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MEDICAL NOTES POWERHOUSE

Medical Notes Powerhouse

The Complete High-Yield Notes for NEET SS & INI SS-ET

Endocrinology, Neurology & Psychiatry

08 VOLUME
of 10 · Volume VIII · CH 388–468

81 CHAPTERS

8 SECTIONS

10 VOLUME SET

SECTIONS IN THIS VOLUME

- Endo — Pituitary & Thyroid
- Endo — Adrenal & Reproduction
- Obesity & Diabetes
- Bone & Metabolism
- Inherited Metabolic Disorders
- Neuro — Cerebrovascular
- Neuro — Neurodegenerative
- Neuro — PNS & Psychiatry

Sources Harrison's Principles of Internal Medicine, 22nd Edition

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Endocrinology — Pituitary & Thyroid

Pituitary tumours, neurohypophysis, thyroid function and thyroid disease

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CH 388 · Approach to Endocrine Disorders

Conceptual framework for endocrinology — scope, three pathologic mechanisms (excess, deficiency, resistance), and prevalence of common adult endocrine disorders. Foundation chapter for the entire endo block.

Endocrinology — Framework

- **Precision medicine** applied early — hormone levels titrate treatment.
- Goal = maintain/restore homeostasis via precise **hormone measurement**.
- **Endocrine** (Starling) = secreted internally; *vs* exocrine = secreted into lumen.
- **Hormone** (Gk = "to set in motion") — dynamic action + feedback control.
- Deficiency → **physiologic replacement**. Excess → **surgical removal of adenoma** or medical suppression.

Scope — beyond classic glands

- **Classic glands**: pituitary, thyroid, parathyroid, pancreatic islets, adrenals, gonads.
- **Brain** → peptide hormones → **neuroendocrinology**; CNS controls pituitary via hypothalamic releasing factors.
- **Heart** → **ANP** (natriuresis at kidney — classic endocrine action).
- **Kidney** → **EPO**, renin-angiotensin; target for PTH, mineralocorticoids, **FGF23**, vasopressin.
- **GI tract** → GLP-1, CCK, **ghrelin**, gastrin, secretin, VIP (carcinoid/islet tumors → syndromes).
- **Adipose** → **leptin** (appetite), adiponectin, resistin.
- **Immune ↔ endocrine**: cortisol = immunosuppressant; cytokines/ILs modulate pit/adrenal/thyroid/gonads.
- **GH + leptin receptors = cytokine receptor family. GPCRs** mediate peptide hormones (also vision, smell, NT).

Three Pathologic Mechanisms

- (1) **Hormone excess** · (2) **Hormone deficiency** · (3) **Hormone resistance**.

Table 388.1 — Causes of endocrine dysfunction (condensed)

Mechanism	Sub-cause	Examples
Hyperfunction	Neoplastic — benign	Pituitary adenoma, primary hyperPTH, autonomous thyroid/adrenal nodule
	Neoplastic — malignant	Adrenal Ca, medullary thyroid Ca, carcinoid
	Ectopic	**Ectopic ACTH, SIADH**
	Genetic	**MEN1, MEN2**
	Autoimmune	**Graves' disease**
	Iatrogenic	Cushing's syndrome, hypoglycemia
	Infectious/inflammatory	**Subacute thyroiditis**
	Activating R mutations	LH, TSH, Ca^{2+}, PTH receptors; **Gsα**
Hypofunction	Autoimmune	**Hashimoto's, T1DM, Addison's**, polyglandular failure
	Iatrogenic	Radiation/surgical hypopit, hypothyroid
	Infect/inflamm	Adrenal TB, hypothalamic sarcoidosis
	Hormone mutations	GH, LHβ, FSHβ, vasopressin
	Enzyme defect	**21-hydroxylase deficiency**
	Developmental	**Kallmann's, Turner's**, transcription factors
	Nutritional	Vit D deficiency, iodine deficiency
	Hemorrhage/infarct	**Sheehan's**, adrenal infarction
Resistance	Membrane R mutation	GH, vasopressin, LH, FSH, ACTH, GnRH, GHRH, PTH, leptin, Ca^{2+}
	Nuclear R mutation	AR, TR, VDR, ER, GR, PPARγ

Mechanism	Sub-cause	Examples
	Signaling pathway	**Albright's hereditary osteodystrophy**
	Postreceptor	**T2DM, leptin resistance**

Hormone Excess — Key Concepts

- Mostly **benign adenomas** (parathyroid, pituitary, adrenal) — well-differentiated, retain secretion.
- **Defective set point** for feedback. e.g., Cushing's disease: ACTH suppresses only at **high-dose dexa**.
- Similar set-point defect in **parathyroid adenoma** + **autonomous thyroid nodule**.

MEN syndromes (Chap. 400)

Table 388.2 — MEN1 vs MEN2

Feature	MEN1	MEN2
Gene	**MEN1** (11q13) — menin	**RET** protooncogene — RTK
Type of mutation	**Tumor suppressor**; 2-hit (retinoblastoma paradigm)	**Activating**; single allele
Tumors	Parathyroid · Pancreatic islet · Pituitary (**3 Ps**)	Medullary thyroid Ca · Pheo · HyperPTH
Screening implication	Family genetic testing	**Prophylactic thyroidectomy** if RET+

Activating mutations — GPCRs / Gsα

- Located in **transmembrane domains** → constitutive Gsα coupling → ↑cAMP **without hormone**.
- **LH-R activating** → male-limited **familial precocious puberty** (premature Leydig testosterone).
- **Gsα activating — early in development** → **McCune-Albright** syndrome.
- **Gsα activating — somatotrope only** → **GH-secreting adenoma / acromegaly**.
- **Graves'** = TSH-R **stimulating autoantibody** mimics activating mutation; ↑thyroid hormone.

