Analysis of the Permeability Characteristics of Cat Intestinal Capillaries

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SUMMARY The permeability characteristics of cat small intestine capillaries were studied using both osmotic transient and lymph-to-plasma protein concentration ratio (L/P) techniques. A vascularly perfused segment of ileum in which superior mesenteric arterial pressure, blood flow, superior mesenteric venous pressure, and lymph flow were monitored was used for both determinations. Intestinal volume was continuously monitored during the osmotic transient experiments. Hyperosmotic solutions of various test solutes were infused at a constant rate directly into the superior mesenteric artery after the establishment of an isovolumetric state. Osmotic conductances were calculated from the initial rate of volume loss and the calculated plasma osmotic pressure change. Reflection coefficients for the various solutes were determined from the osmotic conductance and filtration coefficients within the same preparation. The predicted equivalent pore radius for intestinal capillaries using this approach is 200-350 Å. In another group of cats, the L/P ratio for total plasma proteins was determined prior to and following graded increases in intestinal venous outflow pressure (10-30 mm Hg). At the greatest dilution of lymph proteins, the minimum osmotic reflection coefficient for total plasma proteins ($\alpha_p$) was estimated assuming $\alpha_p = 1 - (C_l/C_p)$, and values of $\alpha_p$ between 0.87 and 0.92 were acquired. Minimum osmotic reflection coefficients for total plasma proteins were then determined during osmotic transients induced by hypertonic glucose (20-70 mM). Values of $\alpha_p$ between 0.56 and 0.74 were acquired during the osmotic transients. The results of these studies suggest that intestinal capillaries are relatively impermeable to endogenous plasma proteins. The discrepancy between the L/P ratio and osmotic transient techniques results, at least in part, from an increased capillary permeability during the osmotic transient.

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MAMMALIAN capillaries have been classified into three types based on ultrastructural characteristics: continuous, fenestrated, and discontinuous (Bennet et al., 1959). Ultrastructural estimates of pore dimensions in the various types of capillaries suggest that selective solute restriction is greatest in continuous capillaries and intermediate for fenestrated capillaries, whereas the pores of discontinuous type capillaries offer the least restriction to transcapillary solute movement (Karnovsky, 1968). Physiological estimates of capillary permeability in various organs have been determined by three different approaches: (1) the osmotic transient method (Pappenheimer et al., 1951; Vargas and Johnson, 1964), (2) the multiple indicator-dilution technique (Chinard et al., 1955; Harris et al., 1976; Yudilevich et al., 1968), and (3) the lymphatic protein flux analysis.

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the physical and physiological factors which can account for the discrepancy between the results of the two techniques.

Methods

Experiments were performed on female cats (2.5-4.1 kg body weight) initially anesthetized with ketamine-HCl (75 mg, im) and maintained in a state of anesthesia with sodium pentobarbital. The experimental procedure has been described previously in detail (Granger et al., 1977; Levine et al., 1978). Briefly, a 14- to 30-g segment of ileum with intact innervation and lymphatic drainage was isolated and autoperfused by the intact superior mesenteric artery. The remaining small intestine, the large intestines, spleen, and omentum were surgically extirpated. A large lymphatic vessel emerging from the mesenteric pedicle was cannulated and lymph flow was determined by observing the movement of lymph in a calibrated pipette (0.1 and 1.0 ml full scale).

A large cannula was inserted into the superior mesenteric vein, and venous outflow drained into a reservoir mounted on a vertically positioned pulley system. Blood from the reservoir returned to the animal by a cannula inserted into the right external jugular vein. Heparinized whole blood from a freshly killed donor cat was used to fill all tubing of the extracorporeal venous circuit. Venous outflow pressure was obtained through a t-connector inserted into the venous outflow circuit immediately distal to the superior mesenteric vein. Venous pressure could be adjusted to any desired level by adjusting the height of the reservoir system.

Systemic arterial pressure was monitored via a cannula inserted into the femoral artery. The femoral vein was cannulated for administration of drugs (sodium pentobarbital, etc.). All pressure cannulae and associated transducers were positioned at heart level, and pressures were continually recorded with a Grass recorder (model 7).

