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Pain in Chronic Pancreatitis: A Salutogenic Mechanism or a Maladaptive Brain Response?

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Abstract
Pain in chronic pancreatitis is frequently refractory to medical and even surgical treatment. This refractoriness leads us to believe that a pancreas-independent, brain-mediated mechanism must be responsible. If so, several scenarios are worth considering. First, chronic pain could be the consequence of undesirable neuroplastic changes, by which pathology becomes established and causes disability. Alternatively, pain may be linked to the salutogenic (from *salutogenesis,* the Latin word for health and well-being) central nervous system response (we defined 'salutogenic response' as the specific modulation of the immune system induced by brain activity changes) to promote healing of the injured viscera. If so, chronic pain could index the ongoing nervous system attempt to promote healing. In this review, we discuss (1) the mechanisms of pain in chronic pancreatitis; (2) potential brain-related salutogenic mechanisms, and (3) the potential relationship of these two factors to the disease status. Furthermore, we consider these aspects in light of a new approach to treat visceral pain: transcranial magnetic stimulation, a noninvasive method of brain stimulation.

Introduction

Chronic abdominal pain is the dominant symptom of chronic pancreatitis. Its incidence is reported to be approximately 50–75 cases per 100,000 patients per year [1]. Along the course of this disease, pain is experienced by 95% of patients [2]. Even though it is a relatively uncommon pathology, chronic pancreatitis has an important clinical and economical impact, and pain in chronic pancreatitis represents a challenge for primary care physicians and gastroenterologists.

Given that pain is the result of increased activity in a specific neural network linking the brain to the pancreas caused by inflammation and injury, an important question is the physiological role of this network activation. Pain during visceral inflammation could be thought of as a disabling and unfortunate consequence of disease. This would mean that visceral afferents carry the signal from the inflamed pancreas to the brain, where pain is perceived, but that does not lead to any kind of meaningful behavioral or neurogenic response. This is most unlikely. At the very minimum, perception of pain will lead to behavioral changes, which may be quite nonspecific for any given illness, but would likely be aimed at minimizing injury. For example, afflicted by pancreatitis pain, the patient will rest more and stop eating, all of which will

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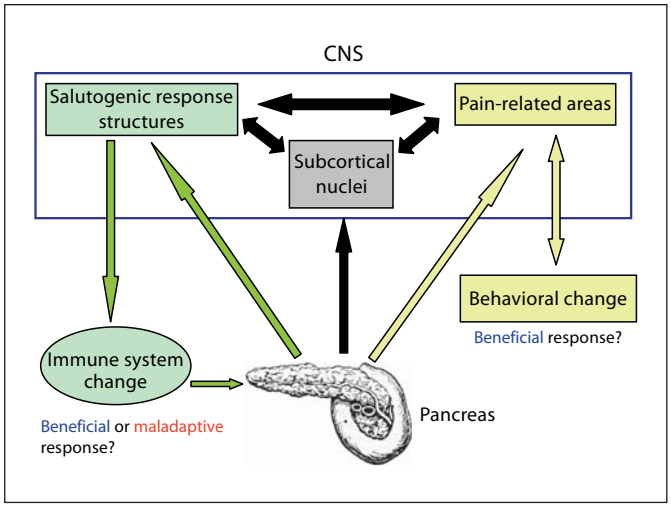

Fig. 1. In this figure, we show that pancreatic inflammation stimulates local nociceptors in the pancreas that convey this information to subcortical nuclei, such as thalamic nuclei, resulting in the activation of a neural cortical network that involves pain-related structures responsible for behavior changes (which may result in a beneficial response as pain forces the individual to rest for recovery, for instance), but may also stimulate potential 'salutogenic response structures', which might increase or decrease pancreatic inflammation, thus generating a maladaptive or beneficial response, respectively.

tend to minimize the risk of further health compromise.

Second, an attractive alternative based on evidence across species is that pain has a profoundly adaptive significance as a promoter of salutogenic bodily responses (although one can say that pain-induced behavioral changes can be viewed as a type of salutogenic mechanism, in this paper we define salutogenic mechanism as the specific modulation of the immune system induced by brain activity changes) [3, 4], some of which may be quite disease or organ specific. The activation of pain-processing brain structures in response to nociceptive inputs from the viscera may activate a two-way pathway and trigger brain-mediated healing-promoting responses (fig. 1). Activation of such salutogenic mechanisms may necessarily be mediated by pain-processing brain structures or be independent of them. In the first instance, pain might be an indicator of the activation of salutogenic bodily responses. In the other instance, pain and salutogenic responses may be both independent, brain-mediated mechanisms (see fig. 1 for a summary of the relationship between pain and salutogenic brain mechanisms). If pain in chronic pancreatitis is a salutogenic mechanism, reducing it by techniques of brain modulation might worsen the pancreatic inflammation.

