Pancreatic pain

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Purpose of review
Pain is the most common symptom of chronic pancreatitis, with a profound socioeconomic impact. Historical management paradigms failed, as they did not adequately address the fundamental underlying mechanisms. The present article describes the neurobiology of pain and sensitization in this condition, in an effort to explain prior failings and provide future directions for managing pain in chronic pancreatitis.

Recent findings
A number of recent advances have been made in understanding the neurobiology of pain for this condition. This has been coupled with clinical advances in assessing sensitization to pain in these patients, which has been shown to predict response to medical and surgical therapy.

Summary
Pain in chronic pancreatitis is complex. Addressing the mechanical and morphological findings in chronic pancreatitis without addressing the underlying neurobiological mechanisms is destined to fail. New advances in our understanding of the neurobiology of pain in chronic pancreatitis helps to explain prior failings and provides future direction for managing pain in patients afflicted by this disease.

Keywords
allodynia, central sensitization, chronic pancreatitis, hyperalgesia, management, pain, pancreatitis, peripheral sensitization, treatment, visceral hypersensitivity

INTRODUCTION

Pancreatic pain is the most common symptom of chronic pancreatitis, reported by up to 90% of patients [1,2]. This pain is classically described as upper abdominal pain that can radiate through to the back, most often persistent as opposed to intermittent in character and commonly exacerbated by foods with high fat content [3]. Its socioeconomic impact is profound, resulting in poorer employment status, excess healthcare cost and a diminished quality of life similar to other serious lung, heart, kidney and liver diseases [3–6]. The largest prospectively collected dataset of patients with chronic pancreatitis and recurrent acute pancreatitis (RAP), the North American Pancreatic Study (NAPS2), reported a predefined pain pattern in 77% of patients. In addition to a large burden of disease as measured by quality of life metrics (Short Form Health Survey, SF-12), 25% of these patients received disability benefits [3,5]. NAPS2 further demonstrated the relentless nature of pain in chronic pancreatitis, with no correlation found between either the severity or the frequency of pain and the duration of chronic pancreatitis. This finding refutes a previously held theory of a pain 'burn out' in chronic pancreatitis, an observation based on older studies [7].

Although the management strategies for exocrine and endocrine pancreatic failure in chronic pancreatitis are well developed, our current strategies for managing pain in chronic pancreatitis are inadequate. Recent advances in the understanding of pain have moved our focus away from anatomical/morphological changes towards the peripheral and central mechanisms involved in processing peripheral nociceptive stimuli (Fig. 1). This paradigm shift has yielded important concepts in pain management, based on the phenomena of peripheral and central sensitization. This article will focus on these neurobiological mechanisms and their potential for providing new directions for assessing and managing pain.

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KEY POINTS

- The pain of chronic pancreatitis cannot be reliably differentiated clinically from other causes of upper gastrointestinal pain.
- Current approaches that attempt to address only the anatomic or morphological changes in chronic pancreatitis are limited in their efficacy.
- The pain of chronic pancreatitis results in nociceptive sensitization, mediated through a combination of process in the peripheral and central nervous system.
- Management paradigms for pain in chronic pancreatitis must include therapies directed at these neurobiological mechanisms.

NEUROPHYSIOLOGY OF VISCERAL SENSORY INNERVATION AND CLINICAL IMPLICATIONS

In patients with chronic pancreatitis, there are larger areas of referred pain with significant overlap between the pancreas and anatomical adjacent organs [8]. Our clinical ability to localize the pain of chronic pancreatitis or for that matter other forms of gastrointestinal pain represents a significant challenge because of the peculiarities of visceral sensory innervation. A single nerve fiber can receive information via its branches from more than one adjacent organ (e.g. stomach, duodenum and pancreas) causing clustering into a single neurosensory unit [9]. This is compounded at the spinal cord where primary sensory nerves from visceral organs terminate in several segments distributed along the vertical axis, thus providing overlap even among organs that are clearly separated from each other in different regions of the abdomen [10]. It is therefore not surprising that it can be clinically difficult to differentiate between the pain of chronic pancreatitis and other common gastrointestinal conditions. This is of particular importance in patients in which there is scant or no objective evidence of pancreatitis and may lead to pursuit of an incorrect therapeutic target.