Osmotic Transients

In these experiments, the superior mesenteric artery was rapidly ligated and cannulated in both distal and proximal directions. The ends of the two cannulae were connected via a polyethylene t-tube, thus allowing for uninterrupted blood flow and measurement of the perfusion pressure of the ileal segment. A cannulating flow probe (3 mm i.d.) was inserted within the extracorporeal arterial circuit, and ileal blood flow was monitored with an electromagnetic flowmeter (BL-310). The arterial loop also allowed a route for infusion of various solutes. The ileal segment then was placed in a triangular plexiglass plethysmograph which was properly sealed. Special care was taken to avoid compression of the mesenteric pedicle to ensure that intestinal blood flow would not be altered. A short length of flexible Tygon tubing connected the sealed plethysmograph to a Lucite reservoir suspended from a force-displacement transducer (Grass FT 10c). Both the reservoir and plethysmograph were filled with warm isotonic Tyrode's solution, thereby allowing for detection of volume displacement within the ileal segment.

Capillary filtration coefficients \( K_{sc} \) were determined in the papaverinized isovolumetric loop by suddenly increasing venous pressure from a control value of 0-2 mm Hg to 10 mm Hg and analyzing the resulting volume changes in the intestine. The volume change following venous pressure elevation is characterized by two distinct components: an initial rapid volume increase and a slower more prolonged phase of volume change. The rapid phase was interpreted to be due to venous distention, and the slower, more prolonged phase was assumed to represent capillary filtration. The slope of the volume gain during the initial 30 seconds of the slow phase provided the initial filtration rate. Dividing this by the changes in capillary hydrostatic pressure (estimated using the precapillary and postcapillary resistance data of Mortillaro and Taylor, 1978) yields a value for \( K_{sc} \).

The capillary osmotic conductance \( L_o \) for various test solutes (NaCl, urea, glucose, mannitol, maltose) was determined after the intestine had reached an isovolumetric state with venous pressure set at approximately 10 mm Hg. Freshly prepared solutions with concentrations of 300, 1000, and 2000 mOsm/liter were prepared for each test solute. The solutions (at 37°C) were infused into the superior mesenteric artery at a constant rate (0.25-1.00 ml/min) once blood flow, lymph flow, and intestinal volume were in a steady state. Due to the potent vasodilatory response of the intestinal vasculature to an elevated plasma osmolality (Levine et al., 1978) papaverine (0.1 mg/kg) was administered to prevent the occurrence of significant blood flow changes during solute infusions. Local arterial plasma osmolality was calculated during the infusion from blood flow, infusion rate, and concentration of the infused solution by assuming that control plasma osmolality was 300 mOsm/liter and that the infused test substance was exactly diluted by whole blood. Infusion of the hyperosmotic solutions (of all solutes) resulted in an elevated plasma osmolality ranging between 40 and 175 mOsm/liter, and a reproducible reduction in intestinal volume. The rate at which a given solute pulled fluid from the intestine \( L_o \) was calculated using the initial rate of volume loss and the predicted change in plasma osmolality (expressed as ml/min per mm Hg osmotic pressure).

The capillary reflection coefficient \( \sigma \) for each test solute was calculated assuming that (see Vargas and Johnson, 1864),

\[
\sigma = L_o/K_{sc}. \tag{1}
\]

The relationship between solute radius \( a \), capillary pore radius \( R_p \), and the osmotic reflection coefficient \( \sigma \) was defined using the equation of
Levitt (1975),
\[ \sigma = \frac{16}{3}(a/R)^2 - \frac{20}{3}(a/R)^3 \]
+ \[ \frac{7}{3}(a/R)^4 - 0.354(a/R)^5. \]  
(Note that, since both \( K_{fc} \) and \( L_o \) were measured in the same preparation, an estimate of capillary surface area was not necessary to determine \( \sigma \).)

**Lymphatic Protein Flux**

In these experiments, the extracorporeal arterial loop and plethysmograph were not used. A larger segment of ileum was used to maximize control lymph flows. The isolated autoperfused ileal segment was moistened with saline-soaked gauze and covered with a plastic sheet to minimize evaporation and tissue dehydration. Plexiglass plugs containing inflow and outflow cannulae were tied into each end of the isolated ileal segment, and the intestinal contents were removed by slow infusion of Tyrode’s solution. Once the intestinal contents became clear, a gentle stream of air was applied to aid in the removal of residual fluid. At 5- to 15-minute intervals thereafter, the air stream was applied and the luminal fluid collected in a 10- to 25-ml graduated cylinder. The luminal fluid collected during these intervals was assumed to represent secreted fluid.

