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Review Series

It has long been appreciated that the experience of pain is highly variable between individuals. Pain results from activation of sensory receptors specialized to detect actual or impending tissue damage (i.e., nociceptors). However, a direct correlation between activation of nociceptors and the sensory experience of pain is not always apparent. Even in cases in which the severity of injury appears similar, individual pain experiences may vary dramatically. Emotional state, degree of anxiety, attention and distraction, past experiences, memories, and many other factors can either enhance or diminish the pain experience. Here, we review evidence for “top-down” modulatory circuits that profoundly change the sensory experience of pain.

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Existence of an endogenous pain inhibitory system

Early evidence for pain modulatory mechanisms came from observations of H.K. Beecher, who noted a remarkable attenuation of pain experienced by soldiers in combat situations (1). Analogous observations have been seen in others, including athletes that continue competition despite significant injuries (see ref. 2). Beecher, a physician who served with the US Army during the Second World War, observed that as many as three-quarters of badly wounded soldiers reported no to moderate pain and did not want pain relief medication (1). This observation was striking, because the wounds were not trivial but consisted of compound fractures of long bones or penetrating wounds of the abdomen, thorax, or cranium. Moreover, only individuals who were clearly alert, responsive, and not in shock were included in his report (1), leading to the conclusion that "strong emotions" block pain (1).

The existence of endogenous mechanisms that diminish pain through net "inhibition" is now generally accepted. Pain modulation likely exists in the form of a descending pain modulatory circuit with inputs that arise in multiple areas, including the hypothalamus, the amygdala, and the rostral anterior cingulate cortex (rACC), feeding to the midbrain periaqueductal gray region (PAG), and with outputs from the PAG to the medulla. Neurons within the nucleus raphe magnus and nucleus reticularis gigantocellularis, which are included within the rostral ventromedial medulla (RVM), have been shown to project to the spinal or medullary dorsal horns to directly or indirectly enhance or diminish nociceptive traffic, changing the experience of pain (3). This descending modulatory circuit is an "opioid-sensitive" circuit (see below) and relevant to human experience in many settings, including in states of chronic pain, and in the actions of pain-relieving drugs, including opiates, cannabinoids, NSAIDs, and serotonin/norepinephrine reuptake blockers that mimic, in part, the actions of opiates (Figure 1). While the precise mechanisms by which drugs produce pain relief is not entirely understood, strong evidence supports the actions of these drugs through the pain modulatory circuit or by mimicking the consequence of activation of this descending circuit at the level of the spinal cord.

"Top-down" modulatory pathways have been shown to underlie the robust and clinically important phenomenon of placebo analgesia, which can be demonstrated in approximately one-third of the population (4). Patients that had undergone removal of impacted molars and who were expecting an analgesic showed reduced pain scores after placebo injection (5). Placebo responders that blindly received the opiate antagonist naloxone indicated pain levels similar to those of the nonresponders, indicating that placebo analgesia required activation of endogenous opioid-mediated inhibition (5). Neuroimaging techniques have now established that the placebo response is likely mediated by activation of pain inhibitory systems, originating from cortical and subcortical regions (6, 7). Human imaging studies with [^{11}C]-carfentanil revealed that placebo analgesia was related to activation of μ-opioid receptors in the rACC, the pregenual cingulate cortex (pCC), the dorsolateral prefrontal cortex, and the anterior insular cortex (7). Changes in regional blood flow revealed that expectation of placebo analgesia activated a neural network from the rACC to include subcortical regions known to be active in opioid-mediated antinociception, such as the PAG (6). Increased regional cerebral blood flow to these sites was associated with a greater placebo response, leading to the suggestion that individual variations in placebo responses may be linked to differences in either concentration or function of μ-opioid receptors (6).

Imaging studies have led to the suggestion of a "pain matrix," brain areas that are consistently activated by noxious stimuli. These areas often include, but are not restricted to, the rACC, pCC, somatosensory cortex 1 and 2, the insula, amygdala and thalamus, and the PAG (8). Interestingly, these regions demonstrate overlap among brain sites activated by opioids and those that are activated by placebo analgesia, and imaging studies suggest that coupling between the rACC and the PAG is mediated through endogenous opioidergic signaling and is essential to both opioid-induced analgesia and placebo-mediated analgesia (9). It should be noted that the concept of a pain matrix is not meant to suggest a rigid regulatory pathway but rather conceptually represents a collection of brain regions that are involved in neurological functions, including cognition, emotion, motivation, and sensation as well as pain. These regions, acting together in the context of modulation of nociception, appear to give rise to the experience of pain (10). It is noted that analgesic drugs as well as expectation, distraction, emotional context, and other factors engage several nodes of the pain matrix to change the pain experience.

