REVIEW

Current understanding of the neuropathophysiology of pain in chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is a chronic inflammatory disease of the pancreas. The main symptom of patients with CP is chronic and severe abdominal pain. However, the pathophysiology of pain in CP remains obscure. Traditionally, researchers believed that the pain was caused by anatomical changes in pancreatic structure. However, treatment outcomes based on such beliefs are considered unsatisfactory. The emerging explanations of pain in CP are trending toward neurobiological theories. This article aims to review current evidence regarding the neuropathophysiology of pain in CP and its potential implications for the development of new treatments for pain in CP.

Key words: Neurobiology; Neuropathophysiology; Pain; Pancreatic pain; Chronic pancreatitis

Core tip: Abdominal pain is the main symptom of patients with chronic pancreatitis (CP), yet the underlying mechanisms are not well understood. The emerging explanations of pain in CP are trending toward neurobiological theories. This article reviews these emerging concepts and their potential implications for the development of new treatments for pain in CP. Three major concepts attempting to explain the pathogenesis of CP pain: Pancreatic nociception and sensitization-induced pain, neuropathic remodeling, and central mechanism of pancreatitis pain are summarized, along with the specific molecules involved in each and potential therapeutic targets.

INTRODUCTION

Chronic pancreatitis (CP) is a persistent and chronic inflammatory disease of the pancreas. Approximately,

80%-90% of patients with CP typically suffer from pancreatic pain[1], which is commonly described as a constant, severe, and dull pain in the mid-epigastrium that radiates to the back and worsens by with high-fat meals. Unsurprisingly, the pancreatic pain can have substantial psychological and economic impact on patients. In addition, a recent study confirmed that the life quality of patients with CP is significantly worsened by pain severity and disease-related complications[2].

The pathogenesis of pancreatic pain is still not fully understood. Thus, management of this pain cannot be specific, leading to unnecessarily high treatment costs and ineffective outcomes. Many theories have been proposed to explain the pain mechanism based on anatomical changes including high pressure within the pancreatic duct, high pressure in the pancreatic parenchyma, and complications of pancreatic and extra-pancreatic structures (*i.e.*, pseudocysts, duodenal and bile duct obstruction, and peptic ulcer). These anatomical changes are believed to be noxious stimuli that activate pancreatic pain *via* nociceptive pathways. However, a number of human studies of CP have demonstrated evidence against the above theories, finding, for example, no relationship between pain and pancreatic duct pressure reduction[3,4], no relationship between pain and increase of parenchymal pressure[5], no pancreatic duct dilation in some patients with severe pancreatic pain[6], and no relationship between pain and severity of CP-related structural changes on imaging[7]. Therefore, the pain of CP patients cannot be explained by mechanical stimulation of nociceptive pathways alone.

Since the late 1990s, investigators have been trending toward neurobiological theories to explain pain in CP[8]. Therefore, the main objective of this paper was to review the current neurobiological theories and emerging concepts that might lead to the development of new treatment regimens for alleviating pain in CP patients.

NEUROPHYSIOLOGY OF THE PANCREATIC PAIN

The pancreas is innervated by a complex structure of two groups of afferent fibers. The first group consists of branches of the abdominal vagus nerve, and the second fibers that run through the celiac plexus and reach the lower thoracic segments of the spinal cord *via* the splanchnic nerves[9]. The latter group is best known for stimulating visceral pain.

The nociceptive pathway in the pancreas begins with nociceptors located at the ends of the primary afferent neurons and function as afferent nerve endings[10]. Unlike those in other visceral organs, these primary afferent neurons convey only pain stimuli. One special subset of theses nociceptors contains a group called "silent nociceptors", which are only activated during inflammatory processes[11]. Furthermore, the pancreatic nociceptors can be activated by various noxious stimuli through mechanosensitive and chemosensitive mechanisms[12]. The former mechanism is located on blood vessels that supply the pancreas and pancreatic parenchyma and can be stimulated by stretching, ischemia, and necrosis. The latter mechanism can be stimulated by inflammatory mediators, but the exact location of this mechanism is not completely known.

