Review Article

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Descending facilitation: From basic science to the treatment of chronic pain

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Abstract

It is documented that sensory transmission, including pain, is subject to endogenous inhibitory and facilitatory modulation at the dorsal horn of the spinal cord. Descending facilitation has received a lot of attention, due to its potentially important roles in chronic pain. Recent investigation using neurobiological approaches has further revealed the link between cortical potentiation and descending facilitation. Cortical-spinal top-down facilitation, including those relayed through brainstem neurons, provides powerful control for pain transmission at the level of the spinal cord. It also provides the neuronal basis to link emotional disorders such as anxiety, depression, and loss of hope to somatosensory pain and sufferings. In this review, I will review a brief history of the discovery of brainstem-spinal descending facilitation and explore new information and hypothesis for descending facilitation in chronic pain.

Keywords

Descending facilitation, rostroventral medial medulla, pain, serotonin, anterior cingulate cortex, mice, chronic pain

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Introduction

Brain activity is able to affect sensory transmission through descending biphasic modulatory systems. Integrative studies using different experimental approaches reveal that descending modulation of spinal sensory transmission is biphasic, including inhibitory and facilitatory influences. Descending influences from supraspinal, central nuclei directly or indirectly modulate spinal sensory transmission and include the anterior cingulate cortex (ACC), amygdala, periaqueductal gray (PAG), and rostroventral medial medulla (RVM). The brainstem RVM is thought to be one of key relay for descending modulation from supraspinal to the spinal cord.[1–3] Due to its potential roles in chronic pain, descending facilitation has attracted much attention recently. Different types of experimental approaches have been used to investigate the mechanisms for descending facilitation, including electrophysiological, pharmacological, behavioral, biochemical, and optogenetic studies (see Table 1). In this review, I will summarize data using whole animal preparation, in vitro spinal and brain slices, and genetically manipulated mice to support the hypothesis that the positive feedback mechanism within the synapses or between different brain regions is a key mechanism for persistent pain caused by injury (Table I).

Brief history of the discovery

Many investigators have focused on the study of descendant inhibition from supraspinal structures, and indeed, activation of brain structures mostly leads to inhibition of spinal nociceptive reflex as well as spinal nociceptive transmission. In electrophysiological experiments, there are a few observations of neurons that electrical stimulation can lead to excitation or increases of spinal neuronal spike.[4] However, it is often treated as unexplained results or modulation of possible inhibitory neurons. The first observation of descending facilitation of pain is that the report of stimulation of the nuclei reticularis gigantocellualaris and gignatocellularis pars alpha in the brainstem can lead to reduction of tail-flick (TF) latency, a typical reflexive response for the

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Table 1. Timelines for the discovery and investigations of descending facilitation and its roles in chronic pain.

Year	Major discovery	Reference
1990	Behavioral report of facilitation of the TF flex by brainstem RVM activation	Zhuo and Gebhart, *Pain* (1990)
1992	Facilitation of spinal unit responses to cutaneous sensory stimuli to RVM activation	Zhuo and Gebhart, *J Neurophysiol* (1992)
1996	Role of facilitation in hyperalgesia	Urban et al., *Brain Research* (1996)
1998	Silent synapses and synaptic facilitation by 5-HT	Li and Zhuo, *Nature* (1998)
1999	AMPA receptor interaction in facilitation	Li et al., *Nature Neurosci* (1999)
2000	Descending facilitation from ACC	Calejesan et al., *Eur J Pain* (2000)
2002	Descending Facilitation of visceral pain	Zhuo et al., *J Neurophysiol* (2002) Zhuo and Gebhart, *Gastroenterology* (2002)
2001	Descending facilitation from RVM in opioid-related pain and tolerance	Vanderah et al., *J Neurosci* (2001)
2003	GluR2 peptide inhibitor and spinal analgesia	Garry et al., *Mol Cell Neurosci* (2003)
2006	Descending 5-HT facilitation in cancer pain	Donovan-Rodriguez et al., *Neurosci Lett* (2006)
2008	Descending facilitation from RVM in muscle pain	Tillu et al., *Pain* (2008)
2013	Descending facilitation maintains neuropathic spontaneous pain	Wang et al., *J Pain* (2013)
2014	Possible cortical projection of facilitation	Chen et al., *Mol Pain* (2014)
2014	Optogenetic stimulation of RVM-induced facilitation in freely moving animals	Cai et al., *Mol Pain* (2014)
2015	Optogenetic stimulation of ACC-induced facilitation in freely moving animals	Kang et al., *Mol Brain* (2015)

TF: tail-flick; RVM: rostroventral medial medulla; HT: serotonin; AMPA: 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid; ACC: anterior cingulate cortex.

investigation of descending modulation in rats.[5] Furthermore, such facilitation becomes more potent after the removal of descending inhibition of the transection or block of bilateral dorsolateral funiculus.[6] Electrophysiological recordings from spinal dorsal horn neurons confirm such descending facilitation, and it is likely to modulate the neuronal threshold to peripheral noxious thermal stimuli.[4] In contrast, descending inhibition is mostly to modulate the maximal responses of neurons. Pharmacological experiments further confirm that facilitation of TF reflex is mediated by different transmitter receptors at the level of the spinal cord.[1] Subsequent works have characterized the synaptic mechanisms for spinal facilitation or potentiation using spinal cord slice preparations.[7] Synaptic and molecular mechanisms have been identified using genetic and neurobiological approaches. Behaviorally, descending facilitation has been implicated in chronic pain conditions as well as increased pain conditions caused by opioids. While it is likely that there may be multiple descending facilitation systems in the central nervous system, it is well accepted that modulation of spinal nociceptive transmission is biphasic, and some excitation can even been long lasting, similar to long-term potentiation reported in the brain.

