

## Pathogenesis and Treatment of Pain in Chronic Pancreatitis

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### 1. Introduction

An inflammatory process of the pancreas, which is replaced by fibrosis and progressive destruction, characterizes chronic pancreatitis (CP). In most patients the early phase is often dominated by pain or recurrent episodes of pancreatitis and complications, whereas in the advanced phase symptoms related to exocrine and/or endocrine insufficiency are also seen (4). Hence, apart from local complications the three major clinical features of CP are pain, maldigestion, and diabetes. However, pain also affects the other complications as for example, postprandial pain may result in patients refraining from eating and in this case enzyme treatment may not be very helpful against malnutrition. Eating habits can also influence diabetes regulation, immune system and life quality. Therefore pain can be regarded as the most severe complication to CP, especially as it is poorly understood and difficult to treat.

#### Characterization of pain

Abdominal pain is present in most patients and the primary cause of hospitalization (51). Pancreatic pain is characteristically described as a constant, severe, dull, epigastric pain that often radiates to the back and typically worsens after meals. However, many different pain patterns have been described. The pain has previously been thought to decrease over time (the so-called “burn-out” hypothesis). However, evidence

against this hypothesis was subsequently provided in two large prospective studies, where no association between the duration of CP and the quality or frequency of pain was found (43). Today the “burn-out” hypothesis is regarded obsolete and most patients have a chronic pain pattern with exacerbations of variable frequency. The economic burden is also of major importance. CP has a profound impact on social life and employment patterns mainly due to the complications, pain being the most severe (33). For society the disease in the U.S. in 2000 accounted for 327,000 hospitalizations, 200,000 emergency room visits and 532,000 physician visits costing 2.5 billion dollars (42).

#### Pain pathogenesis

Even though the pain can be caused by a variety of factors, obstruction of the flow from acinar cells and destruction of the nerves has been thought to be of major importance. This led to a dispute between researchers believing in the so-called “plumbing” and “wiring” hypotheses (51). Those that advocate for the plumbing hypothesis based their findings on the assumption that pain is generated by increased pressure in the pancreatic duct or in the pancreatic parenchyma. This mechanistic understanding of pain has been the most widely accepted theory and it is the theoretical background for most interventions including surgical and endoscopic drainage procedures. Recent studies based on endoscopic manometry have, however, not documented

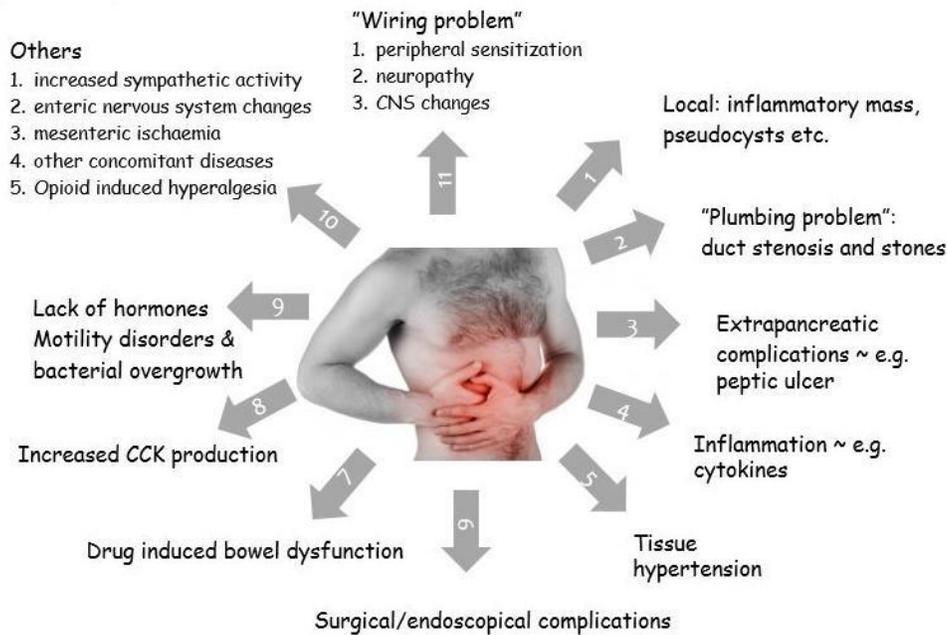
ductal hypertension in CP, and no difference in pressure levels in patients with the presence or absence of pain (44). In a recent study from our group based on magnetic resonance cholangiopancreatography including diffusion weighted imaging we found no association between the degrees of pathological imaging (fibrosis, atrophy, and ductal pathology) and pain (32). However, pancreatic atrophy and ductal pathology were associated with diabetes, and low levels of phosphate and haemoglobin. Hence, the plumbing hypothesis may not be relevant for pain in pancreatitis in general, although relief of obstruction is undoubtedly helpful in selected cases.

