ENDOCRINE BIOCHEMISTRY

LECTURE 2

Structure of Hormones by Location

Slide 1 | Structure of Hormones by Location

Hormones are not only classified by their chemical structure but also by their anatomical origin, which is intimately tied to their function and regulation.

Slide 2 | Hypothalamus

The major endocrine glands, hypothalamus, pituitary, anterior and posterior, thyroid, parathyroid, pancreas, adrenal, cortex and medulla, gonads, and pineal gland, each produce a characteristic set of hormones regulated by specific feedback mechanisms. Understanding the anatomical origin of a hormone is essential for clinical localization of disease. A pituitary adenoma produces excess hormones characteristic of the anterior pituitary G-H, prolactin A-C -T-H, while a hypothalamic lesion affects releasing and inhibiting hormones.

The adrenal medulla produces catecholamines, while the cortex produces steroids, each with distinct clinical syndromes. This anatomical perspective is crucial for diagnosis and management. Primary adrenal insufficiency, Addison's disease, results from adrenal cortex dysfunction, causing low cortisol and aldosterone with high A-C-T-H, while secondary adrenal insufficiency results from pituitary dysfunction, causing low cortisol and low A-C-T-H.

The anatomical source determines the pattern of laboratory abnormalities and the appropriate therapeutic approach. The hypothalamus produces small peptides or catecholamines that regulate the anterior pituitary. Growth hormone-releasing hormone, GHRH, exists in 40 and 44 amino acid forms and stimulates GH secretion.

Somatostatin, 14 and 28 amino acids, inhibits GH and TSH secretion. Dopamine, a catecholamine, inhibits prolactin secretion, forming the basis for using dopamine agonists, bromocryptine, to treat prolactinomas. Corticotropin-releasing hormone, CRH, is a 41 amino acid polypeptide that stimulates A-C-T-H, which in turn stimulates cortisol production.

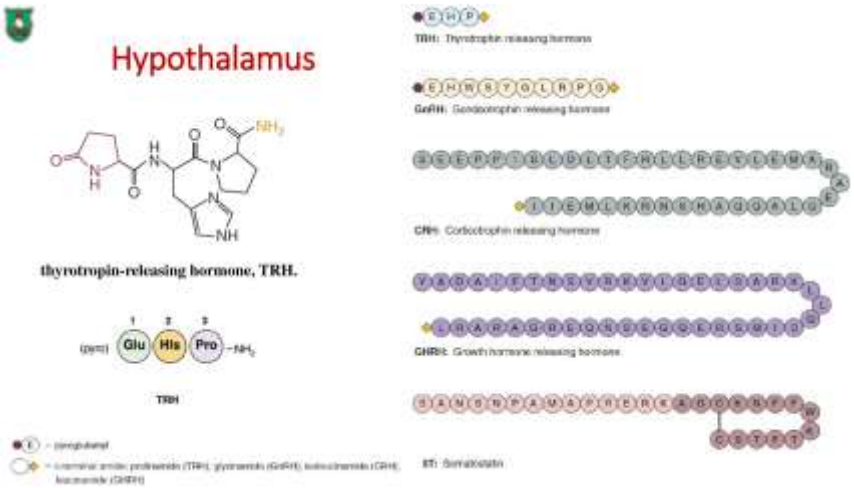
Gonadotropin-releasing hormone, GNRH, is a 10 amino acid decapeptide that stimulates LH and FSH secretion, its pulsatile release is essential, and continuous administration paradoxically suppresses LH-FSH, a phenomenon exploited therapeutically with GNRH agonists for prostate cancer and endometriosis.

Slide 3 | Hypothalamic Peptide Structures

Thyrotrophin-releasing hormone, TRH, is a tripeptide, the smallest hypothalamic hormone, that stimulates TSH and prolactin secretion. Understanding these hormones is essential because they represent the first level of the neuroendocrine axis, hypothalamic lesions can cause hypopituitarism by disrupting multiple releasing hormones simultaneously. The amino acid sequences of hypothalamic hormones, TRH, GNRH, CRH, GHRH, and somatostatin, illustrate that these are peptides of varying lengths, from the tripeptide TRH to the 41 amino acid CRH.

