INTRODUCTION
Pancreatitis constitutes a prevailing clinical condition characterized by inflammatory process in the pancreas affecting both its exocrine and endocrine function. The disease can be classified according to its duration. Based on this, acute pancreatitis represents a mild, self-limited condition accompanied by elevated serum pancreatic enzymes levels. Chronic pancreatitis (CP) is the progressive and irreversible destruction of the pancreas which often (if not always) appears as the result of clinical or subclinical episodes of acute pancreatitis. In this sense, one can consider these two clinical conditions as parts of the same entity in which the transition from the acute to the chronic state can be subtle or even not perceived\(^1\). The main histological findings in CP are the destruction of the pancreatic parenchymal and ductal anatomy, fibrosis, loss of acinar and islet cells and the infiltration of inflammatory cells in the gland. One of the predominant symptoms of CP is pain which is constant or recurrent intense abdominal (often radiating to the back) present in 80-90% of patients\(^2\).

Pain compromises a very common symptom encountered in everyday clinical practice. Defining pain is quite difficult since it is perceived more as a personal experience. In 1979 the International Association for the Study of Pain (IASP) established pain as an unpleasant sensory and emotional experience in relation with a real or potential tissue destruction or described as such \(^3\). Pain can be classified as normal referring to the term noxious. This is the temporal sense triggered by a stimulus of such intensity that causes tissue damage or a small patulous trauma without extensive inflammation or nervous system damage. This kind of pain can be caused by a thermical, chemical or mechanical stimulus and it can be considered as a protective mechanism against harmful factors. Pathological pain is the result of inflammatory reaction provoked by tissue destruction or nervous system harm. Its distinguishing feature is the incongruity between

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**ABSTRACT:** The purpose of the present study is the bibliographic review of chronic pancreatitis (CP) and its underlying pain-induction mechanisms. Chronic pancreatitis is defined as a progressive inflammatory process characterized by destruction or total eradication of the parenchyma and fibrosis. One of its prevailing symptoms is pain. It is severe, dull, epigastric, often radiating to the back, recurrent or permanent. Pain stands for an unpleasant, frustrating sensation evoked by stimuli like harmful agents and inflammation, as a reaction of the human body alerting it for the presence of an intrinsic or extrinsic hazard. In the case of CP pain a great number of causative mechanisms has been proposed. Formerly, it was perceived as originating from the inflammatory and fibrotic process. Pancreatic ischemia related to ductal and parenchymal tissue hypertension and extrapancreatic causes like bile duct and duodenal stenosis have also been proposed. Most recently, emphasis has been placed on the neuropathic component of CP as pain is provoked by peripheral nociceptive mechanisms. Pancreatic neuropathy in terms of neural damage, increased neural density and hypertrophy along with central sensitization (spinal and cerebral hyperexcitability) are also involved in this theory. The various hypotheses highlight its multifactory nature and the need for further exploration.

**Key Words:** Pancreatitis, Chronic pain, Neuropathy, Nociception.
stimulus-reaction in the sense that the stimulus is not adequate to cause pain sensation of such intensity. This is due to the fact that there is a change in the nociceptive system of pain. This results in central hypersensitivity which does not allow for the incoming sensory information to be evaluated correctly\(^4\). Pain can be caused even in the absence of a stimulus and it may not be restricted to the trauma area. Pain also is sorted as acute or chronic and somatic, visceral or neuropathic. Being a multifactory and complex entity, pain consists of three elements. The sensory-discriminative, capable of localizing pain area and assessing its intensity. The affective-motivational quantifies how unpleasant pain is and provokes feelings like fear and distress. The cognitive-evaluative component takes part in memory of the experience and evaluates this\(^5\).

The pancreas has a complicated innervation, the extrinsic and the intrinsic one. Extrinsic innervation consists of both afferent and efferent nerve fibers supplied by the vagus nerve (parasympathetic) and splachnic nerves (sympathetic). Visceral information is transferred to the central nervous system (CNS) either by the vagus nerve to the brainstem or splachnic nerves to the spinal cord. These two types of nerves are considered the ones for signaling pancreatic pain stimuli\(^6\). It is commonly accepted that nociceptive information is mainly transmitted via splanchic nerves. The cell bodies for the axons can be found in the thoracic dorsal root (Level T5-T10 for splanchic nerves) and in nodose ganglia (for vagus nerve). Intrinsic innervation consists of intrapancreatic ganglia and nerve fibers from duodenum’s enteric neurons, the so-called enteropancreatic innervation\(^7\). As far as nociceptive input is concerned, it is regarded that dermatomes between somatic and visceral neurons can converge. Dermatome T10 is thought to converge with pancreatic viscerotomes\(^8\).

