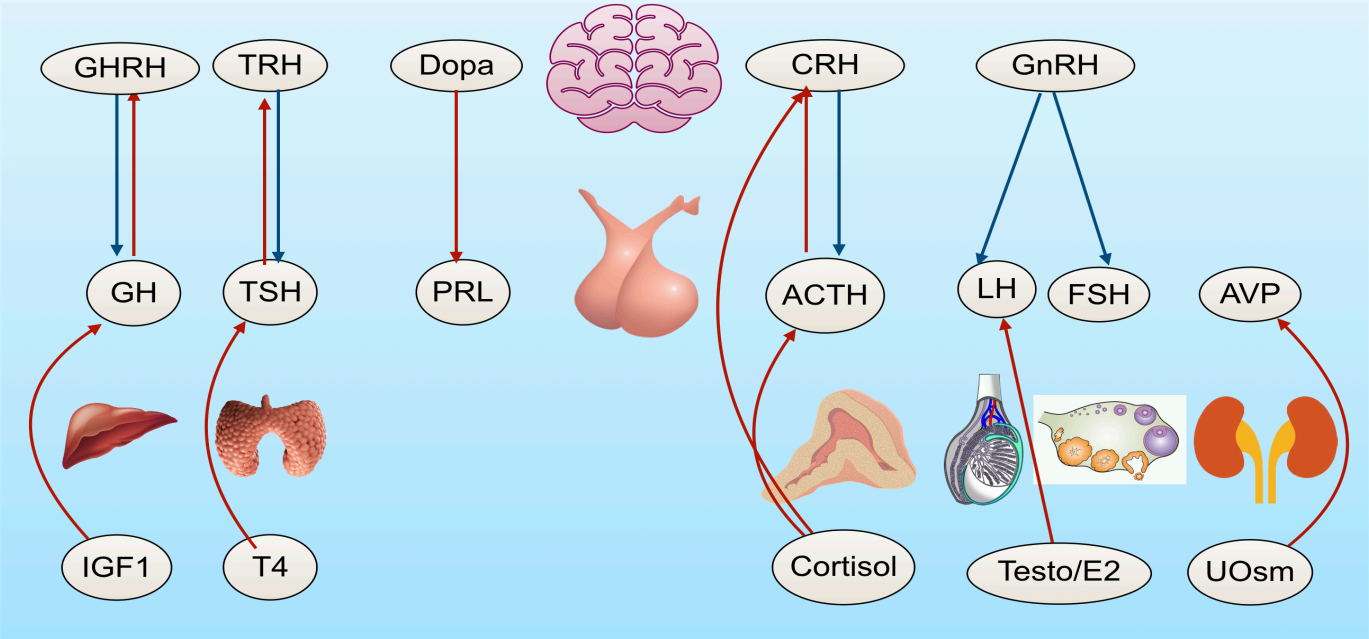
MedEClasses
PEDIATRIC ENDOCRINOLOGY

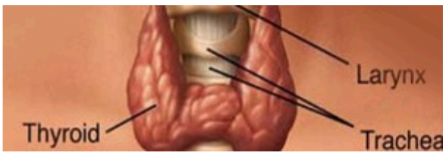


Basic Endocrinology

Growth

Puberty

Thyroid



Bone and Calcium

Electrolyte

Glucose Disorders

Anurag Bajpai

Contributors

Chetankumar Dave Neha Agarwal Riddhi Patel

MedEClasses
PEDIATRIC ENDOCRINOLOGY

Basic Endocrinology

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Preface

Pediatric Endocrinology has witnessed dramatic change 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. Limited exposure during training and lack of learning resources have hindered the spread of the speciality. Pediatric Endocrinology is unique in that comprehensive understanding of physiology is mandatory for successful management. Unfortunately Pediatric Endocrinology textbooks are too voluminous and focused on basic endocrinology to enthuse paediatricians and postgraduate trainees. Practical books provide approach to assessment without 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) was established in 2013 to spread awareness about Pediatric Endocrinology amongst physicians, educationalists and lay public. The society has worked extensively for physician awareness with development of six modules and publications of two books. GROW Society modules have been implemented across the country as 10 full day programs and 100 workshops attended by over 4000 paediatricians. 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 paediatricians and postgraduates in managing children with endocrine disorders. The inaugural six-month online course in Pediatric Endocrinology covering growth, puberty, thyroid, calcium, electrolyte and glucose disorders has been widely subscribed across the globe. This book builds on the resources of the course to provide clinically relevant concise learning on core 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 immense help for neonatologists, intensivists, general pediatricians and pediatric trainees besides pediatric endocrinologists and trainees.