Hormone Deficiency

- Mechanism = **glandular destruction** (autoimmune, surgical, infection, inflammation, infarct, hemorrhage, tumor).
- Common autoimmune: **Hashimoto's** (thyroid), **T1DM** (β cell).
- Also: hormone mutations, receptor mutations, transcription factor defects, enzyme defects, channelopathies.

Hormone Resistance

- Defect in receptor / signaling pathway → **↑ hormone level + ↓ action** = hallmark biochem.
- **Severe inherited** forms — receptor or pathway mutations.
- **Complete androgen insensitivity**: XY genotype + **female phenotype + ↑ LH + ↑ testosterone**.
- **Acquired functional resistance** — common, reversible:
  - Examples:
    - **Insulin resistance** — T2DM.
    - **Leptin resistance** — obesity.
    - **GH resistance** — catabolic states.
  - Mechanism = **receptor downregulation + postreceptor desensitization**.

♥ NEET SS HIGHLIGHTS

♥ **MEN1** (11q13, menin, tumor suppressor) — **3 Ps**: Parathyroid · Pancreatic islet · Pituitary.
♥ **MEN2** (**RET** activating) — Medullary thyroid · Pheo · HyperPTH. **Prophylactic thyroidectomy** indicated.
♥ **Gsα activating mutation**: early → **McCune-Albright**; somatotrope → **acromegaly**.
♥ **LH-R activating** → male familial precocious puberty.
♥ **Graves'** = TSH-R stimulating autoantibody.
♥ **Resistance signature**: ↑ hormone + ↓ action (e.g., XY phenotypic female with ↑LH/↑T = androgen insensitivity).
♥ **Albright's hereditary osteodystrophy** = signaling pathway resistance.

Clinical Evaluation

- Most glands **inaccessible** → exam focuses on **manifestations of excess/deficiency** + palpable glands (thyroid, gonads).
- Approach: presenting symptoms · review of systems · **family + social history** · medications.
- Cushing's clues: **central fat, striae, proximal weakness** — beyond nonspecific HTN/obesity/IGT.
- Hypothyroidism = insidious — fatigue, mental slowing, dry skin (overlap with general population).
- **Lab testing** = quantitative hormone + dynamic testing.
- **Imaging**: CT, MRI, ultrasound, nuclear scans for glandular anatomy/function.

High-Yield Adult Prevalence (Table 388-2)

Table 388.3 — Prevalent endocrine/metabolic disorders + screening

Disorder	Prevalence	Screen / Test
Obesity	40% obese; 70% overweight	BMI, waist circumference
T2DM	>10%	FPG >126, RPG >200, ↑HbA1c — **screen ≥45 y, q3y**
Hyperlipidemia	20–25%	Lipids q5y; lipoprotein analysis
Metabolic syndrome	35%	Waist · FPG · BP · lipids
Hypothyroidism	5–10% / 0.5–2%	TSH, free T4
Graves'	1–3% / 0.1%	TSH, free T4
Thyroid nodules	2–5% palpable; >25% USG	Exam/USG, FNAC
Osteoporosis	5–10% / 2–5%	BMD ≥65 y (or postmenopausal at risk)
HyperPTH	0.1–0.5% (>)	Serum Ca^{2+} → PTH if ↑
Infertility	10% of couples	Semen, ovulatory cycles
PCOS	5–10%	Free testosterone, DHEAS
Hirsutism	5–10%	Free testosterone, DHEAS
Menopause	Median 51 y	FSH
Hyperprolactinemia	15% (in amenorrhea/galactorrhea)	PRL → MRI if not drug-related
Erectile dysfunction	10–25%	PRL, testosterone
Male hypogonadism	1–2%	Testosterone, LH
Gynecomastia	15%	Often no test; consider Klinefelter / drugs
Klinefelter	0.2%	Karyotype, testosterone
Vit D deficiency	10%	25-OH vit D
Turner	0.03%	Karyotype

❦ CLINICAL PEARLS

- ❦ Hormone **excess** = autonomy + set-point defect → confirm with **suppression test**.
- ❦ Hormone **deficiency** = ↓ output despite stimulation → confirm with **stimulation test**.
- ❦ Hormone **resistance** = ↑ hormone + ↓ effect — measure both ligand AND end-organ response.
- ❦ Iatrogenic Cushing's = **most common** cause of Cushing's syndrome overall.
- ❦ **Subacute (de Quervain) thyroiditis** — only **infectious/inflammatory** cause of hyperthyroidism.
- ❦ MEN2 + RET+ child = **prophylactic thyroidectomy before 5 y** (depending on codon).

✦ MNEMONIC

PPP (MEN1) *MEN1 tumor triad*

- **P** — Parathyroid hyperplasia/adenoma (most common, earliest)
- **P** — Pancreatic islet tumors (gastrinoma, insulinoma, VIPoma)
- **P** — Pituitary adenoma (most often prolactinoma)

Gene = MEN1 on 11q13, encodes menin. Tumor suppressor; 2-hit Knudson model.

MPH (MEN2) *MEN2 tumor triad*

- **M** — Medullary thyroid carcinoma (>90%) — C-cell origin
- **P** — Pheochromocytoma (~50%)
- **H** — Hyperparathyroidism (MEN2A only; absent in 2B)

Gene = RET (10q11.2), activating mutation. MEN2B adds marfanoid habitus + mucosal neuromas, NO hyperPTH.