Considering the sensory pathway of pain, how pain is transmitted from the periphery to brain centers and how it is perceived and further analyzed, one can say that a number of different agents is involved. The pain stimulus is carried from the periphery to the center mainly via the myelinated A\(\delta\) and the unmyelinated C sensory nerve fibers. A\(\delta\) nerve fibers are thought to transmit acute pain whereas C fibers are related to demersal, dull pain\(^9\). Through these fibers, stimulation reaches the first-order neurons, the cells of dorsal ganglions. Spinal nerves consist of somatomotor efferent fibers, somato-sensory afferent fibers, visceromotor efferent fibers and viscerosensory afferent nerve fibers. The pain stimulus is then transmitted to the second-order neurons, the cells of the dorsal horn nuclei and the dorsal substantia gelatinosa cells located in dorsal horn. Excitation is carried to the second-order neurons via the posterior roots of spinal nerves and the dorsolateral fasciculus respectively. The stimulus ends up in the third-order neurons, the cells of the thalamus postero-external ventral nucleus via the lateral spinthalamic fasciculus. An acute, stinging pain related stimulus is transmitted to these neurons. Finally, pain excitation will reach the cortex of the central posterior gyrus. In case the stimulus refers to burning pain, it is transferred to the reticular formation’s nuclei cells cited in the cerebral brainstem via the spinthalamic lateral fasciculus. From that point, excitation will alert and inform the CNS of a potential injury exemplified through pain perception. However, the final perception of pain appears to be the result of both facilitatory and inhibitory mechanisms. Inhibitory descending pathways are responsible for preventing pain signals from reaching the CNS and are found in the periaqueductal grey, the locus coerules and the dorsal reticular nucleus in the medulla\(^9,6\). Thus a proper answer to the painful stimulus can be expressed via the motor system’s efferent nerves and the autonomic nervous system\(^9\).

Clarifying the etiology of pain in CP seems a challenge, since a number of different theories has been proposed. Extrapancreatic causes concern bile duct and duodenal stenosis due to fibrosis and inflammation. Pancreatic causes refer to increased intrapancreatic pressure mechanisms, hypercholecystokininemia, the compartment syndrome, pancreatic fibrogenesis, oxidative stress, gene mutations which contribute to the inflammatory process and complications from the pancreas, like pseudocysts and masses.

**Bile duct and duodenal stenosis**

It is accepted that CP causes intense fibrosis, pancreatic and peripancreatic tissue inflammation in its course. Taken together fibrosis and inflammation can provoke stenosis to nearby organs (bile duct or duodenum) by the formation of strictures. Stenosis developed as
a complication of CP has been seen as the source of pain in the disease\textsuperscript{10}. There is evidence that pain can be alleviated by biliary drainage methods applied to common bile duct stenosis. On the other hand, biliary stenosis and its role in the induction of pain have been highly questioned by other authors\textsuperscript{11,3}. Stenosis has also been regarded as a complication of a pathological entity called “groove pancreatitis”. The term was firstly introduced by Stolte et al\textsuperscript{12} to describe a condition found in 19.5% of 600 CP patients. Its main characteristic is a scar or fibrous plate formed between the pancreatic head and the duodenum’s wall. This plate can result in complications like a disturbance in the duodenum’s motility and a duodenal and/or common bile duct stenosis. Nerves and ganglia located between the pancreatic head and the duodenum are compressed by the fibrous plate and this can trigger pain in CP patients\textsuperscript{13}.

**Increased intrapancreatic pressure mechanisms**

Another hypothesis of CP pain generation concerns pancreatic causative mechanisms. Increased intrapancreatic pressure is the pathological entity referring to both ductal and pancreatic interstitial hypertension. This condition of pressure is thought to cause a compartment syndrome which inevitably leads to pain induction\textsuperscript{14}. In the ductal system normal pressure ranges from 7 to 15 mmHg. However in the case of CP patients, ductal hypertension has been found 20mmHg with a maximum of 80 mmHg\textsuperscript{15,16}. This ductal hypertension theory is based on the assumption that the increased secretion of pancreatic juice along with an obstruction because of strictures or calculi/stones leads to an elevated pressure. This CP generation pain mechanism has been supported by many researchers in the past\textsuperscript{17,18}. Another study\textsuperscript{19} also established a relation between intrapancreatic pressure and the intensity of abdominal pain. However, there have been studies that demonstrate the opposite case, namely that pancreatic duct pressure is not the main source of pain. It was found that CP patients still experience pain after pancreatic duct drainage methods have been applied. Pain was perceived as being the same like before drainage or in some other cases long-term pain relief was not achieved. Pain was recorded to reoccur in about 40% of CP patients undergoing a drainage procedure\textsuperscript{20}. At the same time, another study by Vestergaard et al\textsuperscript{21} documented no relation between manometric findings and the severity of CP.

