THE ORIGINAL idea of a blood-brain barrier arose at the turn of the century as an explanation of the properties of the living brain in relation to certain dyes and pharmacologically active compounds, injected either into the bloodstream or directly into the cerebrospinal fluid (CSF) of experimental animals (reviewed by Bradbury, 1979). This developed into the general concept of a cellular barrier between blood and the interstitial fluid of brain (Krogh, 1946), but the hypothesis had no firm structural basis and was abandoned by many when early electron micrographs showed no differences between capillaries in brain and those elsewhere, e.g., in skeletal muscle (Maynard et al., 1957).

In the late 1960's, the use of various heme-proteins and other markers which could be made visible under the electron microscope established unequivocally that the barrier to molecules of 1,800 daltons and above is the endothelium of cerebral capillaries (Reese and Karnovsky, 1967; Brightman and Reese, 1969). Since that time, there has been an explosive increase in experimental work on the properties of transport across the barrier. The final objective must be to elucidate the cellular and molecular mechanisms involved in this transport, and evidence about these is now beginning to appear. A number of reviews and monographs are available which deal both with general features of structure and function (Davson, 1976; Rapoport, 1976; Bradbury, 1979; Fenstermacher and Rapoport, 1984) and with specific aspects of barrier function. Particular topics for which there are recent and excellent reviews are substrate supply to the brain (Pardridge and Oldendorf, 1977; Crone, 1980; Pardridge, 1983), glucose transport (Lund-Andersen, 1979), modulation of transport (Gjedde, 1983; Gjedde and Crone, 1983), mechanism of ion distribution (Fenstermacher, 1975), volume regulation of the brain (Fenstermacher, 1984), comparative physiology (Cserr and Bundgaard, 1984), handling of monoamines (Hardebo and Owman, 1980), peptides, and the blood-brain barrier (Meisenberg and Simmons, 1983; Pardridge, 1984), and function particularly in relation to studies with isolated suspended microvessels (Goldstein and Betz, 1983; Joë, 1984). My objective here will be to consider how the ultrastructure of the cerebral endothelium and adjacent structures differs from that elsewhere and how this gives a basis for the transport properties of the barrier. Also of particular interest in relation to the physiology of the microcirculation in general are the properties of net fluid movement across the cerebral vessels and the recent demonstration of a relation between apparent permeability of the barrier and cerebral blood flow.

Ultrastructure and Function

The Cerebral Endothelium

As has been indicated, the site of the barrier to horse radish peroxidase of molecular weight 40,000 (Reese and Karnovsky, 1967; Brightman and Reese, 1969), cytochrome c of 17,000 (Milhorat et al., 1973), microperoxidase of 1,800 (Reese et al., 1971), and colloidal lanthanum hydroxide is the endothelium of all intracerebral vessels, except those in certain high-permeability regions. Movement across the endothelium in either direction is stopped by the presence of occluding tight junctions in the interendothelial clefts. Tight junctions have been observed in every interendothelial cleft examined, suggesting a continuous belt or zonula occludens around each endothelial cell. In 49 of 100 cross-sections of cortical and cerebellar capillaries (Oldendorf et al., 1977), no intercellular clefts were cut across, indicating that individual endothelial cells can form an uninterrupted cylinder around the lumen. In addition, there normally is no vesicular uptake of peroxidase (Reese and Karnovsky, 1967) or of colloidal iron (Clawson et al., 1966) into cerebral endothelial...
cells, so that pinocytosis can play little role in transport across the normal blood-brain barrier.

When interendothelial junctions in mammalian (Connell and Mercer, 1974; Dermietzel, 1975; Tani et al., 1977) and reptilian brain (Shivers, 1979) have been subjected to freeze fracture, they can be seen to be highly complex, consisting of an anastomosing network of intramembrane ridges of particles and complimentary grooves. The number and complexity of these strands is comparable to those of very tight epithelial junctions (Claude and Goodenough, 1973).