RESIST *Causes of hormone resistance*

- **R** — Receptor mutation (membrane or nuclear)
- **E** — Enzyme/post-receptor defect
- **S** — Signaling pathway mutation (Albright's hereditary osteodystrophy)
- **I** — Insulin/leptin resistance — functional, acquired
- **S** — Suppression of receptor — downregulation
- **T** — Transduction desensitization

Hallmark biochemistry: ↑ hormone + ↓ effect.

✎ MCQ CORNER

Q1. 22 y/o phenotypic female, primary amenorrhea, breast development, absent uterus. Karyotype 46,XY. LH ↑, testosterone ↑. Diagnosis?

A. Turner syndrome
B. Kallmann syndrome
✓ **C. Complete androgen insensitivity**
D. Sheehan syndrome

► *↑hormone + ↓action = resistance. AR mutation → XY female phenotype despite ↑LH/↑T. Classic hormone resistance syndrome.*

Q2. Family with MEN2A. 4 y/o son tests RET-positive. Recommended action?

A. Annual calcitonin only
✓ **B. Prophylactic thyroidectomy**
C. Radioiodine ablation
D. Lifelong thyroxine

► *RET activating mutation → C-cell hyperplasia → medullary thyroid Ca. Prophylactic thyroidectomy in childhood is standard of care; screen for pheo + hyperPTH.*

Q3. Which is the MOST characteristic biochemical signature of hormone resistance?

A. Low hormone, low end-organ effect
B. High hormone, high end-organ effect
✓ **C. High hormone, low end-organ effect**
D. Normal hormone, low end-organ effect

► *Resistance = receptor/signaling defect → compensatory ↑hormone with persistently ↓action.*

Q4. Activating mutation in Gsα limited to somatotropes causes:

A. McCune-Albright syndrome
✓ **B. Acromegaly**
C. Familial precocious puberty
D. Graves' disease

► *Gsα activation in pituitary somatotropes → autonomous GH secretion → acromegaly. Same mutation in early embryogenesis → McCune-Albright (mosaic).*

Q5. Which is NOT part of MEN1?

A. Parathyroid adenoma
B. Pancreatic gastrinoma
C. Pituitary prolactinoma
✓ **D. Medullary thyroid carcinoma**

► *Medullary thyroid Ca = MEN2 (RET). MEN1 = 3 Ps (Parathyroid, Pancreas, Pituitary).*

Q6. Most common cause of Cushing's syndrome overall:

A. Pituitary ACTH adenoma
B. Ectopic ACTH from small-cell lung Ca
C. Adrenal adenoma
✓ **D. Exogenous glucocorticoid administration**

► *Iatrogenic (exogenous steroids) = most common Cushing's overall. Among endogenous causes, pituitary ACTH adenoma (Cushing's disease) is most common.*

◷ LAST MINUTE REVISION

► **3 mechanisms**: excess · deficiency · resistance.
► **Excess** = mostly benign adenomas with abnormal set point.
► **Deficiency** = mostly glandular destruction (autoimmune top cause).
► **Resistance** = ↑ hormone + ↓ effect.
► **MEN1**: 11q13 · menin · tumor suppressor · 3 Ps (Parathyroid, Pancreas, Pituitary).
► **MEN2: RET** · RTK · activating · medullary thyroid + pheo + hyperPTH.
► MEN2 RET+ → **prophylactic thyroidectomy**.
► **Gsα activating**: early → McCune-Albright; somatotrope → acromegaly.
► **LH-R activating** → male precocious puberty.
► **Graves'** = TSH-R stimulating Ab.
► **Subacute thyroiditis** = infect/inflamm hyperfunction.
► **21-hydroxylase deficiency** = enzyme defect hypofunction (CAH).
► **Kallmann + Turner** = developmental hypofunction.
► **Sheehan's** = postpartum pituitary infarct.
► **Albright's hereditary osteodystrophy** = signaling resistance.
► **T2DM, leptin resistance** = functional postreceptor resistance.
► **Complete androgen insensitivity**: XY female + ↑LH + ↑T.
► **Iatrogenic glucocorticoid** = #1 Cushing's overall.
► **Hypothyroidism** 5–10% ; **Graves'** 1–3% ; **PCOS** 5–10% .
► **T2DM** >10% adults; screen ≥45 y q3y with FPG/HbA1c.
► **Hyperprolactinemia** 15% of amenorrhea/galactorrhea — MRI if not drug-induced.

◉ UPDATES

◉ **Immune checkpoint inhibitors** (anti–CTLA-4, PD-1, PD-L1) — new and growing cause of **immune-related endocrinopathies**: hypophysitis, thyroiditis, primary adrenal insufficiency, T1DM-like syndrome.
◉ **FGF23** increasingly recognized as a renal/bone endocrine axis — phosphate regulation.
◉ **Precision endocrinology**: germline panels for MEN, FAP-thyroid Ca, familial pheo/paraganglioma (SDHx, VHL, NF1, MAX, TMEM127).

CH 389 · Mechanisms of Hormone Action — Receptors · Signalin...

Hormone classes, receptor families (GPCR / TK / cytokine / nuclear), signaling cascades, GOF/LOF mutations, feedback loops. Foundational chapter — high yield for receptor disorder MCQs.