THE THEORY OF PAIN IN CHRONIC PANCREATITIS: 'PLUMBING' VS. 'WIRING'

Earlier pain theories in chronic pancreatitis were fostered by commonly observed ductal abnormalities [11]. These 'plumbing' issues were postulated to increased pancreatic tissue pressure via ductal hypertension, resulting in impaired tissue perfusion and ongoing injury via ischemia [12,13]. This theory was corroborated by early studies, reporting elevated

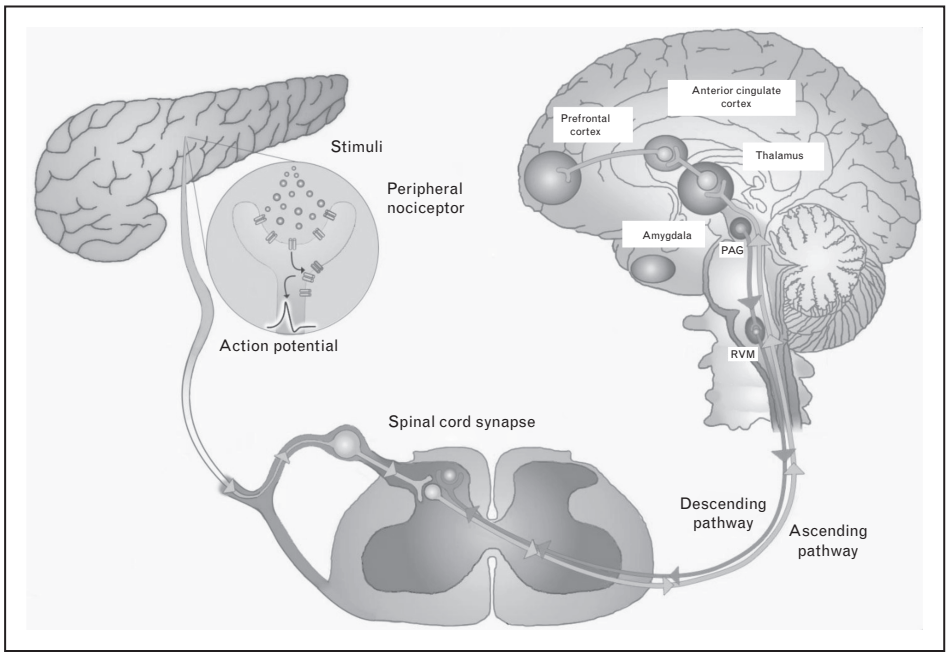

FIGURE 1. Peripheral nociceptive stimulus is a combination of physical or chemical factors, sensed by the primary afferent nociceptor through a combination of specific receptors. The primary afferent nociceptor transmits this peripherally sensed stimulus, via generation of an action potential to the synapse with second order neurons, which originate in the dorsal horn. Nociceptive stimulus is then transmitted via second order neurons to thalamic, limbic and cortical structures via ascending pathways. These central structures are responsible for processing the sensation of pain. PAG, periaqueductal gray; RVM, rostral ventromedial medulla.

pancreatic pressure and impaired perfusion, with subsequent improvement after surgical drainage procedures, correlating to improvement in pain [12,14–16]. Subsequent studies refuted this claim, with no correlation found between ductal pressure and pain response [17,18]. Additional observations also weaken the importance of a pure 'plumbing' problem in the majority of chronic pancreatitis patients. First, ductal abnormalities can be seen in equal numbers of patients with painful and painless chronic pancreatitis [19–21]. Second, significant ductal dilation (>5 mm) is only seen in approximately 30% of patients with chronic calcific pancreatitis [22]. Third, surgical and endoscopic decompression only results in an improved pain response in 50% of patients [23,24]. Finally, the severity and patterns (continuous vs. intermittent) of pain are independent of imaging finding, including ductal dilation [21,25].