The permeability properties of almost all capillaries outside the central nervous system (CNS) depend largely on the presence of water-filled channels which traverse the vessel wall and which are probably interendothelial in position. These allow free passage of all molecules up to the size of inulin (5,000 daltons) and beyond. Since the interendothelial clefts in brain are completely sealed with zonulae occludentes, the transport properties of the blood-brain barrier must be largely those of the plasma membranes of the endothelium. There has been some argument as to whether small polar molecules may diffuse across the barrier relatively faster than predicted for solution in a pure lipid layer, because of a limited water-filled route across the endothelium. The presence of such a route was indicated by Fenstermacher and Johnson's (1966) estimations of reflection coefficients at the blood-brain barrier and by calculations of permeability-surface area (PS) product/diffusion coefficient in water for various polar molecules by Bradbury (1979). The idea has received recent support from the measurement of dilution potentials for NaCl and KCl across cerebral capillaries in the frog (Crone, 1984). The results suggested a small number of neutral or weakly charged pores which did not discriminate between Na\(^+\), K\(^+\), and Cl\(^-\). On the other hand, Rapoport and his colleagues have made extensive studies of PS products at the barrier for a wide range of hydrophilic non-electrolytes. In general, they found a direct proportionality between PS product and the octanol-water partition coefficient (Ohno et al., 1978; Rapoport et al., 1979) (Fig. 1), or as a better alternative, this coefficient divided by the square root of the molecular weight (Fenstermacher and Rapoport, 1984). The smaller molecules did not have a higher than predicted PS product, indicating an absence of pores.

The presence of water-filled channels is also suggested, if the osmotic permeability of a membrane is greater than its diffusional permeability to tracer water. Although indicator diffusion studies of the blood-brain barrier first indicated that this might be so (Paulson et al., 1977), a later mathematical analysis showed that the results could be explained by a nonporous blood-brain barrier, together with an unstirred layer between moving blood and the barrier (Patlak and Paulson, 1981). Overall it can be concluded that if there are water-filled channels, their total effective area is too small to cause an unambiguous physiological effect.

**Electrical and Diffusional Resistance**

This picture of a very tight cellular barrier has been given striking quantitative substance by measurements of the electrical resistance across the walls of capillaries near the surface of living frog brain (Crone and Olesen, 1982). Current was injected into the lumen via a microelectrode, and the intravascular profile of potential was measured with a second electrode placed at various distances from the source. Membrane resistance was calculated from cable theory and was found to average 1900 ohm-cm\(^2\). This specific resistance of brain endothelium is of a size similar to that measured across amphibian tight epithelia, such as skin and urinary bladder, and across amphibian erythrocyte membranes. In line with this high resistance, cerebral interendothelial junctions in both the frog (Bundgaard, 1982) and in a mammal are impermeable to ionic lanthanum (Bouldin and Krigman, 1975).

This potent restraint at the level of the blood vessels leads to the situation whereby solutes, e.g., sucrose and inulin, which freely enter the extracellular space of most tissue and are restricted to it, barely enter the brain at all. Similarly, solutes—which, in other tissues, penetrate into parenchymal cells and which suffer their major hindrance at this entry—in brain are delayed primarily at the capillary endothelium. Since the surface area of endothelium is insignificant compared with that of all the cells and processes within the brain, uptake from interstitial fluid into cells is not rate limiting. Hence, many solutes of differing properties and solubility enter brain from blood according to a single rate constant (Bradbury, 1979). This "ready mixing beyond the barrier has greatly simplified the kinetic analysis of blood-brain barrier permeability.

In addition to lipophilic solutes, a number of polar metabolic substrates cross the plasma membranes of the cerebral endothelium via specific transport sys-
tems. Transport by each of these systems is highly stereospecific, self-saturable, and inhibitable by structurally related compounds. Among systems demonstrated are individual ones for certain hexoses, and for certain monocarboxylic acids (acetic, lactic, pyruvic, and ketone bodies), and three systems, each for a different class of amino acid (Patrick, 1984). The transporter at the blood-brain barrier with the highest capacity is that for glucose. Both intracarotid (Oldendorf, 1971) and isolated capillary studies (Betz et al., 1978) indicate that the rank order of affinities of competitively inhibiting sugars for the transporter is the same as that for the facilitated mechanism in the red cell membrane. Most available evidence suggests that glucose transport into the human erythrocyte is mediated by an integral membrane protein of apparent molecular weight 55,000. Part of the evidence is based on the photo-incorporation of [4-3H]cytochalasin B into the transporter. Baldwin et al. (1984) have applied this technique to osmotically lysed cerebral microvessels isolated from sheep brain and found the cytochalasin to be photo-incorporated into a membrane protein of apparent molecular weight 53,000, this incorporation being inhibited by D-glucose.

