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Review

The Lipoidal Permeability Barriers of the Skin and Alimentary Tract

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The major routes of administration of drugs to humans involve transport either through the intestinal wall or through the skin. Both these barriers are nonpolar in nature and are subserved by membrane lipids. The lipid composition of the brush border of the intestinal wall is unusual, possessing unusually large quantities of glycosylceramide. The lipid composition of the stratum corneum of the skin is also unusual, possessing large quantities of ceramides and free fatty acids. These atypical membrane components are generally more ordered than the other common membrane lipids at body temperature and, thus, are suited for involvement in formation of barriers between the organism and its environment.

KEY WORDS: absorption; skin; brush border; lipids; glycolipids; ceramides.

INTRODUCTION

The delivery of drugs to the human body involves bypassing barriers that have evolved for protection against ingestion of harmful substances and against infection. The barrier function of the skin is obvious and serves to prevent water loss and to prevent intrusion of materials from the environment. The intestinal wall does not provide such an effective barrier, since it is passively permeable to vitamins and many drugs. Extensive experience with oral and transdermal drug delivery has clearly indicated that the primary intestinal and dermal barriers are nonpolar. The molecular architecture which subserves these barriers is lipoidal in nature and involves cell membranes and membrane-like structures. Consideration of the molecular composition of these membranes should provide some insight into the mechanism by which such barriers are constructed and may lead to approaches for bypassing these barriers to deliver drugs.

PLASMA MEMBRANE LIPID COMPOSITION, FLUIDITY, AND FUNCTION

An understanding of the composition and function of the membranes of skin and intestine requires familiarity with the composition and function of cell membranes in general. This section reviews the salient points of this complex subject.

The plasma membrane of the cell is composed of a wide variety of lipids and proteins, with the major structural theme provided by the lipid bilayer. The most common polar lipids found in mammalian plasma membranes are phosphatidylcholine (PC),[2] phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylglycerol (PG), and sphingomyelin (SPM). Plasma membranes also generally contain the neutral sterol cholesterol (~20%). Glycolipids are generally rare components of mammalian plasma membranes (<3%), while ceramide and free fatty acids are almost never found. The structures of some of these common membrane lipids are presented in Fig. 1. When purified and dispersed in water, membrane lipids form a variety of aggregated structures (Fig. 2). PC, PE, PS, PG, and SPM form the lamellar phase, which consists of stacked phospholipid bilayers separated by layers of water. Under certain conditions, PE can form the hexagonal-II phase. This property may be involved in a variety of dynamic membrane phenomena, including endocytosis, exocytosis, and membrane fusion (1).

The acyl chains of most polar membrane lipids can exist in a variety of physical states, the most common of which are the "gel" (stiff chain) and the "liquid crystalline" (fluid chain) states (Fig. 3). An order–disorder transition between these two states occurs at a characteristic temperature (T_M) which depends upon the length and degree of unsaturation of the fatty acyl chains. This transition consists of a "melting" of the phospholipid acyl chains, without any loss of the long-range stacked bilayer structure (2). Table I presents the T_M's for a series of PCs and PEs, along with the crystal melting temperatures of the corresponding fatty acids. The T_M increases with increasing acyl chain length and decreases when the chains are unsaturated. For an equivalent acyl-chain composition, the PEs exhibit higher

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[2] Abbreviations used: Gal-Cer, galactosylceramide; Glc-Cer, glucosylceramide; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PS, phosphatidylserine; SPM, sphingomyelin; T_M, acyl-chain order–disorder transition temperature.