Engagement of descending modulation can facilitate, as well as inhibit, pain. The term "nocebo" has been introduced to describe an effect opposite to that of the placebo, indicated by expectation of a worsening outcome in response to a treatment (11). For example, patients who were expecting pain relief with a NSAID and were then told they were to receive a drug that was hyperalgesic

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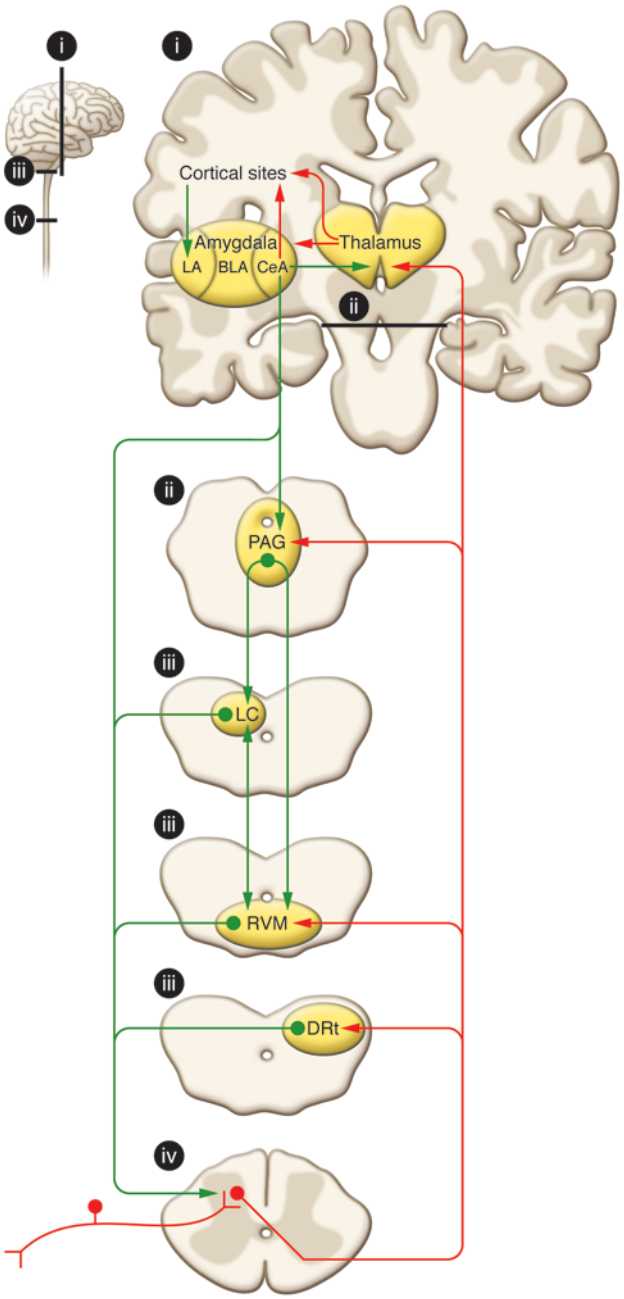

Figure 1
Schematic representation of pain modularity circuitry. Nociceptive inputs enter the spinal dorsal horn through primary afferent fibers that synapse onto transmission neurons. The projection fibers ascend through the contralateral spinothalamic tract. Ascending projections target the thalamus, and collateral projections also target mesencephalic nuclei, including the DRt, the RVM, and the midbrain PAG. Descending projections from the DRt are a critical component of the DNIC pathway. Rostral projections from the thalamus target areas that include cortical sites and the amygdala. The lateral capsular part of the CeA ("nociceptive amygdala") receives nociceptive inputs from the brainstem and spinal cord. Inputs from the thalamus and cortex enter through the lateral (LA) and basolateral (BLA) amygdala. The CeA sends outputs to cortical sites and the thalamus, in which cognitive and conscious perceptions of pain are integrated. Descending pain modulation is mediated through projections to the PAG, which also receives inputs from other sites, including the hypothalamus (data not shown), and communicates with the RVM as well as other medullary nuclei that send descending projections to the spinal dorsal horn through the DLF. The noradrenergic locus coeruleus (LC) receives inputs from the PAG, communicates with the RVM, and sends descending noradrenergic inhibitory projections to the spinal cord. Antinociceptive and pronociceptive spinopetal projections from the RVM positively and negatively modulate nociceptive inputs and provide for an endogenous pain regulatory system. Ascending (red) and descending (green) tracts are shown schematically. Areas labeled "i–iv" in the small diagram correspond with labeled details of the larger diagram.

responded with enhanced pain (12). When subjects were told verbally, nonverbally through the application of conditioning stimuli, or both ways that enhanced pain was to be expected, it was found that expectation of pain resulted in pain to nonpainful stimuli as well as enhanced pain in response to noxious stimuli (13). In order to isolate the effect of expectancy in an imaging study, subjects were presented with visual cues indicating that either a high or low noxious thermal stimulus would be applied but then were actually presented with the high stimulus (14). This procedure revealed changes in the ipsilateral caudal ACC, the head of the caudate, the cerebellum, and the contralateral cuneiform nucleus (nCF), suggesting that increased pain expectancy activates a pain network that modulates afferent input at the level of the nCF (14).

