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The important role of CNS facilitation and inhibition for chronic pain

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Abstract

Multiple studies have demonstrated that the pain experience among individuals is highly variable. Even under circumstances where the tissue injuries are similar, individual pain experiences may vary drastically. However, this individual difference in pain sensitivity is not only related to sensitivity of peripheral pain receptors, but also to variability in CNS pain processing. Peripheral impulses derived from tissue receptors undergo modification in dorsal horn neurons that can either result in inhibition or facilitation of pain. Such influences are particularly apparent in inflammation where not only peripheral, but also central, pain modulatory mechanisms can significantly increase nociceptive pain. Emotional state, level of anxiety, attention and distraction, memories, stress, fatigue and many other factors can either increase or reduce the pain experience. Increasing evidence suggests that 'bottom–up' and 'top–down' modulatory circuits within the spinal cord and brain play an important role in pain processing, which can profoundly affect the experience of pain.

Keywords

chronic pain; facilitation; inhibition

Inflammatory mediators from immune cells of peripheral tissues not only cause inflammation but also pain and hyperalgesia. Cytokines such as IL-1β, IL-6 and TNF-α play an important role in 'rubor, calor and dolor' (redness, warmth and pain), which are all pain-related symptoms [1,2]. Not only can cytokines enhance the activity of pain receptors [3], but they may also induce the expression of pain enhancing genes in dorsal root ganglia [4,5]. Increasing evidence suggests that cytokines can increase pain not only via peripheral, but also via CNS mechanisms [6]. In many different chronic pain conditions cytokines are not only detected in glial cells (microglia and astrocytes) of the spinal cord, but also seem to be linked to chronic pain [7]. Moreover, spinal blockade of cytokine signaling appears to attenuate chronic pain [8]. There is, however, little information available as to how cytokines alter synaptic transmission and neuronal activity in the spinal cord and brain.

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The experience of pain almost always depends on complex central processing of ascending (incoming) signals from peripheral tissues, which are powerfully modulated by descending inhibitory and facilitatory mechanisms. In the spinal cord the main ascending pain pathways are comprised of the spinothalamic tracts, including the lateral sensory discriminative and medial affective systems [9]. Subsequent pain processing in the brain is thought to occur in distributed networks [10] including primary and secondary somatosensory cortex (S1 and S2, respectively) [11], anterior- and mid-cingulate cortex (ACC and MCC, respectively) [12] and insula [13]. Much of the knowledge about supraspinal pain processing comes from functional imaging studies of experimental pain, which frequently report activations of multiple brain areas, including S1, S2, ACC/MCC, insula, prefrontal cortex, cerebellum and supplemental motor area (SMA) [9]. More recently, complex brain networks have been described that become activated during chronic pain [14,15]. Finally, descending pain pathways from the cortex (prefrontal cortex; ACC) to the brainstem and spinal cord can significantly modulate the activity of ascending signals and thus the pain experience [16].

Much of the descending effects of pain modulation occur at spinal synapses, which are critical for central sensitization and pain. Central sensitization refers to increased synaptic efficacy of somatosensory neurons in the dorsal horns of the spinal cord, often following tissue injury or nerve damage. However, synaptic mechanisms underlying central sensitization are only incompletely understood. Growing evidence suggests that proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α, are induced in the spinal cord under various injury conditions and contribute to pain hypersensitivity [6]. Tonic afferent barrage can result in increased synaptic efficiency, reduced pain threshold, pain amplification and enlargement of receptive fields [17].

Synapses are essential for chemical signal transmission between neurons. They can be silent and ineffective, or work at maximum capacity. Synaptic strength is not fixed but dependent on changes in transmitter release from presynaptic terminals or in transmitter responsiveness of postsynaptic membranes. This large variability in synaptic function and structure constitutes synaptic plasticity which is strongly influenced by descending pain modulation. Depending on the intensity, frequency and duration of activity, both increases (sensitization) and decreases (desensitization) in synaptic function can be observed, both of which are central to pain modulation [18,19].

