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Effects of rolipram on the renal microcirculation during sepsis in the rat pup

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Introduction

Microcirculatory failure is a key event during sepsis that is believed to play a major role in multi-organ failure. Acute kidney injury is a complication of sepsis in infants that increases mortality. The phosphodiesterase (PDE)3 inhibitor milrinone is used in infant sepsis to improve cardiac function; however, its effectiveness in septic patients is limited. The goal of this study was to use the kidney as a model vascular bed to evaluated the effects of the PDE4 inhibitor rolipram on renal capillary perfusion and leakage.

Method

We developed a clinically relevant cecal ligation and puncture (CLP) sepsis model in rat pups 17-18 days old to model human infant sepsis. At 18h post sepsis (CLP) or sham surgery (Sham) pups were re-anesthetized with isoflurane. The left kidney was exteriorized and placed on the stage of an inverted microscope to visualize cortical capillaries. Five 10s videos from each animal were captured. Capillaries were analyzed for perfusion and categorized as having Continuous, Intermittent or No Flow. Capillaries with continuous flow were analyzed for red blood cell (RBC) velocity. Evans Blue Dye (EBD) (1% in saline; 2 mg/kg iv) was used to assess vascular leakage (1). To mimic the clinical setting where patients are treated only after the onset of symptoms, rolipram was administered at 6h post CLP.

Results

A decline in renal capillary perfusion occurred by 6h post sepsis. A dose-response study with rolipram (0.1-1.0mg/kg, ip, saline+0.5% DMSO) indicated 0.1mg/kg as the lowest most efficacious dose to improve perfusion at 6h. This dose was then tested with delayed administered at 6h post CLP. At 18h post CLP rolipram increased the percentage of capillaries with continuous flow (Sham, 72±4%; CLP, 46±5%; CLP+rolipram, 70±1%; n=5-6; $P<0.05$ compared to CLP) and improved RBC velocity (Sham, 217±5µm/sec; CLP, 119±10µm/sec; CLP+rolipram, 246±16µm/sec; n=5; $P<0.05$ compared to CLP). Rolipram also reduced capillary leakage (EBD uptake; Sham, 4.4±1.5ng/g; CLP, 12.6±2ng/g; CLP+rolipram, 6.9±2ng/g; n=5; $P<0.05$ compared to CLP).

Conclusions

Sepsis in this infant model produces a rapid decrease in renal microvascular perfusion and RBC velocity. Sepsis also increases vascular permeability. Rolipram mitigated all of these microvascular defects even with delayed administration. These findings suggest that combination therapy with inhibitors of PDE4 and PDE3 may be more efficacious in the septic infant because PDE4 inhibitors also protect against overall microvascular perfusion and microvascular leakage.

References

1. Holthoff JH, Wang Z, Patil NK, Gokden N, Mayeux PR (2013) *J Pharmacol Exp Ther* 347:357-364.