

ADVANCED PEDIATRIC ENDOCRINOLOGY



Volume I

Editor

Anurag Bajpai, MD, FRACP, SCE

Senior Pediatric & Adolescent Endocrinologist,
Regency Center for Diabetes, Endocrinology & Research, Kanpur

Director MedEClasses, General Secretary, GROW Society

Web- dranuragbajpai.com, Email- info.dranuragbajpai@gmail.com



Copyright, Permissions, and Medical Disclaimer

Advanced Pediatric Endocrinology, Second Edition

MedEClasses Private Limited
202, Ratan Presidency Phase II
4/271 B, Parwati Bagla Road
Kanpur 208001, India

Email: medeclasses@gmail.com
Website: learning.growsociety.in

GROW Society
(Growth & Obesity Workforce)
II Floor, Regency Hospital OPD Block
A2, Sarvodaya Nagar
Kanpur 208001, India

Copyright

© 2026 Dr Anurag Bajpai. All rights reserved. This work is published by MedEClasses Publications, Kanpur, for MedEClasses Private Limited.

No part of this publication may be reproduced, stored in a retrieval system, transmitted, or distributed in any form or by any means - electronic, mechanical, photocopying, recording, or otherwise - without prior written permission from the publisher, except as permitted by applicable law.

Responsibility for views

The views and opinions expressed in this book are those of the respective contributors. They do not necessarily reflect the views of the editor, publisher, MedEClasses Private Limited, GROW Society, or any affiliated institution.

Medical disclaimer

Medical knowledge, clinical practice, diagnostic standards, therapeutic recommendations, procedures, investigations, drug dosages, and product information continue to evolve. Although every effort has been made to present accurate, authenticated, and current information at the time of publication, readers should verify the latest recommendations, prescribing information, safety warnings, local protocols, and regulatory guidance before applying the material in patient care.

Clinical decisions and patient management remain the responsibility of the treating physician or healthcare professional, who must exercise independent judgment in light of the individual patient, institutional policy, and prevailing standards of care. The publisher, editor, authors, and contributors accept no liability for injury, loss, or damage to persons or property arising directly or indirectly from the use or application of material contained in this book.

Permissions

Every effort has been made, where necessary, to identify copyright holders and obtain permission to reproduce copyrighted material. If any permission or acknowledgment has inadvertently been omitted, the publisher will be pleased to make appropriate arrangements at the earliest opportunity.

Publication	Advanced Pediatric Endocrinology
Edition history	First Edition: 2021 Second Edition: 2026
Printed by	MedEClasses Publications, Kanpur
Course inquiries	medeclasses@gmail.com

Foreword

The second edition of *Advanced Pediatric Endocrinology*, edited and written by Dr Anurag Bajpai and colleagues once again provides an exceptional “go to” resource of the most up to date and comprehensive information in the field. Its two volume structure follows a similar layout to the very fine first edition. Five years later the multiple updating and enhancements make this text even more compelling than its predecessor.

As in the first edition, the overall principle of the work is to provide a clear but advanced understanding and insight into the field of pediatric endocrinology based on the foundations of applied physiology and related basic sciences. The previous layout of eight sections, including 59 chapters is repeated. The opening Section of six chapters covers physiology, pathology, therapeutics, diagnostics, genetics and an overview of endocrine research. This sets the stage for the subsequent seven Sections, namely Pituitary, Adrenal, Cancer, Bone and Calcium, Ovary, Testis and Metabolic disorders.

A major addition is now the inclusion of a “What’s New” section heading up each chapter, offering brief up to date learning on major new information since 2021. This sets the scene for the entire work, which has been fully revised to include the most recent knowledge in the field in each area - in all cases built on the principle of understanding applied physiology.

Other enhancements include updating of classification systems and evolving concepts in pathophysiology, newer diagnostic approaches and therapeutic guidelines, and strengthening of the clinical algorithm-based approach, with structured diagnostic and management pathways designed to support day-to-day clinical reasoning and to serve as a foundation for next-generation clinical decision-support tools in pediatric endocrinology. As before, the Case Vignettes and tables of Learning Points throughout the work provide further guidance and teaching.

The work remains detailed and comprehensive, while being eminently readable, providing current knowledge on underlying pathophysiology and on modern approaches to diagnosis and management in pediatric endocrinology. It again reflects the encyclopedic knowledge of Dr Bajpai and colleagues, as well as their wealth of experience in the care and management of children with endocrine disorders. I highly recommend this book as an essential addition to the library of pediatric endocrine trainees as well as to established pediatric endocrinologists. It not only provides a highly organized and comprehensive learning source for pediatric endocrinologists in training, but also functions as an excellent reference document, whether it be for seeking guidance for diagnostic dilemmas or for assistance with modern management of pediatric endocrine disorders.

Prof George Werther AO,
MD, FRACP, MSc (Oxon)
Melbourne, Australia
May 2026

Preface

Pediatric endocrinology has continued to evolve at a remarkable pace since the first edition of Advanced Pediatric Endocrinology found its way into the hands of trainees and practising physicians. There remains a genuine hunger for a textbook that respects physiology, stays clinically anchored, and refuses to drown the reader in detail. The first edition aspired to that balance. The second edition must deliver on it more completely.

The field itself has demanded this revision. Nomenclature has shifted in ways that are not merely cosmetic but reflect deeper biological understanding. New gene-disease associations, refined diagnostic thresholds, and transformative therapeutics have reshaped the landscape of our specialty. Every chapter has been substantially rewritten. The foundational sections on Endocrine Physiology, Pathology, Genetics, Therapeutics, and Research have been reimagined to provide the conceptual scaffolding that makes the rest of the book intelligible. Each chapter retains its familiar architecture - pathophysiology, diagnostic pointers and criteria, etiology, assessment, approach, management, case scenarios, and algorithms - designed to distill clinical reasoning into a form equally useful at the bedside and as a framework for the next generation of decision-support tools.

This edition is conceived not only as a textbook but as the contextual knowledge base for a digital paediatric endocrinology ecosystem. The validated Interpreter algorithms that already serve clinicians in everyday practice draw their reasoning from the same physiological logic articulated in these pages. MedESaarthi, our PedEndo AI companion currently in development, will weave these threads together into a clinical decision-support system grounded in this textbook and in our validated algorithms. We hope that future editions will progressively dissolve the boundary between the textbook, the bedside, and the algorithm.

This work would not have been possible without a generation of dynamic young paediatric endocrinologists whose intellectual energy fills these pages - Chetankumar, Neha, Riddhi, Sajili, Proteek, Sayan, Narayanan, Manoj, Vibha, Dhvani, Sandeep, Alapan, Nimisha, Riya, and Kirti. Dr Yuthika's clinical wisdom and editorial eye have once again shaped this work in ways both large and small. I remain deeply indebted to my mentors, Professor George Werther and Professor P S N Menon, whose teaching continues to inform every chapter and every clinical decision within it. To the wider community of GROW Society members, MedEClasses subscribers, ISPAE colleagues, and the trainees who sharpen us with their questions - thank you.

Paediatric endocrinology is, in the end, the privilege of restoring children to growth, to puberty, to metabolic health, and to the futures that biology might otherwise have denied them. If this edition helps a few more children reach those futures, it will have served its purpose.

Happy learning,

Anurag Bajpai, MD, FRACP, SCE
Kanpur, India
July 2026

Contributors

**Dr. Yuthika Bajpai, MD**

Director, Regency IVF,
Regency Healthcare
Kanpur, India

Dr. Chetan Dave, DCH

Pediatric Endocrinologist,
CPED
Rajkot, India

Dr. Neha Agarwal, MD

Pediatric Endocrinologist,
Regency Hospital
Lucknow, India

Dr. Riddhi Patel, MD

Pediatric Endocrinologist,
Cure Hormone, CPAED
Vadodara, India

Dr. Sajili Mehta, MD

Pediatric Endocrinologist,
DMH and KEM Hospital
Pune, India

Dr. Proteek Sen, DNB

Senior Clinical Fellow,
Paediatric Endocrinology and Diabetes
Birmingham Children's Hospital
Birmingham, UK

Dr. Sayan Banerjee, MD

Pediatric Endocrinologist,
Bhagirathi Neotia Women and Child Care
Kolkata, India

Dr. R Narayanan, MD

Senior Resident,
Pediatric Endocrinology, AIIMS
New Delhi, India

Dr. Manoj Agarwal, DCH

Pediatric Endocrinologist,
Shalby Hospital and ATOP
Ahmedabad, India

Dr. Vibha Yadav, MD

Pediatric Endocrinologist,
Regency CDER
Kanpur, India

Dr. Dhvani Raithatha, MD

Pediatric Endocrinologist,
Amrit Hospital
Chapra, India

Dr. Alapan Mahapatra, MD

Pediatric Endocrine Fellow,
Regency CDER
Kanpur, India

Dr. Sandeep Paimode, DNB

Pediatric Endocrinologist,
DVPP'S Medical College
Ahilyanagar, India

Dr. Nimisha Sachan, MD

Pediatric Endocrine Fellow,
Regency CDER
Kanpur, India

Dr. Riya Shah, MD

Pediatric Endocrine Fellow,
Regency CDER
Kanpur, India

Dr. Kirti Pai, MD

Pediatric Endocrine Fellow,
Regency CDER
Kanpur, India

Contents

No.	Chapter	Page
SECTION I Fundamentals of Pediatric Endocrinology		
1	Endocrine Physiology	11
2	Endocrine Pathology	28
3	Endocrine Genetics	43
4	Endocrine Diagnostics	67
5	Endocrine Therapeutics	81
6	Endocrine Research	89
SECTION II Pituitary Disorders		
7	Pituitary Physiology	109
8	Pituitary Assessment	125
9	Multiple Pituitary Hormone Deficiency	135
10	IGF-1 Deficiency	146
11	Impaired AVP Effect	156
12	Syndrome of Inappropriate AVP Secretion	169
13	Hyperprolactinemia	177
14	Sellar Mass	186
15	Tall Stature	197
SECTION III Adrenal Disorders		
16	Adrenal Physiology	209
17	Adrenal Assessment	225
18	Adrenal Insufficiency	235
19	Cushing Syndrome	253
20	Impaired Aldosterone Effect	268
21	Increased Aldosterone Effect	276
22	Steroidogenic Defect	286
23	Adrenal Incidentaloma	302
24	Glucocorticoid Therapy	309
25	Immune Endocrinopathy	318
SECTION IV Endocrinology and Cancer		
26	Endocrine Neoplasia	333
27	Thyroid Carcinoma	346
28	Pheochromocytoma/PPGL	358
29	Late Effects of Cancer Therapy	370

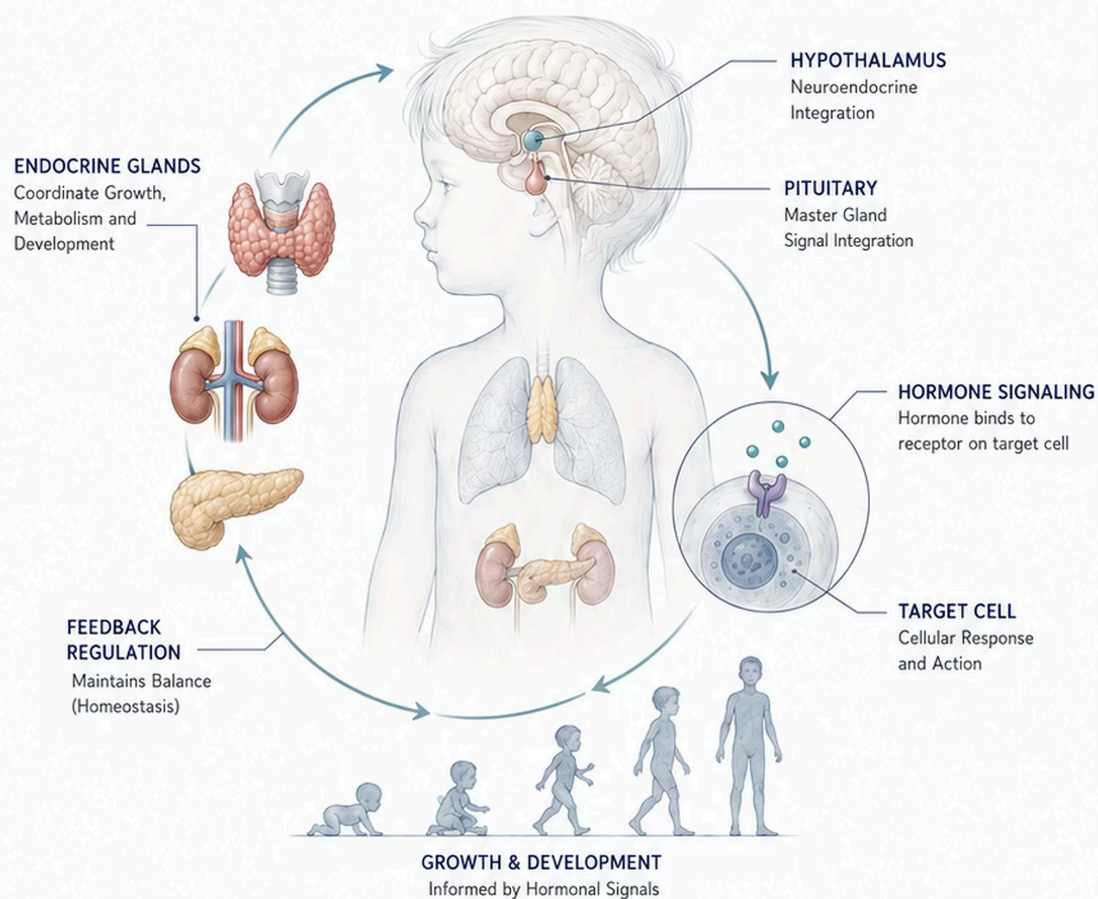
Contents

No.	Chapter	Page
SECTION V Bone and Calcium Disorders		
30	Bone Physiology	10
31	Bone Assessment	33
32	Low Bone Mass	42
33	High Bone Mass	57
34	Impaired PTH Effect	65
35	Increased PTH Effect	79
36	Hypophosphatemic Rickets	91
37	Impaired Vitamin D Effect	105
38	Hypomagnesemia	112
SECTION VI Ovarian Disorders		
39	Ovarian Physiology	124
40	Ovarian Assessment	140
41	Hyperandrogenism	149
42	Oligomenorrhea	164
43	Turner Syndrome	176
44	GnRH Deficiency	193
45	Impaired Estrogen Effect	204
46	Pediatric and Adolescent Gynecology	215
SECTION VII Testicular Disorders		
47	Testicular Physiology	234
48	Testicular Assessment	250
49	Impaired GnRH Effect	259
50	Impaired Androgen Effect	275
51	Klinefelter Syndrome	289
52	Gender Dysphoria	297
SECTION VIII Metabolic Disorders		
53	Increased Insulin Effect	308
54	Neonatal Diabetes	325
55	Monogenic Diabetes	338
56	Type 2 Diabetes	350
57	Genetic Obesity	364
58	Obesity Therapeutics	379
59	Lipid Disorders	391
60	Endocrine effects of chronic disease	412

