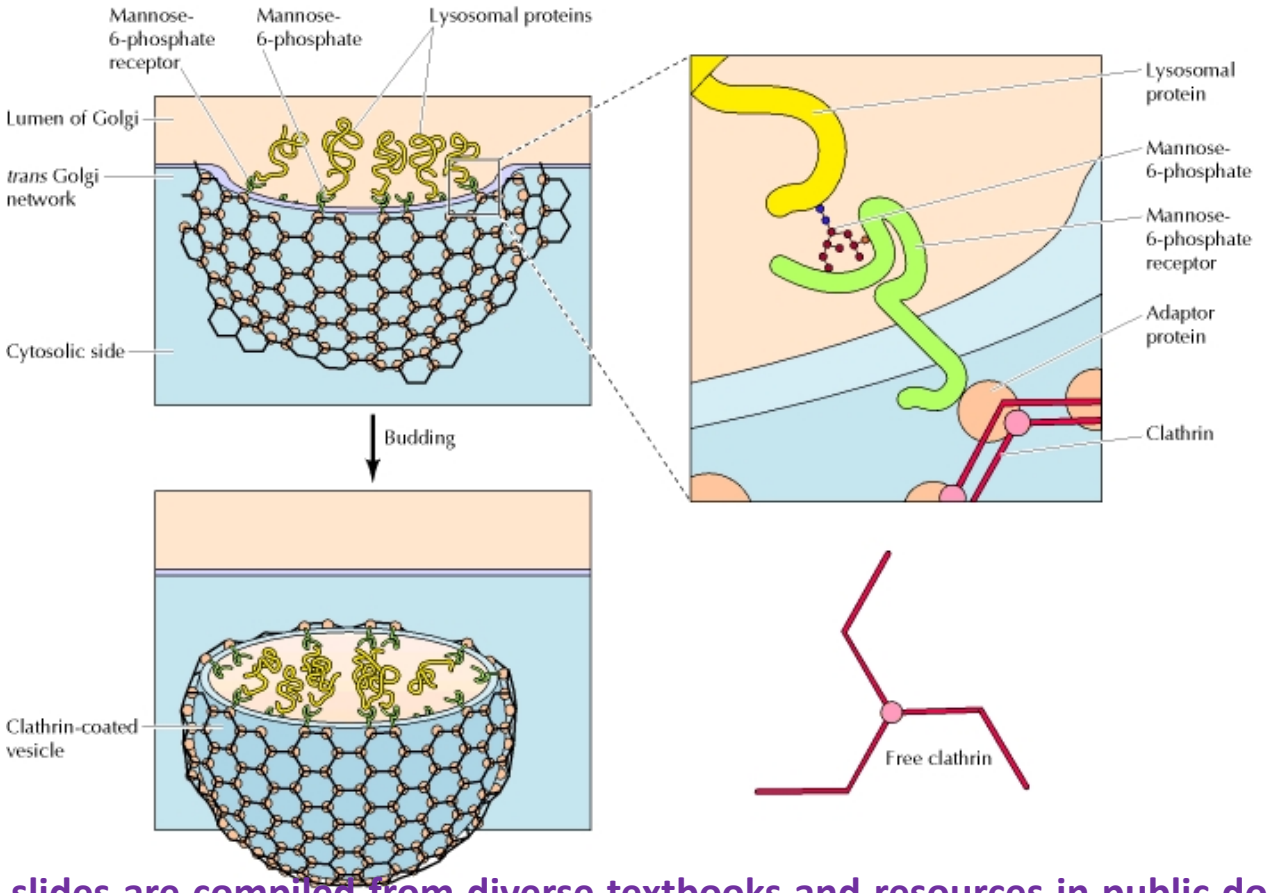
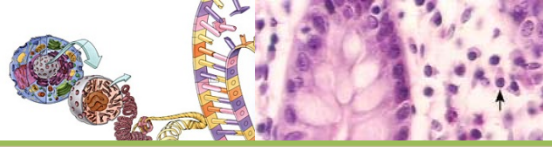
Carbohydrates, Lipids & Membranes

Incorporation of lysosomal proteins into clathrin-coated vesicles



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Carbohydrates

Glycome: The entire complement of sugars present in an organism..Glycomics is its study.

Glycobiology: Study of Structure & function of Saccharides / Carbohydrates in relation to living systems.

Carbohydrates or saccharides are represented by simple formula $(CH_2O)_n$. Much of the basic energy cycle on earth is built from carbohydrate metabolism. Green plants utilize carbon dioxide from atmosphere and driven by the energy of sunlight fix it into carbohydrates. These carbohydrates are stored in the plants as starch or cellulose. Animals that eat plants thus obtain carbohydrates.

Both plants and animals in order to obtain energy carry out oxidative metabolism of carbohydrates that is the reversal of photosynthesis. This step is the primary energy-giving process in metabolism.

$$nCO_2 + n\,H_2O \xrightarrow[\text{Photosynthesis}]{\text{(sunlight)}} (CH_2O)_n + O_2$$

