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Microcirculatory dysfunction during intestinal ischemia-reperfusion

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Oxido-reductive stress is a crucial factor of the tissue response during ischemia-reoxygenation injuries. Reperfusion affects primarily the microvasculature in a manner consistent with an acute inflammatory reaction. In this respect, the salient data suggest an important connection between endothelial cell-derived humoral mediators and the perivascular mast cell system. Increased endothelin-1 and decreased nitric oxide formation, mast cell degranulation and leukocyte accumulation coexist in gastrointestinal ischemia-reperfusion syndromes too. Constitutively produced nitric oxide inhibits, while increasingly formed endothelin-1 significantly enhances the degranulation of the intestinal mast cells. The endothelin-A receptor-dependent mast cell degranulation *per se* plays a secondary role in reperfusion-induced structural injury, but contributes significantly to leukocyte recruitment into the reperfused intestinal mucosa. It is conceivable therefore, that the nitric oxide – endothelin-1 – mast cell cycle is involved in the mechanism of ischemia-reperfusion-induced endothelial cell-leukocyte interactions, where mast cells act to amplify the process of leukocyte sequestration. The alteration in the balance between endothelial cell-derived proadhesive vasoconstrictor and antiadhesive vasodilator factors exerts a significant influence on the mucosal integrity, and the antagonism of endothelin-A receptor activation in this setting tips the equilibrium toward tissue salvage.

Keywords: mast cell, endothelin-1, nitric oxide, ischemia-reperfusion, microcirculation

1. Background

The single-cell epithelial layer of the gastrointestinal mucosa is the most important barrier between the internal milieu and the hostile external environment. In certain circulatory pathologies, this “thin red line” is rapidly deranged and the influx of luminal foreign material leads to acute immune stimulation and inflammation. Intestinal

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mucosal injury may be a result of partial or complete occlusion of the arterial perfusion or could be a complication of systemic low-flow states. The latter, non-occlusive mesenteric ischemia, is a highly lethal consequence of circulatory disturbances associated with a period of decreased cardiac output or hypovolemia, and is thought to result mainly from excessive splanchnic vasoconstriction (15, 43, 44). Paradoxically, the introduction of molecular oxygen exacerbates the ischemia-caused tissue injury, the condition steadily worsening as reperfusion progresses (40, 54, 95). The tissue damage is characterized by progressive shortening of the villus height, loss of villus epithelium, particularly at the tips, and the invasion of inflammatory cells, mainly at the level of the crypts (6, 8, 82).

Although no single process has been identified as the critical event in ischemia-reperfusion (I-R) injuries, it is recognized that an imbalance between intracellular oxidants and antioxidants in favor of the former is a contributory factor in reperfusion-induced mucosal destruction (112). In the 1980s, a series of important studies demonstrated that the superoxide, hydrogen peroxide, and hydroxyl radical generated by the one-electron reduction of oxygen play key roles as effectors of the cellular dysfunction and tissue injury that characterizes reperfusion (2, 41, 95, 96, 101). The intestinal mucosa is one of the richest sources of xanthine dehydrogenase (EC 1.1.1.204), the NAD^+-reducing form of which can be converted into the oxygen radical-producing oxidase form (EC 1.1.3.22) following various durations of hypoxia (92, 95, 96). It has also been revealed that oxidative stress not only initiates but also amplifies the inflammatory response, as the superoxide radical is formed in large amounts from several cellular sources, including NADPH oxidase of neutrophil leukocytes (41, 140). This mechanism has been extensively studied for many years and its possible clinical ramifications have been explored in considerable depth. Reductive stress, by contrast, has not been widely recognized, in spite of the fact that reductive stress is probably both common and of clinical importance; indeed, reductive stress plus oxygen rather than oxidative stress may be the most common mechanism leading to the generation of reactive oxygen species (ROS). One possible link between the two is the reduction of catalytically active iron (Fe^{3+}) and its liberation from ferritin. In the presence of iron, the superoxide anion and hydrogen peroxide react via the Haber–Weiss reaction to form hydroxyl radicals (42, 48, 55, 115). In a general way, reductive stress can adversely affect a variety of enzymatic pathways, including the activation of xanthine oxidase, leading to the post-ischemic generation of ROS (12).

