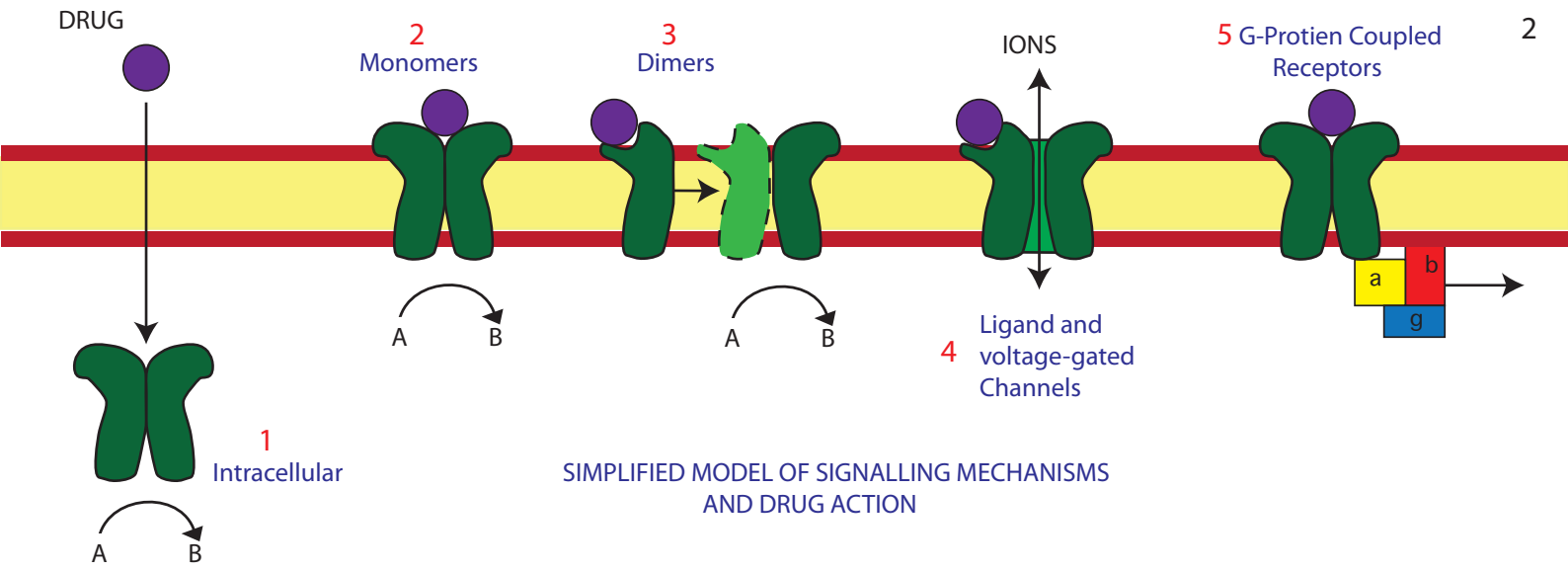


SIMPLIFIED MODEL OF SIGNALLING MECHANISMS AND DRUG ACTION

Intracellular receptors Lipid soluble signalling molecules difuse across the cell membrane and interact with these receptors. The most studied of this class are the Steroid Receptor Superfamily which include; steroids, sterols, thyroxine, retinoic acid and vitamin D. The hormone-receptor complex then modulates gene transciption leading to a biological effect. This explains the lag with drugs such as prednisolone which has an effect lag of ~30mins whilst the transcription takes place and can continue to have effect for days.

