INTERACTION DRUG ↔ BODY

What the drug does to the body
Pharmacodynamics, PD

Drug Action and Mechanism

Absorption, Distribution, Metabolism, Excretion

Pharmacokinetics, PK

What the body does to the drug
Receptors
- intracellular receptors
- membrane receptors
  - Channel receptors
  - G protein-coupled receptors
  - Tyrosine-kinase receptors

Drug/receptor interactions
- agonists and antagonists
- potency and efficacy (effectiveness)
- therapeutic index

Drug effects
- therapeutic effects
- side effects
- toxic effects
Cell-surface (or transmembrane) receptors are membrane-anchored, or integral proteins that bind to external ligand molecules. This type of receptor spans the plasma membrane and performs signal transduction, converting an extracellular signal into an intracellular signal.
This large group of membrane-bound receptors comprises the 7TM or 1TM receptor families. All recruit multiple intracellular signaling cascades known as “second messengers”.
G PROTEIN-COUPLED RECEPTORS (GPCRs)

The largest and most diverse group of membrane receptors in eukaryotes.

Class A (Rhodopsin-like)  most receptors binding monoamines and neurotransmitters
Class B (Secretin receptor family)  binding ligands such as secretin, glucagon, calcitonin
Class C (Metabotropic glutamate/pheromone) Ca-sensitive receptors as the mGlu R

Class D (Fungal mating pheromone receptors)
Class E (Cyclic AMP receptors)
Class F (Frizzled/Smoothened)
G PROTEIN-COUPLED RECEPTORS (GPCRs)

The largest and most diverse group of membrane receptors in eukaryotes.
G PROTEIN-COUPLED RECEPTORS (GPCRs)

They sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses.

**GPCRs** are also known as **seven-transmembrane domain receptors, 7TM receptors** because they pass through the cell membrane seven times.
• The extracellular part of the receptor (N terminal) holds the ligand binding site and can be glycosylated. These extracellular loops also contain two highly conserved cysteine residues that form disulfide bonds to stabilize the receptor structure.

• The intracellular parts of the receptor can be phosphorylated. This serves as additional modulatory mechanism of activity. In addition, lipid anchoring sites allow for its membrane localization.

• Similar to GPCRs, the adiponectin receptors 1 and 2 (ADIPOR1 and ADIPOR2) also possess 7 transmembrane domains. However, ADIPOR1 and ADIPOR2 are orientated oppositely to GPCRs in the membrane (i.e., extracellular C-terminus, cytoplasmic N-terminus) and do not associate with G proteins.
GPCR ACTIVATION AND SUBSEQUENT EFFECTORS

1) ION CHANNELS

Some GPCRs, when activated, modify the intracellular ion concentration

2) ENZYMES and second messengers

Some others amplify the signal giving raise to biologically active second messengers
**GPCR and G PROTEINs**

- GPCR are so called because they are bound to an intracellular G protein
- Guanine nucleotide-binding proteins (G proteins) act as molecular switches inside cells, and are involved in transmitting signals from a variety of stimuli.
There are two classes of G proteins: the **monomeric small GTPases**, and the **heterotrimeric G protein complexes**.

- The heterotrimeric G protein is made up of **alpha (α)**, **beta (β)** and **gamma (γ)** subunits.
- The **alpha (α)** subunit holds the catalytic GTPase activity.
- The **beta (β)** and **gamma (γ)** subunits can form a stable dimeric complex referred to as the beta-gamma complex with regulatory activity.

Their activity is regulated by factors that control their ability to bind to and hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP).
**ACTIVATION/INACTIVATION CYCLE OF GPCR**

**ACTIVATION:** ligand binding results in G-protein exchange of GTP for GDP. The activated G-protein then dissociates into an alpha (G-alpha) and a beta-gamma complex.

- G-alpha bound to GTP is active, and diffuses along the membrane surface to activate target proteins, (often enzymes that generate second messengers).

- The beta-gamma complex is also able to diffuse and activate proteins, typically affecting ion channels.

**INACTIVATION:** it occurs because G-alpha has intrinsic GTPase activity. After GTP hydrolysis, G-alpha bound to GDP will reassociate with a beta-gamma complex to form an inactive G-protein that can again associate with a receptor.
DISTINCT Gα subunits

The many classes of Gα subunits behave differently in the recognition of the effector molecule, but share similar activation mechanisms.