Classes of Hormones

- **5 classes**:
- Categories:
  - **(1) Amino acid derivatives** — dopamine, catecholamines, thyroid hormone
  - **(2) Small neuropeptides** — GnRH, TRH, somatostatin, vasopressin
  - **(3) Large proteins** — insulin, LH, PTH
  - **(4) Steroids** — cortisol, estrogen (from cholesterol)
  - **(5) Vitamin derivatives** — retinoids (Vit A), Vit D
- AA derivatives + peptides → **cell-surface (membrane) receptors**.
- Steroids, thyroid H, Vit D, retinoids → **intracellular nuclear receptors** (lipid-soluble).
- Peptide GFs (IGF1) act locally (paracrine/autocrine).

Hormone & Receptor Families

- **Glycoprotein H family**: TSH, FSH, LH, hCG — share **α subunit**; β subunit confers specificity.
- β subunits arose by gene duplication — high specificity for cognate receptor.
- **hCG cross-reactivity**: high pregnancy hCG → weakly stimulates TSH-R → ↑ thyroid H → ↓ TSH (gestational thyrotoxicosis).
- **Insulin/IGF family**: moderate cross-talk; tumor IGF2 → hypoglycemia (binds insulin R).
- **PTH vs PTHrP**: both bind PTH1R → hypercalcemia + hyperphosphatemia. Distinguish only by specific assays.
- **Nuclear receptors**:
- Two types:
  - **Type 1** = GR, MR, AR, ER, PR (steroids)
  - **Type 2** = TR, VDR, RAR, PPAR (thyroid H, Vit D, retinoic acid, lipids)
- **11β-HSD2** in renal tubules inactivates cortisol → MR selectivity for aldosterone.
- **Apparent mineralocorticoid excess**: 11β-HSD2 saturated in Cushing → cortisol activates MR → Na retention, K wasting.
- ER binds environmental estrogens (resveratrol, octylphenol) → basis for **SERMs (tamoxifen, raloxifene)**.

Membrane Receptor Signaling

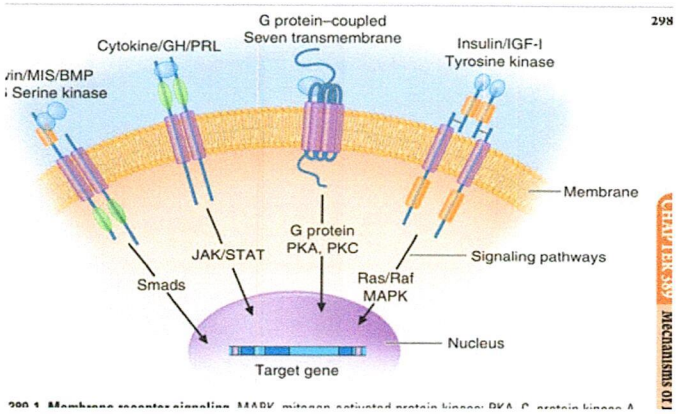


Fig 389.1 — Membrane receptor signaling: GPCR (cAMP/PKA), TK (Ras/MAPK), Cytokine (JAK/STAT), Serine kinase (Smads).

Four major groups

Receptor type	Examples	Pathway
GPCR (7-TM)	LH, FSH, TSH, PTH, ACTH, β-adrenergic	Gsα → cAMP / PKA
GPCR Gq	TRH, GnRH	PLC, DAG, IP3, PKC, Ca^{2+}
GPCR Giα	Somatostatin, α-adrenergic	↓ cAMP; K^+/Ca^{2+} channels
Tyrosine kinase	Insulin, IGF-1, EGF, FGF	IRS, Ras/Raf/MAPK, PI3K/Akt
Cytokine R	GH, PRL	JAK / STAT, MAPK, PI3K
Serine kinase	Activin, TGF-β, MIS/AMH, BMP	Smads

- **Gα subunit**: GTP-bound = active; intrinsic GTPase → GDP = inactive.
- Hormone binding → GDP dissociates → Gα binds GTP, separates from βγ → activates adenylate cyclase / PLC.
- **Gsα GOF mutation** (loss of GTPase) → constitutive activation → McCune-Albright (mosaic), GH adenoma, autonomous thyroid nodule.

GPCR Disease Mutations

Table 389.2 — Genetic causes of GPCR disorders

Receptor	Disorder	Inheritance
LH-R	Leydig hypoplasia (M), 1° amenorrhea (F)	AR inactivating
LH-R	Familial male precocious puberty	AD activating
FSH-R	Hypergonadotropic ovarian failure	AR inactivating
FSH-R	Ovarian hyperstimulation	Activating
TSH-R	Congenital hypothyroidism, TSH resistance	AR/AD inactivating
TSH-R	Nonautoimmune familial hyperthyroidism	AD activating
TSH-R / Gsα	Hot thyroid nodule (somatic)	Sporadic activating
GnRH-R / Kisspeptin	Hypogonadotropic hypogonadism	AR inactivating
CaSR	Familial hypocalciuric hypercalcemia (FHH)	AD inactivating
CaSR	Neonatal severe hyperparathyroidism	AR inactivating
CaSR	Familial hypocalcemic hypercalciuria	AD activating
AVPR2	Nephrogenic DI	XL inactivating
AVPR2	Nephrogenic SIADH	XL activating
ACTH-R (MC2R)	Familial ACTH resistance	AR inactivating
MC4R	Severe obesity	Codominant inactivating
PTH1R	Blomstrand chondrodysplasia (lethal)	AR inactivating
PTH1R	Jansen metaphyseal chondrodysplasia	AD activating

Tyrosine Kinase / Cytokine / Serine Kinase

- **Insulin/IGF-1 R**: autophosphorylation → IRS → Ras-MAPK (growth) + Akt/PKB (metabolic).
- **Insulin R mutation** → extreme insulin resistance (Donohue/leprechaunism, Rabson-Mendenhall).
- **GH R mutation** → **Laron dwarfism** (high GH, low IGF1).
- **AMH R mutation** → **persistent Müllerian duct syndrome**.
- **RET** activating mutation (TK) → **MEN2** (AD).
- Cytokine R (GH, PRL) → JAK/STAT (no intrinsic kinase activity).
- Serine kinase R (activin, TGF-β, MIS, BMP) → Smad signaling.

