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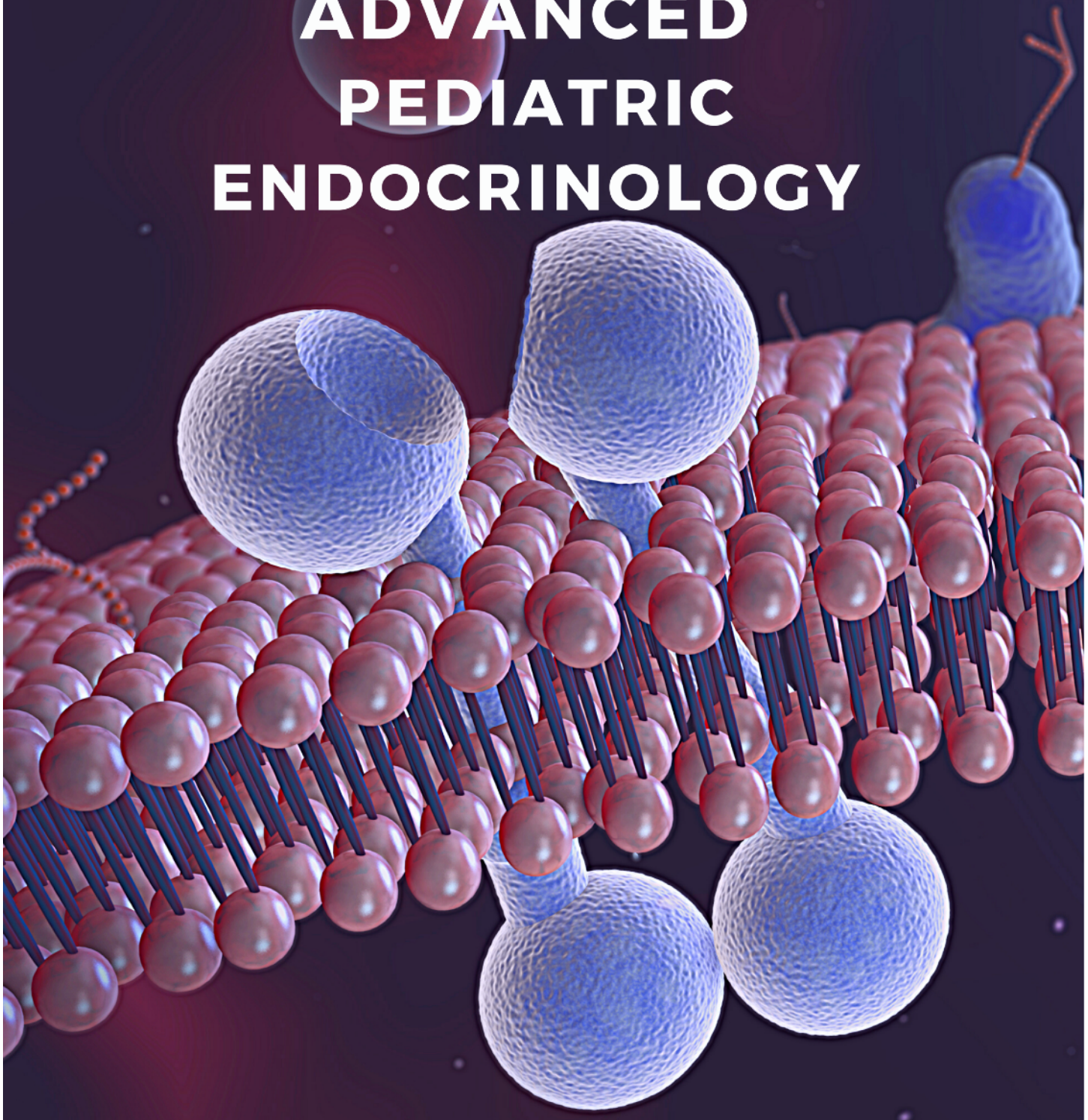

ANURAG BAJPAI

VOLUME I

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MedEClasses
PEDIATRIC ENDOCRINOLOGY

Advanced Endocrinology
Volume I

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Foreword

The practice of endocrinology in children is essentially based on clear understanding of applied physiology and its practical application. In *MedEClasses Text Book of Pediatric Endocrinology* Dr Anurag Bajpai and his colleagues have admirably used these principles to produce a very fine two-volume work covering 63 chapters which comprehensively deal with both common and less common or rare aspects of pediatric endocrinology.

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 six sections, namely Pituitary, Adrenal, Cancer, Bone and Calcium, Ovary, and Testis. Each of these six Sections opens with a chapter on the physiology of the relevant system, followed by a chapter on Assessment, and then specific disorders of that system. The final Section covers Metabolic disorders, each of the six chapters covering important metabolic issues including unusual forms of diabetes, obesity and lipid disorders. The Case Vignettes and tables of Learning Points throughout the book provide further guidance and learning cues for both the advanced trainee and the experienced pediatric endocrinologist seeking diagnostic assistance.

The approach is thus very much based on the principles of applied physiology. The work is detailed and comprehensive, while being eminently readable. It provides current knowledge on underlying pathophysiology and on modern approaches to diagnosis and management.

This is a very high-level text book of pediatric endocrinology, full of detailed and often novel information, as well as very helpful advice about management. This 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 would 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. I commend this text book to all those beginning their journey into a career in pediatric endocrinology, as well as to pediatric endocrinologists seeking a comprehensive and up to date reference source.

Prof George Werther AO, MD, FRACP, MSc (Oxon)

Melbourne, Australia, March 2021

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Preface

Pediatric Endocrinology has witnessed dramatic changes over the last decade with increasing availability of diagnostic tools and trained physicians. Despite these advances Pediatric Endocrine disorders are still missed with devastating consequences. Pediatric Endocrinology is unique in that a comprehensive understanding of physiology is mandatory for successful management. Unfortunately, Pediatric Endocrinology textbooks are too voluminous and focused on basic endocrinology to enthuse trainees. Practical books provide approach to assessment without due importance to physiology. There is, thus, a felt need for a comprehensive book encompassing pathophysiology while retaining a strong clinical focus.

GROW Society (Growth & Obesity Workforce), established in 2013 to spread awareness about Pediatric Endocrinology, has worked extensively for physician awareness with development of six modules, publications of three books, and Pediatric Endocrinology Mobile Application. GROW Society learning modules have been implemented as 10 full day programs and 150 workshops attended by over 5000 paediatrician. The difficulties of onsite programs led to the development of MedEClasses, an innovative E-Learning portal that uses a combination of videos, animations, didactic text and real life cases to empower pediatricians, pediatric endocrinologists, trainees, and postgraduates in managing children with endocrine disorders. The MedEClasses online courses in Pediatric Endocrinology covering Growth, Puberty, Thyroid, Calcium, Pituitary, Ovary, Testis, Adrenal, Fundamentals, Cancer, Metabolic, Electrolyte and Glucose disorders has been widely subscribed across the world. This two volume book builds on the MedEClasses Basic Pediatric Endocrinology Text Book to provide clinically relevant and concise learning on all pediatric endocrinology topics. Each chapter is divided into sections on pathophysiology, pointers and criteria, etiology, assessment, approach, management, and case scenarios. The book is supplemented by animated videos available in the online course. The book would be of help for Pediatric Endocrinologists, Endocrinologists, trainees, and pediatricians with special interest in Endocrinology.

This work would not have been possible without the help of dynamic, young pediatric endocrinologists Drs Chetankumar, Neha, Riddhi, Sajili, Proteek, Sayan, and Narayanan. Dr Yuthika's valuable suggestions have gone a long way in bringing the book into its shape. Hearty thanks for Mr Ravi Shankar Dubey, Hariom, Aditya and Nikhil for making this project seamless and enjoyable. Many thanks to my mentors Professor George Werther and Professor PSN Menon for guiding me through the intricacies of Pediatric Endocrinology and beyond.

