# PRINCIPLES AND PRACTICE OF PEDIATRIC ENDOCRINOLOGY

# PRINCIPLES AND PRACTICE OF PEDIATRIC ENDOCRINOLOGY

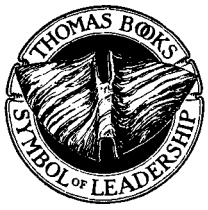
*Edited by*

**MICHAEL S. KAPPY, M.D., PH.D.**

**DAVID B. ALLEN, M.D.**

*and*

**MITCHELL E. GEFFNER, M.D.**

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# FOREWORD

The world of biomedical science is changing as rapidly as it takes for our keystrokes to open a window into cyberspace. Principles, however, remain grounded and provide the basis for learning the new and integrating change into effective, evidence-based, humane medical practice. The editors of *Principles and Practice of Pediatric Endocrinology*, by its very title, have demonstrated their understanding that while downloads and virtual learning are changing the way the current generation acquires information, a text which translates and transmits that information through the experience and judgment of accomplished physician scientists, has a pivotal role in the education of the practitioner. Drs. Kappy, Allen, and Geffner have assembled such a group of accomplished authors and teachers, and the result is a readable, practical, yet scientifically solid and relevant text that should be a valuable asset for pediatric endocrine subspecialists as well as for pediatricians, family practitioners, and other health care providers who care for children and adolescents.

Puberty, for example, is not an endocrine "disease" (notwithstanding the feelings of some parents while their children go through it), but a fundamental aspect of pediatrics, and an understanding of its process and physiology is essential for all physicians, nurses, and others who care for children and adolescents. Thus, the extensive and well-written description of this phenomenon and the illustrative data that describe its variability will serve as a valuable reference well after new genetic mutations are described for some of the rare causes of its pathology. Similarly, the illustrative Atlas cases bring the subject to life and keep the reader grounded in clinical reality.

Conversely, diabetes, which in the type I form is clearly an endocrine disease (notwithstanding that it was not included in one of the earliest, classic pediatric endocrinology texts), has an impact that is so devastating for patient and family that it too needs to be understood by all health care professionals who care for affected children or their family members. Again the authors transmit their vast experience in a practical and useful way that makes the reader want to continue to read and creates a written environment for learning that is so needed for effective care of the affected individuals.

The theme of *Principles and Practice* is reflected in the other chapters as well, and all provide the reader with the balance of science and clinical judgment that teaching is all about. Finally, for this teacher, it is a special honor to comment on the work of so accomplished a panel of contributors, several of whom I had the privilege of working with while they were fellows in our group.

BARBARA M. LIPPE, M.D.

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I would like to thank, first of all, the people at Genentech, Inc., for their generous support of this work, as they did for the 4th edition of the Wilkins textbook that I co-edited with Drs. Blizzard and Migeon in 1994. Ten years between editions is a bit long, but for those of you who contribute chapters for this and other textbooks, it may seem like just a brief moment.

I am, of course, indebted to my two able co-editors, Drs. David Allen and Mitchell Geffner, without whom this book would never have come to fruition. In Denver, the contributions of the staff of the medical library and medical photographics department are much appreciated.

One indulgence afforded editors is the luxury of honoring past mentors, and in that spirit I would like to acknowledge the influences in my life of Lennie Licara, Saul Chavkin, Yvonne Brackbill, Ken Monty, Robert Metzenberg, Harry Harlow, Harry Waisman, C. Henry Kempe, Claude Migeon, Harold and Helen Harrison, Bob Blizzard and Lew Barness. Those whose work formed the foundation of our discipline include Claude Bernard, Walter Cannon, Hans Selye, Lawson Wilkins, Fuller Albright, and many, many others.

I have enjoyed the critical questioning of many students, residents, and fellows over the past 40 years, and believe it enhanced my own education! I am also most grateful for the support of my parents, my wife, children, and grandchildren, and I dedicate my portion of this book to them.

I hope that this book continues in the tradition of the Lawson Wilkins textbook of pediatric endocrinology that included an abundance of clinical descriptions and experience in the diagnosis and treatment of endocrine disorders in childhood and adolescence.

MICHAEL S. KAPPY, M.D., PH.D.

Working on this book has stimulated much positive reflection – on the complexity and rapid advancement of pediatric endocrinology, on the insights of countless brilliant contributors to this progress, on the joy and privilege of caring for children, and on the satisfaction of collaborating with a wonderful community of professional colleagues. For this opportunity, I'm indebted to Michael Kappy for his initiative and confidence, and to Mitch Geffner, with whom it is always a pleasure to work.

