

Mechanisms of Pain in Chronic Pancreatitis



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Introduction

Chronic pancreatitis (CP) is an inflammatory, often painful disease of the exocrine pancreas, which leads to exocrine insufficiency. Its incidence is about 8.2 new cases/100.000 inhabitants per year. Complications encountered in CP include biliary (10-30%) and duodenal (10-25%) obstruction and, as times goes on, maldigestion and diabetes mellitus (1-2).

However, the most disturbing complication of CP is abdominal pain. Surgical management is often indicated in cases with medically intractable pain and this has also repercussions on the economic management of these patients (2-3). Three different typical pain profiles during the evolution of CP have been described: *a*) repeated episodes of acute pancreatitis (acinar necrosis) in early stages, *b*) spontaneous lasting pain relief in association with severe pancreatic dysfunction in late stage of uncomplicated CP, and *c*) persistent severe pain (or frequent recurrent episodes of pain) usually in association with local complications such as pseudocysts, ductal hypertension or extrapancreatic complications such as partial obstruction of the common bile duct, peptic ulcer, and opiate addiction. Clearly, the actual pathophysiology of this abdominal pain remain elusive and several hypotheses have been postulated (4).

Till now, pancreatic and extrapancreatic mechanisms have been implicated in the development of pain in CP (5-7). The "pancreatic causes" may be resembled in: *a*) acute inflammation of the pancreas; *b*) increased intrapancreatic pressure and *c*) neural inflammation. Potential "extrapancreatic causes" are: *a*) common bile duct stenosis by continued inflammation of the head of the pancreas; *b*) duodenal stenosis caused by extensive fibrosis that envelops the wall of the duodenum.

Abstract

Pain is a leading symptom in chronic pancreatitis (CP) and often its management necessitates surgical intervention. Nevertheless the presence of different hypotheses, the pathophysiology of pain is not understood, thus the indications for therapy remain controversial. Increased pressure within the ductal system and for the parenchyma has been suggested to be one of the causes of pain. This controversial theory has been substantiated by the demonstration of a relationship between intrapancreatic pressure and intensity of pain. On the other hand, recent studies have shown the inflammatory involvement of intrapancreatic nerve fibres in a so called "neuroimmune interaction". In fact, infiltration of inflammatory cells around the nerves together with an increase in the number of nerve fibres in the fibrotic pancreatic tissue have been proposed as a possible cause of pain in chronic pancreatitis. Moreover, immunohistological studies have shown that the amount of neurotransmitters, such as substance P and calcitonine gene related peptide, is increased in afferent pancreatic nerves and a close interrelationship between pain and immune cell infiltration of the nerves has been reported in CP. In addition to these hypothesis, extrapancreatic causes such as common bile duct obstruction and duodenal stenosis are discussed. This article review points to the different pathogenic mechanisms of pancreatic pain in CP.

Key words: Chronic pancreatitis, pain, pathophysiology, neurogenic inflammation.

Sommario

PATOFISIOLOGIA DEL DOLORE NELLA PANCREATITE CRONICA

Il dolore è il sintomo principale della pancreatite cronica e spesso il suo trattamento necessita la terapia chirurgica.

Nonostante la presenza di differenti ipotesi, la patofisiologia del dolore nella pancreatite cronica non è ancora stata chiarita, pertanto le indicazioni terapeutiche rimangono controverse. Una aumentata pressione del sistema duttale e/o intraparenchimale è stata suggerita come una causa di dolore. Questa teoria controversa è stata supportata dalla dimostrazione di una possibile relazione tra la pressione intrapancreatica e l'intensità del dolore. D'altro canto, studi recenti hanno dimostrato il coinvolgimento delle fibre nervose intrapancreatiche in un particolare processo infiammatorio definito "neurogenico". Infatti esso è caratterizzato da un'infiltrazione delle cellule infiammatorie attorno alle strutture nervose pancreatiche che risultano alterate nel

numero e nelle dimensioni a testimonianza di un loro coinvolgimento nel processo infiammatorio e doloroso tipico della pancreatite cronica. A supporto di questa ipotesi studi immunohistochimici hanno dimostrato che l'espressione di alcuni neuropeptidi pronocicettivi e proinfiammatori, come la sostanza P e il CGRP, è aumentata nelle fibre afferenti pancreatiche. Esiste inoltre una stretta correlazione tra dolore e grado di infiltrazione delle cellule infiammatorie a carico dei nervi.

