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Recent advances in the understanding and management of chronic pancreatitis pain

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Abstract

Abdominal pain is the most common symptom of chronic pancreatitis (CP) and is often debilitating for patients and very difficult to treat. To date, there exists no cure for the disease. Treatment strategies focus on symptom management and on mitigation of disease progression by reducing toxin exposure and avoiding recurrent inflammatory events. Traditional treatment protocols start with medical management followed by consideration of procedural or surgical intervention on selected patients with severe and persistent pain. The incorporation of adjuvant therapies to treat comorbidities including psychiatric disorders, exocrine pancreatic insufficiency, mineral bone disease, frailty, and malnutrition, are in its early stages. Recent clinical studies and animal models have been designed to improve investigation into the pathophysiology of CP pain, as well as to improve pain management. Despite the array of tools available, many therapeutic options for the management of CP pain provide incomplete relief. There still remains much to discover about the neural regulation of pancreas-related pain. In this review, we will discuss research from the last 5 years that has provided new insights into novel methods of pain phenotyping and the pathophysiology of CP pain. These discoveries have led to improvements in patient selection for optimization of outcomes for both medical and procedural management, and identification of potential future therapies.

Keywords: Central sensitization, Chronic pancreatitis, Pain phenotyping, Peripheral sensitization

Introduction

Pain is the most common symptom of chronic pancreatitis (CP) affecting over 80% of patients during the course of their disease and is the main driver of morbidity in the disease leading patients to seek treatment.[1,2] Current guidelines emphasize a multitiered approach, first emphasizing medical management followed by consideration of procedural or surgical intervention on selected patients with severe and persistent pain.[3] Over recent decades, clinical studies and animal models (Table 1) have been used extensively to investigate CP pain as well as to improve pain management. There still remains much to discover about the neural regulation of pancreas-related pain. Despite the array of tools available, many therapeutic options for the management of CP pain provide incomplete relief and can be associated with negative side effects and additional health risks. In this review, we will discuss research that has provided new insights into novel methods of pain phenotyping and the pathophysiology of CP pain.

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Literature search strategy

The following terms were entered into the Pubmed database with the restriction of publication within the last 5 years: pain, CP, hypersensitivity, hyperexcitability, peripheral sensitization, and central sensitization. These discoveries have led to improvements in patient selection for optimization of outcomes for both medical and procedural management, and identification of potential future therapies.

Pain patterns

Pain in CP has traditionally been grouped into 2 main categories: type A pain is characterized by intermittent pain episodes with pain-free intervals, and type B pain by constant unremitting pain punctuated by acute exacerbations with more severe pain.[39] Type B pain was previously thought to respond more favorably to definitive surgical intervention. Additional efforts have been made to delve into pain aspects of both constancy and severity.[40] Patients with constant pain have been found to have significantly worse quality of life (QOL) and higher rates of medication use, hospitalization, and disability, even independent of pain severity.[40] Unfortunately, the pain experience of patients with CP has not been shown to correlate reliably with imaging findings of the disease.[41] A recent prospective longitudinal study of Dutch CP patients confirmed the finding that patients with constant pain compared to intermittent pain experienced greater pain severity and lower QOL.[42] Importantly, though, the work also showed that most CP patients with pain experience at least one shift in the pattern of their pain when examined longitudinally, confirming that this is a dynamic process for patients and suggesting that pain patterns need to be reassessed over time.[42] Notably, no differences were seen in imaging findings between those with continuous and intermittent pain, underlining the fact that there is no simple proxy for detection of pain pattern or predictor for changes over time.

Pain effect on mental health and QOL

Pain in CP affects many aspects of life including mental health and QOL, a phenomenon that has been well-documented in this

Table 1

Common animal models used to study pancreatitis pain

Model	Basic mechanism	Species used	Features	Behavior assays	References
Cerulein	Supramaximal dosing generates diminished secretion, accumulation of secretory proteins within the pancreas, and pancreatic injury	Rat, mouse, hamster, dog	5–8 hourly injections 1–3 times per wk, >4 wk to histologically relevant symptoms; leads to: fibrosis, atrophy, decreased serum lipase, adipose replacement, necrosis, elevated glucose, leukocyte infiltration	Abdominal von Frey, open field activity	[4–14]
TNBS	Reacts with lysine residues on the epithelium to form a complex which stimulates immunological responses against the tissue	Rat, mouse, hamster, rabbit, dog, cat, pig	Single 1 h infusion period, <3 wk to symptom onset; leads to: edema, hemorrhagic fat/acinar necrosis, organ failure, leukocyte infiltrate, elevated lipase and amylase	Abdominal and hind paw Von Frey, electrically evoked visceromotor reflex, open field activity, voluntary wheel running, vocalizations, catalepsy, elevated plus maze	[7, 15–25]
L-Arginine	The mechanism by which L-arginine causes pancreatitis is not fully understood; possibly works through arginine's production of nitrous oxide	Rat, mouse, hamster	Technically considered a model of pancreatic atrophy. Daily injection for 3 wk then same dose-injection 3 times per week for 3 wk; leads to: pancreatic atrophy, fibrosis, acinar cell destruction, inflammation	Abdominal von Frey	[9, 10, 26–31]
DBTC	Organotins are rapidly excreted via the bile and cause damage to the bile duct epithelium with subsequent necrosis and duct obstruction	Rat, mouse, hamster, rabbit, dog, cat, pig	Single injection or repeated weekly, <6 wk to periductular and interstitial fibrosis; leads to: edema, hemorrhagic fat/acinar necrosis, organ failure, leukocyte infiltrate, elevated lipase and amylase	Abdominal von Frey, abdominal Hargreaves, hot plate	[32–38]

