Fig 2

TOPOLOGY AND BARRIER FUNCTION OF MEMBRANES IN THE LUNG

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SUMMARY

The alveolo-capillary air-blood barrier of the lung is made of two thin cell layers, epithelium and endothelium, that limit the flow of solutes and fluid from blood plasma into the narrow interstitial space and into the very thin alveolar fluid lining associated with surfactant. The conditions for maintaining a thin dry air-blood barrier are discussed. The effect of barrier thickness on gas exchange is discussed by means of the changes in barrier structure that lead to respiratory failure in the respiratory distress syndrome.

INTRODUCTION

The lung and the brain are the two organs where one finds the highest concentration of cell membranes per unit volume of tissue. In the lung these membranes are used to establish an intense contact between air and blood over an area of about 140 m² in the adult, an area which measures some 60 m² even in a 10-year old child. Membranes are used to build a barrier sufficiently thin for efficient gas exchange between air and blood.

Design of a barrier

The tissue barrier separating air and blood consists of four layers (Fig. 1). The capillaries are lined by a continuous endothelium made of simple squamous cells, and the alveolar spaces by an epithelium built essentially of two cell types: the type I cells are very vast squamous lining cells, each covering some $4000 \mu\text{m}^2$ of the alveolar surface, i.e. three times more than the surface of an individual endothelial cell, whereas the type II cells are cuboidal secretory cells, the producers of surfactant. Epithelium and endothelium are separated by an interstitial space of widely variable width and content. The fourth layer of the barrier is a surface lining layer of alveoli, established at the interface to the air; it is the fluid layer which carries surfactant and smoothes out small irregularities of the epithelial surface by distributing mainly into pits and crevices, thus minimalizing the surface curvatures that would give rise to surface tension.

The barrier is hence composed of two cellular layers (endothelium and epithelium) that separate three extracellular fluid compartments: blood plasma, interstitial space (lymph), and alveolar lining layer. The cellular layers themselves are maintained as extremely thin sheets; a thin barrier is maintained only if also the two extracellular fluid layers of the barrier are very thin, i.e. if they are kept as "dry" as possible. Any excess fluid, either in the interstitium or at the alveolar surface, leads to edema and impairs gas exchange.

Fig. 1: Design of air-blood barrier. EP1 = epithelium type 1; EP2 = epithelium type 2 with lamellar bodies (LB); END = endothelium; Jt and Jl = tight and leaky junctions; INC, INF = interstitial cells and fibers; BM = basement membrane; SLL = alveolar surface lining layer.

How is the lung kept dry?

Considering hydrostatic and osmotic pressures a gradient might well exist that drives fluid from the blood plasma in the alveolar capillaries into the interstitial space and, eventually into the surface lining layer. But, normally, there is no such net fluid flow; so the question comes up, how the cellular and membrane barriers prevent this.

We must first clearly distinguish between the barrier function of a membrane - which separates an extracellular from a cytoplasmic

space - and that of a cell layer, such as endothelium, which separates two extracellular fluid spaces. A cell layer can only function as an osmotically active barrier if the intercellular junctions are tight. It is known, however, that the epithelial lining has tight junctions, whereas those in the endothelium of the lung appear leaky (Schneeberger and Karnovsky, 1968); this conclusion was based, on the one hand, on electron microscopic findings, and on the other hand, on tracer studies.

The osmotic behaviour of these barriers has recently been studied by a combined physiological and morphometric approach (Wangensteen et al., 1981). In an isolated perfused lung preparation an "osmotic transient" experiment was performed, in principle. The lung was then fixed by perfusion under controlled conditions at various points of the transient. The conclusion from this study was that the interstitial space of the barrier equilibrated osmotically with blood plasma through large endothelial "pores", probably across the junctions; the epithelial layer, however, separated the interstitial space from the surface lining layer like a semi-permeable membrane, confirming the tightness of this layer (Fig. 1).

From this type of study it appears that the alveolar surface lining layer is well shielded towards the internal fluid spaces by a tight cellular barrier, with two membranes joined by tight intercellular junctions, whereas the solutes of blood plasma have relatively free access to the interstitial space.

