EFFECTS OF CALPAIN INHIBITOR I ON THE MULTIPLE ORGAN FAILURE INDUCED BY ZYMOSAN IN THE RAT

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Zymosan causes an enhanced formation of reactive oxygen species (ROS), which contributes to the pathophysiology of multiple organ failure (MOF). Here we have investigated the effects of calpain inhibitor I (5, 10 or 20 mg/kg) on the MOF caused by zymosan (500 mg/kg, administered i.p. as a suspension in saline) in rats. MOF in rats was assessed 18 hours after administration of zymosan and/or calpain inhibitor I and monitored for 12 days (for loss of body weight and mortality). Treatment of rats with calpain inhibitor I (5, 10 or 20 mg/kg i.p., 1 and 6 hours after zymosan) attenuated the peritoneal exudation and the migration of polymorphonuclear cells (PMNs) caused by zymosan in a dose-dependent fashion. Calpain inhibitor I also attenuated the lung, liver and intestinal injury (histology) as well as the increase in myeloperoxidase (MPO) activity and malondialdehyde (MDA) levels caused by zymosan in the lung, liver and intestine. Immunohistochemical analysis for nitrotyrosine and for poly(ADP-ribose) (PAR) revealed positive staining in lung, liver and intestine from zymosan-treated rats. The degree of staining for nitrotyrosine and PAR were markedly reduced in tissue sections obtained from zymosan-treated rats administered calpain inhibitor I (20 mg/kg i.p.). Furthermore, treatment of rats with calpain inhibitor I significantly reduced the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in lung, liver and intestine. This study provides the first evidence that calpain inhibitor I attenuates the degree of zymosan-induced MOF in the rat.