TRH is P-gluhispro-NH2, where P-glu is pyroglutamic acid that protects the N-terminus from degradation. GNRH is a decapeptide with the sequence P -gluhispro-NH2. These small peptides are rapidly degraded by gastrointestinal proteases, so they must be given by injection if used therapeutically, however, synthetic analogs resistant to degradation, e.g., luprolide, a GNRH analog, have been developed.

The sequences reveal evolutionary conservation. TRH is identical across many species, highlighting its fundamental importance. Somatostatin exists in 14 and 28 amino acid forms, the longer form, somatostatin-28, is more active in the gastrointestinal tract, while the shorter form, somatostatin-14, is more active in the hypothalamus and pancreas, exemplifying how post-translational processing generates tissue-specific functions.



Slide 4 | Anterior Pituitary

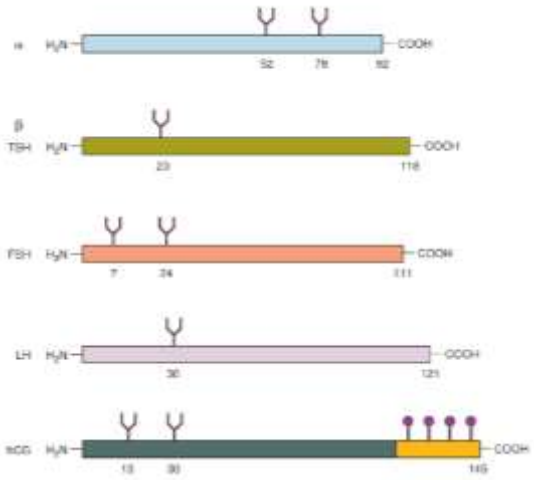
The anterior pituitary produces six major hormones. Growth hormone, GH, somatotropin, is a 191 amino acid protein, with a 176 amino acid variant from alternative splicing, and is the most abundant anterior pituitary hormone, with profound effects on growth and metabolism. Prolactin, PRL, is a 198 amino acid protein structurally related to GH.

The glycoprotein hormones, FSH, LH, and TSH, are heterodimers composed of an identical alpha subunit, 92 amino acids, and a unique beta subunit. This shared alpha subunit explains why measuring total alpha subunit is not diagnostically useful, specific immunoassays directed against the unique beta subunits are required. The beta subunits confer biological specificity, TSH binds to the TSH receptor, while LH binds to the LH receptor.

Slide 5 | Anterior Pituitary - Glycosylation

Post-translational glycosylation affects the folding, secretion, and bioactivity of these hormones, more highly glycosylated isoforms of FSH have longer half-lives but lower receptor binding affinity. This is clinically important in conditions like menopause, where the ratio of glycoforms changes, potentially affecting immunoassay accuracy. The anterior pituitary also produces propiomelanocortin, POMC, a prohormone cleaved to produce ACTH, 39 amino acids, and other peptides.

Glycosylation is a critical post-translational modification for the anterior pituitary glycoprotein hormones. Two main types exist, N-glycosylation, on asparagin residues, and O-glycosylation, on serine or threonine residues. N-glycosylation is more common and occurs in the ER, with glycan chains modified in the Golgi before secretion.



N-glycosylation is essential for proper protein folding, intracellular trafficking, and secretion, without it, the hormone may misfold and be retained. The specific glycan composition, including sialic acid, fucose, galactose, and N-acetylglucosamine, affects half-life and receptor binding affinity. Sialylation increases plasma half-life by reducing liver clearance, while hormones with less sialylation have shorter half-lives but higher biological activity per molecule.

