Published in final edited form as:

Crit Care Med. 2013 September ; 41(9): . doi:10.1097/CCM.0b013e318283cc70.

Mast Cells and Intestinal Injury: A Novel Link Between Hypoxia and Inflammation

Almut Grenz, MD, PhD and Holger K. Eltzschig, MD, PhD

Department of Anesthesiology, University of Colorado School of Medicine, Aurora, CO

Keywords

A2B; adenosine; hypoxia; hypoxia-inducible factor; inflammation

Hypoxia and inflammation share an interdependent relationship (1, 2). On the one hand, inflammatory diseases such as intestinal inflammation, acute lung injury, or infections with pathogens are characterized by alterations in metabolic supply and demand ratio, resulting in an imbalance for oxygen availability and concomitant tissue hypoxia (hypoxia in inflammatory conditions, Fig. 1, right). On the other hand, organ injury primarily caused by hypoxia—such as ischemia and reperfusion injury (3)—will subsequently lead to inflammatory changes that significantly have impact on organ function and disease outcomes (inflammation in hypoxic conditions, Fig. 1, left). Indeed, research over the past decade has revealed that the interdependence of hypoxia and inflammation plays a functional role in many diseases, including critical illness. It is important to point out that hypoxia is not simply a bystander in these pathological conditions but has a profound impact on the microenvironment, for example, by causing changes in gene expression through hypoxia-dependent transcriptional pathways (1). Indeed, there are many examples when hypoxia signaling functions as an endogenous feedback mechanism to attenuate inflammatory hypoxia (3–6).

In this issue of *Critical Care Medicine*, Karhausen et al (7) take a new look at intestinal injury and concomitant hypoxia in the setting of deep hypothermic circulatory arrest (DHCA). DHCA is a surgical technique that is used during major cardiovascular surgery of the aortic arch and during some complex neurosurgical repairs of giant aneurisms of the brain. It includes cooling down body temperature by utilizing cardiopulmonary bypass. Once a temperature of approximately 12°C to 18°C is achieved, blood flow is interrupted to allow the surgical procedure. In addition to neuronal damage (8) and neurologic injury, intraoperative intestinal injury leading to postoperative sepsis and multiple organ failure is among the main concerns for the postoperative recovery and critical care treatment of patients requiring DHCA.

In the present studies, Karhausen et al utilized a technically challenging in vivo model of rat DHCA (9) and performed molecular and functional studies to define the mechanism resulting in intestinal injury. One of the key findings of their study is the observation that DHCA shares many similarities with intestinal ischemia and reperfusion injury. Indeed, studies utilizing nitroimidazole compounds to stain for the occurrence of tissue hypoxia in vivo revealed profound tissue hypoxia localized to the ileal and colonic mucosa, indicating that alterations in oxygen supply and demand during DHCA lead to mucosal hypoxia, and concomitant intestinal barrier dysfunction. These findings were specific for the intestine, as the kidneys and the lungs were spared from ischemia and reperfusion injury. Most likely, the specificity for the occurrence of tissue hypoxia in the intestinal mucosa is related to the fact that the intestinal mucosa is already hypoxic at baseline conditions. Indeed, physiologic

hypoxia of the intestinal mucosa is a reflection of an extremely steep oxygen gradient across the epithelial monolayer that resembles the functional barrier between the anaerobic intestinal lumen and the well-perfused and highly oxygenated submucosal tissue (4). This high degree of physiologic hypoxia puts the intestinal epithelial monolayer into a position that already small additional alterations in metabolic supply and demand—for example caused by inflammation or attenuated oxygen supply during DHCA—will result in profound mucosal hypoxia, resulting in disease pathology similar to intestinal ischemia and reperfusion injury.

Based on the fact that intestinal mast cells have been previously implicated in intestinal ischemia and reperfusion injury, the authors went on to study their functional contribution to intestinal injury during DHCA. Elegant pharmacologic interventions to block intestinal mast-cell activation clearly demonstrate their functional role in DHCA-associated intestinal injury and implicate mast-cell stabilization as treatment in patients requiring DHCA surgery to prevent intestinal injury.

The present findings of DHCA-associated intestinal hypoxia are consistent with previous studies from Karhausen et al on the role of hypoxia signaling during intestinal inflammation (5). Indeed, intestinal inflammation—such as that which occurs during inflammatory bowel disease—is associated with shifts in the metabolic demand and supply ratio for oxygen resulting in profound tissue hypoxia of the inflamed intestinal mucosa. Moreover, intestinal hypoxia is associated with the stabilization of the transcription factor hypoxia-inducible factor (HIF)—the key transcription factor for hypoxia-elicited adaptive responses (2)—and concomitant induction of HIF target genes. Functional studies utilizing conditional knockout mice with deletion of HIF in intestinal epithelial cells or transgenic mice with HIF overexpression indicate that intestinal hypoxia and HIF stabilization function to dampen intestinal inflammation and to protect the gut barrier function (5). Moreover, pharmacologic studies with HIF activators demonstrate robust protection from intestinal injury and inflammation in models of inflammatory bowel disease (6). Several known HIF target genes—such as different control points for extracellular adenosine generation and signaling—have been implicated in protecting the intestine during hypoxia-induced inflammation (10) and inflammatory bowel disease (11, 12), or during intestinal ischemia and reperfusion injury (13, 14). As such, it will be an important future challenge to define the functional role of intestinal hypoxia during DHCA. Based on the present findings by Karhausen et al showing hypoxia in intestinal sections of rats exposed to DHCA (7), one would predict that DHCA is associated with stabilization of HIF and induction of HIF target genes. In line with the above studies from Karhausen et al and other investigators showing a protective role for HIF in intestinal injury, it is intriguing to speculate about the functional role of HIF in stabilizing intestinal mast cells during DHCA-associated intestinal injury. Such studies would be very timely, as pharmacologic HIF activators have been safely used in patients for the treatment of renal anemia (15), and could be considered a novel means for gut protection in a clinical setting—for example, to prevent intestinal injury in patients undergoing cardiac surgery with DHCA.