Pancreatic parenchymal tissue hypertension has also been proposed as a major factor in CP pain generation and its intensity\textsuperscript{22}. The chronically inflamed pancreas causes an extended fibrosis which in turn does not allow the gland to expand and absorb the already created pressure by the increased ductal volume. Increased parenchymal pressure has been observed in CP patients up to 30 mm Hg when the average normal pressure in the gland is 7 mmHg\textsuperscript{4}. A rare case has also been documented\textsuperscript{23} in which parenchymal pressure was up to 662 mm Hg in an alcoholic CP patient. It has also been found that by applying ductal decompression and surgical incision of the gland, pancreatic pressure decreases or even returns to normal levels\textsuperscript{24}. In case parenchymal tissue pressure increases again postoperatively, then pain can reoccur.

**Hypercholecystokininemia**

The elevated pressure is also created by the increased stimulation and exocrine secretion because of the hypercholecystokininemia found in CP. Cholecystokinin (CCK) is thought to generate pain by stimulating pancreatic juice secretion which contributes to the glandular hypertension and ischemia. Elevated CCK levels have been documented in some early stage CP patients compared to controls.\textsuperscript{25} Moreover, it has been speculated that increased CCK levels induce pancreatic pain by acting directly on the CNS, since CCK receptors exist in the vomiting center. However, this center lacks a blood-brain barrier, so its neurons come in contact with CCK in blood and a stimulation of pain is achieved\textsuperscript{26}. On the contrary, another study\textsuperscript{25} exemplifies that there is no connection between exocrine secretion of the gland and increased pain levels in CP. The validity of the increased pressure theory in CP pain induction was also questioned in another study\textsuperscript{27} showing that octreotide used for pancreatic secretion inhibition did not manage to reduce the CP pain intensity.

**The compartment syndrome**

An additional CP pain hypothesis suggests that the compartment syndrome resulting from pancreatic hypertension plays a vital role. In a feline model of chronic pancreatitis\textsuperscript{28}, it was demonstrated that the
increased interstitial pressure can cause a blood flow reduction. This leads to the gland’s ischemia which at least in part has been regarded the source of pain in CP as it is a well known stimulus of pain. Pancreatic fibrogenesis

One of the main histological findings in CP is the development of fibrosis intralobular and perilobular. Fibrosis implies the accumulation of fibroblasts and collagen which replace exocrine parenchyma. Extended fibrogenesis with accumulation of extracellular matrix can lead to irreversible scarring. Even though its pathophysiology still remains unclear, it has been suggested that glandular fibrosis provokes an intraductal hypertension and thereby a chronic pain situation. Pancreatic fibrosis and collagen synthesis is mainly mediated by the pancreatic stellate cells when activated. There is evidence that they are activated in an early stage of CP after the gland’s injury by alcohol consumption. Thus, they produce cytokines and chemokines, contributing to fibrogenesis, pancreatic tissue ischemia and pain. Nevertheless, recent studies emphasize the fact that there does not exist a link between fibrogenesis and intensity of pain thus suggesting other, more significant pain generation mechanisms in CP.

Oxidative stress

The role of oxidative stress has also been implied as a possible mediator in CP pain mechanism. More specifically, it has been suggested that oxygen-derived free radicals are involved in the pancreatic inflammatory process as they are cytotoxic agents, released from inflammatory cells when there is an oxidative burst. Oxidative stress promotes cell or tissue injury directly or indirectly by altering signal pathways or provoking inflammation, ischemia or acidosis.

Gene mutations

More recently, it has been implied that gene mutations can be responsible, at least in part, for the pathogenesis of CP pain, especially the hereditary and idiopathic CP and recurrent acute pancreatitis pain. These concern the gene encoding the cationic trypsino-gen and the gene for the pancreatic secretory trypsin inhibitor. At cellular level they are thought to be responsible for recurrent episodes of inflammation and pain induction.