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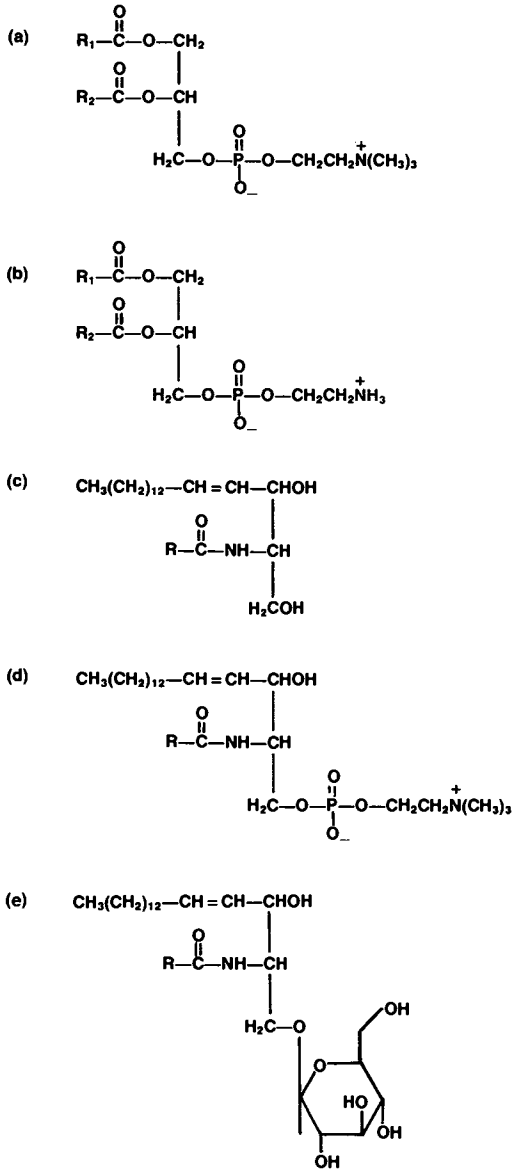

Fig. 1. Chemical structures of some polar lipids: (a) phosphatidylcholine, (b) phosphatidylethanolamine, (c) ceramide, (d) sphingomyelin, and (e) glucosylceramide.

T_M's than the PCs, because the smaller ethanolamine headgroup of the PEs allows tighter acyl-chain packing, resulting in a more stable low-temperature gel state. It should be noted that biological membranes rarely contain polar lipids in which the two acyl chains are identical with respect to chain length and degree of unsaturation. Most natural polar lipids possess one saturated and one unsaturated acyl chain, and these lipids generally exhibit low T_M's. For example, the commonly occurring membrane phospholipid 1-C16:0-2-C18:1-PC undergoes the order–disorder transition at −3°C (3). Most biological membranes exhibit a heterogeneous lipid composition, and this generally results in acyl-chain order–disorder transitions which occur over a broad temperature range.

The order and fluidity of the nonpolar interior of the biological membrane are important for providing an optimal

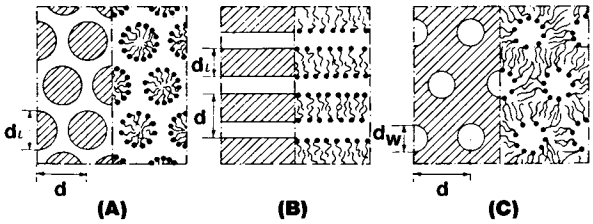

Fig. 2. Structures (cross sections) of some common lipid mesophases. (A) Hexagonal-I phase; (B) lamellar liquid crystalline phase; (C) hexagonal-II phase. (Reprinted from Ref. 61.)

environment for the catalytic and transport activities of membrane proteins. In general, proper membrane functioning requires that the nonpolar interior of the membrane be in the fluid liquid crystalline state. The evidence in the literature for this assertion is extensive, and much of this work has been carried out on easily manipulated bacterial membranes. For example, the microorganism *Acholeplasma laidlawii* takes up fatty acids from its environment and incorporates them directly into its membrane lipids, allowing experimental manipulation of the membrane lipid composition and fluidity. The *A. laidlawii* plasma membrane undergoes a lipid acyl-chain order–disorder transition at a temperature that depends upon the acyl-chain composition (4,5). Growth of this organism occurs only at temperatures at which the membrane interior is partially or completely fluid; no growth occurs at temperatures below the order–disorder transition temperature (4).

