Learning goals for this file:

1) Review receptor theory – affinity, antagonists, agonists
2) Upregulation & downregulation; spare receptors
3) Types of Ligands and Receptor systems
4) Second messenger systems

Note:

- Examples of how different endogenous chemicals in the body use these different receptor systems are given – this is just so the information makes sense with real-world examples
- Additionally, some examples are described in greater detail as DRUG correlates.
- Pay more attention to the drug correlates given in the notes when you study, since of COURSE this is a pharmacology course!!

RECEPTORS & LIGANDS – *REVIEW OF BASIC CONCEPTS*:

Note: for a quick summary on this topic, see the Merck Manual Online:
http://www.merckmanuals.com/professional/clinical_pharmacology/pharmacodynamics/drug%E2%80%93receptor_interactions.html?qt=pharmacodynamics%20receptors&alt=sh

PHARMACOLOGIC ACTION – PHARMACODYNAMICS OF A DRUG:

Receptor concepts:

- **Most receptors are proteins** (or glycoproteins) **located:**
  - **on the cell membrane**
  - **in the cell cytoplasm**
  - **on the nuclear membrane**
  - **on the DNA itself**
- These receptor glycoproteins form highly specific 3-D shapes due to the folding up of proteins – this shape is the **conformation** of the receptor

Ligand affinity:

- Within this conformation the receptor will have "pockets" where the ligands will fit in; the tighter the fit, the better the **"affinity"** for the receptor
  - some drugs have a highly **selective ligand affinity** for specific receptors and subtypes of receptors
  - the **affinity** of a drug reflects its strength of bonding to its specific receptor.
  - A low affinity drug dissociates from its receptor more easily & quickly, creating a more reversible effect.

Ligand binding action:

- **Ligand binding** causes different actions depending on the receptor:
- EXAMPLES:
  - ion channels will open or close
  - cytoplasmic **"second messenger"** molecules are created
  - DNA is stimulated to transcribe mRNA for protein synthesis.
- Overall, cell physiologic functions **are inhibited or stimulated** due to the action of ligand binding.

Drug ligand binding to receptors: some VOCABULARY

- The ligand can be **endogenous** (created by the body, e.g. hormones)
- The ligand can be **exogenous** (taken in from the outside, e.g. drugs)
- Ligand binding effects are called **"signaling"** since the extracellular ligand (DRUG) acts as a "signal" to tell the cell to alter it's physiology.
  - The ligand signal **"transduces"** (TURN INTO) into intracellular messages affecting cell physiologic functioning – thus, achieving your drug effect !!

RECEPTOR ACTIVITY:

1. SPARE RECEPTORS:

- **the more receptors, the more statistical "hits" of ligand and receptor.** Thus, less drug is needed and there is more **sensitivity to the drug**
- **This can also be thought of as increased "receptor density"**
  - an increase in the number of receptor proteins physically located in the cell
- **Another aspect of increased spare receptors is how the receptor "behaves"**
  - the increased "spare activity" may be due to the fact that once a receptor is occupied, the agonist effect is longer lasting that the actual binding/occupying time ("temporal spare receptors").

2. CHANGING NUMBERS OF AVAILABLE SPARE RECEPTORS:

- ***Up regulation:*** Cells can increase the number of available receptors by synthesizing more receptors, or reducing destruction of old receptors.
  - Clinical example:
    - losing weight or eating a low-fat diet will reduce the amount of cholesterol in the liver; the liver now *up-regulates* (increases) the number of hepatocyte receptors for HDL-C and increases reverse cholesterol transport (clearing the blood of LDL-C)
    - *statin* anti-cholesterol drugs also do this, and by will cause the liver to *up-regulate* its receptors, clearing more cholesterol from the bloodstream, thus reducing patient's serum cholesterol.
- ***Down regulation:*** cell synthesizes less receptors, or increases endocytosis of existing cell receptors to destroy old receptors.
  - **Desensitization:** With almost any hormone, large **continuous** amounts of circulating hormone will cause down-regulation, almost like the cell "defending" itself against this onslaught of ligand.
  - Clinical example: insulin resistance (metabolic syndrome, MetSyn)
    - obesity causes more "space" between receptors, thus reducing the number of insulin "hits" and reducing cell's sensitivity to insulin. Weight loss reverses this effect.
    - increased circulating insulin causes adipose cells to destroy insulin receptors by endocytosis, making the cell less sensitive to circulating isulin (Insulin Resistance Syndrome, or "IRS")
    - Overall, either/both obesity and/or hyperinsulinemia worsens IRS