Nuclear Receptors

- **~100 members**; many are **orphan receptors** (ligand unknown — SF-1, DAX-1, HNF4α).
- **Homodimers**: steroid Rs (ER, AR, PR, GR, MR) → palindromic DNA half-sites.
- **Heterodimers with RXR**: TR, VDR, RAR, PPAR → direct-repeat DNA elements.
- Type II (TR, RAR) — **co-repressor** bound when no ligand → silences gene.
- Hormone binding → co-repressor released → coactivator recruited → transcription.

Nuclear receptor diseases

- **AR mutation → Androgen Insensitivity Syndrome (AIS)**; XY female phenotype, testes retained, no Müllerian (AMH preserved).
- **TRβ mutation → Resistance to Thyroid Hormone (RTH)**; AD, **dominant negative**; high T4/T3 + non-suppressed TSH.
- **PML-RARα fusion** → APL; retinoic acid reverses silencing → differentiation therapy.
- **GR mutation** (rare) → glucocorticoid resistance.
- **VDR mutation** → hereditary Vit D-resistant rickets.
- **PPARγ mutation** → familial partial lipodystrophy + insulin resistance.

Hormone Synthesis, Transport, Degradation

- **Precursor processing**: POMC → ACTH; proglucagon → glucagon + GLP1; proinsulin → insulin; pro-PTH → PTH.
- Precursors typically **inactive** — extra regulatory layer.
- Steroid prohormone activation: testosterone → DHT (5α-reductase); T4 → T3 (deiodinase).
- **Half-lives**:
- Examples:
  - **T4 = 7 d** → single daily dose, >1 mo for steady state
  - **T3 = 1 d** → divided BID/TID dosing
  - **ACTH, GH, PRL, PTH, LH < 20 min** → pulsatile
  - **Intraop PTH** drop confirms parathyroidectomy
- **Binding proteins**: TBG (T4/T3), CBG (cortisol), SHBG (sex steroids), IGFBPs, GHBP, follistatin (activin).
- Only **free hormone** is bioactive.
- **SHBG ↓** in insulin resistance / androgen excess → ↑ free testosterone → **hirsutism in PCOS**.
- Estrogen ↑ TBG (pregnancy, OCP); salsalate displaces T4 from TBG.
- **Megalin** = LDL-R family endocytic receptor for thyroglobulin, SHBG-bound steroids, carrier-bound A/D.
- Local degradation: 11β-HSD2 (cortisol→cortisone), deiodinases (T4 ↔ T3), Cyp26b1 (RA in PGCs).

Feedback Regulation

Fig 389.4 — HPA / HPT / HPG / HPS axes share negative feedback architecture: trophic releasing factor → pituitary hormone → target hormone → suppresses both.

- **Negative feedback** = core of all hypothalamic-pituitary axes.
- Examples: T4/T3 → TRH-TSH; cortisol → CRH-ACTH; sex steroids → GnRH-LH/FSH; IGF1 → GHRH-GH.
- **Positive feedback**: estrogen surge → LH surge (mid-cycle).
- Non-pituitary feedback: **Ca → PTH**; **glucose → insulin**; **leptin → hypothalamus**.
- **Suppression test** = workup of hyperfunction (e.g. dexamethasone for Cushing).
- **Stimulation test** = workup of hypofunction (e.g. ACTH stim for AI; insulin tolerance for GH/ACTH).

Major Hormone Functions

- **(1) Growth + differentiation**: GH, IGF1, thyroid H stimulate; sex steroids close epiphysis.
- **(2) Homeostasis**:
- Key homeostatic Hs:
  - **Thyroid H** ≈ 25% basal metabolism
  - **Cortisol** — permissive for many actions
  - **PTH** — Ca/PO4
  - **Vasopressin** — free water / osmolality
  - **Mineralocorticoid** — Na, K, volume
  - **Insulin** — euglycemia
- **Hypoglycemia counter-regulation**: ↓ insulin → glucagon + epinephrine (acute, mins) → GH + cortisol (hours).
- **(3) Reproduction**: 4 stages = sex determination, puberty, pregnancy/lactation, menopause.
- Menstrual cycle: pulsatile LH/FSH → follicle → ↑ E2 + inhibin (suppresses FSH selectively) → LH surge → ovulation.

♥ NEET SS HIGHLIGHTS

♥ **Glycoprotein H** = LH/FSH/TSH/hCG share α subunit; β = specificity.
♥ **hCG ↑ ↑ ↑** in molar/twin pregnancy → gestational thyrotoxicosis (cross-reacts TSH-R).
♥ **AMH** = absence of Müllerian; persistent Müllerian = AMH-R defect.
♥ **AIS** = AR mutation, XY female, testes present, no Müllerian.
♥ **RTH** = TRβ dominant negative; high T4/T3 + unsuppressed TSH.
♥ **Laron dwarfism** = GH-R defect (high GH, low IGF1).
♥ **MEN2** = RET activating mutation (TK receptor).
♥ **FHH** = CaSR LOF (AD); **neonatal severe HPT** = CaSR LOF (AR).
♥ **11β-HSD2 deficiency** = apparent MR excess (HTN + hypokalemia).
♥ PTH intraop monitoring works because PTH t½ < 5 min.

