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Permeability of Ocular Vessels and Transport Across the Blood-Retinal-Barrier

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Summary

This paper reviews quantitative studies on the permeability of retinal and choroidal vessels and the exchange of nutrients over the blood retinal barrier (BRB). The fenestrated capillaries in the choroid are very permeable to low molecular weight substances; sodium permeability in the choroid is probably 50 times that in skeletal muscle. This results in high concentrations and rapid turnover of nutrients in the extra-vascular compartment of the choroid. Free diffusion is restricted by the pigment epithelium barrier. Also the retinal capillaries, with tight junctions between the endothelial cells, have very low permeability even to sodium. The uptake index technique has provided evidence for several carrier systems in the BRB; hexoses, neutral and basic amino acids, and monocarboxylic acids, very similar to those found in the brain. At least for glucose and lactate these carriers operate at both levels of the BRB; the RPE and the endothelium of the retinal capillaries, and in both directions; i.e. inwards and outwards.

The blood-retinal (BRB) and the blood-brain (BRB) barriers are physical hindrances for diffusion between blood and nervous tissue. They are essential for the control of the microenvironment of the tissues:

* by preventing noxious water-soluble molecules from entering the extravascular spaces of the retina and the brain.
* by preventing uncontrolled escape of important ions from nervous tissue.

Due to these barriers there is a need for specific carrier-mediated mechanisms for the exchange of nutrients and metabolites through the cells.

Since the retina in man and several other species has a dual vascular supply, the retinal and the choroidal vessels, the BRB has two parts, the endothelial cells of the retinal capillary walls and the retinal pigment epithelium (RPE). The barrier function depends on tight junctions which restrict intercellular movement of all water-soluble molecules and thus virtually prevent these molecules from entering retinal tissue between the cells.[1] In clinical studies the integrity of the BRB can be evaluated by fluorescein angiography and vitreous fluorophotometry. These methods which provide qualitative, morphological and quantitative information on the permeability of the BRB have increased our understanding of the pathogenesis of many retinal diseases.

The aim of the present paper is to summarise some quantitative experimental studies, performed in our laboratory, on the permeability of the retinal and choroidal vessels and on the exchange of nutrients over the BRB.

Permeability

In our studies on capillary permeability the

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movement of an intra-arterially injected tracer through the capillary wall was determined. The permeability coefficient (P) can be calculated according to the formula:

$$P = -(Q/S)\ln(1-E) \quad (1)$$

where S is the capillary surface area, Q the flow of tracer containing fluid and E the extraction of the tracer. The derivation of the formula assumes that E represents a unidirectionally outflux of tracer, i.e. there is no back-diffusion from tissue to blood. Depending on the speed by which the tracer moves across the vessel wall different experimental designs must be used.

Choroidal vessels

Macromolecules

The permeability of the choroid to plasma proteins has been investigated in rabbits.[2] Steady plasma levels of labelled proteins were obtained by intravenous injections. The animals were killed at different times and the radioactivity in various structures of the eye was measured. For about six hours the amount of labelled protein in the choroid gradually increased. The results indicated an apparent extravascular volume for albumin of 165 µl/g, (plasma equivalents) and a turnover rate constant of 3·5% /min. From these results an albumin extraction of 0·019% was calculated.[3] A permeability coefficient for albumin of 33×10^{-8} cm/s was calculated assuming a plasma flow of 630 µl/min through the choroidal vessels of the rabbit and an estimated capillary surface area of 6 cm.[2] This figure is considerably higher than corresponding figures for fenestrated capillaries in the kidney cortex ($5{\cdot}7 \times 10^{-8}$ cm/s) and for non-fenestrated capillaries in skeletal muscle ($1{\cdot}1 \times 10^{-8}$ cm/s). The permeability of the choriocapillaries to IgG was about 50% of that to albumin. As pointed out by Bill *et al.*[3] this high permeability to macromolecules may play a role in presenting retinol binding protein-prealbumin complex to the RPE.

Small Molecules, the Single Injection Technique

For more diffusible, low molecular weight substances with an expected rapid transcapillary movement, a technique with a high time resolution is required. For this reason we adopted the single injection technique[4] and modified it for studies on the eye.[5,6] After an intra-arterial bolus injection, blood samples are collected from the vein draining the investigated organ (Fig. 1). The bolus contains one or more test substances and one reference substance, selected because of its inability to escape from the intra-vascular volume during the passage through the tissue. Albumin is often used as a reference tracer in organs with non-fenestrated capillaries and it was found to fulfil the criteria of an intravascular tracer also in the fenestrated capillaries of the choroid.

The fractional extraction, E, of the test substance defined as the difference in concentration between the reference and the test substance divided by the concentration of reference substance was used to calculate the permeability coefficient.

