Review

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Proposed New Pathophysiology of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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The most common type of prostatitis is category III, also known as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The current National Institutes of Health definition of CP/CPPS includes genitourinary pain with or without voiding symptoms in the absence of uropathogenic bacteria, as detected by standard microbiological methods, or other identifiable causes such as malignancy. Many different etiologies and mechanisms of pathogenesis of CP/CPPS have been proposed with a suggested role for immunological, neurological, endocrine, and psychological factors. We examined the data supporting the role of each of these areas and also examined the possible interrelationship of these factors in producing the symptoms of CP/CPPS. Prostatitis types IIIa and IIIb are classified according to the presence of pain without concurrent presence of bacteria; however, it is becoming more evident that, although levels of bacteria are not directly associated with levels of pain, the presence of bacteria might act as the initiating factor that drives primary activation of mast-cell-mediated inflammation in the prostate. The gate control theory provides a neurologic basis for the influence of both somatic and psychological factors on pain. Acceptance of chronic pain as a diagnosis may be difficult for the clinician and patient, however it is an important concept in the care of CP/CPPS, which enables the use of pain-directed therapies. Management of CP/CPPS will remain challenging; however, this review provides a better understanding of the condition and improved management strategies based on the newest evidence and concepts available.

Keywords: Prostatitis; Chronic pain; Physiopathology

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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a condition of chronic pelvic pain in men [1]. It has been estimated that between 2% and 14% of men worldwide may have symptoms of CP/CPPS [2,3]. The diagnosis is made on the basis of symptoms of pain with or without voiding symptoms in the absence of other identifiable causes [4]. The etiology of symptoms in a given patient can be from many causes. Whether there are identifiable, repeatable patterns of causes of symptoms, or just individual patients with distinct individual phenotypes are unknown. Because CP/CPPS is a common condition associated with significant physical, mental, and social burden, the medical community has made tremendous efforts to understand the condition and improve management strategies. Despite these efforts, answers remain elusive. Robust tools to measure symptom severity

and disease impact have been developed, but we do not yet know the cause of CP/CPPS, and no reliable treatments have been identified. However, in the last several decades, we have identified some of the factors that play a role in men with CP/CPPS.

Our improved understanding of the etiology and clinical phenotypes associated with CP/CPPS has made the condition less of a clinical enigma. Acceptance of clinical definitions (and classification system) and validated, reliable outcome questionnaire (the CP symptom index) has led to high-quality treatment evidenced from randomized placebo-controlled trials. This article is a very timely review of the topic and provides the clinician with an improved understanding of CP/CPPS and allows better therapy.

THEORIES IN THE PATHOPHYSIOLOGY

1. Infection

The symptoms of CP/CPPS are similar to those of a true prostatic infection. Therefore, infection has been commonly assumed by patients and clinicians alike to be the cause of the symptoms, both historically and to this day. In the Chronic Prostatitis Collaborative Research Network (CPCRN) study, using the 4-glass urine test for localization, men with CP/CPPS and asymptomatic controls showed almost identical numbers of bacteria isolated from urine, prostatic fluid, and post-prostate massage urine [5]. Eight percent of men had uropathogenic bacteria and roughly 70% had some form of bacteria in each group. This indicates that asymptomatic men appear to routinely have bacteria in the prostate, but may not by themselves produce disease or symptoms. Search for other infectious agents such as virus [6] or for other bacteria identifiable by polymerase chain reaction (PCR) [7] in prostate tissue has not proven an infectious cause; there was however an association with improvement on antibiotics in men with bacteria detected by PCR, as compared to those with no detectable bacteria [8].