Questo articolo fa il punto sui differenti meccanismi patogenetici coinvolti nella genesi del dolore da pancreatite cronica.

Parole chiave: Pancreatite cronica, dolore, patofisiologia, infiammazione neurogenica.

In addition, the presence of different hypotheses to explain the genesis of pain in CP directly reflects on the difficult approach to pain treatment and subsequent relief in these patients.

The aim of the present report is to review the data present in the literature and to focus on the potential mechanisms involved in the pathophysiology of pain in CP.

Epidemiology

A remarkably high prevalence of surgery is reported in CP patients in order to decrease pain. But, while surgery was initially reported to be effective, the results for relief of pain have been discussed in the epidemiological series published by Ammann (8) and Lankisch (9), and they concluded that the proportion of patients experiencing pain relief was similar in patients who underwent surgery in comparison to patients who were treated medically. It's important to keep in mind that, often pain measurement in operated patients might be flawed by statistical bias. For example, a higher early mortality in patients with severe disease may reduce the incidence of pain in the follow-up groups (10). In the study of Amman, pain relief was observed after a median of 4.5 years of onset and accompanied by a marked increase in pancreatic dysfunction or calcifications. Similar experiences have been reported by Miyake (11). However, the perception that the painful pancreas will "burn itself out", is not epidemiologically supported by studies from Jensen (12), Malferteiner (13), and Lankisch (9). In a series of 335 patients with CP published by Lankisch, significant pain relief was not obtained in the majority of patients during an observation period of more than 10 years (9). In addition, Malferteiner et al. reported that 58% of the patients with severe pain had marked pancreatic insufficiency, while 35% of the patients with severe pain also had pancreatic calcifications (13). In conclusion, observation that CP will burn itself out, resulting in spontaneous pain relief, have been disputed by epidemiological data that raise the distinct possibility that pain in many patients with CP will continue to last,

despite the progression to pancreatic insufficiency, appearance of calcifications, alcohol withdrawal, or even after pancreatic surgery.

Etiopathogenesis

The pathogenesis of pain in chronic pancreatitis is often multifactorial and this may well explain why all patients do not respond to the same treatment modality (5-7, 14-15). Up to now different hypotheses have been formulated to explain the pathogenesis of pain in CP and these are: 1) pancreatic causes and 2) extrapancreatic causes (Tab. I) (5-7).

Tab. I – CAUSES OF PAIN IN CHRONIC PANCREATITIS

<i>Pancreatic causes</i>	<i>Extrapancreatic causes</i>
Acute inflammation of the pancreas	Duodenal stenosis
Increased pressure in duct and tissue	Common bile duct stenosis
Neuronal inflammation	

Pancreatic causes

Acute inflammation of the pancreas

Acute inflammation is readily apparent when there is severe abdominal pain and tenderness, elevation of serum amylase and lipase, and evidence of acute pancreatic inflammation on CT scan. The causes are likely to be the same as in inflammation associated with acute pancreatitis involving activated enzymes and others injurious substances (15).

