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Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions

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Abstract

The intensity of acute and chronic pain depends on interactions between peripheral impulse input and CNS pain mechanisms, including facilitation and inhibition. Whereas tonic pain inhibition is a characteristic of most pain-free individuals, pain facilitation can be detected in many chronic pain patients. The capability to inhibit pain is normally distributed along a wide continuum in the general population and can be used to predict chronic pain. Accumulating evidence suggests that endogenous pain inhibition depends on activation of the prefrontal cortex, periaqueductal gray and rostral ventral medulla. Quantitative sensory test paradigms have been designed to acquire detailed information regarding each individual's endogenous pain inhibition and facilitation. Such tests include: temporal summation of pain, which is mostly used to assess facilitatory pain modulation by measuring the change in pain perception during a series of identical nociceptive stimuli; and conditioned pain modulation, which tests pain inhibition by utilizing two simultaneously applied painful stimuli (the 'pain inhibits pain' paradigm). Considerable indirect evidence seems to indicate that not only increased pain facilitation but also ineffective pain inhibition represents a predisposition for chronic pain. This view is supported by the fact that many chronic pain syndromes (e.g., fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, headache and chronic fatigue syndrome) are associated with hypersensitivity to painful stimuli and reduced endogenous pain inhibition. However, future prospective studies will be necessary to provide definitive evidence for this relationship. Such research would not only provide important information about mechanisms relevant to chronic pain but would also permit identification of individuals at high risk for future chronic pain.

Keywords

central sensitization; chronic pain; facilitation; fibromyalgia; inhibition; osteoarthritis; pain modulation

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Nociceptive signals that are transmitted from the periphery to the brain require integration and processing within the spinal cord, brainstem and brain. Increased pain sensitivity, a characteristic of chronic pain, may develop either through peripheral mechanisms (peripheral sensitization) or as a consequence of neuroplastic changes in the CNS (central sensitization) [1]. Central sensitization involves: upregulation of sensory neuron-specific sodium channels; NMDA and vanilloid receptors; phenotype switching of large myelinated axons; sprouting within the dorsal horn; and loss of inhibitory interneurons [2]. Although a number of treatment options are available, therapy for chronic pain is less effective than for acute pain, commonly providing significant pain relief for less than 50% of patients [3].

Epidemiologic surveys have estimated the prevalence of chronic pain to be approximately 31% in the general population [4], with low rates of recovery over long-term follow-up

periods [5,6]. The total cost of chronic pain is exceeds US$200 billion annually in the USA [7,8]. Primary care providers, as well as pain specialists, face increasing numbers of patients with chronic pain syndromes, including headache, temporomandibular joint pain (TMD), back pain, osteoarthritis (OA), fibromyalgia (FM), chronic fatigue syndrome and irritable bowel syndrome (IBS). Owing to the negative impact of chronic pain on patients' quality of life and function, as well as increased mortality rates [9–11], optimal treatment of individuals with current chronic pain and identification of persons at high risk for future chronic pain have become increasingly important [12].

Although many chronic pain syndromes are currently defined on the basis of anatomic location, they seem to share numerous common features that could be used for grouping these conditions on the basis of mechanisms rather than anatomy. Such mechanistic classifications include nociceptive pain (pain evoked by a noxious stimulus), pain hypersensitivity syndromes, neuropathic pain and spontaneous pain [13,14]. Pain hypersensitivity syndromes depend on activation of sensitized nociceptors in the periphery by low-intensity mechanical–thermal stimuli (often combined with central sensitization). Neuropathic pain results from ectopic discharge in nociceptors after peripheral nerve injury, and central pain is related to spontaneous activity in neurons of the dorsal horn, thalamus or cortex. Although many chronic nonmalignant pain syndromes such as FM, TMD, OA, chronic headache, idiopathic low back pain, IBS and endometriosis are classified as pain hypersensitivity syndromes, their pathogenesis is only partially understood and physical findings in patients with these disorders are poor predictors for self-reported pain severity and dysfunction. In general, the extent of tissue abnormalities appears to be poorly correlated with the pain intensity reported by chronic pain patients [15,16]. For example, minor radiographic abnormalities of the spine or presence of endometrial tissue in the pelvic cavity may be painless in some individuals but may be associated with severe chronic pain in others [17,18]. Such findings indicate substantial individual differences in pain sensitivity, pain processing and endogenous pain modulation [19].