Neuroanatomical and electrophysiological evidence of endogenous pain inhibition

Although the existence of pain modulatory systems had been surmised for many decades, it was not until electrical stimulation or microinjection of opiates into specific brain regions that the importance and clinical significance of such systems was appreciated. In what may have been the first demonstration of a brain site-specific action for the antinociceptive effect of morphine, Tsou and Jang surmised that since morphine blocks pain at doses that do not affect other sensory modalities, it was likely working through a site specific for pain control. Thus, they microinjected morphine into several regions of the rabbit brain and discovered that a profound antinociceptive effect occurred only when morphine was applied into the PAG (15). Reynolds found that electrical stimulation of the ventrolateral PAG of the rat produced an antinociception so powerful that a laparotomy could be performed in a fully conscious rat, without observable signs of distress to the animal (16).

Electrical stimulation of the PAG was rapidly adapted to humans in efforts to relieve intractable pain (17–19). While PAG stimulation has been largely discontinued because of side effects, such as anxiety, distress, and, in some instances, development of migraine-like headache (20), deep brain stimulation aimed at other regions remains an approach that might control otherwise intractable pain (21). Critically, the reversal of intractable pain by stimulation of the PAG was blocked by naloxone, indicating the activation of an endogenous opioidergic pain inhibitory system (17). These early studies were not rigorous, placebo-controlled double-blind trials, and, as a consequence, the possibility of placebo analgesia cannot be disregarded. Even so, the existence of a placebo effect, as discussed above, is likely dependent on activation of pain modulatory circuits.

Preclinical studies have attempted to delineate the sites and pathways that compose the endogenous pain inhibitory circuit. Considerable overlap has been found between sites that produce antinociception with either electrical stimulation or morphine

microinjection (22–26). Both stimulation-produced antinociception (SPA) and antinociception from morphine microinjection into supraspinal loci are reversed by naloxone, further implicating the activation of endogenous opioidergic systems in these phenomena (27). These studies have revealed descending pain inhibitory projections to the level of the spinal cord, either directly or indirectly from the PAG. Surgical disruption of the dorsolateral funiculus (DLF) abolished supraspinally mediated antinociception (26), and anterograde and retrograde tracing studies revealed that the RVM sends spinopetal projections through this tract (28–30). The precise site of projection of these fibers and their role in inhibition or facilitation remains unclear.

The amygdala in descending modulation

Human imaging studies reveal connections linking the PAG to the amygdala and cortical sites (2, 31). These studies suggest that interactions between the prefrontal cortex and the amygdala provide emotional-affective modulation of cognitive functions in pain, driving tasks such as decision making, assessment of risk/reward versus pain, or punishment avoidance (32). The amygdala plays important roles in emotional responses, stress, and anxiety and is believed to be a critical component of the pain matrix. This region may contribute significantly to the integration of pain and associated responses such as fear and anxiety.

Electrophysiological studies in animals demonstrated that neurons of the central nucleus of the amygdala (CeA) showed excitation with noxious stimulation of the knee joint or deep tissue (33) and enhanced responses after peripheral (34) or visceral (35) inflammation. Sensitization of CeA neurons, mediated through metabotropic glutamate receptors, represents neuroplastic changes that appear to promote chronic pain (36, 37). Administration of a corticotropin-releasing factor (CRF1) receptor antagonist into the CeA of rats inhibited both nociceptive responses as well as anxiety-like behaviors (38). Hemispheric lateralization of the role of the amygdala in pain processing has been recently demonstrated, since, although both the left and right CeA showed responses to brief noxious stimuli, only the right CeA responded with enhancement of firing and increased receptive field size after either ipsilateral or contralateral peripheral inflammation (39). Moreover, peripheral inflammation produced activation of extracellular signal-regulated kinase cascade only in the right CeA, regardless of site of inflammation (40), and blockade of activity of this kinase in the right CeA, but not the left CeA, blocked behavioral signs of enhanced inflammatory pain (40).

The RVM and descending modulation: ON and OFF cells

Electrophysiologic studies and lesioning experiments have revealed that the RVM receives neuronal inputs from the PAG and is likely to be the final common relay in descending inhibition of nociception from supraspinal sites (41). The microinjection of lidocaine into the RVM abolished antinociception arising from electrical stimulation of the PAG (42). Descending projections from the RVM course through the DLF to the spinal dorsal horn and form synaptic connections with primary afferent terminals and second- and third-order neurons that transmit nociceptive signals to supraspinal sites as well as with interneurons and thus are well situated to modulate nociceptive inputs (43–45).