Increased pressure in the pancreatic ducts and tissue

The intrapancreatic ductal pressure might be related to the pancreatic secretion itself and to the presence of an obstruction in the pancreatic duct (16). Several conditions that influence these two parameters are able to modulate pain intensity and frequency in patients with CP (17-18). In fact, many investigators have related the origin of pain to the increased pressure in pancreatic ducts and tissue (19). The "ductal hypertension hypothesis" as an explanation for pain in CP is derived from observations that decompression of a dilated pancreatic duct or pseudocyst frequently relieves pain in chronic pancreatitis patients (20). Pancreatic enzyme supplementation may also relieve pain in some CP patients (21). It is believed that the beneficial effect of pancreatic enzymes is explained by

“cholecystokinin-mediated feedback” regulation between pancreatic exocrine secretion and the activity of proteases in the lumen of the small intestine (21). According to this hypothesis, administration of enzymes reduces hypercholecystokinemia in patients with CP, thus resulting in less stimulation of the pancreas and subsequently lowered intraductal pressure and pain (21). Interestingly, different studies have shown that progressive pancreatic insufficiency, that appears after several years from the first diagnosis, is often associated with a reduction and sometimes a complete pain relief in the patients with CP, thus indicating that probably the disease progression might “burn out” the pancreas itself, as mentioned before (8-9). In contrast, we have to consider that often pain in CP is not related to the consumption of food, and even pain intensity, radiation and duration are not constant (1). In addition, in other studies present in the literature, it has been calculated that around 30% of the patients treated with decompressive surgery exhibited recurrent attacks of pain (22). On one hand, when the patients are “pain free” after surgery, this could be often due to the reduction of alcohol ingestion or due to the progressive pancreatic insufficiency. On the other hand, we must remember that the induction of pancreatic secretion by secretin, cholecystokinin (CCK) or cerulein, as usually done during the standard pancreatic functional tests (Lundh test or serum-pancreolauryl test) is not associated with pain in patients with CP. In fact, recent reports using octreotide- a somatostatin analogue which strongly inhibits pancreatic secretion and therefore should interrupt this postulated “pain circle” described above, failed to reduce the pain syndrome in many patients with chronic pancreatitis (23-24). Ebbehøj et al. (18) have shown in their study a direct relationship between pain intensity and pancreatic intraductal pressure before and after decompressive surgery. In contrast to this study, Manes et al. (19) have investigated the relationship between pain and pancreatic pressure in patients with CP. They studied 12 patients with CP undergoing surgery and five controls with cancer of the pancreatic tail. CP was staged on the basis of morphological and functional (serum-pancreolauryl test) criteria. Patients kept daily records of the intensity of pain on a linear analog scale. Intraoperatively, pressure within the pancreas was assessed by the introduction of a fine needle into the pancreatic parenchyma connected to a pressure transducer. In controls, pressure was determined in macroscopically normal tissue in the head of the pancreas. Pancreatic pressure was significantly higher in CP than in controls. In addition, no relationship was found between the pain score and the pancreatic pressure, but intrapancreatic pressure was positively correlated with ductal changes. Postoperatively, pancreatic pressure fell by 15.3% in four patients with CP in whom pressure assessment was repeated after

surgical decompression. These findings thus concluded that pancreatic parenchymal pressure is not closely related to pain in CP (19).

Neuronal inflammation

Recent concepts have focused on the possible involvement of the nervous system in chronic pain and the inflammatory process in CP. Supporting this fascinating hypothesis, Keith et al. (25) initiated that neural and perineural alteration might be important in pain pathogenesis in CP. They demonstrated that pain severity correlated with the duration of alcohol consumption, pancreatic calcification and more interestingly with the percentage of eosinophil number in the perineural infiltrate, but not with duct dilatation.

A subsequent study demonstrated that there is an increase both in number and diameter of pancreatic nerve fibers in the course of CP compared to normal pancreas. In tissue specimens of patients suffering from CP, foci of inflammatory cells are often found surrounding pancreatic nerves, which in electron-microscopic analysis exhibit a damaged perineurium and invasion with eosinophile granulocytes (26). These abnormalities might allow free access to inflammatory mediators or active pancreatic enzymes in the nerve bundles generating and sustaining the inflammatory response and pain generation. Additionally, an increased production of oxygen radicals in the inflamed pancreas has also been suggested as a contributing mechanism to the development of pain in CP.