DBTC = dibutyltin dichloride, TNBS = trinitrobenzene sulfonic acid.

disease. A recent international multicenter cross-sectional study showed a high prevalence of anxiety (46.8%) and depression (38.6%) in patients with CP, with overlap of these symptoms in many patients (29%).[43] The presence of psychiatric comorbidity in this study associated with lower QOL in all studied domains, and an independent association was seen between decreased QOL and symptoms of depression. Importantly, patients with symptoms of anxiety or depression were more likely to report pain, pain of greater severity, and reported more interference by pain with daily life than nonanxious or depressed counterparts.[43] Another large US cohort study showed significant impairment in both physical and mental health in patients with severe or constant pain.[44] Interestingly, impairment in CP patients with pain also extended to disturbances in sleep, an aspect of life that may have further implications in worsening symptoms of anxiety and depression.

Unfortunately, chronic pain and depression are part of a cycle of mutual perpetuation, which has made deciphering the pathophysiological mechanism difficult.[45] Early explorations in genetic analysis have been assessed to understand hereditary factors that may put CP patients at higher risk for anxiety and depression. A genome-wide association study performed by Dunbar et al[46] evaluated samples from the North American Pancreatitis Study 2 (NAPS2) and compared cohorts of CP patients with and without constant severe pain. Several genetic loci with specific overlap between constant pain and depression were identified.[46] Based on the GWAS catalog, three candidates *SGCZ*, *ROBO2*, and *CTNND2* are implicated in the response to antidepressant.[47] Additional work in this vein has shown possible links between constant and severe pain in patients with CP and genetic predisposition to anxiety and post-traumatic stress disorder.[48]

Dunbar et al[49] also reviewed earlier work showing that the same brain regions are altered in both mood disorders and chronic pain such that there is bidirectional modulation. For instance, individuals with major depression rate heat stimuli as more painful than healthy controls; this decrease in antinociception is associated with decreased functional connectivity in a neural network connecting frontal, temporal, and occipital areas.[50] Similarly, chronic pain patients demonstrate higher levels of anhedonia and depression scores and increased negative affect are associated with striatal hypofunction.[51] Only recently have studies begun to investigate the overlap between pain and mood at mechanistic level in CP. Specifically, pain and depression correlated with elevated *N*-acetyl aspartate and choline in the left hippocampus and left prefrontal cortex regions of the brain.[52] Additional studies are being conducted in animal models to further probe mechanisms that may link depression and anxiety.[53]

Treatment of concomitant anxiety, depression, and other psychiatric comorbidities is essential in patients with painful CP but the feasibility and efficacy of interventions for these comorbid conditions remains little explored.[54] During the coronavirus disease 2019 (COVID-19) lockdown, some patients with CP development comorbid depression and pain. These patients showed improvement with a combination of low-dose antidepressants and analgesics. The results of these studies suggest further investigations are warranted to determine if there is a role for neuromodulator drugs in therapeutic management of CP pain. Other nonpharmacological therapeutic tools used in the mental health field may also be useful for management of CP pain.[55] A pilot randomized controlled study implementing cognitive behavioral therapy (CBT) in adult patients with painful CP showed clear feasibility and acceptability among patients.[56] Data from the study suggested efficacy of the intervention with significant reductions in pain interference, as well as nonsignificant but notable improvements in pain intensity and healthcare-related QOL in the CBT arm compared to the non-CBT arm. A randomized controlled trial examining efficacy in children is presently underway; additional studies in adults are needed to define efficacy in both populations.[57]

