

Unit 1: Endocrine Pharmacology

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Advanced Pharmacology II, subject code MPL201T, is a core Semester 2 subject of M.Pharm Pharmacology. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject completes the systemic pharmacology begun in Advanced Pharmacology I, and it works throughout at the cellular and molecular level the PCI scope demands. Unit 1 is endocrine pharmacology: how hormones act on their receptors and signalling pathways (growth hormone, prolactin, thyroid hormones, insulin and the sex hormones), and the drug classes built on that knowledge (antithyroid drugs, oral hypoglycemic agents, oral contraceptives, corticosteroids and the drugs that regulate calcium). Unit 2 opens chemotherapy with the antibacterial agents, studying each class through its molecular target and, just as carefully, through the resistance mechanisms bacteria evolve against it, then adds the antifungal, antiviral and anti-TB drugs. Unit 3 finishes chemotherapy (protozoal infections, helminthiasis, cancer) and turns to immunopharmacology: the mediators of inflammation and immune response, the hypersensitivity reactions, the pharmacotherapy of asthma and COPD, and the immunosuppressants and immunostimulants. Unit 4 covers the drugs of the gastrointestinal tract and then chronopharmacology, the pharmacology of biological time. Unit 5 studies free radical pharmacology and closes with the recent advances in treating Alzheimer's disease, Parkinson's disease, cancer and diabetes mellitus. As in Semester 1, every class is studied the same way: pathophysiology first, then mechanism at the cellular and molecular level, then uses, adverse effects and contraindications.

1.1 Hormones as messengers: classes and receptor mechanisms

The endocrine system coordinates the body with chemical messengers released into the blood. Three chemical classes of hormone use three broad signalling designs, and the design predicts the drug behaviour:

Hormone class	Examples	Receptor location	Mechanism and time course
Peptides and proteins	Insulin, growth hormone, prolactin	Cell surface	Receptor enzymes or associated kinases (insulin receptor tyrosine kinase, GH and prolactin receptor JAK2 STAT), or G protein coupled receptors (TSH, ACTH, GnRH); fast, minutes, and the hormone cannot be given orally
Steroids	Cortisol, aldosterone, oestrogen, progesterone, testosterone, calcitriol	Intracellular (cytoplasm or nucleus)	Nuclear receptors change gene transcription; slow, hours to days, but oral activity is usual
Amino acid derivatives	Thyroid hormones (from tyrosine), adrenaline	Nucleus for thyroid hormones; cell surface for catecholamines	Thyroid hormones are the exception among amino acid derivatives: they enter the cell and bind nuclear receptors like steroids

Two consequences run through this unit. First, surface receptor hormones work through the second messenger and kinase machinery of MPL104T, so their mechanisms can be stated exactly. Second, the hypothalamus and pituitary sit above most axes, releasing and feedback loops decide hormone levels, and many endocrine drugs work by pushing on the loop (suppressing a pituitary hormone, replacing a missing one, or blocking the peripheral receptor) rather than on the gland alone.

1.2 Growth hormone: JAK2 STAT signalling and the somatotrophic axis

Growth hormone (GH, somatotropin) is a 191 amino acid peptide secreted in pulses by the anterior pituitary, driven by hypothalamic growth hormone releasing hormone (GHRH, stimulatory) and somatostatin (inhibitory), and by ghrelin from the stomach. Its receptor is a cytokine family receptor with no kinase of its own: GH binding dimerises the receptor, the associated **JAK2** tyrosine kinase phosphorylates it, and **STAT5** carries the signal to the nucleus. Many growth effects are indirect, through hepatic and local production of **insulin like growth factor 1 (IGF-1)**, and IGF-1 feeds back to restrain GH at pituitary and hypothalamus.

The pharmacology follows the axis point by point. **Somatotropin**, recombinant human GH, treats GH deficiency in children (failure to grow) and adults, given by daily subcutaneous injection because it is a peptide; adverse effects include raised intracranial pressure, glucose intolerance (GH is a physiological insulin antagonist) and, in children, slipped capital femoral epiphysis. **Mecasermin** is recombinant IGF-1 for the rare patients whose defect is GH insensitivity (Laron syndrome), where GH itself cannot work. In **acromegaly**, GH excess from a pituitary adenoma, the aims are to cut GH secretion or block its receptor: **octreotide** and **lanreotide** are long acting somatostatin analogues acting at somatostatin receptor subtype 2 (sst2) on the tumour, **cabergoline** helps a minority, and **pegvisomant** is a modified GH molecule that binds the receptor without activating it, a true receptor antagonist judged by the fall in IGF-1 rather than GH. In deficiency the hormone is replaced; in excess the axis is blocked at pituitary or receptor; the unit's logic in one axis.