Production of carbohydrates

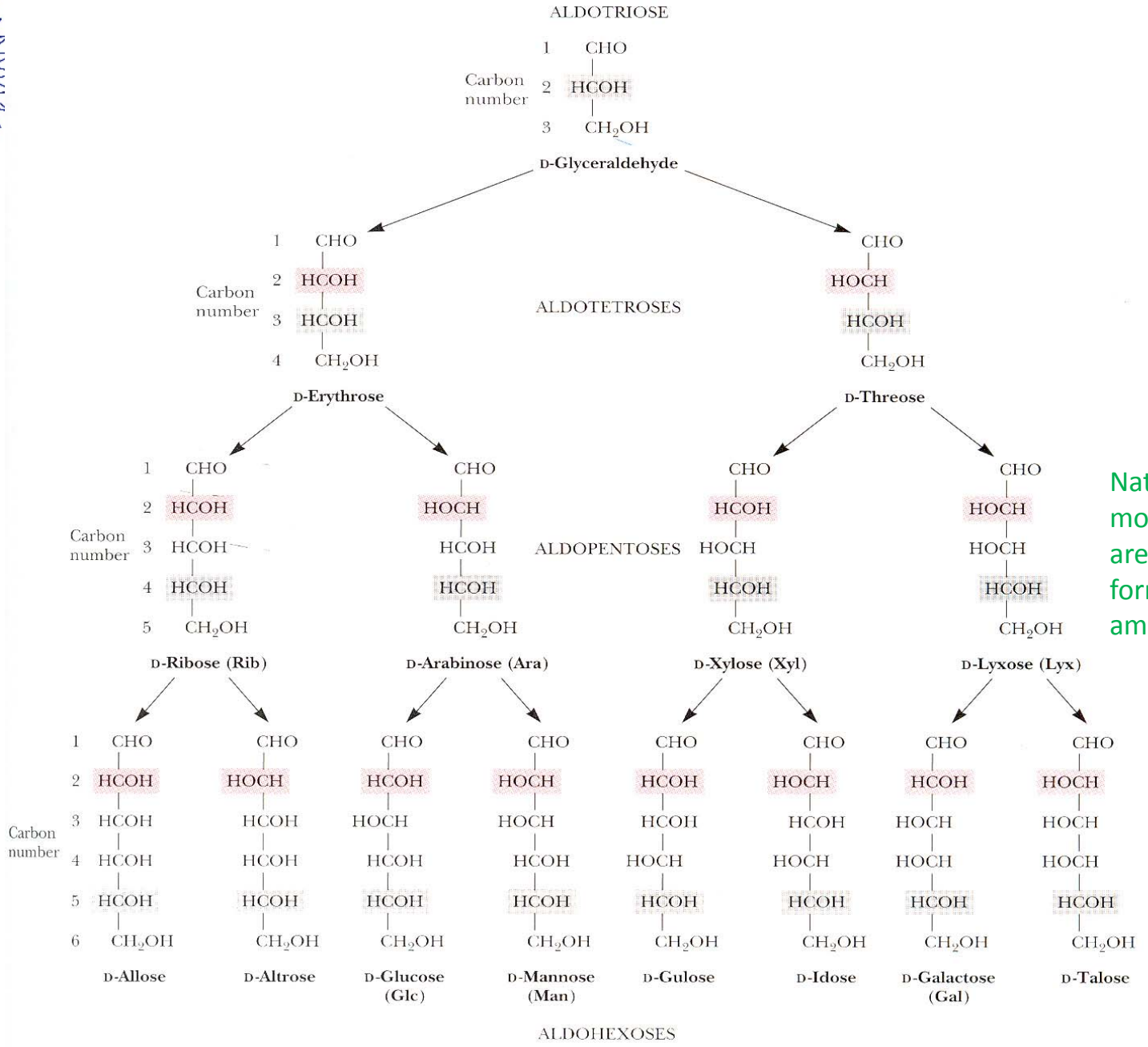
$$(CH_2O)_n + nO_2 \longrightarrow nCO_2 + nH_2O + \text{Energy}$$

Oxidation of carbohydrates

(1) Energy storage and generation are not the only functions of carbohydrates.

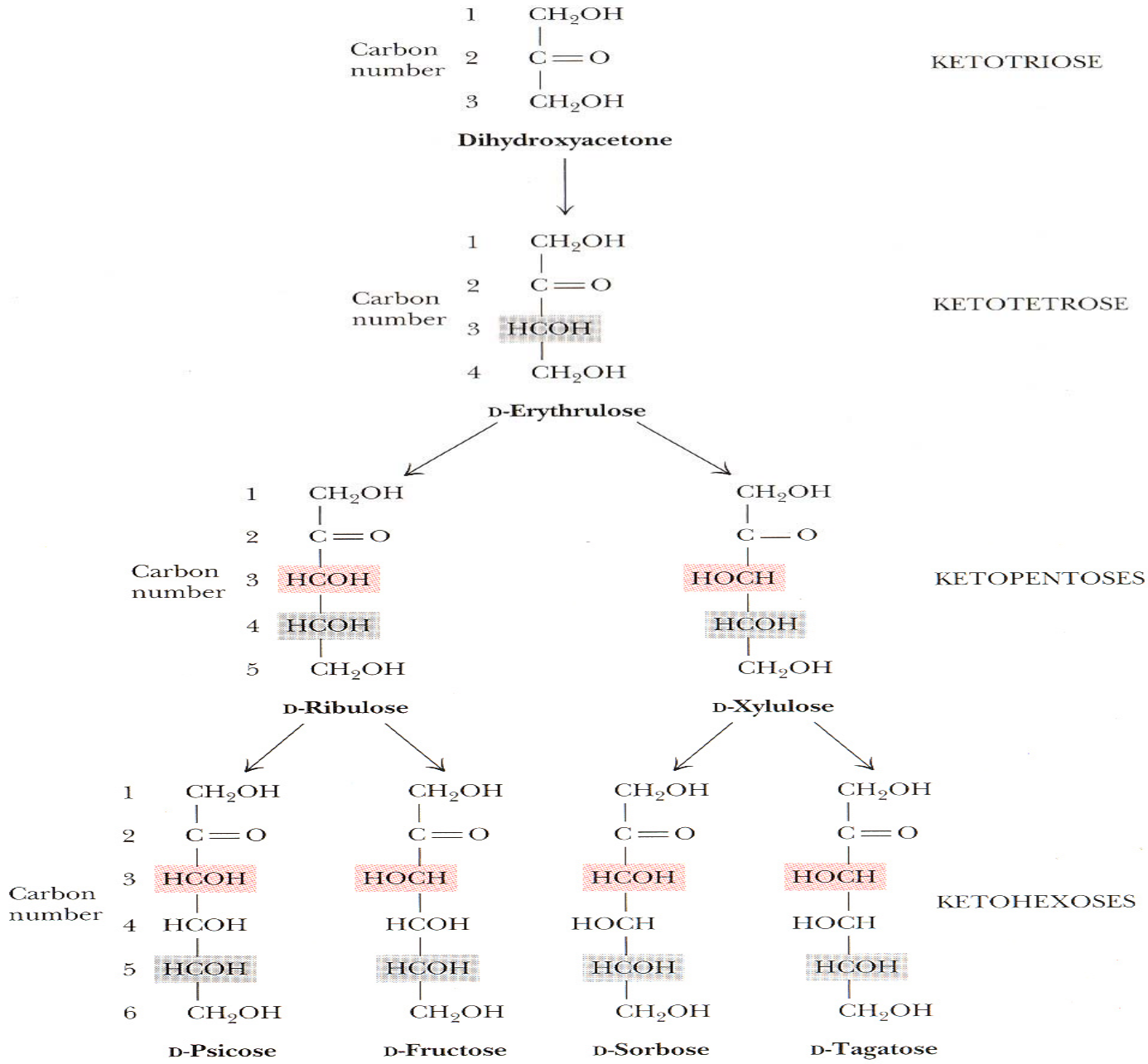
(2) Carbohydrates also form covalent linkages with lipids (to form glycolipids) and with proteins (to form the glycoproteins). These two classes of molecules are important components of cell walls and extracellular structures in plants, animals and bacteria.