In general, cells will possess a membrane fatty acyl composition that assures that the membrane is in a fluid state at the temperature at which the cells must live. Evidence for the universality of this phenomenon can be found in the cases of unusual organisms that live at extreme temperatures. Thermophilic bacteria, which live in high-temperature environments (e.g., hot springs), possess highly saturated membrane lipids and exhibit unusually high membrane order–disorder transition temperatures. *Clostridium thermocellum,* for example, exhibits its membrane T_M at 30°C and grows optimally at 60°C, a temperature well above the

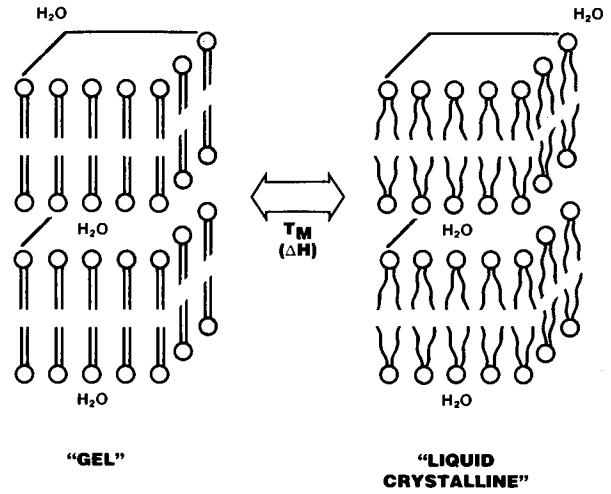

Fig. 3. Order–disorder transition in lamellar aqueous lipid dispersions.

Table I. Order–Disorder Transition Temperatures (T_M) of the Membrane Polar Lipids Phosphatidylcholine (PC) and Phosphatidylethanolamine (PE)[a]

Lipid	T_M (°C)[b]	Ref. No.
di-C14:0-PC	24	53
di-C16:0-PC	41	53
di-C18:0-PC	55	53
di-C18:1-PC	−22	54
di-C14:0-PE	50	53
di-C16:0-PE	60	55
di-C18:0-PE	71	56
C14:0-fatty acid	58	57
C16:0-fatty acid	63	57
C18:0-fatty acid	72	57
C18:1-fatty acid	16	57

[a] Excerpted from Ref. 58. The crystal melting temperatures of the corresponding fatty acids are presented for comparison.
[b] Or melting temperature for fatty acids.

T_M (6). Antarctic fish which live in salt water at 0°C provide an example at the other extreme. These cold-water fish possess plasma membranes with highly unsaturated lipid acyl chains, resulting in a fluid membrane interior at low environmental temperatures (7). Cellular energy must be expended to desaturate fatty acids. Thus in general a cell will desaturate its fatty acids only to the extent necessary to maintain the membrane T_M below the temperature of the environment in which the cell must live, assuring a fluid plasma membrane. This phenomenon is known as homeoviscous adaptation (8).

The necessity for maintaining a fluid plasma membrane is related to the effects of membrane fluidity on the activity of membrane enzymes and transport proteins. This has been illustrated in studies using mutants of the enteric bacterium *Escherichia coli,* in which experimental manipulation of the membrane lipid acyl-chain composition is possible. In these bacterial cells, the activities of membrane-bound enzymes and transport proteins were observed to decrease abruptly as the temperature was decreased below the membrane T_M (9,10). Similar studies with the mammalian membrane ($Na^+ + K^+$)-ATPase indicated that membrane enzyme activity varies with the physical state of the membrane (11,12). These phenomena have been further investigated by isolating membrane enzymes and reconstituting them in model membranes composed of a single phospholipid or a simple lipid mixture. For example, mammalian ($Na^+ + K^+$)-ATPase has been reconstituted into a series of model membranes with various acyl-chain order–disorder transition temperatures (13). In each case, the enzyme became less active at temperatures below the T_M of the lipid in which it was reconstituted. Thus the temperature dependence of the ($Na^+ + K^+$)-ATPase activity does not depend solely upon the absolute temperature, but also upon the temperature dependence of the fluidity of its membrane environment.

