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Association between remote organ injury and tissue polyamine homeostasis in acute experimental pancreatitis – treatment with a polyamine analogue bismethylspermine

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Abstract:
Experimental pancreatitis is associated with activation of polyamine catabolism. The polyamine analog bismethylspermine (Me_2Spm) can ameliorate pancreatic injury. We investigated the roles of polyamine catabolism in remote organs during pancreatitis and explored the mechanism of polyamine catabolism by administering Me_2Spm. Acute pancreatitis was induced by an infusion of 2 or 6% taurodeoxycholate before Me_2Spm administration. Blood, urine and tissues were sampled at 24 and 72 h to assess multi-organ injury and polyamine catabolism. The effect of Me_2Spm on mortality in experimental pancreatitis was tested separately. Liver putrescine levels were elevated following liver injury. Me_2Spm increased the activity of spermidine/spermine N^1-acetyltransferase (SSAT) and depleted the spermidine, spermine or putrescine levels. Lung putrescine levels increased, and SSAT and spermine decreased following lung injury. Me_2Spm enhanced the activity of SSAT and decreased the spermidine and spermine levels. Renal injury was manifested as an increase in creatinine or a decrease in urine output. Decreases in kidney SSAT, spermidine or spermine and an increase in putrescine were found during pancreatitis. In the 2% taurodeoxycholate model, Me_2Spm decreased urine output and raised plasma creatinine levels. Me_2Spm increased SSAT and decreased polyamines. Excessive Me_2Spm accumulated in the kidney, and greater amounts were found in the 6% taurodeoxycholate model in which this mortality was not reduced by Me_2Spm. In the 2% taurodeoxycholate model, Me_2Spm dose-dependently induced mortality at 72 h.
Like pancreatic injury, remote organ injury in pancreatitis is associated with increased putrescine levels. However, Me_2Spm could not ameliorate multi-organ injury. Me_2Spm administration was associated with significant renal toxicity and induced mortality, suggesting that the current dose is too high and needs to be modified.

Key words:
bismethylspermine, multi-organ injury, pancreatitis, polyamines, putrescine, spermidine, spermine