The interstitial space appears to have special design features (Fig. 2) that minimize fluid accumulations (Weibel and Bachofen, 1979). (1) Over about half the capillary surface, the epithelial and endothelial basement membranes are fused, thus excluding a true interstitial space from the thinnest barrier portion. (2) The septal connective tissue fibers establish drainage channels that lead interstitial spaces, towards the lymphatics in the axial and peripheral connective tissue elements of the acinus. (3) The contractile interstitial cells of the septum may possibly regulate the compliance of the interstitial space.

Why is the lung kept dry?

All this effort to maintain a dry thin barrier is made in the interest of establishing and maintaining adequate conditions for efficient gas exchange between air and blood. The gas exchange efficiency of the lung is estimated by the pulmonary diffusing capacity for O_2 , DL_{O_2} , the O_2 conductance of the lung. This parameter lends itself particularly well for considerations on structure-function correlation because it can be estimated by physiological as well as morphometric methods (Weibel, 1973). Fig. 3 shows the model required for estimating DL_{O_2} from morphometric data, collected by means of stereological methods (Weibel, 1979). The important parameters that determine DL_{O_2} are the alveolar surface, S_a , and the harmonic mean barrier thickness, τ_{ht} , which occur as a ratio in the first partial conductance. Normally this conductance is rather large, i.e. the resistance it offers to O_2 flow is small. Any accumulation of fluid will have an adverse

Fig. 2: Design of alveolar septum. Capillaries (C) are winding about fibers (cf) that are anchored in alveolar entrance ring (AR). Interstitial space consists of two parts, one of fused basement membranes (fBL) and one containing fibers and fibroblasts (F) with contractile filament bundles arranged perpendicular to fiber axis. (From Weibel and Bachofen, 1979).

Fig. 3: Model for morphometric diffusing capacity. The serial conductances of tissue, plasma, and erythrocytes (D_t , D_p , D_e) depend on morphometric (surfaces, S ; thicknesses, τ ; volume, V) and physical properties of the barrier.

effect on the two critical dimensions: the barrier thickness increases and the surface decreases (particularly if the alveolar lining layer is increased), and this leads to a potentiated gas exchange disturbance due to the combined effect on the numerator and denominator of the determining ratio S_a/τ_{ht} .

That these are important factors is known from the study of catastrophic respiratory failure as it occurs in the "adult" respiratory distress syndrome (ARDS) due to various forms of shock (Bachofen et al., 1977, 1979); the same syndrome can also develop in children with mature lungs. Due to as yet unknown reasons the endothelial and epithelial sheets lose their sealing function; blood plasma leaks into the interstitial space and eventually into alveoli (Fig. 4). Upon repair of the damage a thick barrier results due to tissue proliferation; gas exchange impairment persists inspite of the resolution of alveolar edema.

Fig. 4: Schematic reconstruction of normal and diseased inter-alveolar septa in ARDS. (From Bachofen and Weibel, 1977).

Unfortunately, no similar study exists as yet on the respiratory distress syndrome of the newborn. Here, the initial damage is different because it is related to an insufficient production of surfactant; this prevents the establishment of a thin barrier of large surface; because of excessive surface tension the alveolar surface cannot expand, and the alveolar lining layer cannot be reduced to its minimal thickness. The structural basis for respiratory failure is therefore very similar, but the pathogenesis is not primarily related to the barrier function of cell membranes, which limits fluid flow from plasma into the interstitial or alveolar spaces. However, this barrier function can be damaged secondarily, in part even by therapeutic measures, for it is known that high O_2 tensions of inspired air can damage membranes and render the endothelial and epithelial barriers leaky (Kistler et al., 1967). The repair of these damaged cell layers then leads to a syndrome similar to the late

stages of ARDS (Kapanci et al., 1969), because it is based on some peculiar properties of lung tissue (Bachofen and Weibel, 1977).

CONCLUSIONS

The purpose of establishing a very thin barrier of large extension in the lung is to ensure adequate conditions for gas exchange between air and blood. This can be maintained only thanks to a good design of the cell and tissue layers constituting the barrier, making use of the sealing properties of cell membranes and of intercellular junctions. If these are damaged, respiratory failure ensues.

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