In chronic pancreatitis, visceral inflammation is sustained and, frequently, pain becomes chronic and refractory to treatment. The fact that total pancreatectomy fails to relieve pain in up to 30% of chronic pancreatitis patients [5] supports the concept that the perceived pain must in part be sustained by a pancreas-independent mechanism. We hypothesize that the chronic inflammation of the pancreas leads, through sustained altered afferent visceral sensory input, to plastic changes in the nervous system that eventually can become self-perpetuating, pancreas-independent, and account for the disabling chronic pain. Is this chronic pain ultimately linked to pancreas-specific salutogenic mechanisms? The cyclic variation of pain levels and flare-ups in chronic pancreatitis might indicate that pain is not only a response to inflammation, but also a modulator of the inflammatory process. Although one can think of a salutogenic mechanism as a beneficial response, it can, on the contrary, increase inflammation. In this context, chronic, disabling pain might be the consequence of pathological changes taking place in the brain, linked to or independent of brain-mediated mechanisms that contribute to sustain the visceral inflammation.

These considerations gain practical, clinical significance in the context of new therapies of noninvasive brain stimulation that can guide brain plasticity (for a review, see Siebner and Rothwell [3] and Pascual-Leone et al. [4]). Noninvasive brain stimulation can enhance or suppress activity in the targeted regions. For instance, for chronic pain syndromes, several studies have shown that repetitive transcranial magnetic stimulation (rTMS) treatment is effective in modifying the dysfunctional brain activity associated with pain and thus results in clinical alleviation of pain [6–8]. In this study, we will not only discuss the use of rTMS treatment to relief chronic visceral pain, but also its potential mechanisms of visceral pain modulation. We speculate in this article that if chronic pain in chronic pancreatitis is an indicator of pathological neuroplastic changes that sustain visceral inflammation, then suppression of brain activity promotes healing. On the other hand, if pain is an obligatory consequence of ongoing nervous system-mediated attempts to promote healing, then facilitation (rather than inhibition) of brain activity by techniques of brain stimulation is desirable.