Experimental methods for investigation of descending modulation

Investigations of descending facilitation have been carried out using different approaches. At the behavioral level, different behavioral responses to peripheral stimuli can be used to evaluated whether activation of certain brain regions induces facilitation of nociceptive transmission. The reduced response threshold (i.e., TF latency) or enhanced responses (colorectal distension) induced electromyographic responses can be recorded.[5,8] These can be combined with local pharmacological administration as well as optogenetic approaches.[9] At the single neuron level, it is important to show that activation of brain regions can facilitate spinal sensory neuronal responses to peripheral stimuli.[4] This allows us to distinguish the effects of potential motor neurons in behavioral studies. Unfortunately, due to the difficulty of approaches and lack of basic funding, there are few laboratories that perform such experiments. At the in vitro slice level, one can record the spinal dorsal horn to measure sensory synaptic transmission. Receptors that are involved in facilitation can be targeted.[7] Future use of optogenetic approaches[9,10] may help to stimulate certain projecting fibers in isolated slices. One simple model for descending

facilitation is to activate the selective projection system to the spinal cord (e.g., serotonin (5-HT)), and the release of 5-HT facilities spinal excitatory glutamate-mediated synaptic transmission by enhancing 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) receptor functions.

Brief summary of brainstem-spinal facilitation system

The investigation of descending facilitatory systems has been carried out systematically in the brainstem RVM. At the level of the whole animal, electrophysiological, pharmacological, and behavioral experiments have been performed to characterize facilitation of responses of spinal sensory neurons to peripheral noxious stimuli as well as behavioral responses to noxious stimuli.[4–6,8,11–13] Facilitation affects spinal nociceptive transmission from cutaneous areas as well as from visceral organs. Furthermore, facilitation is a common form of modulation of sensory transmission, affecting both noxious and non-noxious inputs.[12] These unique features indeed raise the possibility that descending facilitation may serve as a key central mechanism to contribute to injury-related central pain or allodynia.

A key feature of descending facilitation is that it is intensity dependent. Whether facilitation or inhibition is observed, in part, depends on the intensity of stimulation applied. According to effects on spinal sensory neuronal responses, we characterize sites within the brainstem into three different groups: biphasic, inhibitory, and facilitatory sites. At biphasic sites of stimulation, it is typical that electrical stimulation facilitates spinal nociceptive transmission at lesser intensities (5–25 μA) and inhibits responses of the same neurons at greater intensities (50–100 μA). At inhibitory sites, electrical stimulation only reduces and inhibits responses of spinal sensory neurons. At facilitatory sites, we found that electrical stimulation only caused increases in responses of spinal sensory neurons. To determine if facilitatory or inhibitory effects were simply due to different groups of spinal dorsal horn neurons recorded, we also investigate the effect of electrical stimulation at a constant intensity, but at different sites in the RVM on the same spinal neuron. We found that the responses of the same spinal sensory neurons can be either inhibited or facilitated by electrical stimulation applied to different sites in the brainstem. Thus, spinal units receive both facilitatory and inhibitory influences descending from the brainstem.

There is no clear anatomical separation between these different effects produced by stimulation in the brainstem. Biphasic effects are often produced at sites of stimulation adjacent to sites from which only inhibition is produced by similar intensities of stimulation. Further, inhibitory effects are produced at biphasic sites of stimulation adjacent to other biphasic sites from which facilitatory effects are produced. It is unlikely that effects are simply due to activation of fibers passing through the RVM because microinjection of glutamate or selective receptor agonists into the RVM also produces similar biphasic effects.

Facilitation of spinal visceral pain transmission

Most investigations of pain use somatosensory stimuli, since it is easy to use and repeat. However, increasing evidence suggests that visceral pain, pain triggered from internal organs, may not share the same mechanisms with those from skin.[14] For descending facilitation from the RVM, the facilitatory effect on spinal neural responses to visceral noxious stimuli is more robust than cutaneous thermal stimuli[8] (see Figure 1). Activation in the different nuclei can lead to facilitation of spinal responses. Furthermore, in some sites, pure facilitation can be found. The tonic facilitation from the brainstem for visceral pain may explain why some visceral pain is unbearable as compared with well-located cutaneous pain. The physiological significance of such facilitation for noxious stimuli from visceral organs remains to be determined. The frequency and magnitude of descending facilitation found in visceral pain further push aside any doubt of the existence of such potent excitatory system from supraspinal structures.

Facilitation of non-nociceptive transmission: A novel mechanism of feeling a touch

Unlike noxious stimuli, the response to touch is difficult to study in animals. Animals only respond to touch when a touch becomes painful in pathological condition such as neuropathic pain. Electrophysiological recording in vivo from spinal dorsal horn neurons is a useful method to do so. In fact, descending facilitation from the RVM also affect spinal responses to non-noxious brush of the skin (Figure 2). Activation of RVM neurons increases neuronal responses to mechanical brush.[8] Such facilitatory effects may contribute to emotion-related touch in both animals and humans. It is also possible that descending facilitation may affect responses to other sensory stimuli such as itch. Future studies are clearly needed.