In recent years, based on novel animal models and translational studies, localized nerve damage and resultant neuroinflammatory response have emerged as the leading pain theory for chronic pancreatitis, the 'wiring' theory [11]. Infiltration of the perineurium of intrapancreatic nerves is a common histological finding found in patients with chronic pancreatitis and correlates with pain [26–28]. Inflammatory perineurium infiltrates result in direct exposure of an unsheathed nerve to the local environment and inflammatory milieu. Further histological findings in patients with chronic pancreatitis that correlated to pain are increased neural density and hypertrophy [29]. Increased neuronal density has recently been demonstrated in an animal model of RAP, the most prominent emerging pathway for developing chronic pancreatitis [30]. The neuritis found in chronic pancreatitis is composed of a mixture of inflammatory cells: cytotoxic T-lymphocytes, macrophages and mast cells, the latter of which is more common in chronic pancreatitis patients with pain, supporting mast cell infiltration as a key component in peripheral hypersensitivity [31,32]. This interplay between injured nerves and immune cells in pancreatitis has been referred to as 'neuro-immune cross talk' [33–35].

Together, these findings support the concept of nociceptive sensitization in painful chronic pancreatitis, which will now be discussed in greater detail.

NOCICEPTIVE SENSITIZATION

Patients with chronic pancreatitis have lower pain thresholds in response to deep abdominal palpation compared with healthy controls, a principle employed in animal models for studying chronic pancreatitis pain [36,37]. The maladaptive responses resulting in such sensitization occur over time, supported by the clinical observation that patients who experience improved pain response have a shorter duration of pain (<3 years) prior to surgery [24]. Nociceptive sensitization is composed of two components, hyperalgesia and allodynia (Fig. 2), and can occur both in the peripheral and central nervous systems. Typically, peripheral sensitization produces a barrage of signals that in turn leads to central sensitization, so the two are often seen in conjunction in chronic pancreatitis.

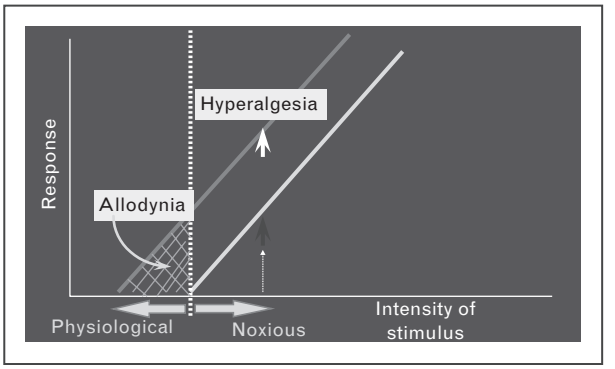

FIGURE 2. Overt time, ongoing noxious stimulus can produce an exacerbated pain response known as visceral sensitization. This results in a patient experiencing an exacerbated pain response to noxious stimulus (hyperalgesia) or perceiving a normal physiological stimulus as pain (allodynia).

A 'wiring' theory can also explain the lack of response to interventional procedures. Thus, neurolytic treatments may be limited or short lived due to the ability of peripheral nerves to regrow, innervating both the pancreas and adjacent organs [38,39]. Isolated central sensitization has not been described as a mechanism of pain in chronic pancreatitis, although in theory it may account in part for pain that persists after pancreatic resection [40].

