Dissection of the Modulatory Role of Nitric Oxide on Neutrophil Migration Reveals Soluble Guanylate Cyclase as a Therapeutical Target in Sepsis

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Introduction and objectives: During severe sepsis neutrophils present a state of unresponsiveness to chemotactic stimuli. This process correlates with a poor prognosis and may collaborate to worsen the clinical outcome in sepsis by precluding an efficient bacterial clearance. Experimental data have implicated nitric oxide (NO) in these phenomena. However NO synthesis inhibition in sepsis leaded to increased mortality despite the restored neutrophil migratory function. This could be at least in part due to an inhibition of the microbicidal role played by NO, suggesting that a better understanding of the roles of NO in sepsis is required. In the present study we investigated the molecular mechanisms triggered by NO that lead to decreased neutrophil chemotactic responses in sepsis. Results: Our data pointed to the involvement of the NO/guanylate cyclase (GC)/protein kinase G (PKG) signaling pathway in this process. Further we found that the NO-GC-PKG signaling modulate CXCR2 internalization probably by upregulating GRK-2 expression. Based on these findings we reasoned that GC targeting could restore neutrophil migration without impairing NO microbicidal activity. In fact, we found that pharmacological inhibition of GC activity in an experimental model of sepsis increased survival, restored neutrophil migration, and increased bacterial clearance. Conclusion: Thus our results suggest a mechanism by which NO interferes with neutrophil chemotaxis and point to GC as a promising therapeutical target in sepsis.

Key words: Neutrophil Migration, Sepsis, Nitric Oxide, Guanylate Cyclase
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