The pathogenesis of CP is strongly related to prolonged exposure to noxious stimuli, which causes chronic inflammation. Noxious stimuli not only stimulate nociceptors, but can also damage pancreatic tissues and nerves surrounding the pancreas[13]. The injured tissues can release pro-inflammatory mediators such as prostanoid, bradykinin, tachykinin, serotonin, and growth factors[14]. Induced by the above mediators, primary sensory neurons then become more sensitive to further stimulation by either noxious (hyperalgesia) or non-noxious (allodynia) stimuli. This process is called peripheral sensitization[15], which indicates that the noxious stimuli can evoke nociceptor plasticity. Moreover, there is another mechanism by which pain can be exacerbated *via* peripheral sensitization, which begins with the activation of silent nociceptors by peripheral inflammation, and the silent nociceptors consequently facilitate and increase afferent activities in the spinal cord.

Once stimulated by pro-inflammatory mediators, the nociceptors will transform the stimuli into action potentials by unbalancing the Na and K currents on the neuronal membrane. The action potentials travel along both unmyelinated C-fibers and small myelinated Aδ fibers of primary sensory neurons[11,12]. These neurons traverse paravertebral and prevertebral ganglia to synapse with secondary sensory neurons at laminae I, II, V, and X of the dorsal horn of the spinal cord at the T5-L2 level. Based on an animal study, the secondary sensory neurons related to the pancreas are primarily located at the T10-T11 level[12]. Consequently, the primary sensory axons release glutamate, substance P, and calcitonin gene-related peptide (CGRP). Glutamate activates both α-amino-3-hydroxy-5-methyl-4-isoxazole propionate and N-methyl-D-aspartate (NMDA) receptors, while substance P activates NK1 receptors[16,17]. These three receptors are located on secondary sensory neurons within the dorsal horn. At this level of stimulation, prolonged stimulation from peripheral sensitization can facilitate excitation of dorsal horn neurons, which can increase spontaneous activities, decrease the firing threshold, and expand the receptive field of the dorsal horn neurons. This process is called central sensitization and can result in hyperalgesia and allodynia[11].

After the activation of secondary sensory neurons, action potentials are generated and transmitted to the thalamus *via* the spinothalamic tract to activate tertiary sensory neurons. These tertiary sensory neurons then transmit the signal to the somatosensory cortex for cognitive integration of pain and the limbic system and hypothalamus for autonomic/affective integration of the pain[18].

Furthermore, the central nervous system (CNS) can modulate pain signaling at the spinal cord level *via* either facilitation, increasing the spinal transmission of pain impulses, or inhibition, decreasing the spinal transmission of pain impulses. The combination of facilitation and inhibition generates the signal that will determine the pain perception in the brain.

After the primary sensory neurons are activated, neurotransmitters (glutamate, substance P, and CGRP) are not only released to the dorsal horn of the spinal cord, but also to primary nerve endings located on the pancreas, where they act as inflammatory mediators that create pancreatic inflammation characterized by vasodilation, edema, and neutrophil infiltration. This process is also known as neurogenic inflammation[19-21]. Additionally, this neurogenic inflammation can facilitate the activation of peripheral sensitization[10].

NEUROPATHOPHYSIOLOGY OF PANCREATIC PAIN

Chronic inflammation in the pancreas has been shown to spread to the pancreatic nerve[22,23]. Additionally, perineural inflammatory cells including eosinophils, CD4+ and CD8+ lymphocytes, macrophages, and mast cells are evidenced in patients with painful CP[24-27]. This finding is consistent with the increased percentage of eosinophils observed in perineural inflammatory cell infiltrates, which may be related to the release of a nociceptive substance[13]. In addition, numerous studies[28-34] have reported the increase of various perineural inflammatory mediators including histamine, serotonin, interleukin, bradykinin, substance P, CGRP, tumor necrosis factor-alpha, and several neurotrophins [*i.e.*, growth-associated protein 43, brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF)]. Specifically, BDNF and NGF up-regulation has been shown in CP patients[24,26].