Pancreatic complications

Complications from the pancreas have also been thought as the origin of pain in CP. Pseudocysts can be responsible for pain especially when they rapidly grow in size and compress adjacent organs. In CP, they tend to disappear either automatically or with octreotide treatment thus ameliorating the pain sensation. Pseudocysts are usually considered the result of acute exacerbations of CP. In this perspective, acute exacerbations can lead to an intense pancreatic and peripancreatic tissue inflammation involving noxious agents and inflammatory cell infiltration which inevitably aggravates pain intensity. Recurrent attacks of acute inflammation seem to promote a cascade of activated enzymes and other substances causing thus a prolonged pancreatic injury and pain intensification. In some cases, an inflammatory pancreatic mass can be developed, mainly in the head of the pancreas. In such a case, this mass is thought to induce or aggravate CP pain, as it can compress pancreatic or peripancreatic nerves and obstruct the common bile duct or the pancreatic duct. In some other cases, pain is the result of CP complications, like a superimposed carcinoma, a relevant pathological condition (mainly gastroparesis) or an irrelevant coexisting entity.

So far pain in CP has traditionally been classified as inflammatory in nature. However, a new insight into its pathogenesis has been offered by the concept of the neuropathic pain syndrome in CP. According to this, it has been speculated that pain in CP has a neuropathic component closely linked to the inflammation process. Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somato-sensory system”. Most recently Demir et al characterized CP pain as of mixed-type with a mainly neuropathic basis. These researchers proposed that pain mechanisms can be classified as central or peripheral based on their location and nociceptive or neuropathic according to whether there is a stimulation of intact or damaged nerve fibers. In their study, CP underlying pain mechanisms were divided into the following categories:

Peripheral intrapancreatic nociceptive mechanisms, including hypertension, agents, receptors and neurotrophic factors.

Peripheral extrapancreatic nociceptive mechanisms, that is DRG neuronal sensitization.
Peripheral neuropathic mechanisms: pancreatic neuropathy referring to eosinophil infiltration, changes in intrapancreatic nerves, neural remodeling and chemokines.

Central (spinal) neuropathy, that is spinal neurons’ excitability.

Central (cerebral) neuroplasticity involving increased cerebral surface activity and altered brain potentials.

**Peripheral intrapancreatic nociceptive mechanisms**

Peripheral intrapancreatic nociception refers to stimulation of pain receptors, neurons located in the gland. An increased presence of nociceptive signals in the periphery (pancreas) is associated with pain generation in CP. A number of various substances has been held responsible for stimulating pancreatic nociception via acting upon C or Aδ nerve fibers. In the past, it was suggested that hypertension, both ductal and pancreatic and toxic agents, like alcohol were the main factors in exciting nociceptive nerve fibers. However, later it was found that even in the absence of these factors CP patients still experienced pain. Thus attention was drawn on other possible explanations. In another study, it was proposed that CP pain can be provoked by other molecules, like cytokines, tryptase, bradykinin along with protons, hydrogen sulfide, serotonin and calcium. These agents are responsible for reducing the threshold for peripheral sensory nerve fibers’ activation. The key mediator of these agents’ upregulation is the damage of acinar cells in the inflamed pancreas.

For example bradykinin, a well-known activator of sensory neurons can indirectly trigger the transient receptor potential vanilloid (TRPV1) by producing arachidonic acid metabolites and lipoxygenase products. TRPV1 is a member of an ion channels superfamily involved in sensory transduction. It is activated by a variety of chemical agents (mainly capsaicin), acid (protons, H+), heat and mediators (bradykinin, substance P, glutamate, prostaglandins and ATP), factors which lower its activation threshold. It is expressed on C and Aδ nerve fibers and it is considered a non-selective cation channel permitting the flow of cations inwards the cell when activated. As a result, neurons depolarize and release neurotransmitters, such as substance P (SP) and calcitonin gene-related peptide (CGRP) in the spinal cord and the periphery. It has been documented that in human CP specimens there is an upregulation of SP- and CGRP-immunoreactive nerve fibers. In the pancreas these two nociceptive activation markers contribute to local inflammation by their vasodilatory and chemotactic features. SP is mainly vasodilatory in nature, causing endothelial cell contraction and plasma extravasation. However, it has been reported that SP can also act as a vasodilator. CGRP is considered a vasodilator contributing to edema formation. Thus, TRPV1 is said to contribute to pancreatic inflammation by provoking vasodilation, and plasma extravasation. It is also considered a mediator of neuronal hypersensitivity and an integrator of responses to inflammatory mediators. In pathological conditions, a change in the expression and sensitivity of the TRPV1 pain channel leads to chronic pain experienced even after the noxious stimulus has disappeared. In a CP study in humans an upregulation of TRPV1 receptors in pancreatic tissues was found even though no connection to pain scores was observed.