This work would not have been possible without the help of dynamic, young pediatric endocrinologists Drs Chetakumar, Neha and Riddhi. Dr Yuthika's valuable suggestions have gone a long way in bringing the book into its shape. Thanks to Shishir Madan for creating the wonderful favicons that brought the book to life. Hearty thanks for Mr Ravi Shankar Dubey, Hariom, Aditya and Nikhil for making this project seamless and enjoyable.

Happy learning,

Anurag Bajpai, MD, FRACP, SCE

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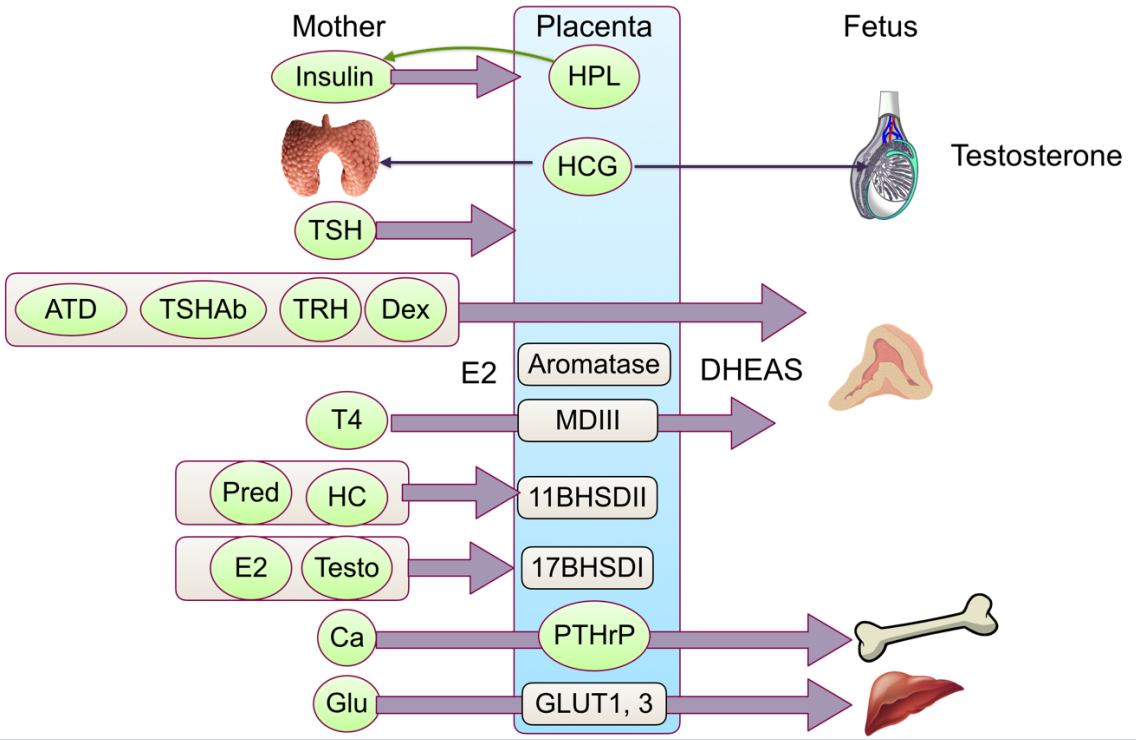

Learning objectives

Understand nuances of endocrine physiology with special emphasis on applied pathophysiology and assessment. Equip yourself to assessment and management of endocrine disorders.

Chapter 1
Endocrine physiology

Anurag Bajpai, Chetankumar Dave

Pediatric Endocrinology is a unique specialty that allows physiological interpretation of disorders and their management. Limited understanding of physiology however complicates assessment and management resulting in labelling of physiological variation as disorders as vice versa.