5-HT: A key transmitter

5-HT is the neurotransmitter of the major projection from the RVM to the spinal cord. Consistent with the biphasic modulatory effects of 5-HT on spinal

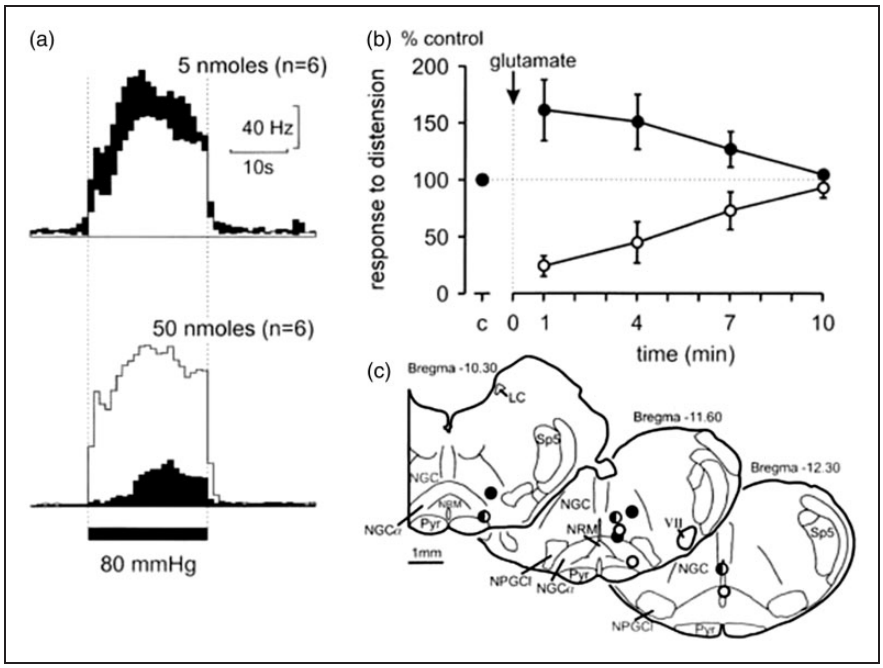

Figure 1. Example of facilitation of responses to non-noxious brush stimulation of the skin produced by stimulation in RMM. (a) Peristimulus time histograms (1-s bin width) and corresponding oscillographic records illustrating a control response to brush of the skin of the hind foot and the effect on responses of the same unit during stimulation in the RMM (intensities given). The brush stimulus is indicated by the horizontal arrows, and the period of RMM stimulation (25 s) is indicated by upward and downward arrows. (b) Graphic representation of the data in (a); the point above 0 represents the response (total number of impulses) in the absence of RMM stimulation. (c) Stimulation site, illustrated on a representative coronal brain section, and receptive field with orientation of brush stimulus indicated. Modified from Zhuo and Gebhart (2002).

nociceptive transmission and behavioral reflexes, we found that 5-HT produced biphasic modulation of excitatory synaptic responses in spinal cord slices (Figure 3). 5-HT at high doses produces inhibition of AMPA/kainite-receptor-mediated excitatory postsynaptic currents (EPSCs), while a low dose of 5-HT or a selective 5-HT2 receptor agonist induces facilitation of fast EPSCs in the lumbar spinal cord (Figure 3). 5-HT at low doses could facilitate fast EPSCs in the presence of a N-Methyl-D-aspartate (NMDA) receptor antagonist, AP-5 (50 μM), indicating that the facilitatory effect is NMDA receptor independent. Furthermore, the facilitatory effect induced by 5-HT at low doses persisted during washout of 5-HT. While activation of 5-HT receptors is important for the induction of the facilitation, continuous activation of these receptors is not necessary for the expression of the facilitation. Application of methysergide after administration of a serotonergic receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, failed to reverse the facilitatory effect of 5-HT.[15] These results indicate that 5-HT triggers long-term plastic changes in spinal dorsal horn synapses, and continuous activation of 5-HT receptors is not required for the expression of the facilitation.

5-HT may affect spinal sensory transmission by acting on presynaptic or postsynaptic receptors.[7] Postsynaptic application of G protein inhibitors, introduced through the recording pipette, abolishes the effect of 5-HT to facilitate synaptic transmission, suggesting that postsynaptic 5-HT receptors are critical for the effect.[15] In support of this notion, we found postsynaptic Ca^{2+}-dependent processes to be required for 5-HT-induced facilitation. In experiments with chelating postsynaptic Ca^{2+} with BAPTA in the pipette solution, the facilitatory effect of 5-HT was abolished, indicating that an increase in postsynaptic Ca^{2+} is required. Additional evidence against a mechanism of 5-HT-induced synaptic facilitation involving modulation of presynaptic glutamate release comes from the observation that while 5-HT application clearly caused AMPA receptor-mediated EPSCs, NMDA receptor-mediated EPSCs were significantly decreased by 5-HT in the same neurons.[16] This result suggests that postsynaptic enhancement of AMPA receptor-mediated currents by 5-HT is selective.

In support of the involvement of descending 5-HT projection pathway in descending facilitation, Cai et al.[10] examined the behavioral effects of selective activation of RVM 5-HT neurons on mechanical and thermal pain behaviors in vivo by using optogenetic stimulation in tryptophan hydroxylase 2-Channelrhodopsin 2 (ChR2) transgenic mice. They found that ChR2-enhanced