Important insights into the nature of descending modulatory circuitry came from studies by Fields and colleagues, in which activity of neurons in the RVM were paired with a behavior elicited by a noxious stimulus (i.e., the tail-flick response to noxious heat) in lightly anesthetized rats (41, 46, 47). These studies led to the identification of a population of RVM neurons that increase firing just prior to the initiation of the nociceptive reflex (i.e., "on-cells"), and another population of neurons was found to decrease firing just prior to the tail-flick (i.e., "off-cells") (48–50). Activity of other "neutral" cells did not correlate with nociceptive stimuli. Both the off-cells and on-cells were found to project to the spinal dorsal horn, indicating that they may exert modulatory influences on nociceptive inputs (51–52).

This dichotomy in neuronal function is consistent with bidirectional pain modulation. Studies performed with electrical stimulation or microinjection of glutamate into the RVM revealed a biphasic function of the RVM, with regard to pain modulation (53–56). Low intensities of stimulation inhibited nociceptive responses, whereas higher levels of stimulation enhanced nociception (53–57). This biphasic role of the RVM in pain modulation was shown with electrophysiologic responses of spinal cord neurons or with behavioral responses and occurred with either cutaneous or visceral stimuli (53–57). The electrophysiologic characteristics of the on-cells are consistent with a pronociceptive function. For example, prolonged delivery of a noxious thermal stimulus increased the firing rate of RVM on-cells as well as enhanced the intensity of the nociceptive response in rats (58). Both enhanced nociceptive responses and increased on-cell activity were abolished by lidocaine microinjected into the RVM (58). Hyperalgesia caused by naloxone-precipitated withdrawal was accompanied by increased on-cell activity (59). Finally, the subdermal injection of formalin into a hind paw of a rat produced exaggerated behavioral responses as well as increased responses of on-cells of the RVM (60).

The activation of descending inhibitory pathways that project to the spinal and medullary dorsal horns has led to the question of the nature of these projections. Opioids administered systemically or into the PAG result in increased activity of off-cells through disinhibition, and it is believed that activation of off-cells is "necessary and sufficient" for analgesia (61–63). In contrast, the on-cells are the only population of cells in the RVM directly inhibited by opioids, suggesting that these cells likely express the μ-opioid receptors (64). These cells are also activated by cholecystokinin (CCK) via a CCK2 receptor (48, 64, 65). Neuroanatomical studies reported a high degree of colocalization of CCK2 receptors with μ-opioid receptors on RVM neurons, presumed to be pain facilitation cells that may correspond with on-cells (66). Additionally, most (i.e., >60%) off-cells, on-cells, and neutral cells have been shown to express glutamate decarboxylase (67). However, the role of GABA in the function of these cells remains unclear.

Descending serotonergic pathways

Early studies with available serotonergic antagonists blocked SPA initiated from the RVM (68), leading to the suggestion that descending inhibition of pain was mediated through serotonergic neurons projecting from the RVM through the DLF (29). Stimulation of the PAG or RVM was found to cause release of serotonin in the spinal cord (69), and intrathecal administration of 5-HT agonists elicited antinociception (70), whereas intrathecal 5-HT antagonists attenuated SPA from the RVM (71). Retrograde labeling studies demonstrated the presence of serotonergic projections to the spinal dorsal horn arising from the nucleus raphe magnus, which is a midline structure within the RVM as well as the nucleus paragigantocellularis and the ventral portion of the nucleus gigantocellularis (72). Together, such studies led to the reason-

able assumption that the RVM provided descending serotonergic pain modulation from the RVM. However, attempts to determine whether either the on-cells or off-cells of the RVM are serotonergic led to the realization that other, nonserotonergic neurons from the RVM may modulate pain (73). In a study of 25 identified RVM neurons, none of the on-cells (i.e., 8 neurons) or off-cells (i.e., 9 neurons) expressed 5-HT, and only 4 out of 8 neutral cells were labeled with 5-HT (73). Moreover, only 20% of RVM neurons were found to be serotonergic (74), and most of the spinal projections from the RVM are either glycinergic or GABAergic. It has been argued that serotonergic RVM neurons are neither on-cells nor off-cells but that they can modulate the activities of these neurons (see refs. 75 and 76). However, a recent study, in which descending serotonergic RVM neurons were selectively ablated through the use of shRNA plasmids and electroporation, demonstrated that descending serotonergic projections from the RVM are important for facilitation of pain in inflammatory or neuropathic pain states, although they are not necessary for opioid-mediated inhibition of acute pain (77). Electrophysiologic studies suggested that GABAergic and glycinergic projections from the RVM mediate antinociception. In addition to the descending serotonergic populations that are activated, the diversity of subtypes of the 5-HT receptors and the complex anatomy of the spinal dorsal horn complicates interpretation of the role of serotonin in pain modulation.