Peripheral sensitization

Peripheral sensitization is the result of increased excitability of primary nociceptors. Based on animal models, evidence for peripheral sensitization exists along all the major steps of peripheral nociception, nociceptive receptor signaling, generation of an action potential and synaptic neurotransmission to second order neurons. Members of the TRP family, expressed on nociceptive neurons, are key cellular receptors responsible for sensing physical or chemical injury in the local environment (Table 1), producing 'trigger currents' that can initiate a full blown action potential [41–57]. The vanilloid receptor TRPV1 is the best described nociceptive receptor

Table 1. Nociceptive stimulus for transient receptor potential family and related receptors

Receptor	Stimulus
TRPV1	Inflammatory molecules: eicosanoids (lipoxygenases products) [41], leukotriene B4 [42]
	Thermal (heat >42°C) [43]
	Moderate acidosis (pH < or = 5.9) [44] and hydrogen sulfide [45]
	Anandamide (endogenous cannabinoid) [46]
	Sensitized by local tissue acidosis, PAR2 [47] and potentially TRPA1 [48]
TRPA1	Inflammatory molecules: prostaglandins [49] and bradykinin [48]
	Irritants: isothiocyanate/thiosulfinate compounds (pungent ingredients of mustard oil and garlic) [48], acrolein [48], formaldehyde [50], cigarette smoke [51] and inhaled anesthetics [52]
TRPV4	Inflammatory molecules: arachidonic acid metabolites [49]
	Osmotic pressure [49,53]
	Thermal (heat >27°C) [54]
	Mechanical pressure [55]
	Sensitized by PAR2 [56]
PAR2	Activated proteases (including trypsin) [44,47,57]

PAR2, protease activated receptor 2; TRPA1, transient receptor potential cation channel, subfamily A, member 1; TRPV1, transient receptor potential cation channel subfamily V, member 1; TRPV4, transient receptor potential cation channel subfamily V, member 4.

in chronic pancreatitis [30,58–60]. It addition to responding to a variety of stimuli, it is sensitized by activation of the protease-activated receptor 2 (PAR2) [47], which is associated with hyperalgesia and allodynia in animal models [61]. The central role that the TRP family plays in chronic pancreatitis is highlighted by two recent findings [30,62]. First, chronic pancreatitis animal models that are either TRPA1 knock outs or employ TRPV1 antagonists demonstrate reduced fibrosis, inflammatory infiltrates and neural hypertrophy, the histological hall marks of chronic pancreatitis. Second, diminished TRPA1/TRPV1 activity is associated with a reduction in sensitization to pain. TRPV1 is also associated with the local release of substance P, a potent inflammatory mediator that contributes to ongoing pancreatic inflammation via neurogenic mechanisms [60,63,64].

Table 2. Medical therapy for pain management in chronic pancreatitis

Abstinence from alcohol[a]
Antisecretory agents
Pancreatic enzyme supplementation[b,c]
Octreotide[b]
Antioxidants[d]
Tramadol[e]
Opiates[e]
Neuropathic agents
Pregabalin[d] and gabapentin[e]
TCAs[e] (nortriptyline and amitriptyline)
SNRI[e] and SSRI[e]

SNRI, selective norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.
[a]Observational data only suggesting improvement in chronic pancreatitis pain.
[b]RCT demonstrated no improvement in chronic pancreatitis pain.
[c]Meta-analysis showing no improvement in chronic pancreatitis pain.
[d]RCT demonstrated improvement in chronic pancreatitis pain.
[e]Extrapolated benefit based on management of other forms of neuropathic pain.

The ability to produce an action potential in response to noxious stimulation is also dependent on the excitability of the neuronal membrane, which is controlled by voltage-gated Na^+ (Nav) and K^+ channels (Kv). Nociceptive neurons express several different types of Kv currents such as those that rapidly activate and slowly inactivate (I_K currents) and rapidly activate and rapidly inactivate (I_A currents). Inhibition of Kv channels is associated with increased neuronal excitability in general. In chronic pancreatitis models, a specific decrease in I_A currents has been shown to be important [65]. The action potential generated in the nociceptive neuron then results in the release of neurotransmitters such as glutamate (which acts via both ionotropic and metabotropic receptors) at the neuronal synapse between the nociceptive and second order neurons in the dorsal horn. Other important neurotransmitters in this communication, such as calcitonin gene-related peptide (CGRP), substance P and brain-derived neurotrophic factor (BDNF), are upregulated in animal models and patients with chronic pancreatitis [37,66–70]. Injection of intrathecal antagonists to these neurotransmitters results in attenuation of pain in the rodent model of chronic pancreatitis [67].