**Cytochemistry of the Cerebral Endothelium**

No other transporting protein has been tentatively isolated from the cerebral endothelium, but increasingly sophisticated ultracytochemical techniques, together with biochemical studies of isolated capillaries, are leading to insights concerning those enzymes which are localized in cerebral capillaries. Some of these may be involved in transport mechanisms. Enzymes which are present at high concentration in tight cerebral endothelium include γ-glutamyl transpeptidase, alkaline phosphatase, the Na⁺,K⁺-ATPase, butyrylcholinesterase, and aromatic-L-amino acid decarboxylase. γ-Glutamyl transpeptidase has become a standard marker enzyme for microvessels prepared from homogenates of brain (Joó, 1984) and outside the nervous system is normally present in secreting epithelia rather than in endothelial cells (Albert et al., 1966). Alkaline phosphatase activity occurs, particularly in the luminal plasma membrane of the endothelium (Kreutzberg and Toth, 1983; Vorbrod et al., 1983). The enzyme is especially active in developing cerebral capillaries and also occurs in transporting epithelia, e.g., those of the proximal renal tubule and small intestine. It is present in the basal plasma membrane of the choroid epithelium but not in the fenestrated endothelium of the plexus (Vorbrod et al., 1983). In contrast, the Na⁺,K⁺-ATPase is present at high concentration in the abluminal membrane of the endothelium (Firth, 1977; Betz et al., 1980) and probably is involved both in the regulation of potassium in interstitial fluid and in the secretion of this fluid. Butyrylcholinesterase has been considered to be specific to tight cerebral endothelium (Joó and Csillik, 1966), but, in fact, is also present in fenestrated capillaries in regions of brain lacking a blood-brain barrier (Kreutzberg and Toth, 1983). Some biochemical studies have associated 5'-nucleotidase with the endothelium (e.g., Betz et al., 1980), but other recent ultracytochemical evidence places it more firmly in glial plasma membranes (Kreutzberg and Toth, 1983), although the enzyme may be present to some extent in all plasma membranes. Adenosine is a possible mediator for metabolic hyperemia in brain. The presence in perivascular glia of 5'-nucleotidase, which hydrolyzes cyclic adenosine monophosphate (cAMP) to adenosine and phosphate, would be particularly favorable to this hypothesis (see below).

The cytochemical picture of the cerebral endothelium is thus much more like that of an actively transporting epithelium, such as proximal renal tubule or small intestine, than that of a typical endothelium. In association with these characteristics, cerebral endothelial cells contain a high density of mitochondria. These are five to six times more numerous per capillary cross-section in brain than in skeletal muscle (Oldendorf and Brown, 1975).

**The Astrocytic Sheath**

Surrounding the endothelium is a basement membrane, and, beyond this, almost the entire cylinder is ensheathed by astrocytic processes (Fig. 2). The function of this near contact between astrocyte and endothelium remains enigmatic, but the presence of a glial link between neurones and capillaries suggests a role in communication. There is now excellent evidence (Stewart and Wiley, 1981; see review by Bradbury, 1984) that the particular structural and functional characteristics of cerebral capillaries are determined by the surrounding central nervous tissue. The glial end-feet must be a natural candidate for mediating such an influence.

An intriguing feature of the astrocytic plasma membrane is the presence of "assemblies" of intra-
membrane particles (Landis and Reese, 1974; Brightman et al., 1983). These particles are 5–7 nm wide and are grouped in orthogonal aggregates. They are revealed on the inner face of the cleaved membrane at freeze-fracture and may connect with the underlying cytoskeleton of filaments. They are particularly numerous in the end-feet of astrocytes, making contact with pia or with blood vessels. Their function is unknown, but their numbers increase greatly during the gliosis, induced by, e.g., cold injury. Cell culture experiments indicate that they may be responding in such injury to a fall in extracellular pH, associated with accumulation of lactic acid and CO₂.