2. The microcirculation is the primary site of ischemia-reperfusion injury

Reperfusion affects primarily the microvasculature, and particularly the postcapillary venules, in a manner consistent with an acute inflammatory response. The most convincing data concerning the significance of this reaction come from intravital microscopy studies. This technology allows real-time imaging of the microcirculation and the exact determination of the consequences of I-R. There is now firm evidence that

the leukocyte-endothelial cell interaction is a critical factor in the mediation of mucosal destruction, i.e. it results in increased microvascular permeability, capillary plugging, and the enhanced production of ROS and other proinflammatory mediators from activated and emigrated leukocytes (28, 41, 49, 75). In animal models of transient intestinal ischemia, inhibition of the accumulation of polymorphonuclear (PMN) leukocytes decreases the magnitude of secondary injury, in experiments with knockout animals, the absence of adhesion molecules significantly reduced the extent of tissue damage (49, 51, 52). This paper reviews the relevant literature, highlighting the microcirculatory consequences of reperfusion injury, and discusses the role of auxiliary mechanisms in leukocyte adhesion. In our view, the cellular and humoral microvascular events are closely interconnected, involving mast cell (MC) degranulation at the site of injury.

3. Leukocytes

Investigations utilizing intravital microscopy have demonstrated that the recruitment of inflammatory cells into the perivascular tissue involves a complex cascade mechanism. The adhesion process consists of several steps, beginning with the rolling of the leukocyte on the endothelial surface of the postcapillary venules until it has slowed down to such a degree that it sticks to the endothelium. At this point, the leukocyte is sequestered from the main vascular flow and firm adherence to the endothelial cells may follow. Subsequently, the leukocyte passes an intercellular junction between the endothelial cells and reaches the abluminal side.

Three families of leukocyte-endothelial adhesion molecules have been identified: the selectins, the immunoglobulin gene superfamily, and the integrins. The selectin family comprises three proteins, designated by the prefixes L (leukocyte), P (platelet), and E (endothelial). It is a class of cell adhesion molecules which mediate leukocyte rolling on the endothelium. P-selectin (CD62P), which is stored in the Weibel–Palade bodies of the endothelial cells, is rapidly mobilized to the plasma membrane in response to proinflammatory mediators such as thrombin or histamine (5, 79). L-selectin (CD62L), is expressed on most types of leukocytes and is shed from the cell membrane by proteolytic cleavage after cellular activation. E-selectin (CD62E) which is not expressed on the endothelial cell membrane under basal conditions, is synthesized after stimulation by inflammatory mediators such as tumor necrosis factor-α (TNF-α) and endotoxin (27). After the leukocyte has been arrested, integrins are activated by chemokines, chemoattractants and cytokines. During the transmigration process, vascular dysfunction may occur due to the inappropriate release of oxidants, proteases and other potent mediators of the activated leukocytes.

4. Endothelial cell-derived vasoactive mediators in microvascular homeostasis and pathologies

4.1. Nitric oxide

Leukocyte reactions are linked by close ties to the actual state of the endothelial lining. Normal microvascular perfusion requires a stable environment; the cells must be maintained in a quiescent state, and intravascular cell adhesion must be regulated. Many of these homeostatic functions are served by the vascular endothelium, which acts as a local integrator of paracrine and autocrine signals. In this respect, one major factor responsible for vascular homeostasis is nitric oxide (NO), synthetized by the constitutively expressed endothelial enzyme NO synthase (eNOS or NOS 1) which oxidizes L-arginine, yielding NO and L-citrulline as products. The bioactivity of NO is particularly sensitive to oxidative stress as superoxide combines readily with NO in a diffusion-limited reaction ($k=1.9\times10^{10}\ M^{-1}\ s^{-1}$) to form peroxynitrite anion and its protonated form, peroxynitrous acid (63). Unlike other intercellular messengers, NO does not bind to receptors, and its effects are transient and local, under stress conditions therefore, the critical balance between vasoconstrictors and vasodilators may be disrupted very quickly. Indeed, it has been suggested that an early endothelial dysfunction is probably a joint result of decreased NO production and the generation of ROS (46, 77, 139). As endogenous NO generation may be reduced by 90% in postischemic tissues, the loss of NO acts as the trigger mechanism (endothelial trigger), and this event becomes aggravated by the involvement of PMNs (i.e. the leukocyte amplification phase). In this sequence of events, the key step towards acute intestinal inflammation could be an abrupt decrease in the local production of NO (77). The role of NO in I-R-induced damage was substantiated by the findings that the nonspecific inhibition of NO biosynthesis mimics the microvascular alterations (i.e. leukocyte adhesion, and endothelial barrier disruption) observed after I-R (72–74), even in the absence of additional inflammatory stimulation (20, 67), and that this effect was reversed by L-arginine and other exogenous sources of NO (1, 68, 97). Similar observations have been made in several tissues, suggesting that this is a universal phenomenon throughout the microcirculation, and this established the role of NO as a general modulator of the adhesive interactions between cells that may participate in the acute inflammatory response (73, 80, 99).