Pain phenotyping

The understanding of pain in CP as a multidimensional experience highlights the importance of an individualized approach to both assessment and treatment of pain. Multiple overlapping factors in CP influence the individual's experience of pain, including biologic factors, psychiatric comorbidities, and

neurologic factors: phenotyping of patients can help to understand patterns of pain experience and also help optimize patient selection for certain treatments.[58] Several different systems of phenotyping have been proposed in independent investigations in an attempt to more accurately classify the range of pain experiences in CP as well as the associated factors predicting outcomes. However, there is overlap between the classification systems and we have not yet fully elucidated how pattern (constant vs intermittent) relates to more recent classification systems (eg, +/– neuropathic pain or +/– central sensitization). A differentiation between neuropathic and nociceptive types of pain in CP patients who reported specific patterns in their experience on pain surveys showed worse overall health and QOL in those with both types of pain, suggesting that patient-reported outcome tools may serve a useful role in phenotyping the pain experience from a patient perspective.[59] Early complementary work in human serum biomarkers has shown that TGFb1 and GP130 may be promising targets for further investigation into biological identification of neuropathic and nociceptive pain.[60]

Despite a lack of correlation between imaging findings and pain experience in CP, pancreatic duct obstruction has long been thought to contribute independently to the pain experience, and is a major target of treatment in this population.[61] Pain response to relief of ductal obstruction is incomplete in many patients, however, and therefore additional sources of pain are thought to be responsible.[62–64] One type of neuroplasticity that may contribute to CP pain is central sensitization, a state of increased responsiveness of neurons in the central nervous system (CNS) that often manifests as pain hypersensitivity.[65] Central sensitization is believed to contribute to the pain experience in patients with painful CP who have incomplete or suboptimal pain response to technically successful relief of ductal obstruction.[66] Its identification is therefore crucial to the process of optimizing patient selection for high-risk invasive interventions with suboptimal rates of response. To date, however, there has been no method of diagnosis or detection of central sensitization feasible in the clinical setting, limiting even the ability to identify this condition.

Central sensitization in the clinical setting

The use of quantitative sensory testing (QST)—a neurosensory testing method designed as a proxy for assessing nociception—adapted into a bedside protocol and focused on pancreas-specific pain has opened the door to identifying CP patients with pain who also have widespread hyperalgesia.[67] The phenomenon of widespread hyperalgesia is suggestive of the presence of central sensitization. Early iterations of experimental QST applied to patients with CP were able to predict outcome to pregabalin therapy.[68] A more streamlined protocol of QST adapted for bedside use called Pancreatic QST (P-QST) has been able to phenotype CP patients with pain into mutually exclusive groups representing nociceptive phenotypes (widespread hyperalgesia, segmental pancreatic hyperalgesia, and no hyperalgesia) independent of psychiatric comorbidity.[69] Those patients with widespread hyperalgesia suggestive of central sensitization were found to exhibit higher rates of constant pain, greater pain overall, and lower QOL in comparison to other phenotypes.[69] Identification of central sensitization as a factor for individual patients has also allowed for elucidation of relationships between psychiatric comorbidity, pain, and other biological factors, an interplay that affects each patient differently over the course of their disease.[58] Overall, this holds promise as a technique to predict outcome to invasive therapies and has implications for use in optimization of patient selection for such procedures.[70,71] The pathogenesis that drives development and progression of central sensitization remains little understood at this time but crucial to the development of future treatments.

Mechanisms of central sensitization in pancreatitis

Increased or persistent nociceptive input to the CNS and persistent activation of nociceptive neurons can drive sensitization of circuits in the brain and spinal cord. Polysynaptic pathways identified through anatomical tracing in animals[72] and neuroimaging studies in humans with CP[73] connect key structures in the CNS to the pancreas that are implicated in the modulation of CP pain. The anterior cingulate cortex (ACC), nucleus tractus solitarius (NTS), insula, and periaqueductal grey (PAG) have all been implicated in processing of pain and emotion.[74–76] Recent preclinical studies focusing on these regions in the context of CP have revealed that key changes in glutamate signaling may drive central sensitization associated with CP pain.

One of the salient features of central sensitization is an enhancement of the functional status of neurons in nociceptive pathways within the CNS. Figure 1 shows the established innervation of the pancreas as well as a recently elucidated NTS-ACC circuit in (laboratory of Y.Q. Li) that has been implicated in the modulation of pain and anxiety symptoms in the trinitrobenzene sulfonic acid (TNBS) rodent model of induced CP.[53,77] Following TNBS infusion into the main pancreatic duct, neurons in the NTS exhibit increased expression of fos, a protein used to identify activated neurons. NTS neurons from TNBS-treated rats also exhibited increased spontaneous post-synaptic currents, indicating hyperexcitability. This is associated with upregulation of the vesicular glutamate transporter (vGlut) 2 and the NR2B and GluR1 subunits of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (ionotropic glutamate receptors), respectively. Chemogenetic inhibition of these neurons (or administration of NMDA and AMPA receptor antagonists to the NTS) attenuates pancreatic hypersensitivity.