Bradbury (1975) has discussed the concept that astrocytes, being epithelial in nature, have a polarity, their basal (vascular) and apical (neuronal) processes being distinct and asymmetrical. This idea has now received experimental support, at least as far as the Muller cells of the retina are concerned. The apical processes of these cells contact the photoreceptors, whereas the basal processes lie in the vitreous humor. Newman (1984) has investigated such cells, dissociated from the salamander retina, with microelectrodes. Almost all the membrane conductance is due to potassium movement, and 94% of the total conductance is attributable to the end-foot membrane. It is known that neuronal activity in the brain releases potassium into the local extracellular fluid. This will tend to depolarize adjacent astrocytic processes. If the basal vascular end-feet of cerebral astrocytes have as high a potassium conductance as neuronal processes, electronic condensation will cause preferential spreading of depolarization will cause preferential spread of depolarization will cause preferential depolarization of the end-foot membranes of gliaJ end-feet.

Filtration Coefficient

The picture already presented of a very tight endothelium would suggest that the blood-brain barrier must have a very low filtration coefficient or hydraulic conductivity, Lp. This is confirmed by two experimental estimations. Fenstermacher and Johnson (1966) measured the changing volume of rabbit brain in response to raising the osmolarity of blood. Sucrose and raffinose were considered to be nonpenetrating. When the concentration of either was raised in blood, the initial rate of water movement out of brain yielded a Lp of 0.8 × 10⁻⁹ cm/sec per cm H₂O. An almost identical value for Lp of the blood-brain barrier has been found by Paulson et al. (1977) in man by the intracarotid injection of a hyperosmotic bolus. Dallas and Fraser (1984) have measured the filtration coefficient of single pial capillaries in the frog. Fluid movements were estimated by introducing carboxyfluorescein into a capillary and measuring its fluorescence with a television microdensitometer. Capillaries were occluded, and the change in fluorescence during superfusion with saline, made hypertonic with sucrose, was compared with that during superfusion with isotonic saline. A minority of capillaries which remained tight had a mean Lp of 3.2 ± 0.5 × 10⁻⁹ cm/sec per cm H₂O. The variability indicated that water- and solute-conducting channels may have been opening up through the tight junctions, and further calculation suggested that the Lp for the water-only pathway (plasma membrane) would be 1.15 × 10⁻⁹ cm/sec per cm H₂O, very close to the average value of total Lp obtained by Fenstermacher and Johnson for capillaries in rabbit brain. This contrasts with a value of 74 × 10⁻⁹ cm/sec per mm Hg in the same units for capillaries in frog skeletal muscle (Curry and Froekjaer-Jensen, 1984) and a mean of 779 × 10⁻⁹ cm/sec per mm Hg for frog mesenteric capillaries [values collected from the literature by Gore (1982)].

Net volume flow across a membrane is determined by the equation

\[ J_P = L_p (\Delta P - \sigma \Delta \pi) \]

where \( \Delta P \) is the difference in hydrostatic pressure and \( \Delta \pi \) is the difference in osmotic pressure due to solutes, if impermeanent. If \( \sigma \) for NaCl is 0.5 (it is probably much higher), a 10 mm difference in NaCl concentration across a brain capillary would produce an osmotic pressure difference of 170 mm Hg. Thus, the potential osmotic pressure due to solutes of small molecular weight is overwhelming, compared with that due to protein. Whereas filtration cannot reasonably account for the production and for the composition of cerebral intestinal fluid, the presence of a tight endothelium, with a high density of Na⁺,K⁺-ATPase in its abluminal membrane and with numerous mitochondria, indicates that secretory mechanisms can generate and maintain ion gradients and may cause bulk flow of fluid.