❦ CLINICAL PEARLS

❦ GR mutation in **promyelocytic leukemia** — PML-RARα → silenced gene → ATRA reverses.
❦ Megalin defect → ↓ thyroid hormone uptake in follicular cells.
❦ Tamoxifen = SERM (antagonist in breast, agonist in uterus → endometrial Ca risk).
❦ Raloxifene = SERM (antagonist in breast + uterus, agonist in bone).
❦ Octreotide = long-acting somatostatin analog (acromegaly, carcinoid, VIPoma).
❦ **Dexamethasone t½ long** → maximal HPA suppression (chosen for diagnostic tests).

✦ MNEMONIC

5-CLASS *Five hormone classes*
A — Amino-acid derivatives (catechols, thyroid H)
N — Neuropeptides (GnRH, TRH, ADH)
L — Large proteins (insulin, LH, PTH)
S — Steroids (cortisol, estrogen)
V — Vitamin derivatives (A, D)
Memorize 5 classes — basis for receptor type prediction.
STAR-G *Gsα GOF clinical effects (McCune-Albright)*
S — Sex precocity (autonomous gonadal activation)
T — Thyroid hyperplasia / nodule
A — Acromegaly (GH adenoma)
R — Rolling pigmentation (café-au-lait, coast of Maine)
G — Growth plate fibrous dysplasia

✎ MCQ CORNER

Q1. A 16 y/o phenotypic female presents with primary amenorrhea, breast development at Tanner stage 4, absent pubic/axillary hair, and palpable inguinal masses. Karyotype = 46,XY. Most likely defect?

A. 5α-reductase deficiency
✓ **B. Androgen receptor mutation**
C. AMH receptor mutation
D. Aromatase deficiency

► *Complete AIS: AR loss-of-function → no androgen action; testes secrete AMH → no Müllerian; breast develops via peripheral aromatization. 5α-RD has ambiguous genitalia + virilization at puberty.*

Q2. A 4 y/o boy has elevated TSH and T4. TRβ sequencing reveals a missense mutation in the ligand-binding domain. Inheritance pattern of his disorder?

A. Autosomal recessive
✓ **B. Autosomal dominant via dominant-negative**
C. X-linked
D. Mitochondrial

► *RTH — TRβ mutant heterodimerizes with RXR and blocks WT receptor function (dominant negative). AD inheritance.*

Q3. A 32 y/o woman with autosomal dominant nonautoimmune hyperthyroidism since childhood. Most likely molecular defect?

✓ **A. TSH-R activating mutation**
B. TPO-Ab positivity
C. Gsα inactivating mutation
D. TRβ mutation

► *Germline activating TSH-R mutation → AD congenital/familial nonautoimmune hyperthyroidism; absent autoantibodies.*

Q4. A 6 y/o with severe early-onset hypercalcemia (Ca 15) since infancy and inappropriately high PTH. Mutation in?

A. PTH1R (Jansen)
✓ **B. CaSR — homozygous inactivating (neonatal severe HPT)**
C. GNAS imprinting defect
D. Vitamin D receptor

► *Biallelic CaSR LOF = NSHPT — severe neonatal life-threatening hypercalcemia, requires parathyroidectomy.*

Q5. A patient with acromegaly is found to have a somatic Gsα mutation in the pituitary somatotroph. What is the biochemical consequence of the mutation?

A. Loss of guanine nucleotide binding
✓ **B. Loss of GTPase activity → constitutive activation**
C. Increased GDP affinity
D. Failure to dissociate from βγ

► *Activating Gsα mutations (e.g., R201) lose GTPase → GTP-bound state persists → continuous cAMP/PKA → GH adenoma. Mosaic germline = McCune-Albright.*

◷ LAST MINUTE REVISION

► 5 hormone classes: AA-deriv, neuropep, large protein, steroid, vitamin-deriv.
► Membrane R = peptides/AA; nuclear R = lipid-soluble.
► Glycoprotein H (LH/FSH/TSH/hCG) share α; β = specificity.
► hCG cross-stim TSH-R → gestational thyrotoxicosis.
► PTH + PTHrP both → PTH1R.
► Type 1 NR = steroid; Type 2 NR = TR/VDR/RAR/PPAR (RXR partner).
► 11β-HSD2 protects MR from cortisol; saturated in Cushing → HTN/hypoK.
► GPCR signal via Gsα(cAMP), Gi(↓cAMP), Gq(PLC-IP3-DAG).
► Gsα GOF → McCune-Albright + GH adenoma + autonomous nodule.
► Gsα LOF imprinted → AHO / pseudohypoparathyroidism.
► TK R: insulin, IGF1, EGF, RET (MEN2).
► Cytokine R: GH, PRL (JAK/STAT).
► Serine kinase R: TGF-β, activin, AMH, BMP (Smads).
► AR mutation = AIS (XY female, no Müllerian).
► TRβ dom-neg = RTH (high T4/T3, non-suppressed TSH).
► GH-R LOF = Laron (high GH, low IGF1).
► AMH-R = persistent Müllerian duct syndrome.
► T4 t½ = 7d (once daily); T3 t½ = 1d (BID); PTH/ACTH/GH/LH < 20 min.
► Negative feedback drives HPT, HPA, HPG, HPS axes.
► Suppression test = hyper; stimulation test = hypo.