3. RECEPTOR VARIETY:

- cells have many receptors
- research & development of new drugs often targets receptors & enzyme systems
- the more we know about basic science, we now have more **therapeutic targets** for pharmacologic intervention!!
- Thus, we must keep up with our continuing education or risk becoming a prescribing dinosaur…oh, no!!

OVERALL DRUG EFFECT: effects of ligand drugs are dependent on →

- concentration of the drug in solution
- maximal effect that can possibly be reached (all receptor sites are occupied)
- strength (affinity, selectivity) of ligand binding

AGONIST DRUGS (LIGANDS): with either **full or partial activity.**

1. **FULL AGONISTS:**
   - a strong (full) agonist causes maximal effects even when occupying a small fraction of available receptors;
   - a weak (full) agonist needs to occupy more receptors to get the same biologic effect.

2. **PARTIAL AGONISTS:**
   - An agonist which, even at full receptor occupancy, cannot elicit a response equal to that of a full agonist
   - Sometimes also called agonist-antagonist or mixed agonist-antagonist
   - Thus, a partial agonist will produce less than maximal effects, even when occupying all available receptors.

3. **REVERSE (INVERSE) AGONISTS:**
   - **What is a "reverse agonist" (also called an "inverse agonist"?**
   - A relatively new term
   - Many receptors have "native" basal activity – if a drug binds to the receptor and stabilizes it, there will be a reduction in agonist activity
   - Thus a reverse agonist has similar effects as antagonists

4. **EFFICACY:**
   - the degree to which a drug is able to induce maximal effects
   - **for drugs affecting receptors, greater efficacy is a higher biologic activity from occupation of fewer receptor sites**

COMPETITIVE ANTAGONIST DRUGS (LIGANDS):

- compete with endogenous agonist for binding on the SAME receptor sites.
- Thus, ***blockade*** of a normal interaction of endogenous chemical and its receptor will prevent the normal biologic activity from occurring.
- Example:
    - the smoking-cessation drug **varncicline (Chantix)** binds to the same nicotine receptors in the brain that are activated with smoking nicotine-containing tobacco and thus the MOA of the drug is to prevent the pleasure from nicotine use and also slow dopamine release (which causes the craving to smoke and thus reduces the cravings)
    - Your patients will know all about receptors: https://www.youtube.com/watch?v=aBNYMwz5oOk (YouTube video)

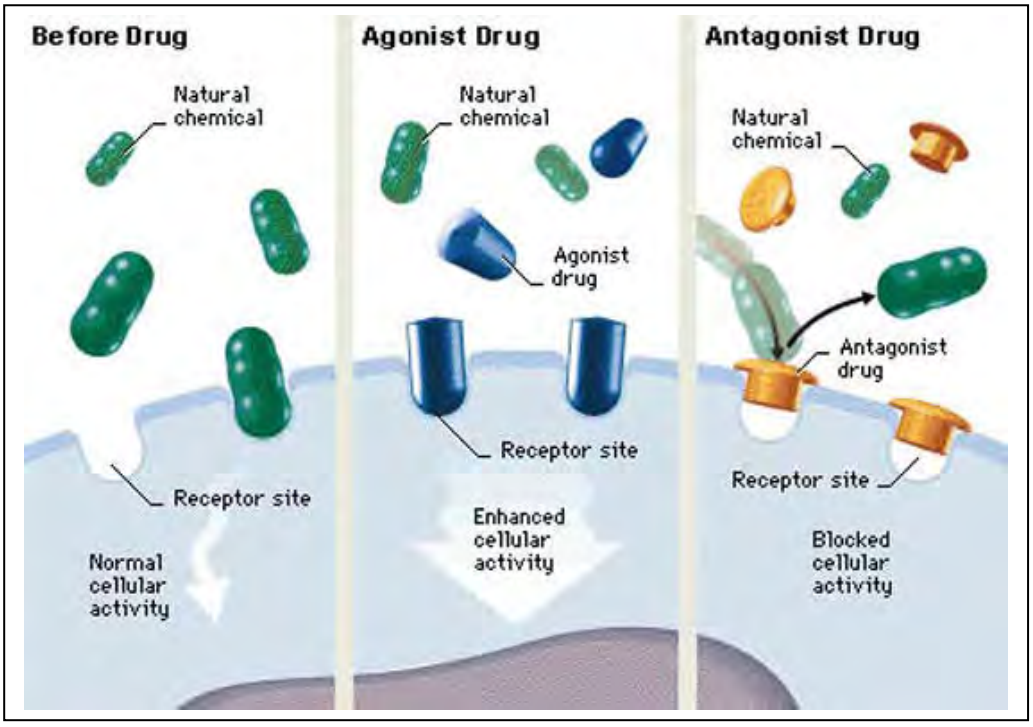
1. REVERSIBLE (EQUILIBRIUM) COMPETITIVE ANTAGONIST:

- effects of agonists/antagonists depend on concentrations of each substance (endogenous substance and the drug)
- the dominant effect will be driven by whichever is present in greater concentration.

2. IRREVERSIBLE (NONEQUILIBRIUM) COMPETITIVE ANTAGONIST:

- the antagonist permanently changes the receptor and doesn't allow agonist action after that
- once the receptor is "claimed" by this antagonist, it cannot work again, & its effect is eventually insurmountable.

Agonist & Antagonist drugs acting at receptors:



NONCOMPETITIVE ANTAGONIST DRUGS (LIGANDS):

- binds to ANOTHER location (doesn't bind to the SAME receptor site) – but it DOES change the agonist receptor site in some way so that it no longer recognizes ligand
- this is an “irreversible” effect (cannot be overcome with increased agonist dosage) since the agonist receptor site is removed from activity by the induced change

PHYSIOLOGIC ANTAGONIST DRUGS (LIGANDS):

- homeostasis involves a “balancing act” between opposing processes; temperature and body pH (as well as other critical factors) are optimal for optimal activity of enzymes
- interdependent, separate pathways that "cancel each other out" on the seesaw
- two different ligand agonists may have separate and opposing biologic effects and thus cancel each other out, or "antagonize" each other (due to activation of two opposing physiologic pathways).
    - Example: effect on the heart rate from an adrenergic (sympathomimetic) agonist (HR increase) working at the same time as a cholinergic (parasympathetic) agonist (HR decrease
    - Example: opposing effects of insulin and glucocorticoids (cortisones).

CHEMICAL ANTAGONIST DRUGS:

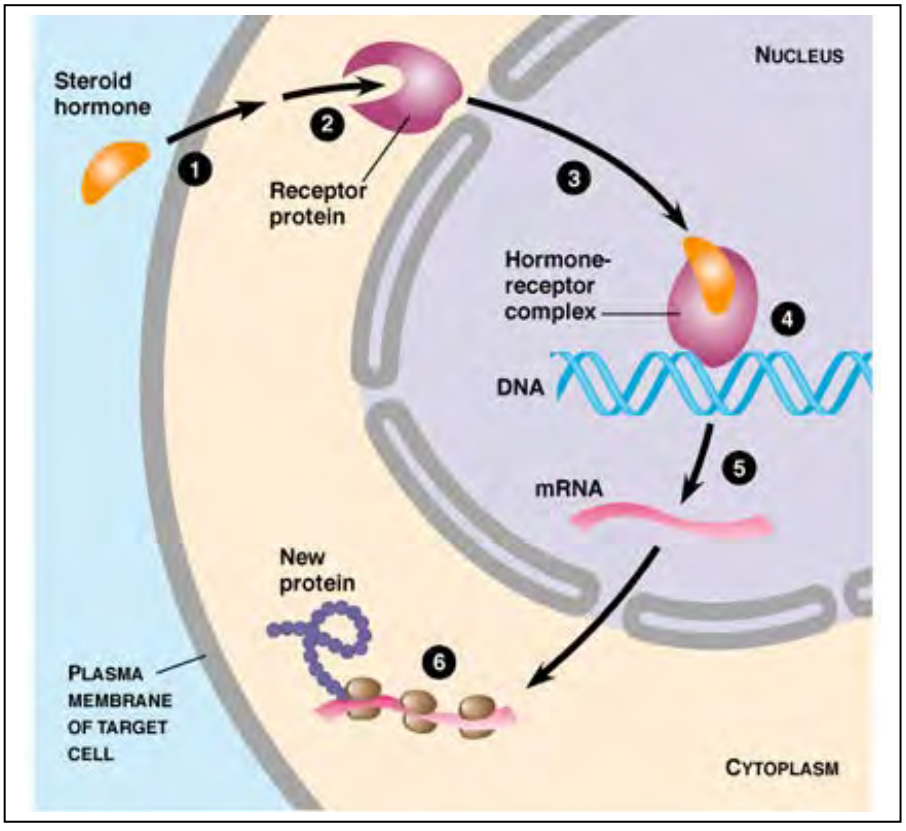
- nothing to do with receptors.
- drug binds to some chemical in the body, preventing its activity
    - Example: protamine binds to heparin and antagonizes its action by chemically neutralizing the heparin, thus it is often called an "antidote" to heparin.

RECEPTORS FORMING TRANSCRIPTION FACTORS:

- What ligands use these?
  - **lipid soluble (lipophilic)** hormones such as **sterol hormones, thyroid hormone and vitamin D (fat soluble vitamin)**

STEROL HORMONES:

- based on cholesterol chemistry and **lipid soluble (lipophilic)**
- Ligand action in the cytoplasm: binds with **cytoplasmic receptors** forming a **hormone-receptor complex** which is also called a **transcription factor**
- Nuclear action:
  - the transcription factor goes to the cell **nucleus** to activate the DNA to cause **transcription** of new proteins, altering cell physiology
  - this is due to **disinhibition** (removal of inhibition) of DNA transcription
  - sometimes this occurs by removal of a protein associated with DNA called "heat shock protein (hsp90) that has been inhibiting DNA transcription
- Action on cell metabolism:
  - It takes LONGER for the action to occur (transcription & translation take at least 30 minutes) – BUT the action will probably be LONGER ACTING since the final cellular products last for hours to days
  - Action of these hormones *also* relies on the **number** & **sensitivity** of the intracytoplasmic receptors.
  - Action on DNA transcription may also affect **upregulation** or **downregulation** of cell receptors
    - Example: cortisols upregulate the number of beta-2 receptors in lung, making lung more sensitive to circulating epinephrine for improved bronchodilatation



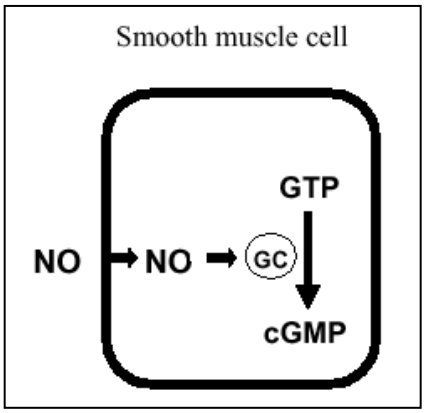
Number 2 shows the hormone-receptor complex,also called a transcription factor. This travels to the nucleus to stimulate transcription by disinhibiting the DNA (removing heat-shock protein). The new proteins that are made by transcription can be proteins in the cytoplasm (enzymes, structural proteins) OR they can be receptors for the cytoplasm or cell membrane.

