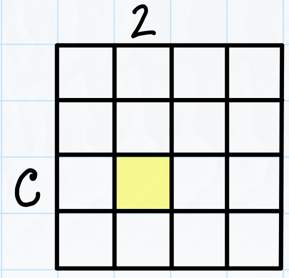
C2.1 CHEMICAL SIGNALLING

Ver. 2

Guiding Questions
How do cells distinguish between the many different signals that they receive?
What interactions occur inside animal cells in response to chemical signals?

Linking Questions
What patterns exist in communication in biological systems?
In what ways is negative feedback evident at all levels of biological organization?



Theme: Interactions + Interdependence

Level of Organization: Cells

Written and drawn by:

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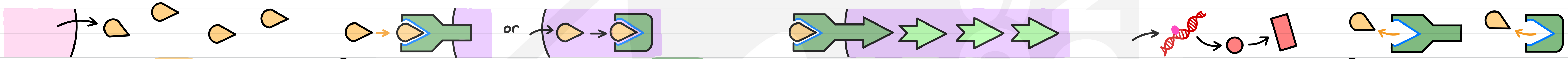
NOTEWORTHY SCIENCE
MARIER

HL LEARNING OUTCOMES

C2.1.1	Receptors as proteins with binding sites for specific signalling chemicals	Students should use the term "ligand" for the signalling chemical.
C2.1.2	Cell signalling by bacteria in quorum sensing	Use the example of bioluminescence in the marine bacterium Vibrio fischeri.
C2.1.3	Hormones, neurotransmitters, cytokines and calcium ions as examples of functional categories of signalling chemicals in animals	Students should appreciate the differences between these categories.
C2.1.4	Chemical diversity of hormones and neurotransmitters	Consider reasons for a wide range of chemical substances being used as signalling chemicals. Include amines, proteins and steroids as chemical groups of hormones. A range of substances can serve as neurotransmitters including amino acids, peptides, amines and nitrous oxide.
C2.1.5	Localized and distant effects of signalling molecules	Contrasts can be drawn between hormones transported by the blood system and neurotransmitters that diffuse across a synaptic gap.
C2.1.6	Differences between transmembrane receptors in a plasma membrane and intracellular receptors in the cytoplasm or nucleus	Include distribution of hydrophilic or hydrophobic amino acids in the receptor and whether the signalling chemical penetrates the cell or remains outside.
C2.1.7	Initiation of signal transduction pathways by receptors	Students should understand that the binding of a signalling chemical to a receptor sets off a sequence of responses within the cell.
C2.1.8	Transmembrane receptors for neurotransmitters and changes to membrane potential	Use the acetylcholine receptor as an example. Binding to a receptor causes the opening of an ion channel in the receptor that allows positively charged ions to diffuse into the cell. This changes the voltage across the plasma membrane, which may cause other changes.
C2.1.9	Transmembrane receptors that activate G proteins	Students should understand how G protein-coupled receptors convey a signal into cells. They should appreciate that there are many such receptors in humans.
C2.1.10	Mechanism of action of epinephrine (adrenaline) receptors	Include the roles of a G protein and cyclic AMP (cAMP) as the second messenger. **NOS**: Students should be aware that naming conventions are an example of international cooperation in science for mutual benefit. Both "adrenaline" and "epinephrine" were coined by researchers and are based on production of the hormone by the adrenal gland; "adrenaline" comes from Latin *ad* = at and *ren* = kidney and "epinephrine" comes from old Greek *epi* = above and *nephros* = kidney, respectively. Unusually, these two terms persist in common use in different parts of the world.
C2.1.11	Transmembrane receptors with tyrosine kinase activity	Use the protein hormone insulin as an example. Limit this to binding of insulin to a receptor in the plasma membrane, causing phosphorylation of tyrosine inside a cell. This leads to a sequence of reactions ending with movement of vesicles containing glucose transporters to the plasma membrane.
C2.1.12	Intracellular receptors that affect gene expression	Use the steroid hormones oestradiol, progesterone and testosterone as examples. Students should understand that the signalling chemical binds to a site on a receptor, activating it. The activated receptor binds to specific DNA sequences to promote gene transcription.
C2.1.13	Effects of the hormones oestradiol and progesterone on target cells	For oestradiol, limit to cells in the hypothalamus that secrete gonadotropin-releasing hormone. For progesterone, limit to cells in the endometrium.
C2.1.14	Regulation of cell signalling pathways by positive and negative feedback	Limit to an understanding of the difference between these two forms of regulation and a brief outline of one example of each.

HL C2.1.1 — Receptors as proteins with binding sites for specific signalling chemicals C.2.1.2 — Cell signalling by bacteria in quorum sensing C2.1.3 — Hormones, neurotransmitters, cytokines and calcium ions as examples of functional categories of signalling chemicals in animals

Cells interact and communicate with each other by sending and receiving signals. The general pathway for cell-to-cell communication is as follows:



① Sender cell releases ligand (specific signalling chemical) into extracellular space

② Ligand travels to target cell and binds to receptor (proteins with binding sites for specific ligands)

③ Binding of ligand typically induces conformational change in receptor, initiating signal transduction

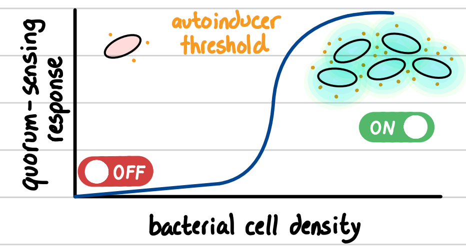
④ Sequence of responses occur in target cell

⑤ Ligand dissociates from binding site of receptor

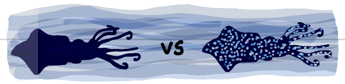
※ Similar to enzyme-substrate specificity, the shape of a receptor's binding site is specific (complementary) to that of a particular ligand, ensuring selective binding and activation (preventing differently-shaped ligands from binding)

Cell-to-cell communication does not only occur in multicellular organisms; Unicellular organisms (such as bacteria) can communicate and coordinate with each other within a population via chemical signalling

↳ Quorum sensing: process of cell-to-cell communication in bacteria which enables coordinated gene expression to changing population density as a means of synchronized activity
※ named 'quorum' as the process operates on a threshold-basis where a minimum amount of a chemical signal (autoinducer) is required to initiate a synchronized, group response.