SP and CGRP seem to be key factors in the so-called neurogenic inflammation. This is defined as the inflammatory process caused by substances released from sensory nerves when activated. So, inflammation process along with hyperexcitability of pancreatic receptors contribute to the pathogenesis of CP pain. Local administration of these two proinflammatory actors can mimic neurogenic inflammation and the use of antibodies and antagonists can block this phenomenon.

SP has also been involved in the direct stimulation of interleukin 8 (IL-8) in macrophages surrounding pancreatic nerves. In alcoholic CP an increased expression of IL-8 in inflammatory cells has been detected. The increased mRNA expression of IL-8 in CP can be mediated by SP release. By exciting post-ganglion sympathetic neurons, IL-8 is capable of inducing hyperalgesia. Being itself a proinflammatory cytokine, IL-8 is said to take part in leukocyte recruitment and activation. In this sense, IL-8 seems to play an important role in the initiation and maintenance of the inflammatory process and chronic pain in CP. CP pain mechanism is also yielded by mast cells involved in nociceptive signaling. This hypothesis is based on evidence that mast cells have been related
to other pathological conditions where pain is a cardinal symptom. Mast cells are usually located around and within the perineurium of pancreatic nerve fibers. Thus they participate in the neuroimmune interaction created between neurons and immune cells, another proposed CP pain induction process. They also release mediators that increase neuronal excitability and pain signal transmission. Neurotransmitters (SP) can provoke mast cells degranulation. These products (tryptase and histamine) are thought to contribute to pain development by sensitizing and/or activating primary afferent neurons in the pancreas. Examining autopsy specimens of patients with painful CP, they exhibited a 3.5-fold increase in pancreatic mast cells compared to those in painless CP patients. In this experimental mice model of CP researchers also demonstrated that wild-type mice were more sensitive to pain in relation with mast cell deficient mice.

Furthermore, pain mechanism in CP has been related to the key receptor of SP, neurokinin-1 (NK-1R). An upregulation of NK-1R in nerves, fibroblasts and inflammatory cells (mostly mononuclear and poly-nuclear) has been documented. In this study, a correlation between NK-1R expression and features of CP pain (intensity and frequency) was established. NK-1R cited in the epineural nerve layer is thought to exert a direct influence on CP pain pathogenesis, since it leads to vasoconstriction and ischemia of pancreatic nerves.

One of the initial facts in pancreatitis is the activation of trypsinogen to trypsin, leading to a proteolytic cascade, the gland’s autodigestion and features of inflammation. Trypsin as a pancreatic protease can cause a sensory neuron hypersensitivity, by acting on the proteinase-activated receptor 2 (PAR-2), which is a pancreas located nociceptive receptor. PAR-2 is expressed in acinar cells and ductal epithelium and it regulates the gland’s exocrine secretion. Moreover, it can be found in endothelial, epithelial, mast cells and dorsal root ganglion neurons. It provokes vasodilation in vascular endothelial nerves and helps neurotransmission in neurons. In an experimental model of pancreatitis, abdominal hypersensitivity could be ameliorated by the administration of proteinase inhibitors, thus blocking PAR-2 involved in pain genesis. The same findings were observed in the study of Hoogerwerf et al. They found that trypsin’s infusion resulted in the dorsal root ganglia neurons’ activation by binding to PAR-2.

Neurotrophic factors have also been investigated regarding their possible role in CP pain pathogenesis. The nerve growth factor (NGF) was the first one to be implied, since it has been found overexpressed in CP tissue samples. It was cited in hypertrophic pancreatic nerves, intrapancreatic ganglia, metaplastic ductal cells and acinar cells. NGF is believed to take part in neural development involving proliferation, maturation and survival of central and peripheral nerves. It has also been involved in the activation of nociceptive nerve fibers causing a hyperalgesia state. This is based on evidence that there is an interaction between NGF and signaling pain systems in adult animals. NGF seems to be a mediator of inflammatory pain states. NGF is also thought to mediate the SP and CGRP synthesis (by increasing the TRPV1 sensitivity) and histamine release thus influencing chronic pain. It can regulate TRPV1 expression either by sensitizing TRPV1-bearing neurons or by upregulating its de novo expression.

