STRUCTURAL NEUROBIOLOGY

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Keywords: Neurones, glial cells, cytoskeleton, membrane lipids, myelin, Ranvier nodes, cell adhesion, cadhedrins, integrins, neurofilaments.

Contents

Summary

This chapter is an overview of the chemical structure of neural plasma membranes and lipids abounding in the nervous system. The myelin sheath that covers the cell extensions of many neurones is a good electrical isolator facilitating nerve impulse propagation. Cell adhesion molecules and cytoskeletal organelles maintain the structural integrity of neural tissues and cells.

1. Neural Plasma Membranes and Membrane Proteins

The principal cellular elements of the central nervous system are neurones and glial cells (see *Neurones, Action Potentials and Synapses*). A prominent structure for their specific function is the plasma membrane. Neurones integrate environmental stimuli and transmit them along the plasma membranes to other cells. These processes are mediated by means of certain specialized structures only existing in the nervous system, which are called synapses. The protein and lipid components in the cell membrane are essential for information transfer. The concept of a lipid bilayer as the cell membrane is now widely accepted and abundantly corroborated by experimental evidence. The forces keeping the protein and lipid components together in the membrane structure are mostly physical in nature, consisting of hydrogen bonds, van der Waals' interactions and electrostatic forces. Cytoskeletal proteins are also essential in the maintenance of membrane structure. A general principle is that the hydrophilic protein components mostly point to the aqueous outer and inner sides of plasma membranes, while the lipid components reside in the hydrophobic inner region. Exceptions for this general structure in nerve cells are transmitter receptors, membrane transporters and ion channels, i.e. protein complexes that extend across the whole membrane (Figure 1). Major lipids in neural membranes have a polar head, mostly consisting of a glycerophosphorylester, and a long hydrocarbon tail pointing to the interior of the membrane.

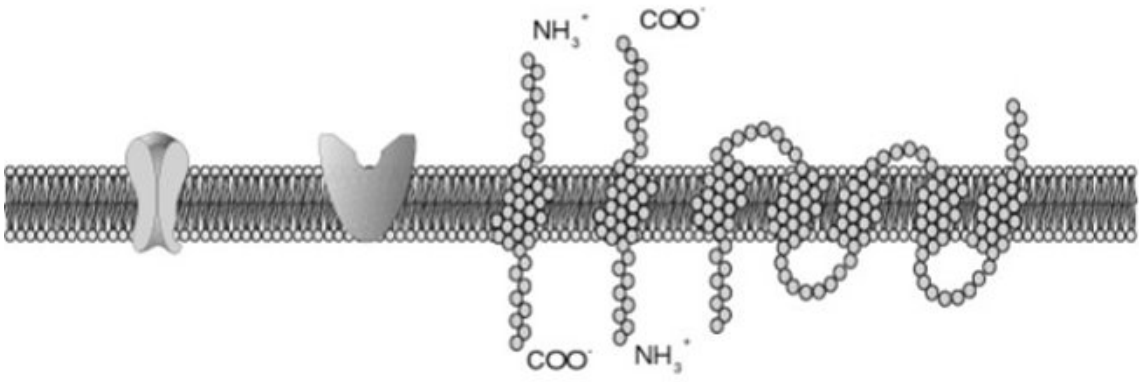

Figure 1. Schematic structure of nerve cell membranes.
As in other cells, the membrane is a lipid bilayer with hydrophilic outer and inner sides and a hydrophobic inner core. The ion channels span the membrane. Their specificity propensities determine whether anions or cations can pass through the central ion pores. The receptor complexes recognize specific messenger molecules, ligands, which participate in information transfer between the cells and their surroundings and neighbouring cells. A few typical integral membrane proteins are shown on the right-hand side of the graph. The abounding bitopic proteins have a single transmembrane domain oriented with the N- or C-termini to the extracellular side. On the other hand, polytopic integral proteins consist of several membrane-spanning regions. Receptors and transporters are often such polytopic protein entities.