For inspiration, I am most indebted to my father, Rich Allen, a dedicated pediatrician in the truest and most profound sense of the word. In spite of my efforts to take a different path, the example he provided in caring for children brought me back to medicine, and then to pediatrics. For whatever perspective and humility that I do have, I give thanks to my mother, Joyce, the most centered and loving individual I have ever known. And for everything else, I thank my wife, Sally, who has unselfishly and constantly supported and encouraged me for over 30 years, and my children, Brittany, Doug, and Nick, who provide immeasurable love and joy and the motivation always to do my best.

Professionally, I first acknowledge the generous spirit of Dr. Robert Blizzard, who spontaneously and from afar took a genuine interest in my career

and provided invaluable advice and support. I also thank Ann Johanson, Ron Rosenfeld, Ed Reiter, Alan Rogol, Barbara Lippe, Margaret MacGillivray, and Ken Copeland, who have inspired and encouraged me to seek academic and leadership challenges. I am indebted to my University of Wisconsin mentors and colleagues Norm Fost and Aaron Friedman, who instilled in me a love for critical thinking and the importance of challenging conventional wisdom. And finally, a sincere thank you to my endocrine coworkers at the University of Wisconsin – Michael MacDonald, Aaron Carrel, Ellen Connor, Gordon Tuffli, Tracy Bekx, Jan Lehmann, and Kiva Adler – who make work in the real world so much fun, and without whose patience and support I could not have pursued so many opportunities.

Twenty years ago, the specialty of Pediatric Endocrinology captivated my interest because of its elegance, diversity, mystery, and intrinsically pediatric focus on the changes of childhood and adolescence. My hope for this book is that it both captures and conveys these qualities for the reader.

DAVID B. ALLEN, M.D.

It goes without saying that I would not be writing this tribute were it not for the invitation from my good friend Mike Kappy to help him carry on the Wilkins torch. It has been a true joy working with Mike and my "grant-reviewing" buddy Dave Allen.

But it all starts at the beginning. I was born to edit – my father being a high school chemistry department chairman in New York and a science review book editor. My mother's love for language – she was a high school French teacher – was, no doubt, another guiding light for this tour de force.

In addition, I thank my three professional mentors from the early days: Sol Kaplan, Barbara Lippe, and Dave Golde. Collectively, they taught me to ask questions and think critically, and, in so doing, they instilled in me the scientific thirst to endure in academia. I also thank Fran Kaufman for her support. I also thank the leprechauns, Laron dwarfs, and Efe pygmies, without whom my research career would have traversed a much different and probably shorter path.

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But the most thanks go to my team at home. My wife, Andrea, is the most patient, understanding, and loving person I know. My children, Jenny and Eric, watched my professional career grow as they grew. Without their unwavering and collective support over the years, I would never have had the opportunity to work on this book or to have achieved the professional success that I have had.

MITCHELL E. GEFFNER, M.D.

## CONTENTS

# PRINCIPLES AND PRACTICE OF PEDIATRIC ENDOCRINOLOGY

# Chapter 1

# ORGANIZATION AND FUNCTION OF THE ENDOCRINE SYSTEM

ALLEN W. ROOT, M.D., AND ALAN D. ROGOL, M.D., PH.D.