Intestinal lymph flow was measured at 5- to 15-minute intervals in the control period. Once lymph flow was in a steady state, intestinal venous pressure was rapidly increased from a control value of 10–30 mm Hg. At 5-minute intervals for 30 minutes, and at 15-minute intervals thereafter following venous pressure elevation, the following measurements were made: plasma protein concentration \( (C_p) \), hematocrit, lymph protein concentration \( (C_L) \), lymph flow, and intestinal secretion (filtration secretion) rate. Lymph and plasma protein concentrations were determined by refractometry (TS meter, American Opticals).

The solvent drag reflection coefficient of the intestinal capillaries to total plasma proteins \( (\sigma_p) \) was determined using one minus the lymph-to-plasma protein concentration ratio at maximum tissue protein washdown, i.e., one minus the sieving coefficient,

\[ \sigma_p = 1 - \frac{C_L}{C_p}. \]  
The theoretical basis for use of \( 1 - C_L/C_p \) as an estimate of \( \sigma_p \) was recently provided by Brace et al. (1977). Since the solvent drag reflection coefficient is approximately equal to the osmotic reflection coefficient under conditions of maximum tissue protein washdown, we can assume that \( 1 - C_L/C_p \) provides a minimum value of the osmotic reflection coefficient.

**Results**

**Osmotic Transients**

Direct intra-arterial infusion of the iso-osmotic (300 mOsm/liter) solutions into the papaverinized isovolumetric ileal loop had no effect on intestinal vascular resistance or intestinal volume at the low infusion rates employed (infusion rates < 10% of control blood flow), with the exception that urea infusions (iso- and hyperosmotic) occasionally resulted in significant increases in intestine volume. Osmotic conductance determinations for urea were acquired only in those experiments in which intestinal volume decreased and no significant vascular resistance changes occurred during urea infusions. Infusion of hyperosmotic solutions of solutes other than urea consistently resulted in a decreased intestinal volume.

Figure 1 illustrates a representative osmotic transient produced by local intra-arterial infusion (0.585 ml/min) of a hyperosmotic glucose solution (2.0 M) into a segment of cat ileum. The calculated change in plasma osmolality (\( \Delta Osm \)) during the infusion was 163 mOsm/liter. Using the initial rate of volume change and the calculated change in blood osmotic pressure \( (\Delta \Pi = \Delta Osm \times 19.3 \text{ mm Hg}) \), the osmotic conductance \( (L_o) \) was estimated as \( 13.9 \times 10^{-11} \text{ ml/min per mm Hg} \). Although papaverine was administered prior to the \( L_o \) determination to minimize osmotically induced vascular resistance changes, blood flow did increase during most \( L_o \) determinations. The capillary filtration coefficient \( (K_{fc}) \) for this experiment was determined following the acquisition of \( L_o \) for all solutes and estimated as \( 6.25 \times 10^{-2} \text{ ml/min per mm Hg} \). The capillary reflection coefficient \( (\sigma) \) for glucose in this experiment, calculated by dividing \( L_o \) by \( K_{fc} \), was \( 22.24 \times 10^{-4} \).

The values of the osmotic conductance \( (L_o) \), filtration coefficient \( (K_{fc}) \), and osmotic reflection coefficient \( (\sigma) \) acquired for urea, glucose, mannitol, and maltose are presented in Table 1. Statistically,
tein washdown data were acquired for an intermediate venous pressure (PV = 20) to demonstrate that tissue protein washdown sufficient for this analysis does not occur until intestinal venous pressure is elevated to at least 30 mm Hg. It is evident from the data for (1 - C_L/C_P) in Table 2 that the osmotic reflection coefficient for total plasma proteins is at least 0.87-0.92. The large reflection coefficients for total plasma proteins acquired in the lymphatic protein flux studies are incompatible with the pore sizes estimated from the osmotic transient study, since one would estimate (from Equation 2) an osmotic reflection coefficient for total plasma proteins of approximately 0.1 for 200-350 Å radius pores.