Also, a changed pattern of intrinsic and possibly extrinsic innervation of the pancreas exists in CP, leading to up-regulation of neuropeptides (27). By immunohistochemistry, antisera against neuropeptide Y, tyrosine hydroxylase, vasoactive intestinal polypeptide (VIP), peptide histidine isoleucine (PHI), calcitonin gene-related peptide (CGRP), and substance P (SP), respectively, were used. In accordance with the findings of Bockman et al. (26), the number and diameter of intralobular and interlobular nerve bundles were increased as compared with control pancreas. The striking changes in the peptidergic innervation pattern in CP concerned these altered nerves. It consisted of an intensification of the immunostaining for CGRP and SP in numerous fibers contained in these nerves. Adjacent tissue revealed a coexistence of SP and CGRP immunoreactive fibers. Because both of these peptides are generally regarded as pain transmitters, these findings provided evidence that changes in pancreatic nerves themselves might be involved in the long-lasting pain syndrome in CP.

Another interesting finding of these studies was the observation of close contacts between neuronal structures and immune cells in chronically inflamed pancreas that led to the concept of neuroimmune mechanisms in the pathogenesis of CP and the accompanying abdominal pain (28).

To confirm this interesting hypothesis in a subsequent report (28), the presence of growth-associated protein-43 (GAP-43), an established marker of neuronal plasticity, was correlated with pain scores in patients with CP. GAP-43 is a neuronal protein known to be involved in the development of axonal growth cones and presynaptic terminals, and the expression of GAP-43 is increased at mRNA and protein level after neuronal lesions. GAP-43 is widespread in both developing and adult central and peripheral nervous system of the rat and is expressed in the hippocampus of rats and humans, regions which continually undergo synaptic remodeling. More recent studies (29-32) showed a modulation of GAP-43 expression after injuries of peripheral nerves and intestinal parasite infection of the rat. In these experimental models, GAP-43 was re-expressed at high levels, reflecting neuronal contribution in inflammation and post-lesional repair. In the chronically inflamed human pancreas, by enzymatic and double fluorescence immunohistochemistry (33), a significant re-expression of GAP-43 in the majority of pancreatic nerve fibers was demonstrated. In a further study (28), by the correlation of GAP-43 with clinical findings, in 29 patients with CP, including the parenchyma-fibrosis ratio, the degree of perineural immune cell infiltration, revealed a strong relationship with individual pain scores. In CP, GAP-43 expression correlated with individual pain scores. Furthermore, the infiltration of pancreatic nerves by immune cells was significantly correlated with the pain intensity, whereas, pain scores did not correlate neither with the degree of pancreatic fibrosis nor with the duration of the disease. The demonstration of a direct relationship between the degree of perineural inflammation and clinical pain symptoms, strongly supports the hypothesis of a neuroimmunologic interaction as an important, if not predominant, factor in pain generation in CP. The lack of a relationship between the degree of pancreatic fibrosis and pain could contradict the common concept that fibrosis leads to increased intraductal pressure in CP and thereby to an involvement in pain pathophysiology during the chronic inflammation of the pancreas (28).

Extrapancreatic causes

Bile duct stenosis and duodenal stenosis due to extensive pancreatic fibrosis and inflammation are often considered putative extrapancreatic causes of pain (34-35). However, only few authors are in accordance with this belief. Recently, Becker and Mischke described in 19.5% out of 600 patients with CP, a pathological condition named "groove pancreatitis" (36). This form of CP is characterized by the formation of scar plate between the head of the pancreas and the duodenum. Scars in the groove leads to complications that are also determined by the topography: disturbance in the motility of the

duodenum, stenosis of the duodenum and a tubular stenosis of the common bile duct, which occasionally leads to obstructive jaundice. These alterations might be responsible of several symptoms present in CP and also for post-prandial pain probably due to the compression of several critical structures, such as nerves and ganglia, present between the pancreatic head and the duodenum (37).