NITRIC OXIDE (NO) GAS AND cyclicGMP (cGMP) FORMATION & ACTION:

- NO used to be called **endothelial derived relaxing factor (EDRF)**
- this is a lipid-soluble gas
  - made by capillary endothelial cells and some parasympathetic neurons
  - causes vasodilatation of blood vessels by relaxation of smooth muscle

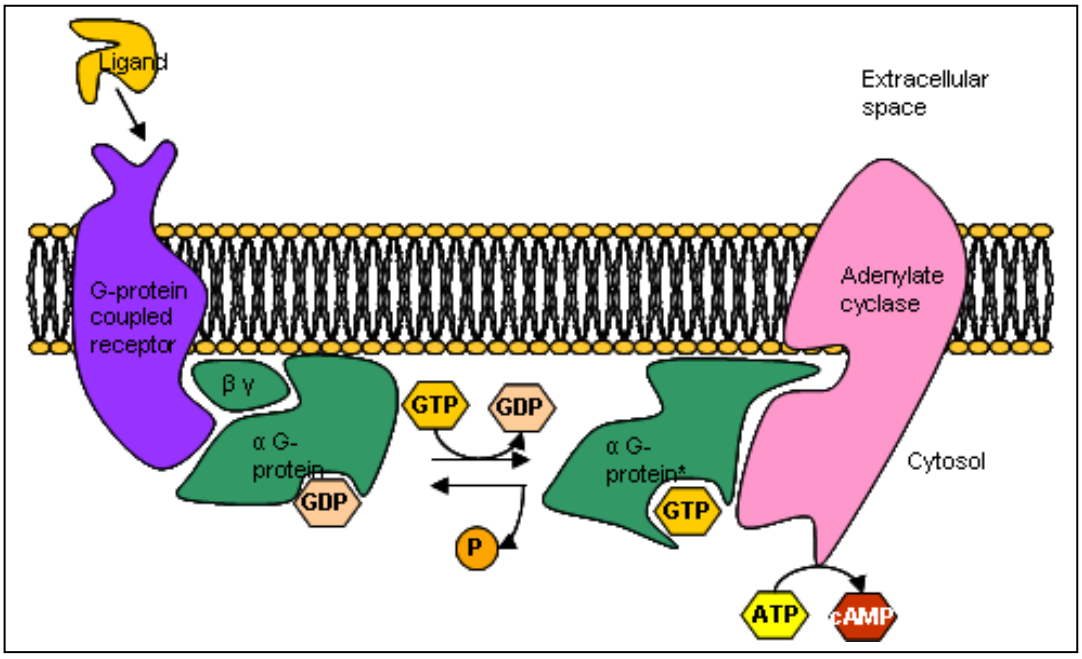
Mechanism – a second messenger system using cGMP:

- Process:
  - NO binds to intracytoplasmic enzyme (guanylyl cyclase, GC) to produce the secondary messenger **cyclic-GMP (cGMP)**
  - cGMP causes *dephosphorylation of myosin light chains and resultant muscle relaxation* with associated vascular vasodilatation
  - The cGMP is then degraded by **Phosphodiesterase enzymes (PDEs)**.
- Drug correlate:
  - **Drugs that turn into NO:**
    - all the **nitrates (e.g. nitroglycerin, nitroprusside)** are converted to NO in the body & are therefore vasodilators by action on vascular smooth muscle
    - smooth muscle relaxation results in blood vessel vasodilatation
  - **Drugs that inhibit PDE (PDEIs):**
    - enhance cGMP activity by inhibiting a subtype PDE enzyme (PDE5)
    - include **Sildendafil (Viagra)** and other drugs for erectile dysfunction
    - improve strength & duration of erection by inhibiting the *degrading* enzyme and allow cGMP to last longer
    - **Drug-drug interaction:** since cGMP activity is *also induced by nitrate drugs, this is WHY* you should NOT take PDE5 inhibitors within 24 hours of taking a nitrate drug due to *additive* effects of overwhelming vasodilatation and possible severe hypotension.
  - **Selectivity of PDEI drugs:** remember about isoenzymes – enzymes exist in multiple "isomer" forms, thus there are subtypes of PDEs in the body
    - Your *therapeutic target* for erectile vascular tissue is PDE5, and you want PDE5 inhibition (PDE5i) and not affect the other PDE enzymes.
    - Newer drugs that compete with sildenafil in the market are **vardenafil (Levitra) and tadalafil (Cialis)** which claim to be *more selective* for PDE5.
    - Pharmacology assays determine the **"selectivity ratio"**
    - One drug side effect for sildenafil & vardenafil is due to the interaction with PDE6 that can cause visual symptoms (a "blue tinge" to the vision).