Helicobacter pylori antibody seropositivity has been associated with numerous disorders, such as coronary heart disease, rosacea, and chronic bronchitis [9-11]. Karatas et al. [12] recently published data from a pilot study that found greater *H. pylori* antibody seroprevalence in CP/CPPS men, as compared to control patients (76% vs. 62%; $p<0.05$). The authors did not correlate their findings with symptom severity or other clinical characteristics. This pilot study supports the hypothesis that *H. pylori* may play a role in CP/CPPS. The infection may be related to the immune response and increased cytokines in seminal plasma and/or expressed prostatic secretion. Further studies are needed to confirm whether a true association between *H. pylori* and CP/CPPS exists.

Nanobacteria have also been suggested as a possible infectious source in CPPS, as they commonly occur in prostatic stones, and anti-nanobacterial therapy has proven effective in small uncontrolled studies [13-16].

In a study of 30,000 male health professionals, men who reported a history of sexually transmitted disease were found to have 1.8-fold higher odds of prostatitis [2]. However, studies that have looked for the presence of sexually transmitted organisms such as *Chlamydia trachomatis, Trichomonas vaginalis, Ureaplasma urealyticum,* or *Mycoplasma hominis* have failed to show persistent infection [17]. Although the presence of an active infection was not evident in men participating in the National Institutes of Health (NIH) cohort study, patients with CP/CPPS were found to have a significantly greater history of urethritis, as compared to age-matched controls [18]. In susceptible men, urethritis could serve as a source of inflammation that could cause chronic pelvic pain well after the resolution of infection.

A more robust infectious candidate is CP1, a newly identified *Escherichia coli* strain isolated from the prostatic secretions of a culture-negative CP/CPPS patient. Rudick et al. [19] showed that CP1 colonized the urogenital tract and elicited pain responses specific to the pelvis in mouse model. Furthermore, resolution of CP1 colonization was associated with continued pain behavior, mimicking a postinfectious chronic-pain response. Interestingly, the pelvic pain response was observed in only 1 of the 2 mouse subspecies tested, and was male specific. The investigators hypothesized that development of CP/CPPS symptoms depends on pathogen and host-specific factors.

2. Inflammation

The term "prostatitis" implies inflammation of the prostate gland. However, it is clear that not all men with CPPS have inflammation related to the prostate. Only about one-third of men with clinical CPPS have been found to have prostatic inflammation on biopsy [20]. In those with inflammation, the degree of that inflammation did not

correlate with symptoms [21,22].

Considerable effort has been made to examine cytokines. Increased levels of interleukin (IL)-1β, IL-8, tumor necrosis factor (TNF)-α, and epithelial cell-derived neutrophil-activating peptide-78 (ENA-78) have been found in expressed prostatic secretions (EPS) of patients with category IIIa prostatitis, but not in those with category IIIb prostatitis [23,24]. Levels of the chemokines, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1-α were significantly elevated in patients with CP/CPPS, as compared to those without urological disease or benign prostatic hyperplasia (BPH), regardless of white blood cell levels in EPS samples [25].

Several chemokines have been identified in the EPS of patients with CP/CPPS, including the MCP-1, which has been found to be overexpressed and nonfunctional in patients with CP/CPPS [26]. Normal MCP-1 (as found in the EPS of asymptomatic control patients) induces monocyte chemotaxis and acts to perpetuate inflammatory response. In contrast, the MCP-1 found in patients with CP/CPPS is nonfunctional and somehow inhibits normal inflammatory response. At first glance, this is somewhat counterintuitive, but the investigators hypothesized that the MCP-1-regulated inflammatory response may be reparative or regenerative in nature (i.e., "healthy" inflammation), and that CP/CPPS symptoms may be a result of decreased or absent "healthy" inflammation. Recently, Desireddi et al. [25] confirmed that controls and BPH patients with or without inflammation had the lowest levels of MCP-1. CPPS IIIa and IIIb patients had MCP-1 values statistically greater than control and BPH patients. IIIa patients also had higher MCP-1 values than IIIb patients. IIIa patients also had higher MCP-1 values than IIIb patients, although the difference was not statistically significant after the Bonferroni adjustment for multiple comparison.