Such evidence has recently become the main focus of many studies attempting to explain the pathogenesis of pain based on three concepts: pancreatic nociception and sensitization-induced pain, neuropathic remodeling (neuropathic pain), and central mechanism of pancreatitis pain. Each of these aspects is complex and involves specific molecules that are described in the following sections.

PANCREATIC NOCICEPTION AND SENSITIZATION-INDUCED PAIN

There is much evidence to support that peripheral and central sensitization is largely associated with the pancreatic pain in CP. The evidence related to the molecules and receptors that have been found to be involved in the sensitization mechanisms will be discussed one-by-one in the following paragraphs.

The transient receptor potential (TRP) family is a group of ion channels localized mainly to the plasma membrane of neurons. Three molecules strongly related to pain and inflammation in the TRP family are TRP vanilloid 1 (TRPV1), TRPV4, and TRP ankyrin 1 (TRPA1)[35]. These three TRP channels are also associated with pain in CP patients through the sensitization of pancreatic afferent neurons and development of neurogenic inflammation. The primary sensory nerve endings that supply the pancreas contain these three types of TRP, which can be stimulated by specific stimuli including inflammatory mediators. After the receptors are stimulated, primary sensory neurons then release substance P and CGRP at both the spinal cord and peripheral sites, thus causing pancreatic inflammation *via* neurogenic inflammation[36-40]. The mechanism of peripheral sensitization (Figure 1) is discussed below.

TRPV1
TRPV1 can be directly activated by many factors, including heat, extra-cellular proton and tissue acidosis, capsaicin, biologically active compounds (anandamide and hydrogen sulfide), and endogenous lipid metabolites from the arachidonic acid pathway[41,42]. Furthermore, TRPV1 can be indirectly activated by pro-inflammatory bradykinin and pro-inflammatory leukotriene[43]. By modulating TRPV1 activity, pro-inflammatory bradykinin can indirectly activate TRPV1 *via* B2 receptors residing on primary sensory neurons. By binding to their leukotriene B4 receptors, pro-inflammatory leukotriene B4 can activate TRPV1 *via* an intra-neural signaling pathway. Furthermore, pro-inflammatory agents can sensitize TRPV1 by reducing the threshold of thermal stimuli (hyperalgesia)[44].

In animal and human studies, TRPV1 plays an important role in explaining pain in CP. After TRPV1 receptor activation by capsaicin in rats with induced CP, peripheral sensitization is evidenced by the significant upregulation of TRPV1 at both mRNA and protein levels in the dorsal root ganglion (DRG) and pancreas-specific sensory neurons[45]. Moreover, the same study found significant reduction of pain behavior and hyperalgesia after administration of a systemic TRPV1 antagonist. Significant upregulation of TRPV1 is also seen in the pancreatic tissue of patients with painful CP; however, no relationship was found between the pain score level and the level of TRPV1 expression[46].

TRPA1
TRPA1 is responsive to various stimuli that can be categorized into five groups: The pungent ingredients of spices, environmental irritants, endogenous agonists of TRPA1[39], cyclopentenone prostaglandins, and general anesthetics[47]. The pungent ingredients of spices include mustard oil[48], garlic[48], and cinnamon[48,49], and environmental irritants include acrolein[48,50], formaldehyde[48,51], and cigarette smoke[36,48]. Cyclopentenone prostaglandins include PGA2, PGA1, and PGJ2[52,53]. Pro-inflammatory agents also sensitize TRPA1 leading to hyperalgesia[54-56].

