Luminal Administration of Biliverdin Ameliorates Ischemia/Reperfusion Injury Following Intestinal Transplant in Rats

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ABSTRACT

Background: Intestinal grafts are susceptible to ischemia/reperfusion (IR) injury, resulting in the loss of mucosal barrier function and graft failure. Biliverdin (BV) is known to exert a variety of cytoprotective functions against oxidative tissue injury. Because the mucosal layer is the primary site of IR injury, mucosa-targeting strategies by luminal delivery of reagents might be beneficial. We tested whether intraluminal administration of BV as an adjuvant to standard preservation solutions protected against IR injury.

Methods: Orthotopic syngeneic intestinal transplants were performed on Lewis rats after 6 hours of cold preservation. Saline containing BV (10 μM) or without BV was introduced into the lumen of the intestinal grafts immediately prior to cold preservation.

Results: Damage to the intestinal mucosa caused by IR injury resulted in severe morphological changes including blunting of the villi and erosion and led to significant loss of gut barrier function 3 hours after reperfusion. These changes to the mucosa were notably ameliorated by intraluminal administration of BV. BV also effectively inhibited upregulation of mRNAs for interleukin-6, inducible nitric oxide synthase, and C-C motif chemokine 2. Additionally, BV treatment prevented the loss of expression of claudin-1, a transmembrane, tight-junction barrier protein. The 14-day survival of recipients of BV-treated grafts was significantly improved as compared with the recipients of saline-treated control grafts (83.3% vs. 38.9%, p=0.03).

Conclusion: This study demonstrated that luminally delivered BV provides beneficial effects during the transplant of rat small intestinal grafts and could be an attractive therapeutic option in organ transplantation.