

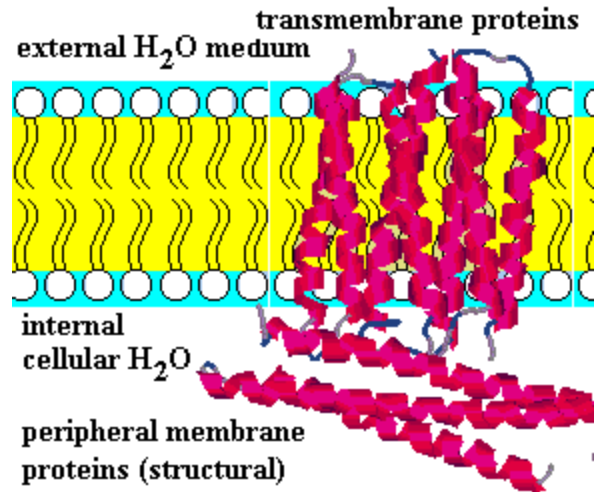
## Chem\*3560 Lecture 36: Review of membrane function

Membrane: Lipid bilayer with embedded or associated proteins.

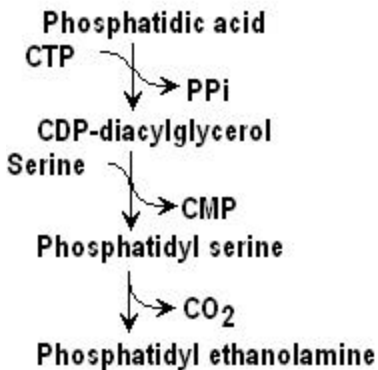
**Bilayers:** 40-70% neutral phospholipid  
 10-20% negative phospholipid  
 10-30% cholesterol  
 10-30% sphingolipid

**Outer leaflet** has more phosphatidyl choline and sphingolipids.

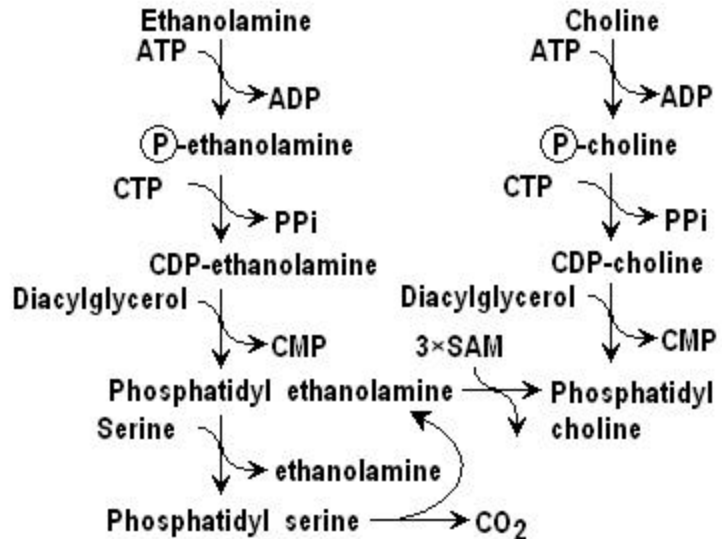
**Inner leaflet** has more phosphatidyl ethanolamine and negative phospholipids (mostly phosphatidyl



### Phospholipid synthesis in bacteria



### Phospholipid synthesis in animals



serine).

The bilayer is **impermeable to polar molecules**, but is pliable and individual molecules are freely mobile within the plane of the bilayer. Fluid bilayers also readily seal themselves into vesicles.

**Membrane fluidity** is indicated by a **transition temperature**, which is a function of chain length and degree of unsaturation of the fatty acids. More *cis*-unsaturation ⇒ lower transition temperature ⇒ more fluidity.

Rapidly growing bacteria synthesize new phospholipids with unsaturated fatty acid content that sets the transition temperature just below the environmental temperature. Animals control fluidity by removing the middle acyl chain and replacing it with an unsaturated fatty acid.

## Membrane proteins provide membranes with function

**Structural reinforcement:** e.g. **Spectrin** is a long extended molecule that forms a framework on the inside of the plasma membrane - a peripheral protein that associates with various transmembrane proteins.

**Protection:** e.g. **Glycophorin** (Greek for sugar-bearing) is rich in short oligosaccharide chains (60% by mass) covalently bonded to amino acid side chains. One type of oligosaccharide is linked to Ser or Thr (O-linked), another type linked to Asn side chains (N-linked). Glycophorin provides a carbohydrate coating that protects the cell exterior and makes it harder for some microorganisms to colonize the cell.