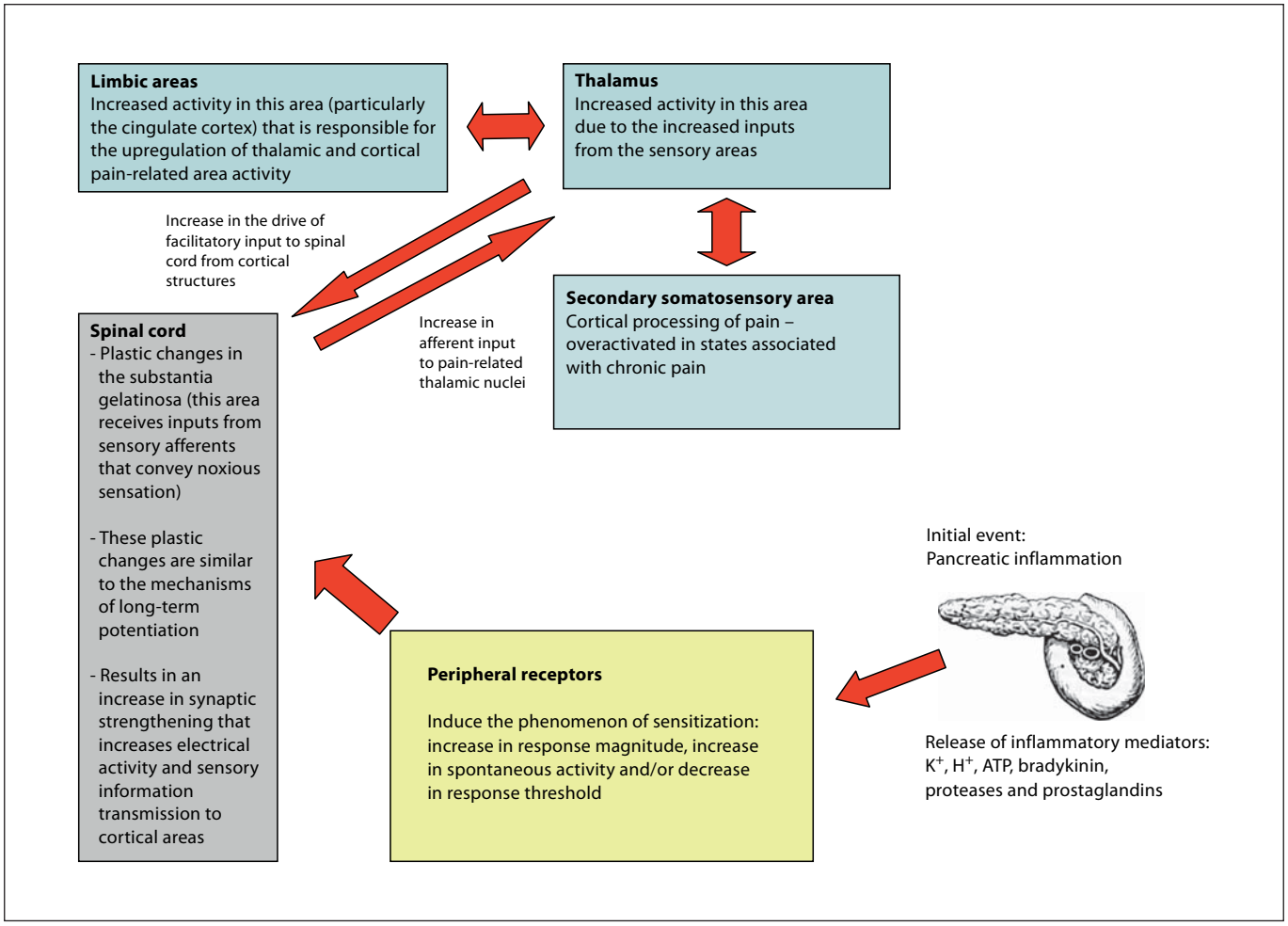

Fig. 2. Nervous system activity changes that follow pancreatic inflammation. These changes occur in all levels of the nervous system: from the peripheral nerves to central nervous structures such as spinal cord, subcortical and cortical structures. Activity changes in these areas are responsible for sustaining chronic pain.

Nervous System Changes Associated with Chronic Pancreatitis Pain: An Overactivated Circuit

In the setting of a chronic inflammation of the pancreas, repeated, pathological activation of the afferent pathways that carry visceral information to the brain is likely to cause neuroplastic changes in the peripheral and central nervous system (CNS). These changes lead to an overactivity of pain-related structures of the peripheral nervous system and CNS that can perpetuate the symptoms of chronic pain (fig. 2 shows a diagram of nervous system changes associated with chronic pain).

Pain in chronic pancreatitis starts with the initial inflammation that is observed in states of acute pancreatitis. Some studies have shown that the initial events associated with pancreatitis are the activation of intracellular proteolytic enzyme zymogens in the acinar cells [9], leading to leakage of trypsin, chymotrypsin and elastase enzymes into the pancreatic tissue [10] that results in a release of inflammatory mediators. These substances activate capsaicin-sensitive sensory neurons resulting in neurogenic inflammation [11]. Neurogenic inflammation leads to changes in the physiology of the peripheral receptors referred to as sensitization – a phenomenon that plays an important role in the pathophysiology of chronic pain.

Sensitization generally occurs after inflammation and results in an increase in response magnitude to any input,

sometimes accompanied by an increase in spontaneous activity and/or a decrease in response threshold. Sensitization of cutaneous nociceptors has long been recognized as an initial, important event to the development of cutaneous hyperalgesia.

In the visceral organs, mechanosensitive visceral afferent fibers, containing low- and high-response thresholds, have the ability to sensitize in response to inflammatory mediators such as K^+, H^+, ATP, bradykinin, and prostaglandins and thus contribute to altered sensations arising from the viscera [12]. Known triggers associated with sensitization are infections, stress and surgical procedures. Interestingly, chronic visceral hypersensitivity can be observed without evidence of overt inflammation [13]. In the case of pancreatitis, the release of proteases by the inflamed, leaky pancreatic cells will in turn extend the injury to adjacent tissues and thus affect (and ultimately sensitize) pain receptors in the other adjacent structures such as omentum, retroperitoneum and duodenum.

Evidence supporting the role of peripheral sensitization with the development of pain in chronic pancreatitis is found in a recent study showing a correlation between pancreatic tissue mast cells and inflammatory mediators with the presence of pain. In this study, using a rat model of chronic pancreatitis induced by pancreatic infusion of trinitrobenzene sulfonic acid, rats with pancreatitis exhibited a marked increase in sensitivity to mechanical probing of the abdomen and increased sensitivity to noxious electrical stimulation of the pancreas. There were significant increases in nerve growth factor protein in the pancreas and in the expression of the neuropeptides calcitonin gene-related peptide and substance P in the sensory neurons from dorsal root ganglia receiving input from the pancreas [14]. The investigators from this study speculated that mast cell degranulation products such as nerve growth factor, which may activate and/or sensitize nociceptive neurons, induce plastic changes in sensory neurons by activating proalgesic receptors and channels such as tyrosine kinase A and transient receptor potential vanilloid 1 receptor, therefore perpetuating pain and chronic inflammation.

The spinal cord can also contribute to the changes in the pain-related neural circuitry. A number of studies have pointed to a possible major role of the dorsal column in viscerosensory processing [15, 16]. A recent review showed that an area of the superficial dorsal horn – the substantia gelatinosa – might undergo plastic changes in the setting of chronic pain [17]. This area receives inputs from sensory afferents that convey noxious sensation and thus can change synaptic connectivity and receptor expression under certain conditions such as following peripheral tissue damage [17]. It has been proposed that these plastic changes in the dorsal horn of the spinal cord are similar to the mechanisms of long-term potentiation [18]. Through a cascade of molecular changes at the cell synapses, long-term potentiation results in an increase in synaptic transmission efficacy thus leading to an augmented response. Therefore, when sensory information arrives from the body to the spinal cord, this overactivated system releases exaggerated quantities of transmitters that ultimately lead to an increased input to pain-related cortical areas [19]. Not only local modulatory changes, but also supraspinal structures (i.e., brain areas) can modify the activity of the substantia gelatinosa under certain pathologic conditions and thus affect pain transmission in the spinal cord by activating corticospinal facilitatory systems [20].