The effect of spinal serotonin can be either inhibitory or facilitatory, depending on the receptor subtype activated (78–82). Spinal administration of an antagonist of the inhibitory 5-HT7 receptor blocked the antinociceptive effect of morphine microinjected into the RVM, whereas pharmacological antagonism of the facilitatory 5-HT3 receptor blocked hyperalgesia induced by CCK administered into the RVM (79). Further, systemic administration of 5-HT7 agonists blocked capsaicin-induced hyperalgesia in mice, whereas 5-HT7 antagonists elicited mechanical hypersensitivity (83). The 5-HT7 receptor has been identified in the dorsal root ganglion and on central terminals of primary afferent fibers (84, 85) as well as on GABAergic interneurons in the dorsal horn of the spinal cord (84), which is consistent with a role in pain modulation (83). Although these observations indicate an important serotonergic role for pain modulation, the precise spinal mechanisms involved remain unclear.

Noradrenergic systems and pain modulation

Electrical stimulation of the PAG or RVM to elicit antinociception increases measured norepinephrine levels in the cerebrospinal fluid, and this effect was blocked by spinal adrenergic antagonists (69, 86–88). These findings suggest a strong contribution of norepinephrine in antinociception associated with descending inhibition. While neither the PAG nor the RVM contain noradrenergic neurons, both regions communicate with noradrenergic sites important to pain modulation, including the A5 (locus coeruleus), A6, and A7 (Kölliker-Füse) nuclei (89–91). These noradrenergic nuclei are a major source of direct noradrenergic projections to the spinal cord (3, 92) and likely may serve to ultimately inhibit the response of presynaptic and postsynaptic spinal pain transmission neurons (3, 92).

Numerous studies have demonstrated that activation of spinal α_2-adrenergic receptors exerts a strong antinociceptive effect (93–95). Spinal clonidine blocked thermal and capsaicin-induced pain in healthy human volunteers (96). PAG activation resulted in inhibition of the nociceptive responses of dorsal neurons mediated through activation of spinal α_2 receptors (97). Activation of α_2-adrenergic receptors has been shown to inhibit nociceptive transmission at the level of the spinal cord through presynaptic activity, inhibiting release of excitatory neurotransmitters from primary afferent terminals, as well as through postsynaptic sites (93). Recordings performed on spinal cord slices revealed that activation of α_2-adrenergic receptors hyperpolarized neurons and was thus inhibitory. Recently, it has also been demonstrated that activation of α_1-adrenergic receptors caused depolarization of GABA interneurons (98), demonstrating an additional mechanism of enhancing inhibition. Activation of spinal α_1-adrenergic receptors also enhances responses of dorsal horn neurons to noxious inputs (97).

Descending modulation and stress-induced analgesia

The mechanisms mediating the suppression of pain by stress have been intensively studied. Watkins and colleagues (99) found that stress induced by brief foot shock of the forepaws of rats produced antinociception as measured in the tail-flick test. Lesions of the DLF made rostral to the entry zone of the peripheral nerves of the forelimbs, which kept intact any direct spinal communications between forelimb and tail, abolished stress-induced analgesia (SIA), indicating that supraspinal sites were necessary to activate a spinopetal pain inhibitory circuit (99). Additionally, it was found that antinociception induced by brief shock of the forepaws was abolished by systemic and intrathecal naloxone, indicating the activation of endogenous opioidergic pain inhibitory systems (99). Stress induced by foot shock reduced firing of RVM on-cells and increased that of off-cells, consistent with opioidergic endogenous pain modulatory systems (100). SIA is associated with elevated PAG levels of β-endorphin (101), and microinjection of μ-opioid receptor antagonists into the PAG or RVM abolished SIA (102–104). Opioid microinjection into the amygdala elicits antinociception that is blocked by lidocaine in either the PAG or RVM (105). These and other studies led to the conclusion that SIA can be opioid sensitive and mediated through descending inhibitory pathways from amygdala, the PAG, and through RVM projections to the spinal cord (106).

However, preclinical studies have also revealed that some aspects of SIA are not sensitive to naloxone and therefore are likely to be mediated via different mechanisms. Recent studies have revealed a role of endogenous cannabinoids in SIA and in descending modulatory pathways. Inhibition of RVM activity by microinjection of muscimol abolished antinociception induced by systemic injection of the cannabinoid agonist WIN55,212-2 (107). Moreover, WIN55,212-2 increased RVM off-cell activity and reduced firing of the RVM on-cells, analogous to the effect of morphine, but these effects were not blocked by naloxone, indicating that these effects are mediated specifically through cannabinoid receptors (107). Studies with a CB1 antagonist revealed that tonic release of endogenous cannabinoids increases off-cell activity and diminishes on-cell firing and may modulate baseline nociceptive thresholds through regulation of RVM activity (107), mechanisms that could also underlie opioid-insensitive SIA. Opioid-insensitive SIA was abolished by systemic administration of CB1, but not CB2, antagonists (108). Microinjection of the CB1 antagonist rimonabant into the dorsolateral PAG abolished such antinociception, further suggesting that SIA is mediated by endogenous cannabinoids (108). Opioid-insensitive SIA was associated with elevated levels of endogenous cannabinoids in the PAG, and SIA was enhanced by microinjection of inhibitors of monoacylglycerol lipase, which hydrolyzes the endogenous cannabinoid 2-arachidonoylglycerol