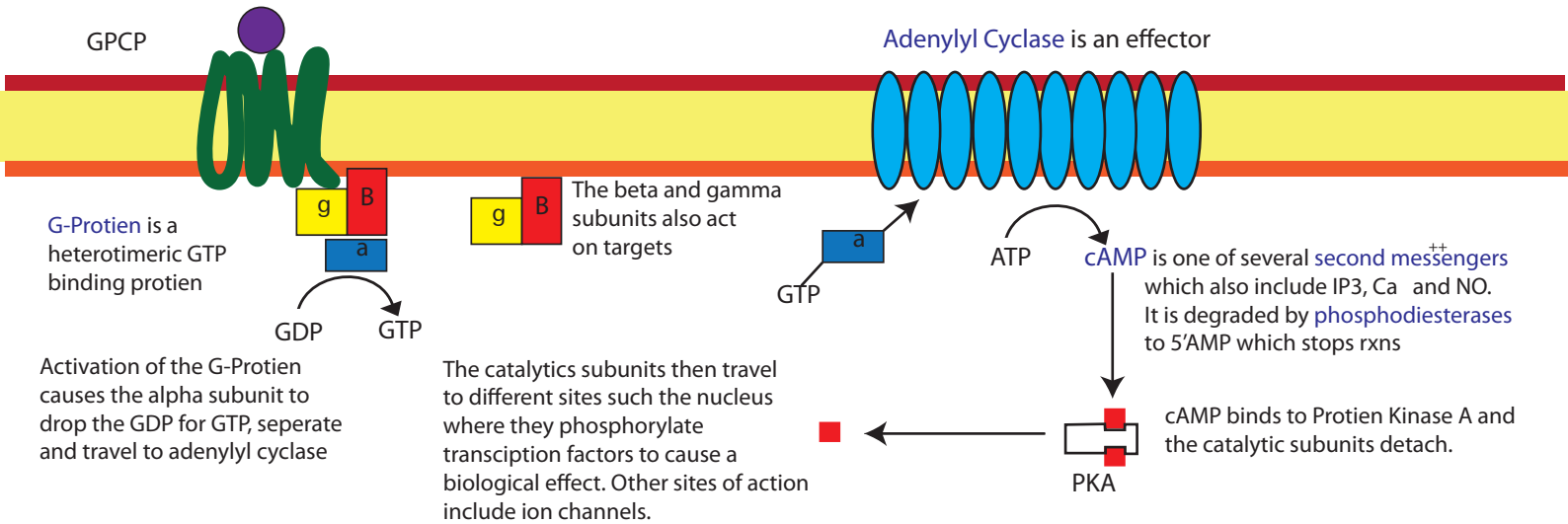
The remainder of the receptors above are transmembrane, and interact with hydrophillic ligands or ions on the cell surface.

Enzyme linked cell surface receptors are a very diverse group that contain intracellular catalytic domains or are closely associated with intracellular enzymes. They may be present either as monomers (for example guanylyl cyclase which binds to atrial natriuretic factor) or dimers such as the tyrosine kinase-associated receptors (which bind to erythropoietin or the interferons) and dimerise on contact with the associated ligand.

Ligand-gated ion channels are involved primarily in fast synaptic transmission between excitable cells. An example is the nicotinic acetylcholine receptor at the neuromuscular junctions.

The last class of recptors are the G-Protien Coupled Receptors. These activate or inhibit adenylyl cyclase, activate phosphilapse C or modulate ion channels. A variety of signals, which include hormones, neurotransmitters, cytokines, pheremones, oderants and photons produce their intracellular actions through GPCR. They are discussed below in greater detail along with second messengers.

The Adenylyl Cyclase/Protien Kinase A Pathway as an example of G-Protien function Hemmings pg 40



Receptors are regulated in number, location and sensitivity. Frequent or continuos exposure leads to short term diminution of the receptor response sometimes called tachyphylaxis (literally "fast-guarding"). There are three main mechanisms for this, intracellular protiens may block access to a G-protien to the activated molecule. An example is Beta-arrestin which blocks continuos activation of the Beta-adrenoceptor. Second, agonist bound receptors may be internalised by endocytosis (eg morphine receptors). Third, continuos activation may lead to depletion of a substrate needed for downstream effects. Long term changes lead to down regulation or up regulation of receptors.

An adverse reaction to a drug is a harmful or unintended response. Overdose, excessive effects and drug interactions may occur in any patient. Adverse reactions occuring only in susceptible patients include intolerance, idiosyncrasy (often genetic in origin) and allergy (usually immunological mediated). See following Pharmacological Basis of Poisoning for further information.

Christopher Andersen 2012