Happy learning,

Anurag Bajpai, MD, FRACP, SCE

Kanpur, India, March 2021

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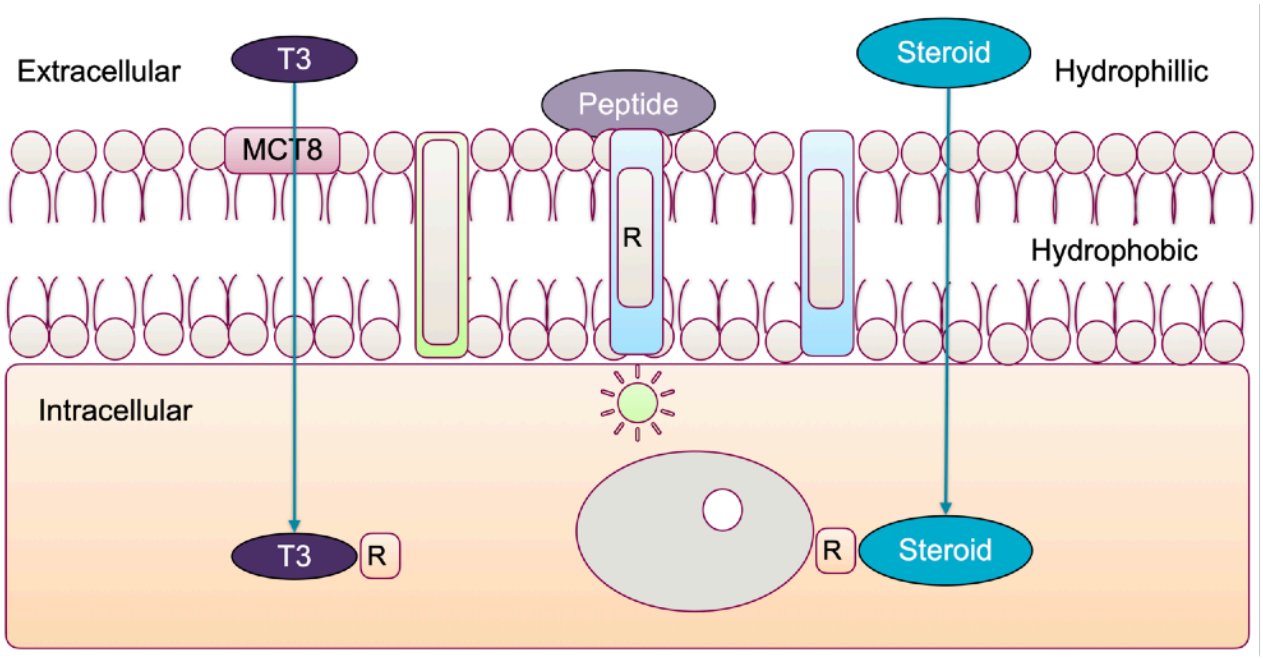
SECTION I - Fundamentals of Pediatric Endocrinology



SECTION EDITORS
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Chapter 1
Endocrine Physiology

Anurag Bajpai, Proteek Sen, Chetankumar Dave

Pediatric endocrinology is one of the most challenging branches of pediatrics due to the complexity of physiology, assessment, and approach. The understanding of endocrine physiology allows the mathematical implementation of endocrine diagnostics and therapeutics.

FUNDAMENTALS

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

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 (GLP1), kidney (renin), bone (CNP, FGF23, osteocalcin), heart (natriuretic peptide), stomach (ghrelin), and adipocytes (adipokines) may be considered an endocrine system.

WHAT IS A HORMONE?

Hormones are molecules secreted in one part of the body that reaches their target sites through the circulation to perform their action. Minuscule amounts of hormones have a significant impact, as illustrated by the fact that 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). PYY produced by the intestine acts on neuropeptide Y, stimulating the orexigenic pathway. Adipocytes produce leptin which acts on leptin receptors in the brain to modulate satiety. Taking the concept further, metabolites like calcium may also be called a hormone. Calcium is released from one site (bones), has distant receptors (calcium-sensing receptors in the kidney, parathyroid, and thyroid) to cause distinct effects (reduced PTH secretion, increased calcitonin release, and urinary calcium excretion). This chapter focuses on conventional hormones.

HORMONE CHARACTERISTICS

Hormone effects represent their direct action, interaction with other signalling pathways, and the influence of the environment. It is characterised by multiple effects of one hormone (pleiotropy), multiple hormones controlling a single effect (redundancy), a combination of multitude 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.

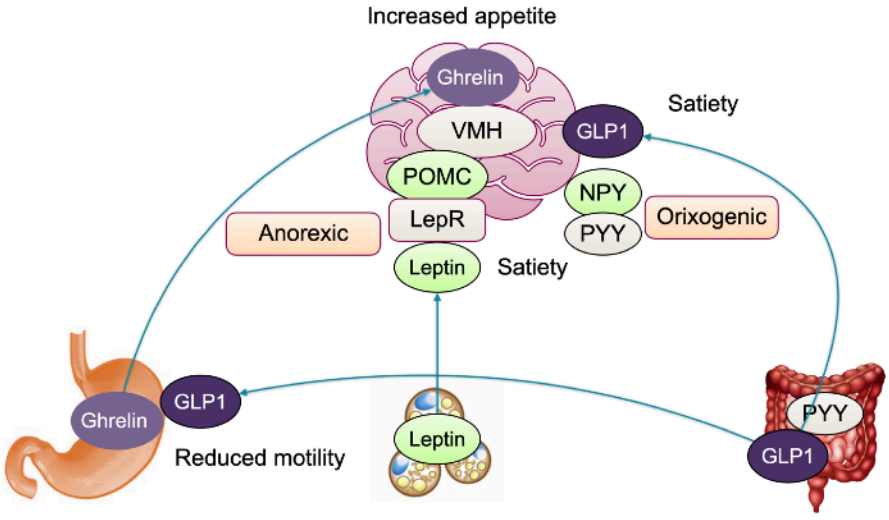

Figure 1.1- The entero-metabolic axis

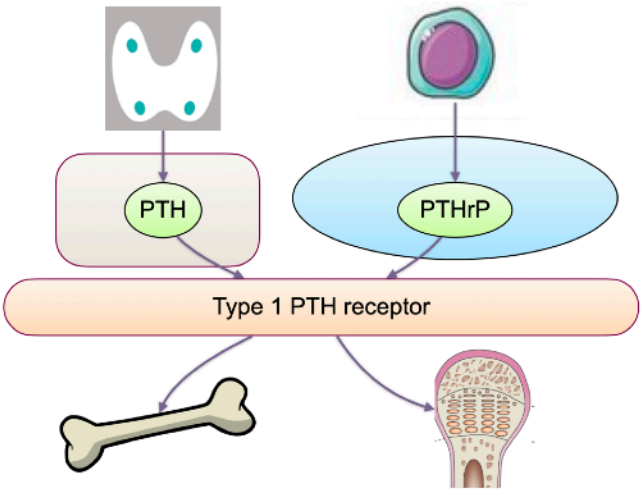

Figure 1.2- Convergence of PTH and PTHrP effects

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 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).

Multiple sites of signaling

Besides acting at sites distant from their origin (endocrine effect), the hormones can act locally (paracrine) and on the cell that produces them (autocrine, Figure 1.3). These actions determines 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 corticotrophin-releasing factor (CRF) produced by the hypothalamus.