Production and Bulk Flow of Interstitial Fluid

It is now pertinent to ask, first, whether there is experimental evidence for the bulk production of
interstitial fluid within the brain, and, second, if this occurs, what the mechanism for net movement of sodium and chloride ions from blood to cerebral interstitial fluid may be, and how may it be influenced. With regard to the first question, Cserr and colleagues have provided much evidence that there is convection within cerebral interstitial fluid. After microinjection into brain, it was found that anatomical tracers moved through the tissue away from the injection site along preferential channels, yielding a pattern of distribution consistent with bulk flow rather than with diffusion (Cserr and Ostrach, 1974; Cserr et al., 1977). Channels of flow outlined by the tracers included the perivascular spaces, spaces between fiber tracts in the white matter and within the subependymal layer of the ventricular ependyma. Most striking was the observation that radiotracers of molecular weights from 900 to 69,000 (differing in their diffusion coefficients by up to 5 times) were cleared from brain according to a single exponential rate constant (Cserr et al., 1981) (Fig. 3). This can only be due to convection, not to diffusion. It suggests a largely centrifugal bulk flow of interstitial fluid, the driving force being the hydrostatic pressure gradient generated by its secretion across the endothelium, but other factors such as to-and-fro movement of cerebrospinal fluid (CSF) in the perivascular spaces due to arterial pulsation need to be excluded. Although metabolic production of water could almost quantitatively account for the apparent flows observed, such water is likely to be immediately reabsorbed into blood by osmotic forces, since it contains no solute. If it is assumed that clearance of large molecules is due entirely to a model of ion transport across the cerebral endothelium which includes furosemide-sensitive coupled influx of sodium and chloride at the luminal membrane and amiloride-sensitive Na\(^+\)-H\(^+\)-exchange at the abluminal membrane, in addition to the ouabain-sensitive Na\(^+\)-K\(^+\)-pump. This model was based on the intracarotid bolus technique for the luminal membrane (Betz, 1983b) and on the isolated capillary preparation for the abluminal membrane (Betz, 1983a). Whereas coupled NaCl influx, together with sodium pumping, might form a good basis for secretion, c.f. various epithelia (Frizzell et al., 1979), the presence of Na\(^+\)-Cl\(^-\)-cotransport is not supported by the experimental evidence. A 50% reduction in chloride influx did not alter sodium influx into parietal cortex (Smith and Rapoport, 1984), and the furosemide inhibition observed by Betz (1983b) apparently required 1 \(\mu\)M of the drug and occurred only at the low sodium concentration of 1.4 \(\mu\)M.

The volume of the vertebrate brain is regulated in the face of maintained osmotic disturbances in the blood, either hypo- or hyperosmolality. This control appears to include regulation of both the extracellular and intracellular volumes, the former being based on net movement of sodium chloride either out of (hypoosmolality) or into (hyperosmolality) the brain [reviewed by Bradbury (1979)]. This regulation occurs in brains with a glial blood-brain barrier—e.g., that of the skate (Cserr et al., 1983)—as well as in the mammal. In the skate, the increased influx of \(^{22}\)Na which occurs into brain when the fish is rendered hyperosmotic takes place across the blood-brain barrier and is probably inhibitable by furosemide and bumetanide, neither drug influencing the isosmotic influx (Mackie et al., 1984). This suggests that coupled NaCl transport across the glial barrier is activated in hyperosmolality. Mammalian brain also takes up sodium chloride in hypernatremia, but this probably occurs from subarachnoid fluid (Pullen and Cserr, 1984), the rate constant for
Apparent Capillary Permeability and Blood Flow

Renkin-Crone Analysis

Since there often is doubt as to the precise area of capillary endothelium across which transport is occurring, the facility of exchange of a solute across the blood-brain barrier, as across other capillaries, is often expressed as a permeability-surface area product, rather than as a permeability coefficient (Bradbury, 1979). This is defined as the unidirectional influx of the solute, mass entering brain per unit time, divided by average capillary concentration. It is often related to unit wet weight of brain and, thus, may be given units of ml/g per min. Since the blood-brain barrier is the main limitation to movement of most solutes from blood into brain, this PS product can be estimated by measuring either the uptake of a radiotracer into brain or its extraction from blood. It is necessary to choose times at which backtransport from brain to blood is not significant.

A complication arises in that, if the extraction of a solute from capillary blood is moderate, its concentration in the venous blood will be less than that in the blood entering the capillary. This progressive reduction in the driving force to solute movement may be allowed for. If it is assumed that all capillaries are cylindrical tubes having uniform dimensions and permeability and receiving uniform perfusion, and that there is no back diffusion, then extraction, E, may be related to PS product and to perfusion flow, Q, by the equation derived by Renkin (1959) and Crone (1963).

\[ E = 1 - e^{-PS/Q} \]

It might be anticipated that PS product would be independent of flow, but in several tissues, including skeletal and myocardial muscle, several solutes of differing molecular and ionic weight show markedly varying apparent permeability with flow (Renkin, 1959; Alvarez and Yudilevich, 1969; Yipintsoi et al., 1970). The phenomenon of an increase in PS product with augmented flow has been ascribed to capillary recruitment, a theory which fits with the presence of unperfused capillaries at low flows and with the PS product reaching a saturation value at high flows, when all capillaries are perfused.