Finally, changes in various areas of the CNS are believed to contribute substantially to the state of CNS overactivation that is observed in patients with chronic pain. Studies on the physiology of pain perception have suggested that various areas in the brain are important for visceral pain representation and processing: (1) the medial thalamus, which mediates spinal input and conveys it to the cortex and also serves to establish modulatory close-loop circuits of corticosubcortical activity; (2) the somatosensory cortex [particularly the secondary somatosensory cortex (SII)], which receives input from the spinothalamic pathway via the thalamus, and is responsible for the sensory-discriminative experience of pain; (3) parietoinsular cortical regions, which are thought to play a crucial role in interoceptive attribution of sensations [21], and (4) limbic areas, which are particularly critical for the motivational-affective experience of pain [22, 23].

The anterior cingulate cortex (ACC), an important component of the limbic system and of the circuit engaged in motivational-affective experience of pain [24–26], receives direct inputs from the medial thalamus and other nociception-mediating subcortical nuclei, bypassing the somatosensory area. The ACC is engaged in anticipatory readiness and anxiety [27]. Levels of anxiety appear to modulate activity of ACC neurons that receive nociceptive inputs [28]. It is thus not surprising that there is an important association between psychological stressors and visceral pain.

Several studies have demonstrated the activation of the SII in the processing of visceral pain. In a magnetoencephalography study, Schnitzler et al. [29] showed that

visceral afferents project to the SII primarily. In addition, PET and MRI studies have shown activation of inferior SI and frontoparietal operculum areas including the SII during the mechanical stimulation of the esophagus [30–32], or rectal stimulation [33]. Data from our pilot trial agree with the notion that the SII might be overactivated in patients with chronic visceral pain and that this overactivity is critical to maintain visceral pain. In our study, visceral pain relief was seen after application of rTMS to the right SII at parameters that suppress activity in the targeted brain region [34]. Pain relief was not observed after stimulation of the left SII, suggesting that there is specificity for the right hemisphere in pain processing. Consistent with these results, patients with brain lesions to the right hemisphere can endure more pain than those with left-hemispheric lesions [35].

The level of activity in pain-related brain areas might be directly correlated to the level of inflammation in chronic visceral inflammatory diseases. A study by Mayer et al. [36] investigating brain activity in two groups of patients with chronic intestinal disease with different levels of inflammatory activity – one group in remission and the other with active colitis – showed that patients with active disease have greater brain perfusion in the limbic circuits associated with their persistent pain. Patients in remission showed less activity in the limbic circuit, but increased activity in the right lateral prefrontal cortex, which perhaps mediated the suppression of the sustained limbic 'hyperactivity'. Similar studies in chronic pancreatitis are lacking. However, our pilot data (unpublished data) suggest that in patients with chronic pancreatitis pain, the level of glutamate as measured by magnetic resonance spectroscopy is increased in the right compared to the left SII area. An increase in glutamate would result in abnormally excitable cortex and possibly be a marker of pain-sustaining maladaptive neuroplasticity.

In summary, peripheral and central sensitization are important contributors for sustaining chronic pancreatic pain. Buscher et al. [37] summarized this notion in a previous study in which they conclude that two mechanisms contribute to pain in chronic pancreatitis: (1) central sensitization and visceral hyperalgesia maintained by persistent nociceptive input from ongoing pancreatic inflammation and (2) autonomous and independent central pain as a result of continuing nociceptive input. These authors performed a study in 10 patients with chronic pancreatitis and stable analgesic opioid medication and 10 matched surgical patients without pain serving as controls. Pain verbal numeric rating scores and thresholds to electric skin stimulation and pressure pain were measured in dermatomes T10 (pancreatic area), C5, T4, L1 and L4. The results of this study showed that pressure pain thresholds were significantly lower in pancreatitis patients than in controls. These findings confirm that chronic pancreatitis patients have pronounced deep hyperalgesia that is present despite opioid therapy [37].

Although central plastic changes are believed to be associated with chronic visceral pain in pancreatitis, the intensity of these changes might be associated with the etiology of pain in clinical pancreatitis. As shown by Mullhaupt et al. [38], the pain pattern can be subdivided into types A and B. The type A is characterized by short episodes of pancreatitis (less than 10 days) separated by long pain-free intervals and type B is characterized by prolonged periods of intermittent severe pain (more than 1–2 months) and is associated with local complications. Therefore, although plastic central changes occur in both patterns of pain, the permanent local inflammatory process associated with type B might have a different impact on brain activity as an ongoing peripheral input might increase activity in pain-related neural networks, thus amplifying brain plastic changes.