In the TNBS model, the majority of activated neurons in the NTS project to ACC pyramidal neurons, which also express fos following induction of CP (Figure 1).[53] In TNBS-treated rats, the fos-expressing ACC pyramidal neurons exhibit increased expression of vGlut1, and a subsequent increase in trafficking and phosphorylation of NMDA and AMPA receptors. Upregulation of phosphorylated NMDA and AMPA receptors in the plasma membrane of neurons is associated with increased neuronal activation and synaptic transmission (eg, glutamate release). Thus, in TNBS-induced CP, rats have increased glutamatergic signaling in the NTS-ACC circuit which correlates with both increased hypersensitivity and anxiety behaviors[53,77]; this is consistent with human studies that detected elevated glutamate levels in ACC of patients with painful CP.[78] This suggests that the ACC could be a therapeutic target. Indeed, local inhibition of ACC neurons, via chemogenetic tools or AMPA and NMDA receptor antagonists, ameliorated both the hypersensitivity and anxiety produced in the TNBS rat model of CP. Interestingly, the insular cortex also exhibits increased activation following TNBS-induced CP.[79] While the synaptic pathway still needs to be determined, hyperactivity within the insular cortex also appears to be driven by upregulation of AMPA and NMDA receptor expression in a vgluT1-dependent mechanism.[79] Like in the ACC, local inhibition of insular activity reduces both abdominal hypersensitivity and anxiety symptoms.[79]

Dysfunction of descending inhibitory pathways also plays a role in the experience of central sensitization. In another rodent model of pancreatitis, intravenous dibutylin chloride (DBTC), rats develop abdominal hypersensitivity that is responsive to gabapentin,[80] which suggests that there may be a centrally mediated mechanism contributing to the pain because its site of action is the CNS. The ventrolateral PAG (vlPAG) has an important role in descending inhibition of ascending nociceptive information. Indeed, electrophysiological recordings assessing vlPAG neurons indicate they have decreased excitability, spontaneous activity, and synaptic strength.[81] Loss of descending inhibition (via reduced vlPAG activity) results in a larger nociceptive signal reaching the