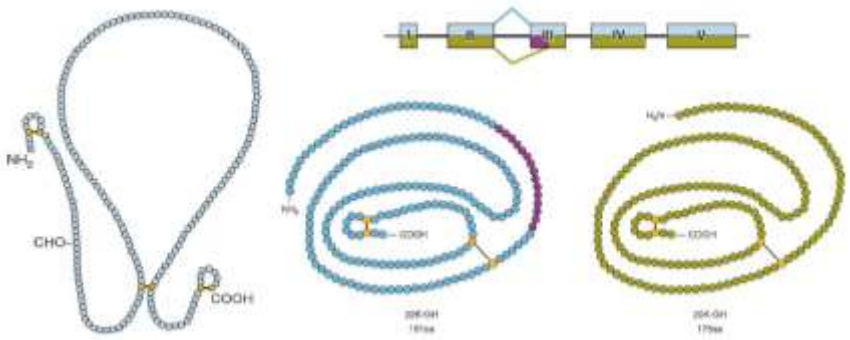
O-glycosylation influences hormone stability and clearance. Understanding glycosylation is clinically relevant because some patients with pituitary adenomas may have normal hormone levels but abnormal bioactivity due to altered glycosylation patterns, and certain immunoassays may not detect all isoforms, leading to false negative results.

Slide 6 | Anterior Pituitary - GH & Prolactin

Growth hormone, GH, and prolactin, PRL, are structurally and evolutionarily related, both being single-chain polypeptides of approximately 22-keta, GH, and 23-keta, PRL. They share a common 4-helix bundle structure characteristic of the cytokine-slash-hematopoietin protein family. This structural homology explains why prolactin can have growth-promoting effects at very high concentrations.

GH exists in multiple isoforms, the most abundant is the 22-keta form, with a smaller 20-keta variant from alternative splicing having reduced bioactivity. GH is not glycosylated in humans, but prolactin can be glycosylated, and glycosylated prolactin is less bioactive but has a longer half-life. Intermolecular disulfide bonds are critical for maintaining the correct three-dimensional structure, their reduction inactivates the hormone.

This structural information is important for pharmaceutical production, recombinant human GH, somatropin, must have the correct amino acid sequence and disulfide bonds to be therapeutically effective. Clinically, this explains why patients with GH deficiency respond to recombinant GH therapy, while patients with receptor mutations, e.g., Laron's syndrome, do not.

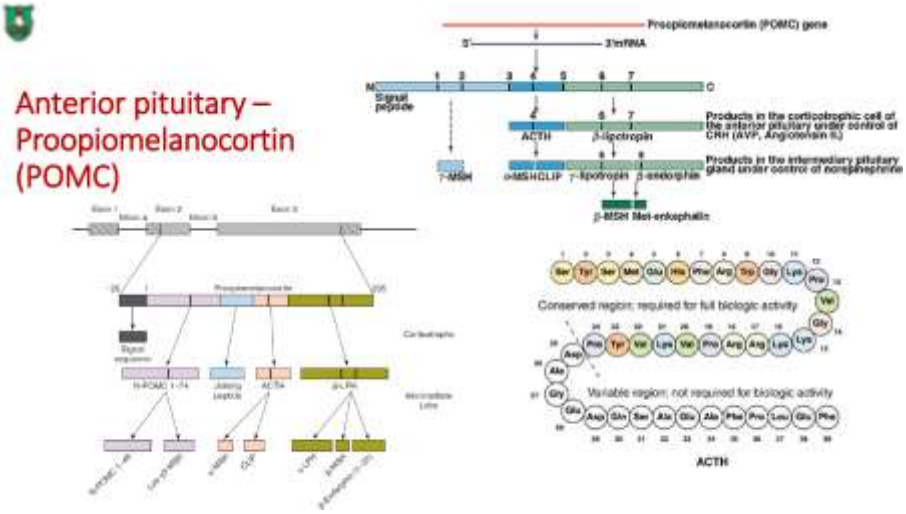


Slide 7 | Anterior Pituitary - Proopiomelanocortin (POMC)

POMC is a classic prohormone differentially processed in a tissue-specific matter to produce multiple biologically active peptides. The POMC gene on chromosome 2 encodes a 241-amino acid precursor synthesized in the anterior pituitary, hypothalamus, and other tissues. In the anterior pituitary, prohormone convertase PC1-3 cleaves POMC primarily to ACTH-39 amino acids and β-lipotropin, β-LPH-91 amino acids.

In the hypothalamus and skin, PC2 further cleaves ACTH to α-MSH, 13 amino acids, and CLIP, and β-LPH to β-endorphin, 31 amino acids, and γ-LPH. This tissue-specific processing means the same gene produces different hormones in different tissues. Clinically, in Addison's disease, loss of cortisol feedback increases POMC secretion, leading to increased ACTH and α-MSH production, causing characteristic hyperpigmentation.