NGF exerts its role by binding to two types of cell surface receptors, the high-affinity receptor tyrosin kinase receptor A (TrkA) and the low-affinity receptor p75. TrkA are located on primary afferent nociceptive neurons. In a study of CP tissue samples it was revealed that NGF mRNA was positively related to the degree of fibrosis, acinar cell injury and ductal metaplasia. However, no relation was established between NGF and pain features. It was TrkA mRNA expression that was linked to the intensity of pain in CP. This study underlines the role of the NGF/TrkA pathway in CP pain syndrome and neural morphological changes. Immunohistochemistry revealed that enlarged pancreatic nerves were the rule and they exhibited strong TrkA immunoreactivity. The electron microscope examination showed that even though pancreatic nerves were preserved, they appeared altered in CP. Their number and diameter were increased and their perineural sheath was destroyed, thus rendering nerves liable to bioactive irritant substances. This neuroimmune interaction is responsible for CP pain pathogenesis. TrkA was also found overexpressed in the perineurium. Even though the underlying mechanisms of nerve changes remain poorly understood, it has been assumed that the NGF/TrkA pathway and its activa-
tion is a key actor. There is growing evidence of the NGF/TrkA pathway influence on CP pain syndrome. A case of patients sharing insensitivity to painful stimuli and loss of sensory neurons due to a mutation in the TrkA gene has been reported. In animal models the use of either anti-NGF antibodies or TrkA-immunoglobulin G fusion protein has the capacity of reducing hyperalgesia.

Another member of the neurotrophin family related with CP pain states is the brain-derived neurotrophic factor. It was found that it can promote excitability in nociceptive sensory neurons either by linking to the p75 receptor or by using the sphingomyelin pathway. Its increased levels in CP and a strong relation with pain intensity have been reported in the study of Zhu et al. It is upregulated in degenerating acinar cells, enlarged nerves, intrapancreatic ganglia and dorsal root ganglia in CP. It has also been suggested that artemin, a member of the glial cell-line derived neurotrophic factor family and its receptor GFRα3 are involved in CP peripheral nociception, since they have both been found overexpressed in CP. A correlation between artemin and the severity of CP pain (frequency and intensity) was established, since this neurotrophic factor is responsible for thermal hyperalgesia and neural growth in the pancreas. Due to neural damage intrapancreatic ganglia and/or Schwann cells produce excessive amounts of artemin thus exciting dorsal root ganglia neurons. These neurons become a source of extrapancreatic artemin which then can be transferred to the gland enhancing the local neural sprouting. These findings point towards the existence of interplay of inflammatory cells, pancreatic nociceptive neurons, neuropeptides and their receptors leading to a state of peripheral nociceptive excitability responsible for CP pain sensation.

Peripheral extrapancreatic nociceptive mechanisms
The importance of extrapancreatically located nociceptive mechanisms in the CP pain origin has also been emphasized. Evidence of this was provided by an experimental animal model of CP. In that study, trinitrobenzene sulfonic acid was administered in rats in order to induce CP. More depolarized resting potentials and suppression of A-type potassium current density were recorded in pancreas-specific DRG neurons compared to controls. Furthermore, increased TRPV1 expression and enhanced capsaacin responsiveness of DRG neurons related to pancreas were demonstrated in this CP model. This DRG neuronal sensitization is said to contribute to pain signals transduction and perception in CP.

Peripheral neuropathic mechanisms
The notion of pancreatic neuropathy as a possible pathogenetic mechanism in CP pain was initially hypothesized based on neural alterations in histopathological tissue samples. Keith et al were the first to report an infiltration of inflammatory cells, mostly eosinophils around intrapancreatic nerves in CP. An important correlation of pain scores with eosinophilic infiltration was demonstrated in that study. This finding was advocated by other studies showing that nerves in CP undergo major changes. Analyzing intrapancreatic nerves it was found that they were increased in terms of their number / density and they were hypertrophic. In addition, a severe neural damage was detected. The perineurium was no longer intact, it was disrupted. Thus its role as a protective barrier did not exist and inflammatory cells could invade the inner part of nerves. There they could secrete noxious factors or agents. Researchers came to the conclusion that pain is not induced by neural constriction due to fibrosis and that these neural changes possibly affect both sensory and motor nerves. The term pancreatic neuritis was introduced in order to exemplify the phenomenon of neural damage, neural sprouting and hypertrophy along with inflammatory cells’ penetration into pancreatic nerves. Pancreatic neuritis was perceived as a responsible factor of CP pain induction.

