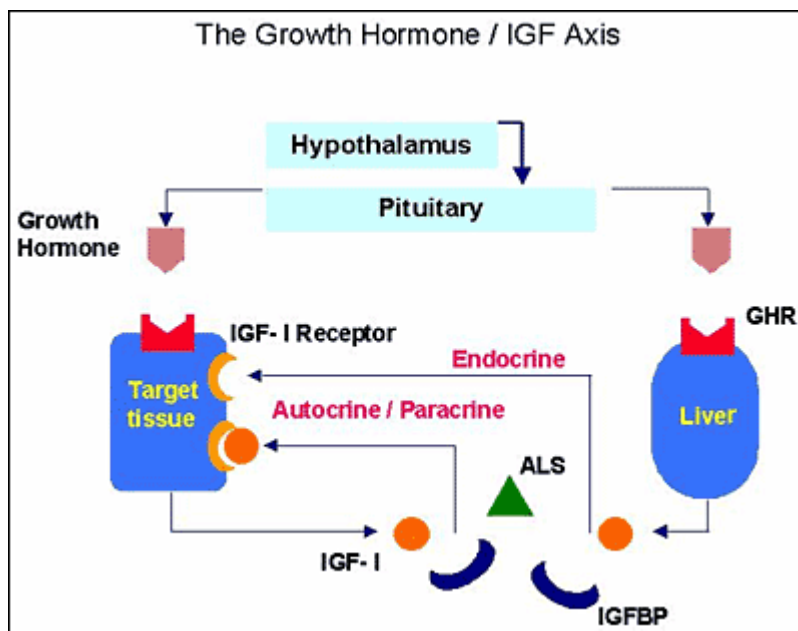
IGF-I mediates growth hormone negative feedback. Nutritional status and supply of dietary energy and protein are also regulators of IGF-I and possibly the main regulators of IGF-I expression in fetal life. GH is secreted by the somatotrope cells located primarily in the lateral wings of the anterior pituitary. The morphological characteristics and number of these cells are remarkably constant throughout life, while secretion changes.

GH secretion occurs in a pulsatile fashion, and in a circadian rhythm with a maximal release in the second half of the night.

Two hypothalamic hormones regulate GH secretion:

- Growth Hormone Releasing Hormone (GHRH) with a stimulatory action at the level of gene transcription and somatostatin (SST) with an inhibitory effect on the GH secretion from the pituitary gland.
- High-dose L-Arginine GH releasing compounds possess a natural dual effect in increasing the release of GHRH and inhibiting SST action, thereby obtaining a very powerful stimulation of GH secretion.

Table 1.



## NON-INSULIN STIMULATING GH AGENTS

IGF is blocked by insulin, both serum and ingested (oral ingestion). This is elucidated by long-term evidence that chronic ingestion of high glycemic and/or high cephalic (insulin-stimulating) foods and beverages leads to weight gain and type 2 diabetes.

The only known safe long-term methodology for re-instating age-reduced growth hormone (GH) levels in humans is administration of high doses of the amino acid L-Arginine. GH-stimulating doses in adults requires oral ingestion of 10,000 mg (10 g) elemental L-Arginine in a low glycemic matrix.

If L-Arginine is administered in a high glycemic format, blunting of GH and IGF occurs. Oral L-arginine can be engineered *not* to elevate insulin levels. This can be accomplished by controlling the glycemic response of the ingested L-Arginine. L-Arginine formulas designed not to over-elevate insulin levels are *low glycemic*. L-Arginine formulas that are not specifically designed to be *low glycemic* will elicit a *high glycemic* response in humans.

High glycemic L-Arginine formulas cause a rise in plasma glucose by 60 % or more. Any potential therapeutic effects of L-Arginine in insulin-resistance, GH, and IGF-1 are eradicated if the formula has a high glycemic response. High glycemic L-Arginine (ARG) formulas *blunt* the positive effects of serum elevation of ARG, including nitric oxide, anti-aging, weight-reduction, and muscle-enhancing benefits.

## FREE FORM VS AMINO ACID CHAIN L-ARG

The type of arginine found in protein-foods is part of an amino acid chain (AAC), and is not considered therapeutic L-Arginine (Free Form). Free Form L-Arginine has been separated from its sister amino acids in the amino acid food chain via a fermenting process, and functions completely differently than AAC.

Only arginine that has been separated from all other amino acids (AAC) will provide therapeutic benefits, such as elevation and re-instation of GH, IGF, improved insulin function, and anti-aging.