Among the biological factors that may be 'master switches' for peripheral sensitization in chronic

pancreatitis, nerve growth factor (NGF) has been studied most extensively. Inhibition of NGF in animal models reduces neuronal excitability by normalizing I_A, suggesting that NGF may induce sensitization by down regulating I_A currents [71]. NGF is one of the best characterized modulators of inflammatory pain and peripheral sensitivity, that is, along with its high affinity receptor (TrkA), upregulated in patients with chronic pancreatitis [72,73]. Antagonists to NGF decrease hyperalgesia and referred somatic pain in animal models [72,74]. It augments pain and sensitization by multiple mechanisms in addition to reducing I_A currents, including upregulating TRPV1 and the neurotransmitters substance P and CGRP [37,58,67]. In recent years, the profibrotic cytokine transforming growth factor beta (TGFβ) has also been shown to cause nociceptive sensitization in chronic pancreatitis and increased neuronal excitability in association with decreased I_A currents [74], a finding that provides a link between fibrosis and pain in chronic pancreatitis. TGFβ may cause upregulation of the neurotrophin artemin in stellate cells, the expression of which, along with its receptor GFRalpha3 in patients with chronic pancreatitis, correlate with pain severity, inflammation, perineural inflammatory infiltrate, neural density and hypertrophy [75]. Prostaglandin E2 (PGE2) is a key inflammatory and profibrotic cytokine, mediating pancreatic fibrosis via its actions on stellate cells [76]. Although it is an important nociceptive signaling mediator that potentiates hyperalgesia, its role in pancreatic pain is less clear [77]. Elevated levels of PGE2 have recently been found in the pancreatic secretions of patients with early chronic pancreatitis who have significant pain but no clear structural abnormalities [78]. This finding may help to explain the severe pain associated with chronic pancreatitis in the absence of significant morphological changes.

Central sensitization

Central sensitization starts in the spinal cord. Increased facilitation or decreased inhibition of second order neuronal impulses results in visceral hypersensitivity [66,69]. Ascending pathways may be facilitated by activated glial cells in the spinal cord in rats with chronic pancreatitis and sensitization [79]. Intrathecal injection of a microglia-activating factor (fractalkine) that increased visceral hypersensitivity can be reversed with injection of a microglia inhibitor (minocycline) [80]. Descending inhibitory pathways facilitated by the rostral ventromedial medulla (RVM) may also play a role, as shown in animal models [81]. The RVM facilitates descending inhibition of pain pathways, by reducing spinal cord concentration of the opioid peptide, dynorphin, elevation of which is associated with visceral hypersensitivity.

A number of experimental findings in humans support the role of central sensitization in chronic pancreatitis. Patients with severe chronic pancreatitis have lower pain thresholds than patients with moderate chronic pancreatitis or healthy volunteers, as measured by pressure and electric stimuli in selected dermatomes, reflecting somatic allodynia, which is a reflection of spinal sensitization [82]. Electrical stimulation of the esophagus, stomach and duodenum, which share some of the same neurosensory origins, produces larger areas of referred pain in patients with chronic pancreatitis [8]. Hyposensitivity to cutaneous stimulation has also been reported in chronic pancreatitis patients, attributed to altered descending inhibitory influences on spinal nociceptive neurons [36,83,84]. Clinical studies in patients with chronic pancreatitis have demonstrated impairment in conditioned pain modulation (CPM) paradigm formally known as the diffuse noxious inhibitory control (DNIC), a phenomenon that reflects descending central inhibition of pain invoked as a countermeasure to noxious stimulation [85].