1.3 Prolactin and the dopamine brake

Prolactin is also a JAK2 STAT cytokine family hormone, secreted by pituitary lactotrophs, but its control is inverted: the hypothalamus restrains it continuously through **dopamine** acting at D2 receptors, and prolactin rises whenever that brake is released. Raised prolactin (**hyperprolactinaemia**) causes galactorrhoea, amenorrhoea and infertility in women and loss of libido and erectile failure in men, and it arises from prolactin secreting adenomas (prolactinomas), from stalk compression cutting off dopamine delivery, and from drugs that block D2 receptors, above all the typical antipsychotics and metoclopramide of earlier units.

Treatment restores the brake. **Cabergoline** and **bromocriptine** are dopamine D2 agonists: they shrink prolactinomas and normalise prolactin, cabergoline being better tolerated and dosed once or twice weekly, bromocriptine older, with nausea, postural hypotension and, at the high cumulative doses once used in Parkinson's disease, fibrotic reactions including cardiac valvulopathy through 5-HT2B agonism. The teaching point is the mirror of Unit 3 of Semester 1: a drug that blocks D2 receptors in the pituitary (risperidone is the commonest offender) manufactures the disease that a D2 agonist cures, because the tuberoinfundibular dopamine pathway lies outside the blood brain barrier and sees both drug families at full strength.

1.4 Thyroid hormones: synthesis, nuclear action and the antithyroid drugs

The thyroid concentrates iodide by the sodium iodide symporter, oxidises it with **thyroid peroxidase (TPO)**, and iodinates tyrosine residues on thyroglobulin to form mono and di iodotyrosine, which TPO couples into **thyroxine (T4)** and **triiodothyronine (T3)**. Proteolysis of thyroglobulin releases the hormones; most T3, the active form, is made outside the gland by deiodinase enzymes removing one iodine from T4 in liver, kidney and target tissues. T3 enters cells and binds **nuclear thyroid hormone receptors (TR alpha and TR beta)** bound to thyroid response elements, changing transcription of genes for metabolic rate, growth, and cardiac and neural function. T4 is therefore largely a prohormone and a circulating reservoir, with a half life of about a week, which is why levothyroxine dosing is forgiving and why antithyroid drugs act slowly.

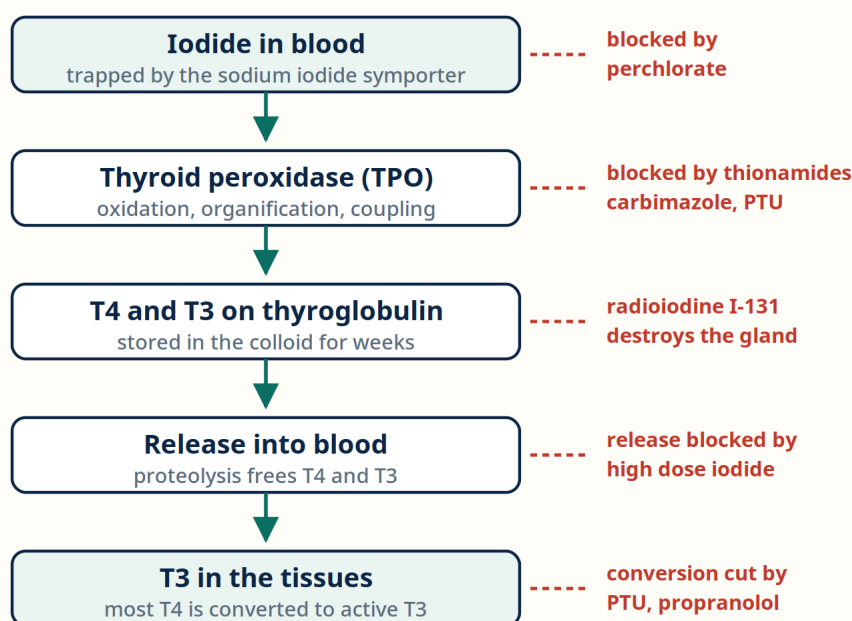
THYROID HORMONE SYNTHESIS AND THE DRUG BLOCK POINTS

```
Iodide in blood
|
| sodium iodide symporter [blocked by perchlorate, thiocyanate]
v
Follicle cell --iodide--> Colloid
|
| thyroid peroxidase: oxidation and organification
| [blocked by thionamides: carbimazole, propylthiouracil]
v
MIT + DIT --coupling--> T4 and T3 on thyroglobulin
|
| proteolysis releases stored hormone
| [release blocked by high dose iodide: Lugol solution]
v
T4 in blood --deiodinases--> T3 in tissues
[conversion reduced by propylthiouracil, propranolol, steroids]
```

