Studies on pathophysiological mechanisms in experimental models of acute renal failure

Akademisk avhandling som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att offentligen försvaras i hörsal F3, Sahlgrenska Universitetssjukhuset/Sahlgrenska, Göteborg, fredagen den 9:e mars, 2007, kl. 9.00

Av Nicoletta Nitescu, Leg. läkare

Fakultetsopponent: Professor Bengt Rippe, Lunds Universitet, Lund

Avhandlingen baseras på följande delarbeten:

I. Nitescu N, Ricksten S-E, Marcussen N, Haraldsson B, Nilsson U, Basu S, Guron G
N-acetylcysteine attenuates kidney injury in rats subjected to renal ischemia-reperfusion. *Nephrol Dial Transplant 21(5):1240-1247, 2006*

II. Nitescu N, Grimberg E, Ricksten S-E, Guron G
Effects of N-acetylcysteine on renal haemodynamics and function in early ischaemia-reperfusion injury in rats. *Clin Exp Pharmacol Physiol 33 (1-2): 53-57, 2006*

III. Nitescu N, Grimberg E, Ricksten S-E, Marcussen N, Guron G
Thrombin inhibition with melagatran does not attenuate renal ischemia-reperfusion injury in rats. *Submitted*

IV. Nitescu N, Grimberg E, Ricksten S-E, Marcussen N, Nordlinder H, Guron G
Effects of thrombin inhibition with melagatran on renal hemodynamics and function and liver integrity during early endotoxemia. *In press Am J Physiol Regul Integr Comp Physiol*

V. Nitescu N, Grimberg E, Ricksten S-E, Herlitz H, Guron G
Endothelin B receptors preserve renal blood flow in a normotensive model of endotoxin-induced acute kidney dysfunction. *Submitted*

Studies on pathophysiological mechanisms in experimental models of acute renal failure

Nicoletta Nitescu, Institute of Clinical Sciences, Department of Anesthesiolgy and Intensive Care, Göteborg University, Göteborg, Sweden

Abstract

Acute renal failure (ARF) affects 5-20 % of critically ill patients and is an independent risk factor for death in this patient population. Reactive oxygen species, thrombin and endothelin-1 (ET-1) are increased in ARF, and could contribute to the development of kidney failure and the poor prognosis. The aim of these studies was to investigate the effects of N-acetylcysteine (NAC; an antioxidant), thrombin inhibition and ET-1 receptor blockade on renal hemodynamics and function in experimental models of ischemic and septic ARF in rats.

N-acetylcysteine was studied in a model of renal ischemia-reperfusion (IR) injury induced by renal arterial clamping. N-acetylcysteine improved glomerular filtration rate (GFR) day 1 and 3 after IR. Furthermore, NAC decreased renal interstitial inflammation. N-acetylcysteine-treated rats had preserved renal glutathione levels and decreased plasma ascorbyl radical concentrations, indicating improved intrarenal antioxidant capacity and attenuated systemic oxidative stress. However, NAC did not improve GFR, total renal blood flow (RBF), or cortical (CLDF) and outer medullary (OMLDF) perfusion measured by laser-Doppler flowmetry, during the first 80 minutes after IR.

Thrombin inhibition with melagatran was examined in endotoxemia induced by lipopolysaccharide infusion, and in renal IR. During the first 3 h of endotoxemia, melagatran improved OMLDF, but did not attenuate the decline in GFR, RBF, CLDF and mean arterial pressure (MAP). In addition, melagatran attenuated the increase in plasma concentrations of aspartate aminotransferase, alanine aminotransferase and bilirubin, and of the cytokine tumor necrosis factor (TNF)-α. Melagatran did not diminish hepatocellular necrosis or the elevated hepatic gene expression of TNF-α, inducible nitric oxide synthase and intercellular adhesion molecule-1, evaluated by reverse transcription-polymerase chain reaction. In renal IR, melagatran did not ameliorate the decline in renal function, or attenuate renal histopathological abnormalities.

We studied the renal effects of selective endothelin type A (ET_A), and type B (ET_B), receptor antagonists during the first 2 h of normotensive endotoxemia with acute renal dysfunction. In saline-treated rats, endotoxin induced an approximate 40 % reduction in GFR, without significant changes in MAP, RBF, or in cortical perfusion and pO_2, measured by oxygen sensitive microelectrodes. In addition, endotoxin increased outer medullary perfusion and pO_2. Neither selective, nor combined, ET_A and ET_B receptor blockade improved GFR. However, in rats receiving selective ET_B receptor antagonist, or combined ET_A and ET_B receptor blockade, endotoxin produced marked reductions in RBF and CLDF, without affecting MAP.

In conclusion, NAC is renoprotective in renal IR presumably by decreasing renal oxidative stress and inflammation, but not by improving kidney hemodynamics early after the ischemic insult. Thrombin seems not to be an important pathogenetic factor in the development of renal IR-injury. Thrombin inhibition with melagatran during endotoxemia preserves renal outer medullary perfusion, ameliorates liver dysfunction and attenuates the systemic inflammatory response. Endothelin-1 has beneficial effects on renal hemodynamics during early normotensive endotoxemia by activation of ET_B receptors that exert a renal vasodilator influence and contribute to maintain normal RBF.

Key words: acetylcysteine, acute renal failure, endothelin-1, endotoxin, ischemia, kidney medulla, reactive oxygen species, renal circulation, thrombin

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