3. Nervous System

Since pain is mediated by the nervous system, it is reasonable to consider abnormalities of the nervous system as a cause of symptoms in patients with CP/CPPS. Men with CP/CPPS were 5 times more likely to self-report a history of nervous system disease, as compared to asymptomatic age-matched controls in the CPCRN Study [18].

The pain of CP may also be a result of neurogenic inflammation in the peripheral and central nervous systems. Nerve growth factor (NGF) was one of the markers that correlated with pain in men with CP/CPPS [27]. NGF is a neurotrophin that has been found to have a role in the regulation of nociceptive nerves, and as a mediator and amplifier of neurogenic inflammation. Researchers in Japan recently analyzed NGF levels expressed in the prostatic fluid of 20 patients with CP/CPPS before and after single, varied, 8-week treatment trials. These were compared to the NGF levels found in 4 asymptomatic control patients [28]. Before initiating treatment, men with CP/CPPS were found to have elevated NGF as measured by enzyme-linked immunosorbent assay; however, the difference between patients and control patients was not significant. After the various 8-week treatment trials (cernitin pollen extract, naftopidil, or magnetic therapy), 13 of the 20 patients with CP/CPPS reported greater than 25% pain improvement, which correlated with a mean statistically significant decrease in prostatic NGF. For the 7 patients who reported less than 25% improvement in pain, mean NGF levels were found to have increased. These results were interesting, but clearly, more comprehensive studies are needed to verify the possible association.

Beyond local causes of pelvic pain, the theory of central nervous system sensitization has been gaining supportive data. Increased concentrations of NGF in a peripheral target can sensitize central neurons to afferent barrages from that target and through enhanced neurotransmission mediated by the N-methyl-D-aspartic acid receptor it can produce long lasting depolarizations [29]. Given the role of NGF in neurogenic inflammation and nociception, and its correlation with pain in CPPS, it is likely that neurogenic inflammation is involved in the pathogenesis of CP/CPPS symptoms. A recent central pain study compared pressure pain thresholds of 55 men with CP/CPPS and 46 asymptomatic control patients over 10 genitopelvic sites and 1 control site (deltoid) [30]. At all sites, clinically and statistically significant differences in pain tolerance were observed between the 2 groups. That is, men with CP/CPPS were universally more sensitive to pressure and could be correctly identified by their thresholds with a sensitivity of 0.82 and a specificity of 0.74. This implied that a difference in systemic pressure sensitivity might exist between men with CP/CPPS and normal, asymptomatic men.

Gabapentin and pregabalin are anticonvulsant drugs that have been used anecdotally in patients with CP/CPPS. They

are commonly used to treat various other neuropathic pain syndromes, including diabetic neuropathy, postherpetic neuralgia, and fibromyalgia. Gabapentin was initially developed as a γ-aminobutyric acid analog but was not found to activate any of the γ-aminobutyric acid receptors. It is an antiepileptic and analgesic drug that has gained particular attention for its efficacy in treating diabetes-related neuropathic pain [31]. It is thought to act through antagonism of the α2-δ subunit of voltage-sensitive calcium channels [32]. Pregabalin also acts on the α2-δ subunit of calcium channels, but with greater binding affinity and potency [33]. Pregabalin has analgesic, antiepileptic, anxiolytic, and sleep modulating activity [34]. The primary known site of analgesic action for both drugs is the dorsal horn of the spinal cord, where they bind to the α2-δ receptor and block the release of glutamate and peptide neurotransmitters, such as substance P and calcitonin-related gene product, thereby decreasing pain signal transmission [35].