Pain modulation

Clinical interest in pain modulation has a long history. One of the first observations of spinal cord neuronal modulation was related to the enhanced nociceptive flexion reflex, following spinal cord transection of animals [20]. Besides such evidence for pain facilitation, inhibition of pain has also been observed in animal studies. One seminal finding of endogenous pain inhibition, was the observation that focal electrical stimulation in the midbrain periaqueductal gray (PAG) produced profound analgesia in the awake rat [21], a finding that has been reproduced in human participants [22,23]. These results suggested that the PAG is an important brain area where ascending pain-related impulses are integrated with descending modulation from the midbrain and the limbic forebrain, including the amygdala, the rostral ACC, insula and orbitofrontal cortex. However, the contributions of the brainstem in descending control of pain are only incompletely understood [24], as these structures also play an important role in pain facilitation or pronociception [25]. In addition, several other regions of the brain have also been shown to affect pain modulation [23,26], including the thalamus, which seems to contribute to pain modulation via the mediodorsal (pain facilitation) and ventromedial (pain inhibition) nuclei [27]. Furthermore, modulation can be influenced by psychological factors, such as expectations [28] and attention [29,30], suggesting the existence of top–down effects on pain processing.

Overall, there is compelling anatomical, electrophysiological and pharmacological evidence that not only the PAG, but also the rostroventromedial medulla (RVM) play important roles in descending modulation of nociception, which can result either in inhibition and/or facilitation of nociceptive and non-nociceptive inputs [31–34].

Role of RVM in descending pain facilitation & inhibition

The modulation of pain depends on at least three types of neurons found in the RVM. Based on their response characteristics to noxious thermal stimulation of animals, these cells have been labeled as 'ON', 'OFF' and 'neutral' [35–37]. Whereas OFF cells seem to be tonically active, ON cells increase firing prior to pain behaviors of animals. The function of neutral cells is unclear but such neurons may represent a subtype of ON or OFF cells [38,39]. In general, activation of OFF cells seems to result in inhibition of nociceptive input [36,37], whereas the response characteristics of ON cells suggests a role in descending pain facilitation [40,41]. Overall, animal experiments resulting in hyperalgesia seem to increase ON-cell activity [42,43], whereas hypoalgesic or analgesic manipulations lead to increased OFF-cell firing. These findings suggest that PAG and RVM may play an important role not only for analgesia, but also in the development and maintenance of chronic pain states, which may occur in the absence of obvious tissue injuries.

Descending pain inhibition

Opioid pathways

Electrophysiological studies have demonstrated the important role of the RVM in the pathway of descending pain inhibition [38]. Descending projections from the RVM extend to spinal cord dorsal horns where they connect to primary afferent terminals, second- and third-order neurons, as well as interneurons [41]. At least part of the descending inhibitory function of the RVM is associated with OFF-cell activity, which can be significantly upregulated by endogenous opioids. Likewise, therapeutic application of opioids can also switch off ON cells that cause pain, and switch on OFF cells, resulting in pain inhibition. Similar increases of OFF-cell activity have been observed after opioid injections into the PAG or RVM [44]. By contrast, opioid injections into the PAG seem to have inhibitory effects on ON cells [45].

Placebo analgesia is a component of most pain therapies and is at least partially dependent on endogenous opioids [46], as well as descending pain modulatory pathways [47]. Neuroimaging studies have demonstrated that placebo analgesia is dependent on activation of pain inhibitory systems from cortical and subcortical areas [48–50], including the rostral ACC and PAG [48]. Increased activation of these brain areas seems to be associated with placebo analgesia [48].

Serotonergic pathways

Several studies have shown that not only endogenous opioids, but also serotonin (5-HT) and norepinephrine, are involved in endogenous pain modulation [51,52]. Norepinephrine and 5-HT can be released via descending pain pathways to modulate nociceptive signaling in the spinal cord. Norepinephrine inhibits pain through $\alpha 2$ adrenoceptors, while 5-HT seems to have pain facilitatory and inhibitory functions [53]. Several lines of evidence support 5-HT's important role in pain modulation, including one study where electrical stimulation of the RVM was associated with 5-HT release in the spinal cord [54]. Furthermore, intrathecal administration of 5-HT agonists or antagonists facilitated [55] or prevented antinociception [56], respectively. Initially, descending pain modulation from the RVM was thought to be solely serotonergic [57]; however, subsequent studies identified RVM neurons that have glycinergic or GABAergic projections to the spinal cord to mediate antinociception [58]. It

appears, that descending serotonergic projections from the RVM are relevant for pain facilitation in chronic pain, but they are not involved in opioid-mediated inhibition of acute pain [59].