**Identity and Adhesion:** e.g. **Integrins and cadherins** provide a mechanism for cells in complex organisms to recognize like or unlike neighbours and their extracellular matrix structural components. These are necessary for the formation of complex tissues.

**Integrins**  $\alpha\beta$  heterodimer exist in different tissue specific combinations (18 different  $\alpha$  chains and 8 different  $\beta$  chains), which bind to different components of the extracellular matrix. Integrins exist in a different conformation when they bind their target ligand, so a cell can detect when it is in appropriate surroundings.

**Cadherins** exist as cell-type specific homodimers, and mediate adhesion between cells of the same type. Adhesion occurs through  $\text{Ca}^{2+}$  bridges between -ve rich regions of polypeptide.

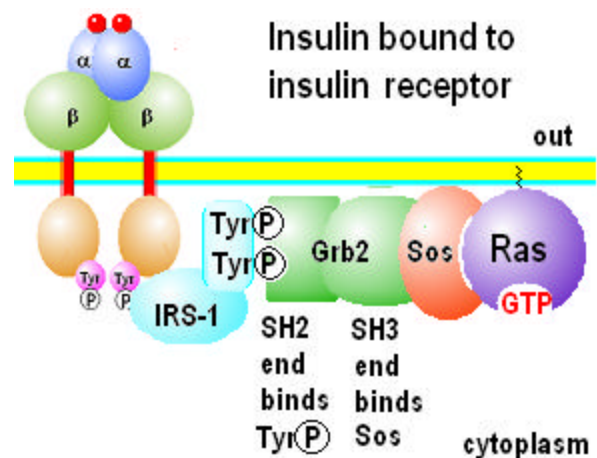
**Vesicle formation and fusion:** e.g. **SNAREs** are transmembrane polypeptides with a long helical section extending into the cytoplasm. Vesicles carry v-SNAREs, fusion targets carry t-SNAREs. SNAREs wind together in a helical bundle to bring the bilayers into close proximity.

**Receptors:** Receptors communicate signals from outside to the inside of a cell; the external signal carrying molecule, such as a hormone or growth factor does not have to enter the cell, but binds to a receptor on the cell surface. This elicits various responses inside the cell, which may be communicated internally by "second messengers" such as cyclic AMP or phosphatidylinositol trisphosphate ( $\text{PIP}_3$ ).

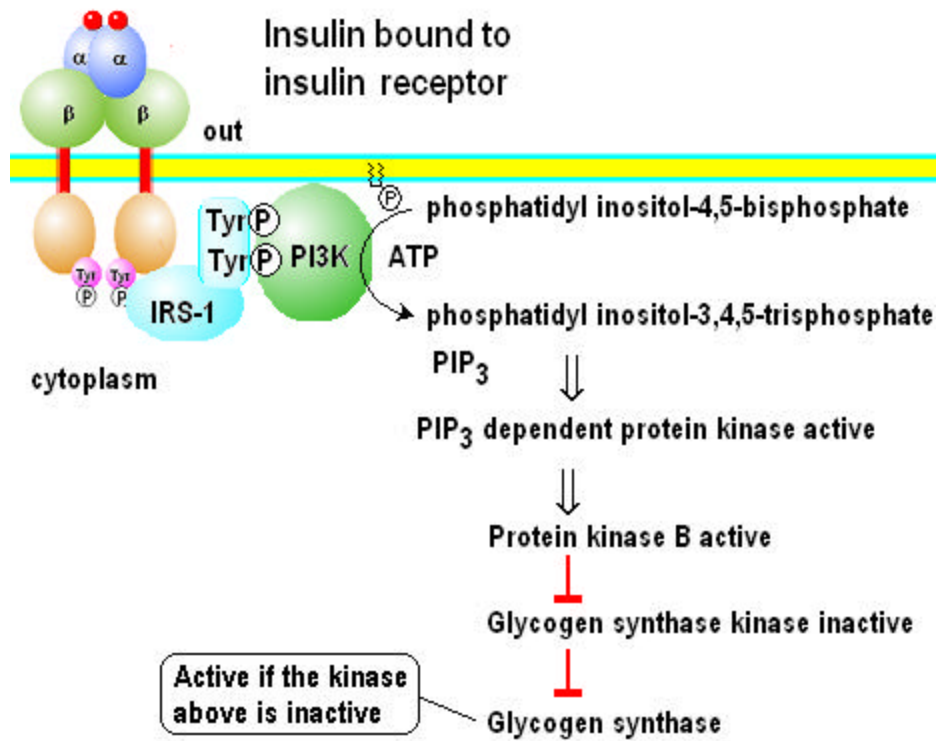
**Death receptors** - Tumor necrosis factor receptor signal for apoptosis

**Receptor Tyr kinases** (e.g. for insulin) - tyrosine phosphorylation creates **link-ups of SH2 domain** proteins on the membrane surface to activate Ras (SH2 domains bind to exposed phosphotyrosine).

