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Membrane Model of Peritoneal Barrier

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Peritoneal tissue, which structure is rather complicated, creates a barrier between blood and dialysate for transport of fluid and solutes during peritoneal dialysis. The aim of this study was to investigate to what extent peritoneal barrier can be modeled as a semipermeable membrane, which permits the application of thermodynamic description of fluid and solutes transport. Using data from the previous studies it has been demonstrated that peritoneal membrane model proved to be useful in interpretation of clinical and experimental on rats investigation. However, limitations of membrane model of peritoneal barrier have been specified.

K e y w o r d s: peritoneal dialysis, peritoneal membrane, transport of solutes, mathematical model

1. Introduction

Peritoneal tissue separating blood from peritoneal cavity represents complicated structure with blood capillaries distributed in the tissue and the interstitial space contains numerous cells and fibers made of long proteins. On the side of peritoneal cavity peritoneum is covered by quite leaky barrier representing mesothelial cells. In addition there are systemic lymphatics transporting fluid and solutes (even cells) from peritoneal cavity to blood. Also, there are local lymphatics located in the interstitium. The main resistance to transport of fluid and solutes between blood and peritoneal cavity is represented by blood capillary walls. According to blood capillary physiology solutes and water can pass the capillary wall because there exist three kinds of pores in the wall: the majority of pores are so-called small pores that allow permeating of solutes, smaller than proteins, and water, ultrasmall pores (aquaporins) permitting only water to be transported, and large pores permitting passage of proteins. The

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large and ultrasmall pores represent less than 10% of all the pores. Because of the quite complicated structure of the peritoneal tissue, which creates a barrier (peritoneal barrier) between blood and dialysate for transport of fluid and solutes, treating the peritoneal barrier as an inert semipermeable membrane seems to be not suitable. However in numerous kinetic studies of fluid and solutes transport in the peritoneal dialysis the thermodynamical description of solute transport has been applied in which the peritoneal barrier is treated as a semipermeable membrane.

2. Membrane Model (Kinetic Modeling)

In the membrane model of the peritoneal barrier no structure of this barrier is taken into account. It is simply assumed that blood and dialysate are separated by a semipermeable membrane and that the transport phenomena can be described with application of the nonequilibrium thermodynamical theory of the transport processes. The fundamental advantage of this approach is that knowing the thermodynamical forces (measured concentrations of solutes, osmolalities, and hydrostatic pressures) the transport parameters can be estimated as it will be shown below.

In addition to the thermodynamical theory of membrane transport the theoretical description used in tracer experiments have to be applied for calculation of dialysate volume, ultrafiltration flow rate and fluid absorption rate.

Change of peritoneal volume V_D in time is equal to the difference between the ultrafiltration flow rate, Q_U, and the fluid absorption rate, Q_A:

$$\frac{dV_D}{dt} = Q_U - Q_A. \tag{1}$$

Eqn (1) cannot be solved without knowing Q_U and Q_A.
Application of the macromolecular tracer (radioisotopically labeled human serum albumin, RISA) allows calculating the tracer elimination coefficient, K_E, which, in turn, can be regarded as an estimation of the fluid absorption rate, Q_A:

$$\frac{dV_D C_{\mathrm{RISA}}}{dt} = -K_E C_{\mathrm{RISA}}, \qquad K_E \approx Q_A \tag{2}$$

and from eqn (2):

$$K_E = \frac{V_{Din} C_{\mathrm{RISA}in} - (V_{Dout} + V_{RES}) C_{\mathrm{RISA}}(T)}{T\bar{C}_{\mathrm{RISA}}(T)} \tag{3}$$

where V_{Din} and $C_{\mathrm{RISA}in}$ represent volume of the dialysis solution in the infusion bag and RISA concentration in the bag, respectively. V_{Dout}, V_{RES} and $C_{\mathrm{RISA}}(T)$ represent

volume of the dialysate removed, the residual volume and T time of the treatment (dwell time), respectively. $\bar{C}_{\mathrm{RISA}}(T)$ is time averaged RISA concentration.