4. Psychosocial Factors

In the CPCRN study, men with CP/CPPS self reported a history of anxiety or depression twice as often as age-matched controls with no pain [18]. The factors that contributed most to the reduced quality of life were pain intensity and quality of life subscale of the NIH-chronic prostatitis symptom index [36]. The general state of anxiety was higher in patients compared to their spouses and remained unchanged two years later [37]. In a Chinese sample, more than 60% of patients were diagnosed with an anxiety disorder using the Hospital Anxiety and Depression Scale (HADS) (control group, 15%) [38]. Elevated anxiety scores in CP/CPPS patients compared to healthy controls were also shown in another study which used the HADS [39] as well as in two studies [40,41] which used the Beck Anxiety Inventory [42]. A case-control-study reported a higher prevalence of anymental health diagnosis and a higher amount of prescribed medication for anxiety in CP/CPPS patients than in healthy controls [43]. Similarly, an additional study with a large sample investigated the existence of any anxiety disorder three years before CP/CPPS was diagnosed [44]. Anxiety disorders were 2.1 times more prevalent in patients than in controls.

Further detailed investigation of psychological variables in this cohort showed that helplessness/catastrophizing predicted overall pain along with urinary symptoms and depression [45]. Another important modifier of the pain experience in men with CP/CPPS is spousal support. Lower perceptions of spousal support also contributed to lower mental component scores on the SF-12 in the CPCRN study [46]. Pain and disability were greater at higher levels of solicitous responses by spouses; the less the spouse tried to distract the patient from the pain, such as by trying to get them involved in other activities, the greater the pain and disability connection [46]. Spousal response also changed the physiology of the patients. In category III prostatitis patients, the degree of spousal concern and support as well as effort to distract patients from their symptoms correlated with lower seminal plasma IL-6 and IL-10 concentrations [27]. Early adverse experiences may contribute to later symptoms of chronic pain. In the Boston Area Community Health Survey, men who reported having experienced sexual, physical, or emotional abuse were more likely (odds ratio, 1.7-3.3) to report symptoms of CP/CPPS in the survey [47]. Stress has physiological consequences, as in addition to many other stimuli such as cytokines, bacterial toxins, and hypoxia, mast cells release their contents in response to stress [48].

5. Endocrine Abnormalities

Endocrine factors also affect both immune and nervous system functions. Testosterone can have a negative effect on NGF. All rat pelvic noradrenergic neurons express the NGF receptors trkA and p75 [49]. NGF induces neurite growth in these neurons. In vitro testosterone impeded the NGF induced growth of long neurites from pelvic ganglion cells cultured from adult male rats [50]. One of the common findings in chronic pain conditions is alterations in the hypothalamic-pituitary-adrenal axis [51,52]. Similar findings have been reported in CP/CPPS. On awakening, serum cortisol levels rise; there is a significantly greater cortisol rise in men with CPPS, as compared to controls [41]. Men with CPPS also have a lower baseline adrenocorticotropic hormone (ACTH) level and blunted ACTH rise in response to stress than men without symptoms [41]. One report has indicated reduced activity of CYP21A2 (P450c21), the enzyme that converts progesterone to corticosterone and 17-hydroxyprogesterone to 11-deoxycortisol [53].

6. Genetic Predisposition to CP/CPPS

The idea of genetic differences that may predispose CP/CPPS patients to develop the condition has been explored in several targets. Differences in the DNA sequence, or polymorphisms, have been identified in the promoter regions of several cytokines. Polymorphisms in the genes or promoters for IL-10 AA and TNF-α are associated with low IL-10 or TNF-α production [54,55]. Shoskes et al. [56] studied cytokine polymorphisms in 36 men with the CPPS and found a higher than expected proportion of the allele associated with low IL-10 expression, which suggests a proinflammatory state. Category IIIa patients were more likely to express the low TNF-α genotype. Patients who did not improve with anti-inflammatory quercetin therapy had a noninflammatory genotype (low TNF-α and high IL-10). These results collectively added further evidence