Ras and steps after Ras **integrate** the signals from several different receptor tyrosine kinases.

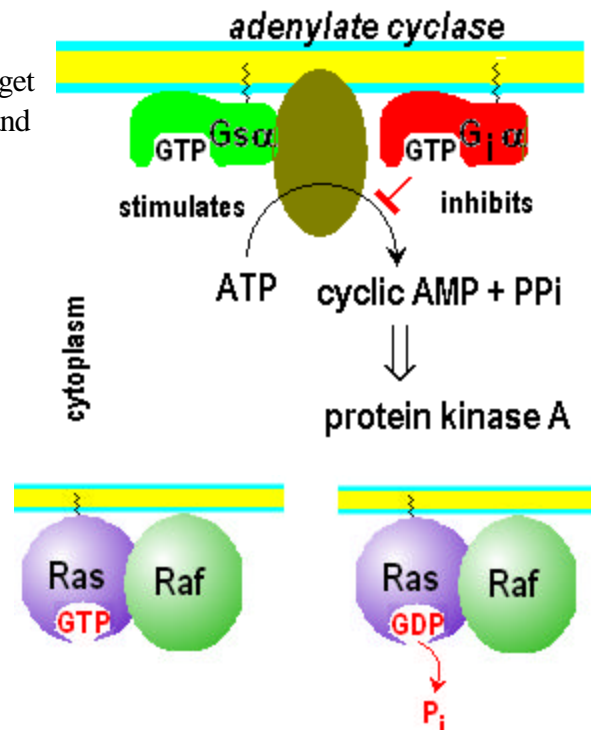


**Insulin receptors** also activate PIP<sub>3</sub> pathway and protein kinase B for **metabolic effects** - glucose uptake in peripheral tissues and promoting activity of glycogen synthase.



**Epinephrine and glucagon receptors** are examples of G-protein coupled receptors; G<sub>s</sub>α-GTP is released to stimulate cyclic AMP and the protein kinase A cascade.

**Enzymes:** e.g. **Adenylate cyclase**; this enzyme is located on the inside of the plasma membrane as a target for the lipid anchored G<sub>s</sub>α. Cyclic AMP is released and can spread throughout the cytoplasm- a so-called **second messenger** that communicates the hormonal signal to the cell interior.



**Signalling:** e.g. **Ras (a small G-protein)** and **heterotrimeric G-protein** are both **lipid anchored** proteins. Their distinguishing feature is **slow GTP hydrolysis**, which times how long they remain in the active state. Some G protein targets enhance the GTPase so that the signal is turned off as soon as it passes to the next step.

**Transport:** includes Translocators, pumps, ion selective channels

Translocators include uniport, symport, antiport mechanisms.

The translocator has a binding site for a limited number of substrate molecules.

After binding substrate, a conformation change must occur to expose the substrate site on the opposite side. The binding site can be saturated, i.e. once occupied and waiting for conformation change, no more substrate can bind. This gives the translocator Michaelis-Menten type kinetics.

Electroneutral translocators move substrates in the direction governed by the concentration gradient. Translocators are electroneutral if the transport equation shown no net movement of charge across the membrane.

GluT2 is a neutral uniporter.

H<sup>+</sup> / pyruvate symporter is neutral (+1-1 = 0 charge moves at each cycle)

Malate<sup>2-</sup>/HPO<sub>4</sub><sup>2-</sup> antiporter (dicarboxylate carrier) is neutral: -2 in and -2 out at each cycle.

Electrogenic translocators move substrates in the direction governed by the combination of concentration gradient and membrane potential. If an appropriate membrane potential exists, electrogenic translocators may be able to move a substrate from low to high concentration.

**Lactose permease** is an electrogenic symport: 1 lactose and 1 H<sup>+</sup> ion moves into the cell for each transport cycle.