(108). Finally, microinjection of a CB1 antagonist into the RVM blocked SIA, whereas inhibition of hydrolysis of endogenous cannabinoids in the RVM enhanced SIA (109). These studies indicate that endogenous cannabinoids, like opioids, regulate pain sensitivity in response to environmental conditions through descending pathways (109). As SIA produces many generalized effects, including release of stress hormones, multiple physiological actions result that may contribute to antinociceptive effects and to pain.

Descending facilitation and experimental chronic pain

Increased descending facilitation in experimental chronic pain models has been demonstrated; but, to date, how this mechanism participates in clinical conditions has not been determined. Emerging preclinical evidence suggests that activation of putative pain facilitation cells maintains descending facilitation and promotes neuropathic pain. The microinjection of lidocaine into the RVM of rats with peripheral nerve injury abolished behavioral signs of enhanced abnormal pain (110–112). Moreover, the surgical disruption of the DLF ipsilateral but not contralateral to nerve injury abolished behavioral signs of enhanced abnormal pain but did not alter normal responses in sham-operated animals (111, 113). Microinjection of CCK into the RVM produced behavioral evidence of enhanced nociception that was blocked by lesion of the DLF (112, 114) and markedly increased on-cell activity (115). Accordingly, microinjection of the CCK2 antagonist, L365,260, into the RVM reversed behavioral signs of neuropathic pain in nerve-injured rats (112).

Microinjection of the potent μ-opioid agonist dermorphin, conjugated to the ribosome-inactivating protein saporin, to rats with peripheral nerve injury produced a selective knockdown of RVM neurons that express the μ-opioid receptor, along with a reversal of behavioral signs of neuropathic pain (111, 116). Additionally, the selective knockdown of CCK2-expressing neurons using CCK-saporin resulted in a substantial reduction in RVM neurons expressing the μ-opioid receptor, whereas the knockdown of RVM neurons expressing μ-opioid receptors with the dermorphin-saporin conjugate resulted in a substantial reduction in numbers of neurons expressing CCK2 (66). Both of these manipulations abolished behavioral and neurochemical signs of neuropathic pain in rats with spinal nerve ligation (66). Furthermore, a recent study demonstrated that blockade of RVM activity by microinjection of lidocaine elicited reward in models of neuropathic pain, suggesting that descending facilitation also likely contributes to tonic-aversive (i.e., stimulus-independent) aspects of such pain (117).

Activation of descending facilitation after peripheral nerve injury has been associated with pronociceptive changes in the spinal cord. Peripheral nerve injury resulted in enhanced capsaicin-evoked release of CGRP from primary afferent fibers in spinal cord sections and upregulation of spinal dynorphin to pathological levels (111, 118, 119). Manipulations that abolished descending facilitation, such as DLF lesions or dermorphin-saporin conjugate given into the RVM, also abolished dynorphin upregulation and enhanced release of CGRP (111, 118, 119). Recent studies revealed that increased concentrations of spinal dynorphin can stimulate neurons through increased calcium influx, unexpectedly mediated through the bradykinin receptors (120). Blockade of spinal bradykinin receptors inhibited behavioral signs of neuropathic pain, visceral pain, and diminished central sensitization (121–123). Collectively, these studies suggest that descending facilitation represents an important mechanism that likely contributes to maintenance of central sensitization after peripheral nerve injury (78, 82).