Other potential mechanisms resulting in pain are microstructural changes caused by the histopathological changes during evolution of the disease. Increasing evidence indicates that pancreatic stellate cells are the major mediators of fibrosis, resulting in the formation of extracellular matrix in the interstitial spaces and in the areas where acinar cells disappear or duct cells are injured. This ultimately leads to progressive loss of the lobular morphology and structure of the pancreas. The process can lead to ischemia and local changes in the gut which by themselves can cause pain, but there is also destruction of the nerves, and therefore neuropathic pain features are likely prevalent (for review see 24). As outlined later in this chapter several recent articles have demonstrated up-regulation of signalling molecules involved in inflammation and pronociceptive mediators, but also neurotropic factors in the pancreatic parenchyma in patients with CP (31). Increased neural density and hypertrophy, sprouting and neuritis of the intrapancreatic nerves, as well as activation of glia and immune cells have also been reported in pancreatic tissue from the patients (11). Finally, as also described in detail later, several studies have reported findings compatible with central sensitization in CP. Among other findings this was manifested as increased areas of referred pain, decreased pain

thresholds and neuroplastic changes in the brain (24, 52). The malnutrition following the exocrine and endocrine insufficiency further aggravates the situation as changes in the immune system and brain-gut axis are likely consequences (6). As many patients are alcoholics with a certain “addictive potential” this will also complicate treatment, especially of the pain.

Importantly, pain due to the disease complications and adverse effects to treatment must not be overlooked as additional sources of pain as these are in many circumstances easier to treat on a permanent basis. In **Figure 1** the many causes for pain are shown and each of these must be thoroughly investigated and treated if possible. This new neurobiological view of pain following CP is somewhat in opposition to the traditional view of pain aetiology, where pain was assumed to arise from pathology in or in close proximity to the pancreatic gland. However, these theories are not mutually exclusive, and aspects of both may contribute in the generation and perpetuation of pain. In addition, adverse effects and complications to medical and interventional therapies may account for a substantial morbidity in many patients and should be considered as an additional source of pain. Therefore, it is important to consider the different mechanisms, when evaluating the origin of pain in pancreatitis patients and it is plausible that the “collective” abdominal pain is a result of a complex interplay of several mechanisms.

In conclusion, the novel and improved understanding of pain pathophysiology in CP advocates a paradigm shift in pain management. Hence, modern mechanism based pain medicine where the pain system is thoroughly investigated and drug therapy tailored to the findings may replace the usual “trial and error approach”. Furthermore, every single patient should undergo careful evaluation according to **Figure 1** to determine the most likely source(s) of pain.



**Figure 1: The different factors and mechanisms that may be responsible for pain in patients with CP**

Notably, invasive based therapies (surgery or endotherapy) should be reserved to special and carefully selected cases demonstrating pathology suitable for interventions with a clear temporal relationship between the appearance of pathology and symptoms. In the following chapter we highlight the recent evidence for a neuropathic source of pain in many patients with CP and propose a theoretical framework for treatment.