K_E can be calculated using eqn (3) because values of the variables on the right hand of this equation can be measured or calculated. Knowing K_E eqn (2) can be solved for V_D:

$$V_D(t) = \frac{V_{Din} C_{\mathrm{RISA}in} - K_E \bar{C}_{\mathrm{RISA}}(t) \cdot t}{C_{\mathrm{RISA}}(t)} \tag{4}$$

and the ultrafiltration flow rate, Q_U, can be calculated using relationships:

$$Q_U = \frac{dV_D}{dt} - Q_A \approx \frac{dV_D}{dt} - K_E \,. \tag{5}$$

Equations (3), (4) and (5) can be used for calculations of V_D, Q_U and Q_A, however there is a need for fenomenological description of the fluid transport which can be used for estimation of parameters governing this transport. Applying the thermodynamical theory the following relationship can be written:

$$\frac{dV_D}{dt} = a_{os}(\Pi_D - \Pi_B) - b_{os}, \tag{6}$$

where Π_D and Π_B represent osmolalities in dialysate and blood, respectively. a_{os} is osmotic conductance, defined as the amount of fluid ultrafiltered to the peritoneal cavity in one unit of time by one unit of osmolality gradient between dialysate and blood plasma and b_{os} represents bulk fluid absorption rate. Integration of eqn (6) yields:

$$V_D(t) - V_D(t_0) = a_{os} \int_{t_0}^{t} \Pi_D(s) - \Pi_B(s) ds - b_{os}(t - t_0) \tag{7}$$

with $V_D(t)$, $\Pi_D(t)$, $\Pi_B(t)$ calculated or measured a_{os} and b_{os} can be estimated from eqn (7) using two dimensional linear regression.

Similarly, solute transport between blood and dialysate can be described using the thermodynamical theory of the membrane transport

$$\frac{dV_D C_D}{dt} = K_{BD}(C_D - C_B) + Q_U S C_B - Q_A C_D \tag{8}$$

where C_B and C_D are concentrations of the investigated solute in the blood and the dialysate, respectively. K_{BD} and S are the diffusive mass transport coefficient (also denoted in the literature as MTAC and PS) and the sieving coefficient, respectively. Integration of eqn (8) yields:

$$V_D(t)C_D(t) - V_D(t_0)C_D(t_0) = K_{BD}\int_{t_0}^{t}(C_D(s) - (C_B(s))ds + \\ + S\int_{t_0}^{t} Q_U(s)C_B(s)ds - Q_B\int_{t_0}^{t} C_D)(s)ds \tag{9}$$

with $V_D(t)$, $C_D(t)$, $C_B(t)$, $Q_U(t)$ and Q_A calculated or measured K_{BD} and S can be estimated using two dimensional linear regression.

In this section it was shown that with application of the volume marker and measurements of concentrations and osmolalities the important fluid and solutes transport parameters can be estimated and applied to interpret results of clinical investigations as well as animal experiments. This approach is also called a kinetic modeling. Examples are given below.

3. Clinical Investigations

Very important problem facing doctors and peritoneal dialysis patients is so called ultrafiltration failure or inability, using standard treatment, to remove excess of fluid from the patient. The definition of the ultrafiltration failure is the net ultrafiltration volume being less than 400 ml in 4 hrs with strong glucose (3.86%) based dialysis solution. There were numerous studies done in the past on causes of the ultrafiltration failure using the kinetic modeling. Below some of the results of studies done in colaboration with the Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden are presented.

The most common mechanism of ultrafiltration capacity loss is usually attributed to increased small solute transport resulting in rapid dissipation of osmotic agent (glucose) gradient [1]. Popular and rather obvious hypothesis is that the increased solute transport (increased diffusive mass transport coefficient, K_{BD}) in some patients (High K_{BD} group) is caused by increased vascular surface area. The increased vascular surface area should be characterized not only by increased K_{BD} but also by increased osmotic conductance, a_{os}. However, kinetic studies [2, 3] demonstrated that increased K_{BD} for glucose (20.4 ± 4.1 ml/min in High K_{BD} group vs. 10.7 ± 2.7 ml/min in control group, $p < 0.001$) was accompanied by decreased a_{os} (0.094 ± 0.041 ml · kg/mOSm · ml in High K_{BD} group vs. 0.133 ± 0.033 ml · kg/mOSm · ml in control group, $p < 0.005$), which also contributes to the ultrafiltration capacity loss.

Intriguing hypothesis emerged from these kinetic studies. Because osmotic conductance, a_{os}, is proportional to $L_p A_V \sigma$, where L_p is total hydraulic permeability of the peritoneal membrane, A_V is the vascular surface area and σ is net reflection coefficient, the increase in $L_p A_V$ has to be accompanied by changes in the capillary wall structure, causing substantial decrease of σ.

