Substance P and Calcitonin Gene Related Peptide Mediate Pain in Chronic Pancreatitis and Their Expression is Driven by Nerve Growth Factor

LianSheng Liu, Mohan Shenoy, Pankaj Jay Pasricha

Division of Gastroenterology and Hepatology, Stanford University Medical Center. Stanford, CA, USA

ABSTRACT

Context Calcitonin gene-related peptide (CGRP), substance P (SP) and nerve growth factor (NGF) play an important role in inflammatory pain in various somatic pain models but their role in chronic pancreatitis (CP) has not been well studied. Objectives The aim of this study was to investigate the effects of intrathecal administration of CGRP and SP receptor antagonists on pain behavior in a rat model of CP and to determine whether NGF drives the up-regulation of expression of these neuropeptides in sensory neurons. Methods Pancreatitis was induced by retrograde infusion of trinitobenzene sulfonic acid (TNBS) into the pancreatic duct of adult rats. Three weeks post infusion continuous intrathecal infusion of the CGRP antagonist alpha CGRP 8-37 or neurokinin-1 (NK1) receptor antagonist CP-96345 or its inactive enantiomer CP-96344 was administered for seven days. The effects of treatment on pancreatic hyperalgesia were assessed by sensitivity of the abdominal wall to Von Frey Filament (VFF) probing as well as by the nocifensive response to electrical stimulation (ES) of the pancreas. In a separate experiment CP was induced and pancreas specific dorsal root ganglion (DRG) neurons labeled with DiI were assessed for CGRP and SP immunoreactivity. Results Intrathecal infusion of CGRP and NK1R antagonists significantly attenuated behavioral pain responses in rats with CP. Further, treatment of CP rats with NGF antibody significantly reduced pancreas specific neurons expressing CGRP and SP in thoracic DRG. Conclusions CGRP and SP mediate pancreatic hyperalgesia in CP and NGF in turn sustains the up-regulation of these neuropeptides in pancreatic sensory neurons.