## 2. Peripheral pain mechanisms in chronic pancreatitis

Pain sensation in CP includes a complex interaction between the peripheral and central nervous system (4). Both arms of the nervous system are known to undergo “neuroplastic” alterations during the chronic inflammation of the pancreas, and this neuroplasticity seems to contribute considerably to the chronic and intensive character of the neuropathic pain syndrome in CP (16). While it is widely

acknowledged that chronic neuropathic pain involves independence of central nociceptive circuits from the input from the periphery, there is also evidence for amelioration of neuropathic pain

following removal of the source of the noxious, painful input from the periphery (18). A leading example related to CP is the significant reduction or even disappearance of pain following pancreatic resection for CP (20). Therefore, it is presumable that the multitude of the peripheral neuropathic alteration that occur during CP may not only be an adaptive mechanism, but even the origin and reason for the severe pain of CP patients. In the following, these peripheral pain mechanisms in CP are divided into *morphological* and *functional* alterations.

### Morphological alterations

The characteristic features of pancreatic neuropathy in CP are 1) increased neural density, 2) neural hypertrophy, and 3) pancreatic neuritis (10). The increased neural density and neural hypertrophy have been recently summarized as “pancreatic neuroplasticity” and pancreatic “hyperinnervation”. Systematic analysis of human CP tissues revealed that intrapancreatic nerves are enlarged in the resected inflammatory mass, irrespective of the etiology of the CP (30). These neuroplastic alterations during pancreatic neuropathy seem to have an impact on the clinical course of the disease, because the extent of

neuroplasticity is closely correlated to the severity of pain in CP patients (31). On the other hand, neuro-inflammation is a characteristic feature of neuropathic pain syndromes (54). The intrapancreatic equivalent of neuro-inflammation during CP is pancreatic neuritis, which is characterized by targeted peri- or endoneural immune cell infiltrations (19). Pancreatic neuritis was reported to be independent of the etiology of CP, i.e. encountered at a similar severity in alcoholic, tropical and idiopathic pancreatitis (30). Recently, immunophenotyping of perineural immune cells in pancreatic neuritis in CP revealed that these immune cell infiltrations are mainly composed of macrophages, cytotoxic T lymphocytes and mast cells. However, it was only mast cells, which were specifically enriched around intrapancreatic nerves of patients who had more severe pain (15). Indeed, mast cells are typically localized in proximity of peptidergic nerve fibers containing substance P (SP), calcitonin-gene-related-peptide (CGRP) and can secrete numerous neuro-excitatory agents including histamine, serotonin, NGF, and proteases including mast cell tryptase. These agents can bind to their corresponding receptors on neurons (H1-4, 5HT-3, tyrosine-kinase-receptor A/TrkA, protease-activated-receptor-1/PAR-1) and hereby trigger pain and neuronal over-activation. Therefore, this recent evidence proposes that CP patients show mast-cell-induced hypersensitivity like patients with irritable bowel syndrome (IBS), ulcerative colitis, migraine or interstitial cystitis (15).

The most likely molecular mediators of pancreatic neuropathy in CP have been considered to be neurotrophic factors and neuronal chemokines. The tissue levels of nerve growth factor (NGF) and the glial-cell-line-derived neurotrophic factor family member artemin and neurturin in CP tissues have been demonstrated to correlate to the extent of neural hypertrophy and the degree of pain sensation in these patients (9, 31). Similarly, overexpression of the neuronal chemokine fractalkine in CP tissues and pancreatic nerves is known to correlate to pancreatic neuritis, and to

the severity and duration of the pain syndrome in CP (12). However, the study of these morphological alterations in a functional manner is limited by the still ongoing lack of animal models that exhibit similar neuroplastic-neuropathic alterations. Nonetheless, in recent *in vitro* models, stimulation of dorsal root ganglia neurons with pancreatic tissue extracts of resected CP patients could mimic the increased neural density and hypertrophy of neurons (14). In the same setting, the blockade of the neurotrophic factor neurturin, similar to the blockade of NGF or TGF-beta-1, could suppress the neurotrophic potential of CP extracts (17). Studies that investigate neurturin as a potential analgesic target in CP are lacking.