Over the last few years, the poor correlation of patients' peripheral tissue abnormalities with chronic pain intensity has shifted the research focus away from peripheral to central pain processing abnormalities [20]. Widespread hyperalgesia and dysfunctional endogenous pain inhibition have been identified as characteristics of many musculoskeletal [21,22] and neuropathic pain conditions [23–25]. These similarities suggest common CNS abnormalities in pain processing among many chronic pain conditions [20,26,27].

Endogenous pain modulation

Pain is a complex sensory, affective, sociocultural phenomenon under the control of CNS facilitatory and inhibitory modulation. Although the intensity of nociceptive input is relevant for pain, subsequent modulation of peripheral impulses in the peripheral and CNS can dramatically reduce the intensity of resultant sensations to almost imperceptible levels or increase pain to nearly unbearable levels. The pain modulatory system includes a CNS network linking multiple brain areas (prefrontal cortex, cingulate cortex and insula) [28], the periaqueductal gray (PAG) and the rostral ventromedial medulla with the spinal cord [29]. The resultant descending modulation of dorsal horn neurons of the spinal cord is thought to provide a protective function [30], because early inhibition can enhance escape behaviors while late facilitation may create conditions that are optimal for healing of tissue injuries [31]. Inhibitory modulation of noxious peripheral signals occurs at both spinal and supraspinal levels and is strongly influenced by psychological features [32]. The capability of human subjects for endogenous pain modulation can be assessed using quantitative sensory tests (QST) sensitive to pain facilitation or pain inhibition. Some of the most frequently used psychophysical tests of endogenous pain inhibition include: conditioned

pain modulation (CPM); offset analgesia (Offset); and habituation. On the other hand, pain facilitation can be assessed by testing temporal summation of second pain (TSSP). Whereas TSSP uses repetitive nociceptive (electrical, mechanical or thermal) pulses at frequencies of ≥0.33 Hz to assess pain facilitation, CPM utilizes two concurrent stimuli (conditioning and test stimulus) to measure the resultant experimental pain inhibition (i.e., counter-irritation) [33–37]. Thus, combinations of these QST measures are commonly used for characterizing CNS pain modulation in pain patients and healthy pain-free individuals.

Pain facilitation

Molecular mechanisms in the dorsal horn of the spinal cord that contribute to augmented pain transmission (facilitation) are well known [38]. Low-level stimulation of nociceptors triggers release of glutamate from the central terminals of primary afferent neurons terminating in laminae I, II and V of the dorsal horn. During intense or sustained nociceptive stimulation, substance P and glutamate are co-released from afferent neurons, enabling TSSP through activation of NMDA receptors. As a result, intracellular calcium levels increase, which activate signaling cascades that lower the firing threshold of dorsal horn neurons. Supporting evidence for this mechanism comes from pharmacological experiments that blocked NMDA channels with dextromethorphan or ketamine, which have been shown to reliably decrease TSSP in laboratory animals and human subjects [39,40]. Although NMDA receptor antagonists have provided some clinical benefits for patients with chronic pain disorders [41], they are generally not well tolerated because of unacceptable side effects including memory problems, dizziness and sedation [42].

Pain inhibition

It has been known for over 100 years that descending inhibition of nociceptive activity in the spinal cord relies on involvement of the prefrontal cortex, midbrain and brainstem [43,44]. Animal and human studies not only emphasize the important role of the ventrolateral PAG for integration of input from the spinal cord, brainstem and cerebral cortex [45,46], but also for pain inhibition [47,48]. Pain modulatory signals from the PAG can reach dorsal horn neurons of the spinal cord either directly or indirectly via the rostroventral medulla [49,50]. Compelling evidence suggests that spinal input to the PAG can elicit pain inhibition through a spinal–supraspinal–spinal loop [51] whose functionality can be assessed by various QST methods including CPM, Offset and pain habituation. This review of endogenous pain inhibition, however, will mostly focus on CPM because of its widespread use in pain research. For more information about other QST of pain inhibition, including Offset and habituation, see [52–54].