In Cushing's disease, pituitary ACTH-secreting adenoma, patients may also experience hyperpigmentation. In congenital POMC deficiency, patients have adrenal insufficiency, hypopigmentation, due to lack of α-MSH, and obesity, due to loss of anorexigenic α-MSH signaling in the hypothalamus. This demonstrates how a single gene product can have multiple, seemingly unrelated effects.

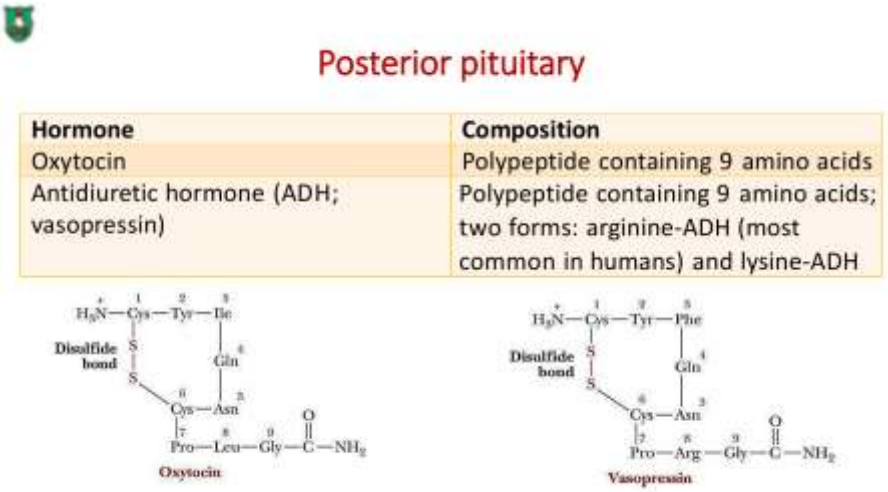


Slide 8 | Posterior Pituitary

Posterior pituitary hormones, oxytocin and antidiuretic hormone, ADH, vasopressin, are unique in that they are synthesized in the hypothalamus, supraoptic and paraventricular nuclei, and transported down the hypothalamal tract for storage and release from the posterior pituitary. Both are known as peptides, 9 amino acids, differing in only 2 amino acids. Oxytocin, Cysteryl-Glnas-N-Cys-Pro-Lu-Gly -NH2, stimulates uterine contraction during labor and myoepithelial cells during lactation for milk ejection, and plays a role in social bonding.

ADH, Cysteryl-Glnas-N-Cys-Pro-Lu-Gly -NH2 in humans, arginine-vasopressin, regulates water balance via V2 receptors in renal collecting ducts, increasing water reabsorption through aquaporin-2 insertion via the CAMP pathway, it also has vasoconstrictor effects via V1 receptors at high concentrations. Clinically, ADH deficiency causes diabetes insipidus, poliuria and polydipsia, which can be central, hypothalamic-slash-pituitary dysfunction, or nephrogenic, renal resistance. Excess ADH causes SIADH, leading to hyponatremia from water retention.

Oxytocin is used therapeutically to induce labor and manage postpartum hemorrhage.