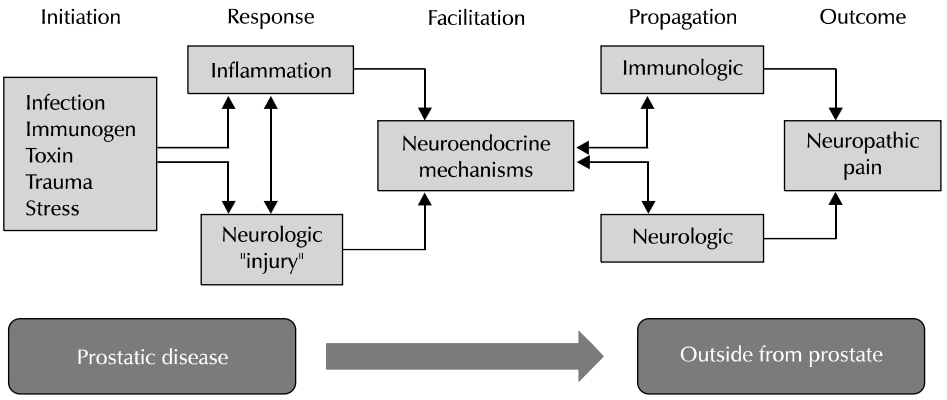

Fig. 1. Hypothetical scenario that could potentially involve most of the proposed and interrelated causes in chronic prostatitis/chronic pelvic pain syndrome.

