PIPADOR REVISION

MRCOG Part 1 Revision Notes

Intracellular Second Messengers

BIOCHEMISTRY • LECTURE 208

VISUAL EXAMINATION REVISION NOTES

2026 Edition

208

MRCOG PART 1 REVISION NOTES | BIOCHEMISTRY

Intracellular Second Messengers

cAMP, cGMP, IP_3, DAG and calcium — generation, actions, termination and application to the myometrium

cAMP	IP_3 + DAG	cGMP	Ca^{2+}
Gs (+) / Gi (−) → PKA	Gq → PLC → Ca^{2+}, PKC	NO / ANP → PKG	100 nM → 1 µM signal

■ KEY FACTS: Learning objectives

- Describe the main intracellular second messengers (cAMP, cGMP, IP_3, DAG, Ca^{2+}) and their generation and termination.
- Describe calcium signalling and calmodulin.
- Apply second-messenger pathways to uterine contraction and relaxation, hormone action and drug therapy.

208.1 cAMP and phosphoinositide pathways

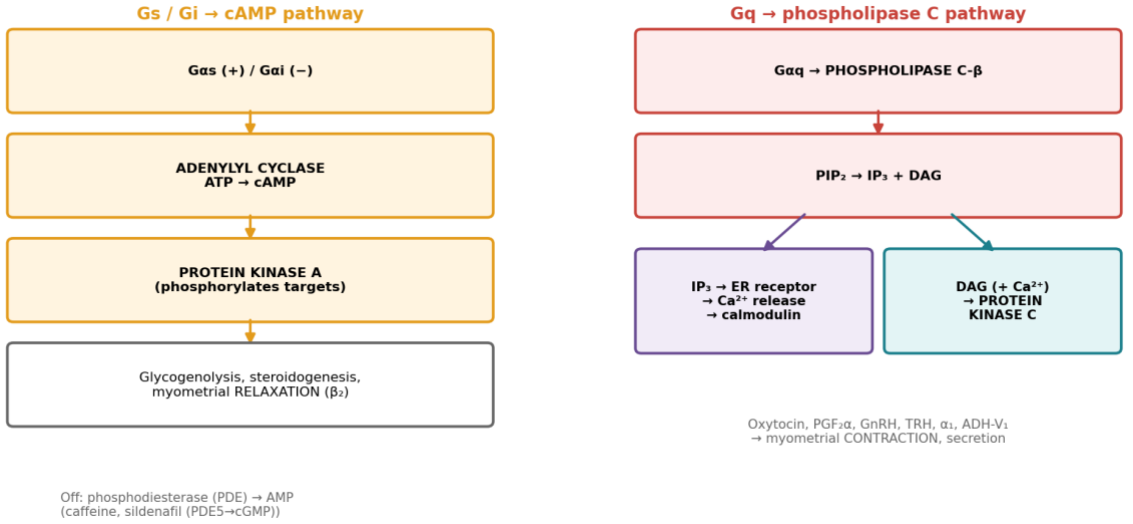


Figure 208.1 — cAMP and IP_3/DAG pathways

Messenger	Generated by	Acts on	Terminated by	Examples
cAMP	Adenylyl cyclase (Gs ↑, Gi ↓; forskolin)	PKA, EPAC, CNG channels	Phosphodiesterases (PDE3/4; inhibited by caffeine, theophylline)	LH → steroidogenesis (StAR); FSH → aromatase; β_2 → myometrial relaxation; TSH; oocyte meiotic arrest
cGMP	Soluble guanylyl cyclase (NO); membrane GC (ANP)	PKG → ↓ Ca^{2+}, smooth-muscle relaxation	PDE5 (sildenafil inhibits)	Vasodilatation (GTN), nitric oxide in pregnancy vasodilatation, penile erection; cGMP maintains oocyte arrest
IP_3	PLC-β (Gq) from PIP_2	IP_3 receptor on ER → Ca^{2+} release	Phosphatases (lithium inhibits inositol recycling)	Oxytocin, $PGF_2\alpha$, GnRH, α_1
DAG	PLC-β	Protein kinase C (with Ca^{2+})	DAG kinase	Secretion, cell proliferation (phorbol esters)

Messenger	Generated by	Acts on	Terminated by	Examples
PIP_3	PI3K (RTK, insulin)	AKT	PTEN phosphatase (PTEN loss → endometrial cancer)	Insulin: GLUT4 translocation, growth