TRPV4
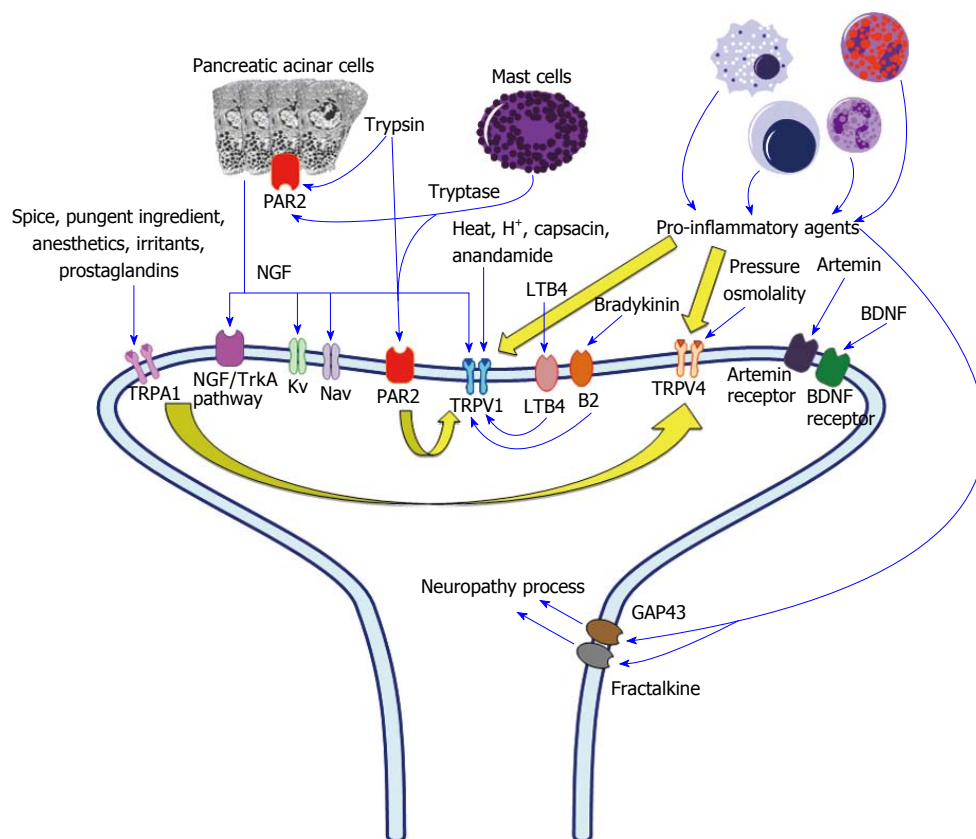TRPV4 responds to changes in tonicity[57,58], moderate

Figure 1 The mechanism of peripheral sensitization. PAR2: Proteinase-activated receptor 2; NGF: Nerve growth factor; TRPA1: Transient receptor potential ankyrin 1; TRPV1: Transient receptor potential vanilloid 1; BDNF: Brain-derived neurotrophic factor; GAP43: Growth-associated protein 43; LTB4: Leukotriene B4.

heat (> 27 ℃)[37], and mechanical pain[37]. Changes in tonicity can cause cell swelling and activate phospholipase A2; this process leads to the generation of arachidonic acid[59], which is an endogenous agonist of TRPV4. In addition, 4α-phorbol 12,13-didecanoate (4αPDD) is a synthetic TRPV4 agonist[60,61]. Similar to TRPV1 and TRPA1, pro-inflammatory agents can sensitize TRPV4 causing hyperalgesia to mechanical stimuli[62-64].

To the best of our knowledge, the first evidence that TRPA1 and TRPV4 contribute to pancreatitis pain was reported in rats with induced acute pancreatitis[48]. Another study also demonstrated that TRPA1 mediates CP pain in mice[54]. In a recent study using mice in which CP was induced through repetitive cerulein injections, TRPV1 and TRPA1 antagonists were important in alleviating neurogenic inflammation in pancreatitis, reducing pain-related behavior, and preventing the transition from acute to chronic inflammation[65]. Therefore, TRPV1, TRPA1, and TRPV4 are likely to be targets for therapeutic pain management in CP patients by reducing peripheral sensitization and neuropathic inflammation.