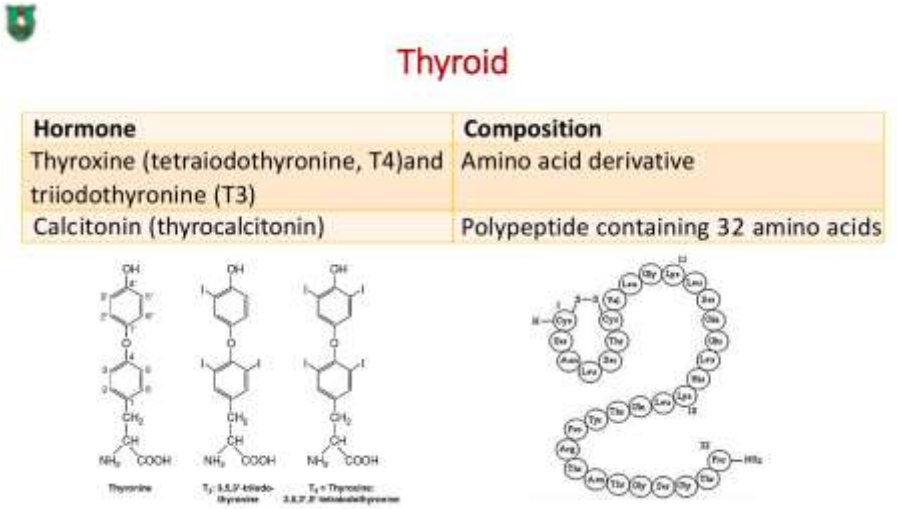


Slide 9 | Thyroid

The thyroid gland produces two major classes of hormones, iodothyronines, T3 and T4, and calcitonin. Thyroxine, T4, contains 4 iodine atoms, while triiodothyronine, T3, contains 3. T4 accounts for 90% of thyroid secretion, while T3 accounts for 10%, but T3 is 3-5 times more potent and is the biologically active form.

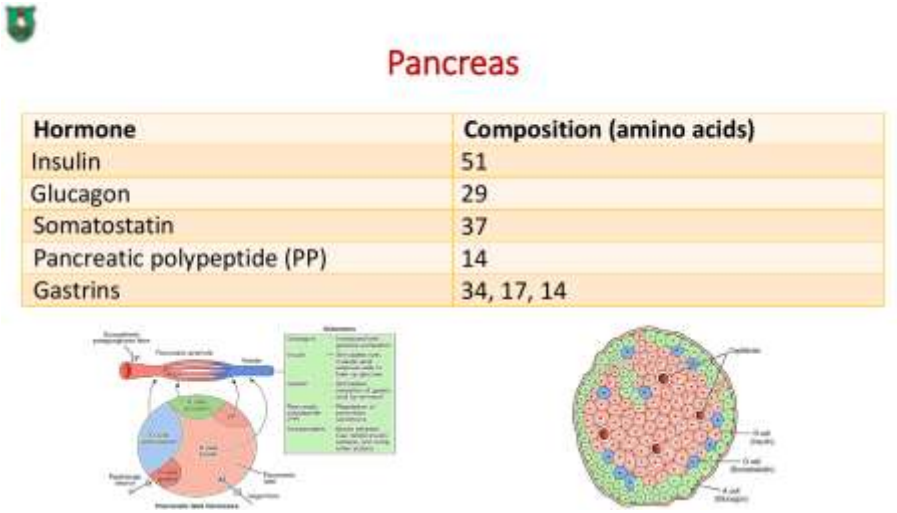
The majority of T3 is produced peripherally through deiodination of T4 by deiodinase enzymes in the liver, kidney, and skeletal muscle, allowing tissue-specific control of thyroid hormone activity. Thyroid hormones are essential for normal growth, development, and metabolism, they increase basal metabolic rate, stimulate heat production, and enhance catecholamine responsiveness. Calcitonin, thyrocalcitonin, is a 32-amino acid polypeptide produced by periphallicular C-cells, it lowers serum calcium by inhibiting osteoclast activity, but its physiological role in humans is minor, patients after total thyroidectomy do not develop significant calcium abnormalities.

Clinically, calcitonin is primarily important as a tumor marker for medullary thyroid carcinoma MTC, which arises from C-cells and secretes large amounts of calcitonin, making serum calcitonin measurement a sensitive screening test and monitoring tool for MTC.



Slide 10 | Pancreas

The endocrine pancreas, islets of Longerhans, produces insulin, glucagon, somatostatin, and pancreatic polypeptide, while intestinal L -cells produce the incretin hormone GLP-1, functionally integrated with pancreatic physiology.



Slide 11 | Pancreas - Insulin & Related Peptides

Insulin is a 51-amino acid hormone with A-chain, 21 amino acids, and B-chain, 30 amino acids, linked by disulfide bonds, it is the primary anabolic hormone, promoting glucose uptake, glycogen synthesis, lipogenesis, and protein synthesis. Glucagon is a 29-amino acid hormone from alpha cells, opposing insulin by promoting glycogen breakdown, gluconeogenesis, and lipolysis. Somatostatin from delta cells is a 37-amino acid hormone in the pancreas, versus 14 amino acids in the hypothalamus, that inhibits insulin and glucagon secretion via paracrine effects.