It is generally believed that capillary recruitment does not occur in brain, in the sense that a proportion of capillaries are intermittently or continuously unperfused under physiological conditions. Indeed, a study in the monkey with water and alcohols, labeled with positron-emitting isotopes (Raichle et al., 1976) showed no variation of PS product with random changes in flow, or for the alcohols when flow was altered by hyperventilation and by administration of 10% CO₂ with 90% O₂. The living frog brain may be transilluminated, enabling movement of red cells to be seen in microvessels to a depth 25 μm or more. No intermittent opening or closing of microvessels can be seen when the state of the brain is healthy (P.A. Fraser, personal communication).

Recently, doubt has been cast on the assumption that clear-cut recruitment does not occur in brain. Weiss et al. (1982) injected fluorescein-labeled dextran of high molecular weight intravenously into pentobarbital-anesthetized rats. At 20 seconds, the head was decapitated into liquid nitrogen, and thin frozen sections were obtained. Fluorescence was present in only about 50% of total capillaries, stained for alkaline phosphatase. Asphyxia caused a large increase in the number of capillaries perfused. Certainly, much evidence is accumulating that the PS product of the blood-brain barrier to a number of solutes increases with flow.

Experimental Evidence for Varying PS Product

In two studies of glucose uptake into the perfused brain, a marked relation between influx into brain and flow was demonstrated. In the first (Zivin and Snarr, 1972), net uptake into the rat brain was found to rise rapidly as flow was increased, reaching half-maximal levels at a total brain flow of about 1 ml/min. In the second (Betz et al., 1973), unidirectional uptake was determined in the dog brain by indicator dilution with [3H]glucose. Uptake (μmol/g per min) increased from 0.5–1.0 when the plasma flow was raised from 0.3–0.8 ml/g per min. Since the Renkin-Crone correction was not used, the increase in uptake might be attributed to flow limitation. This is very unlikely, since the approximate maximal PS product for glucose at the concentration used in the latter study was 0.2 ml/g per min. Flow limitation will not be important for flows above 0.4 ml/g per min (Fig. 4).

It is now well recognized that there is coupling between cerebral blood flow and glucose utilization. This is very tight when flow is related to utilization by different regions of brain at one metabolic state (Sokoloff, 1981) and also occurs, but less predictably, when metabolism is altered (Sokoloff, 1981; Cremer et al., 1983). Since unidirectional influx of glucose in most regions of brain is only about twice the respective glucose utilization in conscious control rats (Cremer et al., 1983), there would be little margin for adequate entry of glucose if metabolism appreciably increased without a change in PS product. Increased flow on its own would be of limited use (Fig. 4). In fact, unidirectional influx, hence PS...
Blood Flow, ml.g

FIGURE 4. Theoretical curves based on Renkin-Crone equation for flow extraction against blood flow (all variables per minute, not labeled). Note that flow extraction represents volume of arterial blood cleared of solute per minute, and is directly proportional to net flux or mass of solute entering brain per minute. Since the equation assumes no back-diffusion, the product is also proportional to unidirectional flux of solute from blood into brain.