The protein-lipid bilayer structure effectively limits the penetration of substances across cell membranes. Only rather small-molecular compounds with relatively good lipid solubility are able to diffuse through the membranes. However, the membrane-spanning transporters and ion 'pumps' effectively facilitate the passage of certain compounds into nerve cells. They thus largely determine which compounds can enter or leave the cells.

These integral protein complexes have transmembrane domains that consist predominantly of nonpolar amino acid residues. The protein complexes forming transmitter receptors (see *Neurones, Action Potentials and Synapses*) and transporters (see *Neurotransmitters and Modulators*) usually traverse the membrane several times. The number of transmembrane domains usually varies from four to eleven. However, the structure may also comprise only one transmembrane domain, e.g. in the receptor-activated tyrosine kinases. The water soluble domains may face either the intracellular or extracellular side but commonly both. The C and N termini are alternatively extra- and intracellular. The transmembrane parts of the molecules are mostly closely packed. The integral functional proteins may have some scope to relocate themselves in the membrane owing to the fluidity of the lipid bilayer. On the other hand, they can be locally fixed to their sites by cytoskeletal proteins that nevertheless allow rotational movements essential for the function of these integral components. The interactions of integral and cytoskeletal proteins are often effected by linker proteins. Of such protein species, the neural adhesion molecules are probably the best known constituents of nervous tissue. They belong to the widely distributed family of cell-membrane glycoproteins. The membrane proteins synthesised in the endoplasmic reticulum travel through a series of successive Golgi compartments to reach their destination. During

this transition, guided and aided by coat proteins, they may undergo post-translational modifications and then fuse with the plasma membrane.

2. Neural Lipids

There are markedly more lipids in the white than in the grey matter of the brain. In the grey matter the total amount of lipids is 5.9% of the fresh weight in the adult human brain, whereas there are 15.6% lipids in the white matter. Of the tissue dry weight about one third is lipid in the grey matter and more than half in the white matter. The lipid composition of grey and white matters in the brain is also markedly different (Table 1). Phospholipids dominate in the grey matter, while in the white matter there are also particularly much cholesterol and cerebrosides. However, the lipid composition is somewhat different in different brain regions, and it varies with age. The lipids that are the principal constitutents of membrane structures dominate in the brain. Characteristic components include phospholipids, glycosphingolipids and sterols.

Lipid component	**Grey matter**	**White matter**
Total lipids	100.0	100.0
Phosphatidylcholine	27.8	13.9
Phosphatidylethanolamine	25.1	22.1
Cholesterol	20.4	25.3
Phosphatidylserine	8.0	7.3
Sphingomyelin	6.4	7.1
Galactosylceramide	5.0	18.3
Gangliosides	3.2	0.2
Phosphatidylinositoles	2.5	0.8
Sulphogalactoceramide	1.6	5.0

Table 1. Typical percentage lipid composition of the grey and white matters in the adult human brain.

Of the phospholipid classes phosphoglycerides are the most common. They consist of a glycerol backbone joined through ester linkages to two fatty acids and a phosphorylated alcohol. The fatty acids most commonly contain 16 or 18 carbons. The alcohols include ethanolamine, choline, serine or inositol (Figure 2). The second phospholipid class is composed of sphingomyelins. They contain a sphingosine backbone, a fatty acid in an amide linkage, and phosphatidylcholine attached through an ester linkage to the primary hydroxyl group of sphingosine (Figure 3). The glycerospingolipids are sugar-containing lipids. They are also sphingosine derivatives, differing from the sphingomyelin by the structure of the moiety attached to the hydroxyl group of sphingosine. Two main classes are cerebrosides and gangliosides. In cerebrosides a single hexose is attached to sphingosine and in gangliosides a chain of sugars, of which at least one is a sialic acid (an *N*- or *O*-acyl derivative of neuraminic acid). In plasma membranes the predominant

sterol is cholesterol, being more abundant toward the outer side. It is also present in lesser quantities in mitochondrial and nuclear membranes as well as Golgi complexes.