Proteinase-activated receptor 2

Proteinase-activated receptor 2 (PAR2) is one of the chief regulators of pancreatic exocrine secretion in pancreatic acinar cells and ductal epithelium. Notably, trypsin is recognized as the strongest activator of PAR2. There is also evidence supporting a relationship between PAR2 and pancreatic pain. PAR2 expression was detected in sensory neurons supplying the pancreas; in fact, primary sensory neurons could be activated and sensitized by administering PAR2-specific proteinase activating peptide and trypsin in an *in vivo* study[66,67]. Moreover, both PAR2-specific proteinase activating peptide and trypsin-induced behavioral pain response have been observed in awake rats[67]. Another study discovered that tryptase, a substance released from activated mast cells, can stimulate PAR2[27], which might explain the relationship between mast cells and pain in CP patients. In an experimental animal model of pancreatitis pain, the administration of two proteinase inhibitors (camostat mesylate and nafamostat mesylate) reduced sensitivity to abdominal pain[68]. Likewise, nafamostat was associated with a significant reduction of pain duration induced by acute pancreatitis[69].

Based on *in vitro* findings, PAR2 activation causes TRPV1 sensitization by enhancing capsaicin; consequently, this process leads to the significant release of CGRP[70]. Similarly, in *in vivo* studies, PAR2 activation resulted in pain-related behavior[55,70,71]. As additional supporting evidence that PAR2 is involved in the development of hyperalgesia, PAR2 was significantly upregulated in DRG neurons along with decreased thermal withdrawal latencies in a rat model of CP[72]. In short, PAR2 agonist peptides, trypsin and tryptase, are related to the pathogenesis of pain in CP *via* nociception and sensitization caused by the interaction between TRPV1 and PAR2.

NGF

NGF, a type of neurotrophin, is a protein important for the growth, maintenance, regulation of survival, and specialization of sensory neurons. Moreover, NGF is an essential mediator of peripheral sensitization[73]. Although the islets of pancreatocytes typically generate NGF, NGF was found to be upregulated and surprisingly expressed in pancreatic acinar cells and ductal epithelium in a rat model of pancreatitis[74]. However, the upregulation of NGF returned to normal after the pancreatic inflammation resolved[16]. Many studies have attempted to explain the mechanism of NGF-induced pancreatitis pain on sensitization *via* modulation of TRPV1 and excitability of K and Na currents[73,75-77]. Another hypothesized mechanism underlying pain in CP is activation of the NGF/trkA pathway[78,79]. In a study of rats with CP induced by trinitrobenzene sulfonic acid, both anti-NGF antibodies and trkA-immunoglobulin G substantially reduced hyperalgesia[80,81].

Artemin

Artemin is a neurotrophin classified as a glial cell line-derived neurotrophic factor. Overexpression of artemin and its co-receptor GFR alpha 3 has been reported to strongly relate to the increased frequency and intensity of pain in rats with CP[82].

BDNF

BDNF is also a member of the neurotrophin family found in the brain and periphery. An *in vivo* study reported that BDNF is upregulated in primary sensory neurons in rats with CP, and that BDNF antagonist treatment was associated with a reduction of pain-related behavior in these animals[83]. Another study of pancreatic tissue in patients with CP found that pain was positively related with BDNF levels and increased in CP patients compared to healthy control. These findings suggest that BDNF is essential to the nociceptive pathway of CP.

Other substances

Studies have also reported associations between pain in CP and other substances that could be related to peripheral sensitization, for example, the over-expression of interleukin 1[84], interleukin 6[85], interleukin 8[86], and fractalkine[87].

Neurotransmitter expression

Previous findings in patients with painful CP indicate overexpression of neurokinin 1[88], neurokinin 2[88], CGRP[16], and substance P[16,88]. Therefore, overexpression of these neurotransmitters may result from activation of nociceptive pathways and peripheral sensitization.