HORMONE AS A MESSENGER

Hormones are chemicals acting on sites distant from production. They are secreted by endocrine glands into the blood stream. Endocrine effect should be differentiated from paracrine (effect around the area of secretion) and autocrine effects (on the secretory cell). This differentiation is however questioned as a hormone can act in an endocrine, paracrine and autocrine fashion. Thus, calcitriol can act on intestine (endocrine effect), renal tubule (paracrine effect) and on its producer renal cells (autocrine effect). Similarly, chemicals like GLP1, osteocalcin and adiponectin that act at organs far from their source of production can be considered hormones.

ENDOCRINE ORGANS

An endocrine organ comprises of a group of hormone producing cells. The concept of endocrine organs has also evolved with increasing understanding. Thus, duodenum that produces GLP1 in response to ingestion of food causing insulin release from pancreas represents an endocrine organ. Organs previously considered inert like adipose tissue (leptin), stomach (ghrelin), bone (osteocalcin), skin (vitamin D), kidney (renin) are increasingly identified as endocrine organs.

HORMONE EFFECTS

Hormones regulate growth and pubertal development, reproduction, fluid, salt, glucose and calcium homeostasis. They link metabolism with nutritional and environmental status. Hormone action is a concerted process involving development of the endocrine gland, synthesis of hormones, their release, transport, activation, action on receptor, formation of second messenger, inactivation and feed-back regulation (Figure 1.1).

Growth hormone secretion is regulated by stimulatory effects of GHRH and inhibitory effects of somatostatin. Environmental factors (adiposity) and other hormones (thyroxine, Estradiol and insulin) also regulate GH production. Growth hormone is transported in the blood bound to growth hormone binding protein and acts on growth hormone receptor at liver to produce insulin like growth factor 1 (IGF1). IGF1 is bound to IGF binding protein and acts on Type 1 IGF receptor to induce chondrocyte growth.

DEVELOPMENT OF AN ENDOCRINE GLAND

The development of most endocrine glands are dual with a neural and mesodermal component (anterior and posterior pituitary, adrenal cortex and medulla, follicular and parafollicular thyroid). This has significant implications on pathophysiology, Anterior pituitary is regulated by the hypothalamic-hypophyseal portal system sensitive to radiotherapy, posterior pituitary is radioresistant as it represents extension of neurons from hypothalamus. Adrenal cortex produces steroid hormones while medulla synthesizes catecholamines. Gonadal development involves combination of steroidogenic cells from the urogenital ridge and germ cells from the hind gut.

HORMONE SYNTHESIS

Hormone synthesis is a complicated process involving multiple steps. Small hormones (epinephrine, cortisol, aldosterone) are synthesized rapidly in response to signal and not stored as a precursor. Large hormones (GH, PTH, prolactin, insulin, and glucagon) require multiple steps for synthesis and are stored in secretory granules (Figure 1.2). Their levels are regulated at the level of release. Insulin is synthesised as large pre-pro hormone. It is cleaved into pro insulin which is stored in secretory granules. After the signal