Another important mechanism of homeoviscous adaptation involves the presence of cholesterol in cell membranes. Cholesterol buffers lipid phase transitions by inserting between lipid acyl chains, thus decreasing transition cooperativity. Addition of cholesterol to a liquid crystalline membrane results in decreased membrane fluidity; addition to a gel state membrane results in increased fluidity (14). Thus the cholesterol content provides another mechanism by which the cell can control the fluidity of its membranes and the activity of its membrane proteins. This role of cholesterol has been experimentally demonstrated in studies of reconstituted lipid/protein model membranes. For example, addition of cholesterol to fluid model membranes containing ($Na^+ + K^+$)-ATPase results in decreased enzyme activity (13).

THE BRUSH-BORDER MEMBRANE OF THE INTESTINAL WALL

The brush-border membrane is a highly invaginated portion of the plasma membrane of the absorptive enterocyte of the intestinal wall. This specialized membrane faces the intestinal lumen and is the primary site of active and passive transport of fats, amino acids, sugars, vitamins, and drugs. The lipid composition of this membrane is atypical in that it contains significant quantities (~33%) of the glycolipid glucosylceramide (Glc-Cer) (15,16). Although the physical properties of intestinal Glc-Cer have not been studied, the physical properties of Glc-Cer from Gaucher's spleen[3] and galactosylceramide (Gal-Cer) from bovine brain are well-known (17–19). Glc-Cer from Gaucher's spleen exhibits its T_M at 83°C, which is significantly higher than body temperature (17). The T_M of Gal-Cer from normal bovine brain is 67°C, which is also above body temperature (20). Bovine brain Gal-Cer has been fractionated by high-performance liquid chromatography into populations with a single acyl-chain length or an acyl-chain composition which is simpler than that of the natural extract. The acyl-chain order–disorder transitions of aqueous dispersions of these isolated Gal-Cer fractions occur at high temperatures which are relatively insensitive to acyl-chain length or degree of unsaturation (19). Thus monoglycosyl-ceramides in general exhibit high T_M's, and intestinal Glc-Cer would be expected to behave similarly. Monoglycosyl-ceramides possess interlipid hydrogen bonding capability via the hydroxyls of the glycosyl headgroup and via the hydroxyl and amide groups of the ceramide backbone (21). It is likely that this interlipid hydrogen bonding capability is responsible for the unusually high T_M's of these glycolipids. Monoglycosyl-ceramides also exhibit metastable polymorphism in the low-temperature gel state; this polymorphism is related to hydration and interlipid hydrogen bonding (22,23). Similar behavior has been observed in other lipids that possess hydrogen bond donating groups, e.g., SPM and PC analogues that possess carbamyloxy linkages (24–27).

The presence of significant quantities of Glc-Cer in the brush-border membrane would be expected to "stiffen" the apolar membrane interior at body temperature. Fluorescence and differential scanning calorimetry studies of brush-border membranes have indicated that these membranes are more ordered than most plasma membranes (28,29). This unusual membrane stabilization may be required for two purposes. First, the brush-border membrane contains sugar and amino acid transport proteins which are powered by transmembrane ion gradients. Maintenance of these ion gra-

[3] In Gaucher's disease, a hereditary deficit of a catabolic glucosidase results in toxic accumulation of Glc-Cer.

dients via a stable membrane is important to assure nutrient transport into the body. Second, the brush-border membrane faces the harsh environment of the intestinal lumen, which is topologically outside the body. This lumenal enterocyte membrane must withstand the variable osmotic environment of the lumen and must be resistant to solubilization by the detergent bile salts.

The enterocyte brush-border membrane also contains a significant quantity of cholesterol, i.e., 20% of the total lipids (15). As described above, cholesterol generally solidifies liquid crystalline membranes and fluidizes gel-state membranes. In the case of the enterocyte brush-border membrane, cholesterol may serve to fluidize the high-T_M Glc-Cer and to solidify the low-T_M phospholipids. It has been shown that Gal-Cer and a common membrane PC are phase-separated at mammalian body temperature, i.e., a Gal-Cer-rich gel phase and a PC-rich liquid crystalline phase coexist (30). Glc-Cer would be expected to behave similarly. Phase separation in PC model membranes has been demonstrated to result in membrane "leakiness" (31,32), and the same undesirable effect would be expected in membranes composed primarily of high-T_M glycolipids and low-T_M phospholipids. A major function of cholesterol in the brush-border membrane may be to promote mixing of the high- and low-T_M lipids, resulting in a homogeneous membrane of intermediate fluidity at body temperature.