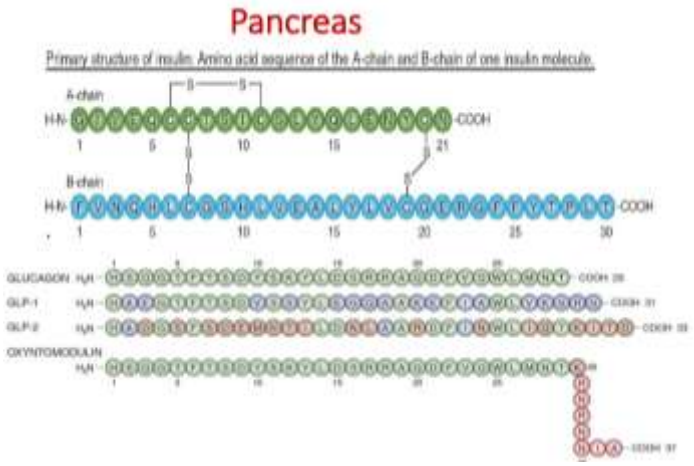
Pancreatic polypeptide, 14 amino acids, regulates exocrine-slash -endocrine secretion and appetite. The insulin-glucagon balance is critical for glucose homeostasis, in diabetes, this balance is disrupted. C-peptide, secreted equimolarly with insulin, allows assessment of beta-cell function, low levels indicate insulin deficiency, type 1 diabetes, while normal or high levels indicate insulin resistance, type 2 diabetes.

The incretin system links the gut to pancreatic function, GLP-1, 30-31 amino acids from intestinal L-cells, accounts for 50-70% of postprandial insulin secretion, suppresses glucagon, induces satiety, and delays gastric emptying. GLP-1 is rapidly degraded by DPP-4, half-life 1-2 minutes, but synthetic GLP -1 receptor agonists, e.g., semaglutide-slash-azempic, are DPP-4 resistant and have become first -line therapies for type 2 diabetes and obesity, with demonstrated cardiovascular and renal benefits. Insulin is synthesized as preproinsulin, containing a 23 amino acid signal peptide that directs the protein to the ER, where it is cleaved to proinsulin.

Proinsulin consists of the A-chain, 21 amino acids, B-chain, 30 amino acids, and the connecting C-peptide. Three disulfide bonds connect the chains, two between A and B chains, and one intermolecular within the A-chain. In the Golgi, prohormone convertases, PC-1-slash -3 and PC-2, and carboxypeptidase cleaves C -peptide, yielding mature insulin.

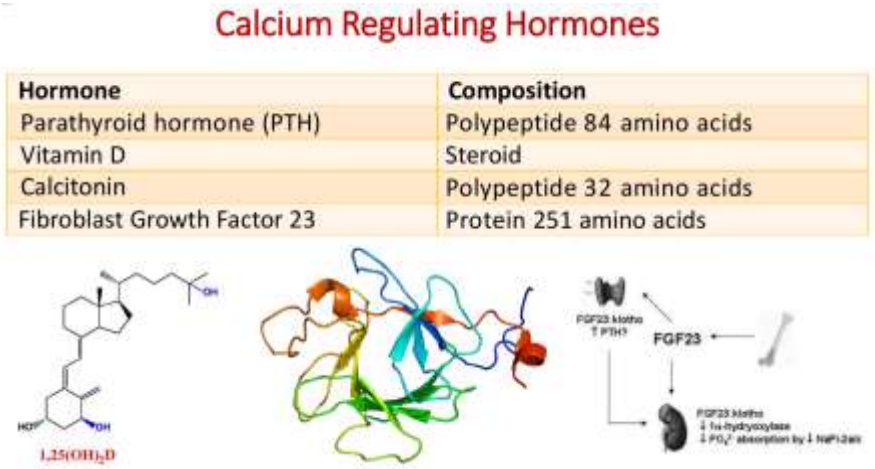
C-peptide is biologically inactive but is secreted equimolarly with insulin and has some vasodilatory and anti-inflammatory effects. C-peptide measurement is a valuable clinical tool for assessing endogenous insulin secretion, even in patients receiving exogenous insulin. In type 1 diabetes, C-peptide levels are very low or undetectable, beta-cell destruction.