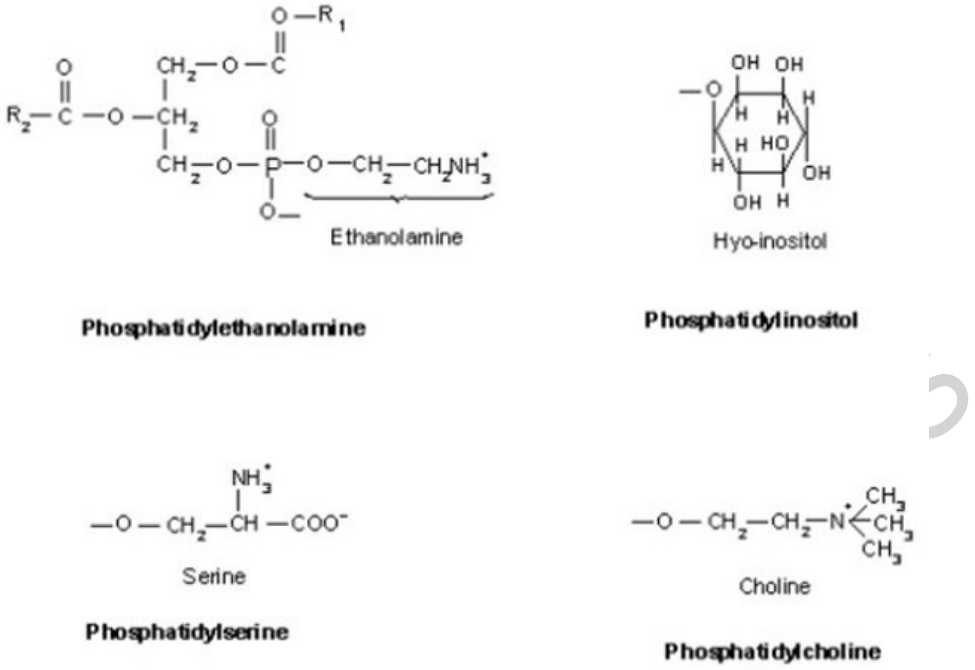

Figure 2. Structure of some common phosphoglycerides abounding in brain lipids. R_1 and R_2 are alkyl chains of fatty acids joined by the ester linkages to glycerol joined to an *o*-phosphoric acid. This phosphoric acid, in turn, is joined by means of an ester linkage to ethanolamine, serine, choline or *myo*-inositol, forming phosphatidylethanolamine, -choline, -serine and -inositol, respectively.

Owing to their abundance, several lipids, such as cerebrosides, gangliosides, phosphoinositides and sulfatides, were first identified in the brain and only later discovered to be present also in other tissues, though generally at much lower concentrations. Trigycerides are generally used as storage fat in other tissues, but they are virtually absent from the brain. Most brain lipids are structural components of cell membranes, but some have also important roles as messengers and in signal transduction at plasma membranes. Membrane lipids have a small polar hydrophilic region and a large nonpolar hydrophobic moiety. This propensity is also the basis for the bilayer structure of cell membranes. Otherwise, lipids are a rather heterogeneous group of compounds with a salient feature of being soluble in organic solvents but not in water.

The lipids are often synthesised in a cellular compartment different from the compartment in which they function. An example of this is vesicular transport in which lipids are first enclosed in vesicles budding from the donor membrane. The vesicles are then transported to the recipient membrane into which they finally fuse to become its integral constituent. Some lipids are also apparently complexed with carrier proteins and may in this manner be transferred to their destination. As stated above, in addition to their participation in the structural integrity of the brain cells, some lipids seem to also

have regulatory roles. For example, arachidonic acid, a polyunsaturated fatty acid that is a major component in phosphoglycerides is also a precursor of a number of important biomessengers. On the other hand, several sphingolipids have also been assumed to participate in a variety of regulatory processes in the cells.