SECTION I

FUNDAMENTALS

Advanced Pediatric Endocrinology • Second Edition



SECTION EDITORS

Anurag Bajpai

Vibha Yadav

CHAPTERS

- 1 Endocrine Physiology
- 2 Endocrine Pathology
- 3 Endocrine Genetics
- 4 Endocrine Diagnostics
- 5 Endocrine Therapeutics
- 6 Endocrine Research



learning.growsociety.in

Endocrine Physiology



Anurag Bajpai, Vibha Yadav, Proteek Sen



WHAT'S NEW

Biased GPCR agonism	Selective signaling for G proteins vs. β -arrestin at GPCRs is now a therapeutic design principle.
Tissue-selective NR modulation	Resmetirom, a liver-selective thyroid hormone receptor- β (TR β) agonist approved for MASH.
Placental endocrine signaling	Extracellular vesicles carrying microRNAs recognized as a mode of feto-maternal communication, programming endocrine axes.
Expanded endocrine organs	Skeletal muscle (myokines), liver (FGF21), bone (FGF23/osteocalcin), and gut microbiome (SCFA/FXR/TGR5) are new endocrine organs.
Minipuberty	Recognized as a diagnostic window for CHH, with an emerging fertility-preservation role for recombinant FSH/LH in neonatal HH.

Pediatric endocrinology translates a small set of core physiological principles into the clinical framework used to evaluate and manage disorders of growth, puberty, calcium homeostasis, fluid balance, glucose metabolism, and stress adaptation. Over the past five years, the field has been reshaped by three major developments: advances in high-resolution receptor pharmacology enabling the development of biased agonists and tissue-selective modulators; a broader understanding of endocrine signaling, extending the concept of endocrine organs to include muscle, liver, bone, and the gut microbiome; and renewed recognition of the perinatal hypothalamic–pituitary–gonadal axis activation, as both a diagnostic window and a potential therapeutic opportunity. This chapter provides the conceptual framework for the rest of the book.

FUNDAMENTALS

The endocrine system regulates calcium homeostasis, bone strength, volume and salt status, glucose homeostasis, growth, puberty, thermogenesis, and links nutrition with metabolism, growth, and puberty.

THE MESSENGERS OF THE BODY

Hormones and neurotransmitters are the key messengers of the body that allow communication between systems. Neurotransmitters secreted by neurons act on their receptors situated just across the synaptic cleft. On the other hand, hormones are secreted via specialized glands into the bloodstream and act distant from their origin. The difference between a neurotransmitter and a hormone is not absolute. Vasopressin and oxytocin produced by the posterior pituitary neurons resemble neurotransmitters in structure but act as hormones. A third category—neurohormones such as GnRH, TRH, CRH, GHRH, somatostatin, and dopamine—is secreted by neurons but

acts through the portal circulation, representing a hybrid of neural and endocrine signaling.

WHAT REPRESENTS AN ENDOCRINE SYSTEM?

The conventional concept of distinct endocrine glands producing hormones has been questioned. Many body systems produce substances that act distantly. Thus, adipocytes produce adiponectin and leptin that influence pubertal development, bone mineralization, and growth. Similarly, the duodenum produces incretins in response to carbohydrate intake to induce satiety, release insulin, inhibit glucagon, and delay gastric emptying. The C-type natriuretic peptide, FGF23, and osteocalcin produced by the bones also have systemic effects. Thus, intestine (GLP-1), kidney (renin), bone (CNP, FGF23, osteocalcin), heart (natriuretic peptide), stomach (ghrelin), and adipocytes (adipokines) may be considered an endocrine system. Recent additions to this expanded view include skeletal muscle (myokines such as irisin, myostatin, and interleukin-6), hepatic FGF21 (regulating energy expenditure and lipid metabolism), and the gut microbiome-derived metabolites such as short-chain fatty acids and bile acid derivatives that signal through FXR and TGR5 receptors to modulate glucose homeostasis and adiposity.

WHAT IS A HORMONE?

Hormones are molecules secreted in one part of the body that reach their target sites through the circulation to perform their action. Minuscule amounts of hormones have a significant impact, as illustrated by the fact that the entire amount of hormones in the body can fit in a teaspoon. The term hormone needs to be expanded in view of the discovery of novel substances with distant effects. Thus, ghrelin produced by the stomach in response to reduced distension increases GH release from the somatotrophs

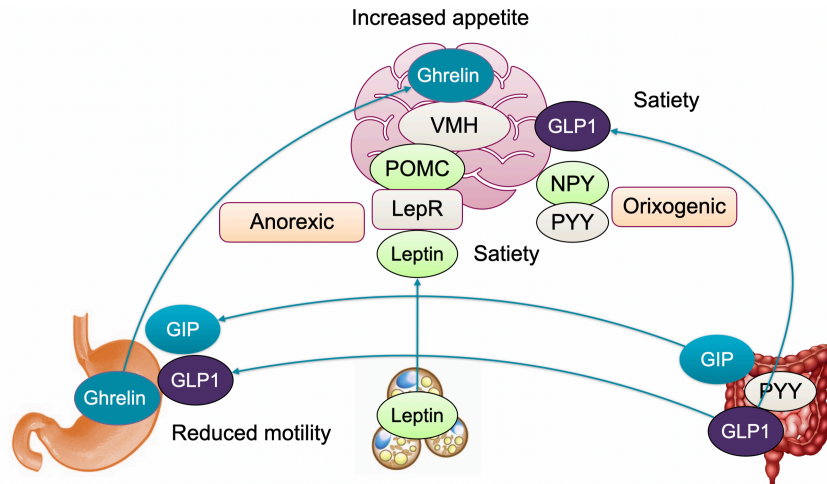


Figure 1.1- The entero-metabolic axis

(Figure 1.1). PYY produced by the intestine acts on neuropeptide Y, inhibiting the orexigenic pathway and promoting satiety. Adipocytes produce leptin, which acts on leptin receptors in the hypothalamic arcuate POMC neurons to modulate satiety. Metabolites such as calcium and bile acids also behave hormonally (signalling via CaSR and TGR5, respectively). This chapter focuses on the classical hormone classes.

Hormone characteristics

Hormone effects represent their direct action, interaction with other signaling pathways, and the influence of the environment. They are characterized by multiple effects of one hormone (pleiotropy), multiple hormones controlling a single effect (redundancy), a multitude of effects (autocrine-paracrine-endocrine), and synergistic action.

Pleiotropy

A hormone can affect multiple systems due to different receptors and signaling pathways. Thyroxine regulates neural function, bone strength, cardiac function, puberty, thermogenesis, growth, and intestinal motility. The recognition of tissue-selective thyroid hormone receptor β (TR β) agonism underlies the 2024 FDA approval of resmetirom for MASH, which exploits hepatic TR β activation to reduce steatosis without cardiac TR α -mediated toxicity—a clinical illustration of hormone pleiotropy being leveraged therapeutically.

Redundancy

Redundancy is an important mechanism that preserves vital metabolic functions. This involves the use of multiple hormones to regulate a critical function. Thus, the prevention of hypoglycemia is the primary goal of glucose homeostasis. This is achieved by four hormones increasing glucose (growth hormone, cortisol, epinephrine, and glucagon) countering the only glucose-lowering substance (insulin). Thus, the deficiency of one hyperglycemic hormone does not cause hypoglycemia. This redundancy is also present for other important parameters (PTH and calcitriol to increase calcium, vasopressin, and renin-angiotensin-aldosterone system to maintain volume and osmolality).

The convergence of signaling pathways

The hormone signaling pathways may converge, allowing the use of a single receptor by different hormones to regulate distinct biological processes. The PTH-related peptide also acts on the PTH receptor (Type 1 PTH R, Figure 1.2). Despite the same receptor, the effects are distinct in terms of the site of action (endocrine for PTH; paracrine for PTHrP), target (calcium levels for PTH; chondrocyte growth for PTHrP), and deficiency (hypoparathyroidism for PTH; severe skeletal dysplasia for PTHrP). Similar convergence underlies the insulin/IGF-1 receptor family, where insulin binds IGF-1 receptor at around 1% potency—clinically relevant in infants of

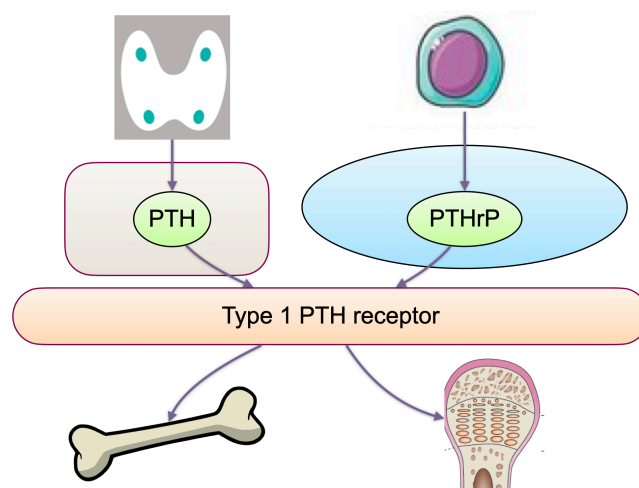


Figure 1.2- Convergence of PTH and PTHrP effects

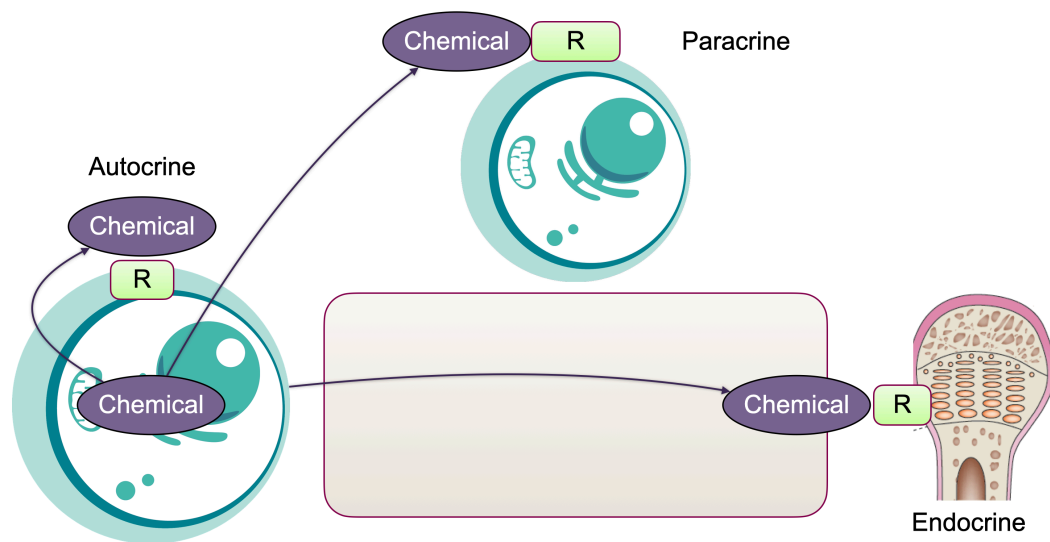


Figure 1.3- Different sites of hormone action

diabetic mothers, where fetal hyperinsulinemia drives IGF-1 receptor-mediated macrosomia. TSH and hCG both act on the TSH receptor while LH and hCG both act on the LH/CGR (LHCGR).

Multiple sites of signaling

Besides acting at sites distant from their origin (endocrine effect), hormones can act locally (paracrine) and on the cell that produces them (autocrine, Figure 1.3). These actions determine their effect.

Autocrine- Autocrine signaling provides rapid feedback for hormonal control.

Paracrine- Paracrine effect reflects the local impact of hormones. The hormone is restricted to the local site by a binding protein. Peptide hormones acting through the paracrine pathway (IGF-1) require binding proteins in contradistinction to those with a predominant systemic effect (insulin). The paracrine effect is crucial in regions with limited blood supply (ovarian follicle, testicular germ cells) and involves high hormone concentration with specific action.