(3) Carbohydrates also aid in recognition between cell types. Recognition events are important in normal cell growth, fertilization and other biological processes.

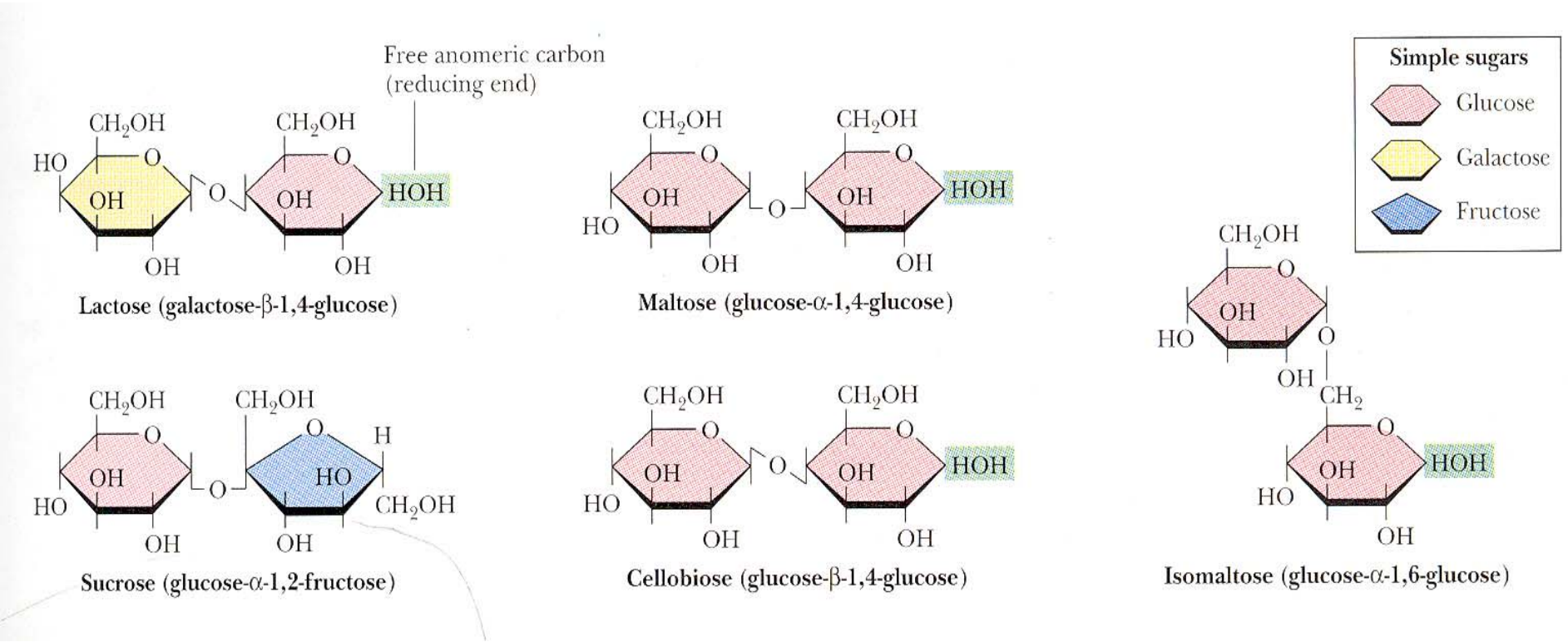


Naturally occurring monosaccharides are mostly of D-form just like the L-amino acids

Structures & names of aldoses having three to six carbons



Structures & names of ketoses having three to six carbons



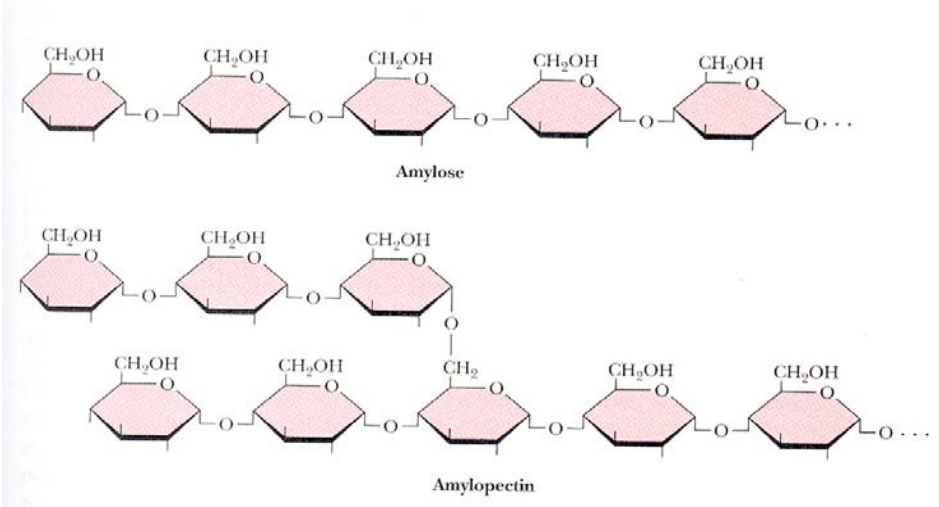
Some naturally occurring disaccharides

Starch

α amylase cleaves α(1 → 4) bonds.