product was decreased in pentobarbital anesthesia (Gjedde and Rasmussen, 1980) and was markedly increased when cerebral metabolism was stimulated by the tremor-inducing drugs cismethrin or decamethrin (Cremer et al., 1981, 1983). Such changes in PS product might be due to an alteration either in the true permeability of the endothelium to glucose or in its effective surface area. Although the transporter, facilitating the entry of ketone bodies into brain, may show adaptive changes in relation to the metabolic needs of the brain, probably mediated slowly via the concentration of ketone bodies in blood (reviewed by Gjedde, 1983; Gjedde and Crone, 1983; Bradbury, 1984), there is no indication as yet that the glucose transporter at the barrier can rapidly adapt in response to neuronal activity or metabolism. On the other hand, there is good evidence that altering cerebral blood flow, with or without a change in metabolism, can change the PS product for a number of nonmetabolized solutes. Bolwig et al. (1977) examined the permeability of the blood-brain barrier in man by indicator dilution. Permeability-surface area products of labeled sodium and chloride ions, urea, and thiourea increased markedly when cerebral blood flow was more than doubled by electrically induced seizures (ECT) or by hypercapnia. In a later study, they found that hypcapnia decreased and hypercapnia augmented PS products for labeled propanolol, thiourea, and phenylalanine (Hertz and Paulson, 1980). Paradoxically, hypcapnia somewhat enhanced the PS product for glucose. In an elegant study, Sage et al. (1981) estimated unidirectional leucine influx and cerebral blood flow in the brain of awake rats. Increasing cerebral blood flow from 1.5-4.5 ml/g by CO2 administration nearly doubled leucine influx over a wide range of leucine concentrations in plasma (Fig. 5). Phelps et al. (1981) examined extraction of [15N]ammonia over a wide range of cerebral blood flows. The PS product for ammonia increased markedly with flow and saturated at a flow of about 2 ml/g per min in a manner reminiscent of glucose in the perfused brain. The results were interpreted as due to "saturation recruitment."

Is Capillary Recruitment the Mechanism?

Two questions arise. Is there a general mechanism whereby PS product is varied in relation to blood flow? If not, how do the mechanisms differ in the various experimental situations studied, i.e., altered arterial PCO2, altered metabolism, including seizures, and spreading depression. As a general mechanism, capillary recruitment would provide a good explanation, but, as discussed, it may not occur in brain as an all-or-nothing phenomenon. However, it is necessary to suppose that capillaries are at any time completely closed. If flows were to be increased through paths with either a high permeability or a high endothelial area, or both, relative to flow through capillaries with low PS products, then the average PS product for the brain region or for whole brain would be increased. Indeed, Hertz and Paulson (1980) found evidence for heterogeneity of capillary flow. Short transit times corresponded to low extractions, and long transit times, to high extractions. To produce the observed effect, flow would have to be relatively increased in the high-extraction vessels.

Evidence concerning an answer to the second question is even more limited. Gjedde et al. (1981) demonstrated an uncoupling between PS product for glucose and cerebral blood flow during the onset of spreading depression. Although blood flow increased markedly, PS product was unaltered. Brain glucose fell, indicating that metabolism had indeed risen. Whether the coupling demonstrated in relation to CO2-induced changes, on one hand, and to
most metabolically mediated changes in flow, on the other, depends on the same mechanism is uncertain. In a comprehensive study, Cremer et al. (1983) estimated not only blood flow with glucose influx and utilization, but also residual tissue blood volume in different brain regions. A particularly tight correlation was noted between maximum glucose transport capacity and blood volume in different brain regions from rats subjected to one experimental condition. This relation was still present when all experimental groups were placed together, but the spread was larger. Since residual blood volume was considered to represent the area of endothelium perfused, the results were taken to support capillary recruitment.

Overall, it would appear that altering cerebral blood flow by varying arterial PCO2 or by altering metabolism must produce a change in PS product by leading to a redistribution of flow, apart from the straight alteration in the magnitude of flow. Whether this redistribution is equivalent in both situations is uncertain at present. Certainly in one situation, spreading depression, the redistribution, if any, must be quite different.

Conclusions and Summary

The blood-brain barrier is now known to be the cerebral endothelium. Except in certain regions, this is a very tight cellular membrane with high electrical resistance, a low filtration coefficient, and low permeability to many polar solutes. It contains specific transport mechanisms for a number of metabolic substrates. The ionic composition of the interstitial fluid of brain is maintained by active transport at the endothelium, and there may well be a slow net secretory production of this fluid.

The astrocytic ensheathment of cerebral capillaries probably induces and maintains the particular properties of this endothelium. It may be a route by which neuronal activity can influence blood flow or permeability or both. The PS product of the cerebral microvessels to glucose and to other solutes may rapidly and markedly change in relation to neuronal activity and metabolism. The mechanism of the increase of PS product is unsettled, but the phenomenon probably may be explained by recruitment or flow redistribution in the microcirculation, or both.

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