### **Functional alterations**

Understanding pancreatic neuropathy in CP at functional level is even more likely to deliver clues for the actual pathomechanism of the neuropathic pain syndrome in CP. From the perspective of autonomic innervation, CP was reported to exhibit “neural remodeling”, i.e. decreased sympathetic innervation, particularly with increasing degree of pain sensation or pancreatic neuritis (10, 11). Hence, it seems that the generation of pain in CP is coupled with the suppression of pancreatic adrenergic input. This observation also seems to be in line with the clinical inefficiency of thoracic splanchnicectomy that involves transection of sympathetic and sensory nerves (10). Concomitantly, nerves in CP tissues provide indicators of glial activation, since they contain reduced amounts of Sox10-immunoreactive peripheral glia and of Nestin-expressing cells in their interior (11). Therefore, at a functional level, sympathetic suppression together with glial activation seem to significantly contribute to the generation of neuropathic pain in CP.

Although current animal models of CP have not yet been reported to demonstrate a human-like neuroplasticity, they still allow the study of molecular agents that may trigger pancreatic nociception during CP. Agents like protons, bradykinin, hydrogen sulfide, serotonin, and calcium are released after acinar cell damage and can result in activation of nociceptive fibers via

their respective receptors (16). In the pancreas, proteinase-activated receptor 2 (PAR-2) and transient receptor potential vanilloid 1 (TRPV1) represent the two leading receptor subtypes that can be directly stimulated by these agents (37, 59, 60). Hoogerwerf et al. showed that trypsin infusion into the pancreatic duct of rats increases FOS immunoreactivity within sensory dorsal root ganglia (DRG) neurons by binding to PAR-2 (37). In a similar model in which trinitrobenzene sulphonic acid (TNBS) was infused into the pancreatic duct, more depolarized resting potentials and suppression of A-type potassium current density was recorded in pancreas-specific DRG neurons (59). In a follow-up study, the authors could reverse these alterations in the same rat model after intraperitoneal injection of NGF-blocking antibodies (63). Importantly, the same animal model has been used to simultaneously study the reactive alterations of central glia, particularly microglia, during CP (41). Overall, NGF seems to be in these preclinical models a major agent suppressing A-type potassium currents in pancreas-specific DRG neurons and triggering neuronal hyperexcitability. However, studies that aimed to target NGF in clinical studies with CP patients are still lacking.

### Summary

Peripheral neuropathic-neuroplastic alterations, together with the abundance of nociceptive/noxious agents in the pancreatic tissue during CP suggest that pain during CP may be induced and maintained by the interaction of both neuropathic and nociceptive mechanisms. Therefore, as also stated in the introduction, pain due to CP should be termed as “mixed-type” pain (16). Understanding the peripheral component of the CP-associated pain syndrome may provide valuable clues for the generation of pancreatic neuroplasticity and mechanisms of visceral pain in several other gastrointestinal disorders.

## 3. Central pain mechanisms in chronic pancreatitis

### Central sensitisation

An increased input of peripheral pain signals to the spinal cord may result in an increased responsiveness of central pain transmitting neurons. This phenomenon is known as *central sensitisation* and refers to an increased synaptic efficacy established in sensory neurons in the dorsal horn of the spinal cord following intense peripheral noxious stimuli, tissue injury, or nerve damage (39, 57). Ultimately, this results in a state where the pain processing is no longer coupled to the presence, intensity, or duration of noxious peripheral stimuli. Various mechanisms have been associated with central sensitisation, which comprises two temporal phases: 1) an early phosphorylation-dependent and transcription-independent phase which results mainly from rapid changes in glutamate receptor and ion channel properties, 2) a later, longer lasting, transcription-dependent phase which drives synthesis of the new proteins responsible for the longer-lasting form of central sensitisation observed in several pathological conditions (58). One of the best characterised mechanisms in the early phase of central sensitisation is activation of the N-methyl-D-aspartic acid (NMDA) receptor, revealing a key involvement of glutamate in this process (56). Blocking of the NMDA receptor by ketamine was shown to reverse hyperalgesia associated with CP in an experimental study (1).