CPM testing generally involves the use of two concurrent stimuli (conditioning and test stimulus) to estimate the resultant pain inhibition of the test stimulus. Although not required, some of the most frequently used test sites include the upper and lower extremities. Importantly, CPM effects are only observed in individuals with intact spinal cords [55] because CPM activates spinal–supraspinal–spinal pathways, with ascending information projecting from the spinal cord toward supraspinal centers and descending projections from the brain via the dorsal columns of the spinal cord, to neurons in the dorsal horns [55,56]. Within the spinal–supraspinal–spinal loop, not only the PAG but also the subnucleus reticularis dorsalis (SRD) of the medulla appears to be critically important for CPM [57,58]. The SRD not only plays an important part in the processing of ascending nociceptive information from peripheral tissues, but also signals back to dorsal horn neurons of the spinal cord [59]. Furthermore, the SRD appears to receive information from several cortical structures including the prefrontal cortex and anterior cingulate cortex, which might explain the influence of psychological factors on CPM [60–62].

Individual differences

Pain is actively modulated by the nervous system at multiple levels of the neuroaxis (see above), and individual variation in pain modulation almost certainly contributes to the well-known variability of clinical and experimental pain [19,34,63]. Individual differences in responses to experimental pain stimuli are normally distributed in the general population and do not seem to significantly change over time [64,65]. Moreover, neuroimaging studies suggest that variability of experimental pain ratings is closely correlated with CNS activity in brain regions associated with pain processing and modulation [66].

Individual differences in pain ratings seem to depend on genetic and environmental factors. Animal work in inbred mice provided evidence for a substantial genetic contribution not only to acute but also to chronic pain and pain inhibition [67–69]. Human genetic studies suggest that single nucleotide polymorphisms of pain-associated genes explain some of the variance in pain, including polymorphisms of the β-adrenergic receptor [70], Δ-opioid receptor [71], GABA receptor [72], Nav1.7 [73] and catechol-O-methyltransferase (*COMT*) genes [74]. Additionally, environmental factors seem to have profound effects on human pain intensity, including early life stressors, which have been shown to alter future pain sensitivity [75–77] and may place individuals at risk for considerable acute [78] and chronic pain [79,80]. Furthermore, pain intensity is influenced by cognitive factors such as catastrophizing, which is associated with lower pain thresholds [81] and increased hyperalgesia/allodynia [82].

Genetic factors in pain modulation

Studies in rodents have provided indirect evidence for the important role of descending serotonergic (5-hydroxytryptophan [5-HT]) pain inhibition [83]. While spinal applications of 5-HT resulted in increased pain inhibition, serotonin receptor antagonists reversed this effect [84]. Effective synaptic concentrations of 5-HT are strongly dependent on the activity of the 5-HT transporter (5-HTT) [85], whose gene (*SLC6A4*) is located on the long arm of chromosome 17 [86]. Polymorphisms of this gene have been associated with many psychiatric disorders [87], including migraine [88], depression [89] and FM [90,91]. Similarly, several mutations of *SLC6A4* have been implicated in CPM effectiveness [92] but this association is controversial at this time. Although one study reported strong genetic association of CPM effectiveness with polymorphisms of the 5-HT promoter region in healthy individuals [92], another study found no significant associations [93]. Although these findings are puzzling, some discrepancies may be explained by methodological differences in CPM techniques. Further research will be necessary to resolve these important issues.

Role of pain modulation in acute & chronic pain

Acute pain

Postsurgical pain has been utilized as a model for the evaluation of endogenous pain modulation. Preoperative experimental pain sensitivity was used to predict postoperative pain in individuals after thoracotomy [94], limb amputation [95], cesarean section [96,97], anterior cruciate ligament repair [98] and laparoscopic cholecystectomy [99]. Presurgical experimental pain sensitivity predicted up to 50% of the variance observed in postoperative pain [97]. The usefulness of this model as a predictor of endogenous pain modulation, however, is controversial at this time. When the CPM of patients was tested before thoracotomy surgery, one study found no correlation between CPM and acute postoperative pain [100]. By contrast, another study reported significant correlations between these

parameters [101]. This discrepancy was most likely related to multiple study-related factors including variability of patients, surgical techniques and test methods.

Chronic pain

A growing volume of animal literature strongly suggests genetic influences on pain sensitivity and pain modulation [102], with highly pain-sensitive animals demonstrating less responsiveness to analgesics [103–105]. Several studies indicate that various biochemical and neural pathways appear to be responsible for individual differences in analgesia, which also influence pain sensitivity [105]. Most of these pathways originate from the medullar raphe nuclei and project serotonergic or non-serotonergic fibers to the dorsal horn of the spinal cord [106]. These findings suggest that high pain sensitivity may place individuals at risk for prolonged pain not only by enhancing pain intensity but also by reducing the general effectiveness of endogenous and exogenous analgesia.