Hyperthyroidism (Graves disease, toxic nodular goitre) is treated at four points of this scheme. The **thionamides, carbimazole** (converted to methimazole) and **propylthiouracil (PTU)**, block TPO and so stop new hormone synthesis; they do nothing to the weeks of hormone already stored in the colloid, which is why clinical control takes three to eight weeks. PTU additionally blocks peripheral conversion of T4 to T3 and is preferred in thyroid storm and the first trimester of pregnancy, but carries a risk of severe hepatotoxicity; carbimazole and methimazole carry the rarer but dangerous risk of **agranulocytosis**, so a sore throat or fever on a thionamide is an emergency blood count, not a minor illness. **Inorganic iodide** in high dose acutely inhibits organification (the Wolff Chaikoff effect) and hormone release and firms the gland before surgery, but escape occurs in about two weeks, so it is a short term tool. **Radioactive iodine (I-131)** exploits the symporter to concentrate a beta emitter inside the gland and destroy it, the commonest definitive treatment, with hypothyroidism the expected long term result. **Beta blockers** (propranolol) control the adrenergic storm of tremor, palpitation and heat intolerance while the slower drugs work.

Hypothyroidism is treated by replacement: **levothyroxine**, synthetic T4, once daily, titrated against TSH; liothyronine (T3) is faster, shorter and rarely needed outside specialist care. The examination trap is interaction: calcium, iron and bile acid resins block levothyroxine absorption, and enzyme inducing drugs raise its requirement.

Thyroid Hormone Synthesis and Its Block Points



Beta blockers calm the adrenergic symptoms while these slower drugs work.

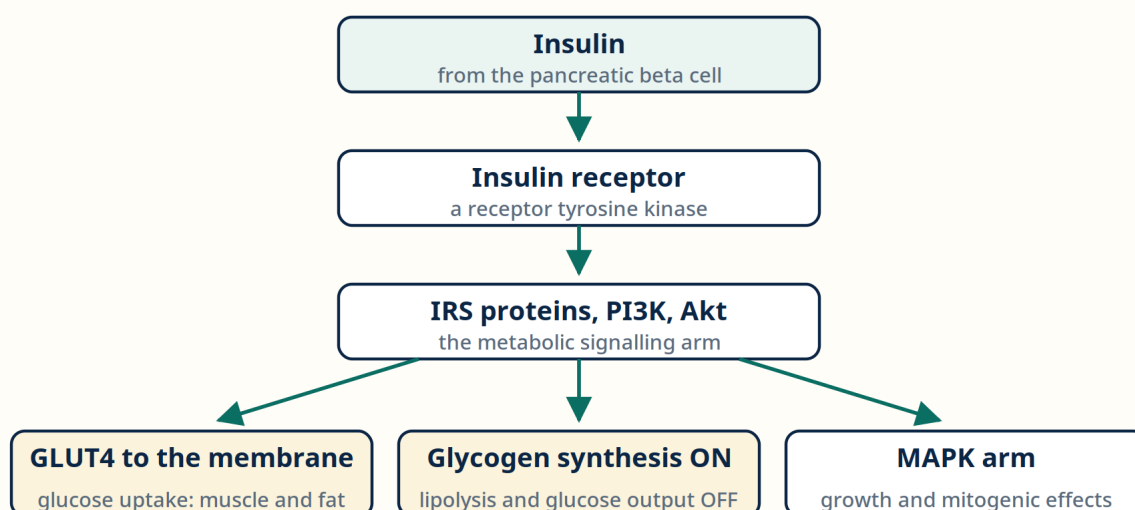
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Figure: Thyroid hormone synthesis in the follicle, and the points where thionamides, iodide, radioiodine and beta blockers act.