Central sensitisation manifests as hyperalgesia (extreme sensitiveness and prolonged aftereffects to painful stimuli), allodynia (pain in response to a non-noxious stimulus) and secondary hyperalgesia (a receptive field expansion that enables input from non-injured tissue to produce pain) (57). Several studies have reported findings compatible with central sensitisation in CP. In one study, increased areas of referred pain to electrical stimulation of the esophagus, stomach, and duodenum (sharing spinal segmental innervations with the pancreas and thus serving

as proxies of true pancreatic stimulation) was reported in CP patients compared to controls (21). Other studies reported decreased pain thresholds to visceral stimulation of the rectosigmoid as well as somatic stimulation of muscle and bone (7, 46) and such hyperalgesia seems to be linked to disease severity in CP patients (3). Taken together, these findings characterise a generalised hyperalgesic state of the pain system and likely mirrors widespread sensitisation of the central nervous system as seen in many other chronic pain disorders (57).

### **Cortical reorganisation and hyperexcitability**

Several experimental and clinical studies have indicated that deafferentation, chronic pain, and hyperalgesia, as seen in CP patients, are associated with a functional reorganisation of the cerebral cortex (26). As an example, people with arm or hand amputations show a shift of the mouth into the hand representation in the primary somatosensory cortex, with the quantity of cortical reorganisation being correlated with subjective pain ratings (25). In patients with CP, damage to the peripheral nerves in the pancreatic gland may to some degree mimic the peripheral nerve pathology seen in patients following amputations. Along this line, experimental pain studies, based on somatic stimulation of the epigastric skin area (sharing spinal segmental innervation with the pancreatic gland) as well as visceral stimulation of the upper and lower gut with concomitant recording of evoked brain potentials and brain source localisation, have indicated that chronic pain and hyperalgesia is associated with functional reorganisation of the cerebral cortex (21, 40, 47). Hence, compared to healthy controls CP patients show reorganisation of the brain areas involved in visceral pain processing including the insula, secondary somatosensory cortex and cingulate cortex parallel to what is seen in phantom pain. In addition to reorganisation of the brain areas involved in visceral pain processing, the excitability of these neural networks is abnormal with evidence of

impaired habituation to noxious stimuli, possibly reflecting a cortical neuronal hyperexcitability (*i.e.*, cortical sensitisation) (50). Finally, the thalamus, as a critical relay site in the pain system, has been implicated in chronic pain. Hence, a disturbance of the thalamocortical interplay seen as global changes in the rhythmicity of the cerebral cortex was observed in patients with neuropathic pain of mixed origin (53). Parallel findings were observed in CP patients in studies based on spectral analysis of visceral evoked brain potentials and resting state electroencephalography (22, 49).

The structural correlate of functional cortical reorganisation and hyperexcitability is found in studies based on advanced magnetic resonance imaging (MRI). In one study using diffusion weighted MRI, microstructural changes in the insular and frontal brain areas was associated with clinical pain intensity and functional scores (29). Patients with a constant pain pattern demonstrated the most severe microstructural abnormalities compared to patients with an attack-wise pain pattern. This translates well to the clinic where patients with constant pain were recently reported to have the most reduced quality of life (43). In another MRI study based on cortical volumetry, brain areas involved in visceral pain processing was shown to have a reduced thickness (28). This finding suggests a central neurodegenerative response to severe and chronic pain.

### **Impaired pain modulation**

The pain system has several inherent mechanisms whereby inflowing pain signals are modulated. Among many mechanisms, descending modulatory pathways from the brain stem and higher cortical structures play a key role in such endogenous pain modulation and controls the afferent input of pain signals at the spinal level. This process can lead to either an increase in the spinal transmission of pain impulses (facilitation) or a decrease in transmission (inhibition), and the balance between these states ultimately determines the quality and strength of

the pain signals perceived by the brain (36). Alterations in the state of descending modulation from inhibition towards facilitation have been implicated in the transition of acute into chronic and neuropathic pain. Thus, several studies, both animal and human, have documented the involvement of brainstem structures in the generation and maintenance of central sensitisation and hyperalgesia (34, 62). In the context of pain and CP, impaired descending inhibitory pain modulation has been reported in studies based on experimental human pain models (3, 46). In addition, brainstem facilitation was reported to maintain pancreatic pain in an animal model of CP (55).