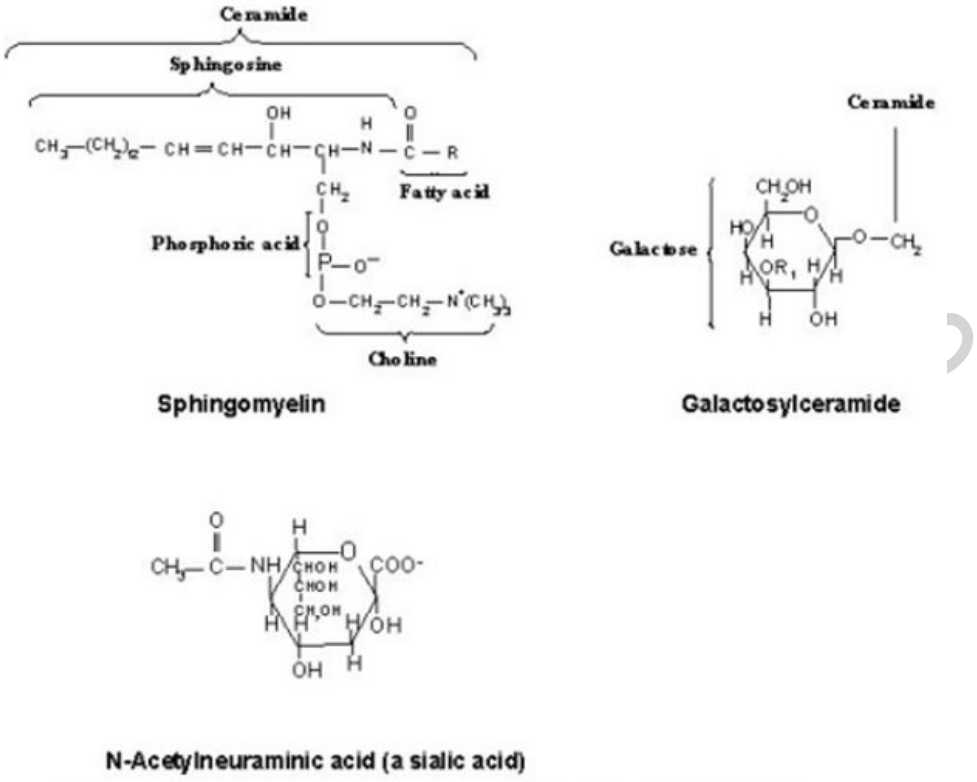

Figure 3. Principles of the structure of sphingomyelin, cerebroside and ganglioside. The backbone in sphingomyelin is an unsaturated aminoalcohol, sphingosine, joined to a fatty acid forming ceramide. Sphingosine is a condensation product of palmitidylaldehyde and decarboxylated serine. The primary alcohol group in ceramide is esterified with phosphorylcholine (or phosphorylcholamine). R denotes the alkyl chain of a fatty acid. In cerebrosides, the group attached to the sphingosine is a hexose. R_1 is either H (e.g. in galactosylceramide shown here) or an esterified sulphuric acid group (sulphogalactosylceramide). In gangliosides, there is instead of a single hexose a chain of sugars, of which at least one is a sialic acid, an *N*- or *O*-derivative of a neuraminic acid; the structural principle is shown in the graph.

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Biographical Sketches

Simo S. Oja is Professor in Biomedical Sciences (physiology), University of Tampere, Director of the Tampere Brain Research Center, and Docent in Biochemistry, University of Oulu, Finland. He was born in 1939 in Kärkölä, Finland. He obtained his Master of Science (M.Sc.) in 1962; Medical Doctor (M.D.) in 1964; Licentiate in Philosophy (Ph.L.) in 1965; Doctor of Philosophy (Ph.D.) in 1966; Doctor of Medical Sciences (M.Sc.D.) in 1967 (all at the University of Helsinki); and Master of Civil and Criminal Law (M.L.) in 1988 (University of Turku).

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He has been Vice President of Finnish Physiologists' Association since 1996. He was a Member of the Executive Committee of the Finnish Brain Research Society from 1984 to 1992, and again from 1998 to the present. He was found qualified and competent for many professorial posts in Physiology, Pharmacology, Biochemistry, and Medical Chemistry in several Finnish universities. Editor *Neurochemical Research*, 1999–present. Has participated in more than 100 international meetings, congresses, and symposia in physiology, pharmacology, biochemistry, and neurosciences since 1974. Has produced about 250 original scientific publications on chemistry, physiology, and pharmacology of brain neurotransmitters.