However, excess NO can be detrimental to the endothelial cells (94). In certain pathological conditions, most notably sepsis, pro-inflammatory cytokines stimulate the expression of an inducible isoform of NOS (iNOS or NOS 2), producing larger amounts of NO that is associated with potent cytotoxic effects. Although these findings have been confirmed in several tissues, including the intestine (3, 18, 24, 45, 84, 107, 116), it is important to note that iNOS can also be rapidly expressed without major inflammatory stimuli, as demonstrated in the peroxisomes of rat hepatocytes in hemorrhagic shock and reperfusion (19).

4.2. The endothelins

Locally formed constrictor vasomodulators likewise play important roles in the physiologic maintenance of the microcirculation (129). The endothelins (ETs) embrace a family of 21-amino acid peptides produced by the endothelial cells (138). Three active isoforms (ET-1, ET-2 and ET-3), and two specific receptors for ET, the ET-A receptor and the ET-B receptor, have been identified and cloned. The ET-A receptor mediates vasoconstriction and has a high affinity for ET-1, whereas the ET-B receptor mediates vasoconstriction (ET-B_2) and vasodilation (ET-B_1 subtype), and has equal affinity for ET-1 and ET-3 (102). These receptors, originally identified in vascular tissues, have also been found in many nonvascular tissues, including the heart, kidney, brain and liver. ET-1 is one of the most powerful vasoconstrictors known to date, and it has been suggested that it may participate in the regulation of the smooth muscle tone in many systems in both physiologic and pathophysiologic settings (71, 119). ET-1 is produced in the splanchnic organs, and both ET-A and ET-B receptors are present in the gastrointestinal circulatory system (65, 120). Similarly to NO, ET-1 may be involved in the hemodynamic events leading to structural cell injury following I-R. Although the level of circulating endogenous ET-1 is very low and exogenous ET-1 is cleared rapidly by the lung and kidneys and by binding to receptors disseminated in the circulation (110, 113), in pathologic conditions the concentration of ET-1 in the local environment may be very high. It has been shown that ET-1 secretion increases several-fold in endothelial and epithelial cells exposed to acute and chronic hypoxia (21, 58, 66, 91, 105, 125) and a prolonged, 2–5-fold increase in endogenous ET levels has been reported after experimental ischemia and hemorrhage (14, 85). Since ET-1 is secreted predominantly in an abluminal direction, toward the underlying smooth muscle cells (102), even small changes in endogenous ET-1 plasma levels may elicit significant involvement of the peptide in local vascular reactions. In general, the levels of immunoreactive ET-1 are elevated in body fluids (i.e. plasma, pericardial fluid and lymph) during local and systemic low-flow states (14, 17, 53, 89, 124, 126, 127) and this suggests that it may mediate vasoconstriction of the regional vascular beds during these conditions (85, 88, 100, 132). *In vivo* and *ex vivo* studies have shown that the number of ET-A receptor binding sites is increased and the responsiveness to the vasoconstrictor effects of ET-1 is enhanced after ischemia (123, 135). The reason for this could be that the activation of glycolysis and hypoxia-inducible factor-1α are both involved in an increased expression of the ET-1 gene in microvascular endothelial cells (57, 87). *In vivo*, the initial ET-1 gene upregulation occurs during ischemia, but this condition is sustained during reperfusion (130).