Endocrine- Hormones have to be produced in much higher quantity (around 1000 times more) than paracrine factors as they traverse a long path before reaching the sites of action. Levels are also higher for systemically acting hormones

than those acting in the hypothalamic-pituitary region. Thus, the amount of ACTH produced by the corticotrophs is 1000 times that of the corticotropin-releasing factor (CRH) produced by the hypothalamus. The amount of cortisol produced by the adrenals is in turn 1000 times that of ACTH due to the need for systemic effect. All the tissues are exposed to the same hormone concentration; the tissue selectivity of a hormone depends on its delivery by the binding protein and the number of hormone receptors. For example, all body tissues have equal exposure to growth hormone. The tissue selectivity of GH action depends upon the release of GH in the tissue by the growth hormone-binding protein, the expression of GH receptor, and the IGF-1 gene and receptor.

OVERLAP OF HORMONE EFFECT

The autocrine, paracrine, and endocrine effects of a hormone are not mutually exclusive. Their interaction produces the overall hormone effect. GH secreted by the somatotrophs acts on the liver to produce insulin-like growth factor-1 (IGF-1) that acts on the IGF1 receptor in the growth plate to enhance chondrocyte growth. This represents the endocrine effect of GH. However, GH receptors in the chondrocyte also produce IGF-1 complementing the systemic effect.

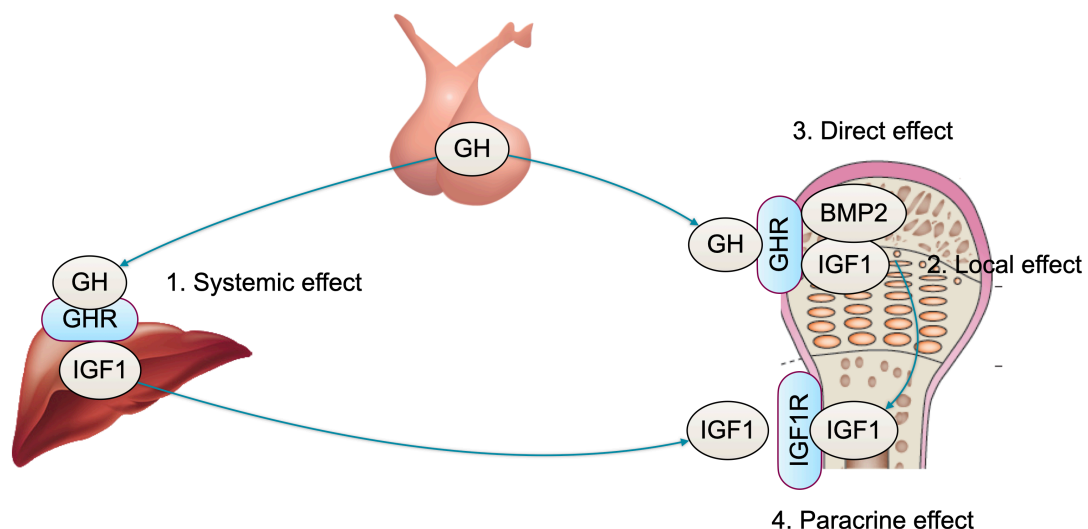


Figure 1.4- The mediators of GH effect

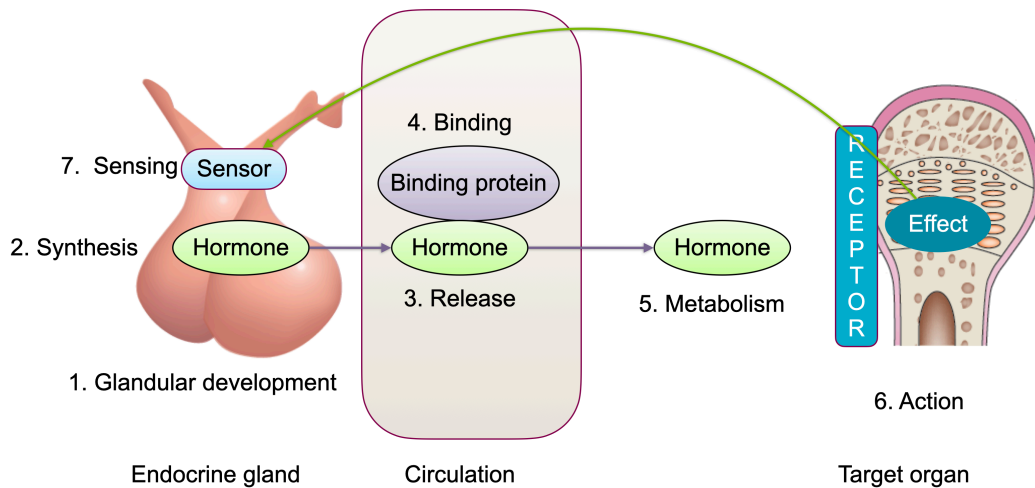


Figure 1.5- The determinants of hormone effect

This, along with the direct GH effect on the chondrocytes, forms the triad of the growth-promoting effect of GH. GH treatment thus increases growth by enhancing systemic and local IGF-1 along with direct effects. IGF-1 treatment, on the other hand, only increases systemic levels with no local production or direct GH effect. Thus, the response to GH in GHD is superior to that of IGF-1 in GH insensitivity. Estradiol, testosterone, calcitriol, and IGF-1 also have significant paracrine effects (Figure 1.4).

DETERMINANTS OF HORMONE EFFECT

The hormone effect requires gland development, hormone synthesis, release, transport to the target site, local metabolism, action, and sensing effect (Figure 1.5).

GLAND DEVELOPMENT

Most endocrine organs (pancreas, adrenal, pituitary, thyroid, and gonads) have a dual origin with distinct regulation, role, and blood supply. Thus, the adrenal cortex synthesizes steroids (glucocorticoids, mineralocorticoids, and androgens) while the medulla produces catecholamines. The two parts of the pituitary developed from the neuroectoderm (neurohypophysis) and pharynx (Rathke's pouch, giving rise to the adenohypophysis) act as different glands. The vasopressin and oxytocin secreting supraoptic and paraventricular neurons of the hypothalamus terminate in the neurohypophysis. On the other hand, the adenohypophysis is regulated by the

hormones transported from the median eminence by the hypothalamic-hypophyseal portal system.

Neural origin and distinct blood supply of the posterior pituitary explain preserved vasopressin function in apoplexy and radiotherapy. Distinct formation and regulation also explain the rarity of simultaneous involvement of the two parts of pituitary (in hypothalamic and stalk lesions). Arginine vasopressin deficiency with pituitary deficiency suggests hypothalamic or stalk involvement. The differential origin of thyroid cells (follicular and parafollicular C cells) explains the different characteristics (more vascular metastasis with medullary), biochemical markers (thyroglobulin for follicular and calcitonin for medullary), and predisposing conditions (radiation for follicular and genetic for medullary) of thyroid carcinoma.

HORMONE STRUCTURE

Hormone structure is the primary determinant of its action and properties. Hormones may be peptides, steroids, or amine derivatives (Figure 1.6). Large peptides are stored in the cell and regulated at the level of release (Table 1.1). They control growth (GH), osmolality (vasopressin), calcium (PTH), glucose (insulin), puberty (gonadotropins), and stress response (ACTH). Small size allows the rapid synthesis of amino acid derivatives to regulate immediate response (thyroxine, epinephrine). Slow production and

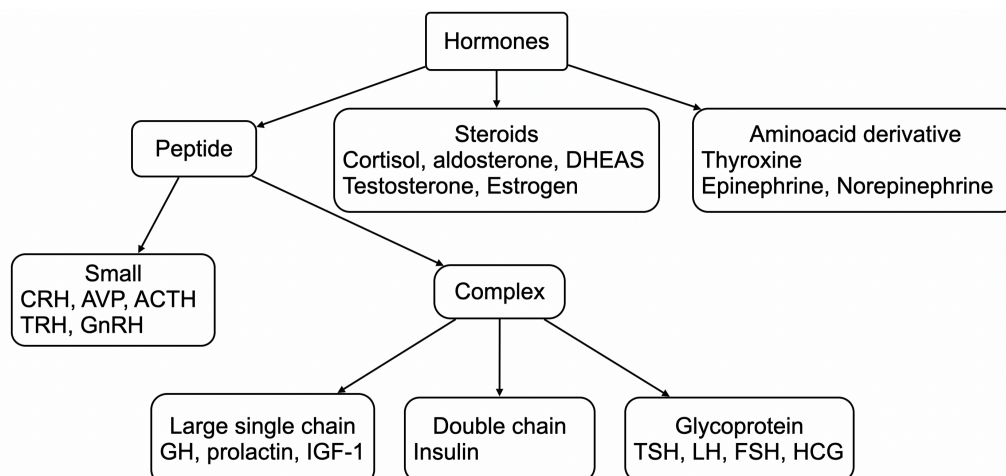


Figure 1.6- Structure-based classification of peptide hormones

Table 1.1- Comparison of different hormone classes

Feature	Peptide	Steroid	Amine	Thyroxine
Size	Usually large	Medium	Small	Small
Protein binding	Low (except GH, IGF-1)	High	Low	High
Receptor	Membrane	Intracellular (rarely membrane)	Membrane	Intracellular
Metabolism	Rapid	Slow	Very rapid	Very rapid
Half life	Short	Long	Very short	Long
Effect	Medium	Slow (genomic), fast (membrane)	Rapid	Rapid

Rapid non-genomic effects via membrane receptors also occur for steroids (GPER1/mPR, mGR) and thyroxine (integrin)

action of steroids make them ideal for regulating puberty (testosterone, estrogen) and metabolic pathways (cortisol).

Peptide hormones

Peptide hormones are large, water-soluble, and circulate in the blood without a binding protein (except GH and IGF-1). The absence of binding proteins makes them susceptible to enzymatic degradation causing a short half-life. Their hydrophilic nature prevents entry into the cell, mandating the need for an extracellular receptor (Figure 1.7). Peptide hormones can be small (hypothalamic peptides: GHRH, TRH, vasopressin, CRH, and GnRH), single large chain (GH and prolactin), multiple chains (insulin and IGF-1), or glycosylated (LH, FSH, TSH, hCG). Glycosylation increases the half-life and duration of action of peptides. Similar structures of peptide hormones allow one hormone to act at other receptors. This is relevant for glycosylated hormones. TSH action on the FSH receptors in severe primary hypothyroidism causes peripheral precocious puberty in girls and macroorchidism in boys (*Van Wyk-Grumbach syndrome*). Placental hCG acts on the TSH receptor causing gestational thyrotoxicosis. hCG-producing tumors in boys cause peripheral precocious puberty in boys. The therapeutic use of peptide-hormone structural mimicry has accelerated with GLP-1 receptor agonists (liraglutide, semaglutide) and the dual GIP/GLP-1 agonist tirzepatide approved for adolescent obesity and type 2 diabetes, while the C-type natriuretic peptide analog vosoritide has become the first precision therapy for achondroplasia by counteracting overactive FGFR3 signaling at the chondrocyte.

Steroid

Steroids derive from a 27-carbon cholesterol backbone. Side-chain cleavage and downstream metabolism yield C21 progestogens and glucocorticoids (pregnane), C19 androgens (androstane, after 17,20-lyase removes the side chain), and C18 estrogens (estrane, after aromatase loses C19 during A-ring aromatization). The steroids are lipophilic and cross the cell membranes freely (Figure 1.8). They cannot be stored in the cells and are produced when needed. The genomic effect of their intracellular receptors explains a lag phase in their response. The binding proteins transfer them to the target sites. Besides transporting the hormones, the binding proteins stabilize their levels, act as reservoirs, and prevent hormone degradation by circulating enzymes. This explains the longer half-life of steroids than peptides. Steroids also signal through membrane-bound receptors (GPER1 for estrogen, membrane progesterone receptors, and recently identified membrane glucocorticoid receptors) that mediate non-genomic effects such as rapid vasodilation and calcium fluxes. These occur within seconds to minutes and are distinct from the slower transcriptional effects.