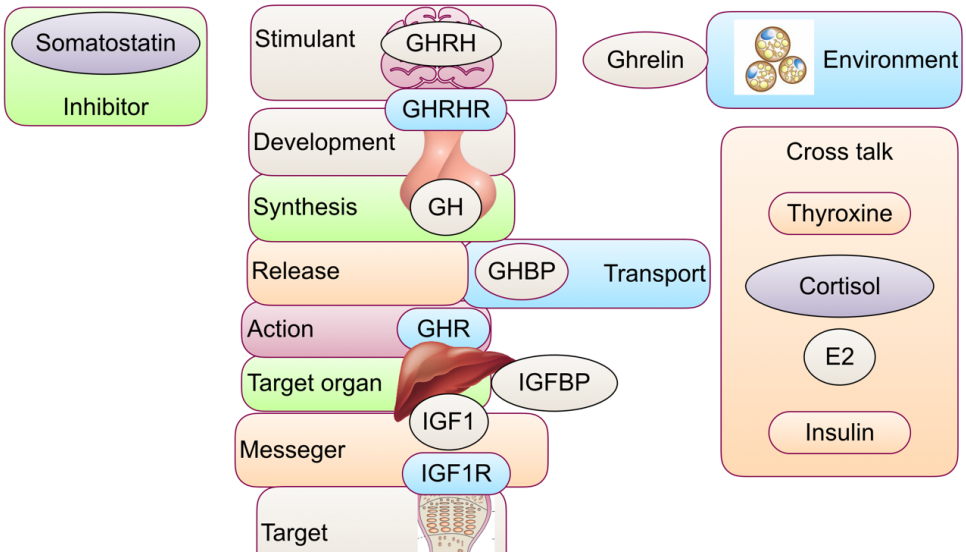

Figure 1.1 GH releasing hormone-GH-IGF1 axis as an example of endocrine regulation

in beta cells, it is cleaved in to insulin and c-peptide via proconvertase and released into circulation.

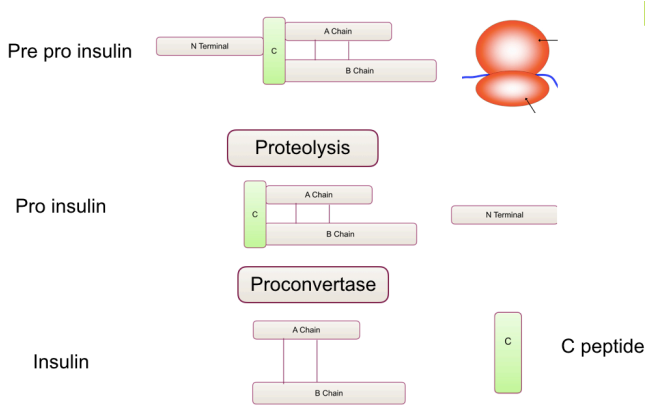

Figure 1.2- The process of insulin synthesis

HORMONE STRUCTURE

Hormone structure has important implications on synthesis, transport, action and metabolism. From a structural point of view hormones can be classified as steroids, peptides and amines (Table 1.1).

Peptide hormones

Peptide hormones are key regulators of growth (GH), adrenal (ACTH), thyroid (TSH), fluid (AVP), gonadal (LH, FSH), calcium (PTH) and glucose (insulin, glucagon) metabolism. Because of hydrophilic nature they transport freely in the circulation without need of a transport protein. This results in their short half-life making their direct assessment difficult. Given their lipophobic nature they do not enter the cells and act on the membrane receptors with immediate action.

Steroid hormones

Steroid hormones play an important role in the regulation of puberty (sex steroids), glucose (cortisol), calcium (calcitriol) and salt homeostasis (aldosterone). They can be produced rapidly and not stored in the cells. They are bound to transport proteins to travel to different parts of the body. Steroid hormones cross the plasma membrane and act on intracellular receptor. This results in a lag period in their action. Local activation (testosterone to estradiol by aromatase, testosterone to dihydrotestosterone by 5ARDII) and inactivation (cortisol to cortisone by 11BHSDII) plays an important role in tissue specificity of steroid hormone action.

Amine hormones

These hormones are small in size and synthesized rapidly. They are involved in regulation of blood pressure (epinephrine), thermogenesis (thyroxine) and fluid homeostasis (AVP). Their actions are mediated by cell surface or nuclear receptors.

Table 1.1- Classification of hormones by structure

Feature	Peptide	Steroid	Amino
Size	Large	Small	Very small
Synthesis	Slow	Slow	Rapid
Storage	Stored in vesicles	Not stored	With other protein
Solubility	Water soluble	Fat soluble	Water soluble
Receptors	Cell membrane	Nuclear	Nuclear and membrane
Half life	Short	Long	Short
Action	Rapid	Slow	Rapid
Transport	Free except GH, IGF1	Bound to SHBG	Bound to TBG, Albumin

HORMONE RELEASE

Hormone release provides an important step for regulation of hormones. Insulin release is triggered by closure of KATP channel in nutrient replete state (increased ATP to ADP ratio) as indicated by increased glucose, aminoacids and lipid levels (Figure 1.3). It is further calibrated by nutrient signals from the intestine (incretin) and nervous system (vagus and sympathetic signals). Same mechanisms are involved in regulation of calcium (PTH) and osmolality (AVP).