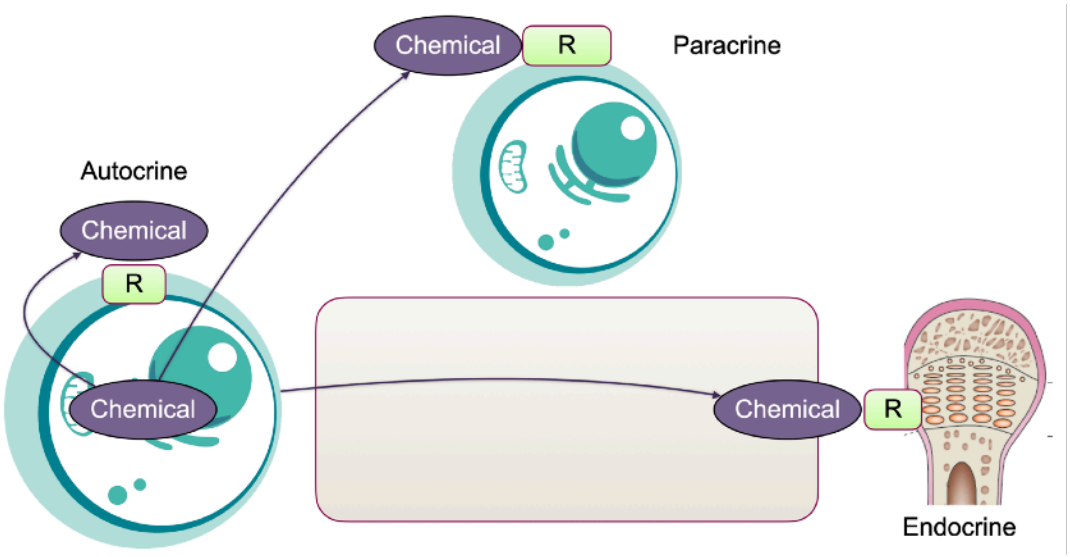

Figure 1.3- Different sites of hormone action

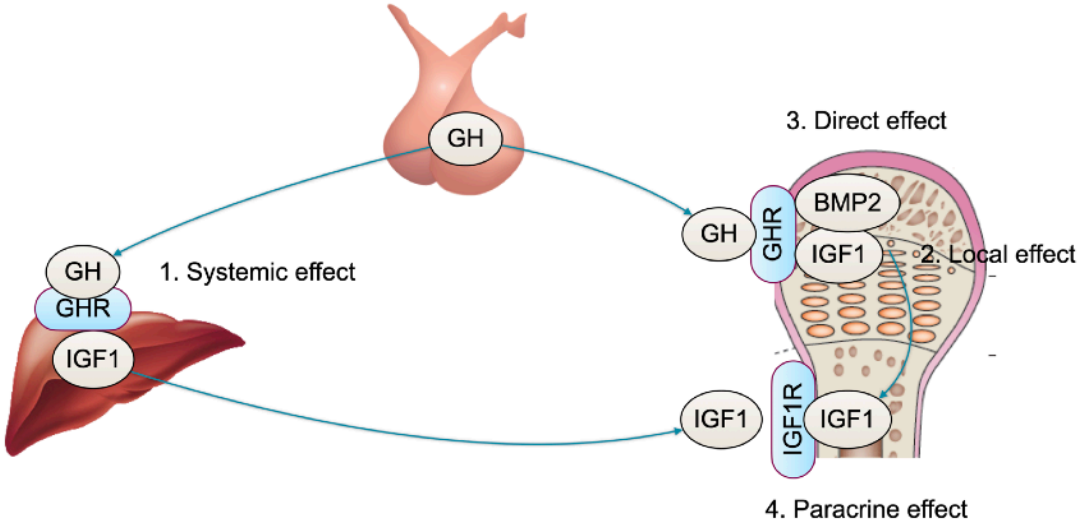

Figure 1.4- The mediators of GH effect

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 receptor. For example, all body tissues have equal exposure to growth hormones. The tissue selectivity of hormone 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 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. 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).

HORMONE ACTION

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 parts of the pituitary developed from the neuroectoderm (neurohypophysis) and pharynx (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.

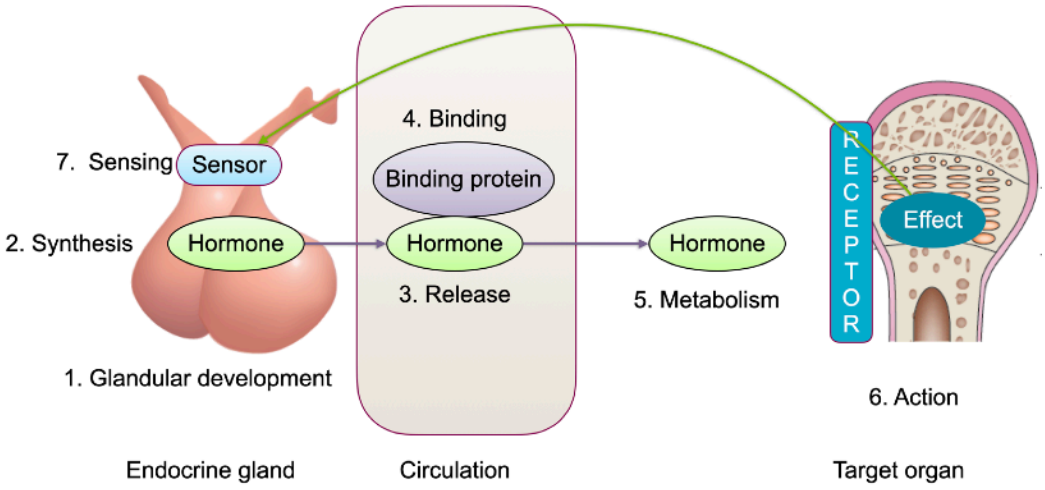

Figure 1.5- The determinants of hormone effect

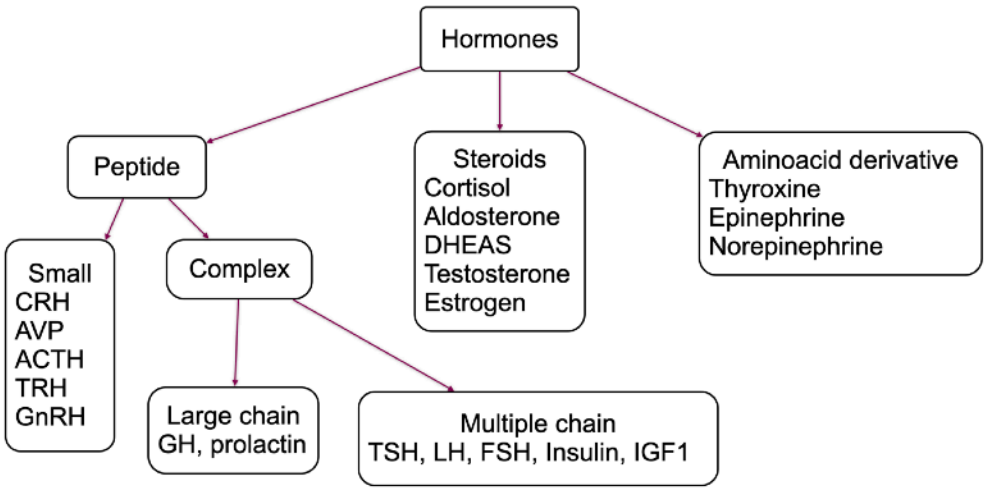

Figure 1.6- Structure-based classification of peptide hormones

Neural origin and distinct blood supply of the posterior pituitary explains preserved vasopressin function in apoplexy and radiotherapy. Distinct formation and regulation also explains the rarity of simultaneous involvement of the two glands (in hypothalamic and stalk lesions). Diabetes insipidus with pituitary deficiency suggests hypothalamic or stalk involvement. The differential origin of thyroid cells (follicular and neuroendocrine) 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 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 IGF1). 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, CRF, 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. Placental HCG acts on the TSH receptor causing gestational thyrotoxicosis. HCG-producing tumors in boys cause peripheral precocious puberty in boys.

