



## 1. PHOSPHOLIPIDS IN THE HUMAN MEMBRANE

### 1.1 Phospholipids Composition

Phospholipids are amphipathic molecules. They contain a polar region and a hydrophobic part. The former is the so-called "head group" of the phospholipid molecule and can be one of several different possible groups, e.g. phosphocholine or phosphoethanolamine (fig. 1).

<% Fig1: Structures of various types of glycerophospholipids (761) %>  
Sphingomyelins (ceramide-1-phosphorylcholines) contain a choline polar head but are not linked to a glycerol backbone.

Furthermore, not all phospholipids have ester linkages as the covalent bond between the glycerol backbone and the tail regions, nor must they contain the linkages -P-O-R-3. In some phospholipids, e.g. the phosphonolipids, the polar group R3 is directly attached to P via P-C bond. Generally all mammalian tissues contain qualitatively the same phospholipids (742).

Phosphatidylcholine predominates in most parts of the human body (tab. 1).  
<% Tab.1: Phosphatidylcholine content in different human organs in percent of the total phospholipid composition (742)%>

The hydrophobic region of a phospholipid consists of the long hydrocarbon chains esterified to the 1- and 2-positions of the glycerol backbone. These chains are at least 14 carbons long in humans (761).

Typically naturally occurring phospholipids contain an unsaturated fatty acid (such as oleic acid, linoleic acid or arachidonic acid) in position 2 and a saturated one (such as stearic acid or palmitic acid) in position 1 (718). Comprehensive analysis of the fatty acids of phosphatidylcholine of whole tissue and subcellular fractions (742) and their possible distribution to the 1- and 2-positions of the glycerol group elucidate the wide variety of different phosphatidylcholine molecules (and of the other types of glycerophospholipids) in the human organism.

### 1.2 Phospholipids for Structuring and Composition of Membranes

Beside glycolipids, cholesterol and proteins phospholipids belong to the main components of biological membranes (519). The total lipid content (40-80 % of dried weight) and the proportion of phospholipids are relatively high in mammalian cell membrane preparations but vary appreciably from one type of membrane to another (182).

Phosphatidylcholine and phosphatidylethanolamine predominate quantitatively in the lipid fraction of most biological membranes (742) and they mainly constitute the matrix of these membranes (fig. 2).

The majority of phospholipids are present in a bilayer structure (519). The bilayer may be discriminated in three parts:  
The polar, hydrophilic groups are arranged at the outer sides of the cellular membranes, whereas the acyl residues face each other at the inside. The hydrophobic core of the bilayer can be subdivided, into the steroid stiff chain and the pliant chain. The pliant chain is a rather disordered region in the middle of the core with high flexibility, the steroid chain is the area where van der Waals forces are very strong (681).  
The different phospholipids need different spaces in the membrane:

1. The size and chemical structure of their polar region influence the tightness with which the acyl chains can pack. Ethanolamine, for example, is

smaller than choline due to N-substitution with methyl groups in the latter, and acyl chains in phospholipids containing ethanolamine can simply for this reason pack more tightly. Furthermore, phosphatidylethanolamine can form an extensive network of hydrogen bonds, which additionally enhances the tightness of packing (761).

<% Fig. 2: Schematic representation of present-day model concepts on the plasma membrane in cross-section with the proteins anchored in it.%>

2. The space is definitely influenced by the type of the acyl chains. With the help of the 'Langmuir balance technique' it was shown that sphingomyelin with its mostly saturated acyl chains occupies an area of 36 Å<sup>2</sup>/molecule. If there are two unsaturated acyl chains, as presented by dilinoleoyl-phosphatidylcholine, the space extends nearly twofold at a pressure of 25 dyn/cm which is assumed to be the intracellular pressure exerted on a bilayer (681).

Below the phase transition temperature (see 1.4.1 Membrane Fluidity) phospholipids containing only fully saturated acyl chains adopt a configuration in which the acyl chain carbons are in extended all-trans conformation. The introduction of a cis double bond precludes the adoption of the trans conformation in at least one position in the chain. A 'kink' is found in the chain, disrupting the close packing which is possible with the all-trans conformation (fig.3). Van der Waals energies are weakened. Correspondingly the presence of even one single double bond is sufficient to exert a profound influence on physical properties (684, 761).