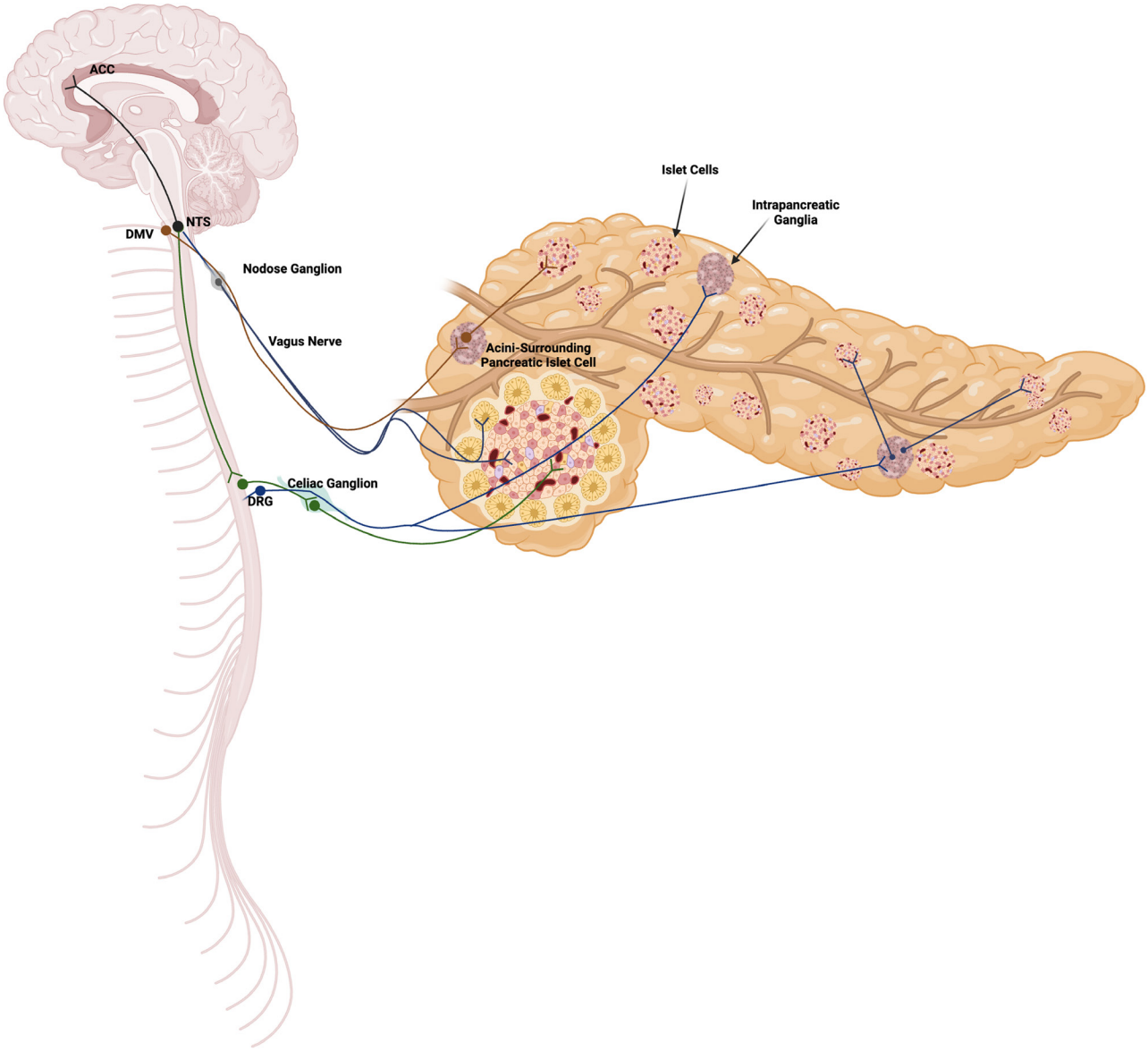

Figure 1. Innervation of the pancreas and novel regulatory pathway. Sensory information, including noxious stimuli, activate sensory neurons innervating all cell types within the pancreas including, neurons in intrapancreatic ganglia, islets, and acini. Sensory afferent cell bodies are located either in thoracic DRG or in the no-dose ganglia. Sensory nerve fibers travel with autonomic nerve fibers that are also innervating the pancreas. Parasympathetic neurons located in the DMV have their axons travel with sensory axons through the vagus nerve. Preganglionic sympathetic nerves (whose cell bodies are in the spinal cord) synapse in the celiac ganglion from which postganglion sympathetic nerves join with sensory fibers from DRG neurons and travel to the pancreas. Novel studies show that pancreatitis induces activation of the NTS neurons (via sensory afferents) which then synapse in the ACC. Both NTS and ACC exhibit increased activity that is associated with increased glutamatergic signaling, an excitatory neurotransmitter, suggesting the hyperactivity of this circuit may contribute to CP pain. Created using BioRender.com. ACC = anterior cingulate cortex, CP = chronic pancreatitis, DMV = dorsal motor nucleus of the vagus, DRG = dorsal root ganglia, NTS = nucleus tractus solitarius.

brain and thus perception of more pain. Direct administration of agonists for the excitatory AMPA receptor activate vlPAG neurons and alleviate abdominal hypersensitivity[81] Together, these studies provide biological evidence and potential treatment targets for central changes that contribute to chronic pain in CP.

Recent advances in understanding of mechanisms of peripheral CP pain

Pathological pain in CP is not only a central phenomenon but initially arises from changes in peripheral sensory neurons. Changes in nociception, including the sensitization of peripheral nerves that transduce noxious stimuli can result in pain that is persistent and difficult to treat. Pancreatic exocrine secretions include pronociceptive proteins. Additionally, during flares of acute pancreatitis, inflammation and tissue damage result in the release of chemical signals that can directly activate sensory neurons or potentiate their response to future stimuli (peripheral sensitization), resulting in neuronal changes that further drive the inflammatory response (neurogenic inflammation).[82] Inflammation in acute and CP has also been shown to be driven by aberrant or upregulated immune responses.[83] There have been a large number of studies focused on the role of immune-dependent mechanisms (eg, danger-associated molecular pattern molecules [DAMPs], cytokines, chemokines, growth factors) involved in the activation and sensitization of the nervous system during pancreatitis, which can contribute to pain.[82]

Nerve damage and neuritis also correlate with CP pain and contribute to the aberrant signaling of pancreatic afferents.[84]

Table 2

Example therapies for painful chronic pancreatitis

Therapy category	Examples
Medical	Alcohol and Tobacco cessation
	World Health Organization Analgesic Ladder (stepwise treatment with nonopioid agents, weak opioids, strong opioids, with or without adjuvants)
Endoscopic	ERCP +/– ESWL
Surgical (drainage or resective therapies)	Puestow Procedure
	Frey Procedure
	Beger Procedure
	Whipple Procedure
	Partial pancreatectomy (of diseased portion of organ)
	Total pancreatectomy with auto-islet cell transplant
Adjuvant	Cognitive behavioral therapy
	Neuroleptic agents (gabapentin, pregabalin, serotonin reuptake inhibitor agents, etc)

Examples of available treatments for painful CP which are commonly offered for painful chronic pancreatitis in a clinical setting. This list represents common clinical practices in the United States, shaped by national and international guidelines for the treatment of pancreatic pain, however is not exhaustive and continues to evolve based on available data and emerging treatments.
ERCP = endoscopic retrograde cholangiopancreatography, ESWL = extracorporeal shock wave lithotripsy.