# ABBREVIATIONS

| | |
|---|---|
| ACTH | Adrenocorticotropin |
| AF-1 | Activation function domain 1 |
| AGRP | Agouti-related peptide |
| ALS | Acid labile subunit |
| AMP | Adenosine monophosphate |
| AP1 | Activating protein-1 |
| ATP | Adenosine triphosphate |
| AR | Androgen receptor |
| AVP | Arginine vasopressin |
| BMP | Bone morphogenetic protein |
| BMPR2 | BMP receptor type II |
| $Ca^{2+}$ | Calcium (ionized) |
| CART | Cocaine- and amphetamine-regulated transcript |
| CG | Chorionic gonadotropin |
| $Cl^-$ | Chloride (ionized) |
| CPT1 | Carnitine palmitoyltransferase-1 |
| CREB | Cyclic AMP response element binding protein |
| CREM | Cyclic AMP response element modulator protein |
| CRH | Corticotropin-releasing hormone |
| DAG | Diacylglycerol |
| DNA | Deoxyribonucleic acid |
| EGF | Epidermal growth factor |
| ER | Estrogen receptor |
| ERK | Extracellular signal-regulated kinase |
| FGF | Fibroblast growth factor |
| FGFR | FGF receptor |
| FSH | Follicle-stimulating hormone |
| GABA | Gamma-aminobutyric acid |
| GASP | GPCR-associated sorting protein |
| Gc | Group-specific component |
| GDP | Guanosine diphosphate |
| GH | Growth hormone |
| GHBP | GH binding protein |
| GHR | GH receptor |
| GHRH | GH-releasing hormone |
| GHRHR | GHRH receptor |
| GM-CSF | Granulocyte/macrophage colony stimulating factor |
| GnRH | Gonadotropin-releasing hormone |
| GPCR | G protein-coupled receptor |
| GPK | GPCR kinase |
| GR | Glucocorticoid receptor |
| GRB | Growth factor receptor-binding protein |
| GRE | Glucocorticoid response element |
| GRK | G protein-coupled receptor kinase |
| GRα | Glucocorticoid receptor α |
| GTP | Guanosine triphosphate |
| hCG | Human chorionic gonadotropin |
| HLGAG | Heparan-like glycosaminoglycans |
| HOP | HSP organizing protein |
| HRE | Hormone response element |
| HSP | Heat shock protein |
| 5-HT | Serotonin |
| Ig | Immunoglobulin |
| IGF | Insulin-like growth factor |
| IGFBP | IGF-binding protein |
| IL | Interleukin |
| $IP_3$ | Inositol-1,4,5-triphosphate |
| IRS | Insulin receptor substrate |
| JAK | Janus kinase |
| JNK | c-Jun amino-terminal kinase |
| $K^+$ | Potassium (ionized) |
| LCFA | Long chain fatty acids |
| LDL | Low-density lipoprotein |
| LRP5 | LDL receptor-related protein-5 |
| LH | Luteinizing hormone |
| MAP(K) | Mitogen-activated protein (kinase) |
| MCH | Melanin concentrating hormone |
| MC4R | MSH-4-receptor |
| MEK | MAP kinase/ERK |
| $Mg^{2+}$ | Magnesium (ionized) |
| MIS | Müllerian inhibiting substance |
| MISS | Membrane-initiated steroid signaling |
| MR | Mineralocorticoid receptor |
| MSH | Melanocyte-stimulating hormone |
| $Na^+$ | Sodium (ionized) |
| NcoR | Nuclear receptor corepressor |
| NFκB | Nuclear factor κB |
| NIS | Sodium/iodide symporter |
| NLS | Nuclear localization signal |
| NOS | Nitric oxide synthase |
| NPC | Nuclear pore complex |
| NPY | Neuropeptide Y |
| NSF-1 | N-ethylmaleimide-sensitive factor |
| PAPS | 3'-Phosphoadenosine 5'-phosphosulfate |
| PDE | Phosphodiesterase |
| PDGF | Platelet derived growth factor |
| PDK1 | 3-Phosphoinositide-dependent protein kinase-1 |
| PGC-1α | Peroxisome proliferator-activated receptor-γ coactivator 1α |
| PIAS | Protein inhibitor of activated signal transducer and activator of transcription |
| PI3K | Phosphatidylinositol 3-kinase |
| $PIP_2$ | Phosphatidylinositol-4,5-biphosphate |
| $PIP_3$ | Phosphatidylinositol-3,4,5-biphosphate |
| PKA | Protein kinase A |
| PKB | Protein kinase B (AKT) |
| PKC | Protein kinase C |
| PLC | Phospholipase C |
| POMC | Proopiomelanocortin |
| PPARγ | Peroxisome proliferator-activated receptor-γ |
| PR | Progesterone receptor |
| PTB | Phosphotyrosine binding |
| PTHrP | Parathyroid hormone-related protein |
| PTHR1 | PTH receptor-1 |
| PTP | Protein tyrosine phosphatase |
| RAN | Ras-related nuclear protein |