208.2 Calcium signalling

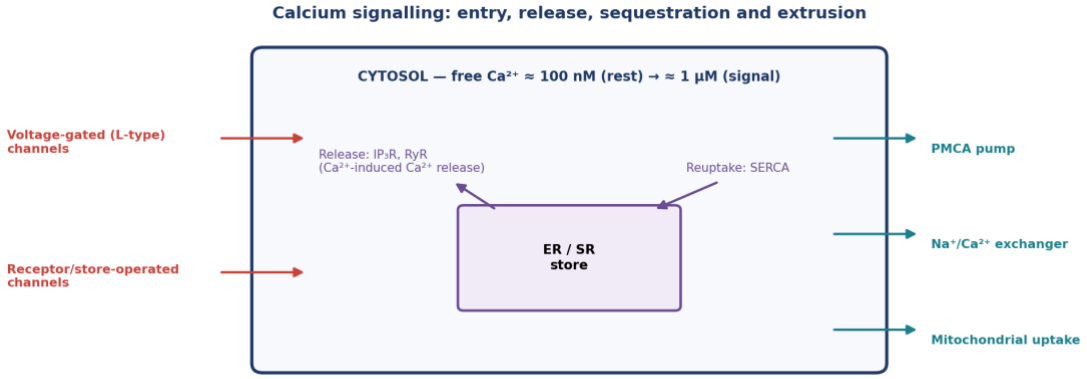


Figure 208.2 — Calcium entry, release and removal

- Resting cytosolic **free Ca^{2+} ≈ 100 nM** vs ≈ 1.2 mM outside — a **10,000-fold gradient** allows rapid signals (oscillations, waves).
- **Calmodulin** (4 Ca^{2+}-binding EF-hands) activates **myosin light-chain kinase** (smooth muscle), CaM kinases, calcineurin, adenylyl cyclases, eNOS. **Troponin C** is the Ca^{2+} sensor in striated muscle.
- Ca^{2+} triggers **exocytosis** (synaptotagmin — hormones, neurotransmitters), egg activation at fertilisation (PLCζ-induced Ca^{2+} oscillations → cortical reaction), gene expression and apoptosis.

208.3 Application — the myometrium

Contraction (↑ Ca^{2+})	Relaxation (↓ Ca^{2+} / ↓ MLCK)
Oxytocin (Gq → IP_3 → SR Ca^{2+}), $PGF_2\alpha$ (Gq), depolarisation → L-type Ca^{2+} channels; Ca^{2+}–calmodulin → MLCK → myosin phosphorylation; connexin-43 spreads signal	β_2-agonists (Gs → cAMP → PKA ↓ MLCK), PGE_2/PGI_2 (Gs), NO → cGMP, progesterone; nifedipine blocks L-type channels; atosiban blocks oxytocin receptor; $MgSO_4$ competes with Ca^{2+}; indomethacin ↓ PG synthesis

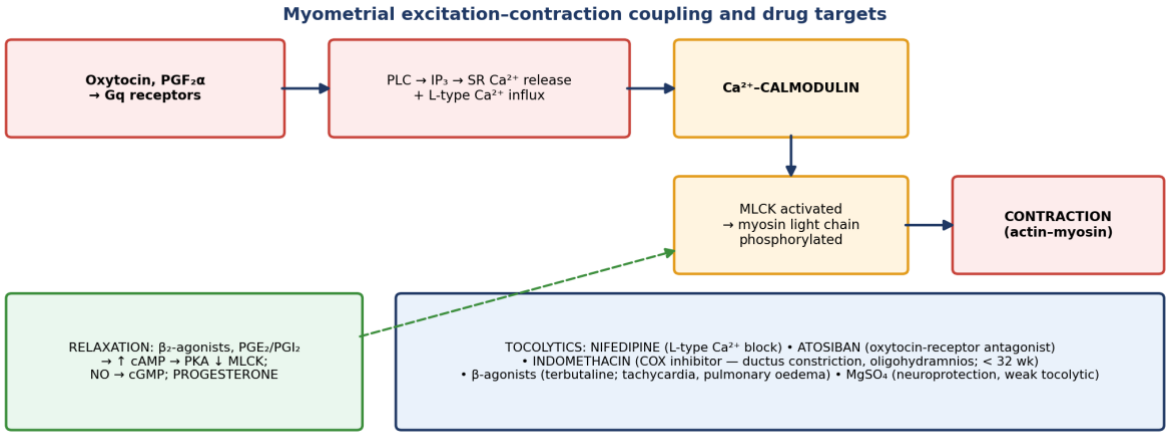


Figure 208.3 — Myometrial excitation–contraction coupling and tocolytic targets

208.4 Must-know summary

■ EXAM TIP

- **cAMP**: adenylyl cyclase → PKA; broken down by PDE (caffeine/theophylline inhibit).
- **cGMP**: NO (soluble GC) and ANP (membrane GC) → PKG; PDE5 (sildenafil).
- **IP_3** releases ER Ca^{2+}; **DAG** activates PKC — both from PIP_2 via PLC-β (Gq).
- Ca^{2+}–calmodulin → MLCK → smooth-muscle contraction; cAMP/cGMP relax.
- PI3K → PIP_3 → AKT; **PTEN** loss in endometrial cancer.

■ MNEMONIC / MEMORY AID

Gs → 'Stimulates cAMP', Gi → 'Inhibits cAMP', Gq → 'Queue for Calcium' (IP_3).