Diffuse noxious inhibitory controls modulation of pain

The concept of diffuse noxious inhibitory control (DNIC) was formulated from observations made with recordings of spinal dorsal horn units in anesthetized rats in response to peripheral stimuli applied to various parts of the body or electrical stimulation of peripheral nerves (124, 125). It was found that peripheral noxious stimuli suppressed the neuronal responses of convergent dorsal horn units to either electrical stimulation of C-fibers or application of noxious heat (124, 125). This inhibitory effect could be evoked from noxious stimuli applied to various parts of the body and thus was diffuse in nature (124, 125). Importantly, DNIC was not demonstrated in dorsal horn units that responded solely to noxious, proprioceptive, or innocuous inputs, indicating a requirement for convergent neurons receiving both noxious and innocuous stimuli (125). In addition, DNIC was abolished by spinal cord section and was diminished by systemic naloxone administration (124–126). Visceral pain induced by i.p. injection of phenylbenzoquinone inhibited vocalization induced by electrical stimuli applied to the tail, and this inhibition was also dose-dependently reversed by systemic naloxone (127). Observations that DNIC was diminished by electrolytic lesion (128) or lidocaine microinjection (129) of the nucleus raphe magnus suggested that there is a contribution from this site to DNIC. However, other studies established that lesions of the RVM or the PAG did not block DNIC (130) and that DNIC was integrated at the level of the dorsal reticular nucleus (130). The dorsal reticular nucleus (DRt) receives nociceptive inputs from spinal projections and communicates with the PAG and RVM as well as the thalamus and amygdala and sends pain modulatory projections to the spinal cord (131–133). Moreover, the DRt sends and receives projections from cortical sites as well, and a single DRt neuron can project to different CNS sites, thus potentially modulating pain through several mechanisms (134). The DRt, along with the PAG and the RVM, form parts of a spinal-supraspinal-spinal feedback loop that modulates pain (134, 135).

Loss of DNIC and chronic pain

These observations suggest that many chronic pain syndromes may be due in part to a loss of DNIC (136). Loss of DNIC could manifest as enhanced through either the loss of endogenous inhibitory control or an enhancement of pain facilitation (136). In one recent study, patients with irritable bowel syndrome (IBS) or temporomandibular disorder (TMD) or healthy volunteers received an experimental pain stimulus in the form of increasing heat applied by a probe placed on the palm and a conditioning pain stimulus in the form of a foot-bath of noxious-cold water (137). The control group demonstrated decreased sensitivity to the noxious thermal stimulus when the foot was immersed in cold water, indicating active DNIC, whereas not only was DNIC absent in the patients with IBS or TMJ, but they showed enhanced sensitivity to the nociceptive stimulus (137). The authors concluded from these data that chronic pain could be caused in part by a deficient pain inhibitory system (137). Deficits in DNIC have been demonstrated in patients with a number of chronic pain syndromes, including, for example, osteoarthritis of the knee (138), chronic pancreatitis (139), rheumatoid arthritis (140), and long-term trapezius myalgia (141).

Additionally, evidence is growing that a loss of DNIC suggests that deficits in endogenous pain modulation may underlie chronic tension-type headache (CTT) as well. In one study with CTT patients and unafflicted volunteers, a training stimulus of noxious thermal heat was applied to the thigh and an electrocutaneous