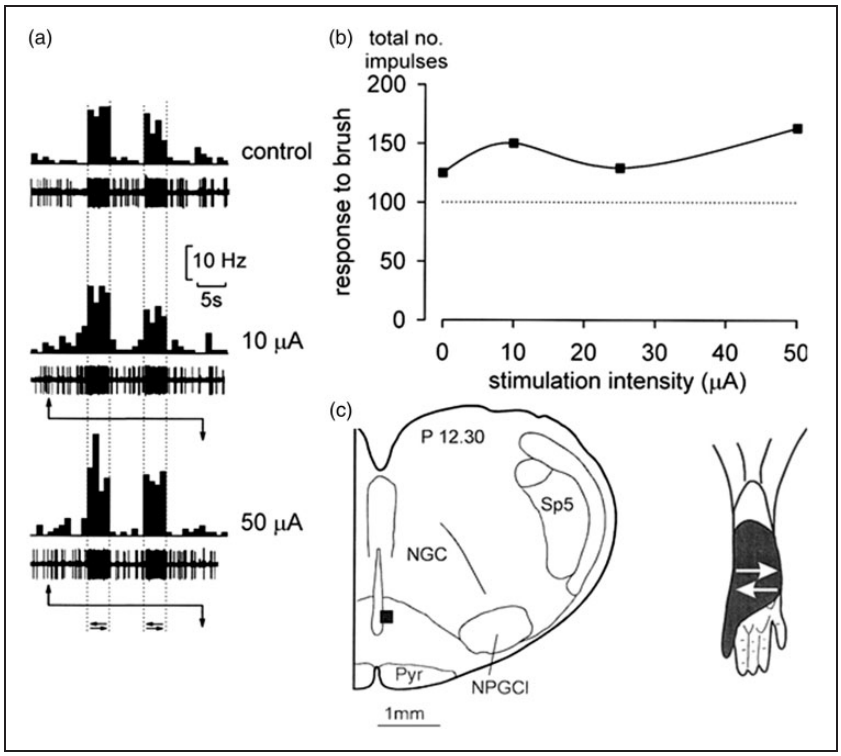

Figure 2. Summary of activation of RVM neurons on visceromotor responses. (a) Mean peristimulus time histograms (PSTHs; 1-s bin width) representing the mean visceromotor response before glutamate administration (unfilled PSTHs) and at 1 min after glutamate administration (filled PSTHs). The period of distention (20 s) is indicated below by the horizontal bar. (b) Graphic representation of the data in (a) and time course of effect. The data are presented as a percentage of the control response (total counts in 20 s). (c) Brainstem sites for glutamate microinjection at a low dose (5 nmol; •) and a greater dose (50 nmol; ○). At three sites (indicated by ◑), both doses of glutamate (5 and 50 nmol) were tested. Modified from Zhuo and Gebhart (2002).

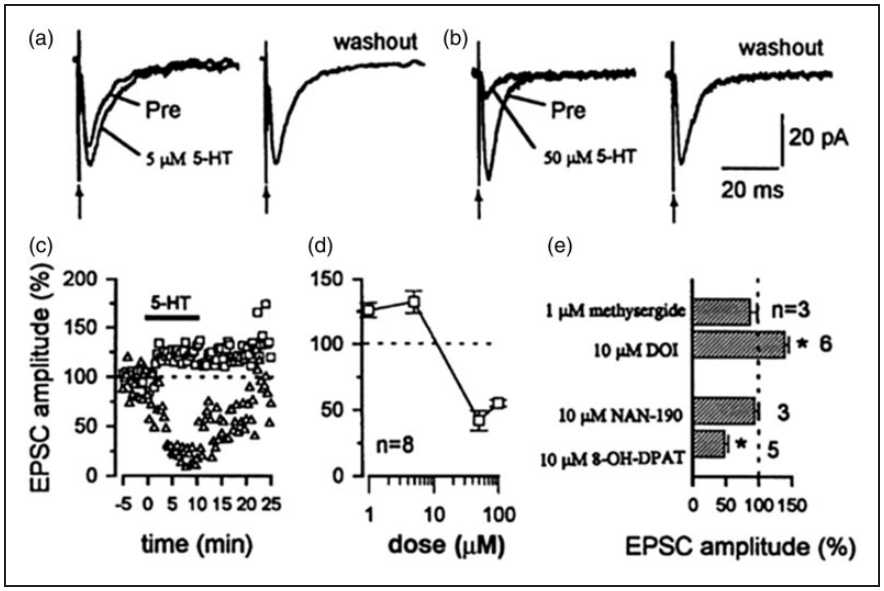

Figure 3. Biphasic modulation of spinal synaptic transmission by 5-HT. (a) and (b) Examples of 5-HT experiments at two doses. Upward arrows indicate the time of stimulation. (c) The effect of 5-HT on amplitudes of EPSCs in experiments shown in a (squares) and b (triangles). (d) Summary data of 5-HT at four different doses ($n = 8$ for each dose). (e) Different effects of 5-HT1A- and 5-HT2 receptor agonists (8-OH-DPAT and DOI, respectively). The effects were blocked by their receptor antagonists NAN-190 (5-HT1A) and methysergide (5-HT), respectively. $^*P < 0.05$. Modified from Li and Zhuo (1998).

yellow fluorescent protein-positive neurons strongly co-localized with tryptophan hydroxylase 2-positive (5-HT) neurons in RVM. The optogenetic stimulation decreased both mechanical and thermal pain thresholds in an intensity-dependent manner, with repeated stimulation producing sensitized pain behavior for up to two weeks.[10] This important study strongly demonstrates that descending 5-HT facilitation from the RVM clearly cause the enhancement of pain responses.

AMPA receptor recruitment and facilitation

AMPA receptors mediate most excitatory transmission in spinal cord synapses.[15,16] There are at least three different types of excitatory synapses. The first one only expresses NMDA receptors, which we call the "silent synapse." In silent synapses, no effective AMPA/kainate receptors are available to detect the release of glutamate from presynaptic terminals. Consequently, these synapses do not conduct any synaptic transmission at the resting membrane potential. In the second type of sensory synapses, only postsynaptic AMPA receptors are functional, and they mostly respond to stimulation at low intensities. In the third type of synapses, both AMPA and kainate receptors are expressed. In previous studies, bath application of low dose 5-HT have found to recruit AMPA receptors in silent synapses as well as AMPA receptor-mediated responses[15]