- **G_i/G_o** inhibit adenylyl cyclase (AC), activate K+ channels or inhibit Ca^{2+} channels
- **Gs** activates adenylyl cyclase (AC), and increase intracellular cAMP levels. cAMP major effect is to bind to and activate cAMP-dependent kinase (PKA)
- **G_q** activates phospholipase C (PLC), which transforms PIP_2 into InsP_3 and DAG. In turn, DAG activates protein C kinase (PKC) while InsP3 increases intracellular [Ca^{2+} ].
### SOME ENDOGENOUS LIGANDS OF GPCRs

<table>
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<th>α SUBUNIT</th>
<th>EFFECOR</th>
<th>LIGANDS AND RECEPTOR TYPES</th>
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</table>
| αs        | Adenylyl-cyclase (+)  
Canali al calcio (+) | noradrenaline (β₁, β₂, β₃); dopamine (D₁,D₂); serotonin (5HT₄); ACTH, FSH, LH, TFH, GnRH, GHRH, Vasopressin, Calcitonin, Prostaculcin |
| αi₁,₂,₃  | Adenylyl-cyclase (-) | noradrenaline (α₂); dopamine (D₂, D₃, D₄); serotonin (5HT₁); acetilcholine (M₂, M₄); somatostatin (SSTR₁-₅) |
| αi₃       | Potassium channels (GIRK) (+) | acetilcholine (M₂, M₄); dopamine (D₂); somatostatin (SSTR₁,₂) |
| αq        | Phospholipase C (+) | noradrenaline (α₁); serotonin (5HT₂₁); TSH, TRH, GnRH, LXs, thromboxans |
| α₀₁,₂     | Calcium channels (-) | noradrenaline (α₂); acetilcholine (M₂, M₄); somatostatin (SSTR₁,₂) |
Some GPCR undergo dimerization. This process can be a **homodimerization** \((M_3, \beta_2, \text{GABA}_B)\) or a more complex **heterodimerization** \((D_2/SSTR_5, AT_1/B_2, SSTR_2/\mu_{\text{opioid}})\).

**Constitutive**
- δ/κ opioid
- Adenosin A1/DopamineD1
- δ opioid/β_2 adrenergic

**Ligand-induced**
- SSTR_5/D_2
- GABA_B/D_5
GPCRs become desensitized when exposed to their ligand for a prolonged period of time. There are two recognized forms of desensitization:

1) **homologous desensitization**, in which the activated GPCR is downregulated;

2) **heterologous desensitization**, wherein the activated GPCR causes downregulation of a different GPCR. This downregulation is regulated by protein kinase-dependent phosphorylation of the intracellular (or cytoplasmic) receptor domain.
Agonist binding also converts the receptor into a substrate for a family of kinases, the G-protein-coupled receptor kinases (GRKs). GRKs phosphorylate only agonist-activated receptors.

Subsequently, the phosphorylated receptor becomes a binding partner for arrestins.

**Arrestins** are normally cytosolic proteins, but they recognise agonist-activated, phosphorylated receptors and bind them. This binding makes the receptor inaccessible for G-proteins (i.e. the arrestin-bound receptor is desensitised), and it targets the receptor for internalization. This is because arrestins do not only bind receptors, but they also bind components of clathrin-coated pits. Thus, arrestin-bound receptors move into clathrin-coated pits and are then internalized.
GPCR desensitization mechanisms

G protein coupling

Agonist binding

Desensitization

β-arrestin binding

β-arrestin signalling

MAPK (ERK and JNK)
Tyrosine kinase
E3 ubiquitin ligase

G protein signalling

↑ cAMP ↓
↑ IP3
↑ Ca^{2+}
This large group of membrane-bound receptors comprises the 7TM or 1TM receptor families. All recruit multiple intracellular signaling cascades known as “second messengers”.
RECEPTOR TYROSINE KINASES (RTKs) are the high-affinity cell surface receptors for many polypeptide growth factors, cytokines, and hormones. RTKs have been shown not only to be key regulators of normal cellular processes but also to have a critical role in the development and progression of many types of cancer.
SCHEMATIC REPRESENTATION OF VARIOUS RTK SUBTYPES AND THEIR RESPECTIVE COGNATE LIGANDS
Ligand binding to the extracellular domain of the TKRs causes dimerization that results in autophosphorylation and activation of the intracellular kinase domain. The ensuing phosphorylation of docking sites on the receptor leads to the recruitment of enzymes, signal transducers and adaptor molecules activating downstream signalling pathways. The signalling pathways regulate a diverse array of processes including transcription, translation, metabolism, cell proliferation, survival, differentiation and motility.
RTKs – TRANSDUCTION SIGNALING CASCADES

[Diagram showing the process of receptor activation, phosphorylation, and signal transmission involving SH2 domains and other enzymes/adapter proteins like Grb2 and Sos.]

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RTKs – TRANSDUCTION SIGNALING CASCADES

(STAT3) - signal transducer and activator of transcription 3

(GRB2) - growth factor receptor-bound protein 2
RAS proteins are small GTPases, which serve as master regulators of a myriad of signaling cascades involved in highly diverse cellular processes. RAS oncogenes have been originally discovered as retroviral oncogenes.

The RAS/RAF/MEK/ERK pathway is the classical RAS/MAPK signaling pathway implicated in growth-factor mediated cell proliferation, differentiation and cell death. RAS activates RAF, which in turn activates mitogen-activated protein kinase kinase 1/2 (MAP2K1/2 or MEK1/2). MEK1 and MEK2 then phosphorylate their two known substrates, ERK1 and ERK2.