Altered anti-inflammatory response of mononuclear cells to neuropeptide PACAP is associated with deregulation of NF-κB in chronic pancreatitis.

Although it is recognized that neurogenic influences contribute to progression of chronic inflammatory diseases, the molecular basis of neuroimmune interactions in the pathogenesis of chronic pancreatitis (CP) is not well defined. Here we report that responsiveness of peripheral blood mononuclear cells (PBMC) to the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) is altered in CP. Expression of PACAP and its receptors in human CP was analyzed with quantitative RT-PCR, laser-capture microdissection, and immunohistochemistry. Regulation of PACAP expression was studied in coculture systems using macrophages and acinar cells. Responsiveness of donor and CP PBMC to PACAP was determined based on cytokine profiles and NF-κB activation of LPS- or LPS+PACAP-exposed cells. Although donor and CP PBMC responded equally to LPS, PACAP-mediated counteraction of LPS-induced cytokine response was switched from inhibiting TNF-alpha to decreasing IL-1beta and increasing IL-10 secretion. The change of PACAP-mediated anti-inflammatory pattern was associated with altered activation of NF-κB: compared with LPS alone, a combination of LPS and PACAP had no effect on NF-κB p65 nuclear translocation in CP PBMC, whereas NF-κB was
significantly decreased in donor PBMC. According to laser-capture microdissection and coculture experiments, PBMC also contributed to generation of a PACAP-rich intrapancreatic environment by upregulating PACAP expression in macrophages encountering apoptotic pancreatic acini. The nociceptive status of CP patients correlated with pancreatic PACAP levels and with IL-10 bias of PACAP-exposed CP PBMC. Thus the ability of PBMC to produce and to respond to PACAP might influence neuroimmune interactions that regulate pain and inflammation in CP.