STEROID

Steroids are formed from a backbone of 21 carbon structures. Removal of two carbon atoms of these produce androgens (C19 steroids) while aromatase removes another carbon forming estrogen (C18 compound). 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.

Table 1.1- Comparison of different hormone classes

Feature	Peptide	Steroid	Amine
Size	Usually large	Medium	Small
Protein binding	Low (GH, IGF1)	High	Low
Receptor	Membrane	Intracellular (rarely membrane)	Extra and intracellular
Metabolism	Rapid	Slow	Very rapid
Half life	Short	Long	Very short
Effect	Medium	Slow	Rapid

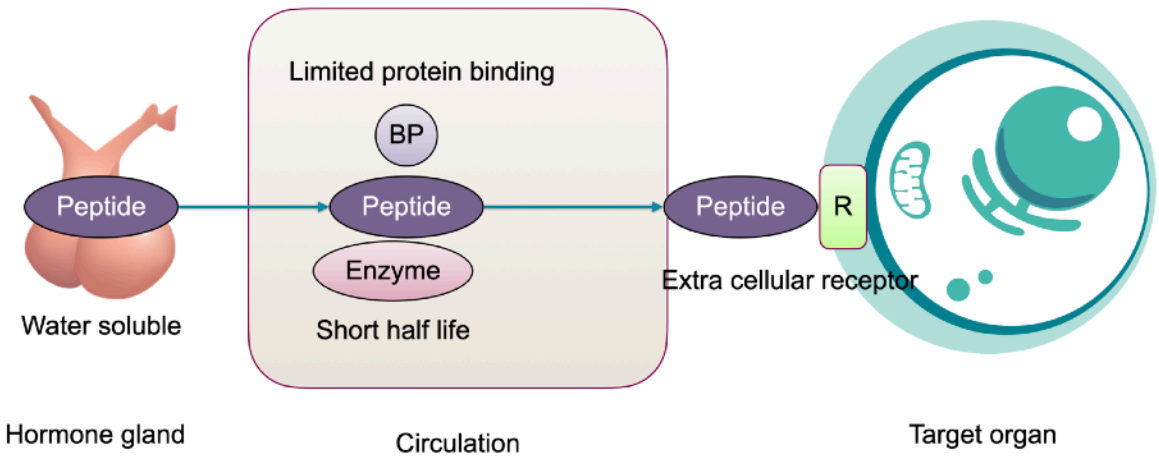

Figure 1.7- Overview of peptide hormones

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).

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. Splicing defects can cause multiple hormone deficiency (diabetes, obesity, hypopigmentation, and ACTH deficiency due to proconvertase deficiency) and glandular damage (INS, vasopressin, and GH splicing defects). 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 clues. 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 levels of release.

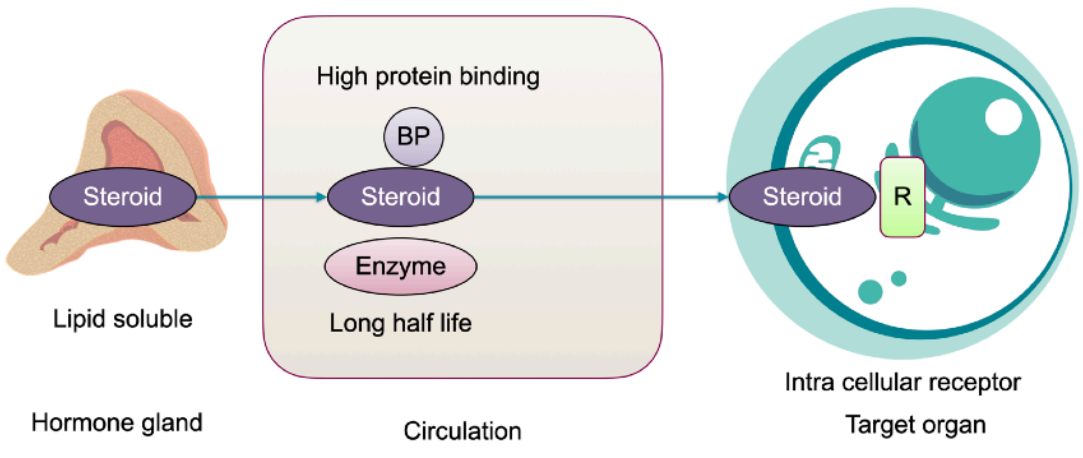

Figure 1.8- Features of steroid hormone

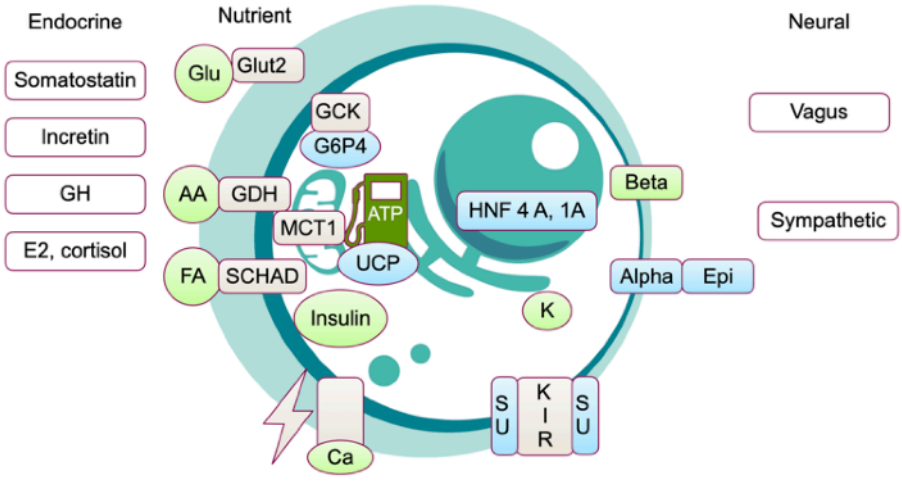

Figure 1.9- Regulation of insulin release

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, 5) and systemic effects (IGFBP3). Steroids need a transport protein due to their hydrophobic nature. The binding protein limits 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 increase in IGFBP1 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 the 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 IGFBP3 levels in impaired GH effect reduces IGF-1 half-life. GH treatment increases both IGF-1 and IGFBP3 levels, enhancing the hormone effect. The IGFBP3 levels, however, do not increase with IGF-1 therapy, causing rapid rise and fall of IGF-1. This explains greater predilection of toxicity and the lower effect of IGF-1 than GH therapy. Increase binding protein levels with pregnancy and estrogen use increase thyroxine and hydrocortisone requirement by increasing the amount of hormone bound to them.

HORMONE METABOLISM

Local hormone metabolism is an important regulator of 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 di hydroxyvitamin D). Testosterone is converted by 5 alpha-reductase 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 a disorder of sexual development to gynecomastia and infertility. Androgen is converted to estrogen in estrogen-responsive tissue (bone, growth plate, and pituitary). The alteration in hormone metabolism provides an opportunity to respond to the environment. Increased monodeiodinase 3 activity in the fetal period and during illness increases T4 inactivation preventing deleterious 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 same affinity to the mineralocorticoid receptor and can cause increased mineralocorticoid effect due to its substantially higher levels than aldosterone. The mineralocorticoid effect of cortisol is prevented by the beta-hydroxysteroid dehydrogenase 2 (11BHSD2) enzyme that inactivates it to cortisone in mineralocorticoid tissues (kidney and sweat gland). The 11BHSD1 enzyme, on the other hand, enhances the cortisol effect in the glucocorticoid responsive tissues by activating cortisone to cortisol. Defects in 11BHSD1 (apparent cortisol deficiency) and 11BHSD2 (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 interacts 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 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).