Years later, more detailed studies were the first to demonstrate a causal relation between pancreatic neuritis and frequency / intensity of CP pain. In this way, pancreatic neuropathy and the neuropathic element of CP pain were established. Neural intrapancreatic damage is followed by a repairing attempt defined as pancreatic neuroplasticity. Increased neural density and hypertrophy are the major neuroplastic changes involved in CP pain initiation and maintenance. A well-known neural plasticity marker, the Growth-associated protein 43 has been found overexpressed in CP tissue samples. Neuronal Growth-associated protein 43 immunoreactivity was closely linked to CP pain scores.
Pancreatic neuropathy also results in an altered innervation of the gland in CP. Both sympathetic and parasympathetic innervations appear seriously diminished especially in patients with abdominal pain and pancreatic neuritis. Neural remodeling is another feature of the pancreatic neuropathic pain theory which may in part explain the reason why denervation techniques are poorly successful in the CP pain treatment. It suggests that since sympathetic nerves appear decreased in CP then pain should be transmitted by afferents other than the ones running with the splanchnic nerves. Neural remodeling stands for both nerve alterations and glia activation resulting in a different type of CP nerve population. Glia cells of the peripheral nervous system, Schwann cells exhibit a proliferation and de-differentiation because of the neural injury in CP. By releasing neurotrophic factors they sensitize nociceptors and promote axonal repair and neural sprouting. Glial activation is demonstrated by alterations in two markers, the glial transcription factor Sox 10 and the neuroepithelial stem cell marker Nestin. In CP there is a down-regulation of neural Sox10 expression indicating a decrease of mature Schwann cells and a dramatic up-regulation of neural Nestin immunoreactivity contributing to neural sprouting.

In an attempt to clarify the way inflammatory cells gather into intrapancreatic nerves, it was suggested that neuronal chemokines have a role in yielding CP pain. The prototype of such molecules is fractalkine. It can influence CP neuropathic alterations and pain, since it is a chemoattractant for immune cells (granulocytes and macrophages), it takes part in glia cells’ activation and pancreatic tissue fibrosis. It exerts fibrogenic and pain-regulating effects. In the same study, an overexpression of tissue fractalkine and its receptor CX3CR1 on protein level together with increased nerve immunoreactivity were recorded. Thus these two were related to the pathogenesis of visceral pain in CP.

Central neuropathy

The continuous peripheral sensitization of the pancreatic nociceptors ends up in spinal neurons’ excitability. This persistent visceral nociceptive input enhances the transmission of nociceptive signals to the brain by the spinal dorsal horn neurons cited in the substantia gelatinosa. Central sensitization is responsible for the two characteristic symptoms of neuropathic pain, that is allodynia (pain sensation caused by non-noxious stimuli) and hyperalgesia (increased pain sensation triggered by a normal pain stimulus). Central hyperexcitability becomes clinically obvious by the increased area of the referred pain sensation, a key element in neuropathic pain. This is due to the fact that afferent nerve fibers from different visceral and somatic organs seem to converge on the same spinal neurons. It is also accompanied by the phenomenon of temporal summation. This means that repeated pain stimuli tend to become more and more painful even though the stimulus’ intensity remains the same. Central hyperexcitability also provokes a state of generalized hyperalgesia. Different causal mechanisms have been proposed for this hyperalgesia state. One possibility is that the ongoing visceral nociceptive input results in a supraspinal (rostral ventromedial medulla) descending facilitation perpetuating chronic pain situation. This was exemplified in the study of Vera-Portocarrero et al. using an experimental rat model of CP. Depleting brainstem cells responsible for the descending inhibitory control, it was found that CP hypersensitivity could be ameliorated. Inhibitory control activated in the presence of ongoing nociceptive input seems to be impaired in CP. Pronounced hyperalgesia has also been attributed to a state of autonomous central sensitization. In this case, due to the enhanced peripheral nociceptive input, central neuroplasticity appears. These changes in central pain processing make pain perception pathological.

