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EMERGING THERAPIES AND NOVEL APPROACHES TO VISCERAL PAIN

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Visceral pain is the most common type of pain associated with disease and it is one of the most frequent reasons why patients present to a doctor's office. Although these patients seek medical care because they are looking for help to alleviate their visceral discomfort and pain, in clinical practice much emphasis has been placed on finding a specific etiology and specific pathological markers for visceral disease. These patients typically undergo many diagnostic tests and procedures. However, often the examination and work-up remain unrevealing and no specific cause of the pain can be identified. In these cases it is important to recognize that pain is not only a symptom of visceral disease, but that the patient is suffering from a "chronic visceral pain syndrome".

Although visceral pain is very common, the recognition of chronic visceral pain as a chronic pain syndrome is fairly new in the clinical subspecialties of gynecology, urology, gastroenterology and cardiology. Much of what we know about the pathophysiological mechanisms of pain is derived from experimental studies of somatic and not visceral

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nociception. Traditionally it was assumed that visceral pain is simply a variant of somatic pain, however, there is growing evidence that, although there are some similarities between the mechanisms of visceral and somatic pain, there are also very important differences.

The purpose of this article is to provide a concise update on the epidemiological and clinical aspects of the visceral pain syndromes, which present an unmet medical need, and to discuss recent advances in the understanding of the pathophysiological mechanisms of visceral pain, highlighting where novel therapeutic approaches might emerge in the near future.

EPIDEMIOLOGY OF VISCERAL PAIN

There is growing epidemiological documentation over the last 15 years that visceral pain syndromes are indeed very common. Patients, who have one visceral pain condition, seem more likely to have other pain conditions as well. Evidence is growing about genetic predisposition and environmental factors.

CHEST PAIN

1 in 25 people consult their General Practitioner with chest pain every year (1). Musculoskeletal chest pain accounts for 20.4% of all diagnoses, followed by reflux esophagitis (13.4%), and costochondritis (13.1%) (2). In this study, stable angina pectoris was the primary diagnosis in 10.3%, unstable angina or possible myocardial infarction in 1.5% (2).

GASTROINTESTINAL PAIN

Between 10% and 20% of the general adult population in the United States report symptoms compatible with Irritable Bowel Syndrome (IBS) (3). The onset of symptoms is often as a young adult, but the prevalence is similar in the elderly. Women are diagnosed more often than men, (2:1) and the prevalence is widely thought to reflect access to health care (3). Several studies find that a sustained, major life event is the strongest predictor of IBS development (4). There is a high cooccurrence of IBS with other gastrointestinal syndromes, such as functional dyspepsia; non-GI pain disorders (fibromyalgia, lower back pain, headaches) and affective disorders (anxiety and depression) (5). Women who have IBS are also more likely to have CPP (35%), and urinary frequency and urgency (65%) (5).

CHRONIC PELVIC PAIN (CPP)

CPP is common in women, affecting as many as 1 in 7 in the United States (6). Studies suggest that a third is due to endometriosis, a third to adhesions and a third have no obvious pathology (7). In all probability the first two are probably over estimated and a central neurological cause is likely.

BLADDER PAIN

Chronic bladder pain, according to a large community-based survey, is common with 1.3% of men and 2.6% of women experiencing ongoing pain associated with bladder function that had been lasting three or more months (8). Co-morbid conditions were found by the same survey to be common. The more restrictive diagnosis of Interstitial Cystitis affects 0.5% of the population with a female predominance of 10:1.

PROSTATE PAIN SYNDROME (PPS)/PROSTATITIS

PPS without demonstrable infection is the most common urological diagnosis among men under age 50, and the third most common in those over 50, with 6 million men affected in the United States (9).

SCROTAL PAIN

The most reliable data is for the incidence of post-vasectomy pain which is between 15–19% (7). Chronic testicular pain (orchialgia, orchidynia) occurs at any age, but is common in the mid to late thirties (7).

