Recombinant human activated protein C improves endotoxemia-induced endothelial dysfunction: a blood-free model in isolated mouse arteries

Titre	Recombinant human activated protein C improves endotoxemia-induced endothelial dysfunction: a blood-free model in isolated mouse arteries
Type de publication	Article de revue
Auteur	Sennoun, Nacira [1], Baron-Menguy, Céline [2], Burban, Mélanie [3], Lecompte, Thomas [4], Andriantsitohaina, Ramaroson [5], Henrion, Daniel [6], Mercat, Alain [7], Asfar, Pierre [8], Levy, Bruno [9], Meziani, Ferhat [10]
Editeur	American Physiological Society
Type	Article scientifique dans une revue à comité de lecture
Année	2009
Langue	Anglais
Date	2009/04/24
Numéro	1
Pagination	H277 - H282
Volume	297
Titre de la revue	AJP: Heart and Circulatory Physiology
ISSN	0363-6135, 1522-1539

Résumé en anglais	Recombinant human activated protein C (rhAPC) is one of the treatment panels for improving vascular dysfunction in septic patients. In a previous study, we reported that rhAPC treatment in rat endotoxemia improved vascular reactivity, although the mechanisms involved are still under debate. In the present study, we hypothesized that rhAPC may improve arterial dysfunction through its nonanticoagulant properties. Ten hours after injection of LPS in mice (50 mg/kg ip), aortic rings and mesenteric arteries were isolated and incubated with or without rhAPC for 12 h. Aortic rings were mounted in a myograph, after which arterial contractility and endothelium-dependent relaxation were measured in the presence or absence of nitric oxide synthase or cyclooxygenase inhibitors. Flow (shear stress)-mediated dilation with or without the above inhibitors was also measured in mesenteric resistance arteries. Protein expression was assessed by Western blotting. Lipopolysaccharide (LPS) reduced aortic contractility to KCl and phenylephrine as well as dilation to acetylcholine. LPS also reduced flow-mediated dilation in mesenteric arteries. In rhAPC-treated aorta and mesenteric arteries, contractility and endothelial responsiveness to vasodilator drug and shear stress were improved. rhAPC treatment also improved LPS-induced endothelial dysfunction; this effect was associated with an increase in the phosphorylated form of endothelial nitric oxide synthase and protein kinase B as well as cyclooxygenase vasodilatory pathways, thus suggesting that these pathways, together with the decrease in nuclear factor-κB activation and inducible nitric oxide synthase expression in the vascular wall, are implicated in the endothelial effect of rhAPC. In conclusion, ex vivo application of rhAPC improves arterial contractility and endothelial dysfunction resulting from endotoxemia in mice. This finding provides important insights into the mechanism underlying rhAPC-induced improvements on arterial dysfunction during septic shock.
URL de la notice	http://okina.univ-angers.fr/publications/ua360 [11]
DOI	10.1152/ajpheart.01133.2008 [12]
Lien vers le document	http://dx.doi.org/10.1152/ajpheart.01133.2008 [12]
Titre abrégé	Recombinant human activated protein C improves endotoxemia-induced endothelial dysfunction

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