◉ UPDATES

◉ **2023** — Mass spectrometry replacing many immunoassays for steroid panels.
◉ **Romosozumab (anti-sclerostin)** — agent class targeting Wnt receptor pathway (related to receptor signaling principles).
◉ **Inavolisib** — PI3K p110α inhibitor for ER+ breast Ca, exploits TK pathway downstream of insulin/IGF.

CH 390 · Physiology of Anterior Pituitary Hormones — PRL · G...

Master gland: 6 hormones across 5 cell types. Anatomy, vasculature, developmental transcription factors, hormone-specific synthesis, secretion, regulation, and action. NEET SS / INI SS-ET high yield.

Anatomy & Development

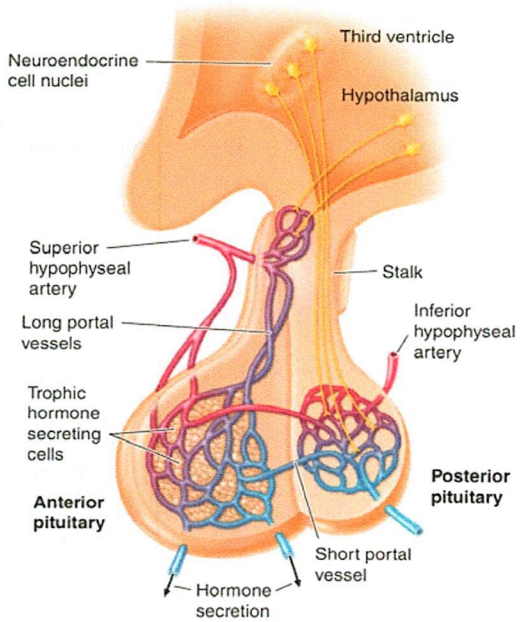


Fig 390.2 — Hypothalamic-pituitary vasculature: long portal vessels (superior hypophyseal artery) feed anterior pituitary; posterior pituitary receives direct neural innervation.

- Pituitary wt = **~600 mg**, within sella turcica.
- Adjacent: cavernous sinus, CNs III/IV/V1V2/VI, **optic chiasm above** (compressive lesion → bitemporal hemianopia).
- **Anterior lobe** = adenohypophysis (from Rathke's pouch — oral ectoderm).
- **Posterior lobe** = neurohypophysis (neural origin); ADH/oxytocin synthesized in hypothalamus, transported via stalk.
- **Long portal vessels** (sup. hypophyseal artery) = main supply to anterior lobe → high concentration of releasing factors.
- Posterior lobe supplied by inferior hypophyseal artery.
- **Stalk section** → loss of dopamine inhibition → **hyperprolactinemia** (only PRL up; others down).

Pituitary Cell Lineages

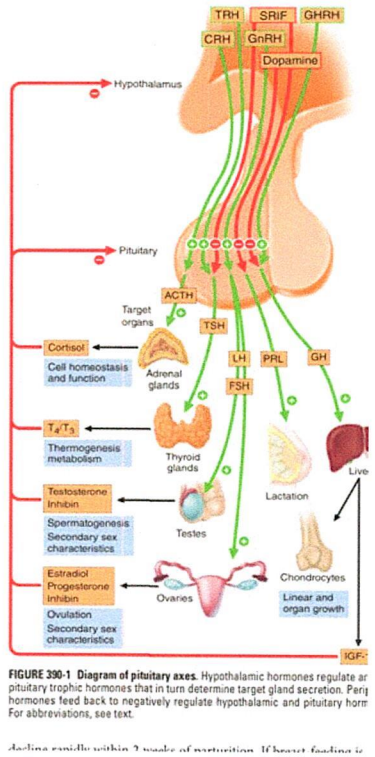


Fig 390.1 — 6 anterior pituitary hormones with target glands and feedback loops.

Table 390.1 — Cell types, TF, hormone

Cell type	TF	Hormone	% pituitary	Week appears
Corticotrope	T-Pit	POMC → ACTH	20%	6 wk
Somatotrope	Prop-1 / Pit-1	GH	50%	8 wk
Lactotrope	Prop-1 / Pit-1	PRL	20%	12 wk
Thyrotrope	Prop-1 / Pit-1 / TEF	TSH	5%	12 wk
Gonadotrope	SF-1, DAX-1	FSH, LH	10%	12 wk

- **Sox2** = pluripotent precursor.
- **Prop-1 → Pit-1** lineage = GH, PRL, TSH (combined pituitary deficiency if mutated).
- **Pit-1 mutation** = GH/PRL/TSH deficiency.
- **Prop-1 mutation** = above + gonadotropin deficiency over time.
- **T-Pit mutation** = isolated ACTH deficiency.
- **SF-1 / DAX-1** mutation = gonadotropin failure + adrenal hypoplasia (DAX-1).

Prolactin (PRL)

- 198 aa polypeptide; homologous to GH + hPL.