1.5 Insulin: receptor signalling and the control of secretion

Insulin is secreted by pancreatic beta cells when glucose rises: glucose enters through GLUT2, its oxidation raises ATP, ATP sensitive potassium channels close, the membrane depolarises, calcium enters, and insulin granules are exocytosed. This secretion machinery matters here because the oral hypoglycemic agents of section 1.6 work by forcing it. Insulin's receptor is a **receptor tyrosine kinase**: insulin binding activates the intracellular kinase, which phosphorylates insulin receptor substrate proteins, and the signal divides between the **PI3K Akt pathway** (metabolic actions: GLUT4 transporters move to the membrane of muscle and adipose cells and take up glucose, glycogen synthesis is switched on, lipolysis and hepatic glucose output are switched off) and the MAPK pathway (growth effects). Failure of this signalling, insulin resistance in muscle, fat and liver, is the core defect of type 2 diabetes; absolute insulin deficiency from autoimmune beta cell destruction is type 1 diabetes, where insulin replacement is life saving and oral agents have no place.

Insulin Receptor Signalling: The PI3K Akt Pathway



Failure of this signalling is insulin resistance, the core defect of type 2 diabetes.

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Figure: Insulin receptor signalling. The PI3K Akt arm produces the metabolic actions of insulin, including GLUT4 movement to the cell membrane.

1.6 Oral hypoglycemic agents

Type 2 diabetes is treated orally with classes that each repair a different defect. None replaces insulin in type 1 disease.

Class and examples	Mechanism	Main advantages	Signature adverse effects
Sulfonylureas: glibenclamide, gliclazide, glimepiride	Close ATP sensitive potassium channels on the beta cell, forcing insulin secretion	Potent, cheap, long experience	Hypoglycaemia (worst with long acting glibenclamide, in the elderly and in renal failure) and weight gain
Meglitinides: repaglinide, nateglinide	Same channel, much shorter action, taken with meals	Controls post meal spikes, flexible with irregular meals	Hypoglycaemia, less than sulfonylureas
Biguanide: metformin	Reduces hepatic glucose output (AMPK linked) and improves insulin sensitivity; does not stimulate secretion	No weight gain, no hypoglycaemia alone, first line standard	GI upset; lactic acidosis risk in renal failure and acute illness, so it is stopped when patients are acutely unwell
Thiazolidinediones: pioglitazone	PPAR gamma nuclear receptor agonists, increase insulin sensitivity in adipose tissue	No hypoglycaemia alone, durable control	Weight gain and fluid retention, worsens heart failure, bone fractures; slow onset over weeks (a gene transcription drug)
Alpha glucosidase inhibitors: acarbose, voglibose	Block brush border enzymes, delay carbohydrate digestion	Targets post meal glucose	Flatulence and diarrhoea from undigested carbohydrate reaching the colon
DPP-4 inhibitors: sitagliptin, vildagliptin	Block the enzyme destroying incretins (GLP-1 and GIP), so glucose dependent insulin secretion rises and glucagon falls	Weight neutral, low hypoglycaemia risk	Generally well tolerated; pancreatitis signal watched

Class and examples	Mechanism	Main advantages	Signature adverse effects
SGLT2 inhibitors: dapagliflozin, empagliflozin	Block sodium glucose cotransporter 2 in the proximal tubule, glucose is lost in the urine	Weight and blood pressure fall; proven heart failure and kidney protection	Genital mycotic infections, volume depletion; rare euglycaemic ketoacidosis

Two principles organise the table. Secretagogues (sulfonylureas, meglitinides) need working beta cells and can cause hypoglycaemia; sensitisers and the newer classes cannot, used alone. And the modern classes are chosen on more than glucose: the SGLT2 inhibitors and the injectable GLP-1 receptor agonists of section 5.10 have outcome evidence in heart failure, kidney disease and cardiovascular events, which is why guidelines now place them early in patients with those complications. **Insulin** itself, in type 2 disease, is added when oral therapy fails or during acute illness; its preparations (rapid, short, intermediate and long acting analogues) are dosed in units and titrated against glucose readings, a practical detail students confuse with the oral agents at their peril.