<% Fig. 3: Conformation of phosphatidyl-glycerol with stearoyl chain in 1-and oleoyl chain in 2-position.%>

Cornell and Separovic (123) found that an increase in the phosphatidylcholine hydrocarbon chain length was accompanied by an increase in bilayer thickness of only 40 % of the value expected for the fully extended chains. The major change was an increase in the area per phospholipid indicating that the ends of the fatty acid chains are highly dynamic and have an increased molecular area. To fulfill its vital functions the membrane must operate differentially on the two compartments it separates, and thus it must be asymmetric. The outer surface must differ chemically from the inner one: Some negatively charged phospholipids (phosphatidylinositol, phosphatidylserine, phosphatidic acid) and the zwitterionic phosphatidylethanolamine accumulate predominantly at the inner surface, while other species such as the strongly acidic phosphatidylglycerol and the zwitterionic sphingomyelin prefer the outer surface of the bilayer (53). Figure 4 shows the asymmetrical distribution of phospholipids in the membrane of human red blood cells (723).

<%Fig. 4: Asymmetrical distribution of phospholipids in membranes of human red blood cells, expressed as mole percent. Abbreviations: TPL, total; phospholipid; PC, phosphatidylcholine; SM, sphingomyelin; PE, phosphatidylethanolamine; PS, phosphatidylserine; and PI, phosphatidylinositol.%>

The asymmetry is maintained by the lack of transmembrane diffusion (585). Apart from the asymmetric disposition of phospholipids (and of cholesterol), the fatty acids are also asymmetrically distributed (684). Asymmetry can be present also in the same layer, where lipids can form domains of different composition and diffusion characteristics (649). These lateral phase operations are characterized by a specific selection of several components which frequently occur in precisely localized positions and are obviously excluded from lateral movements by intramembraneous or exogenous (cytoplasmic and extracellular and intravesicular, respectively) constraints (197). Beside the fact that membrane parts may be laterally divided into distinct phases, the dynamic state of cell and organelle membranes has been demonstrated

by experimentally evidenced exchange processes of phospholipids within a membrane and between several membranes:

1.) Lateral diffusion, rotation of the lipid molecules around their longitudinal axis and rotation around the carbon-carbon bonds of the acyl chains are the main motions, the flip-flop motion is of less importance; the latter describes the movement of a phospholipid molecule from the extracytosolic to the cytosolic part of the bilayer (681, 761). The lack of flip-flop can be explained, at least in part, by the high activation energy that would be required to bring the polar group through the hydrocarbon core of the bilayer (585).

2.) Transfer proteins have been isolated for example from rat and cow livers which facilitate the phospholipid translocation. Exchange studies on sarcoplasmic reticulum have shown that the phosphatidylcholine translocation had  $t_{1/2}$  of either over 15 days (481) or less than 10 min (137), which brings up the possibility that these results reflect "closed" or "open" status of the phosphatidylcholine pore protein (719).

This is important for the extracellular uptake of phospholipids.

The 'phosphatidylcholine translocation' displays stereospecificity, which means that it facilitates the translocation in both directions (719).

In this whole context it is relevant to note that phospholipids can undergo relatively fast transbilayer movements in several biological membranes which do not contain such a strictly organized cytoskeleton such as the microsomal membrane of rat liver (526).

3.) Also an exchange of phospholipid molecules between different membranes takes place. This has been demonstrated, for example, in-vitro between microsomes and mitochondria of rat liver (748). Such transfer processes have been described also to occur between natural and artificial membranes (e.g. between liposomes and rat liver mitochondria) (769).

Membrane synthesis is initiated in the endoplasmic reticulum leading to the formation of precursor vesicles whose fusion with already existing plasma membrane results in formation of a new plasma membrane. During the fusion process the original transmembrane asymmetry of the vesicle is inverted (53) (fig. 5).

<Fig. 5: Proposed mechanism for the biogenesis of plasma membranes of eucaryotic cells (53)>

### 1.3 Protein Distribution in Membranes

In the fluid lipid bilayer various proteins are associated (fig. 2).

Biological membranes contain two types of membrane proteins (680):

1. proteins which are only loosely associated with the membranes and are easily removed ('extrinsic' or peripheral proteins), and
2. those which are firmly bound to the membrane and can only be removed by detergents ('intrinsic' or integral proteins). The latter consist of ectoproteins which are arranged towards the extracytoplasmic side, and of endoproteins which are arranged towards the cytoplasmic side only. Some proteins penetrate the whole lipid bilayer. Most membrane proteins possess a hydrophilic region (protruding from the phospholipid bilayer) and a hydrophobic region embedded in the phospholipid bilayer.