Short polymers made of α(1 → 6) linkages are called Dextrans

Debranching enzymes or bacteria assist in α(1 → 6) cleavage



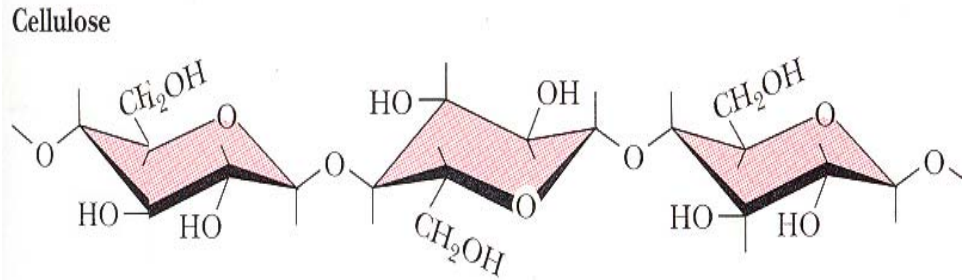
α (1 → 4)

α(1 → 4) & α (1 → 6)
Branching occurs every 12 to 30 residues

Structures of α-amylose and amylopectin

Glycogen, the store house of carbs in animals is like amylopectin with more frequent branching. Glycogen phosphorylase cleaves glycogen. **Hormones Glucagon and Insulin act synergistically to keep the glucose levels under control**
Glucagon -> receptor -> stimulate adenylate cyclase -> cAMP ->activates **PK** -> activates PbK -> converts GPb to GPa -> cleaves glycogen to release glucose. Insulin, among other things, does the opposite of glucagon

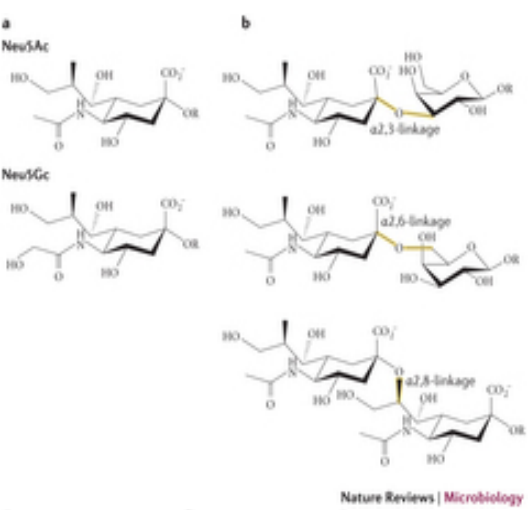
Cellulase, not present in animals, cleaves β (1 → 4) bonds

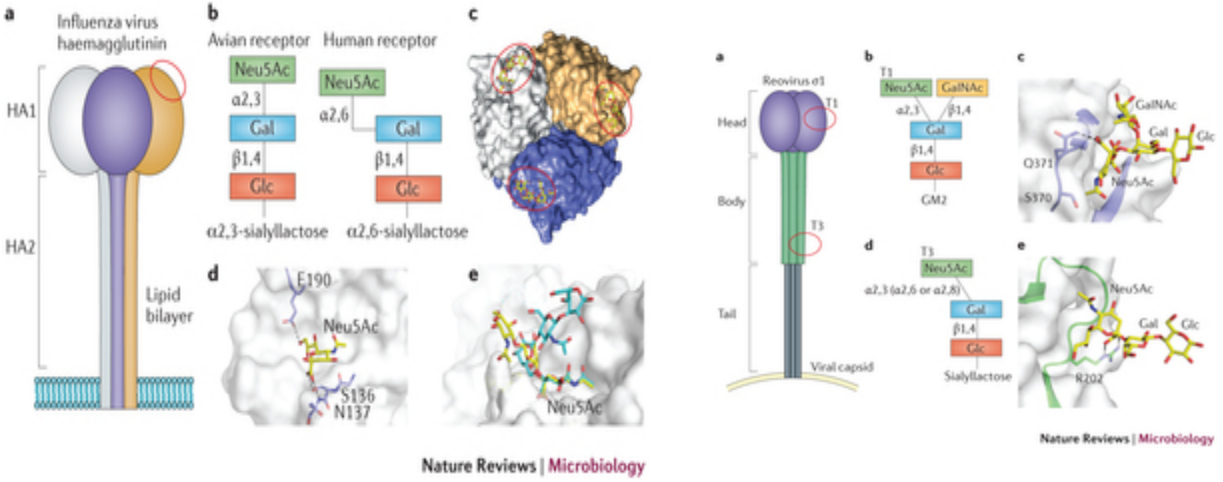


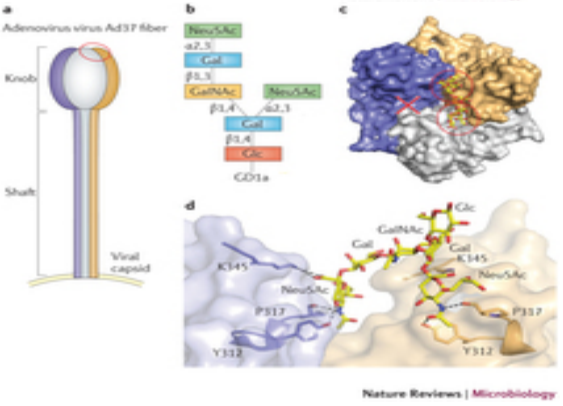
β (1 → 4)

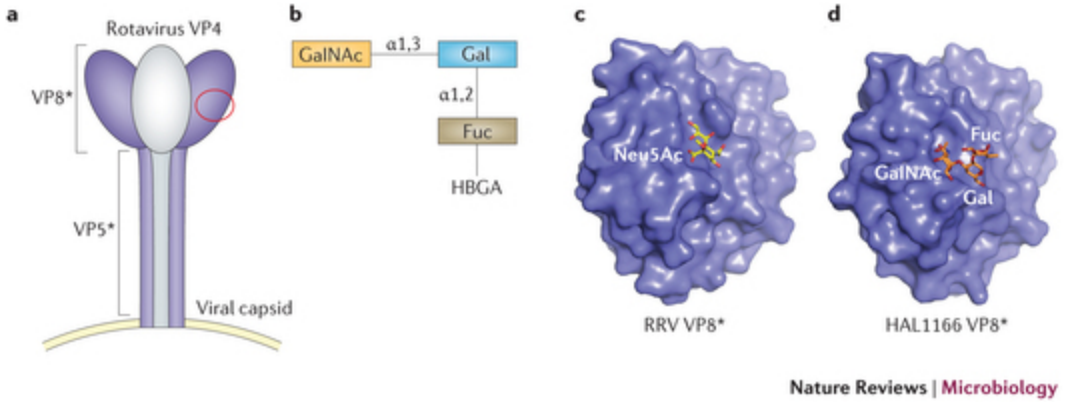
Structure of cellulose

"The sweet spot: defining virus–sialic acid interactions", Stencel-Baerenwald et al., Nature Reviews Microbiology 12, 739–749 (2014). "Sialic acid analogues such as zanamivir and oseltamivir, drugs against influenza, act as viral neuraminidase inhibitors, prevent sialic acid cleavage and virion release"









