

Neurogenic Inflammation in Acute Pancreatitis

Akhil Hegde, Madhav Bhatia

Department of Pharmacology, National University of Singapore. Singapore

Summary

Acute pancreatitis is a clinical condition whose incidence has increased over the past few years. The exact mechanism of its development is not yet clear. Substance P, the proinflammatory neuropeptide, has a role in the initiation of neurogenic inflammation. Substance P and its receptor neurokinin-1 receptor (NK-1R) are involved in the development of local as well as systemic inflammation in acute pancreatitis. This editorial focuses on the role of substance P and its receptors in the development of acute pancreatitis.

Acute pancreatitis (AP) is a clinical condition whose incidence has increased over the past few years [1]. Although several etiologies are responsible for AP, biliary disease and excessive alcoholism are the main causes of the disease. The condition is mild in the majority of patients but about a quarter of the patients may suffer a severe attack. Mortality among these patients is as high as 30-50% [1, 2, 3]. In the United States alone more than 300,000 patients are hospitalized yearly with AP and 3,200 of them eventually die of the disease [4]. Furthermore, AP is a contributing factor in an additional 4,000 deaths annually [4].

AP is a result of a complex cascade of events originating in the acinar cells of the pancreas. The exact mechanism of development is still not clear. However, it is believed that pancreatitis develops due to injury or

disruption of the acinar cells. The disease is initiated, following various pathways, by the activation of intracellular proteolytic enzyme zymogens in the acinar cells [1, 5]. As the protective mechanisms of the body are overwhelmed, tissue injury causes the leakage of trypsin, chymotrypsin and elastase enzymes into the pancreatic tissue [6]. The activated proteases (trypsin and elastase) and lipase break down the cell and tissue membranes leading to edema, vascular damage, hemorrhage and necrosis. They also release inflammatory mediators, which finally result in chronic pancreatitis [5]. Some inflammatory mediators are reported to activate capsaicin-sensitive sensory neurons leading to neurogenic inflammation [7].

Neurogenic inflammation is a term broadly used to include inflammatory responses such as local arteriolar vasodilatation, edema, increased vascular permeability and neutrophil infiltration that result from the activation of primary sensory neurons [8, 9]. It has been reported that primary sensory neurons are a common final pathway in neurogenic pancreatic inflammation [7]. In animal models of cerulein-induced pancreatitis, plasma extravasation is mediated mainly by the activation of primary sensory neurons but other components of neurogenic inflammation such as neutrophil infiltration and parenchymal necrosis are mediated by sensory afferent neurons [7]. Also, innervation of the pancreas is reported to be altered in chronic pancreatitis with increased immunoreactivity for neuropeptides such as substance P (SP) [10]. SP is shown to have a

potent stimulatory effect on the synthesis of cytokines such as IL-1, tumor necrosis factor-alpha (TNF-alpha), and IL-6 by human blood monocytes [11]. All these findings provide evidence of a neuroimmune/inflammatory interrelationship.

For the most part, the pancreas is innervated with SP expressing capsaicin-sensitive C fibers [12, 13]. C fibers are a subpopulation of sensory neurons containing SP, calcitonin gene-related peptide (CGRP), and neurokinin A [5]. The peripheral terminals of these capsaicin-sensitive primary afferents are activated by local depolarization, dorsal root reflexes or axonal reflexes resulting in the release of neuropeptides and further leading to neurogenic inflammation [14]. Some A-delta fibers are also involved in neurogenic inflammation [15] releasing SP and CGRP. SP is an 11-amino acid neuropeptide released from the nerve endings in various tissues [1]. It is an important pain mediator. SP acts as a neurotransmitter (mainly in sensory afferents) and also has a role in the initiation of neurogenic inflammation [16].

The tachykinin 1 gene (Tac 1) encodes for protein preprotachykinin A (PPT-A) [17]. The primary RNA transcript of the PPT-A gene is cleaved to alpha-, beta- and gamma- mRNAs, which code for the synthesis of SP. PPT-A is enzymatically cleaved to produce SP. The neuropeptide SP is present in unmyelinated somatic and visceral afferent nerve fibers, in enteric sensory neurons and in a number of pathways within the central nervous system [18]. It is found in nerve fibers close to the epithelial cells in the gastrointestinal tract. The pancreases of dogs and mice contain SP [19]. SP receptors have been detected on guinea pig acinar cells [20, 21, 22]. No SP receptors are reported to be expressed on rat acinar cells [6].

SP is a proinflammatory mediator involved in acute inflammatory responses [10]. It plays a role in asthma, immune complex-mediated lung injury and inflammatory bowel diseases [23, 24]. It is an important mediator of inflammatory edema, hyperamylasemia, and the histological injury caused by cerulein-induced pancreatitis in rats and mice [25, 26].

This neuropeptide is also a major mediator of neurogenic inflammation in various tissues such as skin, cephalic structures, cardiovascular tissue, the respiratory tract, the genitourinary tract and the gastrointestinal tract [27, 28, 29]. SP controls intestinal motility, blood flow, and ion and fluid transport. It inhibits secretion from the intact pancreas in dogs and rats. It also inhibits basal fluid secretion from isolated rat pancreatic ducts in a dose dependent manner.