In type 2 diabetes, C-peptide levels are normal or elevated, insulin resistance with compensatory hyperinsulinemia. Synthetic insulins are often modified to alter pharmacokinetics, for example, insulin Lispro has a reversed proline lysine sequence at positions B28-B29, reducing hexamer formation and accelerating absorption, making it rapid acting.



Slide 12 | Calcium Regulating Hormones

Calcium homeostasis is regulated by four major hormones, parathyroid hormone, PTH, vitamin D, calcitriol, calcitonin, and fibroblast growth factor 23, FGF23. PTH is an 84-amino acid polypeptide from parathyroid chief cells, it is the primary hormone raising serum calcium by stimulating bone resorption, increasing renal calcium reabsorption, decreasing phosphate reabsorption, and indirectly increasing intestinal calcium absorption via vitamin D activation. Vitamin D, 1,25-dihydroxycholic calciferol, calcitriol, is a steroid hormone derived from cholesterol, its synthesis requires 25-hydroxylation in the liver and 1 -alpha-hydroxylation in the kidney, stimulated by PTH.



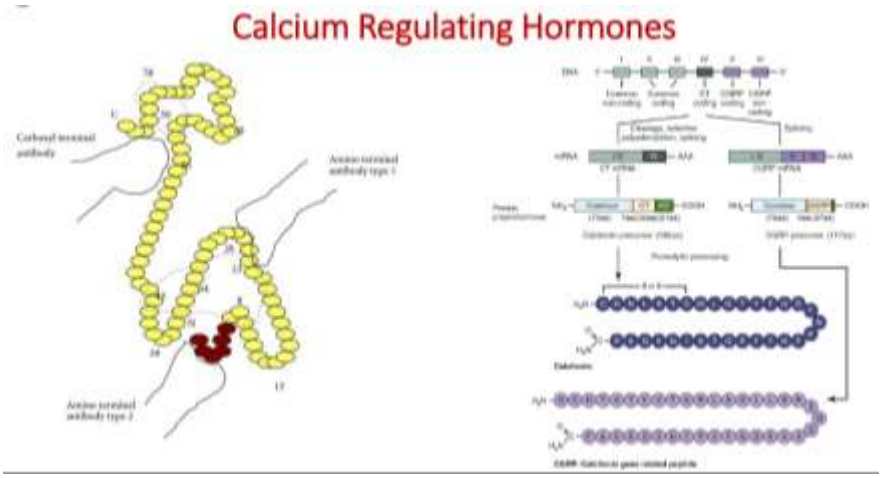
Slide 13 | Calcium Regulating Hormones - Peptide Processing

Calcitriol increases intestinal calcium and phosphate absorption and affects bone and kidney. Calcitonin is a 32-amino acid polypeptide from thyroid C cells that lowers serum calcium by inhibiting osteoclast activity, but its role in human calcium homeostasis is relatively minor. FGF23 is a 251-amino acid protein from osteocytes that decreases serum phosphate by inhibiting renal phosphate reabsorption and reducing vitamin D activation, elevated FGF23 causes hypophosphatemic disorders like X-linked hypophosphatemia.

Understanding this system is essential for diagnosing and managing primary hyperparathyroidism, elevated PTH and calcium, vitamin D deficiency, low calcium, high PTH, low vitamin D, and hypocalcemia of various etiologies. The figure illustrates the complex interplay between PTH, vitamin D, calcitonin, and FGF23 in regulating calcium and phosphate homeostasis, showing hormone sources, targets, and feedback loops. Calcium homeostasis is maintained by a negative feedback loop, low serum calcium stimulates PTH secretion, PTH acts on bone and kidney to raise calcium and stimulates renal 1-alpha-hydroxylase, increasing active vitamin D production, vitamin D increases intestinal calcium absorption, rising calcium levels suppress PTH secretion.

This tight regulation is essential because calcium is critical for muscle contraction, nerve transmission, blood coagulation, and bone health. Phosphate homeostasis is less tightly regulated but is important for bone mineralization and cellular metabolism. FGF23 and PTH have opposing effects on phosphate, both promoting phosphate excretion, with FGF23 also inhibiting vitamin D activation.

