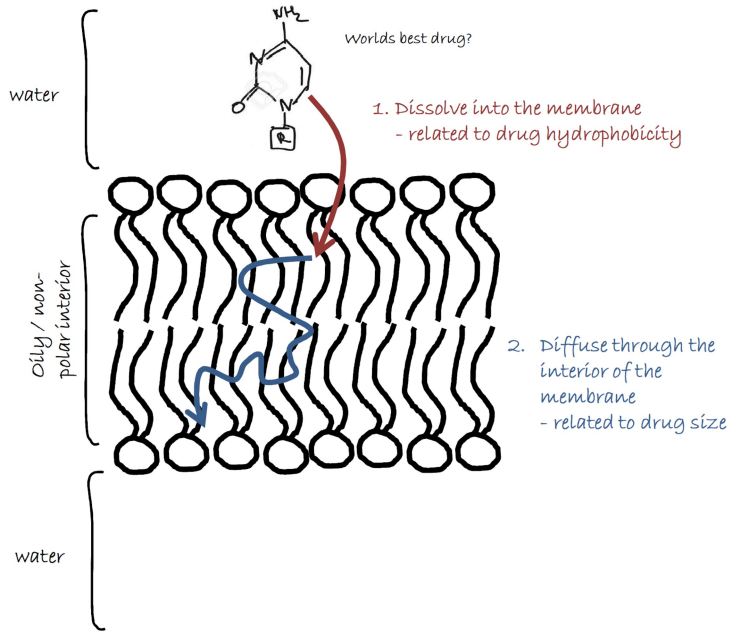
BIOL2174 | ANU

Tuesday, 30 January 2018 7:24 PM

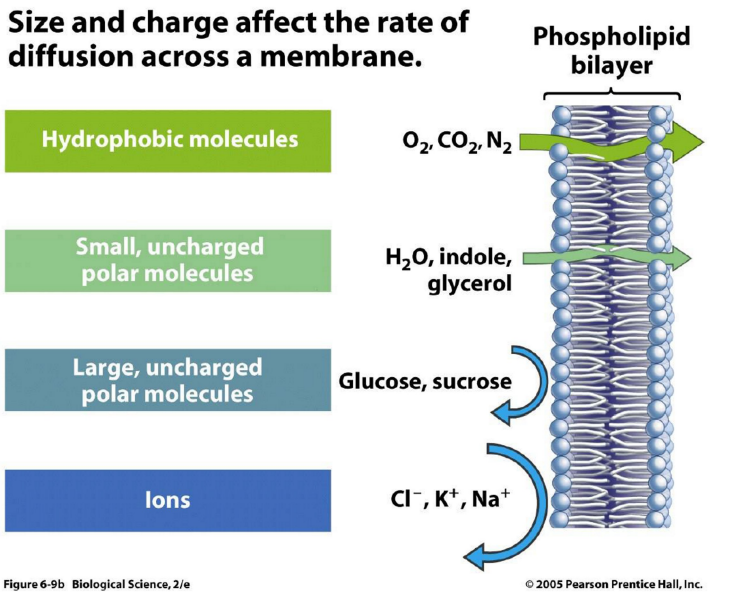
Topic-1 : Permeability

- **Factors influencing rate of diffusion of solutes across the bilayer**



We can understand the rate at which solutes diffuse across the lipid component of membranes in terms of the need for them to:
(i) Partition from the aqueous phase into the oily interior of the membrane bilayer, as reflected in their **oil/water partition coefficient;**
(ii) Diffuse from one side of the bilayer to the other, as reflected in the **size – dependence of the diffusion rate.**
Consequently, the rate of diffusion of small solutes through the lipid phase of biological membranes is determined largely by its hydrophobicity (which determines its oil/water partition coefficient) and its size (which determines its rate of diffusion within the membrane bilayer).

Specifically, the basal membrane **permeability, P**, increases with increasing solute hydrophobicity and decreases with increasing solute size.



The main point of this discussion is that, except simple, small, neutral molecules, essentially everything that is biologically relevant and important cannot readily pass through a simple lipid bilayer membrane.
Molecules that are either hydrophilic or too hydrophobic cannot pass the membrane.