Conclusion

Pain in CP is usually so intense and long-lasting that the follow-up care of patients is often difficult and frustrating. In approximately 75% of cases, CP presents with recurrent or continuous deep and gnawing abdominal pain, characteristically situated in the upper abdomen to the left of the midline passing round or through to the back.

There is still a disagreement over the mechanisms that contribute to the generation of pain, and as regards the best method of managing pain in chronic pancreatitis. Earlier pain hypotheses for example, the increased intraductal and intraparenchymal pressure or post-prandial pancreatic hyperstimulation caused by decreased enzyme secretion and the insufficient functioning of the so-called "negative feedback mechanism", are more and more often questioned as reliable explanations of abdominal pain in patients with CP.

During the last decades much information has been accumulated on the occurrence and distribution of neuropeptides in the gastro-entero-pancreatic system. Additionally, alterations of the enteric nervous system in the regulation of gut functions have been postulated for a number of pathological conditions, including achalasia, Hirschsprung's disease, inflammatory bowel diseases, irritable bowel diseases etc. (37-41).

Our reported findings on possible mechanisms of pain generation in CP, implicate the involvement of neuropeptides released from enteric and sensory afferent neurons and their functional interactions with inflammatory cells in the pathogenesis of both, pain generation and chronic inflammation of the pancreas. This concept of neuropeptides as mediators of "neurogenic inflammation" is also discussed in disorders of the eye, skin, respiratory and gastrointestinal tract (42-43).

Taken together, the present data provides evidence for neuroimmune cross-talk in the pathogenesis of pain and inflammation in CP. Further studies are needed to clarify the interaction of inflammatory cells and nerves in CP.

References

- 1) Beger H.G., Büchler M., Malferteiner P., eds.: *Standards in pancreatic surgery*. New York: Springer-Verlag, 1993, 41-46.
- 2) Beger H.G., Krautzberger W., Bittner R., Büchler M.: *Duodenum-*