Although endogenous pain modulation seems to play an important role in chronic pain, multiple other factors appear to be involved. For example, the incidence of chronic postoperative pain seems to vary greatly depending on the type of surgeries performed. Chronic postsurgical pain has been reported in up to 12% of patients after cesarean section [107], while 19% of patients complained of chronic pain 6 months following knee arthroplasty [108]. Approximately 28% of patients undergoing inguinal herniorrhaphy [109] and 52% of patients undergoing mastectomy experienced persistent pain [110]. The incidence of chronic post-thoracotomy pain syndrome has been estimated to occur in 50–80% of patients [111]. This variability in chronic postoperative pain may be dependent on multiple factors including type of surgery, tissue as well as nerve injury and individual pain modulation.

A large prospective NIH-funded cohort study of orofacial pain (OPPERA) is currently underway to determine whether variability in basal pain sensitivity and pain modulation can predict the development of chronic pain in subjects at risk for TMD [112]. Results from this study are expected to be published in 2012. Information from a small pilot study related to this project has revealed that pain sensitivity and genetic factors predicted the occurrence of TMD in previously pain-free individuals [70]. Significant associations were noted between *COMT* haplotypes predicting pain sensitivity and future TMD.

Long-term studies that assess the contributions of pain sensitivity and endogenous pain modulation to future chronic pain are currently lacking. At this time, the most consistent risk factor for the development of chronic pain appears to be the severity of acute pain after injury. This relationship has been established for chronic pain after arthroplasty, amputation, thoracotomy, spinal cord injury, breast cancer surgery, cholecystectomy, herniorraphy, prostatectomy and cesarean section [97,113–119]. A similar association has also been demonstrated in several prospective studies of patients with herpes zoster infections [120,121]. High pain intensity during the acute episode of herpes zoster infection reliably predicted the development of chronic postherpetic neuralgia after resolution of the zoster rash [121]. By contrast, severity, duration or extent of the zoster rash were much less predictive for postherpetic neuralgia than acute pain intensity [122]. Future prospective well-designed studies will be necessary to assess the role of endogenous pain modulation for chronic pain after injury.

Pain modulation in central sensitivity syndromes

Whereas postoperative chronic pain syndromes appear to be related to tissue damage associated with illness and/or surgery, such associations are not apparent in many chronic nonmalignant pain disorders such as FM, chronic fatigue syndrome, IBS and TMD. Patients

with these disorders generally do not present with consistent tissue abnormalities that could explain chronic pain and localized or widespread hyperalgesia/allodynia. Specifically, the presence of central sensitization and other common features including fatigue, insomnia and distress, have resulted in labeling these chronic musculoskeletal conditions as central sensitivity syndromes (CSS) [123].

CSS are often debilitating illnesses associated with widespread musculoskeletal pain and hyperalgesia. Similar to other chronic pain conditions, such as OA [124] or back pain [125], detectable tissue abnormalities only poorly correlate with CSS pain [126]. A consistent aspect of CSS, however, seems to be augmented CNS processing of nociceptive signals [127,128] and dysfunctional endogenous pain modulation [61,129–131]. Specifically, descending pain inhibition as assessed by CPM has been found to be ineffective in patients with CSS [132,133]. However, this deficiency of CSS patients seems to be relative and not absolute. At least some forms of endogenous pain modulation have been found to be functional in patients with CSS, including spatial summation [134,135] and pain relief through expectation [136]. Thus, failure to appropriately modulate nociception and hyperalgesia may be one of the hallmarks of CSS.