VULVAR PAIN SYNDROME OR VULVODYNIA

The incidence of vulvodynia may be as high as 15% and is most common between the ages of 20 and 60 (10). It is associated with pain with first tampon use (10), bladder pain syndrome and functional bowel disorders (11).

In conclusion epidemiological data support: 1) that there is a significant overlap between the visceral pain syndromes, with one visceral pain syndrome being a risk factor for developing further such syndromes (12) and 2) that the mechanisms involve many systems so that a patient with a visceral pain syndrome is very likely to develop a generalized pain syndrome, such as fibromyalgia or chronic fatigue syndrome (13). The evidence suggests common mechanisms involving the central nervous system and possibly neuroendocrine (14) and neuroimmune mechanisms.

CLINICAL ASPECTS OF VISCERAL PAIN

VISCERAL CHEST PAIN

The properties of visceral pain have clinical implications regarding chest pain.

It may be difficult to establish the cause of chest pain in a patient. For example, cardiac pain and esophageal pain may be almost impossible to differentiate in many cases (15), showing similar referral patterns and similar accompanying autonomic and motor reflex activity. Angina pectoris is the clinical presentation of coronary atherosclerosis. Other cardiac causes of chest pain include peri/myocarditis and mitral valve prolapse. Treatment of angina pectoris is focused on reducing myocardial ischemia and thereby relieving pain, either by reducing oxygen demand (bedrest in acute stage, beta-blockers or regular physical activity) and/or to increase the oxygen supply surgically (coronary artery bypass grafting/ percutaneous coronary intervention) or medically by nitrates and calcium channel blockers. Lipid lowering therapy and thrombolytics are added. Chest pain in spite of optimal medical and surgical treatment is defined as "refractory angina" (16). For these patients, several additional treatment modalities, including spinal cord stimulation, laser vascularization and enhanced external counterpulsation (EECP) have been proposed. Gastro-esophageal reflux disease (GERD) is the most common non-cardiac cause of angina-like chest pain in the clinical setting. Treatment for GERD focus mainly on acid-suppression by proton pump inhibitors, while surgery remains an alternative, in select cases. Several defined esophageal dysmotilities are associated with chest pain. The term, non-cardiac chest pain (NCCP) has been defined as long-lasting chest pain without any (known) cardiac abnormality (17).

Secondly, patients may suffer from dysfunctions of two or more viscera simultaneously, making the differentiation of the cause of a given chest pain episode, even harder. Around 50% of patients with coronary artery disease (CAD) may suffer from coexisting gastroesophageal reflux (GERD) (18). Clinically it is very important to rule out/confirm the presence of myocardial ischemia in patients with chest pain of presumed cardiac origin, even in patients with established CAD. Alternatively, the underlying pathophysiology may be the same, but involving more than one organ. Visceral hypersensitivity (19) is a part of several functional pain entities, such as irritable colon, functional dyspepsia or non-cardiac chest pain (NCCP). Furthermore, esophageal hypersensitivity has been found both in patients with cardiac syndrome X (20) as well as irritable colon.

Thirdly, the presence of viscero-visceral reflexes have been established. Experimentally, acid instillation in the esophagus results in constriction of the coronary arteries in dogs and decreased blood flow velocity in humans, confirming an esophago-cardiac reflex, i.e. linked angina (21). The clinical importance of this phenomenon remains unknown.

VISCERAL ABDOMINAL PAIN

Visceral abdominal pain may derive from abdominal organs, i.e., gastrointestinal tract, upper-middle urinary tract, or organs located in the thorax (see previous section) or pelvis (reproductive organs, lower urinary tract)(22).