Taking protein or amino acids with Free Form L-Arginine is contraindicated as the amino acids found in all protein (AAC) blocks L-Arginine metabolism. Further, protein ingestion causes insulin elevation:

- In humans, consuming 50 grams of beef results in a rise in insulin that is ~ 30 percent that of pure glucose, a very high glycemic, fat-storing sugar.
- In person with type 2 diabetes, the insulin response to 50 grams of beef was identical to that of pure glucose, which further exacerbates the pathology of diabetes and diabetic symptoms.

## ANABOLIC REACTION TO L-ARG

Anabolic activity is mandatory in healthy humans, and particularly so in the athlete. Catabolism (muscle wasting) is common in anorexia, cancer, HIV, aging, and other life-threatening states.

In athletes, anabolic activity is largely responsible for sports performance. Though many athletes have been taught that insulin is a primary mechanism for building muscle, that is not the case.

- Insulin-balance is required for anabolic states, but over-expression of insulin blunts muscle-building and instigates adipose tissue fat-storage.
- Ingestion of lower amounts of protein (30 grams and less ingested at one time) activates appropriate levels of insulin and feeds muscle-building mechanisms.
- Excess supplemental or food protein (more than 30 grams ingested at one time) actually derails the muscle-building process and shunts the excess protein into fat-cells.
- The specific amino acid composition of a food-protein source determines the insulin secreted.

GH blunts fat storage and adipose tissue fat accumulation, as well as internal thermogenesis, while insulin stimulates fat storage and reduced thermogenic fat-burning. Though adequate insulin is required for muscle growth, normal persons have totally adequate insulin levels for anabolic activity. Additionally, when GH levels are high enough (during teen-age years) insulin fat-storing effects are mitigated. It is only after age 23 that GH levels begin to decline, and continue to decline during lifespan.

In supplemental form, the glycemic response of an oral L-Arginine formula determines the level of insulin and blood glucose secreted. Administration of high doses of *low glycemic* Free Form L-Arginine (separate from any protein) creates anabolism and muscle-building, and triggers biochemical *messages* to the body to build more muscle and denser muscle. This also instigates improved insulin resistance, higher muscle mass, and lower body fat levels.

L-Arginine is both dose-dependent and timing-dependent, and is highly metabolically selective, thus inclusion of high glycemic agents renders L-arginine formulas inert.

Copyright © Skinny Science EDU

Copyright © 2006-2009 Skinny Science ®

**SKINNY SCIENCE EDU**  
**MEDICAL NEWS**  
**EDUCATIONAL SERIES**

**L-ARGININE M2 ®**  
**GROWTH HORMONE**  
**IGF & L-ARGININE**

**No. 22884**  
**July 2008**

**This Series is published at**  
**SkinyScienceEDU.com**

**REFERENCES**

*McKusick V, Phillips JI 2003 GROWTH HORMONE 1; GH1. In: McKusick V (ed) Online Mendelian Inheritance in Man. Johns Hopkins University, Baltimore, MD, USA*

*Frankenne F, Rentier-Delrue F, Scippo ML, Martial J, Hennen G 1987 Expression of the growth hormone variant gene in human placenta. J Clin Endocrinol Metab 64:635-7*

*Liebhaber SA, Urbanek M, Ray J, Tuan RS, Cooke NE 1989 Characterization and histologic localization of human growth hormone-variant gene expression in the placenta. J Clin Invest 83:1985-91*

*McKusick V, Phillips JI 2003 GROWTH HORMONE 2; GH2. In: McKusick V (ed) Online Mendelian Inheritance in Man. Johns Hopkins University, Baltimore, MD*

*Marshall J 2002 Control of Pituitary Hormone Secretion - Role of Pulsatility. In: Besser G, Thorner M (eds) Comprehensive Clinical Endocrinology. Mosby, Edinburgh, UK, pp 19-34*

*Doniach I 1985 Histopathology of the pituitary. Clin Endocrinol Metab 14:765-89*

*Chen EY, Liao YC, Smith DH, Barrera-Saldana HA, Gelinas RE, Seeburg PH 1989 The human growth hormone locus: nucleotide sequence, biology, and evolution. Genomics 4:479-97*

*Bodner M, Castrillo JL, Theill LE, Deerinck T, Ellisman M, Karin M 1988 The pituitary-specific transcription factor GHF-1 is a homeobox-containing protein. Cell 55:505-18*

Lemaigre FP, Peers B, Lafontaine DA, et al. 1989 Pituitary-specific factor binding to the human prolactin, growth hormone, and placental lactogen genes. *DNA* 8:149-59

McKusick V, Phillips JI, Hamosh A 2002 Pro-opiomelanocortin. In: McKusick V (ed) *Online Mendelian Inheritance in Man*. Johns Hopkins University, Baltimore, MD, USA

