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Titel des Beitrags: Induction of IkappaB-Kinase by Cholecystokinin Is Mediated by Trypsinogen Activation in Rat Pancreatic Lobules

Abstract:
Background and Aims: Supramaximal concentrations of cholecystokinin (CCK) or cerulein induce the intracellular activation of trypsinogen and the transcription factor NF-kappaB, a key regulator of inflammatory gene expression. Both events occur early in the development of an acute pancreatitis. The aim of this study was to examine the relationship between intracellular trypsinogen and NF-kappaB activation. Methods: We detected NF-kappaB-binding activity in electromobility shift assays, NF-kappaB proteolysis in Western analysis and endogenous IkappaB-kinase (IKKalpha and IKKbeta) activation using immune complex kinase assays following treatment with CCK in rat pancreatic lobules. To block intrapancreatic trypsinogen activation, a potent and cell-permeable serine-protease inhibitor, Pefabloc, was used. Results: CCK-induced IkappaB degradation and subsequent NF-kappaB activation correlated closely with the catalytic activity of IKKs to phosphorylate IkappaBalpha in vitro. Activation is dose-dependent and peaked at 30 min. Doses of Pefabloc sufficient to inhibit trypsin activation reduced CCK-induced activation of NF-kappaB whereas TNF-alpha-induced NF-kappaB activation was not blocked but slightly increased. Moreover, treatment with Pefabloc as well as another serine protease inhibitor, FUT175, inhibited CCK-induced IKK
activation. Conclusion: These results suggest that intrapancreatic activation of trypsinogen may contribute to NF-κB signaling via IKK activation in cerulein pancreatitis. This also explains the fact that only doses of CCK which activate trypsinogen induce NF-κB activation in pancreatic acinar cells. Thus, trypsinogen activation is likely to modulate signaling events in acinar cells in the initial phase of acute pancreatitis.

Stichworte:
NF-κB; IκB-kinase; Trypsinogen; Trypsin activation; Acute pancreatitis; Concentrations of cholecystokinin; Serine protease inhibitor