4. Experimental Studies

Much research has been carried out recently in search for new and better osmotic agent which would replace glucose as an osmotic agent in the peritoneal dialysis to avoid unnecessary glucose load and improve nutrition of the peritoneal dialysis patients. Protein malnutrition is a common problem in end-stage renal disease patients that often suffer reduced circulating levels of essential amino acids [3]. To counteract this problem an amino acid-based peritoneal dialysis solution has been successfully introduced [4]. Amino acids absorbed from dialysis fluid counteract losses of proteins and amino acids to glucose-based dialysis solutions and provide an extra supply of amino acids [5]. Amino acids are also more biocompatible than glucose as regards the effect on peritoneal membrane. However amino acids are quite small molecules (on the average 140 daltons) and therefore are easily transported by diffusion to blood resulting in a rise of amino acids concentration in the blood. The increased concentration of amino acids in blood may have an adverse effect on appetite.

The alternative to amino acids-based may be the dipeptides-based dialysis solution. Dipeptides may have advantage over amino acids as osmotic agents in the peritoneal dialysis solutions since they have about twice as high molecular weight as amino acids and may produce more sustained ultrafiltration. After a protein containing meal, proteins are in part absorbed from the gut as dipeptides, which are rapidly hydrolysed to constituent amino acids. Similarly, after parenteral administration, dipeptides are rapidly metabolized and free amino acids are produced.

We recently performed two studies on dipeptide-based peritoneal solution with rats [6, 7]. These studies were done with slightly different composition of dipeptides in the dialysis solution but the major difference was different way in which anesthesia in animals was performed. In study [6] a single intraperitoneal injection (IP) of pentobarbital was employed and, later, we have found that this method significantly alters the peritoneal permeability and the peritoneal surface layer [8]. In the recent study [7] each rat was anesthetized with a single intramuscular injection (IM) of pentobarbital sodium.

Kinetic studies allowed the estimation of peritoneal volume, ultrafiltration and fluid absorption rates as well as diffusive mass transport parameters for amino acids and dipeptides. The major difference in kinetic parameters observed in dependence of the kind of anesthesia (IP or IM) pertained to the diffusive mass transport parameters, K_{BD}. With IP anasthesia K_{BD} for amino acids ranged from 0.234 ± 0.061 ml/min for tyrosine (molecular weight 180.2 D) to 0.334 ± 0.096 ml/min for glycine (molecular weight 75 D) and increasing molecular weight was accompanied by decreasing values of K_{BD}. Similarly, for dipeptides K_{BD} ranged from 0.172 ± 0.040 ml/min for Val-Lys (molecular weight 281.8 D) to 0.231 ± 0.084 ml/min for Thr-Leu (molecular weight 232.3 D) depending on molecular weight of dipeptides. The observed dependence on molecular weight of amino acids and dipeptides is in general agreement with the thermodynamic theory of the membrane transport, that solutes of higher molecular

weight diffuse more slowly than solutes of lower molecular weight. This finding could support the hypothesis that peritoneal barrier could be regarded as a semipermeable membrane. However, kinetic studies with IM anesthesia [7] resulted in estimations of K_{BD} for amino acids which were much lower than in studies with IP anestesia and, besides, these estimations did not show any dependence on molecular weight of amino acids. E.g. for valine (molecular weight 117) K_{BD} was estimated as 0.098 ± 0.026 ml/min and for histidine (molecular weight 155) K_{BD} was 0.099 ± 0.025 ml/min. These studies demonstrated that IP anesthesia resulted in turning living peritoneal tissue into an artificial semipermeable membrane.

5. Conclusions

Thermodynamic description of fluid and solute transport across a peritoneal barrier treated as a semipermeable membrane is very useful, as it allows estimating parameters important for clinical and experimental investigations. The estimated parameters are "lumped" parameters reflecting complicated transport phenomena existing in the living peritoneal tissue.

Limitations of treating the peritoneal barrier as a semipermeable membrane include among others:

- Diffusive mass transport parameters for solutes depend on the direction of transport (from blood to dialysate and vice versa)
- Diffusive mass transport parameters can not be correlated with molecular weight of the solutes
- Estimations of the transport parameters as constants can be regarded only as a rough approximation.

So, can the peritoneal barrier be regarded as a membrane? The answer can be positive, however, on the condition that it can not be regarded as an inert semipermeable membrane but as a "living" membrane.

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