| | |
|---|---|
| RANK | Receptor activator-NFγB |
| RANKL | Rank ligand |
| RAR | Retinoic acid receptor |
| RCK | Regulators of $K^+$ conductance |
| RER | Rough endoplasmic reticulum |
| RNA | Ribonucleic acid |
| RSK | Receptor serine kinase |
| RTK | Receptor tyrosine kinase |
| RXR | Retinoic acid receptor (9 cis) |
| SERM | Selective estrogen receptor modulator |
| SF1 | Steroidogenic factor 1 |
| SH2 | Src homology 2 |
| SHP2 | SH2 phosphatase 2 |
| SHPS-1 | SH2 domain-containing tyrosine phosphatase substrate-1 |
| SMAD | Mothers against decapentaplegic |
| SMRT | Silencing mediator of retinoid and thyroid hormone receptor |
| SNARES | Soluble N-ethylmaleimide-sensitive factor attachment protein receptors |
| SNX-1 | Sorting nexin-1 |
| SOCS | Suppressor of cytokine signaling |
| SRC | Steroid receptor coactivator |
| SRIH | Somatotropin-release inhibiting hormone = Somatostatin |
| StAR | Steroidogenic acute regulatory (protein) |
| STAT | Signal transducer and activator of transcription |
| SUMO | Small ubiquitin-related modifier |
| TACE | TNF-α converting enzyme |
| TAF | TATA binding protein-associated factor |
| TBP | TATA binding protein |
| TGF | Transforming growth factor |
| TK | Tyrosine kinase |
| TR | Thyroid (hormone) receptor |
| TNF | Tumor necrosis factor |
| TRH | Thyrotropin-releasing hormone |
| TSH | Thyrotropin |
| VDBP | Vitamin D binding protein |
| VDR | Vitamin D receptor |
| WT/wt | Wild-type |

A = Adenine; C = Cytosine; G = Guanine; T = Thymine; U = Uridine

## I. INTRODUCTION

Endocrinology is the science of intercellular and intracellular communication. The endocrine system has expanded beyond the classical "glands of internal secretion" to encompass almost every system and cell in the body. Thus, not only do the pituitary, adrenals, gonads, thyroid, and pancreas synthesize and secrete products that affect other cells, but so do the central nervous system, kidneys, heart, intestines, bone, fat cells, thymus, and mononuclear cells. Endocrine cells synthesize chemical signals that are (1) secreted from the cell of origin into the circulation and affect the behavior/function of a distant target cell (classic endocrine hormones), (2) released into the pericellular space or displayed on the membrane surface of the synthesizing cell in order to affect the behavior/function of an adjacent cell (paracrine signal transmission), (3) released into the pericellular space to affect their own behavior/function (autocrine signal transmission), or (4) retained within the cell of origin (or assimilated into the cytoplasm of the target cell) to direct cellular behavior/function (intracrine transmission) (Figure 1.1). (Another rather unique method of intercellular communication has been described – that through tunneling nanotubes, which are ultrafine tubules that connect adjacent cells from diverse tissues to form complex networks; the membranes of these 50-200 nm in diameter tubules are continuous with the membranes of the connected cells; plasma and vesicular endosomic membrane components but not cytosolic proteins can be transported unidirectionally through the nanotubules [Rustom et al, 2004]. Thus, utilizing a network of nanotubules it might be possible for one cell to affect the function of a neighboring cell several cells distant.)

To recognize the signal, the target cell synthesizes a recognition element or receptor for the chemical messenger. The receptor may be a component of the plasma membrane of the target cell or incorporated into the membrane of a cytoplasmic organelle, or it may reside within the cytoplasm or the nucleus. The signaling molecule may be a polypeptide, a cholesterol or tyrosine derivative, an amino acid, or even a cation, whereas receptors are almost invariably proteins. In this chapter, the authors describe and illustrate the various modes of cellular communication that form the bases of endocrine action.

The endocrine system is organized in a multilayered, hierarchal manner. For example, the