There is now ample evidence that ET-1 plays a crucial role in I-R-induced damage of the intestinal microcirculation. Selective, intra-arterial infusion of ET-1 into the gastric or small intestinal circulation induces extensive ulceration and hemorrhagic damage of the mucosa and mimics the consequences of low-flow-induced ischemia (10, 22, 83). When the microvascular actions of ET-1 were investigated sequentially in all anatomical layers of the small intestine, we were able to show that exogenous ET-1 evoked a marked decrease of the subserosal lymphatic capillary density (LCD) and

functional capillary density (FCD) of the circular and longitudinal muscle and mucosa (10, 83). The decreases in LCD and FCD could be only prevented by ET-A receptor antagonists, suggesting that these effects of ET-1 are primarily mediated by the ET-A receptor subtype. Higher doses of intra-arterially administered ET-1 evoked a profound vasoconstrictor effect, with complete cessation of the local intestinal microcirculation. In a canine model of intestinal autotransplantation, reperfusion progressively decreased the mesenteric blood flow and increased the mesenteric vascular resistance, and the reduction in villus FCD suggested that significant vasoconstriction developed at the level of the precapillary sphincters (133, 134). The antagonism of the ET-A receptors attenuated reperfusion-induced local circulatory failure and subsequent structural injury of the intestinal graft.

There is a growing body of evidence that, in addition to the independent role of ET-1 as a dominant vasoconstrictor, the peptide may also influence the functions of other cell types of the circulatory system. In particular, a number of data suggest that ET-1 contributes to the biological activities of the PMN leukocytes. ET-1 has been reported to induce leukocyte rolling and adherence in the mesentery and submucosal postcapillary and collecting venules of the small intestine through a predominantly ET-A receptor-mediated mechanism in the unmanipulated animal (10, 133). Interestingly, the contractile response to ET-1 in the coronary arteries is also augmented in the presence of PMN leukocytes; this effect was abolished by either an NO donor or a superoxide radical scavenger (103, 104). The peptide increases vascular permeability (29), an event which is also dependent on the presence of leukocytes (47). The exact molecular mechanism of the proadhesive effect of ET-1 is unclear, but other investigators have demonstrated that antibodies against P-selectin reduce the ET-induced leukocyte rolling in the rat (108).

5. Mastocytes – cellular amplifiers of leukocyte responses

One of the most important events in ischemic/low-flow conditions is the production of activators for secondary circulatory responses, The MCs of the gastrointestinal tract are a unique cellular source of both preformed and *de novo* synthesized mediators; they are located mainly around postcapillary venules, from which they can influence local tissue reactions. MCs of the lamina propria of mucosal surfaces (MMCs) and connective tissue MCs (CTMCs) in skin and skeletal muscle are morphologically and functionally different, with distinctive fixation and histochemical properties (25, 26). The heterogeneous expression of granule serine endopeptidases in MC subpopulations was initially described in rodents and later in several other species. It was shown that rat MMCs expressed the soluble beta-chymase RMCP-II, but not the insoluble RMCP-I. Conversely, CTMCs contain RMCP-I and lack RMCP-II (36). The release of RMCP-II from MMC granules in the gastrointestinal tract was first confirmed experimentally in

rats infected with enteric nematodes (86). Immobilization or environmentally induced stress also causes pathological changes in the rat intestinal mucosa, with degranulated intestinal MMCs and increased colonic mucosal levels of RMCP-II (16, 131).

When activated by IgE-dependent or other mechanisms, MCs can produce a diverse array of mediators (e.g. histamine, cytokines, neuropeptides), and a number of experimental data have implicated the role of MC mediation in reperfusion injuries (4, 38, 76, 90). Intestinal I-R also triggers MC degranulation and leads to the discharge of a variety of MC-derived inflammatory compounds into the local mesenteric circulation (7, 9, 30, 62). Ischemia induces a significant fall in the number of MMCs in the mucosal villi; and both the mucosal and plasma histamine and RMCP-II concentrations increase in proportion to the duration of ischemia. We established that MC-induced reactions contribute to the mucosal permeability alterations and postischemic flow response during reperfusion (62, 117).