Acknowledgments

Dr. Grenz received grant support from the American Heart Association. Dr. Eltzschig received grant support from the National Heart, Lung and Blood Institute (R01-HL0921 and R01-HL098294); NIDDK (R01-DK083385); and the Crohn's and Colitis Foundation of America (CCFA).

References

1. Taylor CT. Interdependent roles for hypoxia inducible factor and nuclear factor-kappaB in hypoxic inflammation. *J Physiol (Lond)*. 2008; 586(Pt 17):4055–4059. [PubMed: 18599532]

2. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med*. 2011; 364:656–665. [PubMed: 21323543]
3. Eltzschig HK, Eckle T. Ischemia and reperfusion—from mechanism to translation. *Nat Med*. 2011; 17:1391–1401. [PubMed: 22064429]
4. Eltzschig HK, Sitkovsky MV, Robson SC. Purinergic signaling during inflammation. *N Engl J Med*. 2012; 367:2322–2333. [PubMed: 23234515]
5. Karhausen J, Furuta GT, Tomaszewski JE, et al. Epithelial hypoxia-inducible factor-1 is protective in murine experimental colitis. *J Clin Invest*. 2004; 114:1098–1106. [PubMed: 15489957]
6. Colgan SP, Eltzschig HK. Adenosine and hypoxia-inducible factor signaling in intestinal injury and recovery. *Annu Rev Physiol*. 2012; 74:153–175. [PubMed: 21942704]
7. Karhausen J, Qing M, Gibson A, et al. Intestinal Mast Cells Mediate Gut Injury and Systemic Inflammation in a Rat Model of Deep Hypothermic Circulatory Arrest. *Crit Care Med*. 2013; 41:e200–e210. [PubMed: 23478660]
8. Yang W, Ma Q, Mackensen GB, et al. Deep hypothermia markedly activates the small ubiquitin-like modifier conjugation pathway; Implications for the fate of cells exposed to transient deep hypothermic cardiopulmonary bypass. *J Cereb Blood Flow Metab*. 2009; 29:886–890. [PubMed: 19240742]
9. Jungwirth B, Mackensen GB, Blobner M, et al. Neurologic outcome after cardiopulmonary bypass with deep hypothermic circulatory arrest in rats: Description of a new model. *J Thorac Cardiovasc Surg*. 2006; 131:805–812. [PubMed: 16580438]
10. Rosenberger P, Schwab JM, Mirakaj V, et al. Hypoxia-inducible factor-dependent induction of netrin-1 dampens inflammation caused by hypoxia. *Nat Immunol*. 2009; 10:195–202. [PubMed: 19122655]
11. Aherne CM, Collins CB, Masterson JC, et al. Neuronal guidance molecule netrin-1 attenuates inflammatory cell trafficking during acute experimental colitis. *Gut*. 2012; 61:695–705. [PubMed: 21813473]
12. Frick JS, MacManus CF, Scully M, et al. Contribution of adenosine A2B receptors to inflammatory parameters of experimental colitis. *J Immunol*. 2009; 182:4957–4964. [PubMed: 19342675]
13. Hart ML, Grenz A, Gorzolla IC, et al. Hypoxia-inducible factor-1 α -dependent protection from intestinal ischemia/reperfusion injury involves ecto-5'-nucleotidase (CD73) and the A2B adenosine receptor. *J Immunol*. 2011; 186:4367–4374. [PubMed: 21357264]
14. Hart ML, Jacobi B, Schittenhelm J, et al. Cutting Edge: A2B Adenosine receptor signaling provides potent protection during intestinal ischemia/ reperfusion injury. *J Immunol*. 2009; 182:3965–3968. [PubMed: 19299692]
15. Bernhardt WM, Wiesener MS, Scigalla P, et al. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *J Am Soc Nephrol*. 2010; 21:2151–2156. [PubMed: 21115615]

Figure 1.

Links between hypoxia and inflammation. Shown is an overview of clinical conditions characterized primarily by tissue hypoxia that causes inflammatory changes (*left*) and inflammatory diseases leading to tissue hypoxia (*right*). Reproduced with permission from Eltzschig and Carmeliet (2).