The balance is crucial, in chronic kidney disease, phosphate retention leads to secondary hyperparathyroidism, managed with phosphate binders and vitamin D analogues. Understanding this system is fundamental to managing osteoporosis, hypercalcemia of malignancy, and parathyroid disorders.



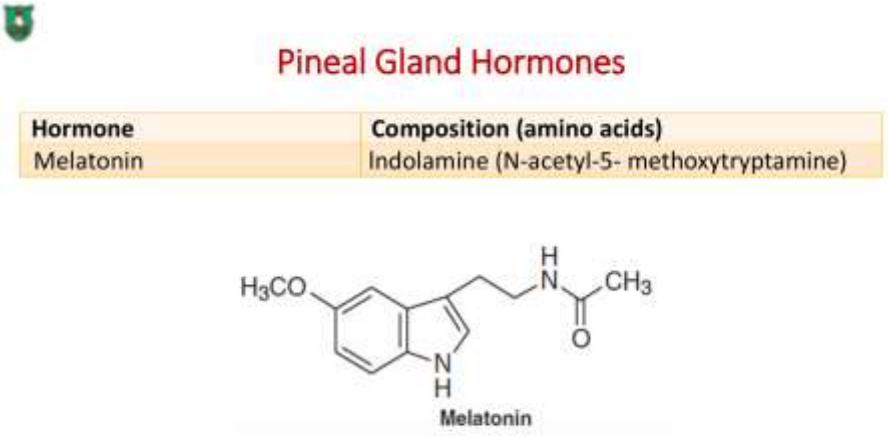
Slide 14 | Pineal Gland Hormones

Melatonin is the primary pineal hormone, an indolamine derived from tryptophan. Its synthesis involves conversion of tryptophan to serotonin, then to N-acetylserotinin, followed by methylation by hydroxyindolomethyltransferase hiamd, to produce melatonin. Synthesis and secretion are driven by the circadian clock in the suprachiasmatic nucleus, SCN.

The SCN receives retinal input about light exposure. In darkness, the SCN signals the pineal gland through a sympathetic pathway, SCN paraventricular nucleus superior cervical ganglion norepinephrine release onto pinealocytes. Norepinephrine activates beta-adrenergic receptors, increasing CAMP, which activates serotonin N-acetyltransferase, NAT, the rate-limiting enzyme.

Thus, melatonin peaks at night and is suppressed by light. Melatonin acts on MT1 and MT2 receptors in the SCN and other tissues to entrain circadian rhythms, promoting sleep. Clinically, melatonin is used as a supplement for jet lag, shift-work sleep disorder, and insomnia, and it has antioxidant properties.

Understanding melatonin physiology is important for counseling patients on sleep hygiene and the effects of light exposure on health.



Slide 15 | Adrenal and Sexual Glands' Hormones

The adrenal glands and gonads both produce steroid hormones. The adrenal cortex produces glucocorticoids, primarily cortisol, mineralocorticoids, primarily aldosterone, and adrenal androgens, primarily DHEA. These are synthesized from cholesterol and regulated by the HPA axis, cortisol, and renangiotensin aldosterone system, aldosterone.

The adrenal medulla produces catecholamines, norepinephrine and epinephrine, from tyrosine, stored in chromaffin granules. The gonads produce sex steroids, testes, Leydig cells, produce testosterone, ovaries, granulosa cells, produce estrogens, estradiol, and the corpus luteum produces progesterone. Sex steroid production is regulated by the HPG axis, GnRH stimulates LH and FSH, which stimulate gonadal steroidogenesis.

Clinically, congenital adrenal hyperplasia CAH causes overproduction of adrenal androgens and underproduction of cortisol and aldosterone, leading to virilization in females and salt-wasting crises. Adrenal Insufficiency, Addison's disease, causes cortisol and aldosterone deficiency, with hyperpigmentation, hypotension, and electrolyte imbalances. Pheochromocytoma, an adrenal medulla tumor, secretes excessive catecholamines, causing paroxysmal hypertension, palpitations, and sweating.

Understanding adrenal and gonadal anatomy and function is essential for diagnosing and treating these disorders.

End of Lecture 2