↳ Quorum sensing is performed by Vibrio fischeri, a bioluminescent bacterium species that lives mutualistically within the light organ of the Hawaiian bobtail squid: squid provides nutrients to V. fischeri and as V. fischeri population density is high within organ, they emit light, used by squid in counter-illumination camouflage in moonlight



view from below

1 V. fischeri release signalling chemical – autoinducer (ligand) into extracellular space

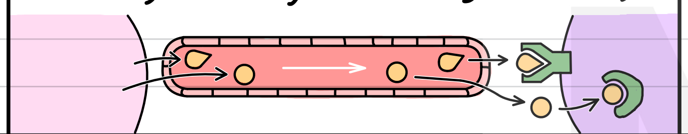
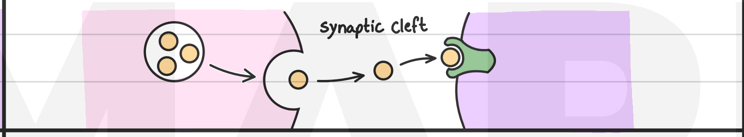
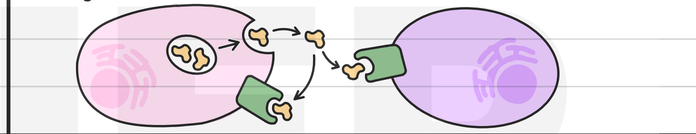
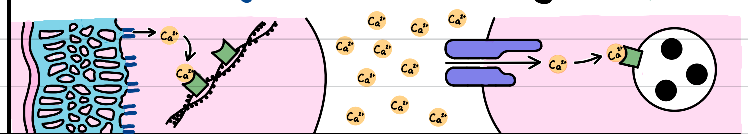
2 autoinducer freely diffuses in and out of cells and accumulates in extracellular environment → as population density ↑, [autoinducer] ↑

3 once concentration of autoinducer reaches threshold, it binds to intracellular receptor LuxR

4 LuxR-autoinducer complex binds to DNA at Lux operon and acts as transcription factor, upregulating transcription of the genes for the enzyme luciferase

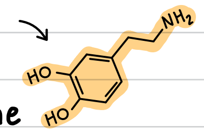
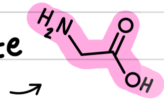
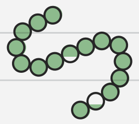
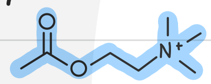
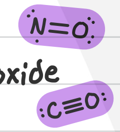
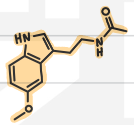
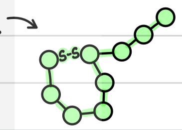
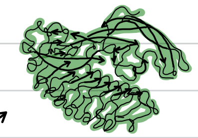
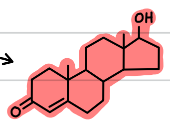
5 Luciferase catalyzes the oxidation ($+O_2$) of luciferin which releases energy in the form of light (bioluminescence)

Signalling chemicals (ligands) in animals can be classified into four functional categories:

	Hormones	Neurotransmitters	Cytokines	Calcium ions (Ca^{2+})
Type of molecule	amines, proteins, steroids	amino acids, peptides, amines, nitric oxide	small proteins, glycoproteins	cation
Mechanism of action	endocrine cells (typically glands) secrete hormones directly into the bloodstream which bind to receptors on the surface or within target cells which may be nearby or far away in the body	presynaptic cell (neuron or sensory cell) secrete neurotransmitters into narrow synaptic cleft which then diffuse only a short distance and bind to receptor on postsynaptic cell (neuron, muscle, or gland)	Many different cell types (such as those in the immune system) secrete cytokines into extracellular space which diffuse and bind to receptors on cells (typically nearby) or the same cell from which it was released	cells pump Ca^{2+} into extracellular space or within organelles (ex: sarcoplasmic reticulum), maintaining a low concentration within cytoplasm. Ca^{2+} enters cytoplasm via facilitated diffusion through gated ion channels, binding to receptors.
				
Response	• promotes or inhibits gene expression and cell activities • effects long-lasting as hormones persist for minutes to hours after secretion	• can promote or inhibit nerve impulses by generating excitatory or inhibitory postsynaptic potentials • effects short-lasting due to rapid removal from receptors	• promotes or inhibits gene expression and alters cellular activity (ex: immune and inflammatory response) • depending on the cytokine, effect can last hours	• can act as second messengers within cells, inducing: contraction in muscle cells, neurotransmitter release by pre-synaptic cells and cortical and acrosome reactions
Examples	insulin, thyroxine, oestradiol, FSH, melatonin	epinephrine	acetylcholine, GABA, dopamine, glutamate	interleukins, interferons, chemokines	• effect typically short-lasting where Ca^{2+} is pumped back