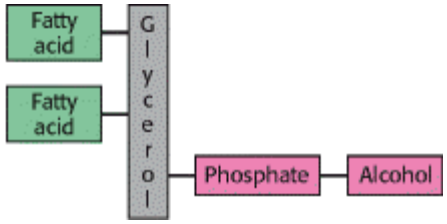
Lipids

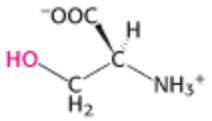
Lipidomics is the study of the structure and function of the complete set of lipids (the lipidome) produced in a given cell or organism as well as their interactions with other lipids, proteins and metabolites (nature.com)

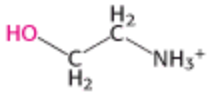
Lipids differ markedly from the other groups of biomolecules. Lipids are water-insoluble but highly soluble in organic solvents such as chloroform. Lipids have a variety of biological roles: they serve as fuel molecules, highly concentrated energy stores, signal molecules and components of membranes.

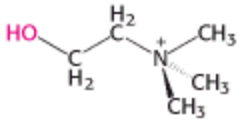
The three major kinds of membrane lipids are (a) phospholipids, (b) glycolipids and (c) cholesterol.

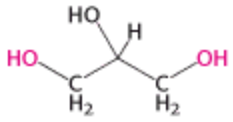
Schematic structure of a phospholipid

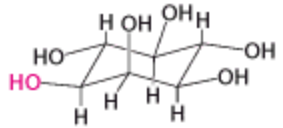


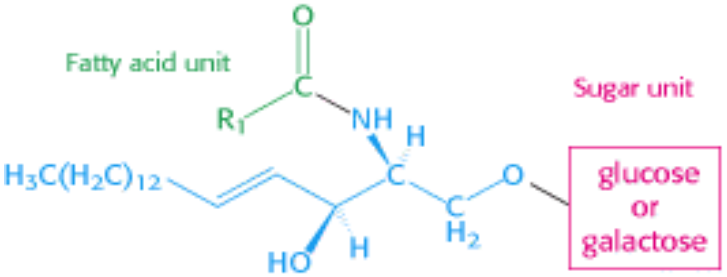

Serine


Ethanolamine

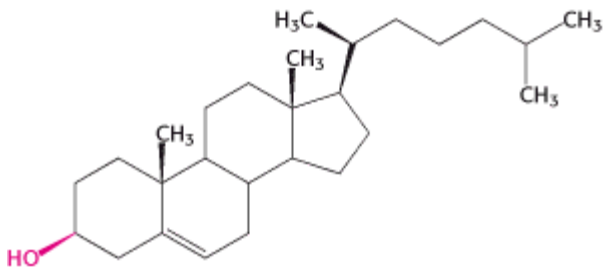

Choline


Glycerol

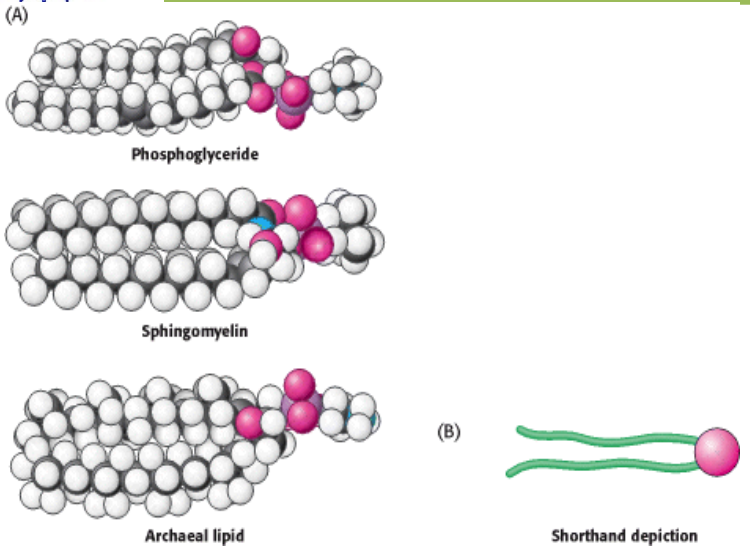

Inositol



Cerebroside
(a glycolipid)


Cholesterol

Membranes



Representations of membrane lipids. (A) Space-filling models of a phosphoglyceride, sphingomyelin, and an archaeal lipid show their shapes and distribution of hydrophilic and hydrophobic moieties. (B) A shorthand depiction of a membrane lipid.