Co-activation of calcium-stimulated adenylyl cyclase subtype 1

Consistent with the silent synapse in adult mouse spinal cord, some synaptic responses (26.3%) between primary afferent fibers and dorsal horn neurons were almost completely mediated by NMDA receptors.[17] Dorsal root stimulation did not elicit any detectable AMPA/kainate receptor-mediated responses in these synapses. While 5-HT alone does not produce any long-lasting synaptic enhancement, co-application of 5-HT and forskolin produced long-lasting facilitation of synaptic responses (Figure 4). Possible contributors to the increase in the cyclic adenosine monophosphate (cAMP) levels are calcium-sensitive adenylyl cyclase (ACs). We found that the facilitatory effect induced by 5-HT and forskolin was completely blocked in mice lacking adenylyl cyclase subtype 1 (AC1), indicating that calcium-sensitive AC1 is important. Our results demonstrate that in adult sensory synapses, cAMP signaling pathways determine whether activation of 5-HT receptors causes facilitatory or inhibitory effects on synaptic responses. This finding provides a possible explanation for regulation of two different signaling pathways under physiological or pathological conditions. Postsynaptic increases in cAMP levels by sensory transmitters may favor 5-HT-induced facilitation. One key source for activation of AC1 in neurons is NMDA receptors.[18,19] It is possible that co-activation of NMDA receptor with 5-HT receptor may lead to significant potentiation in adult spinal cord neurons. The interaction between cAMP and 5-HT may provide an associative heterosynaptic form of central plasticity in the spinal dorsal horn to allow sensory inputs from the periphery to act synergistically

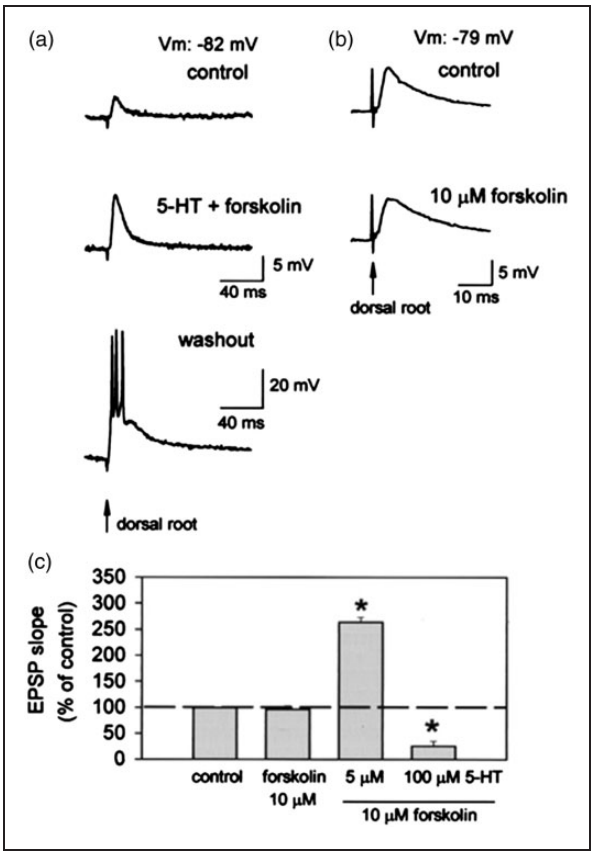

Figure 4. Forskolin and 5-HT synergistically facilitate sensory synaptic transmission. (a) Examples of EPSPs showing synaptic responses before, during, and after co-application of 5 μM 5-HT and 10 μM forskolin. Note that stimulation of primary afferent fibers at the same intensity induced action potentials from the same neuron during the washout. (b) Forskolin (10 μM) alone did not produce any facilitation in a separate experiment. (c) Summarized results for different treatments with forskolin and/or 5-HT. Data are shown as percentages in EPSP slopes during the drug application. While forskolin (10 μM) alone did not induce significant changes in synaptic responses, co-application of 5-HT (5 μM) and forskolin (10 μM) induced long-lasting enhancement of synaptic responses. However, co-application of 5-HT at a high dose (100 μM) with forskolin (10 μM) produced inhibition of synaptic responses during the drug application. Synaptic responses recovered after 10 min washout with normal solution. $^{*}P < 0.05$ indicates significant difference from control. Modified from Wang et al. (2002).