Both hormones and neurotransmitters act as ligands in signalling pathways, yet display large diversity in their chemical composition. This may be due to signalling systems evolving repeatedly in many different organisms, resulting in a wide array of signalling chemicals, with different signalling mechanisms based on their structure and properties. Any chemical can act as a signalling chemical provided:

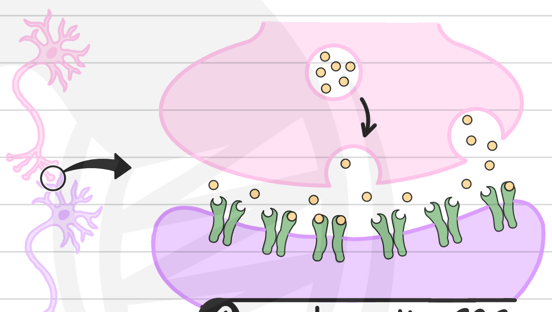
- their shapes and chemical properties are distinctive enough that receptors can bind with them selectively and distinguish them from other chemicals
- small enough to be easily transported into and out of cells and around organism

	Types of Neurotransmitters					Types of Hormones			
	amines	amino acid	proteins / peptides	ester	gases	amines	peptides	proteins / glycoproteins	steroids
Structure	amino acid derivative (modified group)	unaltered amino acid	polypeptide – chain of several amino acids	organic molecule R–C(=O)–OR'	very small gaseous molecules	amino acid derivative (modified group)	short polypeptide chain (2-50 amino acids)	long polypeptide chain (50+ amino acids)	cholesterol derivative (four fused rings)
Examples	dopamine, serotonin, epinephrine 	GABA, glutamate, glycine 	opioids such as endorphins 	acetylcholine 	nitric oxide, carbon monoxide 	epinephrine, thyroxine, melatonin 	oxytocin, GnRH, ADH 	insulin, LH, FSH 	oestradiol, testosterone, progesterone 

Depending on how far signalling molecules are transported from source to target in organisms, their effects can be localized (ex: synaptic signalling by neurotransmitters) or distant (ex: endocrine signalling by hormones)

↳ **Synaptic signalling** : mode of signalling across the junction (synapse) between two cells in the nervous system

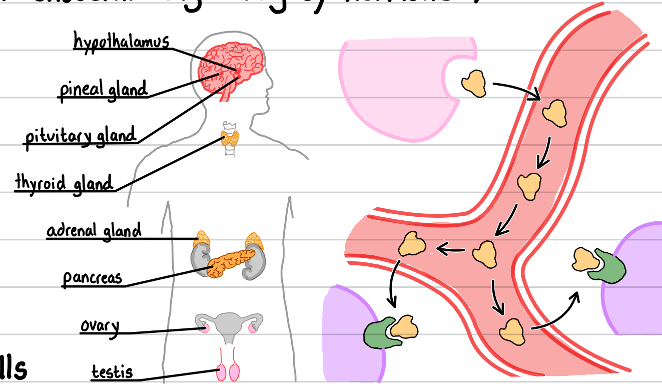
- neurotransmitters are secreted via exocytosis from the presynaptic cell, diffusing across the gap (synaptic cleft), and binding to receptors on the postsynaptic cell membrane
- effects are very localized as neurotransmitters only need to diffuse a very small distance (20-40nm) and only signal the postsynaptic cell



neural signaling C2.2

↳ **Endocrine signalling** : mode of signalling where hormones travel in bloodstream to reach target

- hormones are secreted by endocrine cells into the bloodstream, traveling until they reach and bind to receptors on or in target cells
- effects may be distant and widespread as hormones can travel far from source to signal many different cells



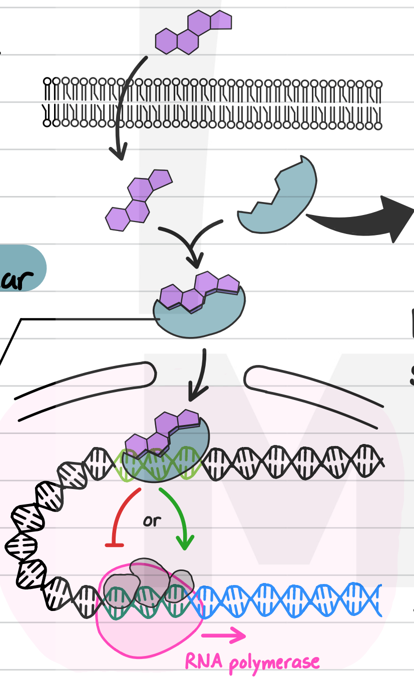
Due to the hydrophobic core of plasma membranes, hydrophilic (polar, charged) ligands cannot penetrate whereas hydrophobic (non-polar) ligands can simply diffuse through readily membranes + transport B2.1
∴ the chemical properties of ligands and their receptor (namely their hydrophobicity/hydrophilicity) will dictate the type of signalling mechanism and transduction pathway - sequences of responses and interactions within the cell

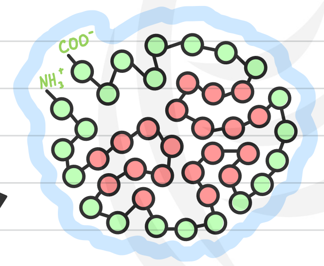
Hydrophobic ligand signal transduction pathway

① hydrophobic ligands such as steroids freely pass into target cells via simple diffusion

② once inside the cell, they bind to an intracellular receptor (either in the cytoplasm or nucleus) forming an activated receptor-ligand complex

③ receptor-ligand complex typically acts as a regulator of gene expression by binding to the DNA at a specific site causing transcription of a particular gene to be promoted or inhibited thus altering cellular activity