These results lead us to conclude that MMCs are very sensitive to hypoxia, with a majority of the MCs in the ileal villi already involved in the response to ischemia after a short period of arterial occlusion (9). These data have suggested that MCs may be involved in the initiation and/or perpetuation of intestinal inflammatory reactions, acting as sentinel cells, providing a chemotactic signal for the mobile PMN leukocytes to eliminate the insult. In 1978, the group of Kitamura has reported that mice with naturally occurring mutations at the Dominant Spotting (W) locus on chromosome 5 or the Steel (Sl) locus on chromosome 10 have a profound deficiency in the numbers of tissue MCs (64). Using this animal strain to examine the MC function, Kanwar et al. have obtained direct evidence that the MCs are critical in leukocyte infiltration and mucosal dysfunction during I-R injury to the small bowel (59–61). A subsequent study demonstrated that MC-derived TNF-α was an important mediator involved in the recruitment of PMNs into sites of IgE-dependent gastric inflammation (98, 128). Additional studies with lymphocyte function-associated antigen-1-deficient mice indicated that administration of a nonspecific MC degranulator compound provoked a dose-dependent leukocyte infiltration and the secretion of cytokine-induced PMN chemoattractant in the skin of wild-type animals, whereas no proinflammatory effect was observed in knock-out mice (109).

These experiments established that the effects of MC mediators on the adjacent vascular and connective tissue are crucial to the recruitment of cellular effectors to the site of mucosal injury (38, 61). In laminar flow chamber studies, perfusion of leukocytes over histamine-stimulated endothelial monolayers induced PMN rolling that was entirely dependent on P-selectin (56). Similarly, intravital microscopy has revealed that histamine induces rapid leukocyte rolling *in vivo* (70), and MCs can induce P-selectin-dependent leukocyte adhesion, as administration of an anti-P-selectin antibody significantly reduced both primary and secondary leukocyte-endothelial interactions in response to MC activation (32).

6. The "nitric oxide – endothelin-1 – mast cell cycle"

Many immune cells, including leukocytes and MCs, are capable of NO production under both physiologic and pathophysiologic conditions (3, 37, 50, 84, 121). The connection between endothelial cell-derived NO and the activation of intestinal MCs has raised the possibility that endogenous NO acts as a homeostatic depressor of MC reactivity that otherwise leads to leukocyte recruitment. Indeed, exogenous NO suppresses histamine release from stimulated MCs *in vitro* (106), and similarly the inhibition of NO synthesis leads to MC degranulation (69, 74). Further, the lack of NO synthesis results in MC-dependent leukocyte adhesion and a parallel rise in microvascular permeability, and NO supplementation may decrease the intestinal permeability secondary to the inhibition of MC activation (69). By means of intravital microscopy Kanwar et al. observed that MCs contribute to the leukocyte recruitment (rolling, adhesion and emigration) to the postischemic tissues *in vivo* (59, 60), and MC stabilization (similarly to NO administration) decreases I-R-induced endothelial cell-leukocyte interactions (35). Thus, it has been proposed that NO functions directly to prevent histamine release from the MCs and thereby it inhibits the recruitment of leukocytes (33).

On the other hand, intestinal MCs have both ET-A and ET-B receptors on their membrane surface (78) and this suggests possible crosstalk between the endothelial cell-derived ET-1 and the MC system. It has been demonstrated that ET-1 may liberate histamine and leukotriene C4 from bone marrow-derived MCs through the activation of ET-A receptors (136, 137). Shigematsu et al. have demonstrated that the mucosal concentrations of ET-1 undergo a significant increase in parallel with the increases in permeability, histamine release and serum RMCP-II concentration in rats with ovalbumin-induced intestinal anaphylaxis (111). Our *in vivo* studies with increasing doses of exogenous ET-1 have shown that the ET-1-induced mucosal morphological changes are correlated to the degree of MC degranulation (13, 118). In these experiments, we used ET-A receptor and ET-B receptor-selective antagonists to investigate the roles of these receptor subtypes in mediating ET-1-induced intestinal MC activation, and provided evidence that pharmacological inhibition of the ET-A receptor reduced MC degranulation and significantly decreased ET-1-induced mucosal injury.