Amino derivatives

Amino derivatives are produced and degraded rapidly. They can act on both the extracellular (epinephrine) and intracellular receptors (thyroxine). Thyroxine is different from epinephrine as it requires a binding protein and a cellular transporter (MCT8). MCT8 deficiency (Allan-Herndon-Dudley syndrome) causes neurodevelopmental impairment despite preserved hepatic and cardiac T3 action; the T3 analog Triac (tiratricol) crosses cell

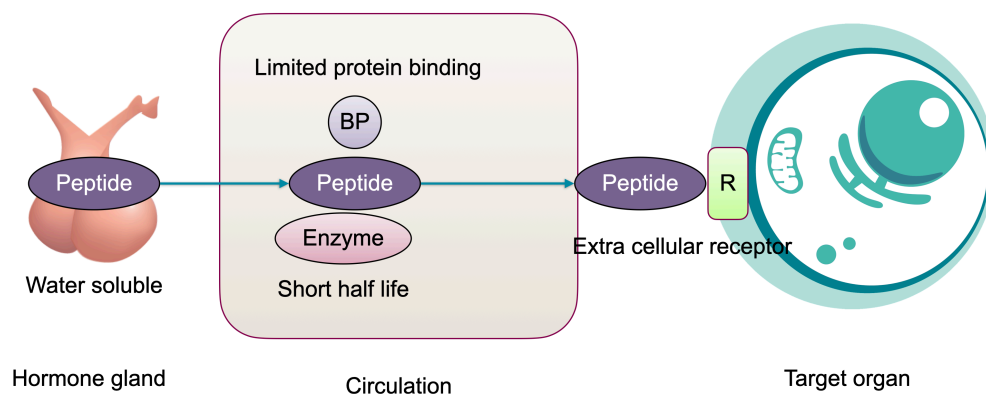


Figure 1.7- Overview of peptide hormones

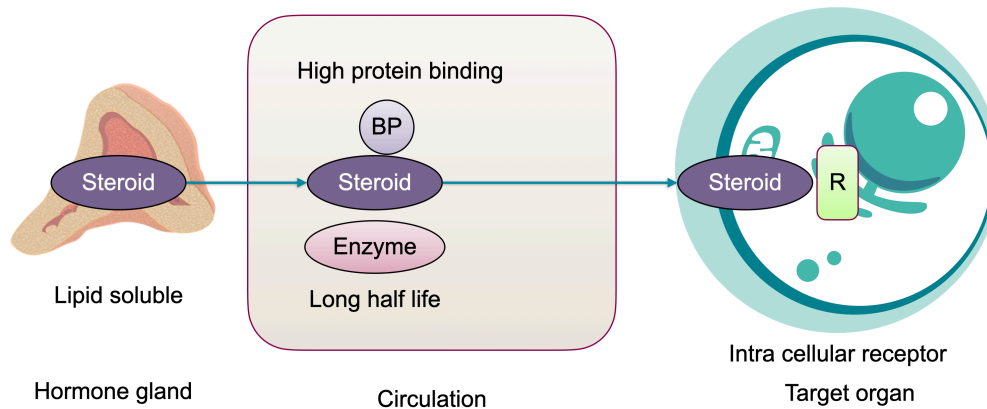


Figure 1.8- Features of steroid hormones Steroids also signal via membrane GPER1/mPR, mGR.

membranes independently of MCT8 and has shown benefit, representing a targeted therapeutic use of structural hormone mimicry.

HORMONE SYNTHESIS

Hormone synthesis depends on their response pattern (rapid for calcium, glucose, fluid, and osmolality; slow for growth, puberty, bone formation). Hormones regulating rapid responses (PTH, insulin, aldosterone, vasopressin, and epinephrine) are pre-synthesized and stored in vesicles. The stimuli trigger their release, the primary site of regulation. Hormones controlling slow responses are regulated at the level of synthesis (gonadotropins, steroids). Peptide hormones are usually synthesized as precursor molecules that are spliced into functional molecules. Defective post-translational processing- for example by proprotein convertase 1/3 (PCSK1)- can cause multiple hormone deficiency (central hypothyroidism, hypocortisolism, diabetes insipidus, hyperphagic obesity, and growth-hormone deficiency, with hypopigmentation due to defective POMC cleavage). Misfolded INS, AVP, and GH precursors cause glandular damage through ER stress. The storage of a hormone depends on its requirements. Thus, the thyroid gland stores thyroxine sufficient for two months to avoid deficiency in adverse circumstances. This explains transient thyrotoxicosis with thyroid damage and a lag phase in response to antithyroid drugs. The tone of hormone regulation determines disease effects. Hypothalamic peptides stimulate the synthesis of pituitary hormones (GH, TSH, ACTH, and gonadotropins) except prolactin that is inhibited by dopamine. Prolactin

levels are therefore high in hypothalamic/infundibular defects with MPHD and low in pituitary defects.

HORMONE RELEASE

The release pattern of the hormone depends on its size, time course, and effects. Variations in the pattern include pulsatility (GH, prolactin, LH, FSH), diurnal rhythms (cortisol, testosterone, thyroxine), menstrual (LH, FSH, 17OHP, and estrogen), and seasonal changes (estradiol, testosterone, vitamin D, and prolactin). These affect hormone assessment. Thus, while pooled samples are required for pulsatile hormones (LH, FSH, cortisol, prolactin, testosterone), timed samples are needed for hormones with diurnal variation (morning sample for cortisol, testosterone, and prolactin). Regulation of hormone release is a major regulator of hormone action.

This may be related to end effects (glucose and calcium-sensing for insulin and PTH), regulator hormone (ACTH for cortisol, GHRH for GH, and TRH for TSH), and environmental cues. The regulation of insulin release represents a combination of nutritional (ATP levels), endocrine (somatostatin, incretin, GH, and cortisol), and neural (sympathetic) effects (Figure 1.9). PTH and vasopressin are the other hormones regulated at the level of release. KNDy (kisspeptin-neurokinin B-dynorphin) neurons in the arcuate nucleus act as the GnRH pulse generator. Neurokinin B (via NK3R) synchronously activates the KNDy network; kisspeptin is released onto GnRH neurons to trigger each pulse; and dynorphin (via κ -opioid receptors) terminates the pulse. This has enabled the development of NK3R antagonists like elinzanetant and

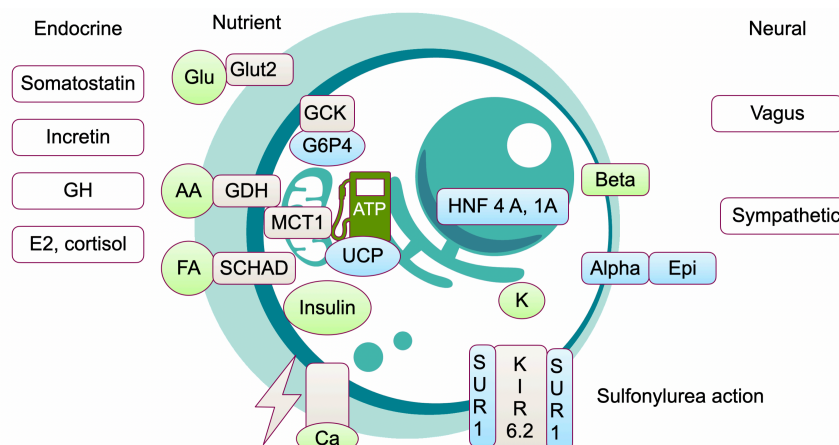


Figure 1.9- Regulation of insulin release

fezolinetant that are approved for menopausal vasomotor symptoms and provides a rational platform for future therapy of central precocious puberty and polycystic ovary syndrome.

HORMONE TRANSPORT

The mode of hormone transport is structure dependent. The hydrophilic peptide and amino hormones freely traverse the circulation and do not need a binding protein. IGF-1 is an exception and has binding proteins involved in paracrine (IGFBP-1 and -5) and systemic effects (IGFBP-3). Steroids need a transport protein due to their hydrophobic nature. The binding protein limits the biological effect of a hormone as only the free fraction interacts with the receptor. This has implications in hormone assessment as conditions affecting binding protein levels make total hormone levels unreliable. The increased binding protein level in pregnancy falsely elevates total cortisol and thyroxine levels. This highlights the need for careful interpretation of hormone levels in the setting. Reduced binding protein levels increase hormone effect (increased free IGF-1 levels with hyperinsulinism-induced decrease in IGFBP-1 and increased free testosterone levels with low sex hormone-binding globulin in PCOS). An increase in binding protein levels may be used to treat hormone excess states (increased SHBG level with estrogen reduces free testosterone levels in PCOS). Besides transport, the binding protein acts as a chaperone taking the hormone to its target area (GH and IGF1 binding protein). Binding proteins also stabilize the hormone levels increasing their duration of action. Low IGFBP-3 levels in impaired GH effect reduce IGF-1 half-life. GH treatment increases both IGF-1 and IGFBP-3 levels, enhancing the hormone effect. The IGFBP-3 levels, however, do not increase with IGF-1 therapy, causing rapid rise and fall of IGF-1. This explains the greater predilection of toxicity and the lower effect of IGF-1 than GH therapy. Increased binding protein levels with pregnancy and estrogen use increase thyroxine and hydrocortisone requirements by increasing the amount of hormone bound to them.

HORMONE METABOLISM

Local hormone metabolism is an important regulator of the action of steroid hormones and thyroxine. This involves activation (testosterone to DHT or estradiol, 25-hydroxyvitamin D to calcitriol, T4 to T3, and cortisone to cortisol) or inactivation (T4 to reverse T3, cortisol to cortisone, and 25-hydroxyvitamin D to 24,25-

dihydroxyvitamin D). Testosterone is converted by 5 α -reductase type 2 in androgen-responsive tissue (genital skin, androgen-dependent follicles) to the potent DHT. Defects in the enzyme cause a spectrum of impaired androgen effects ranging from 46, XY differences/disorders of sex development to gynecomastia and infertility. Androgens are converted to estrogens in estrogen-responsive tissue (bone, growth plate, and pituitary). The alteration in hormone metabolism provides an opportunity to respond to the environment. Increased deiodinase 3 activity in the fetal period and during illness increases T4 inactivation preventing deleterious effects of thyroid activity. The local metabolism of hormones forms the basis of tissue-specific effects. The interchange between the active cortisol and inactive cortisone is a key determinant of the tissue-specific cortisol effect. Cortisol has the same affinity for the mineralocorticoid receptor as aldosterone and can cause increased mineralocorticoid effect due to its substantially higher levels than aldosterone. The mineralocorticoid effect of cortisol is prevented by the 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) enzyme that inactivates it to cortisone in mineralocorticoid tissues (kidney and sweat gland). The 11 β -HSD1 enzyme, on the other hand, enhances the cortisol effect in the glucocorticoid responsive tissues by activating cortisone to cortisol. Defects in 11 β -HSD1 (apparent cortisol deficiency) and 11 β -HSD2 (apparent mineralocorticoid excess) cause cortisol deficiency and mineralocorticoid excess, respectively.

HORMONE ACTION

Hormone action is a critical aspect of endocrine physiology and the target for endocrine pathology and therapeutics. Hormone receptors convert chemical signals into cellular changes. The cell membrane, the major site of the action of hormones, is a lipid-rich structure that restricts the entry of hydrophilic peptide hormones (Figure 1.10). Peptide hormones, therefore, need to have membrane receptors. Steroids cross the membrane to bind intracellular receptors that act as transcription factors. Thyroxine is transported by MCT8 to interact with the intracellular receptors. Hormone receptors can be located in the membrane or inside the cell (Figure 1.11).

Membrane receptors

Membrane receptors mediate the effects of peptides. They have a rapid onset of action, allowing acute regulation. Membrane receptors activate secondary signals through the

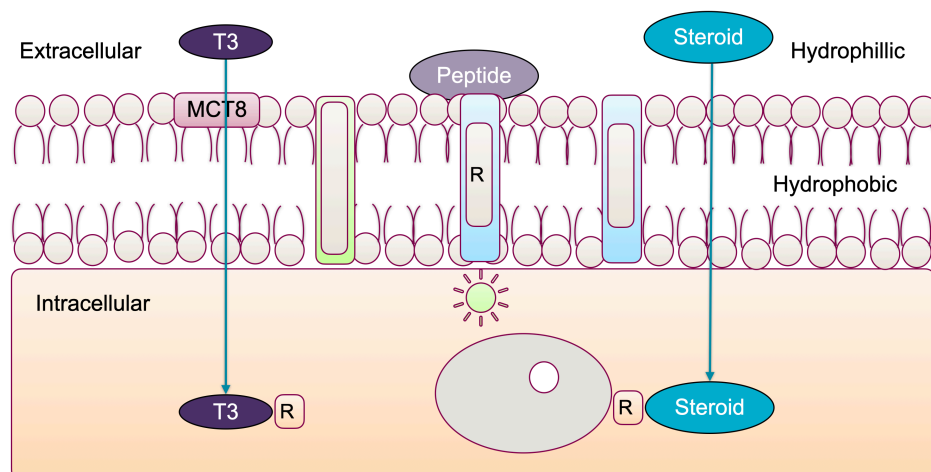


Figure 1.10- Cell membrane and hormone receptors

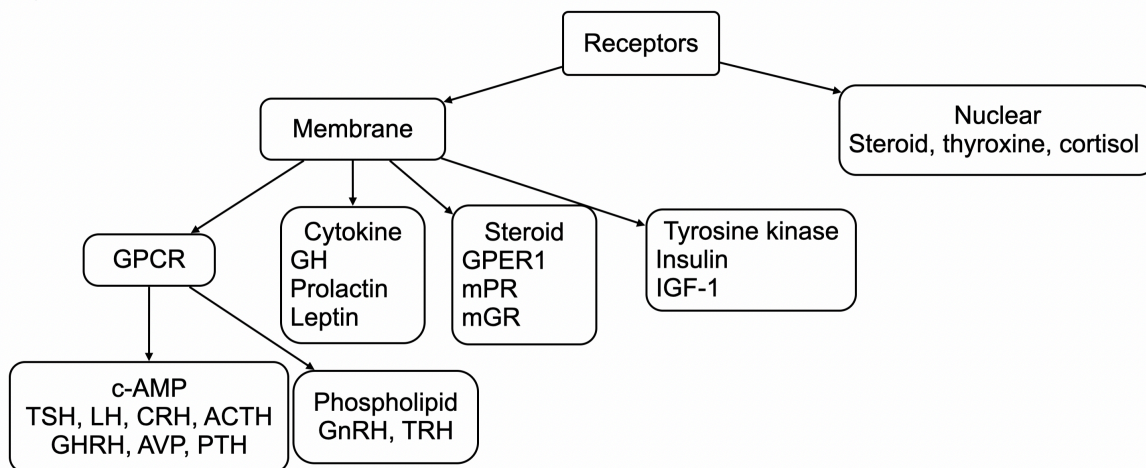


Figure 1.11- Types of hormone receptors

G protein (TSH, LH, FSH, GHRH, PTH, vasopressin), phospholipid (GnRH, TRH), cytokine (GH, prolactin, leptin), or tyrosine kinase pathway (insulin, IGF-1, Figure 1.11).