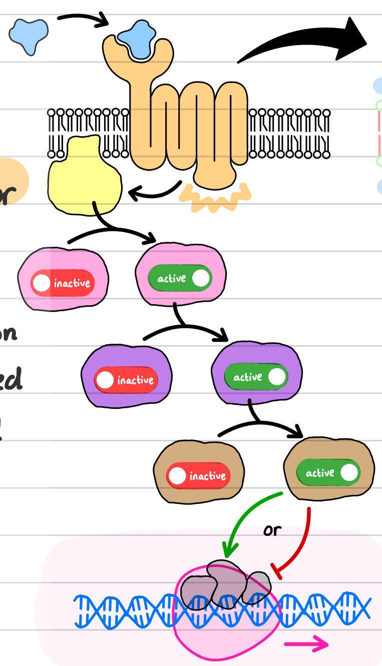
Intracellular receptor is soluble in aqueous cytoplasm/nucleus due to its hydrophilic amino acids facing its periphery and hydrophobic amino acids folded into its core (hydrophobic interactions)

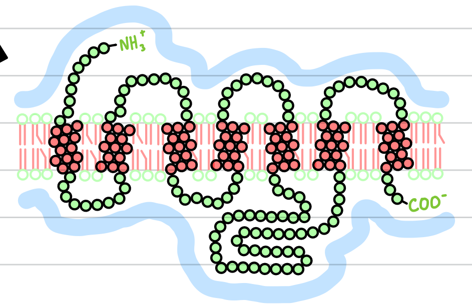
Hydrophilic ligand signal transduction pathway

① hydrophilic ligand such as amines, peptides/proteins bind to extracellular binding site on integral transmembrane receptor

② binding causes conformational change in receptor structure:
- ligand-gated ion channels → pore opens, allowing diffusion
- G protein-coupled receptors → G protein becomes activated
- receptor tyrosine kinase → tyrosine on tails phosphorylated

③ second messenger within cell synthesized/released which triggers signal transduction cascade ultimately resulting in a cellular response, such as changes in gene expression, enzyme activity (metabolic rate), and/or cell movement





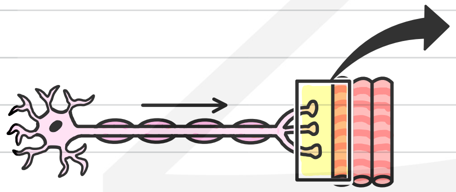
Transmembrane receptor has hydrophilic amino acids protruding into aqueous extracellular space (ligand binding) and cytoplasm (cell protein interactions) and hydrophobic amino acids in the core (interacting with non-polar tails) allowing membrane spanning

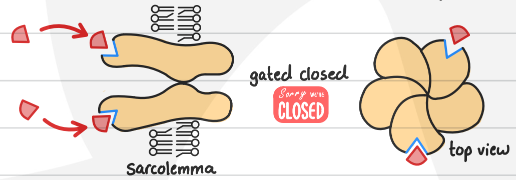
Transmembrane ligand-gated ion channels are receptors located in the membrane of post-synaptic cells in a neural transmission pathway, receiving neurotransmitters from the presynaptic cell at a synapse

neural signalling C2.2
membranes + transport B2.1

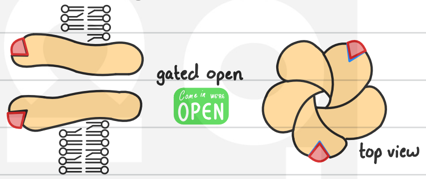
↳ **Acetylcholine receptors**: cholinergic receptors which bind the neurotransmitter Acetylcholine (ACh). Allows the influx of positively charged ions resulting in depolarization and the propagation of an action potential in postsynaptic cell

ex: at neuromuscular junctions, ACh receptors on the sarcolemma bind ACh released from motor neurons, causing muscle fibres to depolarize and initiate skeletal muscle contractions muscle B3.3

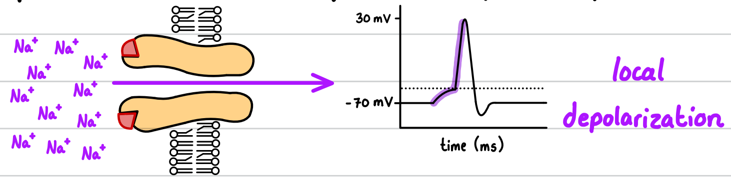




1 Acetylcholine binds at two binding sites on Acetylcholine receptor



2 Binding causes conformational shape change in receptor, opening the gate (pore) for ions



3 cations (Na^+) diffuse through channel into cell, changing voltage across plasma membrane

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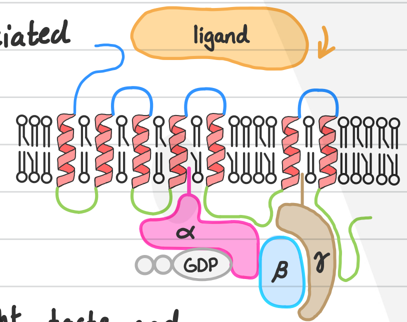
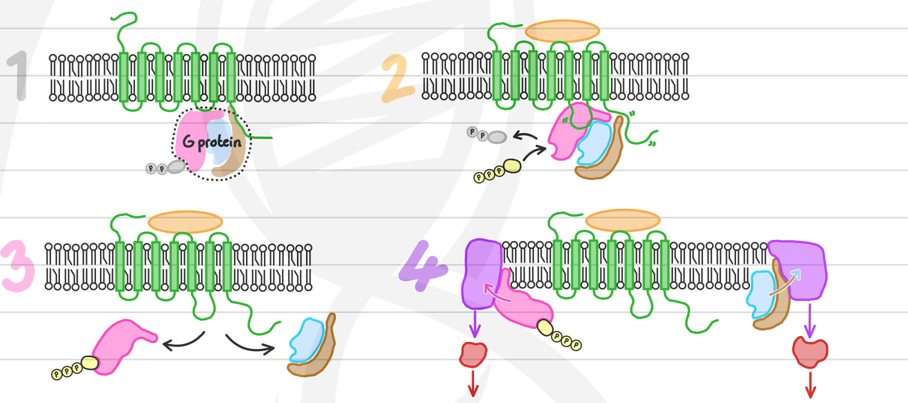
G protein-coupled receptors (GPCR): transmembrane receptor that conveys signals into cells using associated G protein (Guanine nucleotide-binding protein) which acts as a molecular switch for signal transduction