In spite of the stability and order of the brush-border membrane, it is permeable to fat-soluble vitamins and many drugs. This fact is somewhat surprising, considering the low fluidity of this membrane. Apparently, the high cholesterol and glycolipid contents do not adversely affect the partitioning of nonpolar drugs from the lumen into (and through) the brush-border membrane.

THE SKIN

The epidermis is differentiated into three morphologically and compositionally different layers: the innermost basal layer, the intermediate granular layer, and the outermost cornified layer or stratum corneum. The viable cells of the basal and granular layers possess intracellular "lamellar granules," which are membrane-enclosed vesicles containing stacked lipid bilayers (33,34). In the granular layer of the skin, this intracellular lipid material is extruded from the cell, resulting in the presence of intercellular multilamellar lipid bilayers in the nonviable stratum corneum. It is generally believed that this intercellular lipid provides the barrier function of the stratum corneum (33–35). It is interesting to compare the lipid compositions of the three epidermal layers and to consider the possible relationships between the physical properties of these lipids and their functions.

The lipid compositions of the three epidermal layers vary tremendously, as shown in Table II. The innermost basal layer, which contains viable cells, exhibits a lipid composition that differs somewhat from that of most cells and cell membranes. The major basal layer polar lipids, i.e., PC, PE, and SPM, are generally major components of cell membranes. Unusual features are the low cholesterol content (8.7%) and the high contents of glucosylceramide (Glc-Cer) (7.3%), fatty acid (6.7%), and triglyceride (7.5%). The presence of fatty acid and a small amount of ceramide are highly unusual, since undegraded plasma membranes generally do not contain these components.

Table II. Lipid Compositions of Different Cell Populations in Pig Epidermis[a]

	Weight % of total lipids		
	Basal[b]	Granular[c]	Stratum corneum[d]
Phosphatidylethanolamine	11.9	4.1	
Phosphatidyl-(*N*-acyl)-ethanolamine	0.8	5.0	
Lyso-phosphatidyl-(*N*-acyl)-ethanolamine	Trace	1.0	
Cardiolipin	2.1	0.7	
Phosphatidylserine	6.5	2.0	
Phosphatidylinositol	5.6	0.5	
Phosphatidic acid	0.8	0.4	
Phosphatidylcholine	23.6	7.1	
Sphingomyelin	10.7	4.5	
Glucosylceramide	7.3	9.0	
Cholesterol	8.7	21.3	19.6
Cholesterol sulfate	0.3	0.1	
Cholesterol esters	0.9	0.7	0.7
Ceramide	0.9	15.6	49.2
Fatty acid	6.7	16.5	26.0
Triacylglycerol	7.5	2.4	2.6
Hydrocarbon	2.4	8.9	Trace
Unidentified	3.3		1.9

[a] Excerpted from Ref. 59.
[b] Source: Ref. 60.
[c] Source: Ref. 36.
[d] Source: Ref. 45.

The granular layer possesses a lipid composition that is more atypical. Particularly noteworthy is the high concentration of ceramide (15.6%). Ceramide would be expected to be disruptive to plasma membranes, since ceramide exhibits crystalline and isotropic (oil) states but not lamellar liquid crystalline states (W. Curatolo, unpublished observation). It should be noted that granular layer preparations contain material from the viable cells moving into this layer from the basal layer, and from the less viable cells of the upper granular layer which are forming the nascent stratum corneum (36). Thus the reported lipid composition is an average that reflects the compositions of cells from very different levels of this transitional epidermal layer. Also noteworthy in the lipid composition of the granular layer are the high content of fatty acids (16.5%) and Glc-Cer (9.0%) and the low content of the common bilayer-forming diacyl membrane lipids PC (7.1%), PE (4.1%), and SPM (4.5%).