Central sensitization may also involve supraspinal structures. Cortical reorganization on electroencephalograpy (EEG) has been associated with the maladaptive pain response of chronic pancreatitis. Diminished latency of early event related brain potentials in the bilateral insula, anterior cingulate gyrus and bilateral secondary somatosensory area [8,86] and slowing EEG rhythmicity has been associated with chronic pancreatitis patients [87]. A lower peak alpha frequency on EEG is also associated with an increased pain duration in chronic pancreatitis patients [88]. Changes in EEG spectral indices due to slowing of brain oscillations have been associated with the beneficial effects of pregabalin in patients with chronic pancreatitis [89]. In addition to the cortical reorganization seen on EEG, microstructural changes in cingulate and prefrontal cortices that correlated to the degree and pattern (attack vs. continuous) of pain in chronic pancreatitis are observed on functional MRI [90].

STUDYING PAIN AND SENSITIZATION IN CHRONIC PANCREATITIS

Although observational studies in humans have helped to understand chronic pancreatitis pain, detailed molecular and pathological studies are challenging due to the complex interaction between multiple organs, including the gastrointestinal tract, pancreas, peripheral nervous system and

central nervous system. A rodent model of chronic pancreatitis has proven invaluable in the understanding of the molecular and pathological pain pathways in pancreatitis [37]. In this model, an intraductal infusion of trinitrobenzene sulfonic acid (TNBS) is used to induce chronic pancreatitis. The placement of long-lasting electrodes allows for direct noxious stimulation of the pancreas. Mechanical stimulus is applied to the skin overlying the abdomen to assess referred pain, an important component of central sensitization. A similar mouse model has also been adapted by reducing the TNBS dose [66].

Although the concept of visceral hypersensitivity has been well developed in animal models, it is only recently that meaningful strides towards incorporating it into clinical practice have been made. A number of tools have been developed to assess central sensitization, including quantitative sensory testing (QST), EEG and functional MRI [91]. Although important EEG and MRI findings can be found in patients with chronic pancreatitis and central sensitization, the cost and complexity of these tests limit their present use. Conversely, QST has a validated clinical protocol, readily reproducible results that are easier to interpret, a commercially available machine and a CPT billing code, which enables clinical reimbursement and thus potential integration of this technology into clinical practice [36,40]. QST has been validated in evaluating and assessing therapeutic response to a host of pain disorders including chronic pancreatitis [39,82,92]. It involves the application of a stimulus (thermal or pressure) to the peripheral nociceptive neuron (cutaneous) to assess its centrally mediated response (pain). By applying progressively intense stimuli an individual pain curve can be generated. The local pain response is a measure of peripheral sensitization, central sensitization is assessed by employing stimulus to neighboring and distal anatomical sites [36]. CPM, a marker of descending pain modulation, is tested by evaluating a stimulation response before and after a conditioning stimulus is applied, most commonly an ice water bucket immersion [93].

MANAGING PAIN

Medical treatments

A description of the available medical therapies for managing pain in chronic pancreatitis is available in Table 2. A full discussion of all medical therapies is beyond the scope of this article, and we will instead focus on the therapies targeting the neuropathic component of pain in chronic pancreatitis.

Opiates are used to manage pain in more than half of chronic pancreatitis patients [94]. They are known to augment central sensitization and ultimately may fail to control pain, with half of the patients in longitudinal studies of chronic pancreatitis requiring surgery to manage their pain [95,96]. Explanations for opiate failure include tolerance, opioid induced hyperalgesia and narcotic bowel, which by itself can result in chronic abdominal pain. Opioid-induced hyperalgesia is the term used to describe the phenomenon of new or paradoxical worsening of pain in patients on opiates, resulting from an increase in nociceptive sensitization [95].