While differentiation may be difficult in the first phase of “true visceral pain”, always perceived along the midline, it becomes easier in the subsequent phase of pain referral. Diseases of the stomach, gallbladder, duodenum, pancreas, liver, lower esophagus, heart and lungs mainly produce epigastric pain. Liver, gallbladder, and the hepatic flexure of the colon refer pain to the right hypochondriac region while diseases of the spleen, the splenic flexure of the colon, and cancer of the tail of the pancreas produce pain in the left hypochondriac region. Pain in the right or left lumbar/flank regions derives from kidney, ureters, head or tail of the pancreas and colon. Pain in the periumbilical region usually arises from the small intestine, appendix, cecum and body of the pancreas. Pain in the right iliac region originates from the appendix, small intestine, cecum, right kidney and ureter, right uterine tube or ovary. Pain in the left iliac region normally derives from the sigmoid colon, left urinary tract and internal genitalia. Pain in the hypogastric region is usually caused by urinary bladder, internal genitalia and intestinal diseases. Referred abdominal pain is frequently associated with somatic hyperalgesia in the painful area. Generalized abdominal pain accompanied by marked resistance of the abdominal muscular wall and cutaneous allodynia is suggestive of peritoneal involvement (23).

An example of **functional abdominal pain** is Irritable Bowel Syndrome (IBS), the most frequent diagnosis in gastroenterology, characterized by increased pain sensitivity at gut level, in the absence of any detectable organic cause (“visceral hyperalgesia”). Chronic / recurrent abdominal pain or discomfort in IBS is associated with altered bowel habits (constipation, diarrhea, or alternating episodes of both). Therapies include psychotherapy/ behavioral therapy, bulking agents, antidiarrheals, antispasmodics, tricyclic antidepressants and also recently agents that affect serotonergic pathways (24). An example of **organic abdominal pain** is urinary colic from calculosis of the upper urinary tract. Pain derives from acute pelvis dilatation due to impact of the stone in the ureteral lumen, with resulting stretching of nerve endings in the mucosa and increased synthesis and release of prostaglandins, and from hypercontractility of the ureter above the obstacle. It is extremely intense, often accompanied by frequent urination, dysuria, oliguria, haematuria, acute nausea, hypotension and hyperalgesia in the area of referral (lumbar/flank region). Non-steroidal anti-inflammatory drugs (NSAIDs), often associated with spasmolytics, are a first-line treatment of renal colic, but narcotic analgesics are also frequently employed in many countries, especially the weak opioid tramadol (25).

PATHOPHYSIOLOGICAL MECHANISMS OF VISCERAL PAIN

Recently developed models have focused considerable attention on two sites of neural processing: primary afferents and the spinal dorsal horn. Knowledge of how visceral stimuli are transduced, encoded and processed will contribute greatly to understanding mechanisms underlying pathophysiological events that produce chronic visceral pain and hyperalgesia.

DUAL INNERVATION OF VISCERA AND DIVERGENT CENTRAL PROJECTIONS

All viscera are dually innervated by primary afferents that project in the same nerves as parasympathetic (vagus, pelvic) and sympathetic (splanchnic) efferents. Cell bodies are located in sensory ganglia (dorsal root, nodose) which project to separate regions of the spinal cord/brainstem (26). Afferents projecting in the splanchnic nerves innervate thoracic, abdominal and pelvic viscera, respond to stimulation of the mesentery and gut wall, and encode both innocuous and noxious stimuli. Vagal afferents innervate thoracic and abdominal viscera and project to the nucleus of the solitary tract. These afferents encode innocuous stimuli, sense luminal contents in the GI tract, and contribute to the illness response and sensations of nausea. Pelvic viscera (bladder, descending colon, reproductive organs) not innervated by the vagus nerve are innervated by afferents in the pelvic nerve which project to the sacral spinal cord and encode both innocuous and noxious stimuli. Functionally, this dual innervation contributes to differential processing of visceral stimuli by different regions of the neuraxis.