It is, however, well known that depending on the receptor subtype, spinal 5-HT can have inhibitory or facilitatory effects on pain [60]. For example, spinal blockade of inhibitory 5-HT receptors abolished the antinociceptive effect of morphine injections into the RVM, while blockade of pain facilitatory 5-HT receptors prevented hyperalgesia [57]. Although many observations suggest that 5-HT is important for pain modulation in the spinal cord, its specific mechanism is unclear.

Noradrenergic pathways

Direct stimulation of PAG or RVM does not only increase 5-HT but also norepinephrine concentrations in the cerebrospinal fluid, resulting in pain reductions [61]. Furthermore, experimental pain inhibition can be blocked by spinal application of antiadrenergic compounds [62]. Such findings strongly suggest a significant role of norepinephrine in descending pain inhibition. Although neither PAG nor RVM contain noradrenergic neurons, both regions communicate with noradrenergic brain stem nuclei associated with pain modulation, including the locus coeruleus [63]. These nuclei have noradrenergic projections to the spinal cord, which can inhibit the response of dorsal horn pain transmission neurons [64]. Dorsal horn neuron recordings have shown that activated α2-adrenergic receptors hyperpolarize presynaptic neurons and decrease the release of excitatory neurotransmitters from primary afferent terminals, resulting in pain inhibition [65].

Descending pain facilitation

Overall, the signaling characteristics of ON cells seem to be associated with pain facilitation, such as enhancing the magnitude of nociceptive responding in rats [66]. Our understanding of such pain facilitatory mechanisms is still very limited. Pain has important physiological functions, including warning individuals of actual or impending tissue damage. Therefore, pain facilitation represents a physiological mechanism promoting appropriate coping strategies after acute injuries. Some chronic pain conditions, including neuropathic pain, persist long after the initial injury has healed. Thus they do not serve a protective function and therefore serve no adaptive purpose. However, there is increasing evidence for the important role of descending facilitation in clinical chronic pain conditions [67]. For example, after peripheral nerve injury, microinjection with lidocaine into the RVM abolished enhanced pain behaviors in rats [68]. When μ-opioid receptor-expressing RVM neurons were selectively eliminated, neuropathic pain behaviors in rats were reversed [69,70]. Overall, these findings demonstrate the importance of descending pain facilitation for hyperalgesia/allodynia and chronic pain after peripheral nerve injury [60].

Useful tests of pain facilitation

Temporal summation of pain (wind-up)

Wind-up testing is one of the most widely used assessments of pain facilitation in pain patients. Testing of wind-up depends on the application of a series of identical noxious stimuli to determine the increase in experimental pain across trials. Animal studies have shown that wind-up is not a peripheral tissue effect but occurs centrally in second-order neurons of the spinal cord [71]. Wind-up depends on nociceptive input from peripheral nociceptors (C fibers) and glutamate (*N*-methyl-D-aspartate), and tachykinin receptor (NK1) activation is required for this phenomenon. Since the magnitude of wind-up seems to depend on descending pain-modulatory systems, it is often used for examinations of pain facilitation in chronic pain patients [72,73].

Useful tests of pain inhibition

Conditioned pain modulation

Conditioned pain modulation (CPM), which includes diffuse noxious inhibitory controls, relies on the analgesic effect of a conditioning stimulus on a painful test stimulus (‘pain inhibits pain’) [74]. This analgesic mechanism was discovered in anesthetized rats in response to electrical nerve stimulation, when conditioning pain stimuli were applied to various body areas [75]. In general, peripheral noxious stimuli seem to inhibit the responses of dorsal horn neurons to painful electrical stimulation, or to application of noxious heat [76]. This inhibitory effect does not seem to be dependent on noxious stimuli applied to specific body areas. Importantly, CPM can be abolished by spinal cord transection and decreases after naloxone or naltrexone administration [77,78]. Reduced CPM after lidocaine microinjection into the nucleus raphe magnus suggests analgesic contribution from this site [79]. In addition, some studies suggest that CPM is dependent on the nucleus reticularis dorsalis [80]. This nucleus receives nociceptive input from spinal neurons, communicates with the PAG and RVM, and sends pain modulatory projections to the spinal cord [81]. In addition, the nucleus reticularis dorsalis is also connected to cortical sites [82]. Together with PAG and RVM, the nucleus reticularis dorsalis represents part of a spinal–supraspinal–spinal feedback loop that seems to modulate pain [83,84].