Given the limitations of traditional approaches, increasing attention is being paid to the role of neuromodulators for the management of chronic pain. Tricyclic antidepressants (TCAs) and gabaergics modulate the spinal processing of nociceptive signals and are used to manage neurogenic pain across a host of conditions [97]. To date, pregabalin is the only neuropathic pain medication shown to reduce chronic pancreatitis pain in a randomized placebo-controlled trial [98]. Its analgesic effect is associated with a reduction in central sensitization as measured by QST and EEG [89,99]. Pretreatment QST was also shown to predict response to pregabalin, helping to refine patient selection [92]. Pregabalin, which was increased to a maximum dose over 1 week (300 mg twice daily), was extremely well tolerated. In our clinical practice, TCAs are often employed with gabaergics as first line therapies, as they have been proven to diminish pain in a number of neuropathic pain conditions and functional gastrointestinal diseases [100]. At higher doses TCAs have the additional benefit of treating depression, found in over half of chronic pancreatitis patients [101]. However, they are less well tolerated and require a slower titration and, when used in higher doses, require cardiac (corrected QT Interval, QTc) and blood levels monitoring [98,100,102]. Other commonly used neuromodulators include erotonin–noradrenaline reuptake inhibitor such as duloxetine which have yet to be tested rigorously in chronic pancreatitis [103]. Ketamine, an antagonist of the metabotropic N-nitrosodimethylamine (NDMA) glutamate receptor, has gained much attention for the treatment of sensitization in pain. Although it was proven in a recent trial to reduce central sensitization after an IV infusion, these results were not sustained [104]. A clinical trial evaluating a ketamine infusion followed by oral ketamine in chronic pancreatitis is currently underway and may help to define the role for ketamine in these patients [105]. A host of other potential molecular drug targets involved in sensitization (mGluR2/3, CGRP, substance P, BDNF and TRPV1)

for modulating pain in chronic pancreatitis exist and may prove pivotal in tackling this problem [30,67,68,71,106].

ENDOSCOPIC AND SURGICAL PROCEDURES

Endoscopic and surgical drainage procedures are commonly employed to manage chronic pancreatitis pain. Their use should be restricted to patients with dilation of the main pancreatic duct, who can theoretically benefit from ductal decompression. Surgical decompression was superior to endoscopy decompression for providing long-term pain relief in two RCTs, with a long-term pain response of 35%–50% and 15%–25%, respectively [23,107]. The Frey procedure, a modified version of the lateral pancreaticojejunostomy, combines both decompression and partial resection of the pancreas to improve drainage of the head. The Frey procedure has been reported to relieve pain in the short term in 75%–90% of patients [108–110]. Small duct chronic pancreatitis is not suitable for drainage procedures and partial surgical resection, as chronic pancreatitis is a diffuse process than can reoccur in the residual pancreas, ultimately causing recrudescence of pain. Total pancreatectomy and islet cell autotransplantation (TPIAT) has been increasingly utilized for the management of end-stage chronic pancreatitis that is refractory to conventional therapy. It is perhaps the only surgical option that should be considered in small duct disease. TPIAT is however a very invasive procedure with high morbidity and long-lasting complications including insulin dependent diabetes, gastrointestinal dysmotility and persistent pain requiring ongoing narcotic use [111,112]. Patient selection remains one of the most important determinates of outcome and should not be overlooked. Factors that are known to predict outcome include chronic narcotic use (>3 years), multiple prior abdominal interventions and a continuous pattern of pain [24,113,114]. Presurgical QST testing, which can identify patients with significant central sensation and predict response to surgery, may offer a standardized method that could help refine patient selection for this and other invasive procedures, but this has yet to be rigorously proven [39].

CONCLUSION

Quite simply, pain in chronic pancreatitis is complex. An extensive array of pathological and molecular changes occurs in the peripheral and central nervous system, resulting in nociceptive sensitization. Management paradigm focused on the 'plumbing' problems without addressing the 'wiring' is destined to fail in the majority of patients. Incorporation of new neurobiological concepts may lead to more targeted pain therapies, improved outcomes and ultimately reducing or eliminating the need for invasive and morbid procedures in many patients.

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Conflicts of interest

There are no conflicts of interest.

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