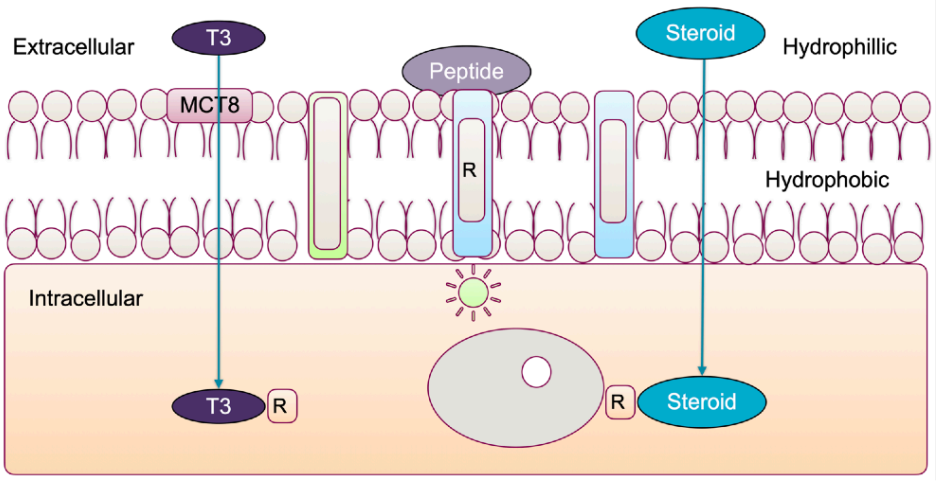

Figure 1.10- Cell membrane and hormone receptors

Membrane receptors of steroid hormones (cortisol, calcitriol, and estrogen) allow their rapid effects.

G Protein-coupled receptor

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

Structure- G protein-coupled receptors have a ligand-binding extracellular N terminal domain, seven transmembrane alpha-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 alpha, beta, and gamma subunits.

Action- Guanosine diphosphate (GDP) present in the native state of the alpha subunit prevents receptor signaling. Hormone binding to the N terminal converts the GDP to guanosine triphosphate (GTP), dissociating the alpha from the beta and gamma subunits. This alpha subunit mediates GPCR effects (Figure 1.12). The intrinsic GTPase activity in the G protein reconverts GTP to GDP, allowing recombination of the beta and gamma units terminating its action. The balance between the inactive and the active state determines the signaling of the G protein-coupled receptor. The alpha subunit of G protein has many forms. The most common Gs alpha unit stimulates adenylate cyclase producing cAMP and is utilised by most peptide hormones (PTH, LH, FSH, GHRH, TSH, vasopressin). The GNAS1 gene regulates the Gs alpha effect. Increased (McCune Albright syndrome) or decreased GNAS1 effect (PHP) causes pubertal, calcium, thyroid, and skeletal disorders. The inhibitory Gs alpha I unit decreases cAMP levels. The Gq11 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 GPCR 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 membrane receptor-associated 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), beta-arrestin (dissociation of the receptor with G protein), ligand effect, and internalization of the receptor. The desensitization may be 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 high phosphorus). Thus, vitamin D deficiency should be excluded before diagnosing PHP.

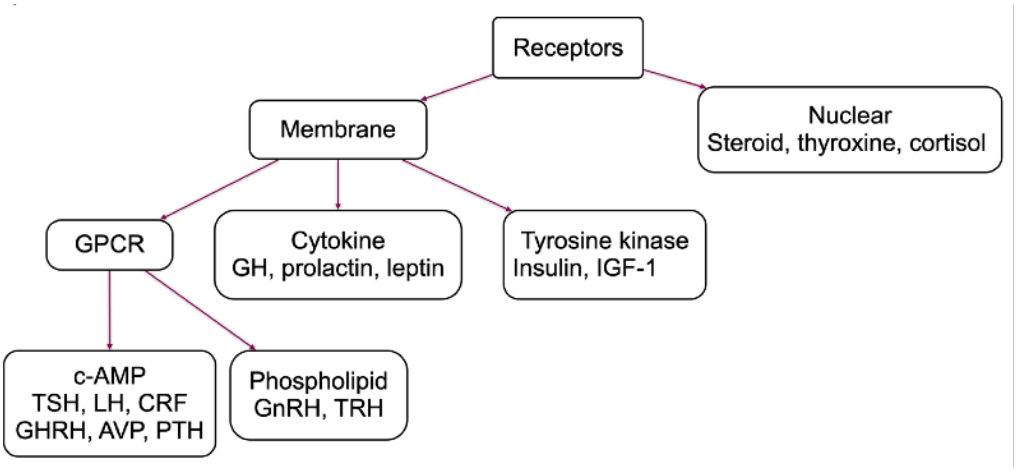

Figure 1.11- Types of hormone receptors

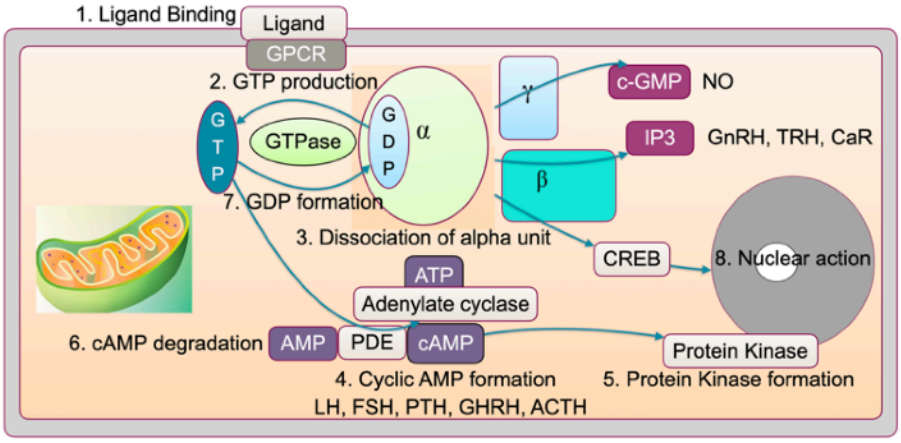

Figure 1.12- G protein coupled receptor action

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.

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 E, nitric oxide, and CREB.

Cyclic AMP- Cyclic AMP is produced by the adenyl 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- 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.

CREB- CREB acts as a transcription factor.

Type 1 Cytokine receptor

The type 1 cytokine receptor are membrane receptors that acts 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 an intracellular domain (Figure 1.13).

Action- The hormone binding to the receptors 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 JAK 2 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 IGFBP3, IGF,1, and ALS. It also activates MAP kinase and insulin response substrate (IRS) allowing calcium and glucose flux.