A diversity of special mechanisms has evolved to transport a broad spectrum of biologically important species:

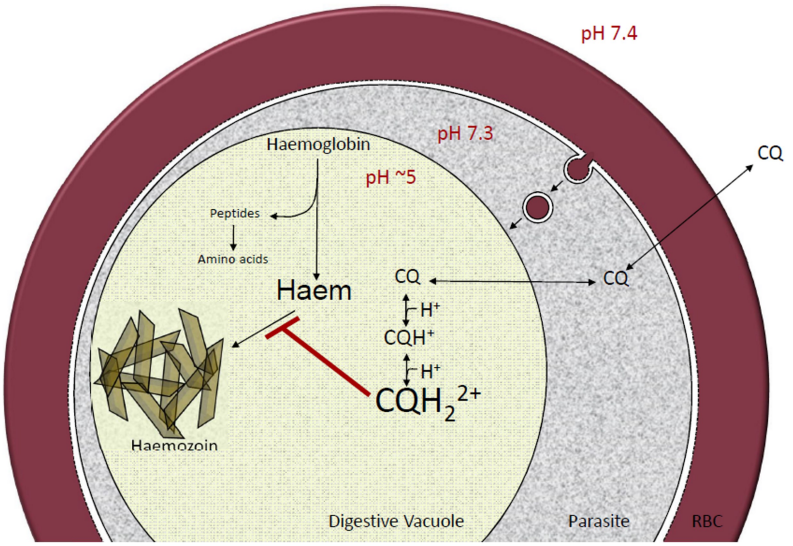
- Ion pumps and channels permit influx and efflux of Na, K, Ca, and Cl
- carrier proteins allows movement of sugars and amino acids across membranes
- Endocytosis and exocytosis of protein molecules.

- **Clinical Examples:**

1. **<u>The antimalarial action of Chloroquine</u>**

Chloroquine is a weak base

Chloroquine accumulates in the vacuole by 'weak base trapping'



- The Malarial parasite has an acidic digestive vacuole.
- Once CQ enters the cell, it becomes doubly charged in the presence of excess H+ (protons)
- The charged CQ species blocks the formation of haemozoin crystals from Haem
- This results in accumulation of high concentrations of toxic haem molecules, which ultimately kills the parasite.

- The delivery of chloroquine at high concentrations to its site of action within the parasite is dependent upon:
(i) The ability of the **uncharged, hydrophobic chloroquine** molecule to diffuse through the various membranes to reach the interior of the food vacuole.
(ii) The inability of the **charged** (and therefore hydrophilic) form of the chloroquine to escape from the acidic vacuole = **WEAK BASE TRAPPING**

CH-2 SUMMARY:

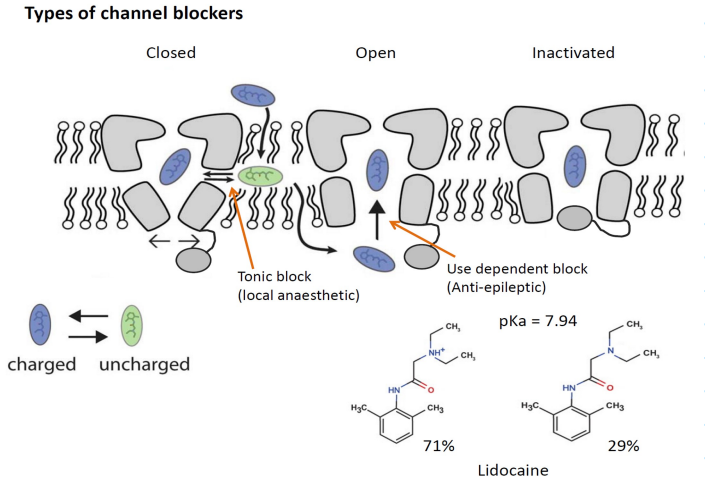
1. Diffusion causes the movement of molecules from a region where their concentration is high to a region where their concentration is low; that is, molecules tend to diffuse down their concentration gradient.
2. Fick's First Law describes diffusion in quantitative terms: the flux of molecules is directly proportional to the concentration gradient of those molecules.
3. Diffusion results entirely from the random movement of molecules.
4. The distance that molecules diffuse is proportional to the square root of time.
5. Because of the square-root dependence on time, diffusion is effective in transporting molecules and ions over short distances that are on the order of cellular dimensions (i.e., micrometers). Diffusion is extremely ineffective over macroscopic distance (i.e., a millimeter or greater).
6. The net flux of molecules diffusing across a cell membrane may be viewed as the net balance between an inward flux (influx) and an outward flux (efflux).
7. The ease with which a species may diffuse through a membrane barrier is characterized by the membrane

permeability, P. Higher permeability permits a larger flux.
8. With the exception of small neutral molecules such as O2, CO2, water, and ethanol, essentially no biologically important molecules and ions can spontaneously diffuse across biological membranes.

Topic-2: Ion Channels

• *How ion channel diversity can be utilised for therapeutic benefit*

Drugs can be developed to target the huge variety of channels to treat the different diseases mentioned before.



Tonic blockers:

Usually uncharged, hence enter the lipid bilayer to directly block the channel via a side gap/ fenestration.