It is clear that the peripheral nervous system and CNS undergo plastic changes in response to the inflammation of visceral organs with the result being increased activity in several pain-related nervous system areas. These plastic changes underlie the pathophysiology of chronic pain in chronic inflammatory visceral conditions, such as chronic pancreatitis. If these neuroplastic changes are desirable, i.e. if they promote health and healing, then we ought to enhance them, and accept the disabling consequences of pain as the least of evils. If, on the other hand, chronic pain is indicative of a dead-end strategy, a failed attempt of the body to overcome an inflammatory visceral process that has ultimately given rise to persistent pain and disability, then suppression of the involved brain region activity may be indicated.

Biological Advantages of Chronic Pancreatitis Pain: Is Pain Associated with a Salutogenic Mechanism?

Pain as a Behavior Modifier

Pain can convey an important evolutionary advantage. At a social level, pain will disable the individuals afflicted with visceral inflammation, illness, or injury, and thus allow the herd, the pack of wolves, the family of chimps, or the nomadic group of hunters to escape from dangers or succeed in food procurement without being slowed down. At an individual level, pain also conveys an

advantage. For example, without pain we would scratch our cornea until we become blind. For visceral sensation, pain may be an important warning that something is wrong in the vital organs that requires an immediate change of behavior in order to promote healing. Additionally, activation of pain-related structures in the brain might trigger physiological changes that help the healing process. Thus, pain might be a part of a complex healing reflex response.

The behavioral responses associated with pain include a change in the feeding and behavior responses [39], leading individuals to rest, sleep more, and avoid potential physical and emotional stresses that can aggravate the pain. These changes help promote the healing even though they are not disease or organ specific. There are other examples of neural responses that lead to behavioral changes that protect the individual and assist recovery and healing. Fever is a classical example. Fever raises the body temperature to the point where bacteria and viruses cannot readily multiply and phagocytic activity is enhanced. However, fever also makes the individual tired, promoting sleep and rest, or thirsty, promoting drinking and increasing renal excretion of possible toxins. In an analogous manner, in addition to behavioral changes, pain could also trigger physiological mechanisms – such as a change in the immune response – that might promote healing and possibly be disease or organ specific.

Pain as an Immune System Modulator

There is a growing body of evidence that the brain can modulate the immune system and ultimately has the capability of activating specific salutogenic mechanisms. For example, there is ample literature demonstrating that focal brain injury, for example due to a stroke, can influence the patient's immune system [40, 41]. A recent study showed that, after stroke (experimentally induced), Wistar rats have an increased activation, as compared with controls, of T and B lymphocytes, characterized by increased proliferative responses of spleen lymphocytes to different mitogens [40]. Similar effects can be demonstrated by patients and animals with refractory partial seizures, revealing a site and hemisphere specificity for this CNS-immune system response [41]. In addition, modulation of cortical activity by noninvasive brain stimulation provides a means to influence immune response and visceral physiology. Evidence that electrical cortical stimulation can modulate the immune system was shown by Moshel et al. [42] in a preliminary study that revealed changes in the number of CD4 and CD8 T lymphocytes depending on the hemisphere of stimulation (the left increased circulating levels of these cells and the right had the opposite effect). More recently, Clow et al. [43] reported that TMS applied to the left or right parietal cortex led to an increase in saliva production and in the secretion of antibody immunoglobulin A into saliva. Furthermore, an animal study showed that rTMS alters the hypothalamic stress axis resulting in an increase in ACTH and corticosteroids levels [44]. It is possible that such brain-mediated salutogenic mechanisms are completely independent of pain-mediating brain regions. However, evidence from several studies supports the hypothesis that activation of brain structures involved in pain perception contribute to the neural response that promotes salutogenesis.

Immune cells produce neuropeptides such as B-endorphins and other neurotransmitters [45] that have an important effect on CNS activity. The CNS, in response to this afferent immune system modulation, can in turn alter the immune system, with this response potentially leading to a maladaptive, vicious circle – i.e., chronic inflammation of the pancreas increases the activity of areas in the brain (including pain-related areas) that in turn increase the inflammatory response in the pancreas and so on. The main question here is whether this vicious circle is necessary for the healing process or is only causing more harm.

Analogous to the somatic system in which a noxious stimulus applied to the skin triggers a reflex arc that results in a motor response to avoid potential harm, a noxious stimulus in the viscera might induce pain as well as a reflex response from the autonomic system that increases or decreases the local inflammation in order to promote healing. If such an analogy is valid, pain is only a component, perhaps secondary, of a complex autonomic reflex response that modulates the immunological response in the inflamed viscera. If overactivity of the nervous system in the setting of pain is associated with a salutogenic mechanism, then pain in pancreatitis should be interpreted as a part of a two-way system in which pain represents the afferent segment while the efferent pathway functions to activate healing mechanisms. Indeed, the term 'neurogenic inflammation' has been used to define the mechanism in which neural and perineural alterations play an important role in pain pathogenesis in chronic pancreatitis [46]. Indeed, it has been suggested that there exists 'neuroimmune cross-talk' in which there is an association between inflammatory cells, nerves and ganglia [46].