Abnormal pain inhibition can be reversible

Clinical OA pain is thought to depend on ongoing nociceptive afferent input from abnormal joint structures. Central sensitization is frequently detectable in OA patients with resultant hyperalgesia and enlarged receptive fields of nociceptive neurons [137]. Although central hypersensitivity is usually reversible following cessation of nociceptive peripheral input, prolonged afferent barrage can result in persistent central sensitization [138–141]. Whether chronic clinical pain associated with central sensitization is dependent on tonic afferent impulse input, is controversial at this time. Several studies seem to indicate that at least some forms of chronic pain and central sensitization are dependent on tonic nociceptive input [37,142–144]. In one study QST was performed in 12 patients with painful hip OA before and at 6–14 months after successful arthroplasty, showing that pain and mechanical hyperalgesia associated with hip OA normalized after surgery [142]. In a second study, not only central sensitization but also central pain inhibition were assessed in 13 patients with painful OA of the hip [37]. Before hip arthroplasty, OA patients demonstrated evidence of mechanical central sensitization and ineffective CPM – using tourniquet forearm pain as the conditioning stimulus and mechanical pain as the test stimulus – which normalized after hip arthroplasty. Lack of central pain inhibition of OA patients before surgery suggests dysfunctional pain modulation (facilitation or inhibition) that normalized after replacement of the abnormal joint. In addition, mechanical hyperalgesia also returned to normal after surgery.

Expert commentary

The mechanisms of most chronic pain syndromes are only partially understood, including many nonmalignant conditions such as OA, FM, IBS and TMD. Intense and/or long-lasting afferent barrage can strongly contribute to central sensitization and often seems to be associated with abnormal endogenous pain modulation. Many patients with chronic pain disorders show evidence to suggest increased facilitation and decreased or absent inhibition of pain. Accumulating evidence has demonstrated that QST of endogenous pain inhibition, specifically CPM, can be used to predict ongoing pain, as well as the risk for future chronic pain, including chronic postoperative pain. Dysfunctional pain inhibition has been associated with chronic pain in patients with CSS or local pain syndromes, such as OA. Individual assessments of pain modulatory systems can be readily accomplished in the laboratory and may represent a sensitive biomarker of current and future chronic pains.

Further investigations of pain modulation in the general population will help refine our estimates of who may be at greatest risk for future chronic pain. Treatments designed to reduce the incidence, severity and impact of chronic pain in susceptible individuals are of great clinical importance and include pre-emptive analgesia [145] and/or multidisciplinary pain management programs [146]. Such approaches could have a considerable impact on acute and/or chronic pain in age-related pain disorders such as OA or after trauma or surgery, specifically for patients with high pain sensitivity and dysfunctional pain inhibition who will require timely and effective pain management interventions.

Five-year view

In most chronic musculoskeletal pain conditions, afferent peripheral input is necessary but not sufficient to explain the presence, duration and intensity of patients' pain. Central sensitization appears to be a hallmark of chronic pain, resulting in enhanced functioning of pain pathways and increased membrane excitability and synaptic efficacy, as well as reduced inhibition of neurons. It depends on the remarkable plasticity of the somatosensory nervous system after afferent barrage, inflammation or neural injury and on ineffective central modulation (increased facilitation or decreased inhibition). Overall, central sensitization increases synaptic inputs to nociceptive neurons, which respond with augmented action potentials, resulting in pain facilitation. Central sensitization is responsible for many, if not most, changes in pain sensitivity observed in chronic pain conditions. Importantly, central sensitization not only changes the sensory response elicited by nociceptive afferents, but also the response to stimuli that usually evoke innocuous sensations. Thus, better understanding of pain pathways that contribute to facilitation or suppress inhibition of central sensitization, is urgently needed. For the time being, prevention or rapid modulation of factors that initiate or prolong central sensitization may represent important strategies. Specifically, prevention and management of injury-related central sensitization, including effective pre- and post-operative analgesia, will most likely be beneficial.

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Key issues

- Many chronic pain syndromes such as fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, headache and chronic fatigue syndrome are associated with hypersensitivity to painful stimuli and reduced endogenous pain inhibition.
- Central sensitization appears to be a hallmark of chronic pain, resulting in enhanced function of pain pathways and increased membrane excitability and synaptic efficacy as well as reduced inhibition of neurons.
- Accumulating evidence suggests that endogenous pain inhibition depends on activation of the prefrontal cortex, periaqueductal gray and rostral ventral medulla.
- Quantitative sensory test paradigms have been designed to acquire detailed information of each individual's endogenous pain inhibition and facilitation.
- Pain inhibition and facilitation can be assessed by testing temporal summation of pain, which is mostly used for testing of facilitatory pain modulation and conditioned pain modulation, which tests pain inhibition by utilizing two simultaneously applied painful stimuli (pain inhibits pain paradigm).
- Treatments designed to reduce the incidence, severity and impact of chronic pain in susceptible individuals are of great clinical importance and include pre-emptive analgesia and/or multidisciplinary pain management programs.