### **Central pain mechanisms in chronic pancreatitis: chickens or eggs?**

As can be seen from the above sections, several lines of evidence indicate that central pain processing is abnormal in CP. However, from the current evidence it is difficult to determine whether these central abnormalities are maintained by a sustained nociceptive drive from the pancreatic gland (i.e. an epiphenomenon) or whether they have become independent of peripheral input (35). However, as outlined in the following section, there is evidence that generalised hyperalgesia independent of the initial peripheral nociceptive drive is the cause of pain in many patients and in these cases treatment should be directed towards the mechanisms involved in neuronal sensitization.

## **4. Theoretical framework for treatment**

Although not well documented, it seems likely that prevention of recurrent pancreatitis attacks, clinical or sub-clinical, by risk-factor modification, will translate into a slowing of disease progression, less exocrine and endocrine insufficiency and most importantly decreased abdominal pain. Therefore pain treatment is a sine qua none in the clinical approach to the patient. For a comprehensive review of pain

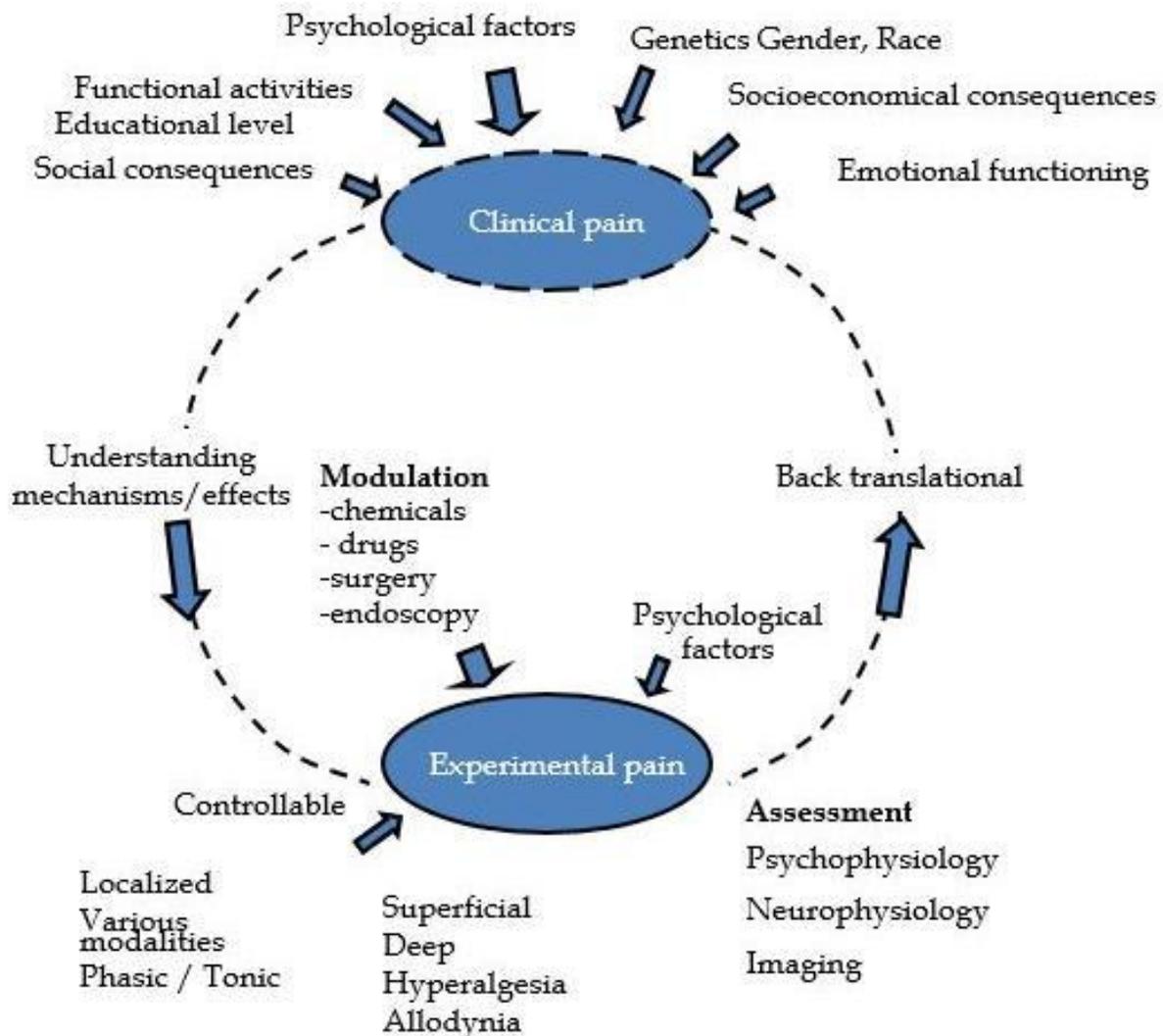
treatment it deserves some comments based on the framework suggested here. As mentioned previously extra-pancreatic causes of pain should always be considered and any complications that can give rise to pain shall be treated as best possible. For example are peptic ulcers reported to have an increased prevalence in chronic pancreatitis. This is possibly explained by reduction of blood flow to the mucosa following attacks of acute pancreatitis as well as deterioration of pancreatic exocrine function and an increased prevalence of *H. Pylori* (13). This again results in a reduction of bicarbonate concentration and hence acidification of the milieu. Another important source of pain is pseudocysts, which should be investigated by an appropriate radiological work-up and treated accordingly. Some patients may have pain as a consequence of obstruction of adjacent viscera (duodenum or common bile duct). Other factors that should always be considered (and treated) are bacterial overgrowth (seen in up to 40% of the patients), mesenteric ischemia and side effects to medications such as opioids (5). As the pain is in most cases multifactorial and neuropathic this should always be considered. Although the new neurobiological view of pain following chronic pancreatitis is somewhat in opposition to the traditional view of pain etiology, these theories are not mutually exclusive, and aspects of both may contribute in the generation and perpetuation of pain. Therefore, it is important to consider the different mechanisms, when evaluating the origin of pain (**Figure 1**), and it is plausible that the “collective” abdominal pain is a result of a complex interplay of several mechanisms. In addition, establishing a stable doctor-patient relationship as well as collaboration with other professions is an important factor for a successful treatment outcome (27). The reader can also refer to the chapter “Medical therapy for chronic pancreatitis: Diet, enzymes, and analgesics” by Joachim Mössner.