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

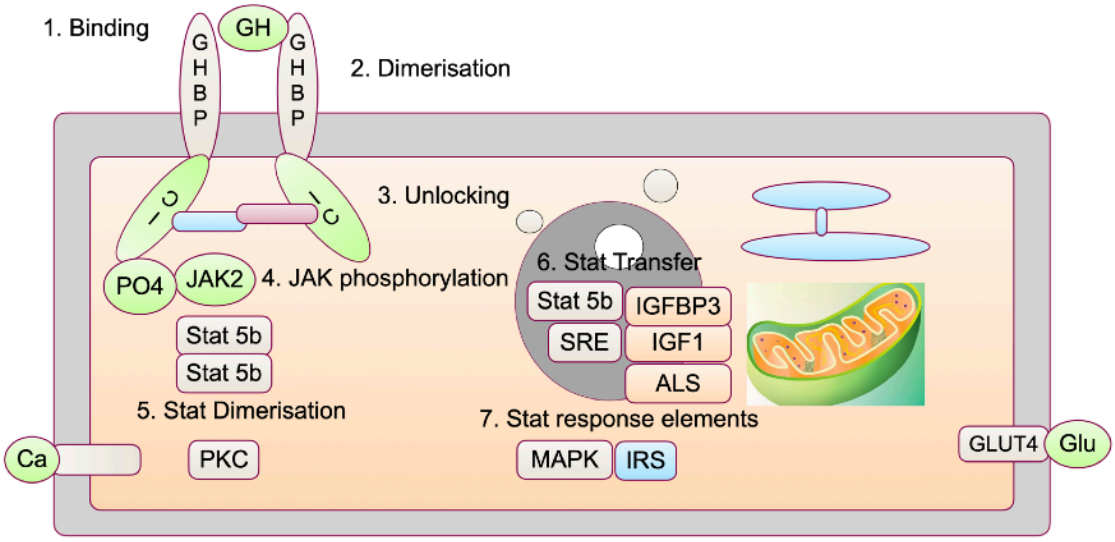

Figure 1.13- Action of Type 1 cytokine receptor

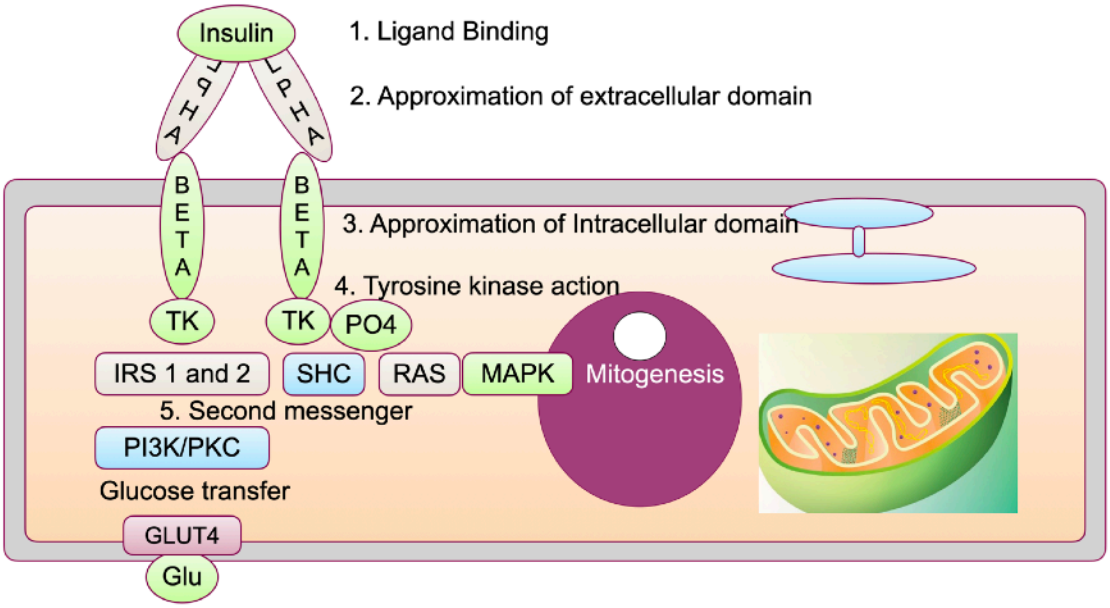

Figure 1.14- Action of Tyrosine kinase receptor

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 (alpha) and intracellular (beta) chains bond to tyrosine kinase. In the inactive state, the alpha chains are separated distancing the beta 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 co-operation). The binding of the hormone approximates the alpha chain bridging the intracellular beta chains allowing tyrosine kinase action to activate subsequent pathways. These include the IRS1 and 2 (cellular glucose entry), SHC, RAS, and MAPK pathways (mitogenesis, Figure 1.14). Structural similarity allows the binding of insulin receptors by IGF1, PDGF, and FGF. The insulin and IGF1 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 a gene product. The ligands of many nuclear receptors are unknown (orphan receptors).

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

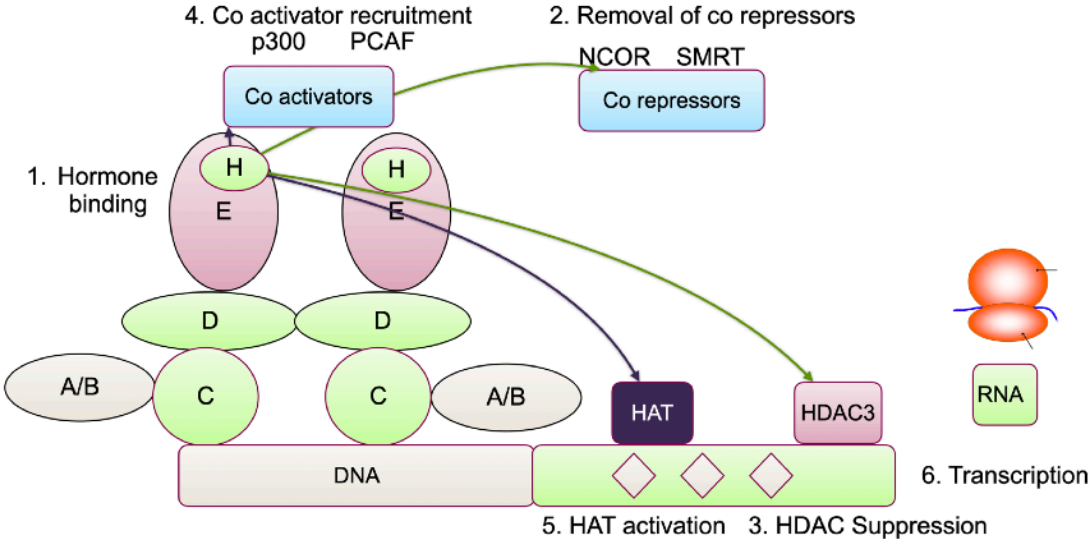

Figure 1.15- The effect of ligand binding

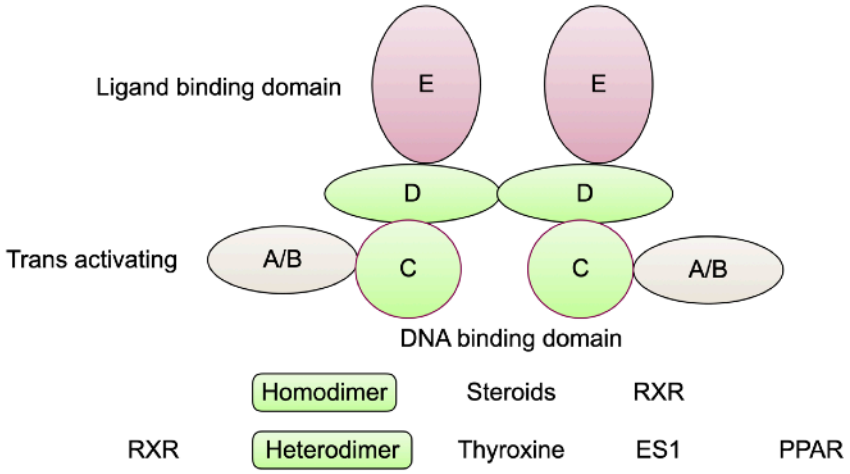

Figure 1.16- Structure of nuclear receptors

receptors (heterodimer, RXR with thyroxine, estrogen, or PPAR gamma 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 corepressors and HDAC and attracts coactivators (p300 and PCAF). The coactivators trigger Esteryl transferase 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).

HORMONES ACROSS LIFE SPAN

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

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 survive without a pituitary, thyroid, or adrenal glands.