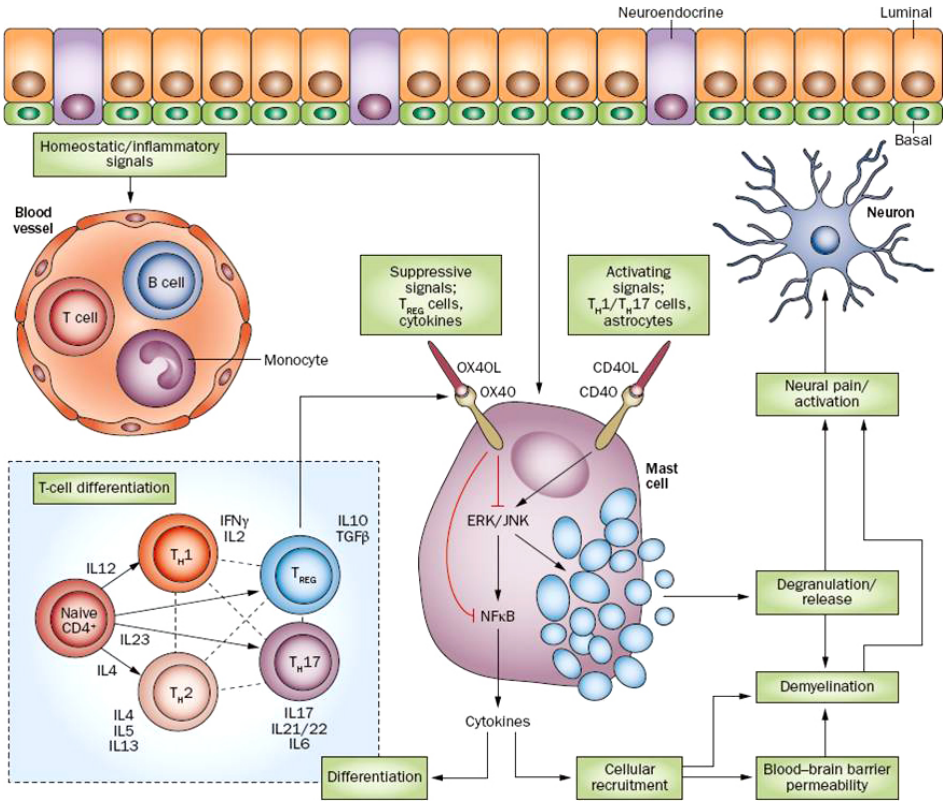

Fig. 2. Hypothetical model of chronic pelvic pain syndrome. Intercellular homeostatic signaling demonstrating differentiation of CD4 T-cells in a context-dependent manner, regulation of mast cell activation by direct interaction (for example, through OX40 receptor), and activation of mast cells and subsequent deactivation, as well as how these signaling cascades interact to stimulate neurons. Reproduced from the article of Murphy et al. Nat Rev Urol 2014;11:259-69 [62] with permission. T_{reg}: regulatory T, ERK: extracellular signal-regulated kinases, JNK: c-Jun N-terminal kinase, NFκB: nuclear factor kappa B, IFNγ: interferon gamma, IL: interleukin, TGFβ: transforming growth factor beta.

that some patients with CP have a predisposition for autoimmune/inflammatory disorders and this subset may best be targeted with anti-inflammatory therapies. Differences have been reported in the frequency of 3 alleles near the phosphoglycerate kinase (PGK) gene, between CPPS patients and controls [57]. The alleles differed in the number of short tandem repeats (STRs). The *PGK1* gene in the region assessed was reported to be associated with familial prostate cancer, hypospadias, and androgen insensitivity. Investigation of single nucleotide polymorphisms in the gene for manganese superoxide dismutase has reported significant differences between men with CP/CPPS and controls but not between category IIIa and IIIb CP/CPPS [58]. The enzyme levels of manganese superoxide dismutase and glutathione peroxidase were higher in control subjects than prostatitis patients, indicating lower antioxidant status in men with CP/CPPS. Also genome wide association study (GWAS) proved to be an essential component of detecting high risk alleles and using that information to understand the fundamental biology of disease [59,60]. Application of GWAS to urologic CPPSs makes logical sense given the lack of a defined mechanism or even objective diagnostic confirmation of disease.

7. Proposed Mechanisms in Development of Pain in CP/CPPS

It is very likely that the etiology and pathogenesis of CP/CPPS involves a pluricausal, multifactorial mechanism.