Upregulation of several proinflammatory and pronociceptive molecules in human CP pancreas and intrapancreatic nerves has been reported which has led to studies in experimental pancreatitis models implicating neurotransmitters (eg, glutamate, ATP), neuromodulatory factors (eg, eicosanoids, cytokines including growth factors, chemokines), and peptides in pancreatitis-related neurogenic inflammation and peripheral sensitization.[15–17,85,86] Recent advancements include further delineation of the role of transforming growth factor β 1 (TGFβ1) as well as identification of novel ion channels, Piezos that may contribute to CP pain.[18,60,87–90]

One specific cytokine that has been independently implicated as a mediator of peripheral sensitization and CP pain is TGFβ1, previously primarily associated with activation of pancreatic stellate cells and promotion of fibrosis.[18,87] CP patients with pain have significantly higher circulating TGFβ1 than those with no pain.[60] A recent study by Pasricha et al[7] has further elucidated the signaling pathway involved in TGFβ1-dependent peripheral sensitization. Overexpression of TGFβ1 in pancreatic acinar cells of mice or infusion of TGFβ1 resulted in sensory neuron hyperexcitability, SMAD3 activation, and increased nociception. Genetic manipulations that downregulate TGFβ1/SMAD3 signaling attenuated neuronal sensitization and pain-associated behaviors in the TNBS model of CP, suggesting that this pathway promotes peripheral sensitization via a direct effect on primary sensory neurons mediated by intra-neuronal SMAD3. Interestingly when administered directly to the CNS, via intrathecal infusion, TGFβ1 reduced hyperalgesia in rats with CP, suggesting that centrally TGF signaling may be antinociceptive. Thus, future therapeutics inhibiting TGF signaling may be more effective if they are engineered to not cross the blood-brain barrier. Recently, the drug pirfenidone which is thought to act on the TGFβ1 pathway has been shown to reduce fibrosis in mouse models of CP.[91] Pirfenidone is already used clinically for idiopathic pulmonary fibrosis and clinical trials for CP are currently in development.[91] Unfortunately, pain was not assessed in the animal study, but it will be an important endpoint to include in the clinical trials of pirfenidone in CP patients.

Chemical (eg, cytokines, chemokines, peptides) associated with neurogenic inflammation, neuronal activation, and sensitization of pancreatic afferents has been studied extensively, but mechanical perturbation such as stretching and crushing associated with increased edema, ductal dilation, strictures, and stones can drive pain as well. Indeed, some patients develop pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP), the development of which involves a problematic level of increased pressure within the main pancreatic duct.[92,93]

The first data implicating specific mechanotransducers (Piezo1 and Piezo2) in mechanically dependent CP comes from a recent series of studies.[88,89] Piezos are mechanically activated cation channel currents that are opened by conformational changes caused by flattening of cell membrane.[94] Romac et al[88] demonstrated that increased pressure within the pancreas can activate Piezo1 expressed on acinar cells, promoting excessive intracellular calcium leading to edema, infiltration of immune cells, and increased exocrine function, thereby driving pancreatitis.

Neuronally expressed TRPV4, a nonselective cation channel that detects arachidonic acid metabolites and osmotic pressure, has previously implicated in regulation of pain in both cerulein and high-fat diet + ethanol models of pancreatitis.[95,96] New data suggest that TRPV4 activation on pancreatic stellate cells occurs following elevation of intrapancreatic pressure and opening of Piezo1.[89] Mechanical stress or application of a Piezo1 agonist increases TGFβ1 in pancreatic stellate cells as well as promotes fibrosis and deposition of extracellular matrix. Importantly, pharmacological inhibition of TRPV4 or genetic deletion protects stellate cells from Piezo1-dependent induction of fibrosis. Based on our own single cell sequencing analysis of mouse pancreatic afferents, TRPV4 mRNA is present in 12% of neurons. However, mRNA for Piezo1 (35%) and Piezo2 (78%) were detected in a larger proportion of pancreas afferents suggesting mechanical stimulation of the pancreas could directly activate nociceptive afferents in a Piezo-dependent manner.

Medical treatment in painful CP

Current guidelines in medical pain management of CP overall follow the analgesic ladder developed by the World Health Organization (WHO).[3] This treatment strategy focuses on step-wide implementation of nonopioid analgesics (including acetaminophen or nonsteroidal anti-inflammatory medications), followed by weak opioid analgesics (such as tramadol or hydrocodone), and reserving potent opioids (oxycodone, hydromorphone) for severe and persistent pain. Adjuvant therapies including tricyclic antidepressants, serotonin and norepinephine uptake inhibitors, selective serotonin reuptake inhibitors, gabapentinoids, and antioxidants have been recommended as agents to trial.[3] See Table 2 for additional information on treatments for painful CP.