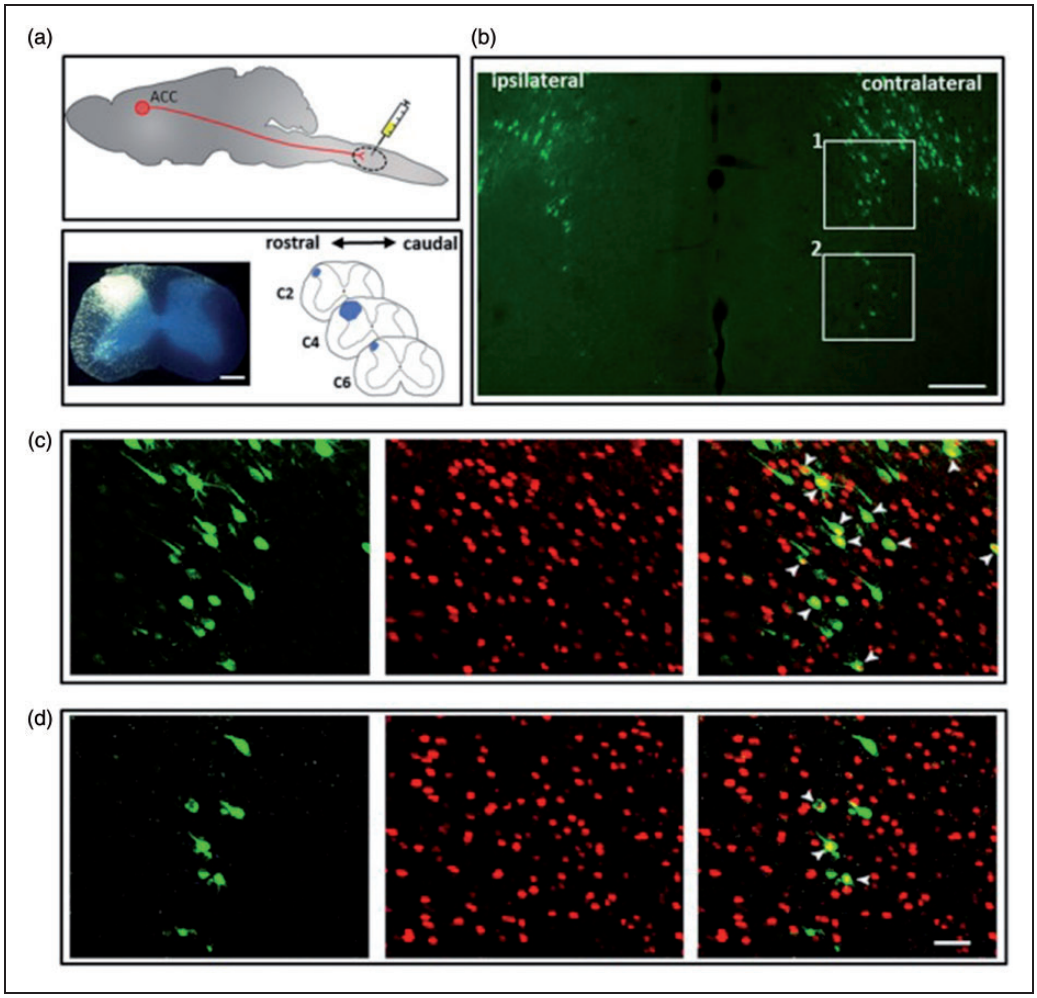

Figure 5. Top-down descending projection from the ACC to the spinal cord. (a) Schematic figures and digitized photomicrograph showing Fluoro-Gold (FG) injection site in the spinal cord and retrograde transportation of FG label neurons in the ACC. (b) Distribution of FG-labeled neurons in both sides of ACC after FG injection into the spinal cord. (c) and (d) Augmented figures showing FG (green) and Fos (red) double-labeling results in rectangle area 1 (c) and 2 (d) in b. Arrowheads on the merged figures indicate FG/Fos double-labeled neurons. Modified from Chen et al. (2014).

with central modulatory influences descending from the brainstem RVM.

Protein–protein interactions for AMPA receptor potentiation

One mechanism for the facilitation of AMPA receptor-mediated responses is the interaction of glutamate AMPA receptors with proteins containing postsynaptic density-95/Discs large/zona occludens-1 domains. GluA2 and -3 (or called GluR2-3) are widely expressed in sensory neurons in the superficial dorsal horn of the spinal cord.[7,20] Glutamate receptor-interacting protein (GRIP), a protein with 7 postsynaptic density-95/Discs large/zona occludens-1 domains that binds specifically to the C-terminus of GluA2/3, is also expressed in spinal dorsal horn neurons.[20] In many dorsal horn neurons, GluA2/3 and GRIP coexist.[20] A synthetic peptide corresponding to the last 10 amino acids of GluA2 ("GluA2-SVKI": NVYGIESVKI) that disrupts binding of GluA2 to GRIP[20] blocks the facilitatory effect of 5-HT.[20] Furthermore, synaptic facilitation induced by phorbol 1, 2-dibutrate is also blocked by GluA2-SVKI, suggesting that synaptic facilitation mediated by protein kinase C activation is similar to that produced by 5-HT in its dependence on GluA2/3 C-terminal interactions.[20]

Facilitation from the cortex

As mentioned above, most investigation of descending facilitation is focused on subcortical structures such as