The fractional extractions in the choroid of ^{22}Na and ^{51}Cr–EDTA showed constantly declining values with time. A likely explanation is back-diffusion of test tracer from tissue to blood. The initial extractions (0·66 and 0·35

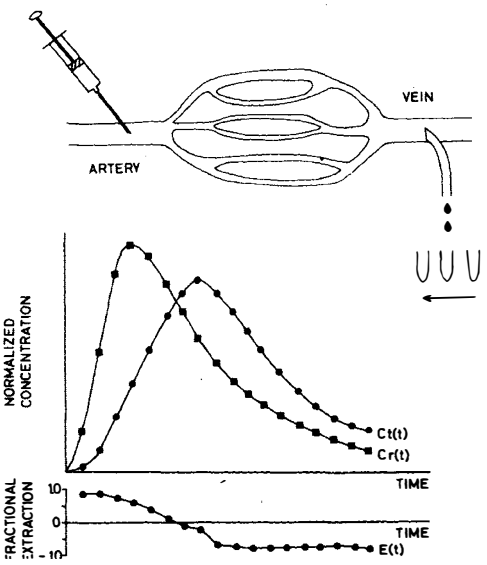

Fig. 1. *Schematic illustration of the single injection technique. The concentrations of the intravascular reference substance, Cr, and the test substance, Ct, are determined in repeated venous samples after an intra-arterial injection. The concentrations are normalised with regard to the concentrations in the injected solution and plotted against time. The extraction of the test substance at any instant, E(t), is then calculated. (E(t)= 1–Ct(t)/Cr(t)).*

respectively), when back-diffusion is minimal, were therefore used for calculations of P, giving values of about 180 and 70×10^{-5} cm/sec for ^{22}Na and ^{51}Cr–EDTA respectively. Even though these values are 50 to 80 times higher than corresponding values in skeletal muscle[7] there are reasons to believe that they are also influenced by back-diffusion and thus underestimate true values for P. However, similar permeability coefficients were found for the fenestrated capillaries of the salivary glands.[8]

To study the wash-out of test tracers from the tissue without interference of recirculation the injected bolus was delayed by use of an external shunting of blood from the abdominal aorta to the carotid artery. Within 20–25 sec, the extravascular compartment was completely cleared of ^{51}Cr–EDTA and only a small fraction, about 3%, of ^{22}Na remained in the extravascular space. This very high permeability of the choriocapillaries, and the rapid turnover in the extravascular space ($T_{1/2}$ for ^{22}Na and ^{51}Cr–EDTA of two and four sec respectively) indicate that molecules such as glucose and amino acids are present at the RPE in concentrations not far from those in plasma. The concentration of glucose in the extravascular space of the choroid has been estimated to be 90–95% of that in blood.[3]

Retinal Vessels

For single injection studies on the retinal vessels access to retinal venous blood is crucial. In the pig there is a venous plexus around the optic nerve, close behind the globe, which drains retinal blood.[9] Thus pigs were used to determine the permeability of the retinal vessels. The venous outflow curves of ^{125}I-albumin and ^{22}Na after a bolus injection into the carotid artery were coincident, that is no extraction of ^{22}Na from retinal vessels could be demonstrated. This is consistent with results obtained in the brain.[10] Thus the permeability of the retinal vessels to ions and low molecular weight substances is too low to be studied with the single injection technique.

Further evidence for the low permeability of the BRB to small substances has been provided by Lightman *et al.*[11] They determined permeability surface area products (PS) for sucrose ($0{\cdot}44 \times 10^{-5}$ ml/g/s) and mannitol ($1{\cdot}25 \times 10^{-5}$ ml/g/s), values which are similar to those found in the brain. They also determined the tissue content of tracers following an intravascular injection and found similar values in the brain and the retina. Although their technique does not separate the relative contribution of the retinal capillaries and the RPE these results indicate that the permeability of both parts of the BRB is of the same order as that of the BBB.

Transport

The Uptake Index Method

We have modified the uptake index (UI) method, previously used in the brain by Oldendorf,[12] for the retina of the rat. For comparisons between BRB and BBB samples from the brain were included.[13,14] A mixture of a ^{14}C labelled test tracer and a highly diffusible reference tracer (^3H_2O) was injected into a carotid artery (Fig. 2). Then tissue samples from the ipsilateral retina and brain were quickly prepared for analysis of radioactivity and the UI was calculated:

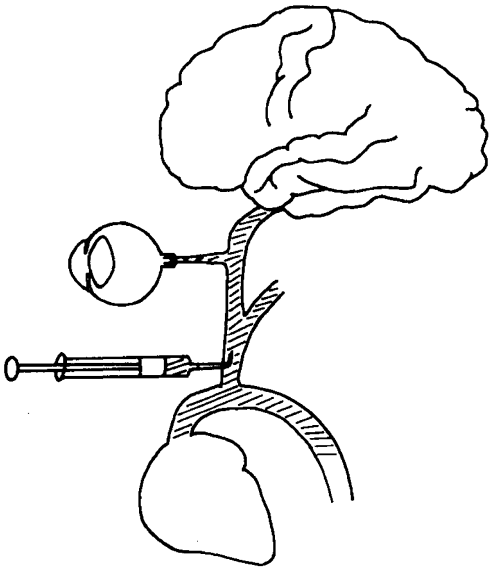

Fig. 2. *Schematic illustration of the uptake index technique. The tissue concentration of the highly diffusible reference substance and the test substance are determined in retinal and brain samples, rapidly obtained after an intra-arterial injection. The UI, which expresses the tissue uptake of the test substance as a percentage of the uptake of the reference substance, is then calculated.*

$$UI\ (\%) = \frac{^{14}C/^{3}H - \text{tissue}}{^{14}C/^{3}H - \text{inj solut.}} \times 100 \quad (2)$$

RUI and BUI express the fractional uptake of the ^{14}C-labelled test substance as a percentage of the fractional uptake of the reference substance ^{3}HOH in retina and brain respectively.

A carrier-mediated transport shows saturability and, as a rule, stereo-specificity. The demonstration of one or both of these characteristics strongly indicates a carrier. If an unlabelled second test substance is added to the injected solution these molecules will compete with the labelled molecules at the carrier for a saturable transport i.e. the UI will be reduced.

If this second test substance is the same as the labelled substance saturability can be demonstrated (self-inhibition). Other unlabelled substances with affinity to the same carrier may also reduce UI (cross-inhibition).

It should be pointed out that the UI technique does not separate between transport at the two parts of the BRB. Thus the possibility of different carriers for the retinal capillary wall and the RPE can not be excluded. A contribution to the retinal uptake from the anterior part of the eye (ciliary epithelium through the vitreous) is probably negligible since the eye is enucleated within five sec following the injection and immediately frozen and the retina is prepared in a frozen condition. The UI technique will only demonstrate carriers able to facilitate passage of substances in the blood-to-tissue direction, and it will not necessarily differentiate between facilitated diffusion and active transport.

The UI technique has provided evidence for several carrier systems in the BRB, and the results demonstrate the similarities between the BRB and the BBB in this respect. Thus in both barriers there are separate carriers for transport of hexoses, including D-glucose,[15] neutral and basic amino acids,[14] and monocarboxylic acids.[16] Some minor differences between the two barriers have been observed, but they may well be due to the limited resolution of the technique.

Stereo-specificity and/or saturability of the passage of glucose through the BRB have been observed in several species.[7,17,18] With the UI technique the presence of a carrier-mediated transport of glucose through the BRB as well as the BBB could be demonstrated.[15] Apart from D-glucose, the carriers accept 2-deoxy-D-glucose, 3-O-methyl-D-glucose, D-mannose and D-galactose, but not L-glucose, D-fructose or D-ribose. The order of affinities seems to be the same in the BRB and the BBB, and phloretin and phloridizin reduce both retinal and brain uptake of D-glucose. The results indicate a larger transport capacity for the BRB.[15]

There is a common carrier for the monocarboxylic acids L-lactate and pyruvate and for the ketone body 3-hydroxybutyrate in the BRB and the BBB. The transport is pH dependent with an increased uptake at lower pH (6·3) suggesting a cotransport of H^+ ions or counter-transport of OH^- ions.[16]

In the BBB three separate, class-specific carrier systems, one each for large neutral amino acids, basic and acid amino acids have been characterised.[19] It has been suggested that amino acids are delivered to the retina mainly from the ciliary epithelium through the vitreous body[20] and that the RPE should have an absorbent transport function of amino acids out of the retina[21] similar to that of the choroid plexus in the brain.[22] With the UI-technique, however, we found in both the BRB and the BBB two separate, stereospeci-

Table *Amino acids with an affinity to the neutral or the basic amino acid carrier in the BRB and the BBB.*

Neutral	*Basic*
L-Phenylalanine	*L-Arginine*
L-Tryptophan	*L-Ornithine*
L-Tyrosine	*L-Lysine*
L-Leucine	
L-Isoleucine	
L-Methionine	
L-DOPA	
L-Histidine	
L-Cycloleucine	
L-Valine	

L-phenylalanine and L-arginine were chosen as representatives for the neutral and the basic carriers respectively. If the UI of one of these compounds was reduced by the adding of an unlabeled amino acid to the injected solution, this second amino acid thereby demonstrates affinity to the carrier.