- GPCR is a polypeptide with 7 membrane-spanning α helices forming 6 loops: extracellular loops for ligand binding and intracellular loops for G protein interaction
- G protein composed of 3 subunits: G_α, G_β, G_γ (inactive when G_α bound to GDP)



↳ GPCR are the largest and most diverse group of membrane receptors in eukaryotes and are involved in light, taste, and smell detection, mood regulation, immune response, nervous transmission, endocrine pathways and more! Below is the general mechanism:

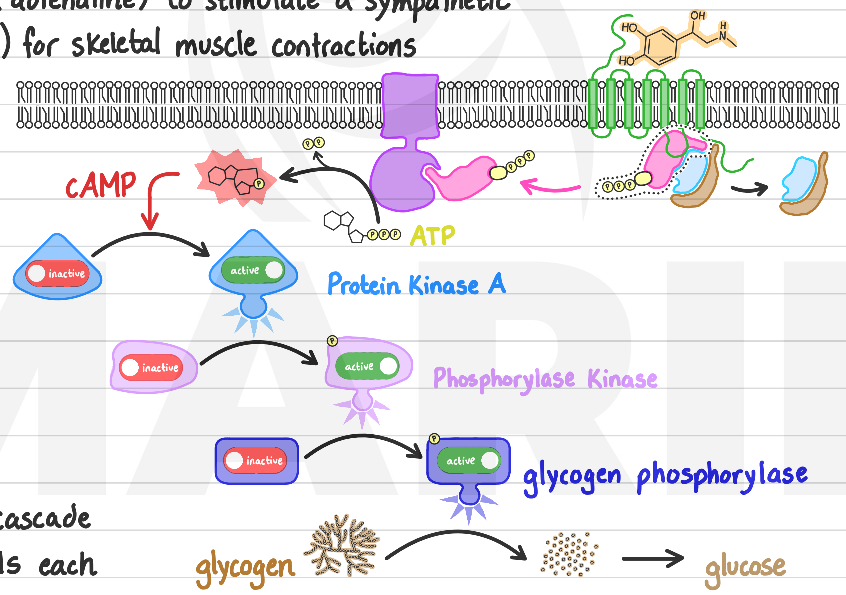
1 G protein inactive as G_α bound to GDP
2 Ligand binds to GPCR causing conformational change in GPCR, displacing GDP from G_α, allowing GTP to bind in its place
3 GTP activates G protein causing dissociation into G_α-GTP and $G_{\beta\gamma}$ dimer and release from receptor
4 G_α-GTP and $G_{\beta\gamma}$ dimer activate effector proteins which relay signal via second messengers in transduction cascade



↳ **Epinephrine (Adrenaline) receptors**: GPCR which bind to epinephrine (adrenaline) to stimulate a sympathetic nervous response, i.e. "fight or flight" where body mobilizes energy (glucose) for skeletal muscle contractions

① Epinephrine binds to epinephrine GPCR receptor inducing conformational change which displaces GDP from G_α in G protein
② GTP binds to G_α inducing dissociation into G_α-GTP and $G_{\beta\gamma}$ dimer
③ G_α-GTP activates membrane-bound enzyme adenylyl cyclase
④ adenylyl cyclase catalyzes conversion of ATP → cyclic AMP (cAMP)
⑤ cAMP as second messenger initiates signalling cascade ultimately resulting in activation of enzyme glycogen phosphorylase
⑥ glycogen phosphorylase catalyzes glycogenolysis (glycogen → glucose)

※ effect of epinephrine can be amplified at each stage of the signalling cascade as each enzyme can catalyze many reactions, thus generating multiple signals each

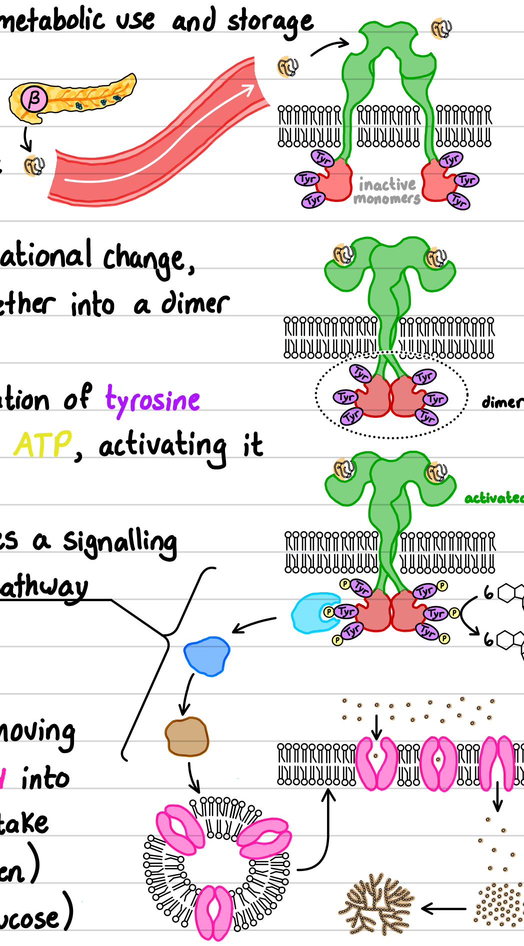


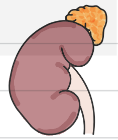
Receptor Tyrosine Kinase (RTK): transmembrane receptor that conveys signals into cells through enzymatic activity (Kinase), specifically by phosphorylating tyrosine from ATP
※ typically, adding phosphate (phosphorylating) a protein activates it (and vice-versa)