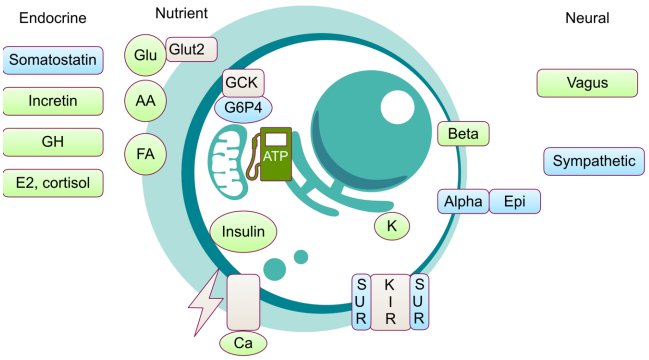

Figure 1.3- Process of insulin release

HORMONE TRANSPORT

Hydrophilic peptide hormones are transported in blood stream without binding proteins. Growth hormone is however bound to extracellular domain of GH receptor while IGF1 is bound to IGF binding protein. Steroid hormones are bound to transport protein (cortisol binding globulin, sex hormone binding globulin, vitamin D binding globulin). Abnormalities in transport proteins have to be considered while assessing hormone levels. Thyroxine is bound to transport proteins (thyroxine binding globulin, albumin and transthyretin). Since hormone action depends on free hormone concentration, fluctuations in transport protein do not alter hormone function. They may however cause diagnostic confusion with inappropriate diagnosis of deficiency with low protein levels (TBG, CBG deficiency, nephrotic syndrome, chronic liver disease) or excess with increased levels (pregnancy, estrogen, oral contraceptives, Table 1.2).

Table 1.2- Conditions affecting transfer protein

Binding protein	Increased	Decreased
TBG	Oral contraceptive, pregnancy, SERM	Androgen, anabolic steroids, cortisol
SHBG	Estrogen, pregnancy, anorexia, hyperthyroidism	Insulin, IGF-1, anabolic steroids, cushing, obesity, hypothyroidism
CBG	Estrogen, pregnancy, OC pills	Newborn, nephrotic syndrome

LOCAL METABOLISM

Site specific action of hormones is mediated by local metabolism and receptor distribution. Local metabolism involves activation (estradiol, T3, dihydrotestosterone) and inactivation (cortisol) of hormones. Conversion of T4 to T3 by monodeiodinase II (MDI II) spares the brain from adverse effects of low thyroid levels during fetal period and illness. Aromatase converts testosterone to estradiol for action at the levels of adipocyte, growth plate, testis, bone and brain in males to allow targeted effects.

HORMONE ACTION

Hormone action involves binding to receptor and production of second messenger. Peptide hormones cannot cross the cell membrane and act on membrane receptors while steroid

hormones cross the cell membrane and act on intracellular receptors regulating transcription and protein synthesis (Figure 1.4). This explains different time course of action for peptide (rapid) and steroid hormones (slow).

Membrane receptors

Membrane receptors possess extracellular and intracellular domain linked to second messenger system (cyclic AMP, inositol triphosphate, calcium-calmodulin system) which trigger subsequent action. The major classes of extracellular receptors include G Protein coupled, tyrosine kinase and cytokine receptors.

G-protein coupled receptors

G-protein coupled receptors are the largest family of receptors utilised by most peptide hormones. They contain a N-terminal extracellular domain, seven transmembrane spanning alpha helices and the C-terminal intracellular region (Figure 1.5). Binding of hormone with its receptor promotes association with a heterotrimeric G protein stimulating dissociation of guanosine diphosphate (GDP) from the α-subunit, allowing GTP to bind to the unoccupied site. G protein–coupled receptors act through the cyclic AMP signal pathway and the phosphatidylinositol signal pathway.