Potentiation of glutamate signaling contributes to both peripheral and central sensitization related to CP pain, raising the possibility that glutamate may be a treatment target. In human studies, glutamate modulators such as acetyl-l-carnitine (ALC) have shown both analgesic and antidepressant effects in non–pancreas-related conditions.[97] There are new murine data suggesting that ALC ameliorates hypersensitivity to both heat and mechanical stimulation as well as decreases ongoing pain

in recurrent acute pancreatitis.[4] In the same model, ALC also reduced microglial activation in the CNS, suggesting it may target both peripheral and central mechanisms that contribute to pain from inflammation within the nervous system.

Gabapentinoid agents including gabapentin and pregabalin work through several different mechanisms,[98–100] but their effect has been promising in terms of ameliorating CP pain both in rat models[80,101] and human clinical studies. Pregabalin has been shown to significantly reduce pain compared to placebo in a randomized controlled trial and has even been shown to have moderate inhibitory effects on central sensitization.[102,103] Antioxidant agents have been explored with little suggestion that they make a significant impact on CP pain; however, in a double-blind randomized controlled trial where antioxidants were combined with pregabalin, a significant reduction in pain, use of analgesics, and hospital admissions were seen in the treatment arm compared to placebo.[104] No analgesic agent is without potential side effects,[105] however, and so the composition and duration of a medical management approach in painful CP must be carefully assessed for each patient in a dynamic fashion throughout their disease course.

Experimental medical treatments for CP pain

Medical therapy for painful CP remains inadequate for many patients, and ongoing efforts are continually exploring new avenues for noninvasive treatments. Two novel therapies, neuronal nitric oxide synthase (nNOS) inhibitor and stem cell infusion, have been investigated recently in animal models of CP. There is a unique enrichment of nNOS in the pancreatic nerves in CP patients that correlates with increasing pain severity.[5] CP neuritis is associated with infiltration of nerves by mast cells which release tryptase. Intraneural tryptase induces upregulation of nNOS in the cerulein model of CP.[5] Treatment with the nNOS inhibitor NPLA reduced abdominal hypersensitivity suggesting that it may be a therapeutic target in CP patients with a neuropathic pain component.[5]

Mesenchymal stem cell (MSC) therapies have shown potential for reducing chronic and neuropathic pain in a variety of conditions including diabetic neuropathy and osteoarthritis, and early studies suggest they may have potential to be therapeutic for CP pain. Chow et al[106] hypothesized that mesenchymal stromal cells engineered to over express human α-1 antitrypsin (hAAT-MSCs), an anti-inflammatory protein and natural protease inhibitor, would improve CP pain. In the TNBS model of CP, administration of hAAT-MSCs reduced abdominal pain hypersensitivity and suppressed TRPV1 expression in sensory neurons (TRPV1 is a pronociceptive ion channel implicated in CP pain).[106] It is not clear whether MSCs are acting directly on nerve terminals within the pancreas or indirectly through actions on other cells because the treatment also reduced pancreatic mast cell density and preserved pancreatic morphology. These promising data suggest nonetheless that clinical trials for MSC therapy in CP may be warranted.

Other medical treatments are being explored though these remain in early stages. A pilot feasibility study in adults with CP using paricalcitol (vitamin D analog) for the amelioration of symptoms of painful CP is underway (NCT 05664880). This work is based on preclinical studies that show the antagonism of inflammatory pathways that may have relevance in human studies to reduce pain in CP.[107] Outcomes including health-related QOL will be measured. Additionally, a safety and feasibility trial of lacosamide, an antiepileptic agent believed to reduce the effect of opioid-induced hyperalgesia, is ongoing (NCT 05603702). It is hoped that this agent may improve existing opioid pain management in painful CP. Numerous clinical trials of antifibrotic agents (some of which have potential in the fibrotic pathophysiology of CP) are underway, though to our knowledge no clinical trial in humans with CP is ongoing at present.[108]

Invasive interventions: endoscopic and surgical treatments

The multifactorial nature of pain in CP includes for many patients a component of anatomical pain secondary to pancreatic duct obstruction by stones or stricture. Rates of durable pain response from relief of pancreatic ductal obstruction however are suboptimal, and data on these rates comes largely from trials comparing different types of invasive intervention.[61,62] Procedural interventions that carry variable rates of risk have been regarded with some hesitancy by providers and patients given the irreversible nature of surgeries and the concern for adequate response with endoscopic therapy. Traditionally, surgical intervention has been reserved for patients who fail attempts at medical and then endoscopic management.[109] However, recent observational and clinical trial data suggests that earlier surgical intervention in patients with painful CP may have significant benefit compared to later surgery, potentially shifting the approach toward recommendation for earlier surgery where such therapy is available.[110,111]