In another series of experiments (n = 6), the lymphatic protein flux method was used to estimate the reflection coefficient of intestinal capillaries for total plasma proteins during simulated osmotic transients. The "osmotic transient" was induced by infusing 2 M glucose directly into the superior mesenteric artery at rates which produced a 19.1-66.8 mOsm increase in local blood osmolality. During the new steady state (PV = 10 mm Hg), venous pressure was rapidly increased to 30 mm Hg, as in the control L/P experiments. The results of these experiments are presented in Table 3. The data suggest that a 20 mm Hg increase in venous pressure results in significantly greater increases in intestinal lymph flow and lymphatic protein flux during the osmotic transient (Table 3) as compared to control (Table 2). In addition, we acquired minimum osmotic reflection coefficients during the osmotic transient group (0.635 ± 0.025) which were significantly (P < 0.001) less than in the control group (0.90 ± 0.068).

### Discussion

The capillaries of the intestinal mucosa classically have been characterized as relatively porous structures. The endothelium of capillaries from the lamina propria of the intestine are seen to be perforated by numerous fenestrations or pores 300-600 Å in diameter (Casley-Smith et al., 1975; Simioneescu et al., 1972, 1976). According to the pore theory of capillary permeability, the passage of water soluble molecules from blood to interstitial fluid is mediated by a two-pore system. For the fenestrated capillaries of the small intestine, the large pores are believed to be represented by fenestrae without diaphragms, whereas the small pores are located in all other fenestrae, the size-limiting structures being the porosity of the diaphragms. It is generally believed that the intracellular fenestrations or pores of intestinal capillaries are too large in themselves to exercise any selective filtration effect at the molecular level; therefore, the delicate dense material of the basement membrane is considered by many to be significant for protein sieving, as in glomerular capillaries.

In the present study, the results obtained with the osmotic transient approach tend to support the ultrastructural estimates of pore dimensions in fenestrated capillaries, i.e., 200-250 Å radius. Using the predicted (from Equation 2) equivalent pore radius from the osmotic transient studies, one would estimate that the osmotic reflection coefficient for macromolecules the size of albumin is less than 0.1 in intestinal capillaries. Although individual macromolecules of known molecular size and configuration were not analyzed in our studies, the lymphatic protein flux analysis of σo for total plasma proteins in the same experimental preparation suggest that intestinal capillaries are at least as impermeable to macromolecules as the continuous type capillaries of skeletal muscle (Taylor et al., 1977; Renkin et al., 1977), since σo in the intestine have a minimum value of approximately 0.90. It is evident, therefore, that the permeability estimates provided by the osmotic transient and lymphatic protein flux meth-
ods are not in agreement when applied to the small intestine.

The range of equivalent pore radii predicted from the intestinal osmotic transient studies is substantially larger and exhibits a wider variation than in previously studied tissues such as heart, lung, skeletal muscle, and brain for which equivalent pores of 35 Å (Vargas and Johnson, 1964), 40-100 Å (Taylor and Gaar, 1970; Wagensteen et al., 1977), 34-45 Å (Pappenheimer et al., 1951; Diana et al., 1972), and 7-9 Å radius (Fenstermacher and Johnson, 1966), respectively, have been predicted. Although the osmotic transient data acquired in the intestine may well represent the true sieving characteristics of intestinal capillaries to small solutes, several limitations of the technique in general and as applied to the small intestine may account for the results obtained. Factors which may influence the osmotic reflection coefficient values include: (1) an unstirred extravascular space, (2) capillary heteroporosity, (3) tissue heterogeneity, (4) overestimation of ΔΠt acting across the capillary, (5) overestimation of Kfc, (6) local vascular resistance and blood volume changes, and (7) osmotically induced changes in capillary permeability. An analysis of possible effects of an unstirred extravascular space and its relation to an overestimation of ΔΠt is presented in the Appendix, since this factor is theoretically a major limitation to the osmotic transient approach.