Membrane receptors of steroid hormones (cortisol, calcitriol, and estrogen) allow their rapid effects. Notable examples include GPER1 (G protein-coupled estrogen receptor 1), which mediates rapid vasodilation; membrane glucocorticoid receptors involved in negative feedback of HPA axis; and the vitamin D receptor-associated membrane-initiated signaling that regulates calcium flux in intestinal enterocytes.

G protein-coupled receptor

G protein-coupled receptors (GPCR) are the most commonly used pathway by hormones, sensory stimuli (odor, light), and therapeutic agents (40% of all drugs).

Structure- G protein-coupled receptors have a ligand-binding extracellular N terminal domain, seven transmembrane α -helices connected with serpentine links, and an intracellular C terminal linked to a G protein. The transmembrane domain is conserved across receptors, while that of the ecto and endo domains is variable. The G protein has a trimeric structure with α , β , and γ subunits.

Action- Guanosine diphosphate (GDP) present in the native state of the α subunit prevents receptor signaling. Hormone binding to the N-terminus prompts the receptor to act as a guanine-nucleotide exchange factor, replacing GDP on the α subunit with GTP. The activated α -GTP dissociates from the $\beta\gamma$ dimer and mediates downstream signaling

(Figure 1.12). The intrinsic GTPase activity in the G protein reconverts GTP to GDP, allowing recombination of the β and γ units terminating its action. The balance between the inactive and the active state determines the signaling of the G protein-coupled receptor. The α subunit of G protein has many forms. The most common G_{α} unit stimulates adenylate cyclase producing cAMP and is utilized by most peptide hormones (PTH, LH, FSH, GHRH, TSH, vasopressin). The *GNAS1* gene regulates the G_{α} effect. Increased (McCune-Albright syndrome) or decreased *GNAS1* effect (PHP) causes pubertal, calcium, thyroid, and skeletal disorders. The inhibitory $G_{\alpha i}$ unit decreases cAMP levels. The $G_{q/11}$ acts through the phospholipase C pathway producing IP₃ and diacylglycerol. GPCR production of CREB (cyclic AMP response element-binding protein), a transcription factor, forms the basis for genomic effects of membrane receptors.

Transfer- The GPCRs are synthesized in the endoplasmic reticulum by ribosomes and transported to the cell membrane by chaperone proteins. Defects in transfer proteins cause hormone resistance despite normal receptor production. MC2R, the receptor for ACTH, is transferred to the cell membrane by the melanocortin 2 receptor accessory protein (MRAP). MRAP defects cause ACTH resistance (Familial glucocorticoid deficiency type 2).

Desensitization- Chronic ligand exposure reduces receptor effect through the G protein-coupled receptor kinase (phosphorylation of receptor), β -arrestin (dissociation of the receptor with G protein), ligand effect, and internalization of the receptor. The desensitization may be

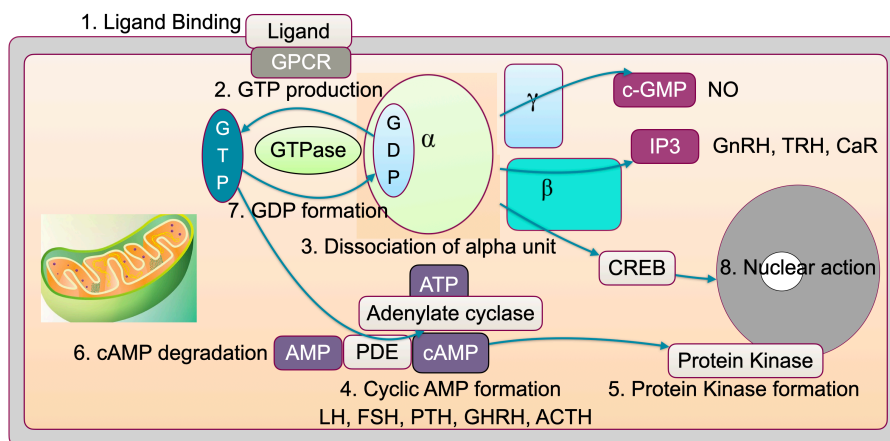


Figure 1.12- G protein coupled receptor action

ligand-specific (homologous) or non-specific (heterologous). Hormone desensitization alters the clinical expression of the disease. Prolonged secondary hyperparathyroidism in vitamin D deficiency induces a post *GNAS1* resistance producing a PHP-like picture (hypocalcemia with elevated phosphorus). Thus, vitamin D deficiency should be excluded, by checking 25OHD, before a diagnosis of PHP is made.

Ligand effects- The modulation of receptor action by modifying ligand structure is an important aspect of endocrine therapeutics. Ligands that activate the signaling pathway (agonists) are used to treat deficiency, while those that oppose it (inverse agonist) help in hormone excess. Antagonists bind to the receptor inhibiting both agonist and inverse agonist action. Biased agonism, selective activation of G protein as against β -arrestin pathways, is being explored for the MC4R (setmelanotide preferentially activates G protein signaling, avoiding blood pressure elevations seen with earlier unbiased MC4R agonists), V2R (for AVP-D therapy), and other GPCRs.

Second messengers- The second messengers amplify the hormone action and are produced in response to G protein action. The key mediators of G protein effects include cyclic AMP, cyclic GMP, IP3 (GnRH, TRH, CaR), protein kinase C, nitric oxide, and CREB.

Cyclic AMP- Cyclic AMP is produced by adenylyl cyclase action on ATP. Its downstream pathways include protein kinase A and B. The enzyme phosphodiesterase terminates the cyclic AMP effect. Increased cyclic AMP effect occurs with activating *GNAS1* mutation (McCune-Albright syndrome) and reduced phosphodiesterase and protein kinase regulator action (Carney's complex).

IP3-DAG- The IP3-DAG system, the second most common G protein-coupled pathway, translates the effects of GnRH, TRH, calcium-sensing receptor, and TSH at a high level.

Cyclic GMP- NO acts through the cyclic GMP pathway. The CNP/NPR-B/cGMP axis is the target of vosoritide in achondroplasia, antagonizing the FGFR3 MAPK pathway to restore endochondral growth.

CREB- CREB acts as a transcription factor.

Type 1 cytokine receptor

The type 1 cytokine receptors are membrane receptors that act through regulating gene expression. They have a slower onset and longer duration of action than the G protein-

coupled receptors. Growth hormone, prolactin, and leptin use the type 1 cytokine receptor.

Structure- The type 1 cytokine receptor comprises linked extracellular and intracellular domains (Figure 1.13).

Action- Hormone binding to the receptor brings the extracellular domains closer, separating the intracellular domains like a scissor. This exposes the receptor phosphorylation site to Janus kinase allowing phosphorylation. The phosphorylation by JAK2 dimerizes and mobilizes the signal transducer and activator of transcription proteins (STAT) to the nucleus, regulating the expression of STAT response elements.

Effects- Binding of GH to the receptor exposes the phosphorylation site activating the JAK-STAT pathway and production of IGFBP-3, IGF-1, and ALS. It also activates MAP kinase and insulin receptor substrate (IRS) allowing calcium and glucose flux. Germline gain-of-function STAT5B or STAT3 mutations cause constitutive activation resulting in lymphoproliferation and autoimmunity, while loss-of-function mutations cause severe GH insensitivity with immune dysfunction (STAT5B deficiency).

Termination of action- The cytokine receptor action is terminated by internalizing the extracellular domain, suppressor of cytokine signaling (SOCS), and protein tyrosine phosphatase.

Tyrosine kinase receptor

The tyrosine kinase receptors have an intrinsic tyrosine kinase that phosphorylates their targets after hormone binding. Insulin and IGF-1 act through the tyrosine kinase receptor.

Structure- The tyrosine kinase receptor is a heterotetramer, with two extracellular (α) and two intracellular (β) chains bonded to tyrosine kinase. In the inactive state, the α chains are separated distancing the β chains.

Action- Ligand binds the receptor first at the low-affinity site, followed by the high-affinity region. This blocks the binding of other molecules to the receptor (negative cooperativity). The binding of the hormone approximates the α chain bridging the intracellular β chains allowing tyrosine kinase action to activate subsequent pathways. These include the IRS1 and IRS2 (cellular glucose entry), SHC, RAS, and MAPK pathways (mitogenesis, Figure 1.14). Structural similarity allows the binding of insulin receptors by IGF-1, whereas PDGF and FGF bind their

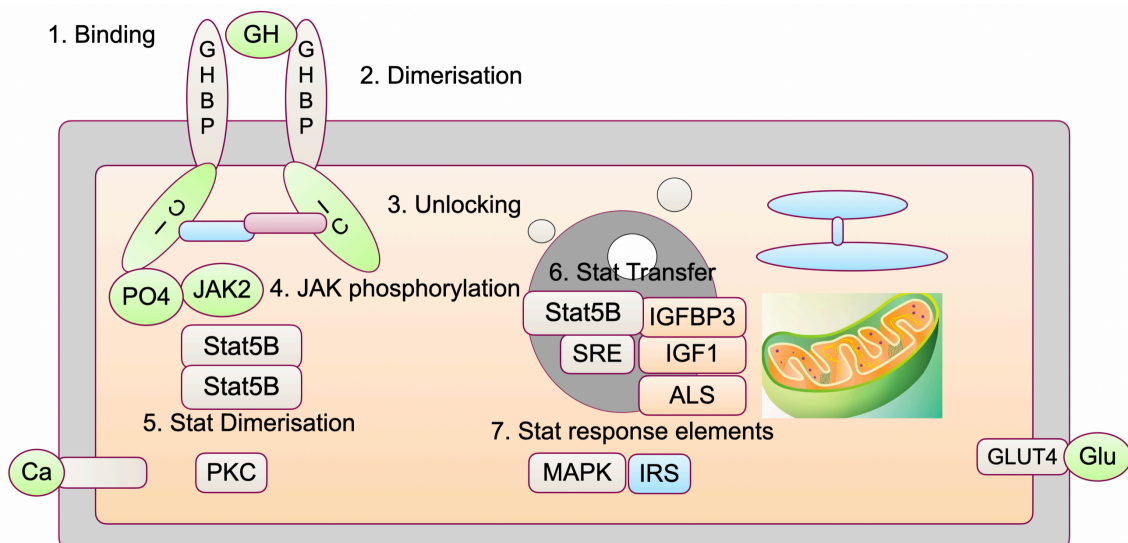


Figure 1.13- Action of Type 1 cytokine receptor

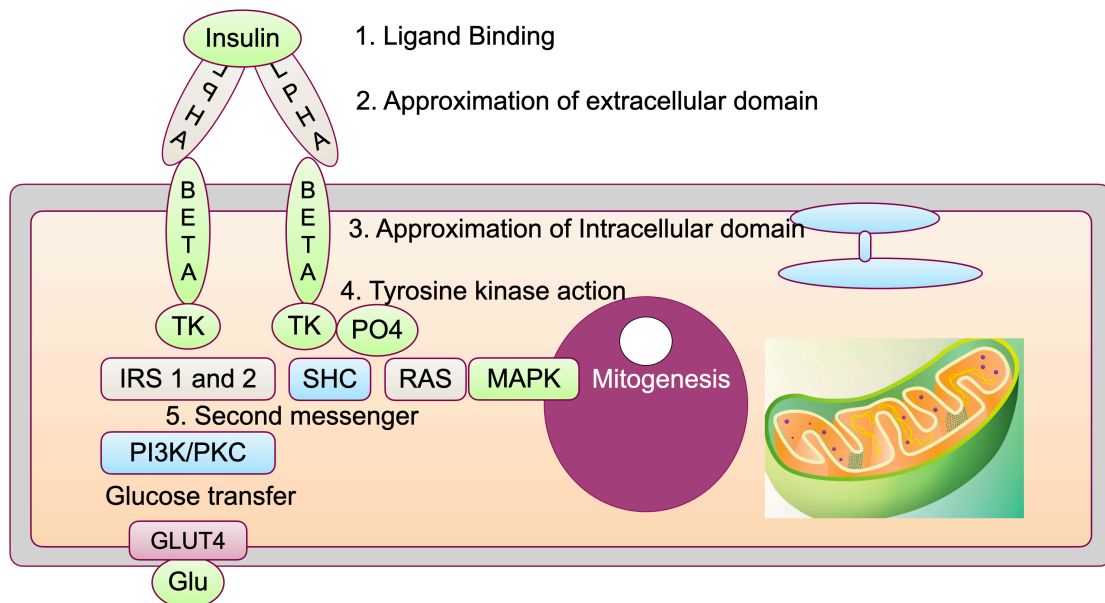


Figure 1.14- Action of Tyrosine kinase receptor

own related receptor tyrosine kinases. The insulin and IGF-1 receptors are similar in structure and use the same MAPK and IRS pathways. Their actions represent the balance of these pathways.

The major effect of IGF-1 is through MAPK, while insulin's effect is directed towards PI3K and glucose metabolism.

Nuclear receptor

The intracellular steroid/retinoic acid/thyroxine receptors act by altering gene expression of hormone response elements. The genomic effect explains the slower onset of action than membrane receptors (Figure 1.15).

Ligands- The ligands of nuclear receptors are metabolites (steroids, vitamins A and D, retinoic acid, free fatty acids, thyroxine, and xenobiotics) and not gene products. The ligands of many nuclear receptors are unknown (orphan receptors).

Structure- The nuclear receptors are made of five functional domains (transactivating A/B, DNA binding C, nuclear localizing D, and ligand binding E domains, Figure 1.16).