↳ **Insulin receptor**: RTK which binds protein hormone insulin in order to signal cellular glucose uptake from blood plasma for metabolic use and storage

homeostasis D3.3

1 insulin released into bloodstream by pancreatic β cells when blood is detected to be hyperglycemic
2 insulin binds to insulin RTK, causing conformational change, bringing the receptor's intracellular domains together into a dimer
3 each tyrosine kinase catalyzes the phosphorylation of tyrosine residues on the neighbouring receptor 'tail' using ATP, activating it
4 each activated phosphorylated tyrosine activates a signalling protein, initiating an intracellular signal cascade pathway
5 signalling pathways ultimately result in:
→ vesicles containing glucose transporter (GLUT4) moving and fusing with membrane, embedding GLUT4 into into the membrane, thus increasing glucose uptake
✓ promotion of glycogenesis (glucose → glycogen)
✗ inhibition of glycogenolysis (glycogen → glucose)

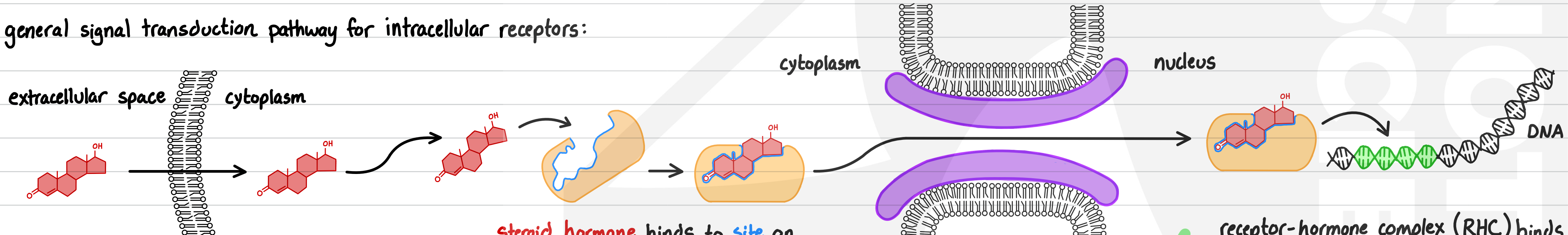


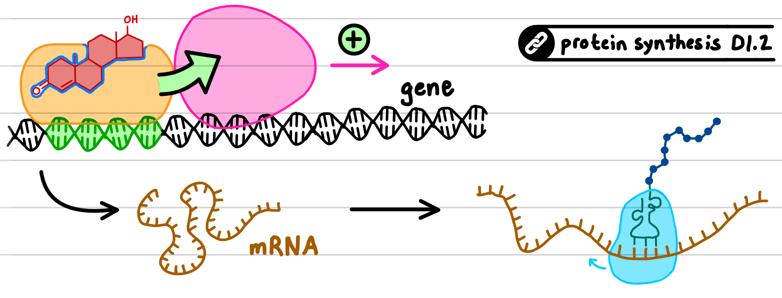


NOS: Naming conventions are an example of international cooperation in science for mutual benefit. While unusual, two terms for same molecule can persist. For example:
Adrenaline = 'ad' (at) + 'ren' (kidney) Epinephrine = 'epi' (above) + 'nephros' (kidney)
both names based on production location - adrenal gland (found above kidney)

Intracellular receptors bind to hydrophobic ligands (such as steroid hormones: testosterone, oestradiol, progesterone) in the cytoplasm or nucleus where they affect gene expression by binding to specific DNA sequences

↳ general signal transduction pathway for intracellular receptors:





1 steroid hormone (ex: testosterone) diffuses through the plasma membrane into cytoplasm

2 steroid hormone binds to site on intracellular receptor forming an active receptor-hormone complex

3 receptor-hormone complex enters nucleus via nuclear pore

4 receptor-hormone complex (RHC) binds to hormone-response element (sequence within promoter region of gene)

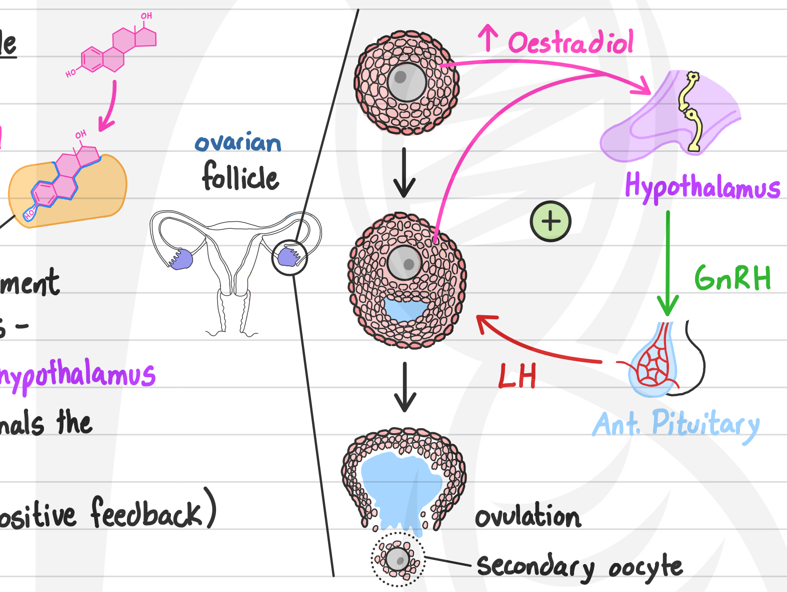
5 RHC regulates RNA polymerase activity such as promoting gene transcription, ultimately synthesizing more of a particular protein, altering cellular activity