Whereas many of the aforementioned factors may account for the large equivalent pore radius predicted by our osmotic transient studies, there is evidence to support a greater permeability of intestinal capillaries to small solutes in comparison to capillaries of cardiac or skeletal muscle. Renkin (1977), in a recent review of capillary permeability, estimated from data of Yudilevich et al. (1968) that the permeability coefficient of glucose (\(\gamma_{\text{glucose}}\)) for the mucosal capillaries in small intestine is four to six times greater than \(\gamma_{\text{glucose}}\) in skeletal muscle. Renkin (1977) also calculated the permeability coefficients of dextrans of various molecular sizes and plasma proteins in dog intestine from the data of Arturson and Granath (1972) and of Granath et al. (1970). A comparison of the intestinal permeability estimates to those of other organs supports our finding that the intestinal capillaries are about as impermeable to macromolecules as the continuous capillaries of dog paw, skeletal muscle, etc. In addition, Wittmers et al. (1976) have demonstrated that the half-time for inulin (4600 mol wt) uptake in rabbit small intestine is very close to what one would predict for a flow-limited substance, i.e., a substance to which the capillary does not offer any significant resistance. These findings are in agreement with our osmotic transient results.

We have recently developed a method for independent analysis of capillary reflection coefficients and permeability surface area products for plasma proteins using lymphatic protein flux data (Taylor and Granger, 1976). In most tissues studied, \(\sigma\) tended to increase with increasing lymph flow, indicating that \(\sigma\) is volume flow-dependent rather than a constant. Brace et al. (1977) subsequently determined that the reflection coefficient in a capillary model, in which the net driving force at the arterial end exceeded that at the venous end, was volume flow-dependent, as indicated by animal experiments, but at high filtration pressures (\(P_v \geq 30\) mm Hg), \(\sigma\) approached a constant which could be described as one minus the sieving coefficient. The results of earlier lymphatic protein studies in the dog (Yablonski and Lifson, 1976; Johnson and Richardson, 1974) suggested that the \(\sigma\) for total plasma proteins is at least 0.72-0.80, i.e., the \(L/P\) ratio was reduced to 0.20-0.28 at high capillary filtration rates. The higher \(\sigma\) for total proteins acquired in this study probably results from the fact that lymph and plasma protein concentrations were determined at the maximum capillary filtration rates prior to the onset of filtration secretion. Moreover, it is likely that the \(\sigma\) for total proteins acquired in the present study are an underestimation of the real value of \(\sigma\), since the sieving coefficient provides a minimum value for the osmotic reflection coefficient. Although total plasma proteins were treated as a single entity in this analysis, our data do indicate that intestinal capillaries are essentially as impermeable to plasma proteins as the continuous capillaries of heart and skeletal muscle. Treatment of total plasma proteins as a single entity merely averages the osmotic reflection coefficient between albumin and globulins (Brace et al., 1977). Even if we assume that \(\gamma\)-globulins comprise all of the total plasma proteins measured, one would predict an equivalent pore radius of 80-90 Å which is significantly less than the osmotic transient estimates. Since the albumin-to-globulin ratio of cat plasma ranges between 1.0 and 1.5, an equivalent pore radius of approximately 50-60 Å would more aptly describe our data.

The results of the lymphatic protein flux experiments during simulated osmotic transients suggest that the discrepancy between osmotic transient and \(L/P\) data is due, at least in part, to a markedly increased permeability caused by the hypertonic solutions used during the osmotic transients. Hypertonic solutions are known to increase the permeability of the blood-brain barrier and various epithelial membranes (Rapoport, 1976; Bindseil et al., 1974). Rapoport (1976) has postulated that hypertonic solutions exert their effects on permeability of the blood-brain barrier by shrinking endothelial cells and that the retracted endothelial cells exert tension on the tight junctions and widen them. Opening of the tight junctions between endothelial and epithelial cells with hypertonic solutions has also been demonstrated ultrastructurally (Rapoport, 1976). Thus, it appears that the capillaries of the small intestine, like those of the brain, are vulnerable to an increase in plasma osmolality. The
increased permeability of the intestinal capillaries during the osmotic transient may result from an osmotic shrinkage of the capillary endothelium which could alter the dimensions of the interendothelial junctions and/or fenestrae. Our results are applicable to those of previous osmotic transient studies, since the increased permeability was observed even when plasma osmolality was increased by only 20 mOsm.