PANCREATIC NEUROPATHIC REMODELING-INDUCED PAIN

In clinico-pathological studies, the intra-pancreatic nerves in patients with painful CP demonstrate immune cell infiltration, indicating pancreatic neuritis[13,89], and characteristics of pancreatic neuropathy, which can be described as the increase of neural density, hypertrophy, and spouting[13,90-92]. Both pancreatic neuritis and pancreatic neuropathy are believed to relate with the inflammatory process, which is a key pathogenic factor in CP as indicated by the following evidence. The increase of fractalkine and its receptor is correlated with fibrosis, neuropathic changes, pain duration of CP and the degree of inflammatory cell infiltrate[87,91,92]. Moreover, the expression of growth-associated protein 43 (GAP43), which is a member of the neurotrophin family, is reported to have a relationship with pancreatic neuropathy, pancreatic neuritis, and pancreatic pain. Consequently, GAP43 may be considered a potential marker of neuronal plasticity during development and injury[87,89,91,92].

Patients with painful CP have been reported to demonstrate significant alterations in pancreatic innervation, with a marked decrease in sympathetic innervation but no statistically significant difference in cholinergic innervation[92]. In the same study, stronger expression of pain-related behavior was also noted in patients with painful CP, indicating neuronal regeneration after neuron injury.

In conclusion, the inflammatory process leaves pancreatic neurons damaged and characterized as showing either neuropathy or neuritis. Correspondingly, these neurons express GAP43, leading to the remodeling of pancreatic innervation. This process might explain pancreatic pain in CP patients. Such a process is similar to pancreatic nociception and sensitization-induced pain in the sense that both processes involve inflammatory mediators. However, the mechanism by which inflammatory mediators induce neuropathic pain is by destroying the neurons, leading to permanent neuronal lesions without involving noxious stimuli and the sensitization process.

CENTRAL MECHANISM OF PANCREATITIS-INDUCED PAIN

Central sensitization

As previously described, several factors can induce pain in CP by triggering the CNS, for instance, chronic stimulation of pain through nociceptive pathways, peripheral sensitization caused by inflammatory processes in the pancreas, and nerve damage. Consequently, prolonged peripheral sensitization can lead to central sensitization, which will be discussed next.

Using quantitative sensory testing in human experiments, researchers found that the brain activity of patients with CP demonstrated increased areas of referred pain and increased heterogeneity of referred pain location compared to the control group after electrical stimulation of the esophagus, stomach, and duodenum[93]. The sensitization caused by CP could decrease the pain threshold and increase the referred pain area[94,95].

Table 1 Potential treatment alternatives and their drug targets

Drug target	Potential treatment alternatives
NGF	Tanezumab
TRPV1	TRPV1 antagonist
PAR2	Trypsin inhibitors
Mast cell	Ketotifen
Interleukin 1	Recombinant interleukin-1 receptor antagonist
Interleukin 6	Interleukin-6 antagonist
Central sensitization	Ketamine, dextromethrophan, pregabalin, tricyclic antidepressants, and noradrenaline reuptake inhibitors

NGF: Nerve growth factor; TRPV1: Transient receptor potential vanilloid 1; PAR2: Proteinase-activated receptor 2.

By using electroencephalography (EEG) to measure brain activities, studies of pain in CP can be categorized as either resting-state EEG or evoked potential (EP) tests[84,96]. In resting-state EEG, alpha activities were found to demonstrate increased amplitude strength in CP patients compared to healthy volunteers[97], and pain duration was negatively correlated with the average peak alpha frequency[98]. Notably, the relationship between chronic pain and the change in alpha activity could be the result of thalamocortical dysrhythmia, which is activated by T-type calcium channels[99]. In EP tests, constant electrical stimulation of the upper gastrointestinal tract significantly decreased latencies of the early EP components in CP patients compared to healthy volunteers[93]. Moreover, hyperalgesia and prolonged latencies of early visceral EPs components in the frontal region of the cortex were seen following electrical stimulation in CP patients compared to healthy subjects[100].