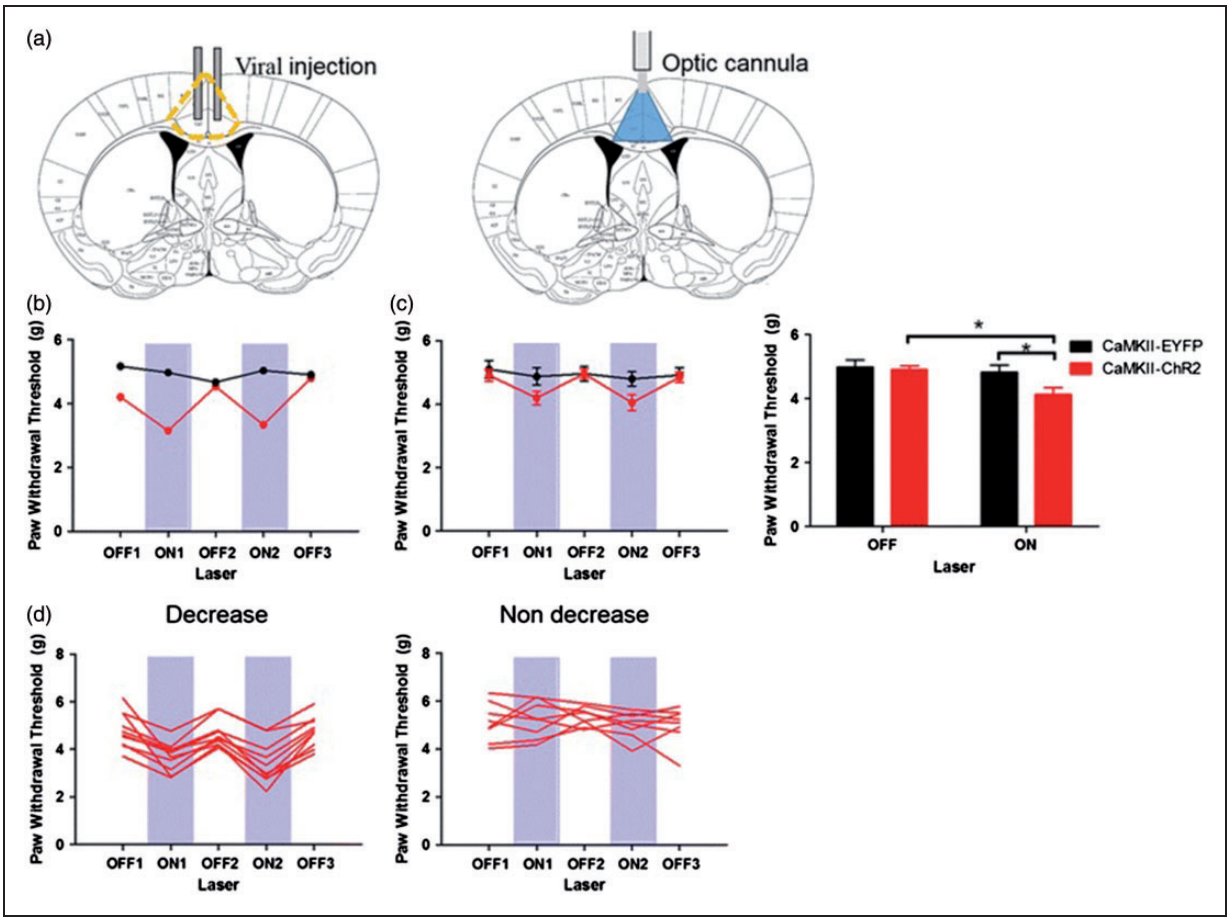

Figure 6. Descending facilitation of behavioral withdrawal by optogenetic activation of ACC pyramidal cells. (a) Schematic diagram of viral injection site (left) and optic cannula placement (right) in the ACC. (b) One example of the effects of blue light in a CaMKII-ChR2 expressing mouse (red) and an EYFP expressing mouse (black) in the von Frey test. (c) Pooled data for ChR2 and EYFP mice. On average, there was a reduction in the mechanical threshold in the ChR2 group. The graph on the right plots the combined data for the two ON and three OFF episodes. There was a significant effect of laser light in the ChR2 group but not in the EYFP group. (d) Not all animals showed a decrease of the mechanical threshold during light activation. Out of 18 animals, 10 showed a decrease while 8 did not. (e) The overlapped pattern of ChR2 expression in each group. Modified from Kang et al. (2016).

the RVM. The possible central control of RVM-spinal facilitation has been less investigated. One possible structure is the PAG. The PAG-RVM is known to play a key analgesic effect in descending inhibition of pain. Few studies report that PAG may exert descending facilitatory effects on spinal transmission. In addition, it has been known that cortical neurons could project to brainstem neurons and lead to the excitation of descending facilitation.[21] Activation of the ACC at high intensities (up to 500 μA) of electrical stimulation did not produce any antinociceptive effect. Instead, at most sites within the ACC, electrical stimulation produced significant facilitation of the TF reflex (i.e. decreases in TF latency). Chemical activation of metabotropic glutamate receptors within the ACC also produced a facilitatory effect. Interestingly, this descending facilitation from the ACC apparently relays at the RVM. In addition, the dorsal reticular nucleus has also been proposed as another possible brainstem relay for descending facilitation from ACC.[22] However, descending facilitation from the dorsal reticular nucleus on spinal sensory transmission has not yet been characterized.

In addition to the ACC-RVM-spinal pathway, recent studies implicate that there may be ACC-spinal direct projection in parallel for descending facilitation modulation. Anatomic studies report that some prefrontal cortical areas, including part of the dorsal ACC, send descending projections to the spinal cord in rats, monkeys, and mice[23–25] (Figure 5). This link provides a possible pathway for ACC neurons to directly regulate the spinal cord neurons. In the present study, in vivo electrophysiological experiments find that activation of ACC enhances spinal sensory transmission, and this facilitation is independent of RVM activity.

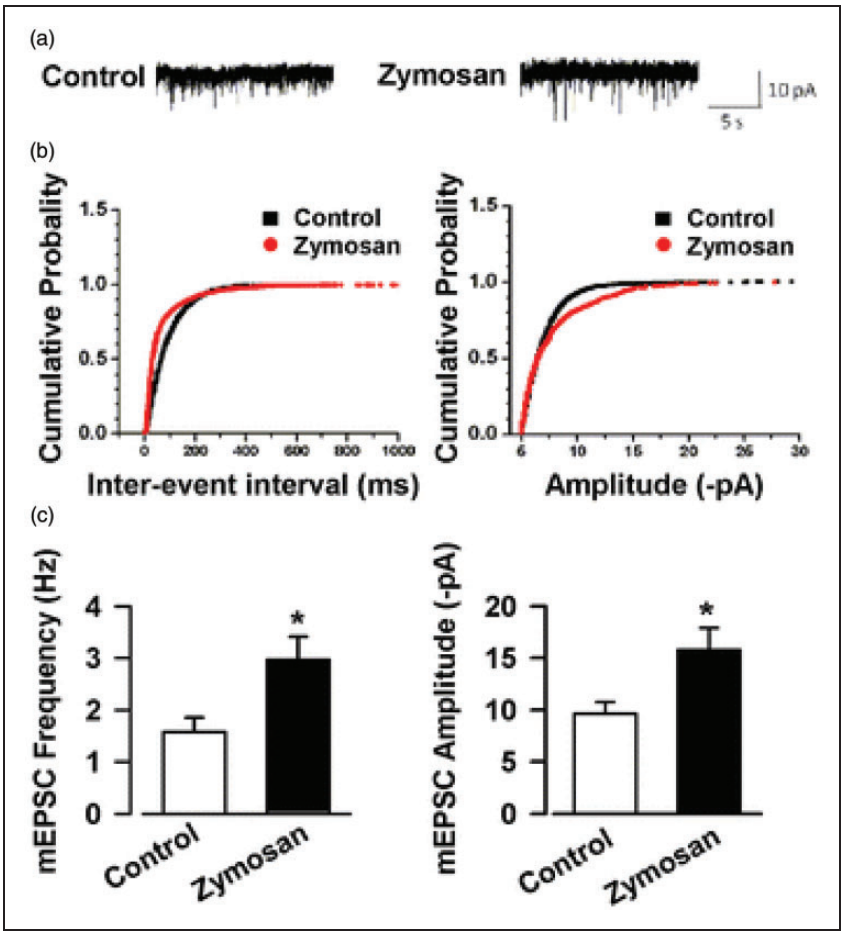

Figure 7. Enhanced excitatory transmission in the ACC by chronic visceral pain. (a) Representative mEPSCs recorded in pyramidal neurons at a holding potential of 70mV from control and zymosan-injected mice. (b) Cumulative inter-event interval (left) and amplitude (right) histograms of mEPSCs recorded in slices of control and zymosan-injected mice. (c) Summary plots of mEPSC data. The frequency (left) and amplitude (right) of mEPSCs were significantly enhanced in the ACC slices of mice injected with zymosan. *$P < 0.05$ versuss control. Modified from Liu et al. (2015).