Since the reflection coefficients for plasma proteins ($\sigma_p$) acquired during the simulated osmotic transients (0.64) are significantly lower than those of the control lymphatic protein flux experiments, yet significantly greater than the $\sigma_p$ estimated from the osmotic transient pore size predictions ($\sigma_p < 0.01$), the increased permeability of the intestinal capillaries to plasma proteins during the osmotic transient will not totally explain the discrepancy between the two techniques. The contradictory results must also be attributed to (1) one or more of the various other factors tending to cause an underestimation of $\sigma$ using the osmotic transient and/or (2) the existence of capillaries which permit free passage of small molecules yet offer significant restriction to the movement of colloids. The existence of such a barrier has been proposed in glomerular capillaries (Renkin and Gilmore, 1973). Glomerular capillaries are of the fenestrated type, and their fenestrations are considered far too large to restrict the passage of proteins (Karnovsky, 1968). The basement membrane is generally considered to be the semipermeable barrier of glomerular capillaries and is gelatinous in nature, thereby permitting free passage of small molecules through its aqueous phase and restricting the movement of colloids. It is conceivable, therefore, that the basement membrane of intestinal capillaries may act as the rate-limiting barrier to diffusion and filtration in the small intestine. Casley-Smith (1975) has suggested that the fenestrated capillaries behave like “tunnel capillaries,” i.e., the interstitial matrix contributes substantially to the overall resistance to fluid and solute movement. The diaphragms covering the fenestrae (over 60% of the fenestrae in the mucosal region have diaphragms) could also serve as the major restrictive barrier to diffusion and filtration across intestinal capillaries (Simionescu et al., 1976). Irrespective of whether the fenestral diaphragms, basement membrane, or the interstitial matrix acts as the semipermeable membrane for fluid and solute movement across intestinal capillaries, a barrier which restricts colloids yet offers virtually no resistance to small solutes is best suited for transporting organs such as the kidney and intestine. Such a barrier would allow for the maintenance of a constant mucosal interstitial fluid volume by restricting colloids to the intravascular compartment, yet would facilitate the transport of newly absorbed solutes (e.g., glucose) from extravascular to intravascular spaces (Granger and Taylor, 1978).

In conclusion, the results of the lymphatic protein flux studies suggest that the fenestrated capillaries of the intestine are as impermeable to endogenous plasma proteins as the continuous type capillaries of skeletal muscle and lung. The osmotic transient data predicts an equivalent pore radius of 200–350 Å for intestinal capillaries. The discrepancy between the lymphatic protein flux and osmotic transient studies results, at least in part, from an increased capillary permeability during the osmotic transient.

Appendix

The validity of the osmotic transient method depends on the assumption that during the first part of the transient the extracellular concentration of the test solute is zero, whereas the capillary concentration is equal to the arterial value. It will be shown here that this assumption is probably not valid for the small intestine because of the very high permeability of the fenestrated capillaries.

Figure 4 shows an approximate scale drawing of the epithelial surface of an intestinal capillary and the extracellular space. The dimensions are based on the measurements of Casley-Smith et al. (1975). The fenestrae are about 500 Å in diameter and the interfenestra distance is about 2200 Å. Using this model, one can make a rough estimate of the time required for equilibration of the extracellular space assuming that, at $t = 0$, the capillary concentration is suddenly raised to $c_0$ and the capillary is well mixed (this is the ideal case for the osmotic transient method).

Consider first the time required to fill the half spheres shown in Figure 4. This can be determined
from the graphical solutions of Schneider (1963) for a spherical shell with an inner radius equal to the radius of the fenestra ($r_f$) and with an impermeable wall at the outer radius (see Fig. 4). This time depends on the permeability ($P$) and area ($S$) of the fenestra which will be written in the form:

$$\text{PS} = \pi r^2 a D/d$$  \hspace{1cm} (1A)

where $D$ (cm$^2$/sec) is the diffusion coefficient of the solute in the extracellular space, $d$ is the length of the fenestra channel, and $a$ is the relative restriction of the fenestra. Since the protein concentration in the lymph was much less than in the plasma (Table 2), it is clear that the fenestra must be nearly impermeable to proteins, presumably because of the presence of a diaphragm. Although the permeability of the diaphragm to small molecules is unknown, it might be expected that a large fraction of its area would be open to small molecules if it were a protein meshwork. It will be assumed that 10% of the fenestra area ($\alpha = 0.1$) is available for the free diffusion of the largest test solute (maltose) used. Using the dimensions of Figure 4 and an $\alpha = 0.1$, the time ($t_\alpha$) for the concentration at the outer surface of the sphere to reach 90% of $c_\infty$ is:

$$t_\alpha \approx \frac{1.5 \times 10^{-8}}{D} \text{ sec.}$$  \hspace{1cm} (2A)