The cells of the basal and granular layers contain intracellular "lamellar granules," and the contents of these granules may partly account for the unusual lipid compositions of these layers. More detailed analyses of the structures of lipids from lamellar granules (and from the stratum corneum) indicated the presence of the unusual lipids acylceramide and acyl-Glc-Cer (Fig. 4) (37–40). These unusual lipids may be involved in promoting the stacking of bilayers in lamellar granules, since the 30-carbon hydroxyacid is long enough to span an entire bilayer, and the ester-linked lino-

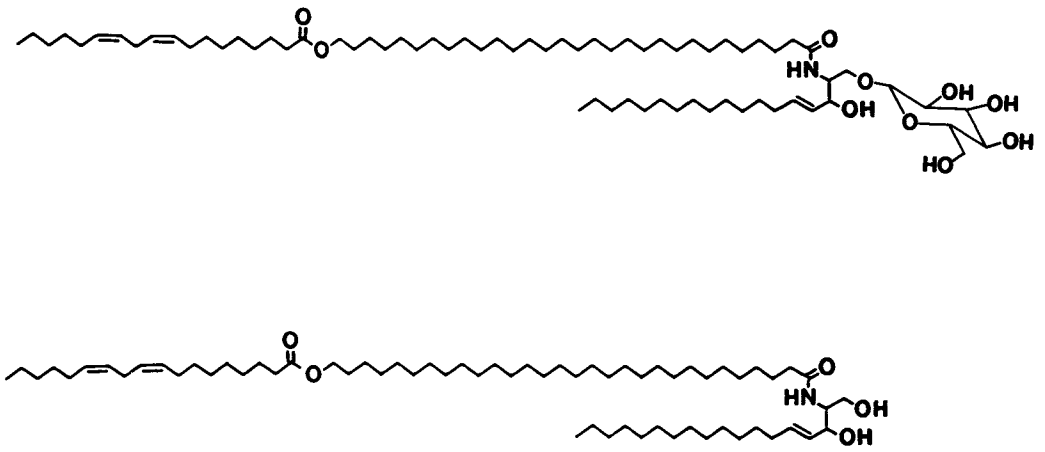

Fig. 4. Structures of an acylglucosyceramide and an acylceramide from rat epidermis (41).

leate group could be embedded in an adjacent bilayer (41). This hypothesis has been supported by the observation that incorporation of acyl-Glc-Cer into PC/cholesterol liposomes resulted in liposome flattening and stacking (42).

The stratum corneum possesses a lipid composition that is highly unusual (Table II). Particularly noteworthy are the exceptionally high contents of ceramide (~50%) and fatty acid (~25%) and the total absence of the common bilayer-forming polar lipids PC, PE, and SPM. Although the major lipids of the stratum corneum are not common membrane components, together they are capable of forming bilayers. Mixtures of ceramides, cholesterol, and a fatty acid (palmitic) have recently been shown to form bilayers in water (43). Fatty acids themselves are capable of forming bilayers (as opposed to micelles) in water when the fatty acids are in the half-ionized "acid-soap" form (44). Thus it is possible and likely that the intercellular multilayered material seen in electron micrographs of the stratum corneum consists of stacked bilayers composed of extracellular lipids.

It is instructive to consider the thermal behavior of the various stratum corneum lipids. The major fatty acids found are palmitic (C16:0), stearic (C18:0), oleic (C18:1), arachidic (C20:0), and behenic (C22:0) acids (45). The melting points of these fatty acids are 63, 72, 16, 75, and 80°C, respectively. The order–disorder transitions of the acid-soaps may occur at slightly different temperatures. Thus the T_M for the acid-soaps of palmitic, stearic, and oleic acids occurs at 51, 61, and 11°C, respectively (44). Ceramide undergoes a crystal-to-isotropic melt at ~80°C and does not exhibit liquid crystalline phases (W. Curatolo, unpublished observation). The crystal structure of ceramide indicates that this lipid undergoes intermolecular hydrogen bonding, and this capacity may provide unusual order to ceramide-containing membranes (46). Considering the fact that stratum corneum lipids consist primarily of ceramide (~50%) and fatty acids (~25%), a rough estimate would place the order–disorder transition of stratum corneum lipid bilayers in the approximate range 50–90°C. The presence of ~20% cholesterol would be expected to result in mixing of fatty acids and ceramide, with a consequent broadening of the lipid thermal transition. In fact, scanning calorimetry studies of stratum corneum membranes and lipids indicate that one or more lipid phase transitions occur in the expected temperature range (47–49).