### 1.4 Function of Phospholipids in Membrane Bilayer

In principle, phospholipids can affect a number of cellular functions, including carrier-mediated transport, the properties of certain membrane-bound enzymes, binding to receptors of biologically active substances (neurotransmitters, peptide-hormones and proteo-hormones, lectins, antigens and antibodies,

lipoproteins, complement factors, chemotactic substances and others), phagocytosis, endocytosis, exocytosis, prostaglandin and acetylcholine production, cell-cell interaction, cell cycle and cell differentiation. The effects of lipid modification on cellular function are very complex and vary often from one type of cell to another. Generalizations are problematic and the response of a membrane to a particular type of modification is difficult to predict.

However, more and more functions of a membrane system as an interplay with the membrane composition are understood and put together like elements in a puzzle. As membrane fluidity belongs to the main factors influencing membrane functions, it will be first described in detail.

#### 1.4.1 Membrane Fluidity

At physiological temperature, x-ray diffraction studies have indicated that the fatty acids of membranes have a "liquid crystalline" structure (194). When the temperature of the membrane is decreased, phospholipids are converted from a "liquid crystalline" phase to a gel phase (194, 683).

The transition temperature and the membrane fluidity depend on (531, 718):

- a) chain length, degree of unsaturation and type of pairing of the hydrocarbon chains of the phospholipids,
- b) the nature and charge of the polar headgroups of the phospholipids,
- c) the phospholipid/sterol ratio and the chemical structure of the sterol, and
- d) the (phospho) lipid-protein interactions.

which will be described by a few examples as follows:

ad a) (519, 649, 683, 761 )

Acyl chain order increases with chain length but decreases with cis-unsaturation. A double bond has the greatest effect when it is introduced into a fully saturated chain, for example, when a stearyl chain is converted to an oleoyl chain; the introduction of a second double bond, like from oleoyl to linoleoyl, has a lesser effect on reduction of viscosity. At higher degrees of unsaturation, the effect becomes progressively less pronounced.

The increase in specific volume, when a cis double bond is introduced, is parallel with a decrease of the thickness of the bilayer (phosphatidylcholine from 0.48 to 0.58 nm, resp. 0.46 to 0.41 nm).

A fluid-phase bilayer (= 45 Å thick) is = 15 % thinner than a gel-phase bilayer. In a more disordered membrane, where the acyl chains do not pack as tightly, even holes or gaps can form between the chains.

ad b) (401, 531, 649)

An increase in the phosphatidylcholine / sphingomyelin ratio is associated with increased erythrocyte membrane fluidity. In fact, natural sphingomyelin and lecithin are at the extreme edges of contribution to rigidification (sphingomyelin) or fluidization (phosphatidylcholine).

The sequential methylation of phosphatidylethanolamine to phosphatidylcholine increases lipid fluidity. Table 2 presents the phase transition temperatures for various species of

phosphatidylcholine (PC) and phosphatidylethanolamine (PE).

<%Tab. 2:%>

The remaining common phospholipids, i.e. phosphatidylserine, phosphatidylglycerol and phosphatidylinositol, are all of a relatively high degree of unsaturation and may, therefore, be considered as fluidizers, similarly to phosphatidylcholine. The sphingoglycolipids (e.g. gangliosides), on the other, have a hydrophobic region which is similar to that of sphingomyelin, and as such act as lipid rigidifiers.

ad c) and d) (519, 585, 649, 683)

Cholesterol is known to restrict the mobility of neighbouring phospholipid fatty acyl chains, creating an ordered surface layer. The acyl chain order increases with cholesterol content above the phase transition temperature and decreases below this temperature.

The effect of proteins on lipid dynamics is in essence similar to that of cholesterol. They also rigidify and increase the order in fluid lipid domains and act conversely below the lipid phase transition.

Moreover, the fluidity can be influenced by such factors as temperature, pressure (osmosis), volume (lipid microviscosity is inversely correlated to the free volume of the lipid constituents), membrane potential, acidity and calcium (649).

In the following sub-chapters the correlation of many membrane functions and membrane fluidity will be continually recognized.