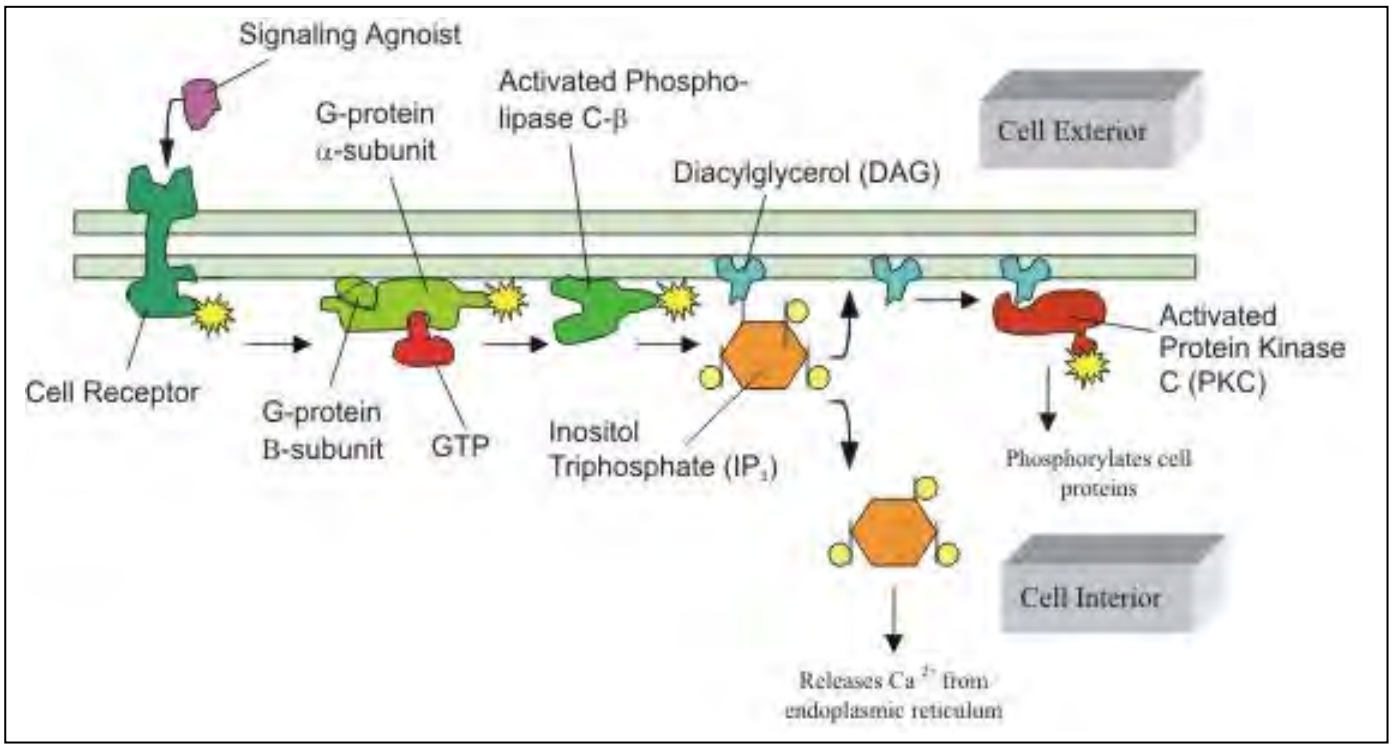
G-PROTEIN RECEPTORS MAKING cAMP:

- What kinds of ligands use this receptor?
  - **non-lipophilic (hydrophilic) ligands** that are not soluble in the cell membrane phospholipid
  - they are "stopped" at the cell membrane and so must interact with *cell membrane* receptors called "G-protein receptors" that are "trans-membrane" in the cell membrane
  - activation of these receptors creates a **second messenger** chemical inside the cell
  - these include **cAMP** or **cGMP** (the little "c" stands for the chemical term "cyclic")
- **cAMP:** the ***most common*** second messenger in the body
  - the ligand creates **GDP** when it activates the cell membrane receptor
  - the GDP then activates an enzyme in the cell membrane called **adenyl cyclase**
  - this enzyme converts ATP to **cyclic AMP (cAMP)**
  - The cAMP has various actions in the cell (usually stimulates metabolism of the cell by activating enzymes like protein kinases)
  - To end the cAMP activity, the cAMP is *degraded* by enzymes called **phosphodiesterase enzymes (PDEs)**
- Examples of ligands using cAMP:
  - Endogenous catecholamines (alpha and beta sympathomimetic receptors), ACh muscarinic receptors, eicosanoids like serotonin & prostacyclin, olfactory odorants, photons (visual receptors), ACTH, MSH, FSH, LH, PTH, thyrotropin, vasopressin (V2 receptors)
- Drug correlates for cAMP:
  - **PDEIs:** inhibition of PDE (PDEIs) stops degradation of cAMP
    - include drugs like caffeine, theophylline, methylxanthines.
    - cAMP concentration remains high longer and works longer.
    - One result is smooth muscle relaxation in bronchial lung tissue → **bronchodilatation**!
  - **Opioids inhibit adenyl cyclase:** cell can't make cAMP → **opioids** cause bradycardia.



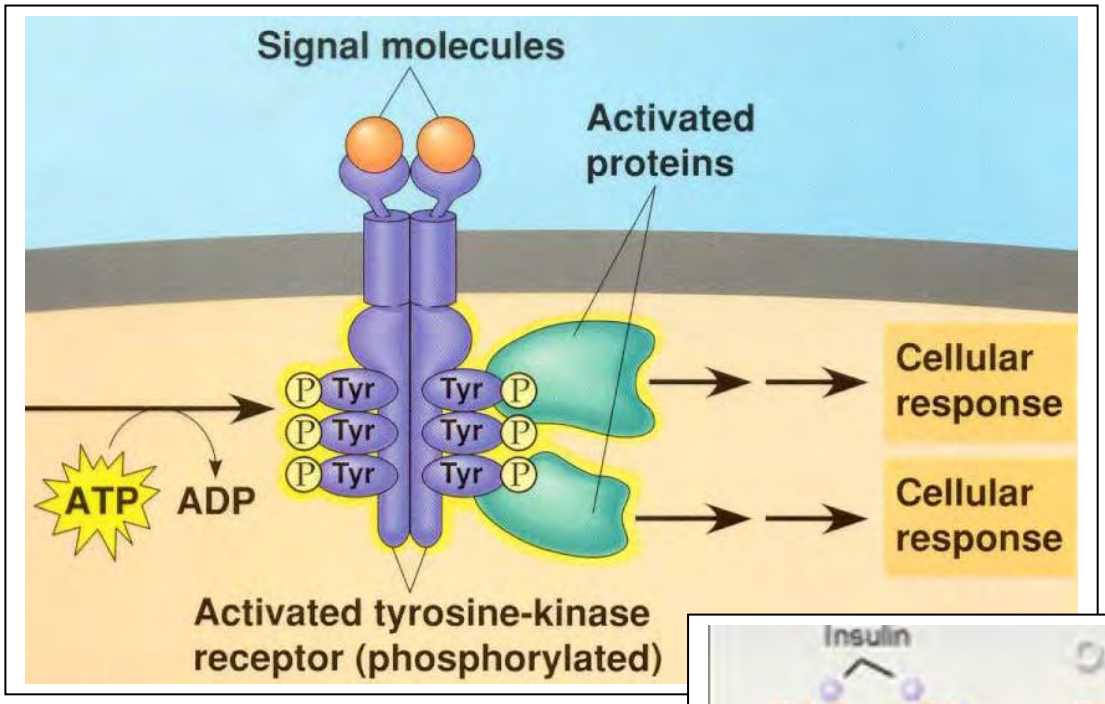
G-PROTEIN CELL MEMBRANE RECEPTORS MAKING DAG-IP3 (DAG-PIP):