fic, saturable carrier systems; one for large neutral amino acids and one for basic amino acids (Table).[14] In the brain, acid amino acids are transported by a separate low-capacity carrier.[19] We were unable to demonstrate such a carrier in either the BRB or the BBB, but the sensitivity of the modified technique may be insufficient for studies on low-capacity transport systems. A specific carrier for taurine was found in the BRB, but not in the BBB.[14] In all other respects the similarities between the results obtained for the BRB and those obtained for the BBB were striking, and a reasonable conclusion is that in the BRB, as in the BBB, amino acids are transported by carrier-mediated facilitated diffusion. Thus these results do not support the concept of an absorptive, active transport system for amino acids in the tissue-to-blood direction as proposed by Reddy *et al.*[23] The co-existence of carriers for facilitated, bidirectional diffusion and carriers for active, mainly indirectional transport of amino acids through the BRB is definitely unexpected and a question where further research is needed.

Arteriovenous Differences:
Tracer studies like the single injection technique and the UI technique ideally assumes a unidirectional flux over the barrier. Obviously it is of great interest also to measure the net flux of the molecules under investigation. If choroidal and retinal venous blood can be collected the relative contribution to the retinal nutrition, of transport across these two parts of the barrier, can be estimated. The possibility of sampling choroidal venous blood in cats[24] and retinal venous blood in pigs[25] has been utilised for this purpose.

In the pig the a-v-differences for glucose was 0·07 mmol/l and 0·44 mmol/l for the choroid and retina respectively at an arterial concentration of 3·69 mmol/l.[25] Thus a glucose-carrier operates at the two sites of the BRB. The net extraction of glucose from the choroidal and retinal blood (2% and 12%) corresponds to 121 nmol/min and 28 nmol/min calculated for blood flow values of 1732 mg/min and 64 mg/min for the two tissues. Since the choroid can be expected to utilise only a minor fraction (less than 4%) of the glucose consumed by the two tissues together, about 80% of the glucose consumed by the retina was delivered from the choroid.[25] The extracted fraction of glucose is much larger[15] than the net extraction which indicates that the carrier operates in both directions.

An unusually high rate of anaerobic glycolys has been shown *in vitro*.[26] It was estimated that glucose and oxygen consumption in the retina of the pig was 110 μmol/min/100 g and 224 μmol/min/100 g respectively. Thus 63% of the glucose was not oxidised which indicates a high rate of lactate production also *in vivo*. Negative a-v-differences for lactate in retinal and choroidal blood show a net outflow to the blood under normoglycemia,[25] as has been demonstrated for the brain.[27]

The Effect of Diabetes on the BRB
It is well known that breakdown of the BRB is part of clinical diabetic retinopathy. It has even been suggested that an increase in BRB permeability to sodium fluorescein preceeds any other sign of diabetic retinopathy.[28] Other investigators, however, have been unable to confirm this observation.[29,30]

Attempts to study the barrier function with vitreous fluorophotometry in an animal model—short-term, untreated-streptozotocin-induced diabetes in rats—have also given conflicting results.[31-33] Some of the problems involved in these fluorophotometry studies can be avoided by using radioactively labelled tracers instead of fluoroscein for quantitation of BRB permeability. In one such study we were unable to demonstrate any increased permeability of either the BRB or the BBB after 1–2 weeks untreated diabetes in rats.[34] The results, however, suggested that untreated diabetes may cause an intraretinal accumulation of weak acids, such as para-amino-hippuric acid. An outward-directed transport of weak acids and anions through the BRB has been described,[35] and the possibility that fluorescein is transported out of the eye by this carrier may explain the variable results obtained with fluorescein in diabetic rats.

Diabetes may have other effects on the BRB than increased permeability. The possibility of an effect on the transport of glucose across the BRB as well as the BBB has been discussed. Insulin causes long-term regulation

of the number of glucose carriers in the cell, and short-term activation/translocation of those in adipocytes and skeletal muscle.[36,37] Thus insulin-dependent glucose transport seems to be influenced/regulated by insulin levels in plasma. Glucose transport through the BRB and BBB, however, is not regulated by insulin, but previous studies have indicated that the glucose carrier in the BRB and the BBB may become adapted to chronic hyperglycemia through reduced V_{max} (maximum rate of transport) for the BBB[38,39] or increased K_m (concentration at which transport rate is half of maximum) for the BRB.[40] DiMattio *et al.*[41] however, could not verify that short-term diabetic hyperglycemia has an effect on the transport kinetics of the glucose carrier in the BRB, and in a recent study we observed that hyperglycemia induced by a three min glucose infusion has the same effect on glucose transport through the BRB and the BBB as two to three weeks untreated diabetes.[42] The results could well be explained by competitive inhibition, although a rapid change—within minutes—of the kinetic characteristics of the glucose carriers cannot be excluded with such techniques. Still, our studies on diabetic rats have not provided any evidence that increased barrier permeability or disturbed glucose transport is an early sign in experimental diabetes.

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