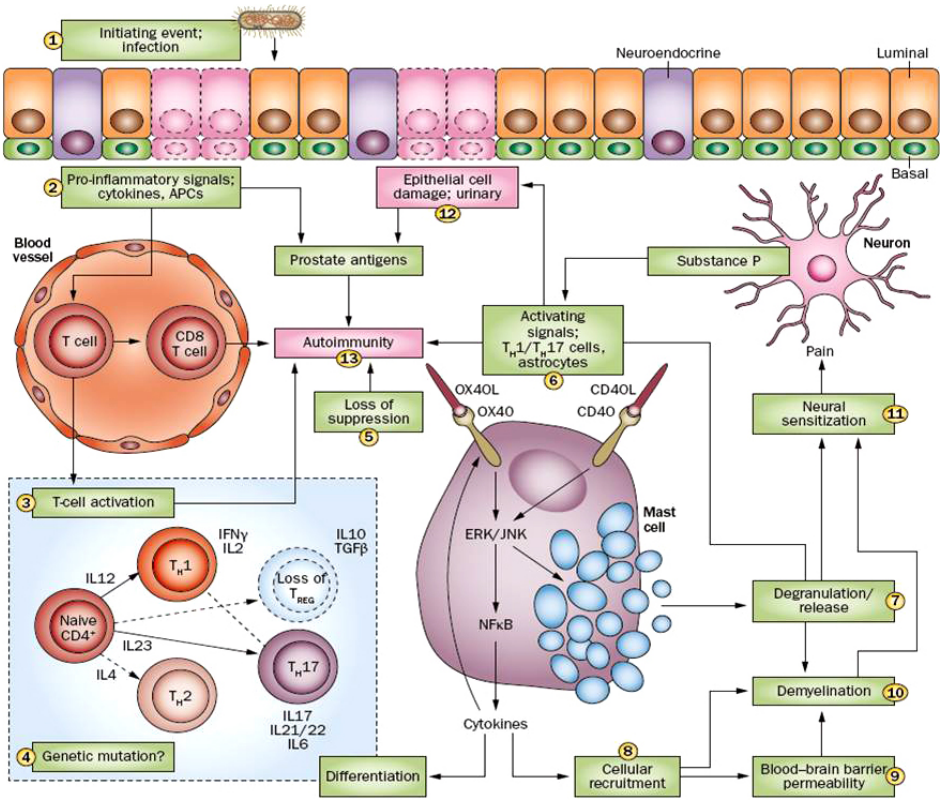

Fig. 3. Hypothetical schematic representation of a modulated immune system in chronic prostatitis/chronic pelvic pain syndrome. An initiating event, such as bacterial infection, drives prostatic epithelial cell damage (1) and promotes the secretion and activation of proinflammatory cytokines, chemokines and presentation of antigens via antigen-presenting cells (APCs) (2). These signaling cascades result in CD4 T-cell activation, which is initially of Th1-type (interferon gamma, IFNγ) but Th17 activation is also implicated in the pathway, possibly at later stages of chronic pain development (3), followed by a loss of interleukin (IL)10-secreting suppressive regulatory T (T_{reg}) cells and a skewing towards Th1/17 responses (4). The loss of suppression of mast cells as a result of unchecked T-cell activation then results in a positive feedback loop in the mast cell (5, 6), resulting in degranulation and release of proteases such as tryptase, chymase, and allergy mediators such as histamine (7), and secretion of cytokines (such as IL6, IL17, tumor necrosis factor-α, and IL6), resulting in the recruitment of inflammatory cells (8) and potentially disrupting the blood–brain barrier (9) and demyelinating neurons (10). Taken together, these processes result in neuronal activation and sensitization (11). The mast cell mediates these events and positive feedback loops enhance these processes. Further epithelial cell damage is one consequence of such increased mast cell activity (12). Prostate antigens generated from damage to the epithelium in the presence of an activated CD4 T-cell response, with unchecked mast cell degranulation and increased numbers of CD8 T-cells can result in the development of autoimmunity, which further exacerbates these mechanisms (13). Reproduced from the article of Murphy et al. Nat Rev Urol 2014;11:259-69 [62] with permission. TGFβ: transforming growth factor beta, ERK: extracellular signal-regulated kinases, JNK: c-Jun N-terminal kinase, NFκB: nuclear factor kappa B.

An initiating stimulus such as infection, reflux of some "toxic" or "immunogenic" urine substance, perineal/pelvic "trauma", and/or psychological stress starts a cascade of events in an anatomically or genetically susceptible man, resulting in a local response of either inflammation or neurogenic injury (or both). Further immunologic or neuropathic (possibly interrelated) mechanisms mediated by neuroendocrine pathways propagate or sustain the chronicity of the initial (or ongoing) event. The final outcome is the clinical manifestation of chronic perineal/pelvic pain-associated symptoms associated with local and central neuropathic mechanisms (Fig. 1) [61].

Many factors, such as infectious agents, hormonal changes, physical trauma, urine reflux, and dietary habits initiate the process of CP/CPPS in susceptible males. Mechanism in the development of neuropathic pain was interpreted in Fig. 2 [62]. Numerous lines of evidence and ongoing investigations underline the role of the adaptive immune response and activation of autoimmunity in the development of CP/CPPS (Fig. 3) [62]. Melzack and Wall's gate control theory, although not entirely correct, presents a more accurate model to describe pain. This theory proposes that neural mechanisms in the dorsal horn of the spinal cord act like a gate that can increase or decrease the flow of nerve impulses from peripheral fibers to the spinal cord cells that project to the brain. The neurophysiologic events that gate or modulate the pain impulse may be influenced by numerous peripheral and central factors. The gates may be affected by: (a) the level of firing of the visceral afferent nerves, (b) afferent input from cutaneous and deep somatic structures, (c) endogenous opioid and nonopioid analgesic system, and (d) various central excitatory and inhibitory influences from the brainstem, hypothalamus, and cortex (Fig. 4) [63]. This theory provides a neurologic basis for the influence of both somatic and psychological factors on pain; that is, the perception of pain may increase or decrease with anxiety, depression, physical activity, mental concentration, marital discord, and so on. Although chronic pain may be difficult for the clinician and his patient to accept as a diagnosis, it is an important concept in the care of CP/CPPS. In allows the use of pain-directed therapies that albeit not curative, permit the patient to progress toward a more normal life that is not dominated by pain.

