Kinin B1 receptor plays a pivotal role on pathophysiology of sepsis

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Abstract

The sepsis is a dysregulated response of the body to an infection. The failure of neutrophil migration to the infectious focus is observed in sepsis induced in experimental models. This failure of neutrophil migration is determinant for the worse prognosis of the animals. The kallikrein-kinins system has already been implicated in the pathophysiology of sepsis, especially in the hemodynamic scenario since its receptors participate in the hypotension that occurs in sepsis. Therefore, this work aimed to investigate the role of B1 and B2 receptors for kinin in the development of pathophysiological responses involved in polymicrobial sepsis in mice. In an experimental model of sepsis, we demonstrated that B2 receptor does not modulate neutrophil migration to the peritoneum. The B1 receptor plays an important role in the pathophysiology of sepsis by CLP demonstrated by the absence of deficiency of neutrophil migration to the peritoneum in B1R KO animals with infection control, signs of lower systemic inflammation and lung damage and, finally, presented lower lethality. The protected phenotype of B1R KO animals is also repeated in WT animals treated with B1 receptor antagonist. B1R KO animals, 3 hours after CLP, showed a greater amount of neutrophils expressing CXCR2 in the circulation compared to WT animals, and this phenomenon partially corroborates the reduced neutrophil recruitment failure in this context. The deletion of B1 may be related to activation of the PI3Kγ enzyme in the cytosol of circulating neutrophils and this enzyme may modulate neutrophil recruitment in sepsis. We also demonstrate that activation of B1 receptor impairs the chemotaxis of LPS-activated human neutrophils and this phenomenon appears to involve the CXCR2 receptor. We conclude that the B2 receptor has no dominant function in CLP-induced sepsis but the B1 receptor participates in the pathophysiology of polymicrobial sepsis through the failure of neutrophil migration to the peritoneum. Thus, B1 receptor deficient animals better control infection and systemic inflammation and the use of B1 antagonist drug becomes a possible therapeutic target for sepsis.

Keywords: Sepsis, B1 receptors, neutrophils, chemotaxis