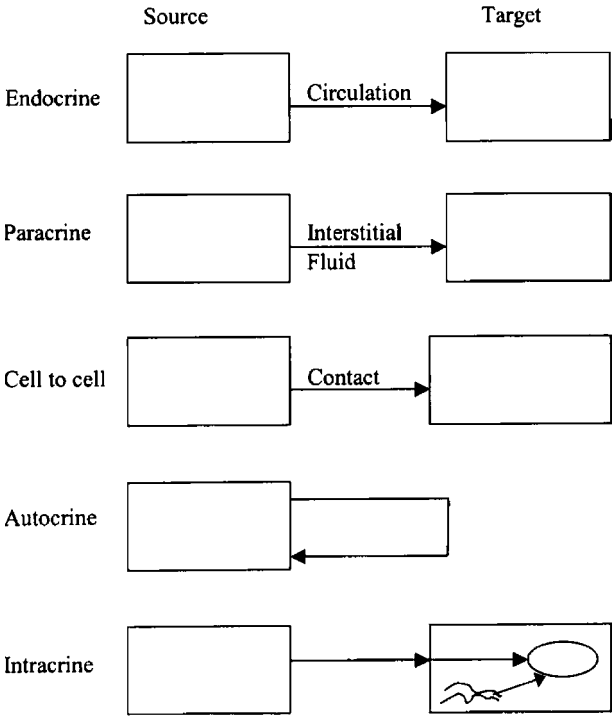


FIGURE 1.1 – Modes of inter- and intracellular communication: Endocrine, paracrine/cell-to-cell, autocrine, intracrine. Classically, endocrine glands secrete a product into the circulation to act upon a target cell either at the cell membrane or within the nucleus. Cells may also secrete product into the interstitial fluid to act upon a near or adjacent cell (paracrine transmission). Cellular product may be expressed on the cell membrane and interact with a receptor on an adjacent cell (cell-to-cell interaction). A cell may secrete a product that interacts with a receptor on the membrane of the same cell (autocrine transmission). Lastly, a protein product may enter the target cell to act. or it may be synthesized and act within the cell of origin (intracrine transmission).

hypothalamus releases a number of small peptides that regulate the synthesis and secretion of anterior pituitary (adenohypophyseal) hormones (Figure 1.2A); the adenohypophysis then secretes a variety of protein hormones that act directly at the tissue level (growth hormone, prolactin) or regulate function of a peripheral endocrine organ (thyrotropin, adrenocorticotropin, luteinizing, and follicle-stimulating hormones). In turn, the peripheral endocrine glands secrete products that act systemically to maintain homeostasis. Throughout this system there is a series of feedback loops that provide for its functional regulation. Within a specific organ, there are paracrine and autocrine regulatory mechanisms; e.g., in the anterior pituitary lobe there are cells that synthesize a number of peptides (such as activin, insulin-like growth factor-I [IGF-I], transforming growth factor-$\alpha$) that modulate the activity of adjacent mammotrophs, gonadotrophs, and corticotrophs (McArdle and Evans, 2001). Furthermore, within the adenohypophysis the folliculostellate cells form a network that coordinates pituitary function by integrating the temporal secretion of many of the hormones of the anterior pituitary lobe (Fauquier et al, 2002).

The integration of central and peripheral regulatory mechanisms that influence the endocrine system can be appreciated by examination of the growth hormone (GH)/IGF-I unit (Root and Root, 2002). GH (OMIM 139250, chromosome 17q22-q24) is released from the somatotroph episodically at the rate of 10-20 pulses per 24 hours with low trough concentrations between periods of GH release; there is enhanced secretion of GH within the first 120 minutes of the onset of sleep. The secretion of GH is more orderly in the male than the female in whom trough concentrations of GH are higher and secretory peaks of GH less well defined than in the male. These patterns of GH release are regulated by central nervous system neuropeptides, neurotransmitters, and neuromodulators, and by hypothalamic peptides and neurotransmitters with GH releasing and GH release-inhibiting properties (see Figure 1.2A). They are further modified by peripheral signals such as IGF-I, adrenal, thyroid, and gonadal hormones, and metabolic products such as glucose and fatty and amino acids. GH-releasing hormone (GHRH – OMIM 139190, chromosome 20q11.2) is the primary hypothalamic stimulus to GH secretion. Somatostatin (SRIH – OMIM 182450, chromosome 3q28) is the principal hypothalamic peptide that inhibits GH release. Dopamine, $\alpha_2$-adrenergic agonists, gamma-aminobutyric acid, and galanin are among the neurotransmitters that increase GH secretion, acting primarily upon hypothalamic neurons that secrete GHRH. The secretion of GH can be augmented by neurotransmitters that inhibit SRIH release, e.g., $\beta_1$-adrenergic agonists, muscarinic agonists, serotonin, and L-arginine. Ghrelin (OMIM 605353, chromosome 3p26-p25) is a GH secretagogue synthesized both in the hypothalamic arcuate nucleus and adenohypophysis and in the