That some visceral afferents innervate more than one visceral organ could account for the comorbidity of visceral pain disorders (27). Bifurcating afferents may become active following inflammation of one or more related organs. Alternatively, convergence may occur in the dorsal horn with separate afferents from both organs converging on a single dorsal horn neuron. In either case, the result is poor localization and discrimination of the source of visceral pain.

PRIMARY AFFERENTS AND DORSAL HORN PROCESSING

Signal transduction at the primary afferent terminal is dependent on activation of receptors in the afferent fiber membrane. The contribution of ionotropic (contain intrinsic ion channels) and metabotropic (coupled to second messenger systems such as those initiated by G proteins) receptors to visceral nociceptive processing is discussed further below.

TRPV1 Receptors—TRPV1 receptors, which are activated by capsaicin and protons, are coexpressed with CGRP and SP in 60–80% of visceral afferents (28). TRPV1 activation increases GI wall protection by increasing the mucosal barrier via release of CGRP and activation of cyclooxygenase (COX) (29). In contrast, tissue injury or bacterial toxins can increase anandamide, a ligand for intestinal TRPV receptors. Activation of these receptors and subsequent neuropeptide release further increases inflammation of the ileum or bladder.

A related receptor-activated ion channel, TRPA1, is present on subsets of primary afferents with TRPV1 receptors and is source of mustard-oil related neurogenic inflammatory effects. Numerous other drugs have been demonstrated to have a role in clinical pain management that act by blocking other ion channels – particularly those associated with sodium or calcium ion passage (e.g. mexilitine, pregabalin). Anecdotal reports of efficacy have not been fully tested in clinical visceral pain studies, but some controlled trials are ongoing.

Purinergic (P2X) Receptors—ATP, which is released from all tissue types when there is tissue damage, binds ionotropic P2X receptors. Expression of nociceptive-specific P2X3 receptors is upregulated in colonic nerve fibers of individuals with IBS (30). Furthermore, activation of P2X3 receptors on bladder afferents increases bladder contraction, micturition and bladder afferent activity, resulting in pain. Results of studies in P2X3 knockout mice suggests that interfering with ATP/P2X receptor binding may alleviate problems with voiding frequency and urgency in IC patients.

P2X4 receptors, expressed by microglia in the spinal cord, also bind ATP following injury. This activates the microglia, releasing inflammatory cytokines that contribute to central

sensitization. Although much work has recently focused on the role of glial cells in chronic pain, their contribution to visceral pain mechanisms is still unclear.

5-HT Receptors—Serotonin, released from a variety of cells intrinsic to the GI tract as well as migrating inflammatory cells, activates 5-HT_3 and 5-HT_4 receptors. 5-HT_3 receptor antagonists decrease peristaltic activity which is useful for diarrhea predominant IBS, but constipation as a side effect diminishes therapeutic potential. 5-HT_4 agonists appear to reduce symptoms in constipation predominant IBS patients (31). However, vascular effects of serotonergic drugs have limited their clinical usefulness. There may be a role for other monoamine-related mechanisms as alpha-2 adrenoceptor agonists have had analgesic effects in both clinical practice and pre-clinical models.

NMDA Receptors—NMDA receptors are expressed in primary afferents and dorsal horn neurons. Most models of visceral pain show NMDA receptor activity at the afferent and/or spinal cord level (32). While NMDA receptors are involved in signaling acute innocuous and noxious visceral pain and inflammatory visceral pain in animals, they do not appear to signal innocuous stimuli in humans during esophageal stimulation. Other glutamate-activated receptors such as AMPA channels or the metabotropic glutamate receptor families clearly have a role in nociceptive systems, but specific roles in visceral pain systems are yet to be precisely defined.

Acid Sensing Ion Channels (ASICs)—ASICs respond to decreases in pH and possibly contribute to mechanosensation from viscera. Cardiac afferents that express ASIC3 evoke large depolarizing currents to tissue acidosis that accompanies cardiac ischemia, suggesting that these receptors mediate anginal pain (33). In the GI tract, ASIC1a has an inhibitory effect, ASIC2 has mixed effects and ASIC3 appears excitatory (34).