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 its resistance. IGF-1 secretion matures by 12 weeks and is the major regulator of fetal growth through the Type 1 IGF1 receptor. Insulin acts on IGF 1 receptor with a 5% affinity of IGF-1. This explains increased (infant of diabetic mother) and reduced growth (neonatal diabetes) with fetal insulin disorders.

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 disjuncted in TSH deficiency. Maternal T4 is partially inactivated by placental monodeiodinase type III. Despite this, a substantial amount of thyroxine is transferred to the fetus resulting in 40% T4 of maternal levels in athyreotic fetuses. This is sufficient to prevent fetal brain damage due to increased cerebral mono 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.

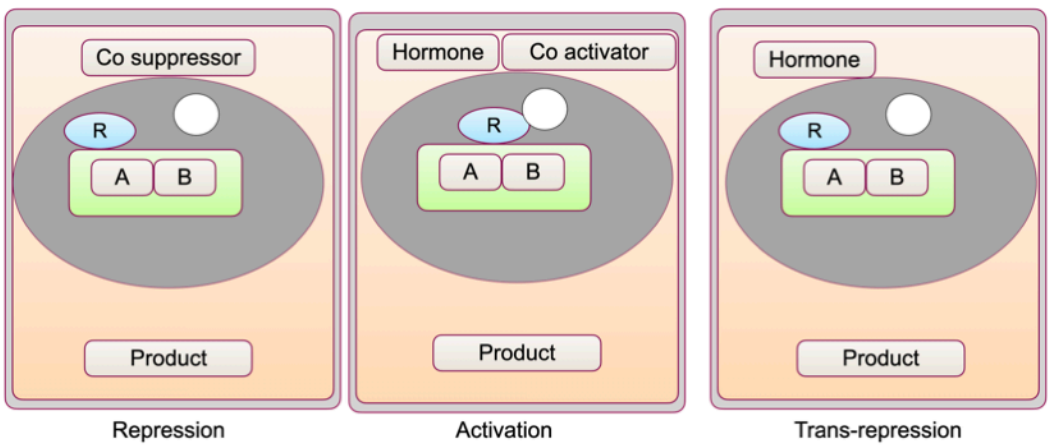

Figure 1.17- The effect of ligand binding on gene expression

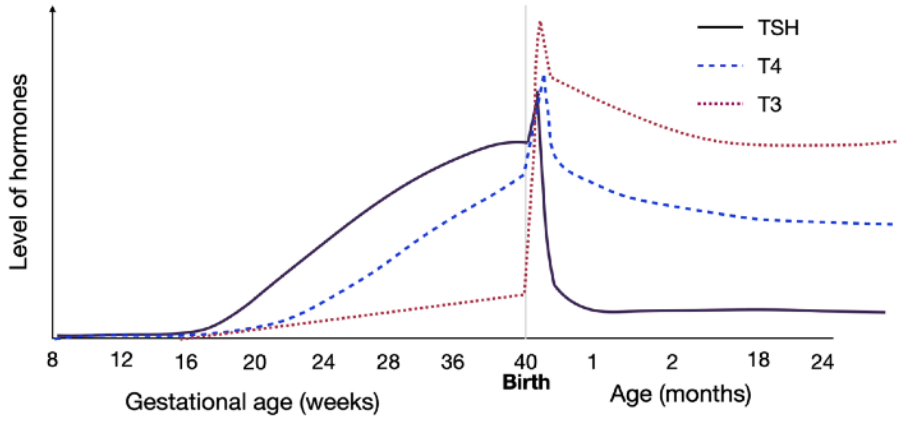

Figure 1.18- Thyroid hormone levels across gestation

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 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 MDI 3) and reduced activation to T3 (reduced MDI 1). T3 levels are low till 32 weeks of gestation (Transient 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 Mullerian regression), testosterone (causing virilization and sustaining wolffian growth), and insulin-like factor 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 the 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 till 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 is supported by the mother. 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 beta-hydroxysteroid dehydrogenase activity and high 17 lyases and sulfatase activity of the fetal zone causing 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, ensures normal maternal calcium levels via bone resorption and enhanced intestinal absorption. The fetal parathyroid gland develops independently from the mother.

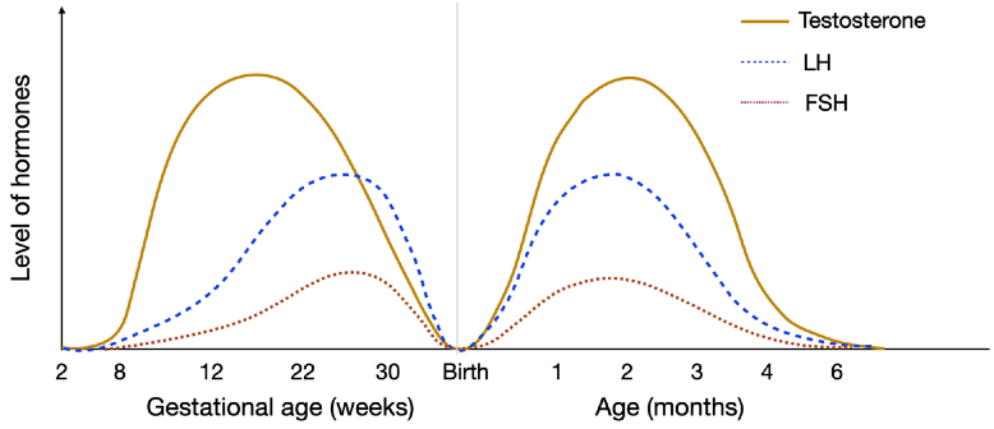

Figure 1.19- Maturation of Fetal hypothalamic-gonadal axis in male fetuses

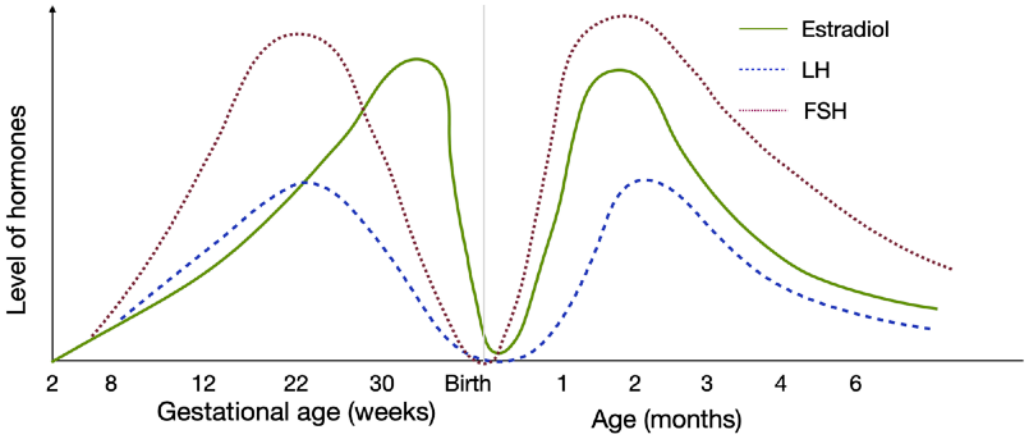

Figure 1.20- Maturation of Fetal hypothalamic-gonadal axis in female fetuses

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 hypovitaminosis D may develop hypercalcemia.

Fetal Glucose Physiology

The fetus derives all its glucose from the mother through passive transfer by placental GLUT 1 and 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 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.

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 (blocking antibody) and thyrotoxicosis (stimulating antibody).

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 11 beta-hydroxysteroid dehydrogenase II inactivates hydrocortisone and prednisolone with no effect on dexamethasone. Therefore, hydrocortisone and prednisolone are preferred for treating maternal disorders in pregnancy (rheumatic 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 La antibodies). 11BHSD II inactivates hydrocortisone and prednisolone with no effect on dexamethasone. Placental 17BHSD 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 virlisation. Very high androgen maternal androgens (ovarian tumor) may overwhelm aromatase causing fetal virlisation.