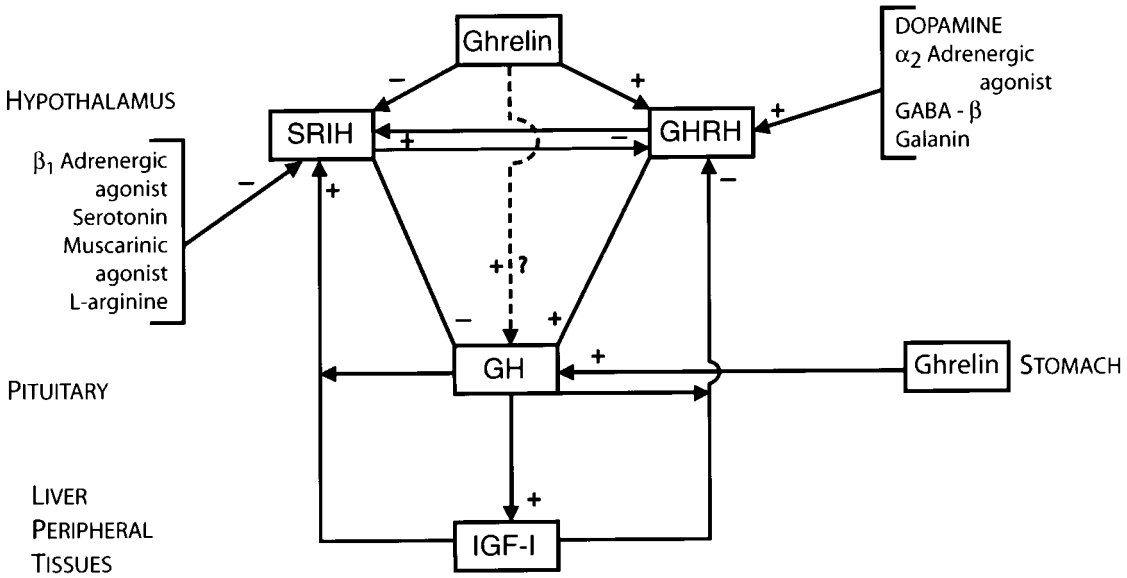


FIGURE 1.2A – Regulation of growth hormone synthesis and secretion. The secretion of growth hormone (GH) is stimulated by GH-releasing hormone (GHRH) and an endogenous GH secretagogue (GHS), most likely hypothalamic ghrelin. Its secretion is inhibited by somatostatin (SRIH). A number of neurotransmitters modulate the release of GH – acting upon hypothalamic GHRH, GHS, and SRIH, or directly upon the pituitary somatotroph. GH stimulates the peripheral synthesis of insulin-like growth factor-I (IGF-I), which exerts inhibitory effects upon GH secretion, acting in both the pituitary and hypothalamus. GH also exerts autoregulatory effects upon its own release In addition, numerous nutritional and metabolic elements also influence GH synthesis. (Reproduced with permission from Root and Root, 2002.)

intestinal tract, primarily by the P/D1 cells of the oxyntic glands of the human gastric fundus. It is a 28 amino acid peptide in which the third amino acid serine bears an n-octanoyl group (Casanueva and Dieguez, 2004). Although ghrelin stimulates GH release, its physiologic role in the regulation of GH secretion is unclear as it exerts primary effects upon energy homeostasis through its orexigenic properties (*vide infra*).

GHRH, ghrelin, and SRIH bind to distinct G protein-coupled receptors (GPCRs) (*vide infra*) in the plasma membrane of the pituitary somatotroph (Figure 1.2B). Acting through a stimulatory GPCR (GHRHR – OMIM 139191, chromosome 7p15-p14), GHRH increases activity of adenylyl cyclase and intracellular levels of cyclic adenosine monophosphate (AMP) and protein kinase A (PKA – OMIM 188830, chromosome 17q23-24). By activation of voltage sensitive calcium channels, the rate of influx of ionized calcium ($Ca^{2+}$) is augmented, thereby acutely raising its intracellular concentrations and leading to depolarization of the membrane and release of GH. Nitric oxide may also mediate some of the effects of GHRH on GH release (Anderson et al, 2004). GHRH also increases synthesis of GH by increasing transcription of GHI. After binding of ghrelin to the GH secretagogue receptor (OMIM 601898), the activity of phospholipase C (PLC) is increased, resulting in hydrolysis of membrane-associated phosphatidylinositol-4,5-biphosphate ($PIP_2$) and generation of diacylglycerol (DAG) and inositol-1,4,5-triphosphate ($IP_3$), further increasing intracellular $Ca^{2+}$ concentrations and amplifying GH release. Through its GPCR (somatostatin receptor subtype 2, OMIM 182452, chromosome 17q24), SRIH activates an inhibitory G protein that suppresses adenylyl cyclase activity, thereby lowering intracellular cyclic AMP values, and that also increases intracellular levels of potassium ($K^+$), thereby repolarizing the somatotroph membrane and halting egress of GH.

There are two major isoforms of human pituitary GH: 22-kDa GH with 191 amino acids and 20-kDa GH with 176 amino acids, the latter isoform without amino acids 32-46 of the larger GH