Prostaglandin Receptors—Prostaglandins, synthesized in response to tissue injury by COX, sensitize afferents to mechanical and thermal stimuli and contribute to spinal processing of pain (35). In the GI tract constituitive COX1 is involved in gastric mucosal protection, and inducible COX2 contributes to afferent sensitization. Thus while nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis and attenuate inflammation and pain, they also damage the gastric mucosa. Current generation COX2 selective inhibitors have limited therapeutic potential due to side effects. Cytokines and other neuroactive substances associated with inflammation (e.g. IL6, TNF-alpha) also have clear role when visceral inflammatory processes have been identified. Newly available anti-inflammatory agents are only now being utilized in clinical trials of visceral pain.

Corticotropin Releasing Factor (CRF) Receptors—CRF is involved in the stress response, activating the hypothalamic-pituitary-adrenal and sympathoadrenal axes. In animals, acute stress, colitis or central CRF administration increases colorectal distention-evoked nociceptive responses and colonic motility which can be reversed by CRF1 antagonists (36). In humans, peripheral CRF increases colonic motility and hypersensitivity to distention, effects that are exacerbated in patients with IBS. These same effects are decreased by a CRF antagonist. With regard to the bladder, CRF receptor agonists and antagonists alter cystometric parameters, and CRF-related neuropeptides are expressed in areas involved in micturition and the stress response (37). A related family of neuropeptides which activate the CRF2 receptor, the urocortins, may also have a role in visceral hypersensitivity-related processes.

NK-1 Receptors—SP is expressed in a greater percentage of visceral afferent fibers than somatic afferent fibers. Inflammation of viscera increases central and peripheral NK1

receptor expression, and visceral hyperalgesia is attenuated in NK1 receptor knockout mice. Receptor antagonists act peripherally and centrally to attenuate visceromotor responses and receptor internalization induced by colorectal distention (33). Other neuropeptides that have similar potential for a role in visceral pain sensation include CGRP, somatostatin and cholecystokinin.

Opioid Receptors—Opioids constitute a major class of analgesic to treat visceral pain. While kappa opioid agonists have a peripheral site of action, mu agonists act at peripheral, spinal and supraspinal sites to attenuate pain originating in viscera (38,39). Nociceptin-Orphanin receptor agonists have also been used in pre-clinical models, investigating visceral hypersensitivity associated with inflammation with promising potential for therapeutic effects.

ADDITIONAL CONSIDERATIONS

Additional issues must be taken into account when designing and interpreting studies of visceral pain mechanisms. First is the effect of sex and gender. A number of visceral pain syndromes are more prevalent in one sex; thus gonadal hormone status and quantitative and/or qualitative changes in underlying mechanisms should be considered. Second, humans are not equivalent to experimental animals. Hence, similar studies may yield disparate findings, and species differences produce problems translating animal data to human studies. Finally, not all human diseases have equivalent animal models. Caution must be taken so as not to over interpret animal data into the human condition.

MODULATION OF VISCERAL NOCICEPTIVE PATHWYS: THE FUTURE - CHALLENGES, OPPORTUNITIES AND CLINICAL IMPLICATIONS

The visceral pain syndromes have previously been neglected and underestimated. They have only reached clinical and scientific recognition in the last 15–20 years, due to the overwhelming evidence of recent epidemiological data highlighting the widespread existence of these pain syndromes. Patients with visceral pain, present a previously unrecognized and underserved population in need of adequate pain management. In the United States, patients suffering from some of these previously un-recognized pain syndromes (such as chronic prostatitis, interstitial cystitis and vulvodynia) have organized patient support groups, which have urged the US government and the National Institutes of Health to fund research studies aimed at a better understanding of the pathophysiology of these pain syndromes and to fund clinical research studies aimed at identifying specific treatment approaches for these visceral pain syndromes.