An improved understanding of pain mechanisms in CP will undoubtedly pave the way for new treatments and future strategies should be based

on modern mechanism based and personalized pain treatment. In the clinical setting, many patients with chronic abdominal pain suffer from co-morbidity, such as nausea, narcotic addiction, physical and emotional disability, and malnutrition. Therefore, a detailed characterization of pain symptoms is often difficult to obtain and is often blurred by symptoms from the associated co-morbidities as well as medication. This is particularly problematic when underlying pain mechanisms are under investigation. In order to bypass this problem experimental pain models based on quantitative sensory testing can be used (23, 45). Quantitative sensory testing provides information on sensory function at the peripheral and central level of the nervous system by recording subjects' responses (subjective or objective) to different external stimuli of controlled intensity. The primary advantages are that a pain stimulus can be controlled, delivered repeatedly, and modulated, and that the responses can be assessed qualitatively and quantitatively with psychophysical, neurophysiological or different imaging methods (**Figure 2**). As outlined in the previous sections these methods have proven to be an important instrument to characterize basic physiology as well as mechanisms underlying pathological pain disorders in chronic pancreatitis. A major problem in pain medicine is the lack of knowledge about which treatment suits a specific patient. In a recent study, we tested the ability of quantitative sensory testing to predict the analgesic effect of pregabalin and placebo in patients with chronic pancreatitis (48). A positive pregabalin effect was associated with pre-treatment sensitivity to electric tetanic stimulation of the upper abdominal area (sharing spinal segmental innervation with the pancreatic gland). Hence, patients expressing lower pain thresholds in the "pancreatic viscerotome" were more likely to benefit from pregabalin treatment compared to patients with normal sensitivity. These findings suggest sensitization of spinal neurons in the segment innervated by pancreatic visceral

afferents to be an important predictor of pregabalin efficacy in the patients. This method may be used to tailor pain medication based on patient's individual sensory profile and thus comprises a significant step towards personalized pain medicine.