SP and its receptor neurokinin-1 (NK-1R) are involved in the development of local as well as systemic inflammation. SP binds to G-protein-coupled NK-1 tachykinin receptors present on effector cells such as acinar cells [30] and immune cells [31] leading to inflammatory edema and hyperamylasemia [32]. During acute pancreatitis, sensory nerves may be stimulated to release intrapancreatic SP which, in turn, activates NK-1 receptors. SP bound to NK-1R on postcapillary venules leads to intercellular gaps in the endothelium of blood vessels [33]. Plasma and small proteins infiltrate the interstitial tissue through these gaps causing edema [33].

SP binding to NK-1R also results in neutrophil accumulation in the pancreas [33] and mast cell degranulation leading to the release of proinflammatory mediators which cause neutrophil adhesion, migration and production of reactive oxygen species [34, 35, 36]. Together, the neuropeptide and its receptor form one of the major players responsible for the pathological events leading to pancreatic injury [25]. SP also binds to NK-2 and NK-3 receptors but with a low affinity. However, NK-2 and NK-3 receptors have not yet been detected on pancreatic acinar cells [26].

Various reports in the last few decades have implicated SP in pancreatitis. SP receptors have been detected on guinea pig acinar cells and SP is reported to stimulate amylase secretion from those acinar cells [20, 21, 22]. We have shown that, in mice with pancreatitis, there are elevated levels of SP and an increased number of NK-1 receptors on the acinar cells in the pancreas [25]. In

addition, NK-1R knockout mice were protected against pancreatitis and associated lung injury [25]. These knockout mice showed significantly less pancreatic and lung injury as compared to wild type mice in cerulein-induced pancreatitis [25]. Knockout mice which have the preprotachykinin-A (PPT-A) gene, the precursor for SP, are also protected against acute pancreatitis and subsequent lung injury [26]. Thus, the severity of pancreatitis is alleviated in mice lacking NK-1 receptors [25] as well as the preprotachykinin gene [26]. SP also determines lethality in a choline-deficient, ethionine-supplemented (CDE) diet model of acute hemorrhagic pancreatitis via NK-1 receptor activation [37]. All these data indicate a strong role for SP in pancreatitis via NK-1R [25]. Further proof is given by the report that knockout mice which have neutral endopeptidase, the SP hydrolyzing enzyme, are more prone to acute pancreatitis due to the lack of biotransformation of SP by the enzyme [38].

Recently it has been reported that activation of the transient receptor potential vanilloid 1 (TRPV-1), the capsaicin receptor, present on primary sensory afferents, promoted neurogenic inflammation in the rat pancreas via the release of SP and NK-1R activation [33]. Furthermore, capsazepine, a selective TRPV1 antagonist, is reported to reduce cerulein-induced pancreatitis in mice [5, 39]. This beneficial effect is achieved by inhibiting the activation of sensory neurons, reducing the internalization of NK-1R in pancreatic acinar cells and reducing SP release [5, 39]. As capsaicin is known to cause plasma extravasation in the pancreas, the activation of capsaicin-sensitive sensory neurons may be responsible for triggering and propagating the neurogenic inflammation [5]. It is thought that cerulein-induced pancreatitis caused activation of TRPV1 on sensory neurons in the pancreas releasing SP to further propagate the downstream inflammation [5].

Since SP and NK-1 receptors play a major role in acute pancreatitis, pharmacological intervention against NK-1 receptors could be

a promising lead for therapy. Several groups have investigated this aspect. Figini *et al.* in 1997 [29] used an NK-1R antagonist to block plasma extravasation caused by SP from the postcapillary venules in the mouse pancreas [29]. Our group has recently evaluated the possibility of NK-1R as a potential target for the treatment of acute pancreatitis [40]. We investigated the effect of CP-96345, a specific NK-1R antagonist, on pancreatic and lung injury in cerulein-induced pancreatitis in mice. The NK-1 antagonist was observed to protect mice, prophylactically and therapeutically, against acute pancreatitis and associated lung injury [40]. Thus, NK-1R antagonists may potentially be useful in the treatment of acute pancreatitis and its subsequent systemic complications.

Until now, most of the data has originated from animal studies. Detailed investigation of neurogenic pancreatitis in humans is obviously difficult. Significant progress has been made in understanding the pathophysiology of pancreatitis in recent years. The mechanism by which SP affects the severity of pancreatitis is still not clear. Understanding the mechanism of neurogenic pancreatitis along with the critical role of NK-1R and SP can provide new insight and many more avenues to treat this clinical condition successfully. However, more work needs to be done in order to take these therapies to the clinic.

Keywords Neurogenic Inflammation; Pancreatitis; Receptors, Neurokinin-1; Substance P

Abbreviations AP: acute pancreatitis; NK: neurokinin; NK-1R: neurokinin-1 receptor; PPT-A: preprotachykinin A; SP: substance P; TRPV-1: transient receptor potential vanilloid

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Correspondence

Madhav Bhatia
Department of Pharmacology
National University of Singapore
Yong Loo Lin School of Medicine
Bldg MD2, 18 Medical Drive
Singapore 117597
Phone: +65-6874.8256
Fax: +65-6873.7690
E-mail: mbhatia@nus.edu.sg

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