1.7 Sex hormones and oral contraceptives

The **sex steroids** oestrogen, progesterone and androgens are made from cholesterol under hypothalamic pituitary control (GnRH, LH and FSH) and act on intracellular steroid receptors that regulate transcription, the slow, durable signalling of section 1.1. Oestrogens grow the endometrium, maintain bone and shape lipid profiles; progesterone prepares and holds the endometrium and is secreted in the luteal phase; their cyclical interplay is the menstrual cycle, and its pharmacological override is contraception.

Combined oral contraceptives pair an oestrogen (ethinylestradiol) with a progestin (levonorgestrel, desogestrel and others). Taken daily, the steady steroid signal suppresses pituitary FSH and LH by negative feedback: no follicle matures, the LH surge never fires, and ovulation does not occur; progestin additionally thickens cervical mucus and thins the endometrium. The benefits beyond contraception include lighter, regular, less painful periods and lower risks of ovarian and endometrial cancer. The adverse ledger is dominated by the oestrogen: a several fold rise in **venous thromboembolism** (highest in the first months, with third generation progestins somewhat above levonorgestrel pills), a small rise in arterial events in smokers over 35, nausea and breast tenderness, and the interaction trap: enzyme inducing drugs (rifampicin, carbamazepine) speed steroid clearance and cause contraceptive failure, while ordinary antibiotics do not. **Progestin only pills** avoid oestrogen risk but demand strict timing; long acting progestins (implants, injections, intrauterine systems) remove the daily adherence problem entirely.

Emergency contraception with levonorgestrel delays ovulation and works only before the LH surge. On the androgen side, testosterone is replaced in hypogonadism, abused as an anabolic steroid with suppression of the axis it mimics, and blocked therapeutically by **finasteride** (5 alpha reductase inhibitor, benign prostatic hyperplasia and hair loss) and the antiandrogens used in prostate cancer.

1.8 Corticosteroids: the glucocorticoid receptor and its price

Cortisol is secreted by the adrenal cortex under ACTH, itself under hypothalamic CRH, with negative feedback at both levels: the **hypothalamic pituitary adrenal (HPA) axis**. The glucocorticoid receptor sits in the cytoplasm held by heat shock proteins; cortisol binding frees it, the complex enters the nucleus and changes transcription in two directions: **transactivation** of metabolic genes (gluconeogenesis enzymes, the source of steroid diabetes and much of the toxicity) and **transrepression** of the inflammatory transcription factors NF kappa B and AP-1, shutting down cytokines, adhesion molecules, COX-2 and inducible nitric oxide synthase. That second arm is the anti inflammatory and immunosuppressive action for which synthetic corticosteroids (prednisolone, methylprednisolone, dexamethasone, chosen by potency,

duration and mineralocorticoid activity) are prescribed across every specialty: asthma, rheumatoid disease, transplant rejection, cerebral oedema, replacement in adrenal failure.