Advances in endoscopic therapy

The main goal of endoscopic therapy in painful CP with pancreatic ductal obstruction has been to relieve a perceived obstruction by removing stones or dilating a stricture. Therapies for ductal clearance overall have changed little in recent years; patients and providers often continue to elect endoscopic approaches prior to surgical intervention to establish whether relief of ductal obstruction is likely to help with pain in their individual situation and to avoid a higher-risk irreversible procedure. Adjunctive therapies for stent placement and dilation of strictures include electrohydraulic lithotripsy, and use of extracorporeal shockwave lithotripsy (ESWL) to help fragment stones prior to their removal. An ongoing randomized, single-blind, parallel-group, sham-controlled clinical trial aims to assess whether pancreatic duct decompression (via endoscopic retrograde cholangiopancreatography [ERCP] with or without ESWL) is an effective treatment for painful CP.[71] An experimental endpoint of the study is to determine whether the use of P-QST phenotype (presence of hyperalgesia) can predict response to therapy. The issue of optimal timing in endoscopic therapy has also arisen: a single small study comparing early endotherapy with a wait-and-see strategy showed increased atrophy of the pancreas in the wait-and-see group as well as a trend toward improved pain control in the early endotherapy group.[112]

Advances in surgical therapy

Surgical approaches have also largely remained stable in recent years, with drainage or resection procedures including Frey, Puestow, Beger, and Whipple surgeries respectively serving as the main interventions offered. A recent unblinded randomized controlled multicenter trial from the Dutch Pancreatitis Study Group compared early surgery versus endoscopy-first approach in the treatment of painful CP, and found higher rates of pain relief at the end of 18 months of follow-up in the early surgery group compared to endoscopy-first by integrating the Izbicki pain scores during that time.[111] Interestingly, it is noted that when the endoscopy-first group is limited to those patients who experienced relief of ductal obstruction, there is no significant difference in rates of pain relief. In the overall cohort, no significant differences were seen in treatment complications, mortality, hospital admissions, QOL, or pancreatic function.

The total pancreatectomy with islet cell autotransplantation (TPIAT) has been increasingly offered to pediatric patients, especially those with hereditary etiologies of CP, and to both

children and adults with refractory pain as the outcomes have shown durable pain relief, sustained islet cell graft relief, and improvements in QOL.[113–115] Currently offered only in major tertiary care centers with islet cell isolation capability, an ongoing observational study—the Prospective Observational Study of TPIAT (POST)—is a multicenter effort aimed at clarifying the risks and benefits as the practice of this procedure becomes more widely disseminated.[116] TPIAT has significant risks including insulin dependence, new pain, and other gastrointestinal issues. A novel therapeutic approach termed "chemical pancreatectomy" is being investigated in animal models as a future treatment that could potentially achieve the same result (removal of exocrine pancreas as a noxious stimulus) without invasive surgery and fewer side effects. Infusion of acetic acid results in nonregenerative, near-complete ablation of the exocrine pancreas while preserving islets; postchemical pancreatectomy islets exhibit improved glucose tolerance and insulin secretion. While still in the early stages, Saleh et al have demonstrated that ductal infusion of 1% to 2% acetic acid resolves inflammation and pain-associated behaviors in mice and nonhuman primates.[117,118] This innovative nonsurgical therapy may be translatable to humans through ERCP and may offer a nonsurgical solution to alleviate pain and prevent pancreatic diabetes progression.

Extra-pancreatic procedural approaches

Extra-pancreatic procedural approaches that target the peripheral nerves innervating the pancreas include vagus nerve stimulation, celiac plexus neurolysis, and transverse abdominus plane (TAP) block. There are also rare reports in which spinal cord or dorsal root ganglion stimulation has been used.[119–121] However, evidence for efficacy of these procedures is inconclusive and these procedures are not universally recommended given risks and perceived lack of durable benefit.[3,66]

Gaps in knowledge and paths forward

There remains much work to be done in elucidating a better understanding of the pathophysiology of pain in CP, and subsequently to develop treatments and targeted approaches to address the pain experience. To date, there exists no cure for CP, and no way to mitigate the progression of disease except for omission of risk factors including toxins (alcohol, tobacco, triglyceride levels) and reducing the recurrence of inflammatory events. A multidisciplinary approach is often helpful to determine the best approach for individual patients though standardization of such an approach has not yet occurred. Small studies concentrated in geographic areas with sophisticated care systems for patients with CP have been designed to assess the benefits of such an approach, and preliminary data suggest improved outcomes overall.[122,123] Additional study is needed to disseminate algorithms for coordinated care in patients with painful CP. The incorporation of adjuvant therapies to treat comorbidities including psychiatric disorders, exocrine pancreatic insufficiency, mineral bone disease, frailty, and malnutrition, are likely to improve the overall health of patients with painful CP and have beneficial effects on the pain experience in this disease as well.

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Author contributions

AEP and JLS conceived, edited, and revised the manuscript the manuscript. JW and OLB performed literature review and wrote the first draft of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

Our review did not involve any clinical or animal experiments and was analyzed only using published open-source studies, therefore did not involve the approval of the Institutional Review Board.

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