Action- The hormone enters the cell and binds to its receptor culminating in the formation of a dimer.

Dimerization involves binding of two similar (homodimer; steroids and retinoic acid receptor, RXR) or dissimilar receptors (heterodimer, RXR with thyroxine, estrogen, or PPAR γ receptor). The ligand-receptor complex then migrates to the nucleus and binds to the hormone response elements. Without the hormone, the co-repressors (NCOR and SMRT) deacetylate the DNA region preventing gene transcription. Hormone binding releases the co-repressors and HDAC and attracts coactivators (p300 and PCAF). The coactivators trigger histone acetyltransferase activity (HAT), exposing the hormone response element, allowing transcription and production of target proteins. This shift from suppression to activation amplifies the hormone effect. Hormone binding to the receptor may also suppress the expression of some genes (trans-repression). Thus, the effect of nuclear receptors represents the balance of gene suppression, activation, and trans-repression (Figure 1.17). Tissue-selective nuclear receptor modulation underlies two major 2024 therapeutic advances: resmetirom, a liver-selective TR β agonist approved for MASH, and the continued development of selective estrogen and androgen receptor modulators (SERMs and SARMs) that exploit tissue-specific co-regulator recruitment.

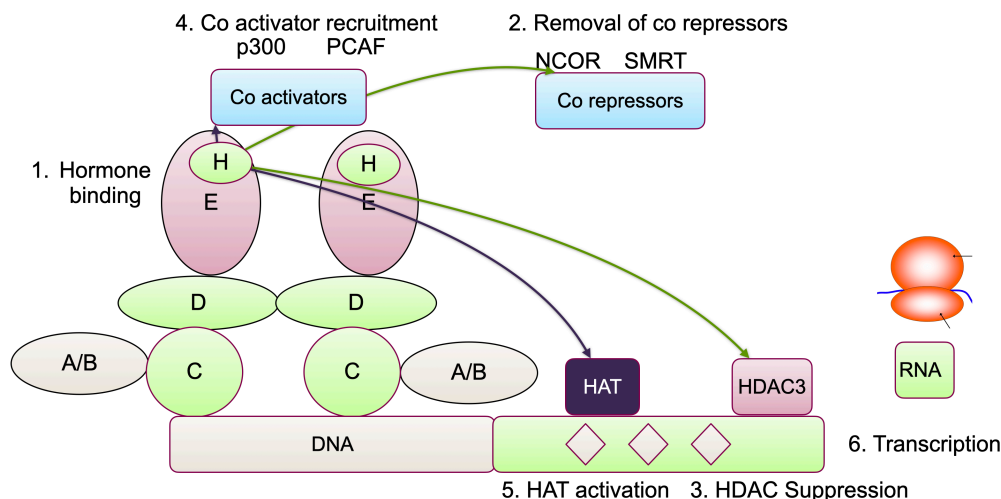


Figure 1.15- The effect of ligand binding

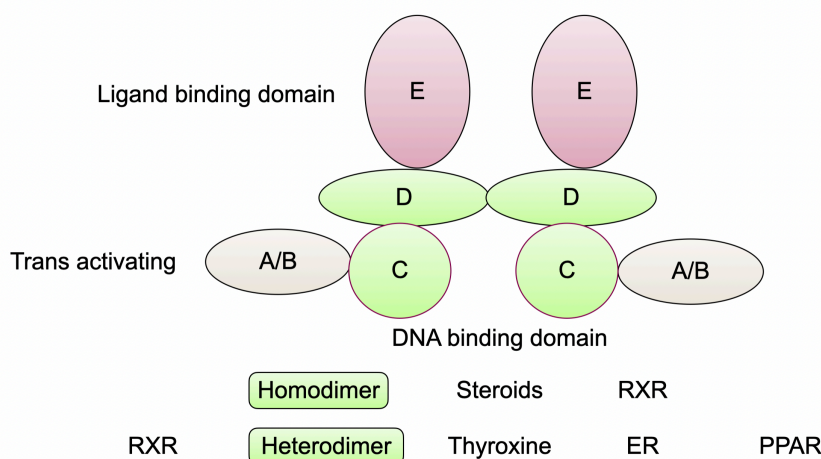


Figure 1.16- Structure of nuclear receptors

HORMONES ACROSS THE LIFE SPAN

The fundamental characteristic of pediatric endocrinology is the dramatic change in hormone levels and action across ages. These have implications for endocrine assessment (reference levels), manifestations (physiological versus pathological), and treatment (need and doses).

FETAL ENDOCRINOLOGY

Fetal metabolism is directed towards anabolism, allowing rapid growth and accumulation of glycogen, fat, and calcium. The fetus depends on the mother to regulate temperature, glucose, calcium, and electrolytes and can survive without a pituitary, thyroid, or adrenal glands functioning at adult levels.

Fetal hypothalamic-pituitary axis

The hypothalamic-pituitary axis develops from 6-8 weeks, with complete maturation by 18-20 weeks. The axis is dormant in the fetal period except for the hypothalamic-pituitary-testicular axis.

GHRH-GH-IGF-1 axis- GH has a limited effect on fetal growth due to relative resistance. IGF-1 and IGF-2 secretion matures by 12 weeks and is the major regulator of fetal growth through the type 1 IGF1 receptor. Insulin acts on the IGF-1 receptor with a ~1% affinity of IGF-1. This explains increased (infant of diabetic mother) and reduced growth (neonatal diabetes) with fetal insulin disorders. Imprinted genes IGF2 (paternal) and H19 (maternal) regulate placental nutrient transport and fetal growth—

disruption underlies Beckwith-Wiedemann (overgrowth) and Silver-Russell (IUGR) syndromes. Recent work has confirmed PAPP-A2 as a critical regulator of IGF-1 bioavailability, with biallelic PAPP-A2 mutations causing short stature with elevated total IGF-1 but reduced free IGF-1.

Hypothalamic-pituitary-thyroid axis- The fetal thyroid gland develops around seven weeks of gestation before TRH and TSH production. Initial thyroid growth is hypothalamus-pituitary independent. TSH regulates folliculogenesis. Follicular growth is disrupted in TSH deficiency. Maternal T4 is partially inactivated by placental deiodinase type III. Despite this, a substantial amount of thyroxine is transferred to the fetus resulting in ~40% of maternal levels in athyreotic fetuses. This is sufficient to prevent fetal brain damage due to increased cerebral deiodinase 2 activity. This provides a window of opportunity to treat congenital hypothyroidism and highlights the need to maintain normal maternal thyroid levels during pregnancy.

Fetal hypothalamic TRH production starts around 8-9 weeks and that of T4 around 16 weeks. The hypothalamic-pituitary-thyroid axis matures by 14-15 weeks, with the feedback mechanism establishing itself by 18 weeks. The fetal thyroid axis is directed towards anabolism, avoidance of thermogenesis, and preservation of brain function by enhanced inactivation of T4 to reverse T3 (increased DIO-3) and reduced activation to T3 (reduced DIO-1). T3 levels are low until 32 weeks of gestation (transient

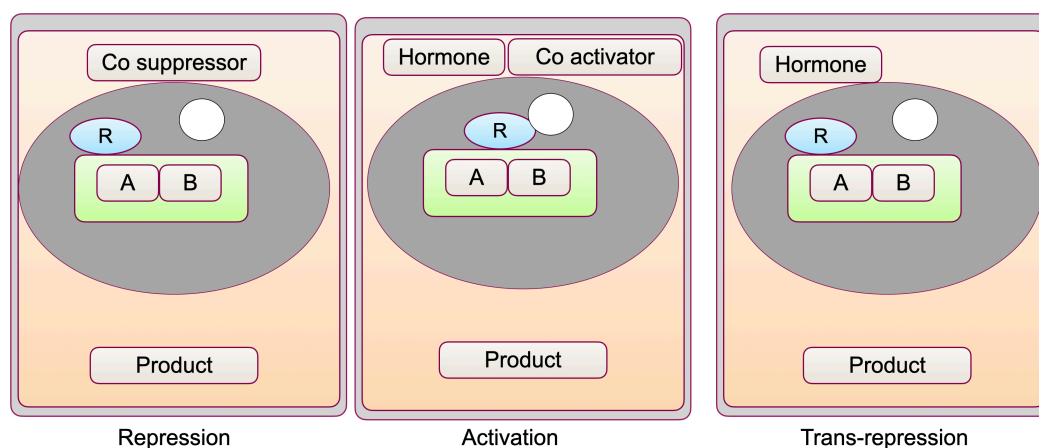


Figure 1.17- Repression, activation and trans-repression by nuclear receptors

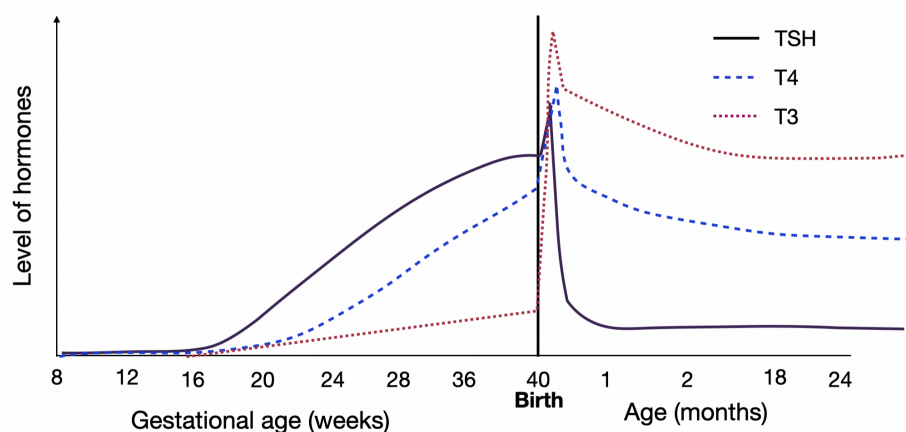


Figure 1.18- Thyroid hormone levels across gestation

hypothyroxinemia of prematurity). This is a physiological response and does not warrant treatment. TSH level rises from 24 weeks to reach 7-10 mIU/L by term (Figure 1.18).

Hypothalamic-pituitary-gonadal axis- The hypothalamic-pituitary-testicular axis is active in the antenatal period producing AMH (causing Müllerian regression), testosterone (causing virilization and sustaining Wolffian growth), and insulin-like peptide 3 (inducing testicular descent). Testosterone is detectable from eight weeks of gestation and peaks by 12 weeks (Figure 1.19). Its production during this period is controlled by placental hCG, with LH taking over after ~15 weeks of gestation. This phase is vital as labioscrotal fusion is achieved between 8-12 weeks. Inefficient testosterone action during this period causes atypical genitalia, while later defects cause micropenis with normal genitalia. hCG prevents the development of hypospadias in a male fetus with hypogonadotropic hypogonadism. In contradistinction to the testis, fetal ovarian hormone production is quiescent. The LH and FSH levels increase from 12 weeks of gestation to peak by 22-24 weeks to menopausal levels (Figure 1.20). They decrease after this period to low levels at birth. LH and FSH levels should be interpreted in light of gestational age. Female fetuses have an FSH predominant response due to lower GnRH pulse frequency. Fetal gonadotropin levels are higher in girls than boys due to lower AMH levels. The fetal ovary does not produce estrogen until term. Estrogen levels are, however, high due to transplacental passage.

Hypothalamic-pituitary-adrenal axis- Cortisol and aldosterone have a limited role in the fetal period as blood pressure, glucose, and electrolyte metabolism are supported by the mother. The fetal adrenal acts as a factory supplying

DHEA to the placenta for the production of estriol. The fetal adrenal has a large fetal and very small definitive zone. Low 3 β -hydroxysteroid dehydrogenase activity and high 17,20-lyase and sulfotransferase activity of the fetal zone cause massive production of DHEAS that is aromatized to estriol by the placenta. Placental aromatase deficiency, therefore, causes maternal and fetal virilization. Cortisol is produced between 8-12 weeks of gestation to inhibit ACTH-induced androgen production and virilization of the female fetus. Fetal aldosterone production is negligible.

Fetal calcium physiology

The fetus is dependent on the active maternal transfer of calcium by placental transporters (TRPV5, TRPV6, and calcium ATPase), producing a materno-fetal gradient of 1 to 1.4. Over 80% of the transfer occurs in the third trimester predisposing preterm infants to hypocalcemia. PTHrP and calcitriol ensure normal maternal calcium levels via bone resorption and enhanced intestinal absorption. The fetal parathyroid gland develops independently from the mother. Maternal calcium disorders have a reciprocal effect on postnatal calcium levels. Maternal hyperparathyroidism suppresses fetal PTH production, causing postnatal hypocalcemia, while infants born to a mother with hypoparathyroidism may develop hypercalcemia. Biallelic TRPV6 pathogenic variants have recently been recognized to cause transient neonatal hyperparathyroidism with hypocalcemia, rib fractures, and skeletal demineralization—an important differential of osteogenesis imperfecta in the preterm infant.