Treating patients with visceral pain remains a significant clinical challenge and current therapeutic interventions are often empirical. Pharmacological pain management is typically with drugs, that have shown efficacy for the treatment of chronic neuropathic pain states. Very few drugs have been specifically approved for the treatment of visceral pain syndromes. Examples are Elmiron (pentosan polysulfate sodium), which is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis and Zelnorm (tegaserod maleate), which was on the market for a brief period of time (subsequently withdrawn due to side effects) and was indicated for the short-term treatment of women with IBS.

Based on the epidemiological evidence and convincing basic science data, showing specific potential targets for visceral pain therapy, there is growing interest in the pharmaceutical industry to expand basic science and clinical research efforts for this underserved patient population. The European Agency for the Evaluation of Medicinal Products suggested to

include patients with chronic visceral pain in their recommendations “Guidance on clinical investigation of medicinal products for treatment of nociceptive pain” (Available at: http://www.emea.europa.eu/pdfs/human/ewp/061200en.pdf).

The task to include patients with visceral pain syndromes into clinical trials requires very thoughtful trial design. Difficulties in clinical trial design for this patient population are the clinical observations, that many of the visceral pain syndromes have periods of flares and remission. In other patients, symptoms become more severe and frequent over time. Thus it is difficult to establish a baseline for the symptoms over a longer observation period. It has been suggested by some investigators to circumvent this problem by evaluating the response to an evoked painful visceral stimulus, such as bladder distension, either in normal volunteers, or in subjects with visceral pain (40). Conceptually, however, it is not clear, if pharmacological studies evaluating the response to an evoked visceral stimulus can be used to predict the response to spontaneous visceral pain, since the neurophysiological mechanisms are likely to be different. A further challenge is the complexity of the visceral pain syndromes. Often patients suffer not only from visceral pain, but also from other symptoms: for example interstitial cystitis is characterized by urinary urgency, frequency and pain. Thus, determination of the global endpoint for such studies requires careful consideration.

There is a growing body of literature demonstrating that different visceral pain syndromes, as well as pain syndromes in other body regions, often occur together in the same patient. Thus, efforts to understand the pathophysiology and to design therapeutic modalities have recently shifted from an organ-based approach to a more global approach (12). It is important to keep track of these comorbidities for clinical trial design, since the pathophysiological mechanisms in subjects with different comorbidities might be different.

Many visceral pain syndromes occur preferentially in women in their reproductive ages (41). There is a desperate need to provide adequate pain management for this patient population, and on the other hand this age group provides specific challenges to clinical trial design.

Recent clinical research studies that have tried to refine or test existing therapies in visceral pain populations (for example: 42, 43). The trial design of these studies, including the challenges and pitfalls, can serve as basis for future studies using currently available drugs and pharmacological agents in development. Several of these studies have obtained frustrating results, and it appears that many therapies are effective in only a subset of patients. Thus, a key issue will be to identify subgroups of patients based on aspects such as the clinical symptoms, quantitative sensory testing parameters, biomarkers and comorbid conditions, who respond to particular therapeutic approaches. A similar approach has been used successfully for drug development for other pain conditions (for example: cluster headache and migraine headache subjects would obviously not be combined in a clinical trial to test a new drug).

Modulation of visceral nociceptive pathways can occur at peripheral, spinal and supra-spinal sites and a wide variety of potential drug targets exists as reviewed above. Compounds, which hit several targets, might be the best option for a successful approach in the short term. However, there is emerging evidence that a more refined approach may be achievable(44). These are very exciting times for the area of visceral pain (45), since visceral nociceptive pathways are being identified and compounds are being discovered that are likely to modulate these visceral nociceptive pathways. While there are challenges to clinical trial design for this patient population, as outlined above, knowledge of these challenges should result in well planned, successful studies in the near future.

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