Central neuroplasticity

Focusing on cerebral pain processing in CP, increased cerebral surface activity and altered brain potentials, key features of neuropathic pain, have been reported. CP patients exhibit an increased theta wave activity on electroencephalogram during painful visceral stimulation. Modified CNS activity is also advocated by the reorganization in cortical projections of the nociceptive system because of the recurrent pain syndrome in CP. A discrepancy in latency and topographic distribution exists when CP patients’ brain potentials are compared to controls. Analysis of the typical visceral-sensory areas of the cerebral cortex (the bilateral insula, the anterior cingulated gyrus and
the bilateral secondary somatosensory areas) in CP patients strongly supports the hypothesis of changes in brain pain processing\textsuperscript{56}. An overactivity detected in the right secondary somatosensory cortex has been attributed to the increased glutamate levels in CP patients. This increase in glutamate seems responsible for the excitable cortex activity and can account for a pain-sustaining central neuroplasticity. The same study provides a link between peripheral and central neuropathy in CP. Researchers hypothesized that pain mechanisms can either be a maladaptive or salutogenic response to the disease. Pancreatic inflammation and neuropathy act as a stimulus for local nociceptive nerves. Once they are activated, they transmit visceral nociceptive information to the CNS. So, a neural network is activated, generating pain and increasing or decreasing the glandular inflammatory process. In this sense, a vicious circle of inflammation / pain can be created and sustained or pain can be the body’s warning of pancreatic malfunction.

It could be claimed that pain in CP still remains a challenge since its underlying mechanisms are poorly understood. A variety of pain-induction mechanisms has been proposed and new theories are still evolving. Pancreatitis-induced pain is probably multifactorial in origin and a network of peripheral and central processes is involved. It is hypothesized that the persistent pancreatic inflammation in CP causes a release of mediators which sensitize pancreatic nociceptive receptors thus they increase in response. The ongoing nociceptive input results in plastic changes in the spinal cord and central sensitization. Thus nociceptive information is transmitted to central pain-related areas, the viscerosensory areas of the cerebral cortex, where pain sensation is perceived and further processed. Understanding the underlying CP pain pathogenesis will provide the basis for more effective future medical approaches to this refractory chronic condition. It is a field needing further exploration, so that CP pain management will no longer be unsuccessful, leading patients to hospitalizations, medical interventions and drug overuse.

**Mηχανισμοί πόνου στην χρόνια παγκρεατίτιδα.**

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ΠΕΡΙΛΗΨΗ Σκοπός της παρούσας εργασίας είναι η βιβλιογραφική ανασκόπηση της χρόνιας παγκρεατίτιδας και των βασικών μηχανισμών επαγωγής πόνου. Ορίζεται ως μια χρόνια φλεγμονώδης διαδικασία με καταστροφή ή πλήρη εξάλειψη του παρεγχυματικού ιστού και ίνωση. Ένα από τα κυριότερα συμπτώματα της χρόνιας παγκρεατίτιδας είναι ο πόνος, αμβλύς επιγαστρικός που αντανακλά στην πλάτη, επαναλαμβανόμενος ή συνεχής. Αναφέρεται σε μια δυσάρεστη, ενοχλητική αίσθηση που παράγεται από ένα ερεθισμό όπως φλεγμονή και βλαπτικούς παράγοντες. Μια αντίδραση του ανθρώπινου σώματος, που προκαλείται από τη φλεγμονώδη διαδικασία και την ίνωση. Η παγκρεατική ισχιαμία σε σχέση με την αυξημένη πίεση παρεγχυματικού ιστού και πόρων και εξωπαγκρεατικών αιτίες όπως η στένοση του χοληδόχου πόρου και του δωδεκαδακτύλου έχουν επίσης συμβάλει στην πρόκληση του πόνου. Πρόσφατα, έμφαση έχει δοθεί σε νευροπαθητικό στοιχείο όπου ο πόνος προκαλείται από περιφερικούς μηχανισμούς αλγαισθησίας. Η παγκρεατική νευροπάθεια, η αυξημένη πυκνότητα νευρικών ινών και η υπερεκμία μαζί με κεντρική ευαισθητοποίηση (υπερδιέγερση νοσοκομικών μυελών και εγκεφαλίου) συμβάλλουν επίσης σε αυτή τη θεωρία. Οι διάφορες υποθέσεις για τον μηχανισμό επαγωγής του χρόνου παγκρεατικού πόνου υπογραμμίζουν την πολυπαραγοντικότητά του και την ανάγκη για περαιτέρω διερεύνηση.

Λέξεις Κλειδιά: Παγκρεατίτιδα, Χρόνιος πόνος, Νευροπάθεια, Αλγαισθησία.
REFERENCES


