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PERSPECTIVES

Flow-dependent changes in microvascular permeability – an important adaptive phenomenon

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The exchange of solutes between the blood and tissue is increased by vasodilatation of arterioles to increase the number of vessels perfused, a reduction in diffusion distances in the tissue and the maintenance of concentration gradients across the walls of the exchange vessels. Most textbooks describe these as the primary mechanisms by which the metabolic demands of the tissues are met. However, in isolated skeletal and heart muscle preparations, in which all available exchange vessels are open and the surface area for exchange is close to maximum, the diffusion capacity for small solutes (measured as an effective permeability–surface area product, P_S) increases as the blood flow increases. The magnitude of the increase is 2- to 3-fold for solutes the size of glucose and sucrose, but may be larger for smaller solutes. The mechanisms determining these blood flow-dependent increases in diffusion capacity remain poorly understood (Renkin, 1984).

The possibility that there is a general increase in the permeability of the microvessel wall when exposed to increased blood flow has not been generally supported. In fact, Neal & Bates (2002) in this issue of *The Journal of Physiology*, using an elegant modification of the microperfusion method, demonstrate that in individually perfused microvessels there appears to be no relationship between perfusion rate and the hydraulic conductivity. In whole organs, Renkin (1984) has demonstrated that, in the presence of large inhomogeneities in blood flow, the effective P_S of a microvascular bed would increase either as perfusion rate increased, or as heterogeneity was reduced at higher flows. However, he found that, in the heart, flow non-uniformities could account for less than 50 % of the increase in effective P_S of solutes such as glucose.

In this context, the paper by Montermini *et al.* (2002) in this issue of *The Journal of Physiology*, describing the direct effect of perfusion rate on the permeability of the walls of capillaries and venules to a solute similar in size to sucrose, is an important contribution to our understanding of the mechanisms by which solute exchange is regulated. Taken together with other recent papers from Michel's laboratory showing that the permeability coefficients of the walls of individually perfused microvessels to potassium ions increase with increasing rates of perfusion, these investigations provide some of the most convincing data to support the hypothesis that a flow-dependent increase in small solute permeability is a real physiological mechanism contributing to increased solute delivery (Kajimura *et al.* 1998; Kajimura & Michel, 1999*a*,*b*).

Montermini *et al.* (2002) estimate the permeability of a single microvessel to the fluorescent solute sodium fluorescein (MW 376, Stokes–Einstein radius 0.45 nm), while perfusion rate was varied over a wide range, keeping all other conditions constant. They demonstrate that the measured increases and decreases in microvessel permeability are very rapid and occur within seconds of changes in perfusion rate, far more rapidly than the classical receptor-activated inflammatory pathways (e.g. bradykinin, platelet-activating factor, histamine) that increase microvessel permeability over a period of minutes.

An important clue to the nature of this flow-dependent component of permeability is the calculation that it involves the opening of pores close to 1 nm in radius. If charge effects are ignored, pore theory predicts that electrolytes and low molecular weight solutes of MW < 500 and solute radius < 0.5 nm could diffuse through a population of such small pores, but that the same pores would have a high resistance to water flow and the diffusion of larger solutes. This model would explain the observation by Neal & Bates (2002) and others that increased perfusion does not increase hydraulic filtration coefficients. However, as the authors themselves admit, this prediction of a population of small pores needs to be tested experimentally and the ultrastructural basis for them explored.

Studies in cultured endothelial cells and in isolated perfused venules (Yuan, 2000), in which increased permeability to both water and large solutes with increased shear stress in the range reported by Montermini *et al.* (2002) has been demonstrated, indicate changes in pathways larger in radius than the small-pore pathway described by Montermini *et al.* (2002). The mechanisms underlying these different responses to shear under different experimental conditions also require further investigation. It is striking that the same experimental conditions that Montermini *et al.* (2002) found to modulate the permeability response to high flow (inhibition of nitric oxide synthase in rat venular microvessels; noradrenaline-stimulated increases in intracellular cAMP in frog vessels), also attenuate the increase in permeability to water and large solutes after exposure to acute inflammatory mediators. Much work therefore remains to be done to understand the different signalling mechanisms that modulate these different permeability changes.

Together these studies add to our understanding of the mechanisms whereby the endothelial barrier adapts to local tissue requirements. In organs with a very high tissue-to-blood exchange rate (e.g. kidney, gut and some secretory glands), the microvessels have a fenestrated endothelium and consequently a much higher permeability to small solutes and water than those with a continuous endothelium such as mesentery and muscle. In skeletal muscle subjected to a long-term change in metabolic demand (e.g. exercise training), the normal response is growth of new blood vessels (Hudlicka, 1998). In contrast, the mechanism described by Montermini *et al.* (2002) may serve to increase solute delivery on a time scale approaching the moment-by-moment changes in metabolic demand or local blood flow. In skeletal muscle, a direct effect of perfusion rate to increase solute permeability would act in conjunction with an increase in the surface area available for exchange (2- to 3-fold relative to rest) and solute delivery by the blood (1.5- to 2-fold). If perfusion were increased uniformly in vessels over the range investigated by Montermini *et al.* (2002), the increase in permeability would be at least 3-fold for solutes of molecular mass < 400 Da. With heterogeneity of flow, a more subtle action of the mechanism to directly increase permeability with increased flow, acting in individual microvessels, would offset some of the loss of diffusion capacity due to non-uniformities in blood flow. In either situation the phenomenon of flow-dependent permeability becomes an important physiological mechanism by which blood–tissue exchange of small hydrophilic solutes could be regulated.

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