PIPADOR REVISION

MRCOG Part 1 Revision Notes

Intracellular Receptors

BIOCHEMISTRY • LECTURE 207

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG PART 1 REVISION NOTES | BIOCHEMISTRY

207 Intracellular Receptors

Nuclear receptor structure, steroid and thyroid hormone receptor mechanisms, isoforms, selective modulators and disorders

≈ 48	Zinc fingers	Hours–days	HRE
Human nuclear receptors	DNA-binding domain	Genomic response time	Hormone response element

■ KEY FACTS: Learning objectives

- Describe the structure of nuclear (intracellular) receptors and their domains.
- Describe the mechanism of steroid and thyroid hormone receptor action, including co-regulators and non-genomic effects.
- Describe receptor isoforms, cross-reactivity and selective modulators used in O&G.
- Describe disorders of intracellular receptors.

207.1 Structure

Domain	Function
N-terminal (A/B) — AF-1	Ligand-independent transactivation; most variable; isoform differences (PR-A vs PR-B)
DNA-binding domain (C)	Two zinc fingers; recognises hormone response elements (palindromic or direct repeats)
Hinge (D)	Nuclear localisation signal; flexibility
Ligand-binding domain (E) — AF-2	Hormone binding, dimerisation, co-activator/co-repressor recruitment; binds heat-shock proteins when unliganded

207.2 Mechanism of action

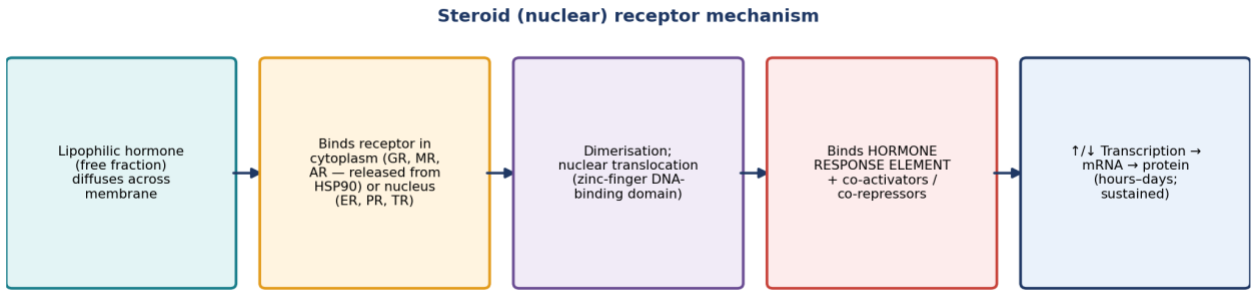


Figure 207.1 — Nuclear receptor signalling

Class	Receptors	Behaviour
Type I (steroid receptors)	ER, PR, AR, GR, MR	Unliganded receptor bound to HSP90 (cytoplasm for GR/MR/AR; mainly nucleus for ER/PR); ligand → release, homodimer, HRE binding
Type II	Thyroid (TR), vitamin D (VDR), retinoic acid (RAR), PPAR	Bound to DNA even without ligand (often repressing via co-repressors); heterodimer with RXR; ligand switches to activation

Class	Receptors	Behaviour
Orphan receptors	SF-1 (steroidogenesis, gonadal development), DAX-1, LRH-1	Ligand unknown/not required — SF-1/DAX-1 mutations → adrenal and gonadal failure

Non-genomic effects occur within seconds–minutes via membrane-associated receptors (e.g. **GPER** for oestrogen, membrane progesterone receptors in sperm/oocyte, rapid vasodilatation).

207.3 Receptor isoforms and selectivity

Receptor	Isoforms / key points
Oestrogen receptor	ERα (uterus, breast, hypothalamus, liver, bone), ERβ (ovary granulosa, prostate, brain, vessels); ER status guides breast cancer therapy
Progesterone receptor	PR-B activator; PR-A represses PR-B and ER — ↑ PR-A:PR-B in myometrium at term = functional progesterone withdrawal
Androgen receptor	X-linked; binds T and DHT (DHT higher affinity)
Glucocorticoid vs mineralocorticoid receptor	Cortisol binds MR with equal affinity — selectivity provided by 11β-HSD2 (kidney, placenta)
Thyroid receptor	TRα (heart, bone, brain), TRβ (liver, pituitary feedback); T_3 binds 10× more avidly than T_4

Selective modulator	Mechanism	Uses
SERMs (tamoxifen, raloxifene, clomifene)	Ligand-induced conformations recruit different co-regulators in different tissues	Breast cancer, osteoporosis, ovulation induction
SPRMs (ulipristal, mifepristone)	PR modulators / antagonists	Emergency contraception, fibroids; medical abortion, IOL after fetal death
Anti-androgens (cyproterone, spironolactone, flutamide)	AR antagonists	Hirsutism, prostate cancer — teratogenic for male fetus
Fulvestrant	ER degrader	Advanced breast cancer

207.4 Receptor disorders

Disorder	Defect
Complete/partial androgen insensitivity	AR mutations — 46,XY with female/ambiguous phenotype
Resistance to thyroid hormone	TRβ mutations — high T_4/T_3 with non-suppressed TSH
Glucocorticoid resistance	GR mutations — hypertension, hyperandrogenism
Vitamin D-dependent rickets type 2	VDR mutations — rickets, alopecia
Hormone-dependent cancers	ER/PR-positive breast and endometrial cancers — targeted by endocrine therapy (tamoxifen, aromatase inhibitors, progestogens for early endometrial cancer)

207.5 Must-know summary

■ EXAM TIP

- Domains: AF-1, **zinc-finger DNA-binding**, hinge, ligand-binding/AF-2.
- Type I (ER, PR, AR, GR, MR): HSP90 release → homodimer → HRE. Type II (TR, VDR, RAR): **RXR heterodimer**, DNA-bound when unliganded.
- PR-A represses PR-B (term myometrium); 11β-HSD2 protects MR from cortisol.
- SERMs/SPRMs: tissue-selective via co-regulators.

■ MNEMONIC / MEMORY AID

'Steroids Stroll In' — lipophilic, intracellular, slow but sustained.