- preserving resection of the head of the pancreas in patients with severe chronic pancreatitis. *Surgery*, 1985, 97: 467-473.
- 3) Büchler M.W., Friess H., Müller M., Wheatley A.M., Beger H.G.: *Randomized trial of duodenum-preserving pancreatic head resection versus pylorus-preserving Whipple in chronic pancreatitis*. *Am J Surg*, 1995, 169: 65-69.
 - 4) Manes G., Pieramico O., Uomo G.: *Pain in chronic pancreatitis: recent pathogenetic findings*. *Minerva Gastroenterol, Dietol*, 1992, 38:137-143.
 - 5) Kloppel G.: *Pathology of chronic pancreatitis and pancreatic pain*. *Acta Chir Scand*, 1990, 156: 261-265.
 - 6) Hilsted J., Worning H.: *Pain in chronic pancreatitis*. *Pain*, 1990, 43:390.
 - 7) Jansen J.B.: *Pain in chronic pancreatitis*. *Scand J Gastroenterol*, 1995, 212:117-125.
 - 8) Ammann R.W., Akovbiantz A., Largiader F., Schueler G.: *Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical surgical series of 245 patients*. *Gastroenterology*, 1984, 86:820-828.
 - 9) Lankisch P.G., Lohr-Happe A., Otto J., Cruzefeldt W.: *Natural course of chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease*. *Digestion*, 1993, 54:148-155.
 - 10) Hayakawa T., Kondo T., Shibata T., Sugimoto Y., Kitagawa M.: *Chronic alcoholism and evolution of pain and prognosis in chronic pancreatitis*. *Dig Dis Sci*, 1989, 34: 33-38.
 - 11) Miyake H., Harada H., Kunchika K., Ochi K., Kimura I.: *Clinical course and prognosis of chronic pancreatitis*. *Pancreas*, 1987, 2:378-385.
 - 12) Jensen A.R., Matzen P., Malchow-Moller A., Christoffersen I.: *Pattern of pain, duct morphology, and pancreatic function in chronic pancreatitis. A comparative study*. *Scand J Gastroenterol*, 1984, 19:334-338
 - 13) Malfertheiner P., Büchler M., Stanescu A., Ditschuneit H.: *Pancreatic morphology and function in relationship to pain in chronic pancreatitis*. *Int J Pancreatol*, 1987, 2:59-66.
 - 14) Malfertheiner P., Pieramico O., Büchler M., Ditschuneit H.: *Relationship between pancreatic function and pain in chronic pancreatitis*. *Acta Chir Scand*, 1990, 156: 267-271.
 - 15) Hacker J.F., Chobanian S.J.: *Pain of chronic pancreatitis: etiology, natural history, therapy*. *Dig Dis*, 1987, 5:41-48.
 - 16) Bradley E.L.: *3d. Pancreatic duct pressure in chronic pancreatitis*. *Am J Surg*, 1982, 144:313-316.
 - 17) Ebbehøj N.: *Pancreatic tissue fluid pressure and pain in chronic pancreatitis*. *Dan Med Bull*, 1992, 39:128-133.
 - 18) Ebbehøj N., Borly L., Bulow J., Rasmussen S.G., Madsen P., Matzen P., Owre A.: *Pancreatic tissue fluid pressure in chronic pancreatitis. Relation to pain, morphology, and function*. *Scand J Gastroenterol*, 1990, 25:1046-1051.
 - 19) Manes G., Büchler M., Pieramico O., Di Sebastiano P., Malfertheiner P.: *Is increased pancreatic pressure related to pain in chronic pancreatitis?* *Int J Pancreatol*, 1994, 15: 113-117.
 - 20) Ebbehøj N., Borly L., Madsen P., Matzen P.: *Pancreatic tissue fluid pressure during drainage operations for chronic pancreatitis*. *Scand J Gastroenterol*, 1990, 25:1041-1045.
 - 21) Ditschuneit H.: *Treatment of pain in chronic pancreatitis by inhibition of pancreatic secretion with octreotide*. *Gut*, 1995, 36:450-454.
 - 22) Ihse I., Borch K., Larsson J.: *Chronic pancreatitis: results of operations for relief of pain*. *World J Surg*, 1990, 14: 53-58.
 - 23) Malfertheiner P., Mayer D., Büchler M., Dominguez-Munoz J.E., Schiefer B., Ditschuneit H.: *Treatment of pain in chronic pancreatitis by inhibition of pancreatic secretion with octreotide*. *Gut*, 1995, 36:450-454.
 - 24) Büchler M.W., Binder M., Friess H.: *Role of somatostatin and its analogues in the treatment of acute and chronic pancreatitis*. *Gut*, 1994, 35:S15-19.
 - 25) Keith R.G., Keshavjee S.H., Kerenyi N.R.: *Neuropathology of chronic pancreatitis in humans*. *Can J Surg*, 1985, 28:207-211.
 - 26) Bockman D.E., Büchler M., Malfertheiner P., Beger H.G.: *Analysis of nerves in chronic pancreatitis*. *Gastroenterology*, 1988, 94:1459-1469.
 - 27) Büchler M., Weihe E., Friess H., Malfertheiner P., Bockman E., Müller S., Nohr D., Beger H.G.: *Changes in peptidergic innervation in chronic pancreatitis*. *Pancreas*, 1992, 7:183-192.
 - 28) Di Sebastiano P., Fink T., Weihe E., Friess H., Innocenti P., Beger H.G., Büchler M.W.: *Immune cell infiltration and growth-associated protein 43 expression correlate with pain in chronic pancreatitis*. *Gastroenterology*, 1997, 112:1648-1655.
 - 29) Youn S.H., Maeda T., Kurisu K., Wakisaka S.: *Growth-associated protein-43 (GAP-43) in the regenerating periodontal Ruffini endings of the rat incisor following injury to the inferior alveolar nerve*. *Brain Res*, 1998, 787:41-48.
 - 30) Fu S.Y., Gordon T.: *The cellular and molecular basis of peripheral nerve regeneration*. *Mol Neurobiol*, 1997, 14: 67-116.
 - 31) Nahin R.L., Ren K., De Leon M., Ruda M.: *Primary sensory neurons exhibit altered gene expression in a rat model of neuropathic pain*. *Pain*, 1994, 58:95-108.
 - 32) Stead R.H., Kosecka-Janiszewska U., Oestreicher A.B., Dixon M.F., Bienenstock J.: *Remodeling of B-50 (GAP-43)- and NSE-immunoreactive mucosal nerves in the intestines of rats infected with *Nippostrongylus brasiliensis**. *J Neurosci*, 1991, 11:3809-3821.
 - 33) Fink T., Di Sebastiano P., Büchler M., Beger H.G., Weihe E.: *Growth associated protein-43 and protein gene product 9.5 innervation in human pancreas: changes in chronic pancreatitis*. *Neuroscience*, 1994, 63:249-266.
 - 34) Levy P., Lesur G., Belghiti J., Fekete F., Bernades P.: *Symptomatic duodenal stenosis in chronic pancreatitis: a study of 17 cases in a medical surgical series of 306 patients*. *Pancreas*, 1993, 8:563-567.
 - 35) Prinz R.A., Aranha G.V., Greenlee H.B., Kruss D.M.: *Common duct obstruction in patients with intractable pain of chronic pancreatitis*. *Am Surg*, 1982, 48:373-377.
 - 36) Becker V., Mischke U.: *Groove pancreatitis*. *Int J Pancreatol*, 1991, 10:173-182.
 - 37) Hiraoka T., Watanabe E., Katoh T., Hayashida N., Mizutani J., Kanemitsu K., Miyauchi Y.: *A new surgical approach for control of*