#### 1.4.2 Membrane Passage

Biological membranes delimit both the cell and its organelles 'from outside and from inside'. As a consequence, all membrane reactions have to pass through the membranes insofar as these reactions exceed the cellular or subcellular space. All the information, molecules and substances reach the cell through the membranes, so that these have to accomplish two contradictory tasks: on the one the membranes delimit the cells and the organelles and, on the other, the cell membranes are transmitting the signals and substances for the exchange processes between these unities.

For the molecular transport through the membrane both the lipid bilayer and a kind of pore system are at disposal. The passage of substances may happen

a) according to the rules of passive diffusion,

b) as facilitated carrier-mediated diffusion,

c) as active transport .

d) and as endocytosis or exocytosis (389).

The fluid mosaic model of a biological membrane offers three possibilities of direct participation of phospholipids in the membrane transport:

a) facilitated bilayer transport of polar molecules (e. g. of ions) by forming inverted micelles,

b) fusion, and

c) transport by changing the membrane morphology (e.g. by forming channels with nonbilayer structures) (128).

It is considered as sure that certain pairs of fatty acids in phospholipids require a certain kind of tissue and membrane specificity. As a consequence of their varying interactions with stearins, of the structural difference in their polar component (charges ranging from extremely negative to positive) and of different structures of hydrocarbon chains, phospholipids are able to regulate the multiple biological functions of the membrane. This applies in particular to permeability and to ion passage (quoted from 97, 117, 133, 183, 194, 365, 624, 680, 724).

The effects of increasing phospholipid unsaturation in increasing passive diffusion, for a series of defined phospholipid molecular species, has been shown to follow closely the increase in molecular area (143).

In carrier-mediated transport this pattern is not always followed (684) (tab. 3).

<%Tab. 3: Effect of polyunsaturated fatty acid enrichment on carrier-mediated transport in cultured cells (658)%>

When the membrane lipids are rich in unsaturated fatty acids, transport can proceed at rates up to 20 times faster than it does when the membrane lipids are poor in unsaturated fatty acids (194). Or, with other words, when the density of the phospholipid structures is loosened the exchange rate is accelerated (680).

### 1.4.3 Activity of Membrane-Bound Proteins and Receptors

Many enzymes, receptors and transport systems are linked to or embedded within membranes of cells and sensitive to the structure and physico-chemical properties of the lipids with which they interact. Because of this, the functions of these membrane-bound proteins and receptors can be regulated to some extent by changes within the lipid portions of biological membranes. The sensitivity may involve conformational changes that affect the binding sites of receptors of neurotransmitters and hormones, of transport systems (such as the calcium pump of the sarcoplasmic reticulum) or of the active site of enzymes. Lateral mobility and clustering, their vertical orientation in the lipid bilayer or their interaction with other membrane components may be affected. Thus, the membrane lipid structure mechanism may involve either bulk lipid fluidity, localized changes in specific lipid domains, or a combination of both (482, 658, 761).

The presence of lipids provides a medium for reaction; in general, they are needed for normal function, in single cases additionally for stimulation (117). Analogous to Zakim (761)

- 1) the many proteins which are embedded in the lipid bilayer and which are dependent from its physico-chemical properties
  - 2) can be influenced in their functions by changes in the chemical composition of lipids and
  - 3) since the composition of membrane phospholipids is not fixed but modifiable by diet and disease states, they can be manipulated by diet/drugs.
- Listed in table 4 are some enzymes whose activities are showing lipid, especially phosphatidylcholine requirements (117). This list is not meant to be exhaustive but to illustrate that many vital processes are catalyzed by enzymes that are embedded within membranes.

<%Tab. 4: Enzymatic activities showing lipid requirements%>

It is interesting to note that enzymes of the electron transport system, lipid metabolism, transport and information transmission are prominent.

The enzymes in table 4 belong to that group of membrane-located enzymes which show a decline or a complete loss of their activity when membrane lipid is extracted or modified but some have been fully or partially restored by the addition of lipids (708, 409).

The implication of such a lipid dependence could be that there is some interaction between the lipids and the enzyme system which is critical either for maintaining a specific configuration of the enzyme or for facilitating interactions between the enzyme and the substrate (182).

The demonstrated requirements are predominantly for polar lipids and in a few cases perhaps for a particular polar lipid or for a restricted group of lipids (182).

For some enzymes it has been shown that the fatty acid composition of the added lipid may determine the effectiveness of reactivation. In general, lipids containing a high proportion of unsaturated lipids are most effective in reactivation (117).