Recent research has shown that inflammatory response might be mediated by a CNS reflex, i.e., the presence of inflammation would send afferent signals via the

vagus nerve that would result in a response in the efferent part of the vagus nerve to increase acetylcholine release in the vicinity of macrophages that ultimately determines the intensity of the inflammatory response [47]. In addition, the vagus nerve is not only proinflammatory, but can also induce an anti-inflammatory response as shown by in vivo electrical stimulation of this structure [48]. The vagus nerve might therefore not only convey afferent input from the inflamed viscera, but also transmit a feedback response from the CNS that might be mediated, in part, in pain-related areas. Evidence for the role of cholinergic modulation of pancreatic inflammation has been shown by the following studies:

- Alcoholic pancreatitis is associated with excessive cholinergic tone that would potentially lead to inflammatory changes and pain [49]. However, it is still unknown whether this increased cholinergic tone is an attempt of the CNS to control the inflammatory process induced by alcohol consumption.
- A previous study in an animal model of pancreatitis induced by cerulein showed that vagotomy or pretreatment with mecamylamine (a nicotinic receptor antagonist) worsens the severity of pancreatitis – as indexed by histological examination. On the other hand, pretreatment with the selective α7 nicotinic receptor agonist 3-(2,4-dimethoxybenzylidene) anabaseine strongly diminishes the severity of pancreatitis [50]. Therefore, this study supports the anti-inflammatory role of the vagus nerve via the nicotinic pathway.
- Although vagus nerve activity seems to be anti-inflammatory in pancreatitis, another important peripheral nervous structure – capsaicin-sensitive afferent sensory neurons – seems to have the opposite effect as it increases local inflammation. It has been shown that peripheral sensory neurons treated with capsaicin release substance P resulting in an acute overstimulation, a burning pain sensation [51], pancreatitis pain [51] as well as a strong inflammatory response [52]. In fact, disruption of the capsaicin-sensitive neuron-associated immune response decreases pancreatic inflammation and also reduces lung injury. In contrast, stimulation of the nicotinic anti-inflammatory pathway only ameliorates inflammation and injury in the pancreas. This suggests a specific response from the nervous system in controlling inflammation and injury which might also have a corresponding somatotopic representation in the brain.

Therefore, an important issue here is to define the factors that trigger the 'proinflammatory nerve pathway' – that consists of a reflex arc involving the stimulation of specific sensory neurons (sensory C-fibers by capsaicin, for instance) that results in the release of bioactive substances from nerve terminals [53] – and the 'anti-inflammatory nerve pathway' – that consists of the vagal nerve releasing acetylcholine and decreasing inflammation. In either case, both of these pathways relay information to the spinal cord and CNS. Therefore, the ultimate control of the inflammatory response might come from the CNS.

Further evidence points to the relationship between pain and immune system changes. Hoogerwerf et al. [54], in a study examining autopsy specimens of patients with painful chronic pancreatitis, found that humans with painful chronic pancreatitis had a 3.5-fold increase in pancreatic mast cells as compared with those found in painless chronic pancreatitis patients. Also in this study, the authors further explored this association and showed that wild-type mice with chronic pancreatitis were significantly more sensitive to pain as compared with mast-cell-deficient mice. In addition, a recent review underscored this relationship showing an association with growth-associated protein 43, an established marker of neuronal plasticity, in the CNS and peripheral nervous system of adult rats with behaviors associated with pain [55]. However, the direction of this relationship is not clear – i.e., whether more inflammation causes more pain – as shown by a recent study that demonstrated that proteinase-activated receptor 2, a receptor activated by trypsin and tryptase and abundantly expressed in the gastrointestinal tract including the C-fiber terminals, plays a significant role in the processing of visceral pain but not in the inflammation associated with pancreatitis [56] – or more pain induces more inflammation via brain modulation, or yet, a combination of these two mechanisms.

Finally, the regulation of cytokines can be significantly controlled by the CNS. Therefore, the initial pancreatic inflammation may modulate pain through the release of cytokines, which secondarily induces a release of cytokines in the glia within the brain and spinal cord and facilitates neural transmission in pain-related areas [57]. This increase in activity in pain-related areas in turn could modulate immune responses.

In summary, there are definite links between CNS activity, immune response, and visceral function. The areas of the brain involved in pain perception appear to play a critical role in this link, and brain stimulation to several of these areas has been shown to modify different aspects of immune and visceral function.