It is conceivable that the NO–MC axis is involved in the mechanism of endothelial cell-leukocyte interactions, the MCs acting as an amplifier of the process of leukocyte sequestration. Accordingly, the interaction between ET-1 and MCs suggests that a shift in the equilibrium between endothelial cell-derived vasoconstrictor and vasodilator factors significantly influences the mucosal MC responses, and this mechanism could play important roles in ischemia-induced endothelial cell-leukocyte interactions.

7. Unanswered questions

Although there is now a general consensus regarding the separate roles of NO, ET-1 and MCs in stimulating leukocyte accumulation during I-R, important questions remain to be resolved. Since MCs have the possibility to act in homeostatic and pathological roles, the precise function of these cellular components in the time scale of I-R-induced tissue changes is difficult to delineate. The microvascular response to reperfusion can consist of a rapid exacerbation of injury after a severe ischemic episode or, alternatively, a more slowly developing adaptation that occurs after a less severe insult. In this case, the alterations in vascular status are partly a result of the upregulation of stress-induced vascular mediators such as iNOS-derived NO, and the outcome of the MC reaction may be different. Moreover, MCs or MC-derived mediators may influence tissue remodeling and repair in the mucosa (31, 34). The number of MCs in the rapidly growing tissues rises and histamine derived from MC or non-MC sources plays a significant role in tissue regeneration and in angiogenesis of the inflammatory granulation tissue (39, 114, 122). Additionally, in an experimental model of bacterial peritonitis, MC-deficient mice exhibited a significantly greater mortality than did normal mice (23, 81). Histidine decarboxylase (HDC) is the enzyme responsible for histamine synthesis in mammals, and is an important factor of mucosal repair (11, 31). Studies with a recently developed HDC-deficient mice strain could help to shed light on the role of MC reactions in this respect (93).

8. Conclusions

Increased ET-1 and decreased NO formation, leukocyte accumulation and MC degranulation are phenomena that coexist in gastrointestinal I-R injury. It is proposed that the alteration in the balance between endothelial cell-derived proadhesive vasoconstrictor and antiadhesive vasodilator factors has a significant influence on the MC responses, and the antagonism of vasoconstrictor ET-A receptor activation tips the equilibrium toward tissue salvage by decreasing MC degranulation and subsequent leukocyte accumulation (Fig. 1).

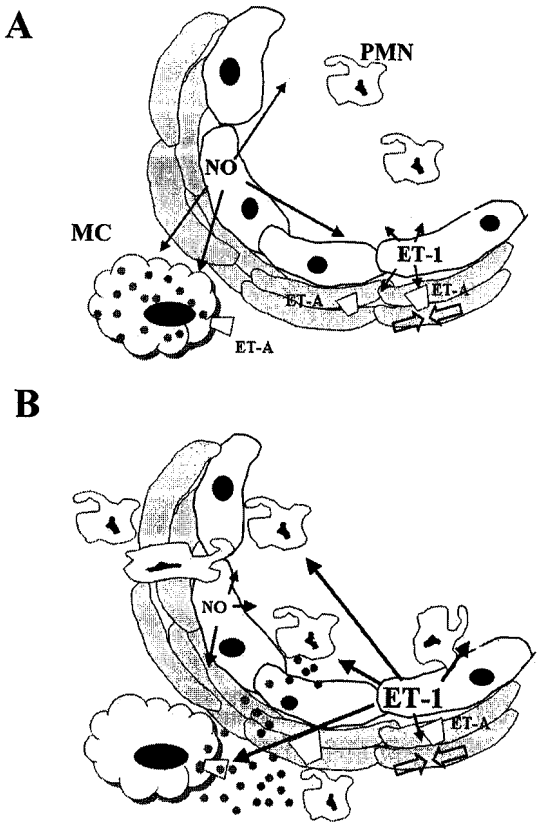

Fig. 1. Schemes simulating normal (**A**) and compromised (**B**) microcirculatory flow conditions. Nitric oxide (NO) is antiadhesive to the leukocytes (PMNs) and prevents mediator release from the mast cell (MC). **B**: Ischemia-reperfusion injury is accompanied by decreased NO formation, increased endothelin-1 (ET-1) release, leukocyte adhesion and transmigration. Endothelin-A receptor (ET-A) activation leads to mast cell degranulation, and mast cell-derived mediators amplify leukocyte recruitment into the perivascular tissue

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