Therrien M, Drouin J 1991 Pituitary pro-opiomelanocortin gene expression requires synergistic interactions of several regulatory elements. *Mol Cell Biol* 11:3492-503

Therrien M, Drouin J 1993 Cell-specific helix-loop-helix factor required for pituitary expression of the pro-opiomelanocortin gene. *Mol Cell Biol* 13:2342-53

Poulin G, Turgeon B, Drouin J 1997 NeuroD1/beta2 contributes to cell-specific transcription of the proopiomelanocortin gene. *Mol Cell Biol* 17:6673-82

Boutillier AL, Monnier D, Koch B, Loeffler JP 1994 Pituitary adenylyl cyclase-activating peptide: a hypophysiotropic factor that stimulates proopiomelanocortin gene transcription, and proopiomelanocortin-derived peptide secretion in corticotropic cells. *Neuroendocrinology* 60:493-502

Suda T, Tozawa F, Yamada M, et al. 1988 Effects of corticotropin-releasing hormone and dexamethasone on proopiomelanocortin messenger RNA level in human corticotroph adenoma cells in vitro. *J Clin Invest* 82:110-4

Seidah NG, Chretien M 1981 Complete amino acid sequence of a human pituitary glycopeptide: an important maturation product of pro-opiomelanocortin. *Proc Natl Acad Sci U S A* 78:4236-40

Vale W, Spiess J, Rivier C, Rivier J 1981 Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science* 213:1394-7

Brownstein MJ, Russell JT, Gainer H 1980 Synthesis, transport, and release of posterior pituitary hormones. *Science* 207:373-8

Antoni FA, Holmes MC, Kiss JZ 1985 Pituitary binding of vasopressin is altered by experimental manipulations of the hypothalamo-pituitary-adrenocortical axis in normal as well as homozygous (di/di) Brattleboro rats. *Endocrinology* 117:1293-9

al-Damluji S 1993 Adrenergic control of the secretion of anterior pituitary hormones. *Baillieres Clin Endocrinol Metab* 7:355-92

Korbonits M, Kaltsas G, Perry LA, et al. 1999 The growth hormone secretagogue hexarelin stimulates the hypothalamo-pituitary-adrenal axis via arginine vasopressin. *J Clin Endocrinol Metab* 84:2489-95

Arvat E, Maccario M, Di Vito L, et al. 2001 Endocrine activities of ghrelin, a natural growth hormone secretagogue (GHS), in humans: comparison and interactions with hexarelin, a nonnatural peptidyl GHS, and GH-releasing hormone. *J Clin Endocrinol Metab* 86:1169-74

Cohen LE, Radovick S 2002 Molecular basis of combined pituitary hormone deficiencies. *Endocr Rev* 23:431-42

Niall HD, Hogan ML, Sauer R, Rosenblum IY, Greenwood FC 1971 Sequences of pituitary and placental lactogenic and growth hormones: evolution from a primordial peptide by gene reduplication. *Proc Natl Acad Sci U S A* 68:866-70

Owerbach D, Rutter WJ, Martial JA, Baxter JD, Shows TB 1980 Genes for growth hormone, chorionic somatomammotropin, and growth hormones-like gene on chromosome 17 in humans. *Science* 209:289-92

Masuda N, Watahiki M, Tanaka M, et al. 1988 Molecular cloning of cDNA encoding 20 kDa variant human growth hormone and the alternative splicing mechanism. *Biochim Biophys Acta* 949:125-31

McKusick V, Phillips JI, Rasooly R 2003 CHORIONIC SOMATOMAMMOTROPIN HORMONE 1; CSH1. In: McKusick V (ed) *Online Mendelian Inheritance in Man*. Johns Hopkins University, Baltimore, MD

McKusick V, Rasooly R 2003 CHORIONIC SOMATOMAMMOTROPIN HORMONE 2; CSH2. In: McKusick V (ed) *Online Mendelian Inheritance in Man*. Johns Hopkins University, Baltimore, MD

Rasooly R 2003 CHORIONIC SOMATOMAMMOTROPIN HORMONE-LIKE 1; CSHL1. In: McKusick V (ed) *Online Mendelian Inheritance in Man*. Johns Hopkins University, Baltimore, MD

Fox SR, Jong MT, Casanova J, Ye ZS, Stanley F, Samuels HH 1990 The homeodomain protein, Pit-1/GHF-1, is capable of binding to and activating cell-specific elements of both the growth hormone and prolactin gene promoters. *Mol Endocrinol* 4:1069-80

Tansey WP, Catanzaro DF 1991 Sp1 and thyroid hormone receptor differentially activate expression of human growth hormone and chorionic somatomammotropin genes. *J Biol Chem* 266:9805-13