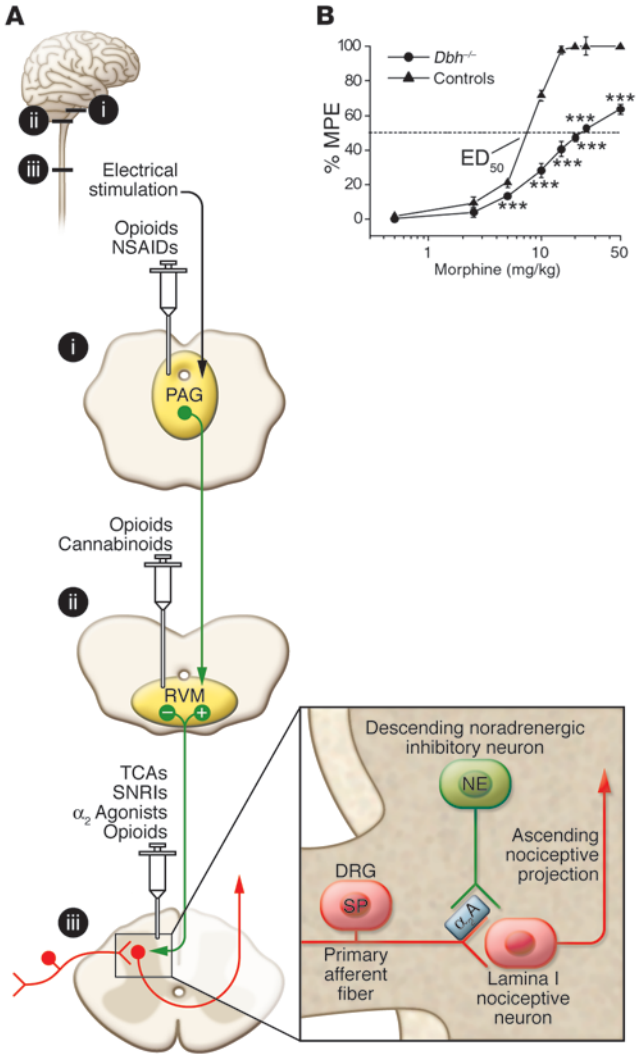

Figure 2
Schematic representation of bulbospinal pain inhibition and potential targets of analgesic activity. (**A**) Descending pain inhibition from the PAG can be initiated by electrical stimulation or direct microinjection of opioids. Recent evidence also indicates a role for COX inhibitors in the PAG as well. Opioids and cannabinoids inhibit pain by enhancing the baseline firing rate of off-cells and eliminating the off-cell pause in response to nociceptive stimuli. Inhibition of on-cell activity may abolish enhanced pain states. The on-cells and off-cells might correlate with pain facilitatory (+) and inhibitory (–) neurons in the RVM, respectively. At the level of the spinal cord, opioids can inhibit transmitter release from primary afferent terminals as well as activity of pain transmission neurons. Norepinephrine (NE) release from spinopetal noradrenergic fibers from medullary sites also inhibits pain transmission. Tricyclic antidepressants (TCAs) and other norepinephrine reuptake inhibitors enhance the antinociceptive effect of opioids by increasing the availability of spinal norepinephrine (box). Areas labeled "i–iii" in the small diagram correspond with labeled details of the larger diagram. α_2A, α_2-adrenergic receptor; DRG, dorsal root ganglion; SNRI, serotonin/norepinephrine reuptake inhibitor; SP, substance P. (**B**) Mice deficient in dopamine β-hydroxylase that do not produce norepinephrine show a diminished antinociceptive effect of morphine compared with control animals, suggesting that the presence of norepinephrine, presumably released in the spinal cord, is required for the full expression of morphine antinociception. The dashed line represents the 50% effect, and the corresponding dose is the ED_{50} (that is the dose producing a 50% effect). % MPE, percentage maximal possible effect. ***$P < 0.001$ compared with the control group. Error bars represent SEM. Copyright National Academy of Sciences, USA (151).

noxious stimulus was applied to either the forearm or the temple (142). The control group demonstrated decreased pain perception with the conditioning stimulus, whereas the CTT patients did not, indicating a deficit of DNIC (142). Similarly, a more recent study using pain from an occlusion cuff and temporal summation from repeated pulses from a pressure algometer demonstrated deficiency in DNIC in CTT patients (143). In a recent study performed with rats, it was shown that persistent morphine exposure resulted in increased sensitivity to sensory thresholds and loss of DNIC in trigeminal neurons sensitive to dural stimulation (144). Here, it was hypothesized that loss of DNIC may contribute to development of medication-overuse headache (144). The DNIC paradigm has been used as a clinical tool to predict who might be at risk for enhanced postsurgical pain (145, 146).

Descending modulation and pain-relieving drugs

The existence of a descending pain modulatory system provides many targets for the development of analgesic drugs or adjuncts that enhance the effects of existing analgesics (Figure 2). Opioids act throughout the neuraxis and can relieve pain through activities at cortical and subcortical sites, at which affective and somatosensory aspects of the pain experience can be modified, as well as by activating descending pain inhibitory circuits. Activation of descending noradrenergic projections from the locus coeruleus and other noradrenergic sites, described above, produces antinociception. Accordingly, α_2-adrenergic receptor agonists have been shown to produce antinociception as well as to potentiate the antinociceptive effect of opioids (94, 147). Moreover, by increasing spinal noradrenergic activity, tricyclic antidepressants and other selective noradrenergic reuptake inhibitors, such as duloxetine, enhance the analgesic effect of opioids and show clinical efficacy against neuropathic pain (148). It was recently also shown that the clinical efficacy of gabapentin may be due to its activation of descending noradrenergic systems and release of norepinephrine in the spinal cord (149). The COX inhibitors exert an analgesic effect by inhibition of PGE_2 synthesis, thus reducing peripheral and central sensitization. Recent studies also indicate that inhibition of COX in the PAG promotes an opioid-mediated descending pain inhibition (150).

Summary

The advent of neuroimaging studies and technological advances allowing increased spatial and temporal resolution has contributed greatly to our changing perceptions of how pain is integrated and modulated in the central nervous system. From early animal studies that described a linear system of pain modulation from the PAG through the RVM and descending to the spinal cord, we now envision a complex pain matrix that includes important cortical regions and elements of the limbic system as well as midbrain and medullary sites. These structures that likely participate in pain modulation reflect interacting brain regions that participate in pain processing as well as autonomic regulation and sensory and emotional management. The concept of top-down pain modulation system accounts for or contributes to pain relief, as seen with

the placebo effect, stress, DNIC, and the actions of pain-relieving drugs, such as opioids, NSAIDs, reuptake blockers, and possibly gabapentinoids. These modulatory pathways help to explain how personal experience and emotional state as well as societal beliefs may alter the experience of pain. Clinical evidence supports the emerging view that dysfunctions of descending modulatory pathways, resulting in reduced inhibition/enhanced facilitation (e.g., loss of DNIC), can result in the enhanced pain observed in many chronic pain conditions. While not yet clinically proven, enhanced descending facilitation may also play an important role in maintaining chronic pain. Increased knowledge of the components of these clinically validated pain modulatory circuits may offer approaches to develop improved pain therapy.

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