As observed with functional magnetic resonance imaging, pain sensation is processed and localized in somatosensory cortex, insula, anterior cingulate cortex, prefrontal cortex, and thalamus. Recently reported evidence indicates that plasticity, *i.e.*, functional or structural changes, in the CNS may be associated with pain in chronic syndromes. The structural reduction of cortical thickness[101] and microstructural changes in the insula and frontal cortex[102] also have been observed in magnetic resonance imaging studies.

The above findings support the hypothesis that the pain experienced by CP patients can be triggered by central sensitization, which is derived from sustained and increased peripheral nociceptive drivers. Moreover, recent studies have demonstrated that descending inhibitory modulators are significantly impaired in patients with CP compared to healthy controls[95,103]. Descending facilitation from the brainstem was also reported to be a critical factor in pancreatic pain in rats with CP[20].

POTENTIAL APPLICATIONS

Generally, drug discovery involves finding a new drug with the ability to increase or decrease the activities of selected targets or unrelated targets. The greater our

understanding of the neuropathophysiology of pain in CP, the better our opportunity to identify potential treatment alternatives. Currently, there are two groups of potential treatment alternatives and their drug targets, which are summarized in Table 1. The first group of potential treatment alternatives is directed at attenuating the peripheral sensitization process by targeting related molecules and receptors, such as NGF, TRPV1, PAR2, trypsin, tryptase, interleukin 1, and interleukin 6. The second group of potential treatment alternatives focuses on attenuating the central sensitization process.

Anti-NGF antibody demonstrated a significant effect on attenuating the changes in the excitation of pancreatic nociceptors in rats with CP[81]. Tanezumab, a humanized monoclonal antibody with specific binding to NGF, is able to relieve chronic pain in many conditions, for instance, chronic low back pain[8,104], interstitial cystitis[8,105,106], and osteoarthritis knee pain[8,107,108]. However, to the best of our knowledge, there has not been any human study to date using anti-NGF in CP.

A TRPV1 antagonist remarkably reduced both visceral pain behavior and referred somatic hyperalgesia in rats with CP[45]. Since not only TRPA1 but also TRPV4 are related to the peripheral sensitization of pain in CP, theoretically both TRPV1 and TRPV4 antagonists should be able to attenuate pain in CP. Nevertheless, we have not seen any study using a TRPV4 antagonist in CP.

Although PAR2 is the receptor that induces peripheral sensitization of pain in CP, direct PAR2 antagonists are very difficult to create[8]. As already mentioned, both trypsin and tryptase are agonists of the PAR2 receptor. Therefore, one researcher proposed that PAR2-sensitized pain can be inhibited indirectly by using trypsin inhibitors and a mast cell stabilizer (ketotifen)[8].

In the inflammatory process, interleukin 1 and interleukin 6 are associated with pain in CP. As a result, antagonists of both these interleukins may be able to attenuate pain. Researchers found that a recombinant interleukin-1 receptor antagonist[109] and interleukin-6 antagonist[85] can have an effect on attenuating pancreatitis-induced pain in rats with CP.

Central sensitization of pain in CP can be influenced by NMDA receptors, thalamocortical dysrhythmia, and impaired modulation pathways. Consequently, we can attenuate pain in CP by modifying the activities of these influencing factors. Several known drugs can reduce the effect of central sensitization, such as ketamine[8,110,111], dextromethrophan[8,112], pregabalin[113-115], tricyclic antidepressants[84], and noradrenaline reuptake inhibitors[84].

CONCLUSION

Chronic pain is an important issue that significantly lowers quality of life in patients with CP. The theories for underlying causes of pancreatic pain in CP have been shifting away from anatomical changes of pancreatic structure to changes in neurobiological structure, which include peripheral sensitization-induced pain, neuropathic remodeling, and central sensitization of

pancreatic pain. Furthermore, researchers have identified numerous molecules related to pancreatic pain in CP, for example, TRPV1, TRPA1, TRPV4, PAR2, NGF, artemin, BDBF, GAP43, and fractalkine. As a result, the neuropathophysiological mechanisms of pain in CP show strong potential as targets for drug discovery to relieve the pain and improve quality of life in this patient population.

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