Since the volume of the entire extracellular space is about five times the volume of the half spheres, the time ($t_{ec}$) for this space to become 90% equilibrated is roughly five times $t_\alpha$:

$$t_{ec} \approx 5t_\alpha = \frac{7.5 \times 10^{-8}}{D} \text{ sec.}$$  \hspace{1cm} (3A)

Since $D$ is probably greater than $10^{-6}$, the time required for 90% equilibration of the extracellular space is less than 0.075 sec. In contrast, the osmotic transients that are observed experimentally (Fig. 1) occur over times of the order of minutes. Even if only 2% of the fenestra was available for diffusion of the test solute ($\alpha = 0.02$), the equilibration time would be less than 0.4 sec, still much less than the time constant for the osmotic transient. It is obvious from this calculation that the observed transients cannot be due to gradients across the capillary wall because the extracellular space equilibrates much too rapidly. The transients must be due to a slower process, possibly related to the time for diffusion to the larger extracellular spaces of the villus from the rapidly equilibrating space close to the capillary. The observed weight change could be accounted for by an osmotic removal of water from the cells. This is consistent with the observation that glucose, mannitol, and maltose are equally effective (since they are all relatively impermeable to cell membranes), whereas urea (which has a significant cell membrane permeability) is less effective.

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**PERMEABILITY OF INTESTINAL CAPILLARIES/Granger et al.** 343
Autoregulation of Renal Blood Flow in Spontaneously Hypertensive Rats

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SUMMARY The relationship between renal blood flow (RBF) and arterial pressure was determined in nine anesthetized, spontaneously hypertensive rats (SHR) of the Okamoto-Aoki strain and seven Wistar-Kyoto rats (WKY). The rats had similar body weights and the average age was 14–15 weeks. Measured in vivo with a noncannulating electromagnetic flow transducer, RBF was quite stable in both groups in the pressure range of 165 to 105 mm Hg; renal vascular resistance (RVR) was directly related to pressure. Within this pressure range, RBF was approximately 6.7 ml/min in SHR and 7.3 ml/min in WKY. When perfusion pressure was reduced from 105 to 65 mm Hg, RBF decreased progressively, roughly in proportion to pressure. RBF and RVR did not differ significantly in SHR and WKY at each level of pressure. An even more striking resemblance in the overall pressure-flow relationships was evident after RBF and RVR in each experiment were normalized to their respective values at the pressure of 115 mm Hg. The observations demonstrate that SHR autoregulate RBF in vivo as efficiently as WKY, and that the sensitivity and reactivity of the renal vasculature to acute alterations in perfusion pressure are not modified appreciably in these SHR. The increased RVR in 15-week-old SHR can be explained as an appropriate autoregulatory response of the vasculature to the elevated arterial pressure. Circ Res 44: 344–349, 1979

OUR knowledge of renal hemodynamics in genetically hypertensive rats is limited to only a few reports, which is surprising in view of its potential influence on hormonal mechanisms and excretion of salt and water. Clearly, renal vascular resistance (RVR) is elevated in spontaneously hypertensive rats (SHR) of the Okamoto-Aoki strain (Okamoto and Aoki, 1963), because renal blood flow (RBF) is either in the normal range (Arendshorst and Beierwaltes, 1978; Azar et al., 1976; Baer and Stell-Vick, 1978; Beierwaltes and Arendshorst, 1978) or reduced (DiBona and Rios, 1977a). With respect to the response of RVR to acute changes in arterial pressure, SHR have been reported to be abnormal, since their kidneys fail to autoregulate blood flow (Collis and Vanhoutte, 1977; Tobian et al., 1975). In contrast, our recent clearance data in SHR suggest an appropriate autoregulatory adjustment of RVR in response to a reduction in renal perfusion pressure (Arendshorst and Beierwaltes, 1978).

The present study reports short-term responses of RBF, measured continuously with an electromagnetic flow transducer, to acute, stepwise decrements in perfusion pressure in SHR and WKY. RBF was autoregulated with the same efficiency in SHR and Wistar-Kyoto rats (WKY) when pressure varied between 165 and 105 mm Hg. At each level of perfusion pressure, mean values for RBF and RVR did not differ appreciably between groups.
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