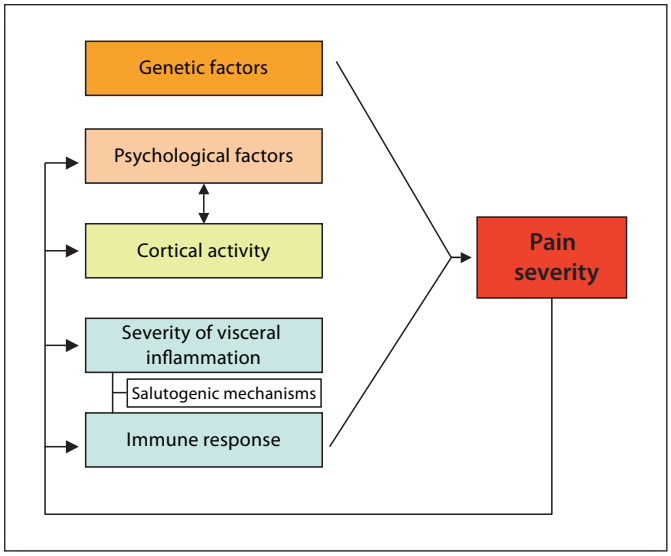

Fig. 3. Factors that contribute to the experience of chronic pain and the interrelation between these factors and pain. For instance, psychological factors alter cortical activity and vice versa and both factors can modulate pain severity. Furthermore, severity of visceral inflammation is associated with the severity of immune response that in turn modulates cortical activity that in response might modulate back inflammation severity, ultimately, resulting in a regulation of pain severity.

Factors Determining Pain Response: Psychological and Genetic Factors

It has been established that pain levels vary substantially across patients with chronic pancreatitis and this variation does not depend only on the degree of pancreatic inflammation but might depend on other factors, such as psychological and genetic differences.

The affective component of pain is an important factor in determining pain levels. Patients may have similar levels of overactivity in pain-related brain areas, but rate pain differently. In an elegant study, Vase et al. [58] showed that pain induced by distention of the rectum with a balloon can be decreased equally by placebo or lidocaine when compared to the natural history. Interestingly, they then performed the same procedure but using an opioid antagonist – naloxone – and found that this drug does not block the placebo effect. The authors concluded that there is a causal link between expectation and pain perception that is not mediated by endogenous opioids. One possible explanation is that expectation does not alter the experience of pain but simply the rating of pain severity – i.e. patients with the same pathophysiological change in pain-related structures may feel pain differently depending on their expectation. Alternatively, if the placebo response can truly induce a decrease in pain through physiological changes, then expectation might ultimately reverse the altered brain activity associated with pain [59].

One important determinant of pain levels in chronic pancreatitis might be the phenomenon of psychological amplification. Psychological amplification refers to an amplification of the severity of the physical symptoms due to psychological processes. Vandvik et al. [60] showed that, compared to patients with low somatic comorbidity, patients with high somatic comorbidity have a higher frequency of extraintestinal symptoms, such as stress-related symptoms, higher health anxiety, more mood disorders, more neuroticism and more adverse life events. Psychological factors may modulate visceral hyperalgesia as demonstrated by a study whereby patients become overaware of the luminal distension [61]. Therefore, psychological amplification might be an important factor in sustaining the refractory pain in a subset of patients with chronic pain and pancreatitis.

Another possible reason to explain why pain levels are different across patients with similar pancreatic inflammation is related to different individual characteristics across subjects. Because pain is associated with overactivity of the CNS, patients who are 'primed' for altered cortical plasticity would be the candidates to develop these symptoms. Indeed it has been demonstrated that dystonia – a disease linked to a specific genetic alteration – is an example of genetic changes leading to altered plasticity [62, 63]. In the case of chronic pancreatitis, patients with specific genetic factors, when faced with chronic altered afferent input from the inflamed pancreas, could be more prone to develop the type of plastic changes that result in a neural substrate for chronic pain and visceral inflammation (see fig. 3 for a summary of the factors that might determine pain response).

Modulating the Pain-Related Neural Circuitry with Brain Stimulation in Chronic Pancreatitis: Is This Advantageous?

The development of noninvasive techniques of brain stimulation makes it possible to modulate brain activity in a safe and painless way. For this reason, several researchers and clinicians have become interested in the use of these methods for the treatment of neuropsychiatric disorders, including chronic pain. Although reducing

pain seems, at first glance, the only beneficial advantage of brain modulation, changes in brain activity induced by brain stimulation might modulate salutogenic mechanisms as well. One of the techniques that have been proposed for the treatment of chronic pain is TMS.