Many enzymes such as ATPases, adenylate cyclase, 5'-nucleotidase, acetylcholinesterase, desaturases, succinate dehydrogenase, B-N-acetyl-D-glucosaminidase and drug metabolizing enzymes show modulation of activity by changes in fatty acid unsaturation (684).

Various regions of enzymes move during the catalytic cycle, and these movements may be critical for catalysis. These enzymes generally have higher catalytic activities in phospholipid environment of low versus high viscosity (761).

Membrane enzymes could be modulated differently in the two bilayer leaflets which has been demonstrated in detail for adenylate cyclase, for example (684). Adenylate cyclase consists of a number of functional subunits, distributed in the different halves of the lipid bilayer, which are interrelated in a complex manner (for reviews see references 120, 402).

#### 1.4.4 Cell Differentiation and Proliferation

The influence of phospholipids on cell differentiation and proliferation will only be highlighted by presenting a few characteristic points:

- Maturation of the hepatic endoplasmic reticulum is correlated with an increased production of phosphatidylcholine that contains greater amounts of unsaturated fatty acids. This microsomal phospholipid synthesis seems to be not only essential to the membrane structuring but also as to increase the enzyme activities during development (180).

- The available literature does not indicate any general profile for the change in membrane lipid fluidity or protein mobility during the cell cycle. While in a lot of different cell types such as lymphocytes, fibroblasts and hepatocytes (142) a lower microviscosity in mitosis than in the S-phase or interphase was seen neuroblastoma cells acquire in mitosis a higher membrane microviscosity (122).

Differentiation is affected by a progressive increase in microviscosity of the cell membrane (649).

#### 1.5 Functions of Phospholipids in Monolayers

##### 1.5.1 Phospholipids in Lipoproteins

Lipids occur in the blood as water-insoluble complexes which are transported only after binding to certain apoproteins. Phospholipids, which are lipophilic and hydrophilic, serve as solubilizers. Lipoproteins accordingly represent the transport forms of lipids in the blood. On the basis of their migration rates during electrophoresis, their density and their flotation in ultracentrifugation, lipoproteins are classified in chylomicrons, VLDL, LDL, IDL and HDL particles (29). Common to all lipoproteins is that the phospholipids as solubilizers surround these particles as monolayers (fig.6).

<%Fig. 6: Cross Section of a VLDL (664)%>

Beside transporting lipids through blood lipoprotein-phospholipid exchange processes occur which probably contribute to the enrichment of phosphatidylcholine and sphingomyelin in the external phase of some plasma membranes (139).

##### 1.5.2 Biliary Micelles .

Another polar medium by which unpolar substances (mainly cholesterol) are transported is the biliary fluid. Bile is an aqueous solution with detergent-like molecules called 'bile salts', phosphatidylcholine and unesterified cholesterol; other components are conjugates of bilirubin and a mixture of proteins of diverse origin (96). Cholesterol is transported in small bile salt-cholesterol micelles and with , minimum-sized mixed bile salt - phosphatidylcholine-cholesterol micelles. All molecules are in rapid exchange from micelle to micelle via the intermicellar monomeric concentration of each lipid. The predominant subclasses of phosphatidylcholine are the 1-palmitoyl-2-oleoyl and 1-palmitoyl-2-linoleoyl species.

##### 1.5.3 Emulsification

One function of bile is that of providing a reservoir of detergents and emulsifiers for efficient fat digestion in the gut (96).

The fine distribution of the fat droplets in the aqueous digestive secretion reduces the surface potential between oil and water and induces the formation of an emulsion, in which the lipids can easily be split by lipases.

For the intestinal resorption the emulsified fats are transferred into a micellar form (387). Again, these micelles consist mainly of lipids, bile acids and phosphatidylcholine.

## 1.6 Pool Function of Phospholipids In Membrane

### 1.6.1 Eicosanoid Precursor

Membrane phospholipids also play a major role in the prostaglandin synthesis: the principal prostaglandins, thromboxanes and leucotrienes are formed from precursors like eicosatrienoic and eicosatetraenoic acid. These precursors exist in the cell as components of the membrane lipids. They are both formed from essential linoleic acid by extending the chain and by desaturation (12, 583). In the case of the a.m. eicosanoid formation, the phospholipid fatty acyl modifications probably exert their effect primarily through a change in substrate availability. The chemical basis of the mechanism is the same, a change in membrane lipid composition (658).