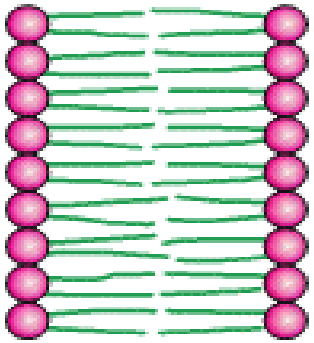
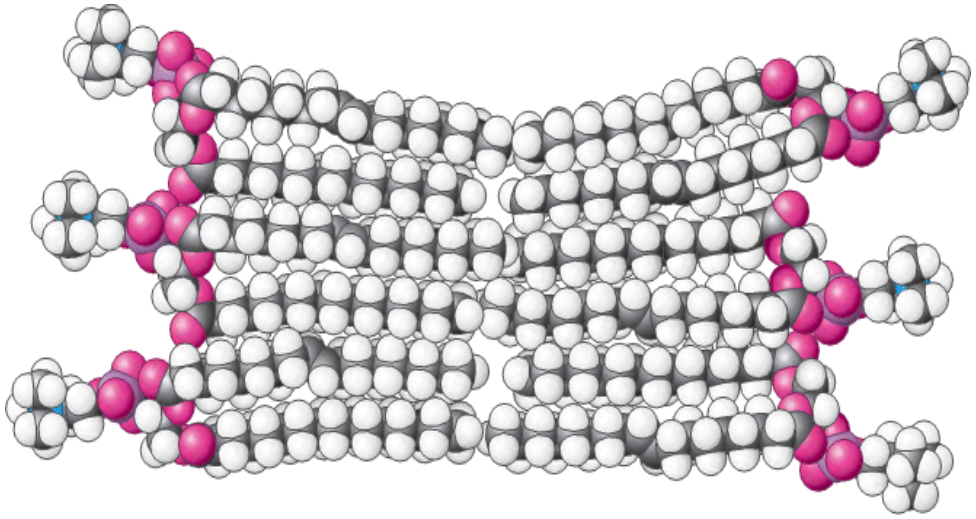
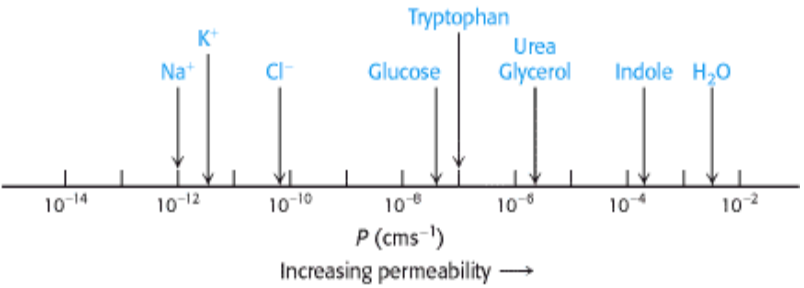
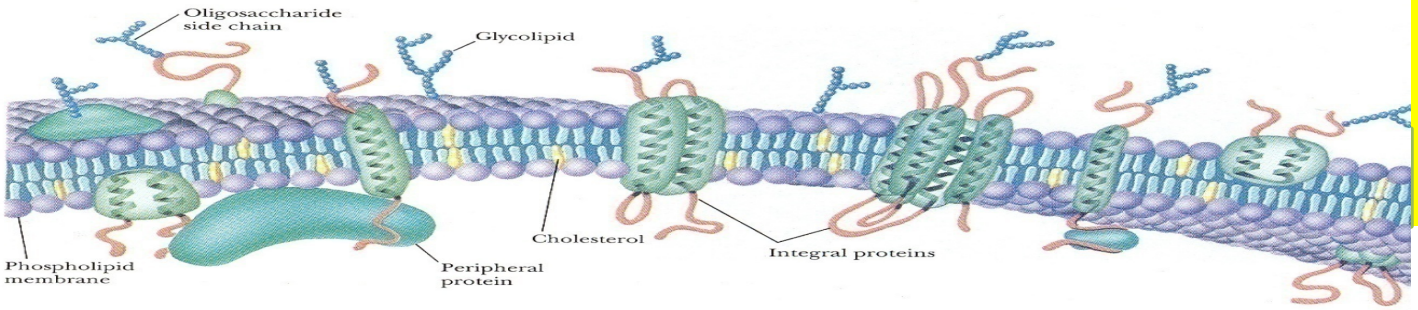


Diagram of a section of a **bilayer membrane**



Space-filling model of a section of a Phospholipid Bilayer Membrane





Membranes

Membranes are as diverse in structure as they are in function. However, they do have in common a number of important attributes:

(1) Membranes are sheet-like structures, only two molecules thick that form closed boundaries between different compartments. The thickness of most membranes is between 60 Å (6 nm) and 100 Å (10 nm).

(2) Membranes consist mainly of lipids and proteins. Their mass ratio ranges from 1:4 to 4:1. Membranes also contain carbohydrates that are linked to lipids and proteins.

(3) Membrane lipids are relatively small molecules that have both hydrophilic and hydrophobic moieties. These lipids spontaneously form closed bimolecular sheets in aqueous media. These lipid bilayers are barriers to the flow of polar molecules.

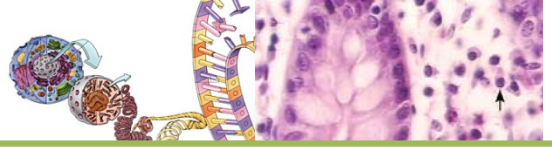
(4) Specific proteins mediate distinctive functions of membranes. Proteins serve as pumps, channels, receptors, energy transducers, and enzymes. Membrane proteins are embedded in lipid bilayers, which create suitable environments for their action.

(5) Membranes are noncovalent assemblies. The constituent protein and lipid molecules are held together by many noncovalent interactions, which are cooperative.

(6) Membranes are asymmetric. The two faces of biological membranes always differ from each other.

(7) Membranes are fluid structures. Lipid molecules diffuse rapidly in the plane of the membrane, as do proteins, unless they are anchored by specific interactions. In contrast, lipid molecules and proteins do not readily rotate across the membrane. Membranes can be regarded as two-dimensional solutions of oriented proteins and lipids.

(8) Most cell membranes are electrically polarized, such that the inside is negative [typically - 60 millivolts (mV)]. Membrane potential plays a key role in transport, energy conversion, and excitability.

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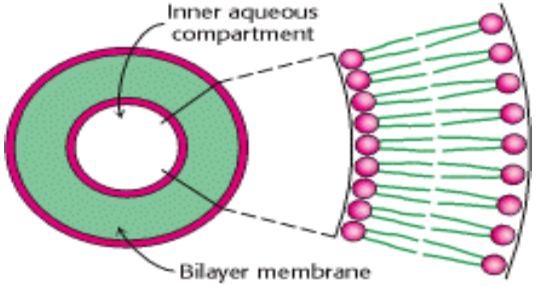
Some milestones across membranes

(From www.nobelprize.org)



A liposome, or lipid vesicle, is a small aqueous compartment surrounded by a lipid bilayer.

