* G proteins and their receptors – GPCRs
* Cyclic adenosine monophospahte – cAMP pathway
* RTKs lead to the binding of two transmembrane proteins – lead to phosphorylation – standardised form of signalling – some prokaryotes use too
* G-Protein-linked receptors or G-Protein Coupled Receptors (GPCRs) – very conserved too
* GPCRs
  + Have receptors such as photorodopsin, olfactory receptor
  + Important to break down or make up of glucose to provide energy to cell
* In glucose metabolism, epinephrine analogs
  + Agonists act like epinephrine
  + Antagonists block the action of epinephrine
  + Adrenalin is what we concern about
  + Now we know that adrenergic receptors are not in adenylate cyclases anymore
  + Before thought receptor does all the signalling in the cell – now found out that transducer in the middle that controls things
  + Alpha 2 – flight
  + Beta 1 and 2 – get more air into lung
* Signalling has 3 components
  + Receptor
  + Transducer – G proteins are heterotrimers – multiple units coming together – quaternary – 3 components that are anchored
  + Effector – adenylate cyclase
* Beta2-Adrenergic receptor
  + In the cell – very compact – moving around – so fluid which we need to think in 3D
  + All the 7 sequences are embedded in the membrane as alpha-helixes – give it hydrophobicity – make sure they are embedded in membrane
  + The loops in between allow the shape to be formed to receive the signals
  + Glycosylation enhances the signalling
  + The twisting opens up new active site on the other side
* GCPR structure
  + Rhodopsin has light receptor whereas beta2AR binds to adrenaline as an agonist
  + They are conserved – co-evolved – using similar mechanisms to transmit the signal
* G proteins
  + Has 3 domains
  + 2 of them are attached onto the inside of the cytoplasm
  + 1 of them is detached
  + Alpha, beta, gamma are the subunits
  + GDP when bounds become GTP and becomes active – can activate or inhibit adenylate cyclase
  + GTPase – enzyme that takes off a phosphate and turn GTP to GDP – phosphatase
* Activated G Protein activate Adenylate Cyclase (AC) – converts ATP to AMP by nucleophilic attack
* cAMP is a signalling molecule
* Need to have so many checkpoints – to make sure that the signal is meant to go where it is supposed to go – don’t want random reaction going on – can only go in one direction – 2nd Gibbs free energy – need to transform the receptor, G Protein – cost a lot of energy – need to fill the gap of energy in small steps – cAMP is a ligand within the cell
* The four domains of AC come together to turn ATP to cAMP – the nucleophilic attack needs to happen such that the conformation allows it to happen
* Steps in G protein signalling
  + Hormone binds to GPCR – then it binds to GDP making GTP
  + ATP is converted to cAMP – causing cellular response
  + G protein catalyses hydrolysis of its bound GTP to generate GDP again
  + The movement from GDP to GTP is a very short time – because protein itself has phosphatase activity that is very weak so it wants to go back to its original time – need to reset because another one gonna come – overactivation means cell will act in activated fashion as well
* Ending cAMP signalling
  + Last bit of the G Protein signalling
  + Don’t want to continually signal because cannot respond to next signal
  + Protein Kinase – A (PKA) is responsible to control AC activity – make sure it is not always in excited state
* Drugs affect cell signalling
  + Inhibitor – keep AC in active – body feels like need to run even no adrenaline
* Toxins affect cell signalling
  + Stimulatory external signalling comes in – GTP converted to GDP
  + Cholera toxin inhibits conversion of GTP to GDP so it activates AC and cellular response – uncompetitive inhibitor – lock the substrate into the protein
  + Inhibitory external signal – inhibits AC – eg. pertussis toxin causes whooping cough – keep GDP inactive
* Alternative pathway to cAMP signalling – phosphoinositide pathway
  + Transduction path
  + 3 secondary messenger generated from phospholipase (PLC) – IP3, calcium, and DAG (diacyl-glycerol)
  + Still G protein
  + PLC – cuts glyceride bond – break down lipid
  + Glycerophospholipid
* Phosphoinositide signalling
  + If have glycerophospholipid, got one phosphate group
  + PIP2 has 2 phosphateds
* Cellular processes controlled by phosphoinositide – table in slide 24 – acetylcholine is very important – basic principle of immunology, embryology are the same
* Nitric oxide (NO) as secondary messenger – very important in the brain and other cells – regulate neurotransmission, vasodilation, stimulating defence to microbial infection
* Need 2 different receptors for hormones because that one hormone can do two different things
* One signal can have multiple impacts following in the same direction – complimentary effect