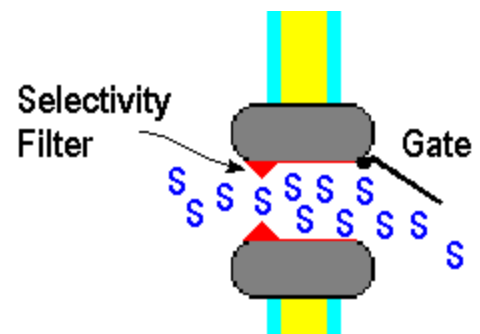
The **ATP:ADP translocator** is an electrogenic antiport.

Pumps or active transporters use an energy yielding reaction such as ATP hydrolysis to drive the conformation change needed for transport in a particular direction. The conformation change may also change binding affinity for substrate as well as changing which side of the membrane it's exposed to, e.g. Na<sup>+</sup> /K<sup>+</sup> ATPase.

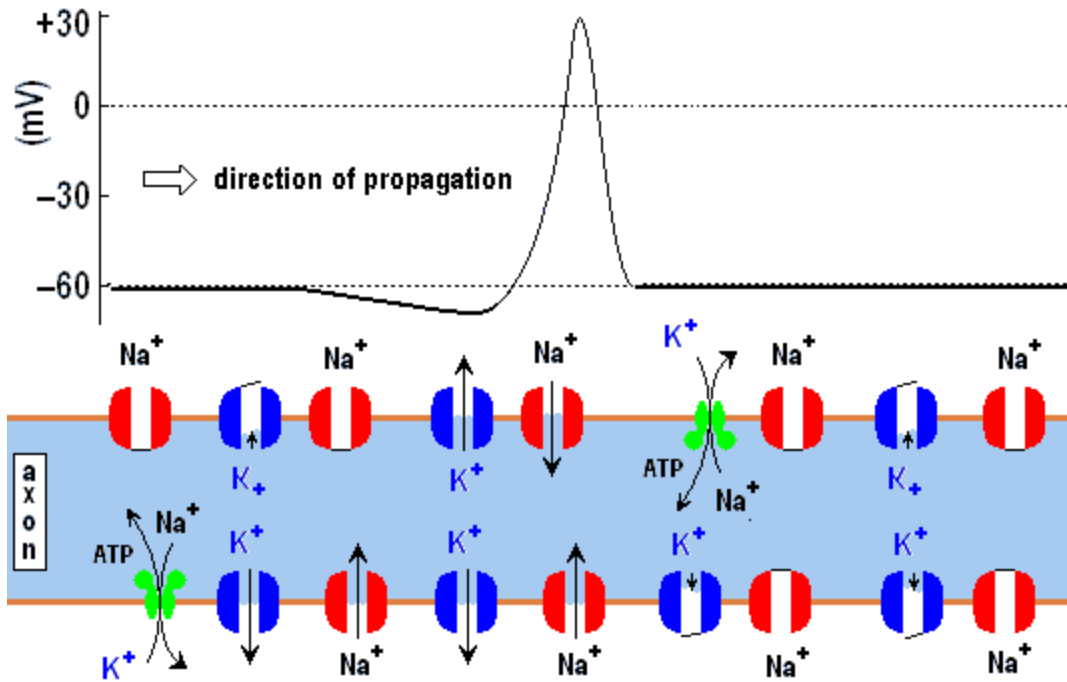
If the pump is reversible, it may be able to use an electrochemical gradient to force the condensation of Pi with ADP to make ATP, e.g. FoF1 ATPase.

Ion selective channels are holes through the membrane that include a selectivity filter, which determines which ion passes through. The ion does not have to stay bound in the selectivity filter, and the channel does not have to change conformation for each ion passed, so large numbers of ions can be passing through at the same time. A gate controls whether the channel is open or closed. The purpose of a channel is to allow for controlled changes in permeability to particular ions, so that membrane potential can be changed.

In a multi-ion system, both the concentration gradient and the relative permeability for each ion contribute to the overall membrane potential.



## Transmission of nerve impulses



**The resting potential**  $-60$  mV is due to the higher background permeability to  $K^+$

The **action potential** is initiated by perturbation in local potential that causes  $Na^+$  channels to open.

Altered permeability increases potential to  $+30$  mV. Open channels rapidly inactivate themselves, and meanwhile  $K^+$  channels open. This brings the potential back down to about  $-75$  mV.

Channels to the left and right experience the perturbation due to the action potential.

The wave shown is propagating left to right, so channels on the left were open less than 5 ms ago and are still inactive. Therefore they do not reopen due to the voltage spike in the middle. Channels on the right have not yet fired, so the perturbation will trigger them to open. As a result the wave propagates left to right.

Note that this graph of potential is drawn with respect to **position along the axon**, not time. Since the wave is travelling left to right, the time scale runs right to left.