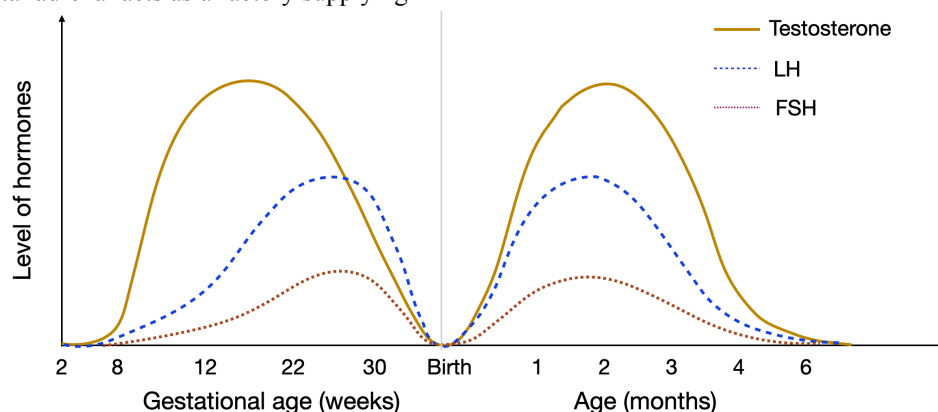


Figure 1.19- Maturation of Fetal hypothalamic-pituitary-gonadal axis in male fetuses

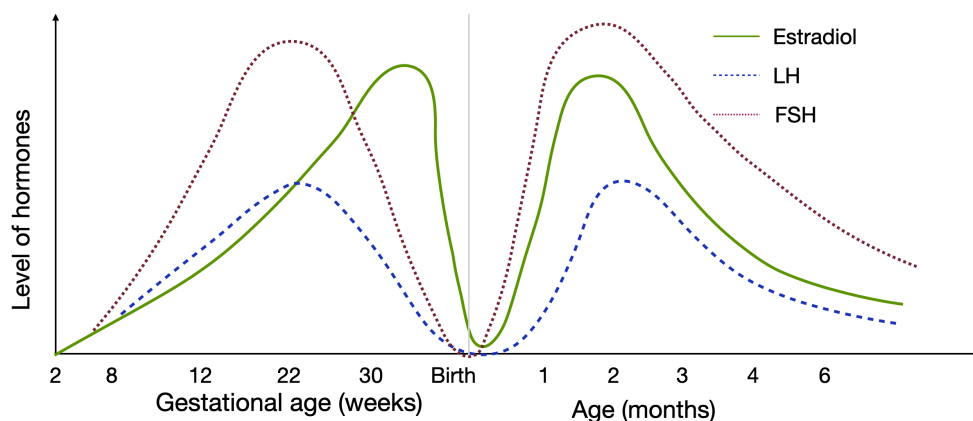


Figure 1.20- Maturation of Fetal hypothalamic-pituitary-gonadal axis in female fetuses

Fetal glucose physiology

The fetus derives all its glucose from the mother through passive transfer by placental GLUT-1 and GLUT-3 transporters (materno-fetal gradient of 1.25 to 1). Maternal hypoglycemia has a devastating impact on the fetus. The placenta secretes human placental lactogen (hPL) to induce insulin resistance in the mother increasing fetal glucose supply. High fetal glucose levels increase insulin and inhibit glucagon production. This high insulin to glucagon ratio triggers fetal growth and glycogen deposition. Most glycogen is accumulated in the third trimester. Preterm neonates have limited stores predisposing to hypoglycemia.

PLACENTAL ENDOCRINOLOGY

The placenta plays a vital role in feto-maternal endocrinology. Besides acting as a mechanical barrier, the placenta is an active endocrine organ. Emerging evidence also implicates placental extracellular vesicles (exosomes) carrying microRNAs, proteins, and metabolic signals as a mode of feto-maternal communication that may program metabolic risk in offspring—a mechanism under active investigation in the "developmental origins of health and disease" (DOHaD) paradigm.

Placenta as a conduit

The placenta allows the transfer of T4, TRH, TSH receptor antibody, calcium, and glucose (Figure 1.21).

Transplacental transfer of maternal thyroxine protects the athyreotic fetus from hypothyroidism-induced brain damage. TSH receptor antibody crosses the placenta causing transient hypothyroidism (TSH-blocking antibody, TBII) and thyrotoxicosis (TSH-stimulating antibody, TSI).

Placenta as a sieve

The placenta acts as a mechanical barrier for PTH, insulin, and TSH protecting the fetus from fluctuations in maternal levels. Placental enzymes determine the transfer of steroids from fetus to mother and vice versa. The placental 11β -hydroxysteroid dehydrogenase type II inactivates hydrocortisone and prednisolone with no effect on dexamethasone. Therefore, hydrocortisone and prednisolone are preferred for treating maternal disorders in pregnancy (rheumatoid arthritis, autoimmune disorders). Simultaneously, dexamethasone should be used to treat fetal disorders (lung maturation to prevent respiratory distress syndrome and heart block due to anti-Ro and anti-La antibodies). 11β -HSD II inactivates hydrocortisone and prednisolone with no effect on dexamethasone. Placental 17β -HSD type II protects the female fetus from maternal hyperandrogenism and the male fetus from high maternal estradiol levels. Placental aromatase prevents maternal virilization. Aromatase deficiency therefore causes fetal and maternal virilization. Very high maternal androgens (ovarian tumor) may overwhelm aromatase causing fetal virilization.

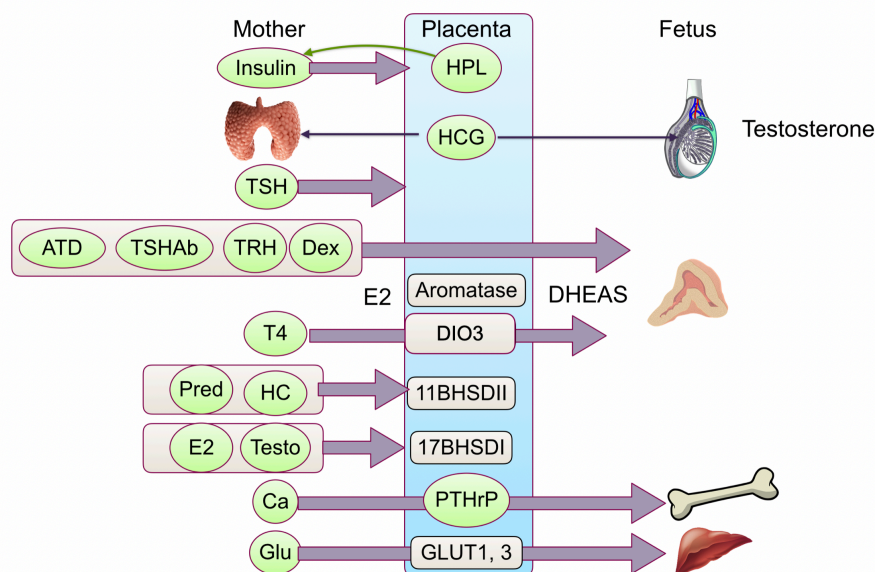


Figure 1.21- Role of placenta in relation to fetal endocrinology

Placental hormones

Placental hCG sustains fetal Leydig cell function until ~12 weeks of gestation. hCG has structural homology with TSH increasing T4 level. Estradiol increases thyroxine-binding globulin and increases total T4 levels. Placenta secretes human placental lactogen (hPL), which increases fetal glucose supply by inducing maternal insulin resistance. PTHrP is the primary determinant of fetal calcium transport. Placental corticotropin-releasing hormone (pCRH), produced in exponentially rising amounts during the third trimester, is unique to primates and is thought to function as a biological "placental clock" timing the onset of labor; elevated mid-gestation pCRH predicts preterm birth.

POSTPARTUM CHANGES

Birth is a watershed moment transitioning from a dependent and metabolically inactive fetus to an independent and active neonate. Immediate challenges include maintaining temperature, glucose, and calcium, requiring a shift from an anabolic to a catabolic state.

Postnatal hypothalamic-pituitary axis

The levels of GH, TRH, TSH, T4, and prolactin increase after birth with a reduction in cortisol, LH, and FSH.

Postnatal GHRH-GH-IGF1 axis

GH increases in the immediate postnatal period (up to 40 ng/mL) due to a fall in somatostatin levels. This has a limited effect on growth due to concomitant GH resistance. The postnatal GH resistance explains the lack of growth failure in children with GHD in early infancy. The metabolic effects of GH are, however, active predisposing GH deficient children to hypoglycemia.

Postnatal thyroid metabolism

The postnatal period is characterized by thermogenesis and catabolism induced by increased thyroid levels (increased DIO-1, decreased DIO-3, and TRH surge). This postnatal surge has implications on neonatal thyroid assessment. TSH, T4, and T3 levels are elevated in the first three days of life, highlighting the need for neonatal screening after this period. TSH levels remain high up to three weeks of life, indicating a higher cutoff during this period. Blunted TRH surge in preterm neonates may cause false-negative screening results highlighting the need for repeat screening at 3-4 weeks of life.

Postnatal hypothalamic-pituitary-gonadal axis

Gonadotropin levels decrease at birth with the loss of placental estrogen suppression and rebound around two weeks of age. This stage of minipuberty represents the transient postnatal reactivation of the HPG axis. In boys, LH peaks at 4-10 weeks (1-10 IU/L) with testosterone reaching 60-400 ng/dL, returning to baseline by 4-6 months. In girls, the activation is FSH-predominant, more prolonged (up to 18-24 months; median 6 months), with fluctuating estradiol and transient breast tissue. Biologically, minipuberty drives Sertoli cell proliferation (establishing ~90% of the adult pool), germ cell maturation, penile growth, and INSL3-mediated testicular descent.

Minipuberty offers a window to evaluate the HPG axis without pharmacological stimulation until puberty. In a 4-10-week-old boy with micropenis, bilateral cryptorchidism, or midline defect, an undetectable LH and testosterone <0.5 nmol/L is diagnostic of CHH; concurrent low AMH and

inhibin B argue against anorchia. Therapeutically, this window permits recombinant hCG plus FSH (or pulsatile GnRH) to correct micropenis and cryptorchidism while recruiting the latent Sertoli and germ cell pools, with rises in testicular volume, AMH, and inhibin B. Long-term fertility data are pending, and current consensus positions this as established for phenotypic correction but investigational for fertility preservation. Interpretation requires strict attention to timing and gestational-age adjustment, as prematurity amplifies and prolongs the response.

Postnatal adrenal physiology

The most dramatic postnatal endocrine change involves the adrenal gland, which shows rapid involution of the fetal zone and maturation of the definitive zone. Neonatal adrenals produce a large amount of sulfated and structurally related steroids causing errors in immunoassay results. This highlights the need for extraction-based assays or structure-based liquid chromatography-tandem mass spectrometry in the period. The neonatal distal nephron has relative aldosterone resistance for the first 1-2 weeks. This, together with placental clearance of fetal salt, explains the typical 7-14-day delay before salt-wasting CAH presents with hyperkalemia, hyponatremia, and shock.

Postnatal calcium metabolism

The decline in calcium levels triggers PTH release while inhibiting calcitonin production, maintaining calcium levels. Predisposed individuals (prematurity, birth asphyxia, and infant of diabetic mother) develop hypocalcemia in this transitory period. Calcitriol has a minor role in maintaining neonatal calcium levels in the first two weeks of life. Therefore, infants born to vitamin D deficient mothers do not develop hypocalcemia before two weeks of life.

Postnatal glucose metabolism

The glucose supply of the fetus from the mother abruptly stops at parturition, predisposing to hypoglycemia. Increased epinephrine and glucagon, along with a reduction in insulin, induce glycogenolysis to maintain glucose levels. This is followed by increased gluconeogenesis and ketogenesis. Blood glucose falls dramatically in the first 24 hours despite these defence mechanisms. The transition is complete by 48 hours; hypoglycemia beyond this period is pathological.

MATERNAL ADAPTATION

Besides the demands of pregnancy, mothers must supply glucose, calcium, and energy to the fetus. This involves a concerted effort of the endocrine system to induce maternal insulin resistance (human placental lactogen), bone resorption (PTH-related peptide), and energy consumption. This highlights the need for increased caloric and calcium consumption in pregnant women and the role of maternal malnutrition in exacerbating fetal undernutrition. Placental hCG acts on the TSH receptor to induce mild thyrotoxicosis lowering TSH levels by ~1 mU/L. Increased estradiol elevates binding globulin increasing thyroxine and cortisol requirements. Increased binding globulins also increase total thyroid hormone prompting a change in cut-off to ~one and a half times the upper limit of non-pregnant levels.

CHILDHOOD

Childhood is a period of stable growth and endocrine parameters. Gonadotropins are suppressed throughout childhood under hypothalamic inhibitory control. This inhibition is maintained by GABAergic tone on KNDy/kisspeptin neurons and by makorin ring-finger protein 3 (MKRN3), whose loss-of-function mutations are a leading genetic cause of familial central precocious puberty inherited in a paternally transmitted pattern due to maternal imprinting. Additional pubertal-timing genes include DLK1, KISS1, KISS1R, TAC3, and TACR3. This makes the assessment of testicular function difficult during childhood. AMH and inhibin B are markers of testicular function at this age.

PUBERTAL CHANGES

Puberty is characterized by dramatic changes with the achievement of 40% of adult bone mass, 25% growth, and 100% reproductive potential. Besides the increase in gonadotropins and sex steroid levels, puberty witnesses changes in the GH-IGF1, insulin-glucose, PTH-calcitriol, thyroid, and adrenal axes.

GH-IGF-1 axis

GH secretion increases two- to threefold during puberty under the influence of sex steroids. GH levels may be low in delayed puberty and become normal after puberty. This causes a false diagnosis of GHD in prepubertal individuals and highlights the need for sex hormone priming in the setting. IGF-1 levels increase during puberty, highlighting the need for age-specific cutoffs.

Body composition

Puberty is associated with fat deposition in the abdomen in boys and mammary and gluteal regions in girls. Increased sex steroids induce insulin resistance causing acanthosis, metabolic dysfunction-associated steatotic liver disease, and type 2 diabetes.