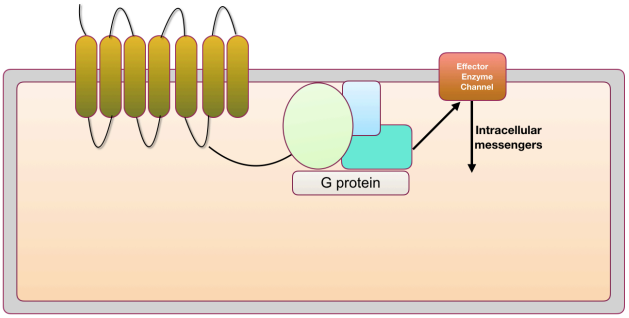

Figure 1.5- Action of G Protein coupled receptor

Type 1 cytokine receptors

Certain hormones like growth hormone, prolactin, and leptin mimic cytokine action and act on type 1 cytokine receptor. These receptors require homodimerization for activation (Figure 1.6). Activated receptors stimulate Janus associated kinase (Jak kinases) to phosphorylate tyrosine residues on the cytoplasmic region of the receptors.

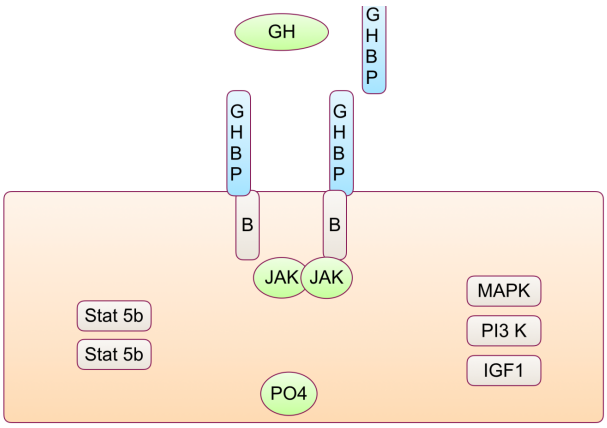

Figure 1.6- GH acting through Type 1 cytokine receptor

Tyrosine kinase receptors: These receptors are connected to tyrosine kinase. Binding of the hormone to the receptor transfers phosphate from adenosine triphosphate (ATP) to tyrosine residues of the receptor stimulating second messengers (Figure 1.7).