Nickel BE, Nachtigal MW, Bock ME, Cattini PA 1991 Differential binding of rat pituitary-specific nuclear factors to the 5'-flanking region of pituitary and placental members of the human growth hormone gene family. *Mol Cell Biochem* 106:181-7

Nachtigal MW, Nickel BE, Cattini PA 1993 Pituitary-specific repression of placental members of the human growth hormone gene family. A possible mechanism for locus regulation. *J Biol Chem* 268:8473-9

Jones BK, Monks BR, Liebhaber SA, Cooke NE 1995 The human growth hormone gene is regulated by a multicomponent locus control region. *Mol Cell Biol* 15:7010-21

Shewchuk BM, Liebhaber SA, Cooke NE 2002 Specification of unique Pit-1 activity in the hGH locus control region. *Proc Natl Acad Sci U S A* 99:11784-9

Frohman LA, Burek L, Stachura MA 1972 Characterization of growth hormone of different molecular weights in rat, dog and human pituitaries. *Endocrinology* 91:262-9

Baumann G, Winter RJ, Shaw M 1987 Circulating molecular variants of growth hormone in childhood. *Pediatr Res* 22:21-2

Baumann G, Stolar MW, Amburn K 1985 Molecular forms of circulating growth hormone during spontaneous secretory episodes and in the basal state. *J Clin Endocrinol Metab* 60:1216-20

Herington AC, Ymer S, Stevenson J 1986 Identification and characterization of specific binding proteins for growth hormone in normal human sera. *J Clin Invest* 77:1817-23

Leung DW, Spencer SA, Cachianes G, et al. 1987 Growth hormone receptor and serum binding protein: purification, cloning and expression. *Nature* 330:537-43

Baumann G, Shaw MA 1990 Plasma transport of the 20,000-dalton variant of human growth hormone (20K): evidence for a 20K-specific binding site. *J Clin Endocrinol Metab* 71:1339-43

Baumann G, Amburn KD, Buchanan TA 1987 The effect of circulating growth hormone-binding protein on metabolic clearance, distribution, and degradation of human growth hormone. *J Clin Endocrinol Metab* 64:657-60

Ross RJ, Esposito N, Shen XY, et al. 1997 A short isoform of the human growth hormone receptor functions as a dominant negative inhibitor of the full-length receptor and generates large amounts of binding protein. *Mol Endocrinol* 11:265-73

Thorner MO, Perryman RL, Cronin MJ, et al. 1982 Somatotroph hyperplasia. Successful treatment of acromegaly by removal of a pancreatic islet tumor secreting a growth hormone-releasing factor. *J Clin Invest* 70:965-77

Mayo K, Vale W, Rivier J, Rosenfeld M, Evans R 1983 Expression-cloning and sequence of a cDNA encoding human growth hormone-releasing factor. *Nature* 306:86-88

Gubler U, Monahan J, Lomedico P, et al. 1983 Cloning and sequence analysis of cDNA for the precursor of human growth hormone-releasing factor, somatocinin. *Proc Natl Acad Sci U S A* 80:4311-4314

Mayo K 1992 Oct Molecular cloning and expression of a pituitary-specific receptor for growth hormone-releasing hormone. *Mol Endocrinol* 6:1734-1744

Barinaga M, Yamamoto G, Rivier C, Vale W, Evans R, Rosenfeld M 1983 Transcriptional regulation of growth hormone gene expression by growth hormone-releasing factor. *Nature* 306:84-85

Fukata J, Diamond D, Martin J 1985 Aug Effects of rat growth hormone (rGH)-releasing factor and somatostatin on the release and synthesis of rGH in dispersed pituitary cells. *Endocrinology* 117:457-467

Campbell R, Scanes C 1992 Dec Evolution of the growth hormone-releasing factor (GRF) family of peptides. *Growth Regul* 2:175-191

Shen L, Pictet R, Rutter W 1982 Aug Human somatostatin I: sequence of the cDNA. *Proc Natl Acad Sci U S A* 79:4575-4579

Siler T, VandenBerg G, Yen S, Brazeau P, Vale W, Guillemin R 1973 Oct Inhibition of growth hormone release in humans by somatostatin. *J Clin Endocrinol Metab* 37:632-634

Brazeau P, Vale W, Burgus R, et al. 1973 Jan 5 Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. *Science* 179:77-79

Tannenbaum GS, Epelbaum J, Bowers CY 2003 Interrelationship between the Novel Peptide Ghrelin and Somatostatin/Growth Hormone-Releasing Hormone in Regulation of Pulsatile Growth Hormone Secretion. *Endocrinology* 144:967-74

Copyright © Skinny Science EDU

Copyright © 2006-2009 Skinny Science ®