- **Tonic dopaminergic inhibition** = unique among pituitary hormones.
- Receptor = **type I cytokine receptor** (JAK-STAT, like GH and IL-6).
- **Stalk section** → hyperprolactinemia (loss of DA).
- **D2 receptor** mediates inhibition — basis for cabergoline/bromocriptine.
- **TRH** stimulates PRL release (within 15–30 min) — clinical: 1° hypothyroidism with high TRH may cause mild hyperprolactinemia + galactorrhea.
- Peak = **non-REM sleep**, 04:00–06:00; t½ ≈ 50 min.
- Normal: F 10–25 µg/L, M 10–20 µg/L. Pregnancy ↑ ~10×.
- **Effects**:
- Actions:
  - Induces + maintains lactation
  - Suppresses GnRH → ↓ LH/FSH → hypogonadism (amenorrhea, ↓ libido, infertility)
  - Blocks granulosa cell aromatase → anovulation
  - Luteolytic effect → short luteal phase
  - Lobuloalveolar breast proliferation (synergy with estrogen, progesterone, IGF-1)
- **PRL-R mutation** = PRL insensitivity, hyperprolactinemia, oligomenorrhea, agalactia (homozygous).

Growth Hormone (GH)

- **Most abundant pituitary hormone**; somatotropes = up to 50% cells.
- 5 genes encode GH-related proteins; pituitary hGH-N → 22 kDa GH (191 aa).
- Placental hGH-V → HCS (human chorionic somatotropin).
- **Mammosomatotropes** coexpress GH + PRL — may give rise to dual-secreting tumors.
- **Regulators**:
- Stimulation/inhibition:
  - ↑: GHRH (44 aa, pulses → GH pulses), ghrelin (gastric, octanoylated)
  - ↓: somatostatin/SRIF (basal tone)
  - ↑: sleep onset, exercise, stress, hypoglycemia, fasting, l-arginine, dopamine, α-adrenergic
  - ↓: hyperglycemia (suppresses GH to <0.7 µg/L F, <0.07 µg/L M), free fatty acids, IGF-1, glucocorticoids, β-blockade
- **GHRH-R mutation** = profound dwarfism.
- **SST2/SST5** = inhibit GH + TSH; **SST5** = inhibits ACTH.
- **Pegvisomant** = GH-R antagonist (acromegaly).
- Pulsatile; peak at night with sleep; declines with age (~15% of pubertal by middle age).
- Higher 24-h integrated GH in **women** (estrogen ↑ GH but causes peripheral resistance).

GH actions

- **Direct**: ↑ protein synthesis, ↑ lipolysis (↓ omental fat), ↑ lean body mass.
- **Antagonizes insulin** → impaired glucose tolerance.
- ↑ Na, K, water retention; ↑ inorganic phosphate.
- **Indirect via IGF-1** (mainly hepatic):
- IGF-1 details:
  - ↑ in puberty, peaks 16 yr, ↓ >80% with aging
  - Higher in F than M
  - Low IGF-1 in hypocaloric states, cachexia, malnutrition, sepsis (GH resistance)
  - IGFBP-3 = GH-dependent major carrier
  - **Mecasermin** (rhIGF-1) approved for GH-resistance syndromes
- **Laron syndrome** = GH-R mutation → high GH + low IGF-1.
- IGF-1 overdose → hypoglycemia, hypotension, intracranial hypertension, TMJ pain.

ACTH

- Corticotropes ~20% of pituitary; ACTH = 39 aa derived from **POMC (266 aa)**.
- **POMC products**: ACTH, β-lipotropin, β-endorphin, met-enkephalin, α-MSH, CLIP.
- POMC suppressed by glucocorticoids, induced by CRH + AVP + IL-6 + LIF.
- **CRH** (41 aa, PVN) = main stimulator → GPCR on corticotrope.
- Circadian: **peak 06:00, nadir midnight** (amplitude varies, frequency fixed).
- **Cushing's**: midnight cortisol ↑ (loss of nadir) — morning cortisol may be normal!
- **Glucocorticoid dosing**: bigger AM dose mimics physiology; **HS dose** = max HPA suppression (blocks AM ACTH peak).
- **Inflammation**: TNF, IL-1/2/6, LIF → ↑ CRH/AVP → ↑ ACTH → ↑ cortisol → restrains inflammation.
- **ACTH-R = MC2R** (melanocortin-2) — defect → familial ACTH resistance.

Gonadotropins (LH, FSH)

- Gonadotropes ~10% of pituitary.
- Both glycoproteins — **shared α subunit** with TSH/hCG; β subunit = specificity.
- **GnRH** (10 aa) — pulses every 60–120 min trigger LH/FSH pulses.
- **Kisspeptin (KISS1 gene)** regulates GnRH — basis for puberty initiation.
- **Continuous GnRH = desensitization** → therapeutic basis for:
- GnRH agonist uses:
  - Central precocious puberty (leuprolide)
  - Prostate cancer (chemical castration)
  - IVF ovulation control
  - Endometriosis, fibroids
- **FSH-specific regulators: inhibin ↓ FSH** (selectively); **activin ↑ FSH**.
- Estrogen feedback = chronic ↓ (negative); preovulatory surge = positive feedback → LH surge.
- Progesterone slows GnRH pulse frequency but enhances response.
- Testosterone feedback partly via aromatization to estrogen.

Actions

- **F**: FSH → follicle growth + estrogen; LH → ovulation + corpus luteum.
- **M**: LH → Leydig → testosterone; FSH → Sertoli → spermatogenesis.

TSH

- Thyrotropes ~5% pituitary.
- **TRH** (pyroGlu-His-Pro-NH2) = stimulator.
- Negative regulators: **T3/T4** (predominant), dopamine, somatostatin, glucocorticoids.
- **Long-standing untreated hypothyroidism** → thyrotrope hyperplasia → pituitary enlargement on MRI (mimics adenoma!).
- Pulses are **low amplitude** + long t½ → single TSH measurement adequate.
- Receptor on follicular cell = GPCR → cAMP → T4/T3 synthesis.