Oestradiol and Progesterone are steroid female sex hormones responsible for a wide-range of effects including regulation of menstrual cycle, triggering development of female secondary sex characteristics, maintenance of reproductive tissues and pregnancy. reproduction D3.1 ※ note: oestradiol and progesterone are also naturally found in males (although in lower concentrations) and are involved in many aspects such as mood, spermatogenesis, and more.

↳ Oestradiol plays key role in the menstrual cycle including regulation of Gonadotropin-releasing hormone (GnRH) release

Oestradiol's role at the end of follicular phase of menstrual cycle

1. granulosa cells of developing follicle in ovary secrete Oestradiol
2. Oestradiol diffuses into neurons of hypothalamus and binds to Oestradiol intracellular receptor, forming a complex
3. receptor-Oestradiol complex binds to oestradiol-response element in DNA and promotes gene expression of signalling proteins - inducing a surge in GnRH secretion by GnRH neurons in hypothalamus
4. GnRH binds to receptors on cells in anterior pituitary and signals the expression and release of Luteinizing Hormone (LH)
5. LH promotes follicle development and Oestradiol release (positive feedback)
6. LH surge ultimately results in ovulation

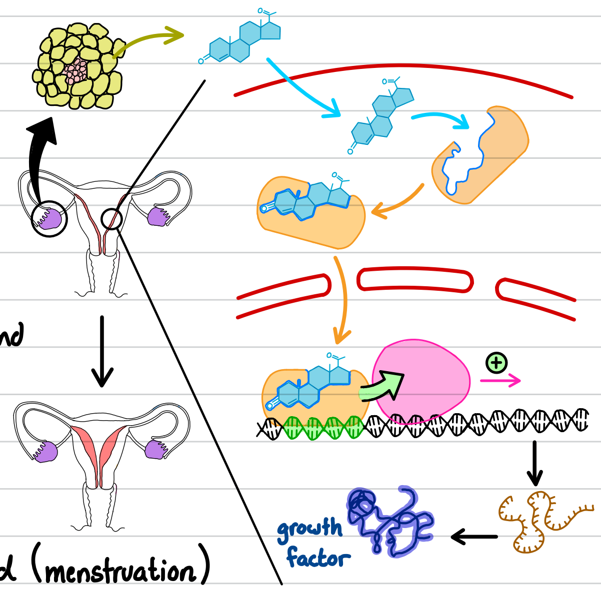


↳ Progesterone plays key role in the menstrual cycle including the development and maintanance of endometrium

Progesterone's role during luteal phase of menstrual cycle

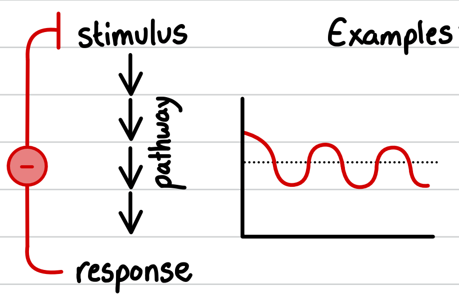
1. Progesterone secreted by corpus luteum in ovaries
2. Progesterone diffuses into cells of endometrium (uterine lining)
3. Progesterone binds to progesterone intracellular receptor within the cytoplasm, forming a receptor-progesterone complex
4. receptor-progesterone complex moves into nucleus via nuclear pore and binds to progesterone response element in promoter of target gene
5. Complex acts as transcription factor, promoting transcription of genes for cell growth and proliferation (such as growth factors)
6. endometrial cells grow and divide, causing it to thicken

※ if progesterone levels fall, endometrium breaks down and is shed (menstruation)



Cell signalling pathways can be regulated by both negative and positive feedback where the amount of a product in a pathway can impact how much more is produced.

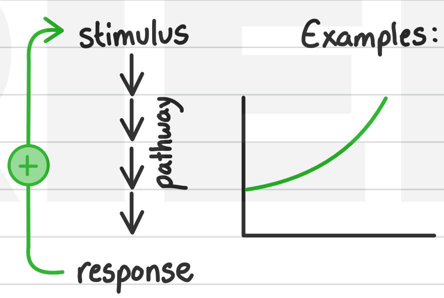
↳ negative feedback : end-product inhibits more of its own production ⊣ reverses change and leads to stabilization of system



Examples:
- ⊖ thermoregulation via thyroxin
- ⊖ blood glucose level regulation via insulin and glucagon
- ⊖ osmoregulation via ADH
- ⊖ heart rate and blood pressure
- ⊖ blood pH regulation via ventilation
- ⊖ oestradiol and progesterone levels in menstrual cycle

(first three: homeostasis D3.3; heart rate/blood pH: integration of body systems C3.1; oestradiol and progesterone: reproduction D3.1)

↳ positive feedback : end-product stimulates more of its own production → amplifies change in system



Examples:
- ⊕ ovulation via LH surge during menstrual cycle
- ⊕ childbirth via oxytocin
- ⊕ fruit ripening via ethylene
- ⊕ lactation via prolactin and oxytocin