Use dependent blockers:

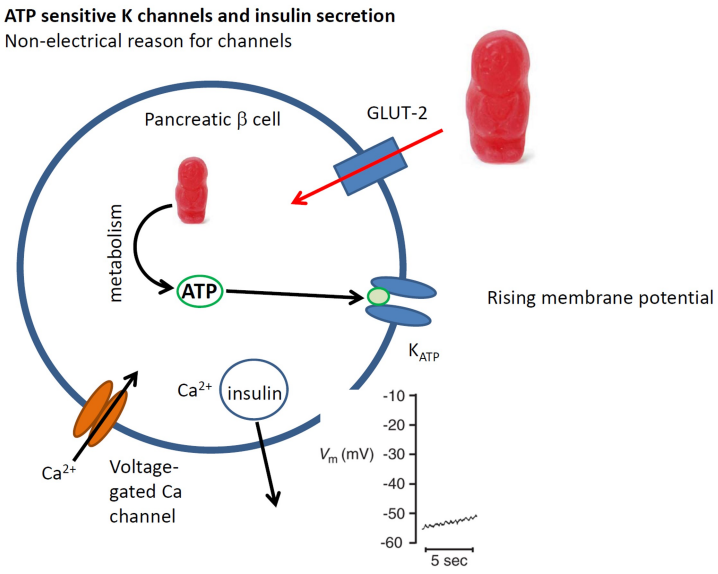
Use-dependent block by charged drugs is explained by the idea that the activation gate in the channel must open before charged drug molecules can gain access to the blocking site.

Initially, there is little reduction in the current, however, subsequent depolarizations produce smaller and smaller currents.

Point to note:

Uncharged molecule can easily access the pore (but doesn't block so effectively)
Charged molecule blocks the pore more effectively (eg: it repels the entry of +vely charged Na+ ions into the channel and sits effectively in the pore - but it cannot easily access the pore through the lipid bilayer)

Clinical example:



The b-cells in the islets of Langerhans in the endocrine pancreas play a critical role in the regulation of the plasma glucose concentration. The b-cell secretes the hormone insulin in response to increased plasma levels of glucose, which stimulates the uptake, metabolism, and storage of glucose in muscle and fat cells.

- When the plasma glucose concentration rises, glucose is transported into the b-cell (by the GLUT-2 transporter), and glucose metabolism results in an increase in [ATP]i.
- The K-ATP channel is blocked by a high concentration of intracellular ATP ([ATP]i).
- This closes K-ATP channels and thus reduces membrane K1 permeability.
- As a result of the reduced K1 permeability, the b-cell depolarizes and generates bursts of APs.
- Voltage-gated Ca21 channels are activated during this glucose-induced electrical activity, and Ca2+ ions enter the cell through the open Ca2+ channels.
- The resulting increase in [Ca21]i activates insulin secretion.

Sulfonylureas, such as glibenclamide, selectively block K-ATP channels and thereby enhance insulin secretion. For this reason sulfonylureas are used in the treatment of type 2 diabetes mellitus

CH-8 SUMMARY

1. Ion channel types are characterized by their selectivity and by their structures and pharmacology.
2. The various types of ion channels play specific, critical roles in normal cell function, and channel defects can have serious pathophysiological consequences.
3. Voltage-gated Ca21 channels can generate the upstroke of APs. In addition, Ca2+ channels can influence a large variety of cellular activities because Ca2+ ions regulate many cellular processes.
4. Several distinct types of Ca21 channels can be distinguished on the basis of their physiological and pharmacological properties.
5. Ca2+ antagonist drugs reduce Ca2+ entry into the cell by blocking voltage-gated Ca2+ channels. These Ca2+ channel blockers are widely used as therapeutic agents in the management of cardiac arrhythmias, coronary artery disease, and hypertension.
6. TRPC channels are all nonselective cation channels with different permeabilities to Ca2+ and Na+. TRPC channels are regulated by ligand-gated receptors or Ca2+ stores in the cell.
7. K1-selective ion channels, which are found in all cells, are diverse in their activity, structure, and distribution. Neuronal K1 channel diversity contributes to the regulation of AP firing patterns.
8. Many neurons express KA channels, which generate transient outward currents. These channels activate relatively rapidly during depolarization and then inactivate. In neurons that generate bursts of APs, the length of the interval between APs in the burst is regulated by the activity of KA channels.
9. The three subtypes of Ca21-activated K1 (KCa) channels (large, intermediate, and small conductance) are all opened by intracellular Ca21. The BKCa channels have one of the largest single-channel conductances. The current through KCa channels helps to repolarize individual APs and can also play a role in terminating a burst of APs.
10. The hERG K1 channels are voltage-gated channels with slow activation and deactivation and fast inactivation. These channels contribute to repolarization of the cardiac AP.