The Nobel Prize in Physiology or Medicine 2013

for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells

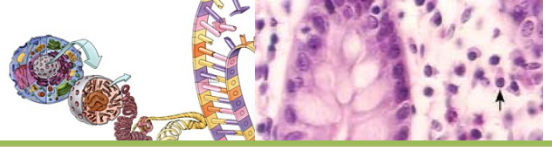
James E Rithman
Yale U, USA
b. 1950, (USA)

Randy W Schekman
UCB, USA
b. 1948 (USA)

Thomas C Sudhof
Stanford U, USA
b. 1955 (Germany)

Summary

The 2013 Nobel Prize honours three scientists who have solved the mystery of how the cell organizes its transport system. Each cell is a factory that produces and exports molecules. For instance, insulin is manufactured and released into the blood and signaling molecules called neurotransmitters are sent from one nerve cell to another. These molecules are transported around the cell in small packages called vesicles. The three Nobel Laureates have discovered the molecular principles that govern how this cargo is delivered to the right place at the right time in the cell. Defective vesicle transport occurs in a variety of diseases including a number of neurological and immunological disorders, as well as in diabetes. Without this wonderfully precise organization, the cell would lapse into chaos.

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The Nobel Prize in Physiology or Medicine 1994 was awarded to Alfred G. Gilman and Martin Rodbell "for their discovery of G-proteins and the role of these proteins in signal transduction in cells"

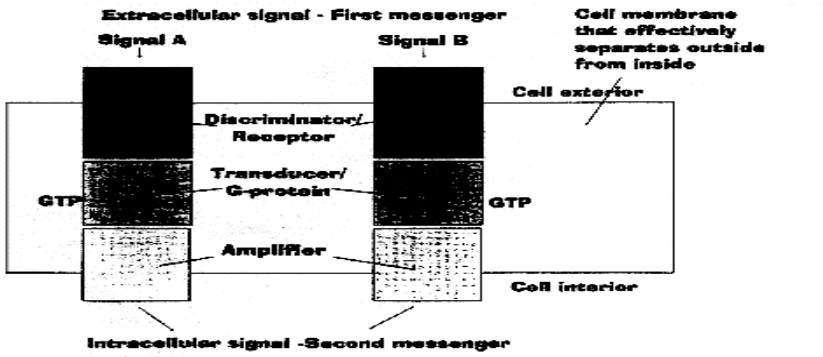
Summary

It has been known for some time that cells communicate with each other by means of hormones and other signal substances, which are released from glands, nerves and other tissues. It is only recently that we have begun to understand how the cell handles this information from the outside and converts it into relevant action - i.e. how signals are transduced in cells.

The discoveries of the G-proteins by the Americans **Alfred G. Gilman**and **Martin Rodbell** have been of paramount importance in this context, and have opened up a new and rapidly expanding area of knowledge.

G-proteins have been so named because they bind guanosine triphosphate (GTP). Gilman and Rodbell found that G-proteins act as signal transducers, which transmit and modulate signals in cells. G-proteins have the ability to activate different cellular amplifier systems. They receive multiple signals from the exterior, integrate them and thus control fundamental life processes in the cells.

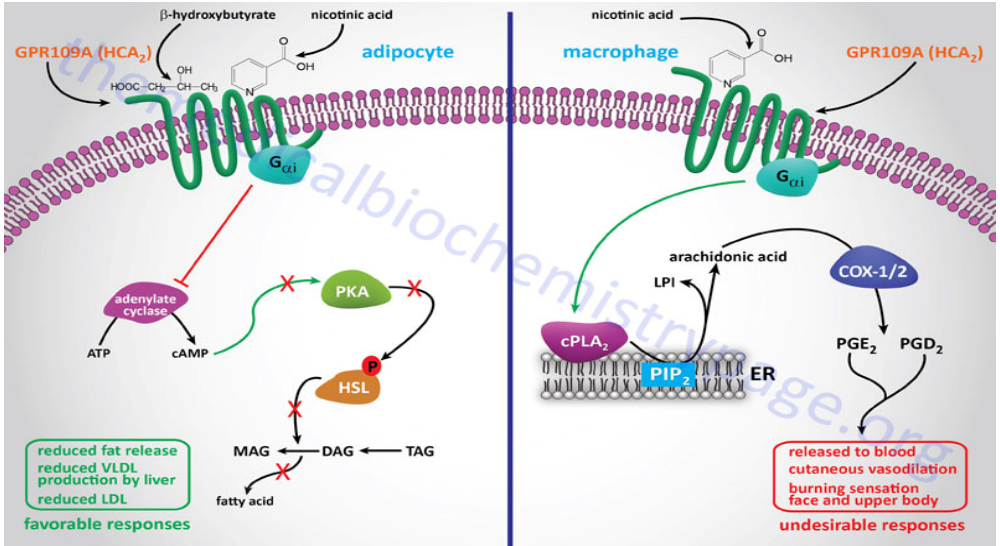
Disturbances in the function of G-proteins - too much or too little of them, or genetically determined alterations in their composition - can lead to disease. The dramatic loss of salt and water in cholera is a direct consequence of the action of cholera toxin on G-proteins. Some hereditary endocrine disorders and tumours are other examples. Furthermore, some of the symptoms of common diseases such as diabetes or alcoholism may depend on altered transduction of signals through G-proteins



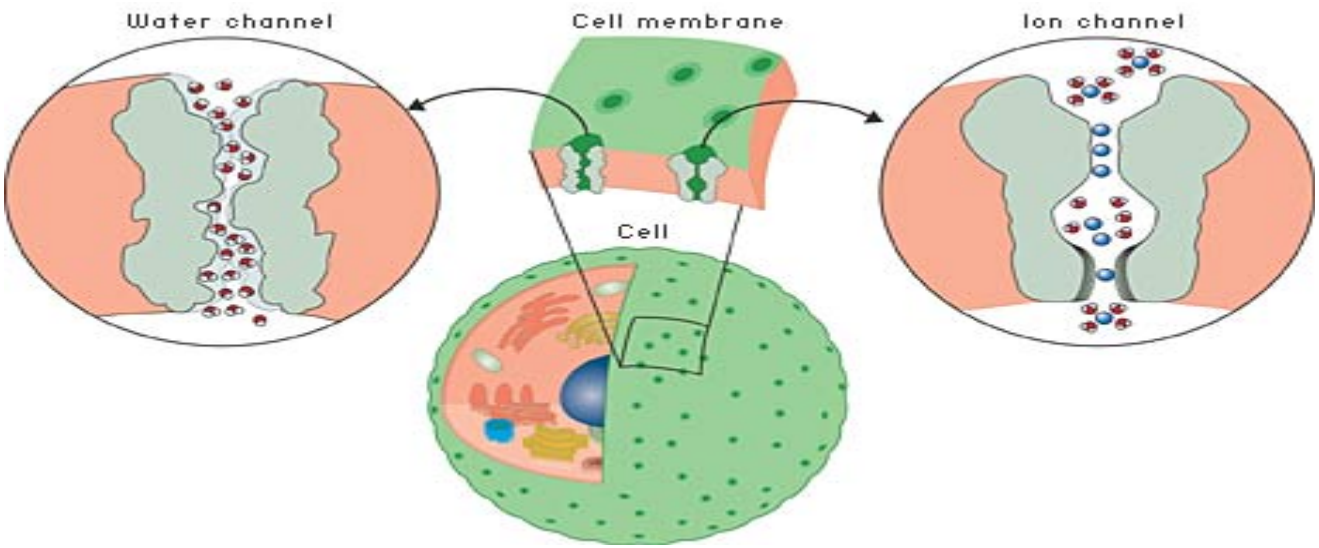
The Nobel Prize in Chemistry 2012 was awarded to Robert J. Lefkowitz and Brian K. Kobilka "for studies of G-protein-coupled receptors"