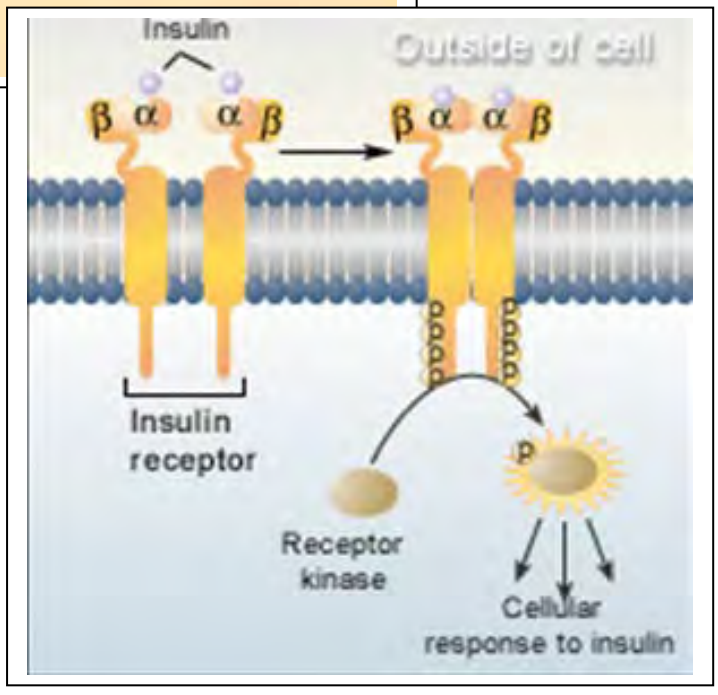
- What kinds of ligands use this receptor?
  - **non-lipophilic (hydrophilic) ligands** that are not soluble in the cell membrane phospholipid (these are usually **protein** ligands)
  - they are "stopped" at the cell membrane and so must interact with *cell membrane* receptors called "G-protein receptors"
  - activation of these receptors creates a **second messenger** chemical inside the cell
  - these include **diaglycerol-inositol-tri-P** also called **DAG-IP3** and **DAG-PIP**
- Process of creating second messenger DAG-IP3:
  - G-protein receptor (located "trans-membrane" in the cell membrane) is activated by ligand
  - cell membrane phospholipid is broken down → DAG-IP3
  - ionized **Calcium** is released from cell storage sites to activate **kinase** enzymes in the cell that induce metabolic cellular changes
- Process of ending the action:
  - DAG is either turned back into phospholipid or arachidonic acid
  - IP3 is inactivated in the cytoplasm
  - excess free Ca++ is pumped back into storage sites by cellular pumps
- Examples: cadmodulin (muscle myosin activity)



PROTEIN KINASE CELL MEMBRANE RECEPTORS:

- What kinds of ligands use this receptor?
  - **non-lipophilic (hydrophilic) ligands** that are not soluble in the cell membrane phospholipid (these are usually **protein** ligands)
  - they are "stopped" at the cell membrane and so must interact with *cell membrane* receptor
  - two ligands cause a conformational change in this receptor to activate a **protein kinase enzyme** that uses ATP energy to create **activated proteins** and a cellular response
- Examples of endogenous substances using this system:
  - **insulin**, EGF(epidermal growth factor), PDGF (platelet derived growth factor), ANF (atrial natriuretic factor), & TGFB (transforming growth factor-beta).





LIGAND GATED CHANNEL (ION CHANNEL) (VOLTAGE GATED) RECEPTORS:

- What kinds of ligands use this receptor?
  - **non-lipophilic (hydrophilic) ligands** that are not soluble in the cell membrane phospholipid
  - they are "stopped" at the cell membrane and so must interact with *cell membrane* receptor
  - agonist effects induce a conformational change in this receptor to **OPEN ion channels**
- Examples of endogenous substances using this system:
  - neurotransmitters such as ACh (nicotinic receptors), GABA (gamma aminobutyric acid), excitatory amino acid neurotransmitters (glycine, glutamate).