Topic-3: Channels and Transporters

- **The general functional characteristics of uniporters**

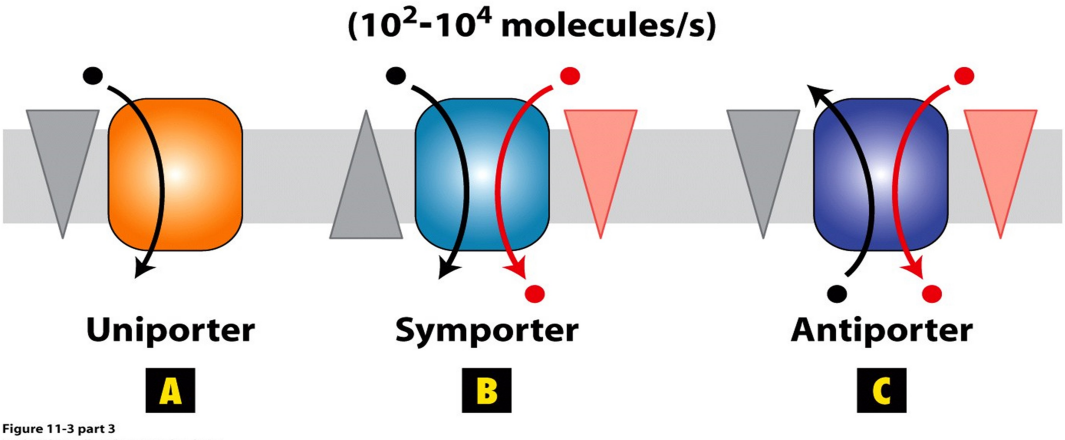


Figure 11-3 part 3
Molecular Cell Biology, Sixth Edition

Uniporter	Symporter	Antiporter
Uniporter carrier proteins work by binding to one molecule of substrate at a time and transporting it with its concentration gradient.	The **symporter** works in the plasma membrane and molecules are transported across the cell membrane at the same time in the same direction, and is, therefore, a type of **cotransporter**.	An **antiporter** (also called exchanger or counter-transporter) is a cotransporter and integral membrane protein involved in secondary active transport of two or more different molecules or ions across a phospholipid membrane such as the plasma membrane in opposite directions.

- **The physiological roles of GLUT 1-4**

GLUT1	GLUT2	GLUT3	GLUT4
• Widely distributed in foetal tissues • Expressed at high levels in erythrocytes (red blood cells) and in the endothelial cells of barrier tissues such as the blood-brain barrier. • Responsible for the low level of basal glucose uptake required to sustain metabolism in many cell types	• Expressed in kidney (renal tubular) cells and intestinal cells, as well as in the liver and in pancreatic beta cells.	• Expressed in neurons and in the placenta.	• Expressed in adipose tissue and striated muscle (skeletal muscle & cardiac muscle). • Regulated by insulin. • Insulin recruits GLUT4 to the plasma membrane of adipose and muscle cells from intracellular storage sites. • States of insulin resistance such as type 2 diabetes are associated with impaired regulation of GLUT4 gene expression and function

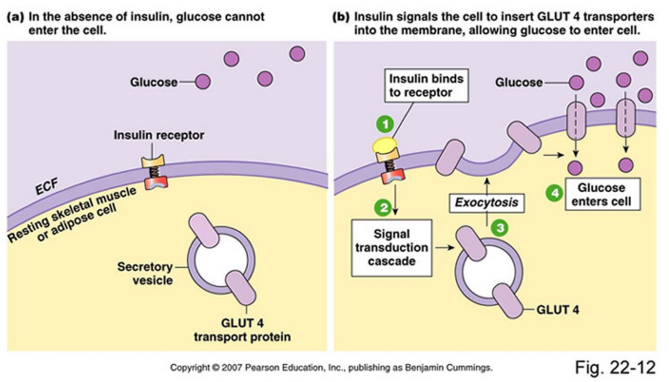


Fig. 22-12

When Insulin binds to its cell receptor, it generates a signalling cascade to recruit GLUT4 transporter via vesicles, to the plasma membrane.
This allows higher uptake of glucose molecules into the cell.

However, in the absence of insulin, glucose cannot be absorbed into the cell.

- **GLUT1 deficiency**
  - *Cause:* Mutations in the GLUT 1 gene are responsible for **De Vivo disease**
  - De Vivo disease or 'Glucose Transporter type 1 deficiency' is characterized by a low cerebrospinal glucose concentration (hypoglycorrhachia) which results from impaired glucose transport across the blood-brain barrier.
  - Children with this disease present with seizures, ataxia (gross incoordination of muscle movements), microcephaly, developmental delay.
  - *Treatment:* A ketogenic diet provides ketones as an alternative fuel to the brain, instead of glucose.