GPCRs are smart receptors on cell surfaces: Human body is a fine-tuned system of interactions between billions of cells. Each cell has tiny receptors that enable it to sense its environment, so it can adapt to new situations. **Robert Lefkowitz** and **Brian Kobilka** are awarded the 2012 Nobel Prize in Chemistry for groundbreaking discoveries that reveal the inner workings of an important family of such receptors: G-protein–coupled receptors.

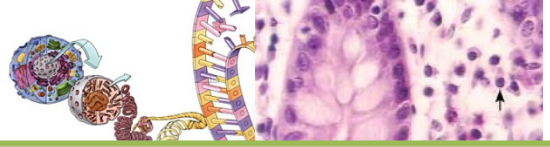
GPCRs are popular drug targets



The Nobel Prize in Chemistry 2003 was awarded to **Peter Agre** "for the discovery of water channels“ and **Roderick MacKinnon** "for structural and mechanistic studies of ion channels"



The dividing wall between the cell and the outside world – including other cells – is far from being an impervious shell. On the contrary, it is perforated by various channels. Many of these are specially adapted to one specific ion or molecule and do not permit any other type to pass. Here to the left we see a water channel and to the right an ion channel



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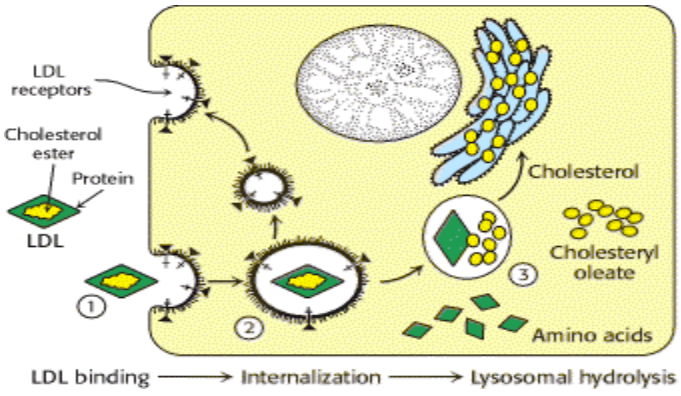
The Nobel Prize in Physiology or Medicine 1985 was awarded to Michael S. Brown and Joseph L. Goldstein "for their discoveries concerning the regulation of cholesterol metabolism"

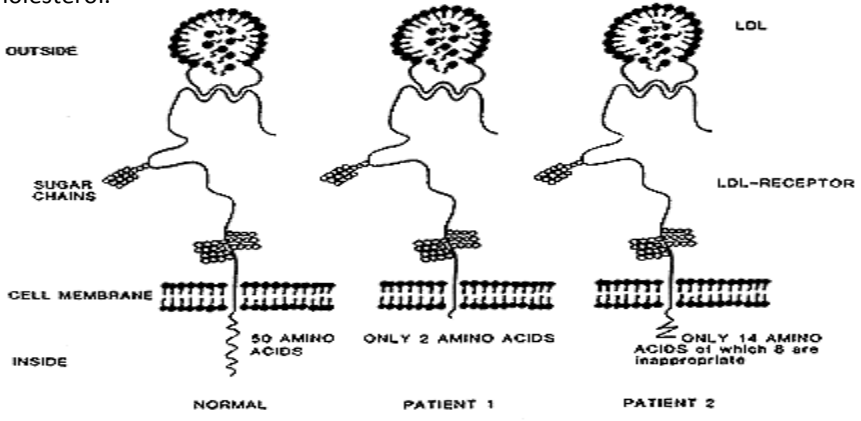
Summary

Michael S. Brown and **Joseph L. Goldstein** have through their discoveries revolutionized our knowledge about the regulation of cholesterol metabolism and the treatment of diseases caused by abnormally elevated cholesterol levels in the blood. They found that cells on their surfaces have receptors which mediate the uptake of the cholesterol-containing particles called low-density lipoprotein (LDL) that circulate in the blood stream. Brown and Goldstein have discovered that the underlying mechanism to the severe hereditary familial hypercholesterolemia is a complete, or partial, lack of functional LDL-receptors. In normal individuals the uptake of dietary cholesterol inhibits the cells own synthesis of cholesterol. As a consequence the number of LDL-receptors on the cell surface is reduced. This leads to increased levels of cholesterol in the blood which subsequently may accumulate in the wall of arteries causing atherosclerosis and eventually a heart attack or a stroke.

Brown and Goldstein's discoveries have lead to new principles for treatment, and prevention, of atherosclerosis.



Receptor-Mediated Endocytosis. The process of receptor-mediated endocytosis is illustrated for the cholesterol-carrying complex, low-density lipoprotein (LDL): (1) LDL binds to a specific receptor, the LDL receptor; (2) this complex invaginates to form an internal vesicle; (3) after separation from its receptor, the LDL-containing vesicle fuses with a lysosome, leading to degradation of the LDL and release of the cholesterol.



LDL-receptors. When the LDL via its apoprotein wanders to the receptor it is internalized by the normal healthy receptor. The two abnormal receptors are unable to complete the internalization.

BJ-L7.15