Bone metabolism

Estrogen increases calcium absorption, lowers bone resorption, and increases bone formation enhancing bone mineral density. There is a lag of 2-3 years between the achievement of adult height and peak bone mass predisposing adolescents to fracture.

HORMONE CROSS TALKS

The endocrine effect represents the balance between stimulant, inhibitor, environment, other hormones, synthesis, release, transport, action, and feedback. The key factors affecting the endocrine function include the evolutionary burden, hormonal cross-talk, nutrition, and illness.

HORMONES AND EVOLUTION

The hormone milieu has evolved over thousands of years under a deprivation state with a scarcity of food, warmth, water, salt, and calcium. Therefore, the endocrine system has adapted for conservation with limited capacity to react to excess (Figure 1.22). This is illustrated by four hormones to counter hypoglycemia (growth hormone, epinephrine, glucagon, and cortisol) and only one for hyperglycemia (insulin). Similarly, regulation of sodium (dominant role of sodium retaining RAAS with a minor role of salt-losing atrial natriuretic peptide), calcium (tonic role of PTH and calcitriol and insignificant effect of calcitonin to reduce the level), and fluid (physiological role of retaining AVP and trivial role of losing ANP) are directed towards preventing deficiency. The abundance of these substrates has caused high blood pressure and glucose, explaining the modern pandemic of non-communicable diseases. The endocrine system was built to defend against scarcity. The pediatric endocrinologist is asked to manage its failure to defend against abundance.

HORMONAL CROSS TALKS

Multiple hormone systems interact with each other to achieve homeostasis. Significant contributors to this interplay include pleiotropy (one hormone acting on many parts), redundancy (many systems working for one effect), and synergy. Hypothalamic hormones control their counterpart pituitary hormones (TRH-TSH, CRH-ACTH, GnRH-LH/FSH, GHRH-GH, and dopamine-prolactin). There are, however, significant cross-talks with clinical implications. TRH increases prolactin in primary hypothyroidism, which in turn inhibits gonadotropin production, causing hypogonadism. Cortisol inhibits TSH and GH secretion while estradiol stimulates GH production. Regulation of fluid and osmolality status by AVP, the RAAS, and natriuretic peptide is a classic example of hormone cross-talk. Hypovolemia and hyperosmolality trigger AVP and RAAS while inhibiting ANP production. Both AVP and RAAS have a mutually

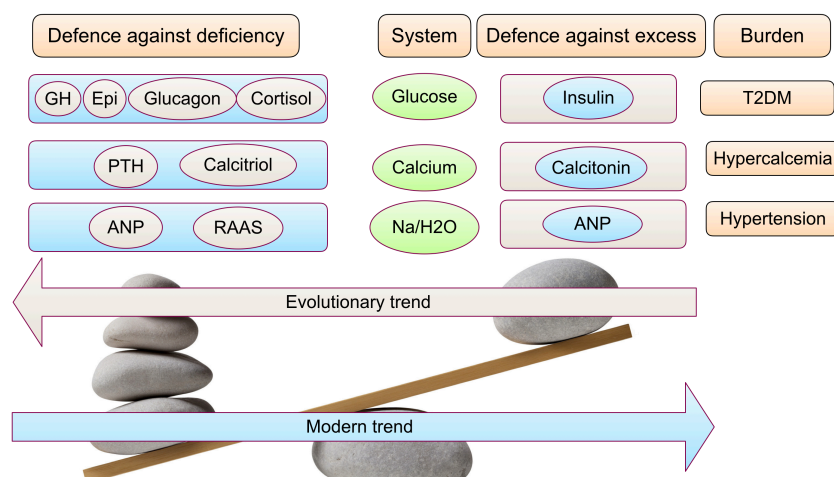


Figure 1.22-Evolutionary basis of modern diseases

stimulatory effect. Thus, angiotensin II stimulates AVP release, which increases ACTH-dependent aldosterone secretion, potentiating both actions. In hypervolemic states, ANP inhibits both AVP and aldosterone production increasing volume and sodium loss.

The muscle–bone–gut–liver metabolic network has emerged as a major regulator of energy homeostasis: exercising muscle secretes myokines (irisin, IL-6, myostatin) that drive adipose browning and bone formation; osteocalcin released from bone stimulates β -cell insulin secretion and muscle glucose uptake; gut-derived incretins (GLP-1, GIP) and FGF19 modulate hepatic glucose and lipid handling; and hepatokines (FGF21, fetuin-A) feed back to muscle and adipose tissue to regulate insulin sensitivity. Disruption of this network through inactivity, dysbiosis, or hepatic steatosis causes the clustering of obesity, MASLD, sarcopenia, and type 2 diabetes.

NUTRITIONAL EFFECT

There is a need to link endocrine functions with nutritional status given the energy demand of growth and puberty (Table 1.2). Leptin is the crucial link between nutrition and endocrine function. Understanding the effect of nutrition on hormone assessment is vital to allow appropriate evaluation of reports.

Overnutrition

Excessive body fat gives the body a signal to grow, enter puberty, and increase the metabolic rate.

Growth- Obesity increases growth due to insulin resistance. Increased insulin acts on the type 1 IGF receptor and increases free IGF1 levels by lowering IGFBP-1 levels. Obesity is a state of relatively preserved IGF-1 with suppressed GH secretion, causing a false diagnosis of GHD. GH requirements are lower in obese children. This along with disproportionately greater GH dose based on body weight, has led to the recommendation of body surface area-based dosing in obesity.

Thyroid- Obesity stimulates TRH increasing TSH despite normal T4. This is an adaptive mechanism and the effect and not the cause of obesity. Thyroid replacement is not needed with mildly elevated TSH levels (below 10 mU/L).

Adrenal- Adiposity causes pseudo-Cushing syndrome due to increased 11β -HSD1 activity and CRH production. Premature activation of the adrenal androgen axis causes adrenarche discordant to gonadarche.

Puberty- Leptin is the gatekeeper for puberty. Its levels should be above a threshold level for puberty to start; higher levels in themselves do not trigger puberty. Obese girls have early but disjointed puberty with an increased gap between thelarche and menarche. Increased aromatase activity in obese boys delays pubertal onset and results in relative hyperestrogenemia with gynecomastia.

Bone mineralization- Obesity has been considered a high bone mass state due to elevated IGF1 and estradiol levels. Recent studies have shown adverse effects of obesity on bone health in the presence of metabolic complications. This is related to the central effects of leptin and insulin resistance. Mechanistic work has identified that chronic low-grade inflammation, sclerostin elevation, and marrow adiposity together contribute to the paradox of preserved areal BMD with impaired bone quality and elevated fracture risk in adolescents with severe obesity.

Glucose metabolism- Increased visceral fat deposition causes insulin resistance, MASLD, type 2 diabetes, and polycystic ovarian syndrome. Low birth weight individuals have limited capacity to store fat and develop metabolic complications at a lower body mass index than those with normal or high birth weight. Asian Indian adolescents demonstrate a distinctive "thin-fat" phenotype with greater visceral adiposity, insulin resistance, and early MASLD at lower BMI than White counterparts, supporting lower BMI cutoffs for screening in Indian pediatric populations.

Undernutrition

Undernutrition represents a state of energy conservation with the postponement of growth, puberty, and bone mineralization.

Growth- Undernutrition is a GH-resistant state with low IGF1 and high GH levels. GH levels may be spuriously high in malnutrition, causing a missed diagnosis of GHD. IGF1 levels are unreliable and should not be assessed in undernourished children.

Thyroid- Undernutrition causes low T3 (increased DIO-3 action) and TSH levels (increased cerebral DIO-2 action).

Table 1.2- Effect of nutritional status on hormone levels

Hormone levels	Over nutrition	Under nutrition
<i>Growth hormone</i>	Decreased	Increased
<i>IGF-1</i>	Increased	Decreased
<i>TSH</i>	Increased (≤ 10 mU/L)	Decreased
<i>Free T4</i>	No change	Normal or mildly decreased
<i>T3</i>	Normal to increased	Decreased
<i>Cortisol</i>	Increased (11β -HSD1)	Increased (stress response)
<i>PTH</i>	No change	Increased with low vitamin D
<i>DHEAS</i>	Increased	Decreased
<i>Leptin</i>	Markedly increased	Decreased
<i>Adiponectin</i>	Decreased	Increased
<i>Estrogen in boys</i>	Increased (adipose aromatase)	Decreased
<i>Testosterone in girls</i>	Increased	Normal or increased

Adrenal- Stress response as part of undernutrition causes mildly elevated ACTH and cortisol levels.

Puberty- Undernutrition delays puberty due to decreased leptin levels. Delayed puberty in undernutrition is characterized by absent thelarche and absent/delayed adrenarche (pubic hair), in contrast to hypogonadotropic hypogonadism where adrenarche is typically preserved.

Bone mineralization- Bone mineralization is compromised due to vitamin D deficiency and secondary hyperparathyroidism in undernutrition.

Glucose metabolism- Malnutrition modulates the development of diabetes resulting in severe hyperglycemia without ketosis (Type 2 diabetes, malnutrition-related diabetes mellitus; recognized as a separate type by the IDF in 2022).

ILLNESS EFFECT

Hormones play an important role in combating acute illness and stress. The key response to stress is a shift of metabolic pathways from catabolism to energy conservation.

Adrenal- The main regulator of the stress response is cortisol, and the inability to mount a stress response is the most frequent cause of an adrenal crisis. This mandates the need for stress dosing in children with adrenocortical insufficiency.

Thyroid- Acute illness increases DIO-3 activity lowering T3 levels. TSH levels are low due to enhanced DIO-2 action and the inhibitory effects of hypercortisolism and dopamine. This constellation of low T3, normal/low T4, and low TSH is characteristic of non-thyroidal illness and not a marker of central hypothyroidism. Recovery from illness is characterized by an increase in TSH, causing a diagnostic dilemma of primary hypothyroidism. Thyroid function should not be assessed in hospitalized subjects unless mandatory. Thyroid hormone treatment should be started only with persistent and significant elevation of TSH with low T4 levels.

GH-IGF-1 axis- Acute illness produces a state of acquired GH resistance shifting metabolism from anabolism to substrate mobilization for immune and repair functions.

Low IGF-1 in this setting reflects illness, and GH testing should be deferred until recovery.

Vasopressin- Non-osmotic AVP release in sepsis, pneumonia, meningitis, and post-operative states produces the syndrome of inappropriate antidiuresis (SIAD) with hyponatremia and concentrated urine despite euvolemia.

Gonadal axis- Stress suppresses hypothalamic GnRH pulsatility via CRH, cortisol, and inflammatory cytokines, producing functional HH. In adolescents this manifests as delayed puberty and menstrual irregularity. Recovery follows resolution of the underlying illness and does not require hormonal therapy.

FURTHER READING

1. Bajpai A, Sen P, Dave C. Endocrine Physiology. MedECclasses Online Course in Pediatric Endocrinology. learning.growsociety.in
2. Rosen ED, Carter-Su C. Principles of hormone action. In: Williams Textbook of Endocrinology. Eds: Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ. 14th Edition, Elsevier, 2020.
3. Kublaoui B, Levine MA. Receptor transduction pathways mediating hormone action. In: Sperling Pediatric Endocrinology. Sperling MA (Ed.). 5th Edn, Elsevier 2021, Philadelphia. pp 30-85.
4. Lodefalk M, Nilsson O. Puberty—new insights and challenges. *Acta Paediatr.* 2024;113(3):381-390.
5. Grigorakis N, Karampela I, Dalamaga M. The role of placental extracellular vesicles in pregnancy and in the programming of offspring health: A narrative review. *Curr Obes Rep.* 2024;13(2):347-362.
6. Kuiri-Hänninen T, et al. Activation of the hypothalamic-pituitary-gonadal axis in infancy: minipuberty. *Horm Res Paediatr.* 2014;82(2):73-80.
7. Suntharalingham JP, et al. DAX-1 (NR0B1) and steroidogenic factor 1 (NR5A1): new insights. *Best Pract Res Clin Endocrinol Metab.* 2015;29(4):607-619.

LEARNING POINTS

Hormone effect is the product of gland development, synthesis, release, transport, metabolism, receptor action, and feedback sensing. These steps form the basis of disease and treatment.

Counter-regulatory redundancy due to evolutionary burden explains modern patterns of non-communicable diseases in a calorie-abundant environment.

Local metabolism creates tissue-specific effects: 11 β -HSD2 protects the mineralocorticoid receptor from cortisol, 5 α -reductase generates DHT, and deiodinases fine-tune thyroid hormone action.

Fetal endocrinology is directed at anabolism and thermogenic protection: the HPG-testicular axis is active; the HPA axis acts as a DHEA factory; thyroid activity is suppressed via DIO-3.

Birth reverses multiple axes: GH, TSH, and prolactin surge; cortisol, LH, and FSH fall.

Minipuberty (boys: onset 1–2 weeks, peak 4-10 weeks, declining by 6 months; girls: up to 18-24 months) is a unique diagnostic and therapeutic window.

Nutrition modulates every endocrine axis: obesity causes a GH-resistant, TSH-elevated, pseudo-Cushing state; undernutrition causes a GH-resistant, low-T3, delayed-puberty state.

When a hormone effect is abnormal, walk the seven steps: gland → synthesis → release → transport → metabolism → action → sensing. Each step has a class of disease and a class of treatment.

Illness disrupts hormones: non-thyroidal illness (low T3, low-normal T4, low TSH) must not be misdiagnosed as central hypothyroidism.