pain in chronic pancreatitis: complete denervation of the pancreas. Am J Surg, 1986, 152:549-551.

38) Bishop A.E., Polak J.M., Bryant M.G., Bloom S.R., Hamilton S.: *Abnormalities of vasoactive intestinal polypeptide-containing nerves in Crohn's disease.* Gastroenterology, 1980, 79:853-860.

39) Goldin E., Karmeli F., Selinger Z., and Rachmilewitz D.: *Colonic substance P levels are increased in ulcerative colitis and decreased in chronic severe constipation.* Dig Dis Sci, 1989, 34:754-757.

40) Mantyh P.W., Mantyh C.R., Gates T., Vigna S.R., Maggio J.E.: *Receptors binding sites for substance P and substance K in the canine gastrointestinal tract and their possible role in inflammatory bowel disease.* Neuroscience, 1988, 25:817-837.

41) Mantyh C.R., Gates T.S., Zimmerman R.P., Welton M.L., Passaro E.P., Vigna S.R., Maggio J.E., Kruger L., Mantyh P.W.: *Receptor binding sites for substance P, but not substance K or neuromedin K are expressed in high concentrations by arterioles, venules, and lymph nodules in surgical specimen obtained from patients with ulcerative colitis and Crohn disease.* Proc Natl Acad Science, 1988, 85:3235-3239.

42) Weihe E., Krekel J.: *The neuroimmune connection in human tonsils.* Brain Behav Immun, 1991, 5:41-54.

43) Di Sebastiano P., Fink T., Di Mola F.F., Weihe H., Innocenti P., Friess H., Büchler M.W.: *Neuroimmune appendicitis.* The Lancet, 354, 9177:461-465, 1999.

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