Abnormal wind-up & CPM in chronic pain patients

Many studies of chronic pain syndromes indicate that endogenous pain modulation may be inefficient [85,86]. Abnormal CPM and wind-up have been demonstrated in several chronic pain syndromes, including knee osteoarthritis [87,88], chronic tension-type headache [89,90], fibromyalgia [91,92], chronic pancreatitis [93,94], rheumatoid arthritis [95,96] and low back pain [97,98]. Recently, abnormalities of wind-up and CPM have been used as clinical tools to predict risks for enhanced postsurgical pain [99,100]. In addition, the incidence and severity of chronic postoperative pain could also be predicted by CPM assessment obtained before surgery [101]. Measurements of abnormal pain modulation were superior to pain thresholds or magnitude estimation of suprathreshold noxious stimuli for determining the risk for chronic postoperative pain.

Descending pain modulation as a pharmacological target

A number of commonly used analgesics directly or indirectly affect descending pain modulation, including COX inhibitors, which seem to produce analgesic effects mostly by inhibition of prostaglandin E2 synthesis but can also initiate opioid-mediated descending pain inhibition in the PAG [102]. Opioids not only activate cortical and subcortical receptors, but also descending pain inhibitory circuits. Similarly, 32-adrenergic receptor agonists, such as clonidine, and norepinephrine-reuptake inhibitors, such as duloxetine, have been shown to increase antinociception and to augment the antinociceptive effect of opioids [103,104]. Some of the analgesic effects of gabapentinoids, such as gabapentin and pregabalin, may also be due to their activation of descending noradrenergic pain pathways with subsequent release of norepinephrine in the dorsal horn of the spinal cord [105].

Conclusion

Accumulating evidence supports the important role of CNS pain modulation for both analgesia and hyperalgesia. Multiple cortical and subcortical brain and brainstem regions integrate and process sensory, autonomic and emotional information, resulting in activation of the PAG and RVM, with subsequent inhibition or facilitation of pain-related dorsal horn neurons. This top–down modulation is relevant for experimental, as well as clinical pain, and influences the effects of pain-relieving drugs, such as opioids, NSAIDs, 5-HT–

norepinephrine-reuptake inhibitors and gabapentinoids. These pain modulatory pathways are affected by memories and mood, as well as sociocultural background.

Future perspective

Evidence is emerging for the importance of dysfunctional descending modulatory pathways in hyperalgesia, as well as chronic pain. A better understanding of central pain modulation may allow new insights into chronic pain mechanisms that may ultimately result in improved pain therapy.

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Executive summary

Pain modulation

- There is compelling evidence for pain facilitation and inhibition originating from several fore- and mid-brain areas, which can be modulated by psychological factors such as expectations and attention.

Role of rostral–ventral medulla for descending pain facilitation & inhibition

- Activation of ON cells of the rostral–ventral medulla is associated with pain behaviors in animals, whereas OFF cells seem to be tonically active and inhibit nociceptive input.

Descending pain inhibition

- Opioid pathways:
  - Therapeutic opioid applications switch on OFF cells and switch off ON cells.
- Noradrenergic pathways:
  - It appears that serotonergic projections from the rostral–ventral medulla play a role in pain inhibition.
- Serotonergic pathways:
  - Serotonin seems to be involved in pain inhibition as well as pain facilitation.

Descending pain facilitation

- Signaling of ON cells seems to be associated with pain facilitation.

Tests of pain facilitation

- Temporal summation of pain (wind-up) can be used as measure of central pain facilitation in chronic pain patients.

Tests of pain inhibition

- Conditioned pain modulation and wind-up are frequently used as measures of central pain inhibition and facilitation. These tests were often found to be abnormal in patients with chronic pain disorders.

Pain modulation as pharmacological target

- Many analgesics, including opioids and norepinephrine-reuptake inhibitors, seem to affect descending pain inhibition.