In support of descending facilitation from the ACC in freely moving animals, Kang et al.[9] used optogenetic methods to selectively activate ACC pyramidal versus inhibitory neurons in mice (Figure 6). They found that selective activation of pyramidal neurons rapidly and acutely reduced nociceptive thresholds and that this effect was occluded in animals made hypersensitive using Freund's Complete Adjuvant. Conversely, inhibition of ACC pyramidal neurons rapidly and acutely reduced hypersensitivity induced by Freund's Complete Adjuvant treatment. These results provide direct evidence of the pivotal role of ACC excitatory neurons, and their regulation by parvalbumin expressing interneurons, in nociception.[9]

ACC: A cortical amplifier of pain

ACC synapses are highly plastic.[19,26] Activity-dependent immediate early genes, such as c-fos, Egr1, and adenosine 3′,5′-monophosphate response element binding protein, are activated in ACC and insular cortex neurons after tissue inflammation or digit amputation.[27–29] Furthermore, these plastic changes persist for a long period of time. AMPA receptor and NMDA receptor functions undergo potentiation in ACC neurons of animals with chronic pain[30–34] (see Figure 7 for visceral pain model). In addition, the release of glutamate is also increased.[30,35,36,37,39] Thus, ACC serves as a key cortical control for descending facilitation systems, including those from RVM.

Pathological implications of descending facilitation

It is known that supraspinal neurons are activated by noxious stimuli or after injury, including those neurons located in the RVM and ACC.[19,38,39] Even under physiological conditions, such brief noxious stimuli may be

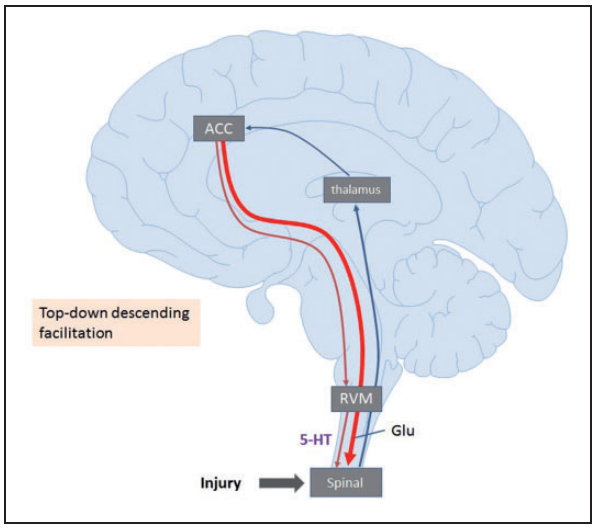

Figure 8. Descending facilitation from the ACC. ACC pyramidal cells send projection fibers to the brainstem RVM and activate RVM neurons that send descending projection to the spinal cord dorsal horn. 5-HT is a likely key neurotransmitter for such facilitatory effect on spinal sensory synaptic transmission. Enhanced postsynaptic AMPA receptor-mediated synaptic responses contribute to facilitated effects produced by 5-HT in the dorsal horn. ACC neurons also send its projection directly to the dorsal horn and potentiate spinal sensory synaptic transmission. Glutamate is likely one of these facilitatory transmitters. It may cause the potentiation by presynaptic and/or postsynaptic mechanisms. For the cortical inputs, ACC neurons receive at least sensory input through ascending projection from the spinal cord through the thalamus.

sufficient to activate descending facilitation from the RVM as well as the ACC. Facilitated nociceptive transmission at the level of the spinal cord may assist animals to escape dangerous conditions.

Under pathological conditions, long-term activation of descending facilitation may contribute to chronic pain, including behavioral allodynia, hyperalgesia, and spontaneous pain after the injury. A positive feedback mechanism has been proposed to explain that enhanced pain transmission may directly contribute to the suffering of chronic pain in patients. Using various animal models, descending facilitation has been implicated in cancer pain conditions, chronic muscle pain, neuropathic pain, opioid induced pain, headache, as well as inflammation-related pain.[40–46,48,49] Especially for the ACC-spinal top-down facilitation, it has been proposed that it may also contribute to emotion disorder caused pain[25,47] (Figure 8).

Summary and future directions

Understanding molecular and cellular mechanisms for central changes in various pain-related states holds hope for improved understanding and, thus, treatment of chronic pain. At the synaptic level, it is important to understand molecular and cellular mechanisms for long-term plastic changes in the ACC, RVM, and spinal dorsal horn after peripheral tissue insult; at the network level, descending facilitation as well as descending inhibition provide a key mechanism to link pain-related neurons located at different regions of the brain. For facilitation, it will convey the cortical excitation back to the level of spinal dorsal horn, a gate region for the entrance of painful information from the outside. The information of descending modulation will provide clues for testing new drug targets—for example, blocking descending facilitatory influences at different levels of the central nervous system (e.g., the ACC and RVM). It is clear that improved understanding of endogenous facilitatory systems provides not only knowledge about basic physiological mechanisms related to sensory transmission, modulation, and neuron plasticity but also knowledge that can lead to improved management of persistent and chronic pain states in patients.

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