### 1.6.2 Choline Donator

Cerebral choline is made by hydrolysis of acetylcholine, phosphorylcholine, membrane phosphatidylcholine and sphingomyelin as well as by the uptake of plasma choline (198). A small de novo synthesis is also possible (342). After the passage of the blood brain barrier choline may be used for the synthesis of acetylcholine in cholinergic neurons (58). It possibly also induces postsynaptic effects at nicotinic and muscarinic receptors (652).

## 1.7. Blood Corpuscles

In erythrocytes phosphatidylcholine comprises about 30 % of the total phospholipid complement and is distributed asymmetrically over the two layers: 76 % is found in the outer layer and 24 % in the inner one (526).

A crucial part for structure and function of the erythrocytes plays the degree of unsaturation of phosphatidylcholine. The unsaturation index (i.e. the number of double bonds per fatty acyl residue in the phosphatidylcholine) should be 0.5-1.0, otherwise the packing of (phospho)lipid molecules within the erythrocyte membrane is no longer efficient and leads to abnormal structure and behaviour up to hemolysis of the cells (526).

Experimentally it was shown that the cells turned echinocytic when the amount of di saturated phosphatidylcholine was increased, and stomatocytic on replacement by dilinoleoylphosphatidylcholine (fig. 7).

<Fig. 7: Changes in the shape of the erythrocyte outer membrane layer according to the fatty acid composition of the phosphatidylcholine molecules (526)>

Even if the applied phosphatidylcholine could undergo a relatively fast trans-bilayer movement, 76 % phosphatidylcholine in the outer layer compared to the interior pool still result in predominant localization of the substituting molecules in the outer layer.

The maximal substitution of phosphatidylcholine is about 53 %.

Beside the degree of unsaturation of phospholipid acyl chains the shape of red blood cells is influenced by the cholesterol/phospholipid ratio and the phosphatidylcholine/sphingomyelin ratio (121).

The normal molar ratio of cholesterol to phospholipid in the erythrocyte membrane is about 0.8-0.9. In diseases such as advanced cirrhosis of the liver spur cells are seen on dry smears with erythrocyte cholesterol/phospholipid molar ratio of about 1.22 (602). By exchange between the membranes of blood

cells and the serum lipoproteins the cholesterol/phospholipid ratio can be regulated/normalized (649).

The rigidifying effect of cholesterol, is similar on macrophages (104), monocytes (542) and lymphocytes (130, 542). In general, it appears that cholesterol acts as a natural modulator of immune responses (649). Unstimulated lymphocytes have an unusual fatty acid distribution of phosphatidylcholine. A high percentage of saturated fatty acids are formed in the 2-position of this phospholipid; stimulation, however, increases the content of polyunsaturated fatty acids in this position (519). It is apparent that the overt lymphocyte stimulation needs an optimum microviscosity for maximal response (170).

### 1.8 Surfactant

According to Hills (268) the surface of the gastric mucosa is covered with a hydrophobic coating due to the presence of surface-active phospholipids, the phosphatidylcholines in particular, both in the gastric mucosa and in the gastric juice. Probably a monolayer of the surfactant molecules is bound to the cell surface, thus protecting it against luminal acid (270). Hydrophobicity is most pronounced in the region of the acid forming mucosa; conversely, those regions of the gastrointestinal tract absorbing aqueous luminal fluid do not possess a similar hydrophobic mucosal surface (268).

Surface active phospholipids identified in gastric juice and along the gastrointestinal tract are also absorbed onto other mucosal surfaces to render them hydrophobic, these including alveolar (267), placental (124), eustachian (269), tracheal (266) and peritoneal (233) epithelium/mesothelium.

Protection against gastric luminal acid is one important function of a surfactant. Other main functions are:

- regulation of surface tension (622) (mainly down-regulation to prevent collapse of tissue such as of alveoli)
- anti-oedematous function (249) (to prevent shifts of liquid e.g. from the lung interstitium to the alveoli)
- anti-glue function (21, 617) (e.g. to prevent adhesion in the peritoneum or to support mucociliar clearance)
- improvement of immunological effects (522) (such as broncho-pulmonal defence by alveolar macrophages)
- regulation of exchange of substances (157, 166) (e.g. increase of ultrafiltration in CAPD).