Importantly, surgeons and gastroenterologists often overlook pain mechanisms as they have limited expertise. Hence, they often approach the patient with either surgery or endoscopy and in case of failure the patient is left to symptomatic treatment at the general practitioner. This is very unsatisfactory as modern pain treatment is based on a thorough knowledge to pain mechanisms and the variety of treatment modalities. In many centres pain is still treated depending on the macrostructural appearance of the pancreas as briefly outlined above, but as procedures are neither evidence nor mechanistically based, the outcome is variable and often unsatisfactory. Even though studies have compared, endoscopy and surgery (8) no placebo-controlled studies have been performed and this question the effect of invasive treatments. Surgery has been stated to be the most effective treatment of pain in CP, and recent studies suggest early surgery for CP may even increase the likelihood of complete postoperative long-term pain relief (61). As an example total pancreatectomy with islet cell transplantation is an emerging approach to treat patients with pancreatic pain. However, there has been no documentation that such advanced surgery is better than placebo as no studies have included sham surgery (or sham endoscopy) of the pancreas. As pain often resolves during the natural course of disease future studies should try to characterize pain pathogenesis better to select the right patients. In patients with neuropathic origin for the pain the surgical (or endoscopic procedures) may do more harm and deteriorate several hormonal systems regulating metabolism, gut motility etc.



**Figure 2: Schematic overview of factors influencing a patient's perception of pain in the clinic (top) and illustration of concepts in experimental assessment of pain (bottom).** Experimental pain is better suited to investigate not only the pain mechanisms but also the effects of treatment. It is essential that intensity, duration, frequency and localization of the experimental stimuli are controlled. When a given experimental stimulus results in a stable and reproducible response it is possible to modulate the stimulus. The evoked pain sensation can be assessed in a subjective manner by use of visual analogue scales (VAS) or questionnaires, but to go beyond this one dimension way of assessing pain subjective measurements can be combined with objective methods such as electroencephalography or functional magnetic resonance imaging. To mimic the clinical situation where many mechanisms come into play, various modalities (electrical, thermal, mechanical or chemical) as well as a combination of phasic and tonic models as well as models inducing hyperalgesia are typically used. Phasic models are short lasting and have limitations compared to the complex clinical conditions, whereas models inducing hyperalgesia can act as proxies for the clinical manifestations (back translational) and hence are more clinical relevant than superficial pain models.

Correspondingly surgical procedures to treat phantom pain in amputees have been abandoned by most centres. Hence, there has been a shift towards a more complex neurobiological understanding of pain generation and treatment. As the inflammation and fibrosis is invariably

linked to damage of the pancreatic nerves along with peripheral and central sensitisation of the pain system, an important outcome of such neural generated pain is that once the disease has advanced and the pathophysiological processes are firmly established, the generation of pain

become self-perpetuating and independent of the initial nociceptive drive. Hence, a small cross-sectional study found that generalised hyperalgesia (i.e. a clinical measurable proxy of central sensitisation) was associated with failure of thoracoscopic splanchnic denervation (2). The authors proposed that in hyperalgesic patients the generation of pain was independent of the initial peripheral nociceptive drive and consequently denervation of peripheral nerves was ineffective.

## Conclusion

The improved understanding of pain mechanisms focusing on neuropathic pain may pave the way for new treatments. Analgesics specifically targeting neural or humeral mediators of pain, such as nerve growth factor and transient receptor potential vanilloid-1 antagonists, are currently being tested in clinical trials and hold promise for the future, although these drugs have yet to be tested in patients with pancreatitis.

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