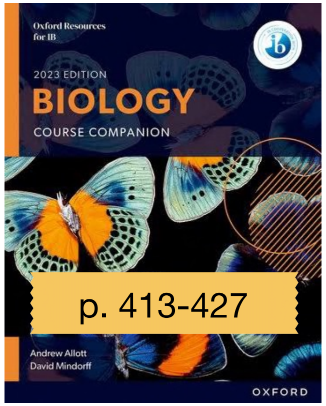
(first two: reproduction D3.1; fruit ripening: integration of body systems C3.1)

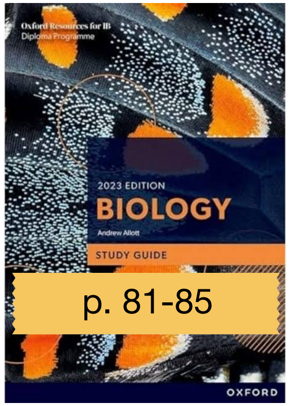
※ typically reinforces stimulus in order to drive a process/event to completion

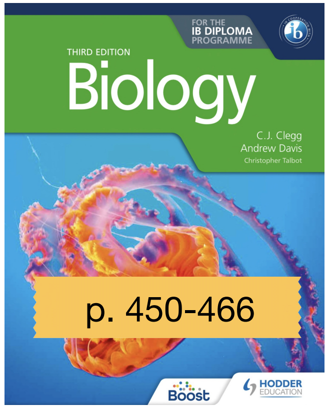
Resource Links

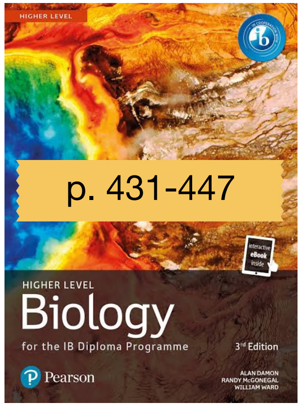
each resource is hyperlinked

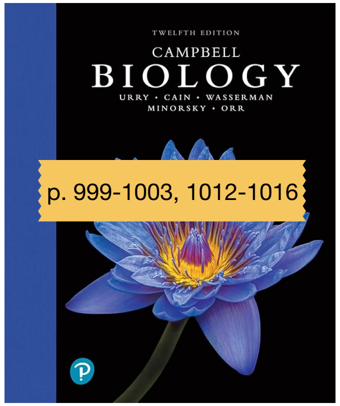
Textbooks



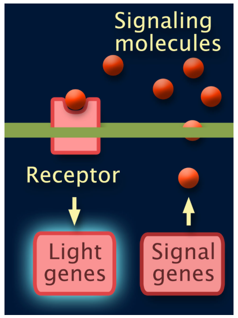








Simulators / Interactives



Quorum sensing

Signalling pathway diagrams

Articles

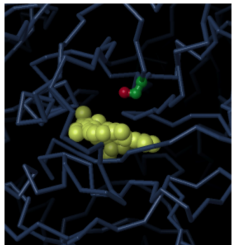
Bramhachari, N. P. V., & Sheela, G. M. (2018). Vibrio fischeri Symbiotically Synchronizes Bioluminescence in Marine Animals via Quorum Sensing Mechanism. In Springer eBooks (pp. 207–219). https://doi.org/10.1007/978-981-13-2429-1_13

GPCRDB: an information system for G protein-coupled receptors. Isberg, V., Vroling, B., van der Kant, R., Li, K., Vriend, G. and Gloriam, D. Nucleic Acids Research, 2014

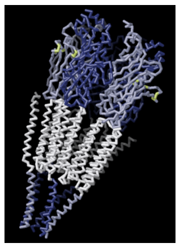
Lights. camera. action! How the Hawaiian bobtail squid brings a creative vision to its maritime world of small big. . . (n.d.). https://www.labxchange.org/library/items/lb:LabXchange:c4a7aa61:html:1

Pándy-Szekeres, et al. (2022). GPCRdb in 2023: state-specific structure models using AlphaFold2 and new ligand resources. Nucleic Acids Research, 51(D1), D395–D402. https://doi.org/10.1093/nar/gkac1013

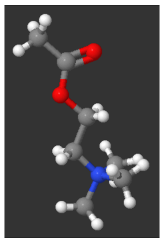
3D models



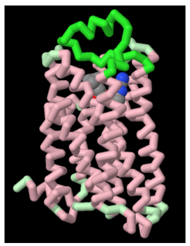
Luciferase



Acetylcholine Receptor

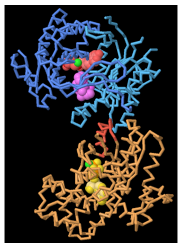


Acetylcholine

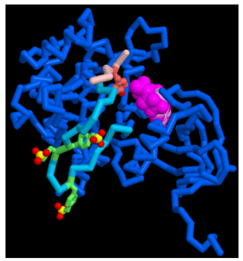


GPCR

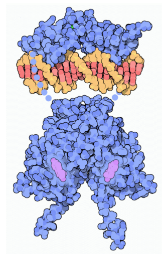
G protein



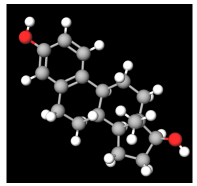
Adenylyl Cyclase + G protein



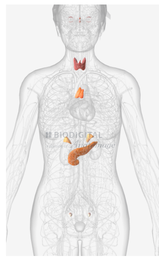
Insulin receptor



Estrogen receptor



Estradiol



Endocrine system