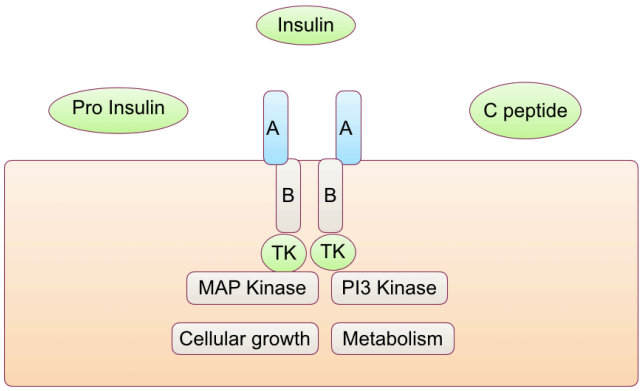

Figure 1.7- Mechanism of action of insulin receptor

Intracellular receptors

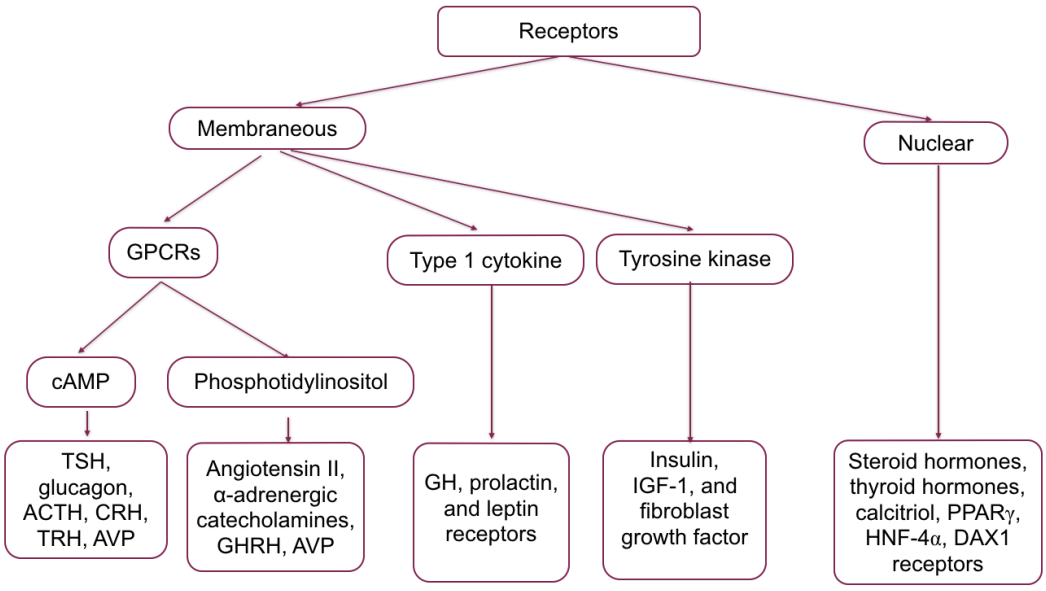

Figure 1.4 Classification of Hormone receptors

Steroids, vitamin D and thyroxine traverse the cell membrane and act on intracellular receptors. The ligand-receptor complex binds to hormone response element stimulating transcription (Figure 1.8). Steroids like estrogen and glucocorticoids also act on cell membrane receptors with rapid response. Many hormones bind to more than one receptors causing myriad effects. Estradiol binds to ER alpha and beta besides the membrane receptor producing organ specific effects. This Differential affinity of ligands to a receptor determines its effect. Both DHT and testosterone bind to the same androgen receptor though the affinity is much higher for DHT.

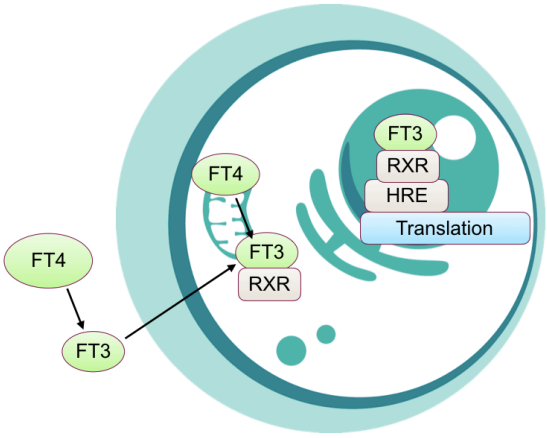

Figure 1.8– Mechanism of action of Thyroid receptor

HORMONAL REGULATION

Hormone levels are maintained within a narrow range by a complex interplay of regulators, hormone sensing and feedback.

Regulator

Most hormones are regulated by stimulators and inhibitors. The predominant tone of regulation predicts the likely etiology of a disorder. Anterior pituitary hormones (GH, TSH, ACTH, LH, FSH) are stimulated by hypothalamic peptides with the exception of prolactin that is inhibited by dopamine. Hypothalamic lesions therefore cause hypopituitarism with hyperprolactinemia. Prolactin levels are low in pituitary lesions making prolactin a discriminatory investigation in hypopituitarism. Regulatory agents represent a therapeutic option with the use of inhibitors in excess (somatostatin in hyperinsulinism) and stimulants in deficiency states (kisspeptin in hypogonadotropic hypogonadism).

Hormone sensing

Appropriate sensing of hormone effect by target organs or sensors is of paramount importance for hormonal regulation. Abnormal sensing of hormonal effect results in unregulated hormonal levels and pathology.

Hormonal feedback

Feedback regulation is critical part of hormonal regulation. Excess hormone effect is sensed by the body triggering negative feedback to bring its level back in the normal range. Most feedback processes inhibit the trophic hormone (negative feedback), positive feedback is characteristic of proliferative phase of menstrual cycle where elevated estradiol levels further enhance LH levels triggering ovulation. Feedback mechanism emphasizes the need for interpretation of hormonal levels in the context of its effect.

Hormonal metabolism

Hormone metabolism plays an important role in termination of its actionIncreased metabolism can unmask covert deficiency of the hormone.

FURTHER READING

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Learning Points

- Hormones are substances produced at one part of the body that act on distant sites.
- Chemical structure of hormones predict their metabolism, action and time profile.
- Trasnport proteins are important determinants of hormone metabolism and action.
- Hormone action is mediated by receptors.
- Hormone regulation involves interaction of hormone regulators, feedback and sensing.