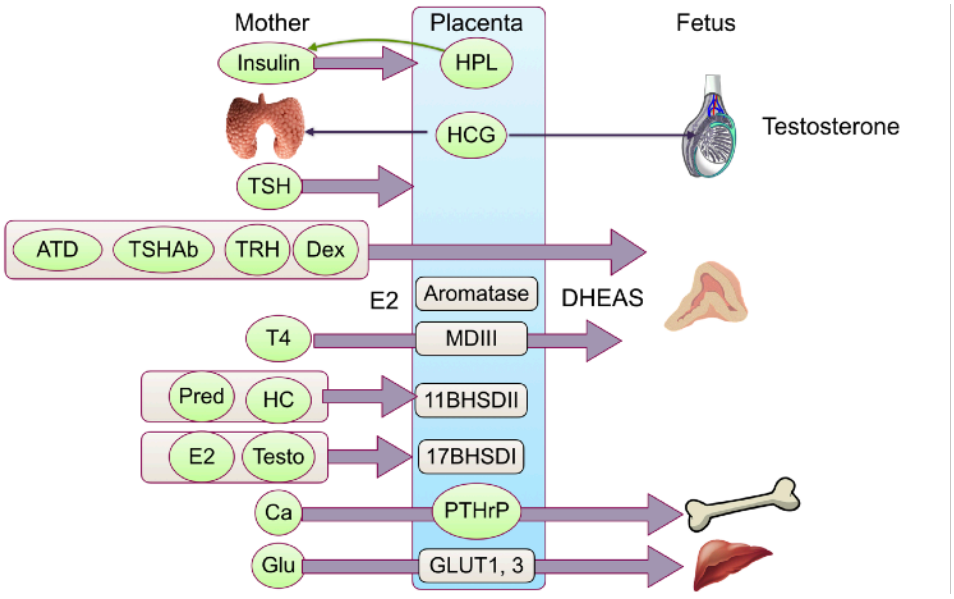

Figure 1.21- Role of placenta in relation to fetal endocrinology

Placental Hormones

Placental HCG sustains fetal Leydig cell function till 12 weeks of life. HCG has a 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.

POST PARTAL 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 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 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 MDI 1, decreased MDI 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

The gonadotropin levels decrease at birth and rises around two weeks of age due to mini puberty.

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 the immunoassay results. This highlights the need for extraction and structure-based mass spectroscopy in the period. Salt regulation is aldosterone independent in the first two weeks of life, explaining lack of salt wasting in congenital adrenal hyperplasia during this period.

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, induces 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 the period is pathological.

MATERNAL ADAPTATION

Besides the demands of pregnancy, mothers have to 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 requirement. Increased binding globulins also increase total thyroid hormone prompting a change in cut-off to one and a half times above the non-pregnant levels.

CHILDHOOD

Childhood is a period of stable growth and endocrine parameters. Gonadotropins are suppressed throughout childhood under hypothalamic inhibitory control. 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% 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 axis.

GH-IGF-1 Axis

GH secretion increases two folds 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. IGF1 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, nonalcoholic fatty 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. Dramatic lifestyle changes have offset the gains of evolution. The abundance of these substrates has caused high blood pressure and glucose, explaining the modern pandemic of non-communicable diseases.

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, RAAS system, and natriuretic peptide is a classic example of a hormone cross talk. Hypovolemia and hyperosmolality trigger AVP and RAAS while inhibiting ANP production. Both AVP and RAAS have a mutually stimulatory effect. Thus, angiotensin II stimulates AVP release, which increases ACTH-dependent aldosterone secretion, potentiating both the actions. In hypervolemic states, ANP inhibits both AVP and aldosterone production increasing volume and sodium loss.

NUTRITIONAL EFFECT

There is a need to link endocrine functions with the nutritional status given the energy demand of growth and puberty (Table 1.4). Leptin is the crucial link between nutrition and endocrine function. Understanding the effect of nutrition on hormones 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 levels. Obesity is a GH-sensitive state with low GH and high IGF1 levels, 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 11BHSD1 activity and CRF 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 dysjuncted puberty with an increased gap between thelarche and menarche. Increased aromatase activity in obese boys delays pubertal onset and pregnancy.

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.

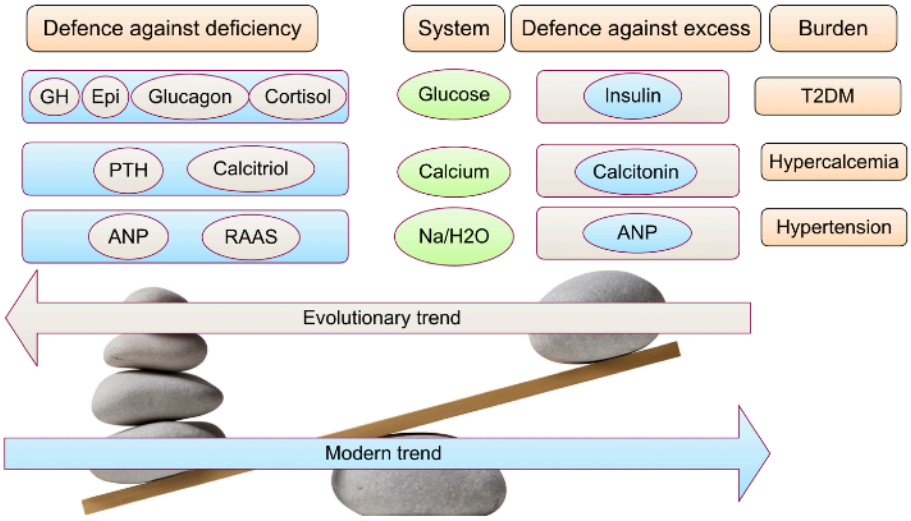

Figure 1.22- Evolutionary basis of modern diseases

Table 1.4- Effect of nutritional status on hormone levels

Hormone levels	Over nutrition	Under nutrition
Growth hormone	Decreased	Increased
IGF-1	Increased	Decreased
TSH	Increased	Decreased
Thyroxine	No change	Increased
Cortisol	Increased	Increased
PTH	Same	Increased with low vitamin D
DHEAS	Increased	Decreased
Estrogen in boys	Increased	Decreased
Testosterone in girls	Increased	Normal or increased

Glucose metabolism- Increased visceral fat deposition causes insulin resistance, nonalcoholic fatty liver disease, 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.

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 MDI3 action) and TSH levels (increased cerebral MDI2 action).

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 pubic development as against normal pubic hair development in hypogonadotropic hypogonadism.

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 (malnutrition-dependent diabetes mellitus).

Illness affect

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 stress response is the most frequent cause of the adrenal crisis. This mandates the need for stress dosing in children with adrenocortical insufficiency.

Thyroid- Acute illness increases MDI3 activity lowering T3 levels. TSH levels are low due to enhanced MDI2 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 increase in TSH, causing a diagnostic dilemma of primary hypothyroidism. Thyroid functions 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.

FURTHER READING CHANGE

1. Bajpai A, Sen P, Dave C. Endocrine Physiology.. MedEClasses Online Course in Pediatric Endocrinology. learning.growsociety.in
2. Rosed ED, Carter-Su C. Principles of hormone action. In: Williams Textbook of Endocrinology. Eds: Melmed S, Auchus R, Goldfine A, Koenig R, Rosen C. 14th Edition, Elseiver, Manesar. Pp 13-41.
3. Kublaoui B, Levine MA. Receptor transduction pathways mediating hormone action. In: Sperling Pediatric Endocrinology. Sperling MA (Eds.). Elseiver 2021, Philadelpia. 5th Edn, pp 30-85.