TMS has been shown to be a powerful tool to modulate brain plasticity [64, 65]. When applied repetitively, it can induce changes in brain activity that can outlast the period of stimulation itself [66]. The induced effects depend on various stimulation parameters, but particularly on stimulation frequency. Low-frequency rTMS suppresses the activity of the targeted brain region, while high-frequency rTMS tends to promote a facilitation of the targeted area [66]. Clinically, several studies have shown that the cortical activity modulation by rTMS can be successfully used in the treatment of various neuropsychiatric disorders [67–71], as well as the treatment of chronic pain [6, 7, 72, 73]. The notion that brain modulation may be an effective therapy for chronic pain syndromes is further supported by the fact that chronic electrical epidural stimulation of the precentral cortex can improve drug-resistant neurogenic pain [74, 75]. Presumably this is due to inhibition of nociceptive neurons at cortical levels through non-noxious fibers from the motor cortex or a secondary modulation of thalamic nuclei. TMS has the advantage of being noninvasive and safe if appropriate guidelines are followed [76]. Two recently published studies using rTMS applied to the motor cortex reported suppression of pain in patients with therapy-resistant chronic somatic pain syndromes [6, 77]. In addition, Lefaucher et al. [7] studied 60 patients suffering from intractable pain. These patients underwent one session of active or sham rTMS in random order. The authors showed that pain reduction was significantly greater following real rather than sham rTMS.

Our group has investigated whether rTMS is effective in the relief of chronic visceral pain in patients with chronic pancreatitis [34]. The effect of low- and high-frequency rTMS was studied. Five participants with idiopathic chronic pancreatitis underwent (in random order) six sessions of rTMS with different parameters: right 1-Hz rTMS, left 1-Hz rTMS, right sham, left sham, right 20-Hz rTMS, and left 20-Hz rTMS. Each participant had had chronic daily pain for at least 3 years. Baseline pain scores on a visual analogue scale were obtained during the 2 weeks prior to treatment. Pain levels were assessed daily throughout the TMS sessions. Daily chronic and 'as needed' analgesic intake was also recorded. The interval between each session was 1 week to avoid carryover effects. Participants and raters were blinded to the stimulation condition.

Three out of 5 participants had a significant response with a mean pain reduction of 59% after rTMS applied to the right SII at a frequency of 1 Hz, as compared to baseline. This improvement lasted 3–5 days. Other stimulation conditions, including sham treatments, either had no effect or were associated with a worsening of the pain score. When the results were analyzed together, only right 1-Hz rTMS resulted in a consistent improvement in pain across participants [34]. It needs to be underscored, however, that these preliminary findings have to be replicated in future studies with larger sample sizes. Furthermore, the effects on pain reduction after a single session of rTMS were transient – lasting a few days only. Therefore, further studies need to explore other strategies of stimulation – such as multiple sessions of stimulation – to increase the duration of its effects.

Another noninvasive neuromodulatory method is transcranial direct current stimulation (tDCS). In tDCS, a very-low-level current is passed between an anode and a cathode electrode attached to the scalp. The patient perceives practically nothing, but a faradizing current is induced in the brain that changes the neuronal membrane potential and can shift the level of brain activity in the targeted brain regions. Applied over the sensorimotor cortex, tDCS can have substantial analgesic effects in patients with neuropathic pain due to spinal cord injury [78]. The study of tDCS in patients with visceral pain seems worth pursuing.

More invasive tools of neuromodulation include spinal cord stimulation, direct cortical stimulation, and vagus nerve stimulation. Spinal cord stimulation has recently been reported to have substantial effects on visceral pain [79]. Another neuromodulatory approach is stimulation of the vagus nerve. The vagus nerve may have a critical role in inflammation as shown by studies demonstrating its role in inflammatory activity [80] and its stimulation is efficacious in reducing the symptoms of depression and seizures [81–83]. Therefore, stimulation of this structure might, in addition to modulating the central activity of the nervous system, also modulate the immune system activity to some extent.

One important aspect is whether the analgesic effects of brain stimulation may also have an anti- or proinflammatory effect and whether this might be beneficial or not (fig. 1). Independent of pain modulation, brain stimulation itself can have a modulatory effect in the immune system through the release of humoral substances as well as modulation of peripheral nerves such as the vagus nerve. Therefore, neuromodulation approaches might be

used to modulate not only pain but also the inflammatory process associated with chronic pancreatitis.

Past research indicates that modulation of immune response by changes in brain activity is specific to the site and hemisphere of the brain. Therefore, in order to use brain stimulation to interfere actively with visceral inflammation, the site of stimulation is a critical parameter. Because the results of studies on the immune response after brain stimulation or in the setting of a brain lesion are mixed, it makes it difficult to predict (1) the optimum site of stimulation and (2) whether a possible change in the immunological system induced by brain stimulation would have a clinical impact.

Conclusion

The field of brain stimulation for chronic pancreatitis is a new field that has yet to be explored in a substantial manner, and will likely be expandable to other visceral and gastrointestinal disorders. Because of the development of new tools of brain stimulation and of new tools and devices to investigate brain activity, this field has the potential to yield new approaches in a short period of time. However, with this development, new questions will arise, such as the role of brain stimulation and its relationship with immune system modulation and visceral function. Previous data support the concept that brain cortical areas may actively change immune responses and visceral function, and therefore might play an important role in the visceral physiology. The investigation of new treatments that can change brain activity need to address whether changing brain plasticity results in immune system changes and whether such changes are beneficial or detrimental and, importantly, clinically relevant.

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