Activated protein C improves LPS-induced cardiovascular dysfunction by decreasing tissular inflammation and oxidative stress.

Titre	Activated protein C improves LPS-induced cardiovascular dysfunction by decreasing tissular inflammation and oxidative stress.
Type de publication	Article de revue
Auteur	Sennoun, Nacira [1], Ferhat, Meziani [2], Dessebe, Olivier [3], Cattan, Valérie [4], Solène, C. [5], Montemont, Chantal [6], Gibot, Sebastien [7], Asfar, Pierre [8], Regnault, Véronique [9], Lecompte, Thomas [10], Andriantsitohaina, Ramaroson [11], Lacolley, Patrick [12], Levy, Bruno [13]
Editeur	Lippincott, Williams & Wilkins
Type	Article scientifique dans une revue à comité de lecture
Année	2009
Langue	Anglais
Date	2009/11
Pagination	246 - 255
Volume	37
Titre de la revue	Critical care medicine
ISSN	0090-3493
Mots-clés	bioinformatics [14], Biological [15], biomedical [16], citation [17], Europe [18], health [19], journal [20], life [21], medical [22], UK [23]

Résumé en anglais	BACKGROUND:: Recombinant human activated Protein C (APC) is used as an adjunctive therapeutic treatment in septic shock. APC seemingly acts on coagulation-inflammation interaction but also by decreasing proinflammatory gene activity, thus inhibiting subsequent production of proinflammatory cytokines, NO and NO-induced mediators, reactive oxygen species production and leukocyte-endothelium interaction. The hemodynamic effects of APC on arterial pressure and cardiac function are now well established in animal models. However, the specific effects of APC on heart and vessels have never been studied. OBJECTIVES:: To investigate the potential protective properties of therapeutic ranges of APC on a rat endotoxic shock model in terms of anti-inflammatory and cytoprotective pathways. DESIGN:: Laboratory investigation. SETTING:: University medical center research laboratory. INTERVENTIONS:: Rats were exposed to lipopolysaccharide (LPS) (10 mg/Kg iv.). Endotoxic shock was treated with infusion of saline with or without APC (33 mug/kg/h) during 4 hrs. Hemodynamic parameters were continuously assessed and measurements of muscle oxygen partial pressures, NO and superoxide anion (O2) by spin trapping, of NF-kappaB, metalloproteinase-9 (MMP-9) and inducible NO synthase (iNOS) by Western blotting, as well as leukocyte infiltration and MMP-9 activity were performed at both the heart and aorta level (tissue). MAIN RESULTS:: APC partially prevented the reduction of blood pressure induced by LPS and improved both vascular hyporeactivity and myocardial performance. This was associated with a decreased up-regulation of NF-kappaB, iNOS and MMP-9. LPS-induced tissue increases in NO and O2 production were decreased by APC. Furthermore, APC decreased tissue leukocyte infiltration/activation as assessed by a decrease in myeloperoxydase and matrix metalloproteinase 9 activity. CONCLUSIONS:: These data suggest that APC improves cardiovascular function i) by modulating the endotoxin induced-proinflammatory/prooxydant state, ii) by decreasing endothelial/leukocyte interaction and iii) by favoring stabilization of the extracellular matrix.
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