The observation of lipid thermal transitions above body temperature in the stratum corneum is consistent with ultrastructural observations that indicate the presence of extracellular multilamellar material. Since integral membrane proteins require a fluid lipid environment, it is unlikely that the stratum corneum lipid which undergoes these transitions is a constituent of any intact cell membrane that exhibits metabolic or transport activity.

Table III. Lipids of Pig Epidermis and Oral Mucosa (Weight %)[a]

	Epidermis	Gingiva	Palate	Floor	Buccal
Phospholipids	24.1	42.3	39.1	44.2	38.2
Cholesterol sulfate	0.2	2.0	1.7	3.2	7.8
Glycosylceramides	2.3	2.1	1.8	5.8	16.5
Acylglycosylceramides	3.2	2.1	2.8	0.0	0.0
Acylceramides	1.7	0.4	0.2	0.0	0.0
Ceramides	12.2	6.6	3.3	0.7	0.8
Cholesterol	15.4	21.0	33.6	19.5	13.6
Fatty Acids	13.6	5.0	1.3	0.6	1.6
Triglycerides	24.7	16.9	15.9	11.1	15.7
Cholesterol esters	2.6	1.1	0.2	15.0	5.9

[a] Source: Ref. 50.

THE ORAL EPITHELIA

The lipid compositions of epithelia from the gingiva, palate, floor, and buccal regions of the mouth of the pig are presented in Table III (50). These data represent the lipid compositions of the entire epithelial surface (all layers), and the composition of the epidermis is also presented for comparison. In general, the gingiva and palate exhibit lipid compositions that resemble that of the epidermis. These two regions of the mouth possess significant quantities of acylglycosylceramide, acylceramide, and ceramide, all of which are characteristic lipid components of the epidermis. The floor and buccal regions possess little or none of these components but, instead, possess significant quantities of glycosylceramide, as does the brush-border membrane of the intestinal wall. The observed lipid compositions are consistent with the observation that the epidermis and gingiva are significantly less permeable to water than the floor and buccal regions of the mouth (51,52).

CONCLUSION

The skin and the oral and intestinal mucosa are all topologically outside the body, and it is clear that these surfaces must serve important functions relative to the interaction of the body with its environment. The major functions of the skin are to prevent intrusion of noxious agents and to retain body water. The intestinal wall, on the other hand, is partially responsible for flux of water into and out of the body and for active and passive absorption of vitamins and nutrients. These very different functions of the skin and intestine are subserved by lipoidal structures with different compositions.

The intestinal brush-border membrane possesses a lipid composition that provides unusual stability. However, this membrane possesses a variety of essential transport proteins, and these proteins require a fluid membrane in order to function. Thus the physical state of the brush-border membrane must be finely balanced to provide the required level of both order and fluidity. This balance is subserved by a mixture of "fluid acyl-chain" phospholipids and "stiff acyl-chain" glycolipids, whose mixing is aided by the presence of cholesterol. The ordered character of the glycolipids is the result of their ability to undergo extensive interlipid hydrogen bonding.

The stratum corneum of the skin has as its major function the provision of a highly ordered essentially impenetrable barrier. Unlike the intestinal epithelium, the skin does not have to balance opposing requirements for order and fluidity. The barrier of the stratum corneum is subserved by a mixture of highly ordered lipids, most of which are below their T_M's at body temperature. The unusual sphingolipid ceramide is a major component which, like the glycolipids of the intestinal wall, is capable of undergoing interlipid hydrogen bonding.

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