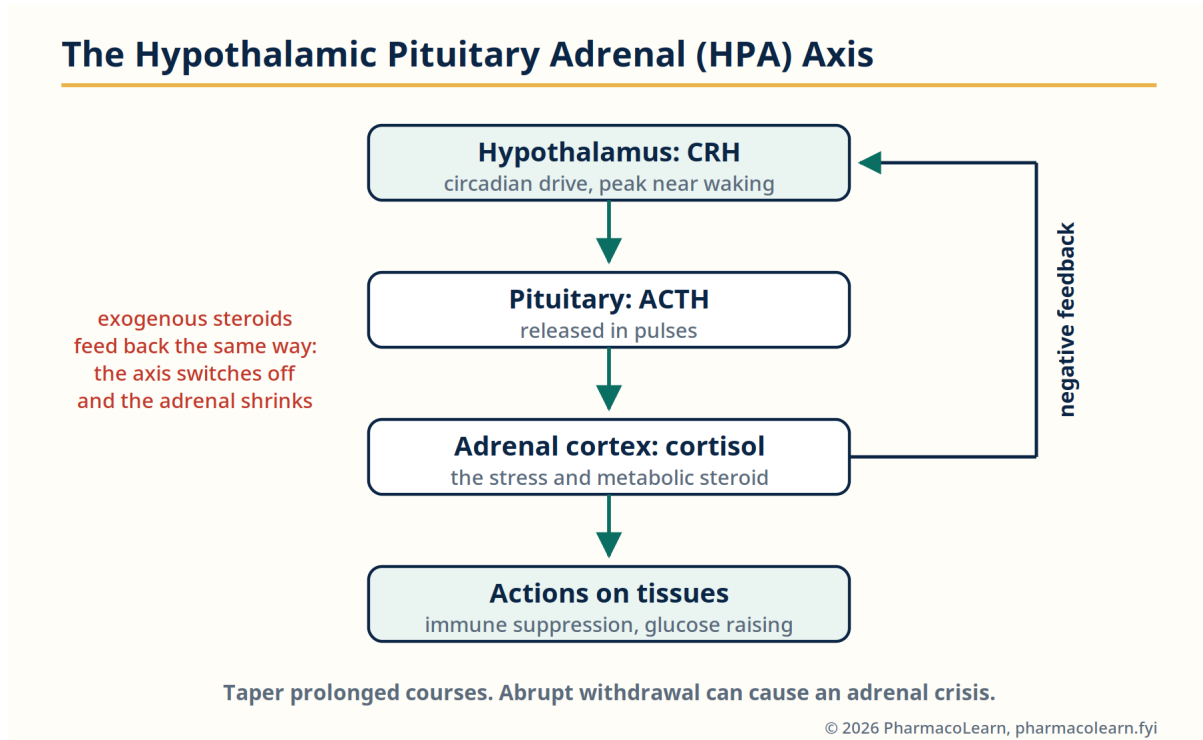


Figure: The hypothalamic pituitary adrenal axis. Exogenous corticosteroids feed back like cortisol and, given for weeks, leave the adrenal unable to respond when they stop.

The price list is the physiology read backwards: hyperglycaemia and diabetes, central obesity and muscle wasting, hypertension and fluid retention (mineralocorticoid spillover), osteoporosis and growth suppression, cataracts and glaucoma, thin skin and poor healing, mood change and psychosis, and two dangers students must never miss. First, immune suppression reactivates latent infections, tuberculosis above all in this country. Second, **HPA suppression**: exogenous steroid switches off CRH and ACTH, the adrenal cortex atrophies, and abrupt withdrawal after prolonged therapy can produce an adrenal crisis of hypotension and collapse; steroids are therefore tapered, and patients carry steroid cards warning that illness or surgery needs extra cover. **Mineralocorticoid** replacement (fludrocortisone) is the other half of adrenal replacement, acting at the mineralocorticoid receptor to retain sodium through the epithelial sodium channel, the same channel amiloride blocks from the diuretic side in Semester 1.

1.9 Drugs affecting calcium regulation

Blood calcium is held in a narrow range by three hormones working on gut, bone and kidney. **Parathyroid hormone (PTH)** raises calcium: it increases bone resorption, renal calcium reabsorption and phosphate excretion, and switches on renal activation of vitamin D. **Calcitriol** (active vitamin D) raises calcium and phosphate by increasing intestinal absorption. **Calcitonin** opposes resorption weakly and is a minor physiological player but a usable drug. Drugs exploit each arm:

- **Bisphosphonates** (alendronate, risedronate, zoledronic acid) bind bone mineral and poison osteoclasts; nitrogen containing members block the mevalonate pathway enzyme farnesyl pyrophosphate synthase inside the osteoclast. They are the mainstay of osteoporosis and of hypercalcaemia of malignancy; poor oral absorption and oesophagitis dictate the fasting, upright dosing ritual.

- **Denosumab** is a monoclonal antibody against RANK ligand, the osteoclast activating signal, blocking resorption from outside the cell.
- **Teriparatide**, a PTH fragment, paradoxically builds bone when given as a daily pulse (intermittent exposure favours formation, continuous exposure favours resorption) and is reserved for severe osteoporosis.
- **Cinacalcet** is a calcimimetic: it makes the parathyroid calcium sensing receptor more sensitive, so the gland behaves as if calcium were higher and PTH falls; used in secondary hyperparathyroidism of renal failure.
- **Vitamin D preparations** (cholecalciferol for deficiency, calcitriol and alfacalcidol where renal activation fails) and calcium salts complete the set; **calcitonin** survives mainly for acute hypercalcaemia, where saline, bisphosphonates and glucocorticoids do the heavier work.

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