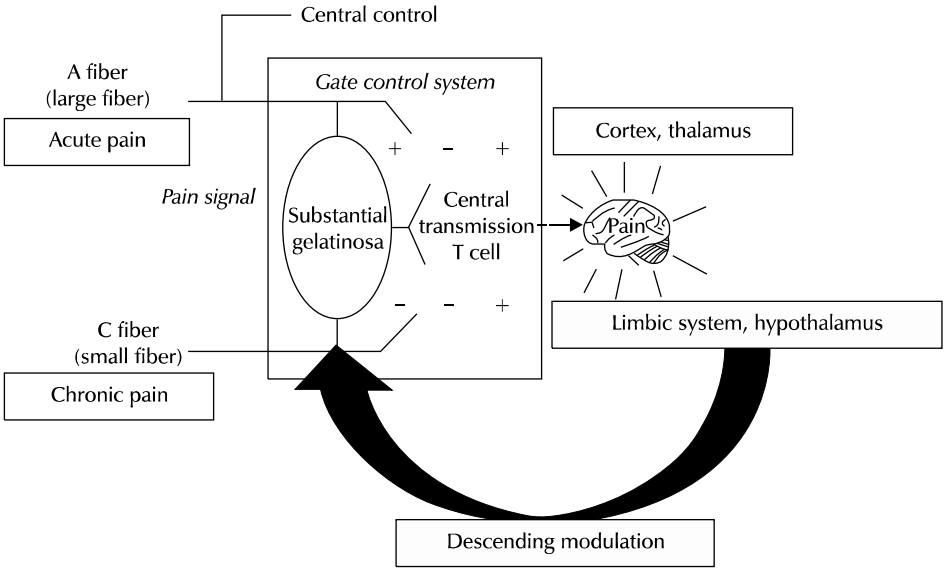

Fig. 4. The gate control theory of pain. This theory is based on the following propositions. (1) The transmission of nerve impulses from afferent fibers to spinal cord transmission (T) cells is modulated by a spinal mechanism. Gating mechanism in the dorsal horn. (2) The spinal gating mechanism is influenced by the relative amount of activity in large-diameter (L) and small-diameter (S) fibers: activity in large fibers tends to inhibit transmission (close the gate) while small-fiber activity tends to facilitate transmission (open the gate). (3) The spinal gating mechanism is influenced by nerve impulses that descend from the brain. (4) A specialized system of large-diameter, rapidly conducting fibers (the central control trigger) activates selective cognitive processes that then influence, by way of descending fibers, the modulating properties of the spinal gating mechanism. (5) When the output of the spinal cord transmission (T) cells exceeds a critical level, it activates the action system-those neural areas that underlie the complex, sequential patterns of behavior and experience characteristic of pain.

CONCLUSIONS

Gram-negative Enterobacteriaceae and enterococci are responsible for most cases of bacterial prostatitis. Nonbacterial prostatitis syndromes are caused by an interrelated cascade of inflammatory, immunologic, neuroendocrine, and neuropathic mechanisms that begins with an initiator in a genetically or anatomically susceptible patient. Urologists are responsible for treating a chronic pain condition that occurs in their area of interest. In genitourinary area, we must become on some level a pain doctor. Finally, it offers hope that with future research the psychoneurologic dysfunctions responsible for chronic pain may be identified and lead to definitive, curative treatments.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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