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CHRONIC PAIN (R STAUD, SECTION EDITOR)

Descending Control Mechanisms and Chronic Pain

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Abstract

Purpose of Review The goal of the review was to highlight recent advances in our understanding of descending pain-modulating systems and how these contribute to persistent pain states, with an emphasis on the current state of knowledge around "bottom-up" (sensory) and "top-down" (higher structures mediating cognitive and emotional processing) influences on pain-modulating circuits.

Recent Findings The connectivity, physiology, and function of these systems have been characterized extensively over the last 30 years. The field is now beginning to ask how and when these systems are engaged to modulate pain. A recent focus is on the parabrachial complex, now recognized as the major relay of nociceptive information to pain-modulating circuits, and plasticity in this circuit and its connections to the RVM is marked in persistent inflammatory pain. Top-down influences from higher structures, including hypothalamus, amygdala, and medial prefrontal areas, are also considered.

Summary The challenge will be to tease out mechanisms through which a particular behavioral context engages distinct circuits to enhance or suppress pain, and to understand how these mechanisms contribute to chronic pain.

Keywords Pain modulation · Brainstem · Persistent pain · Inflammation · Hypersensitivity

Introduction

Current pharmacological treatments for chronic pain have limited efficacy and undesirable side effects, particularly when used long-term [1]. Relief of *acute* pain is relatively straightforward, and pharmacological approaches range from over-the-counter pain relievers such as nonsteroidal anti-inflammatory drugs (NSAIDs), to prescription drugs, such as opioids, which can provide powerful pain control. Management of *chronic* pain conditions, on the other hand, is much more challenging. Many chronic pain conditions are without apparent underlying physical injury, or develop after a primary injury has healed, making targeted treatments or surgical interventions difficult. Moreover, pharmacological therapies used for acute pain are generally less effective in chronic pain conditions. For example, opioids, one of the most powerful classes of analgesics, become less effective over time, and the accompanying side effects, such as constipation, respiratory depression, and dependence, become more severe. The risk of addiction is also a factor. Alternatives, such as serotonin-norepinephrine reuptake inhibitors and anticonvulsants, act centrally, and show benefits in treating some pain conditions, although these approaches themselves have undesirable side effects.

These clinical challenges highlight the complexity of pain as a sensory experience, and argue for understanding the circuitry underlying different persistent pain states as the basis for therapeutics. The present review will discuss recent findings related to the role of "descending control systems" in persistent pain. These systems, with important links in the brainstem and descending projections to the dorsal horn, are known to modulate spinal nociceptive processing. "Bottom-up" and "top-down" inputs to the descending pain-modulating system allow sensory information (bottom-up) and cognitive and emotional factors

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(top-down) to influence nociceptive processing and pain perception [2–4].

Dysfunction in Descending Control Contributes to Persistent Pain States

There is now increasing evidence that persistent pain states are, at least in part, a reflection of dysfunction in descending control systems [5, 6]. This is most amply documented using the "conditioned pain modulation" (CPM) paradigm, in which a painful stimulus delivered to one part of the body suppresses the pain resulting from a standardized noxious stimulus applied at a remote site. An impaired ability to mount a CPM response is a frequent characteristic of patient populations with chronic pain [6–8]. This concept is supported by complementary studies in animal models measuring "diffuse noxious inhibitory control" (DNIC), the phenomenon of descending inhibition of the dorsal horn sensory neurons when a painful stimulus is applied to a remote body part outside of the recorded neuron's receptive field [9]. The mechanism of DNIC involves a complex brainstem circuit that includes both an ascending limb from the dorsal horn to caudal brainstem, and a descending limb from both the caudal medulla and the rostral ventromedial medulla [10, 11]. A reduction in DNIC has been demonstrated to be associated with hyperalgesia in models of postsurgical pain, nerve injury, traumatic brain injury, and opioid-induced sensitization [12–15] (Fig. 1).

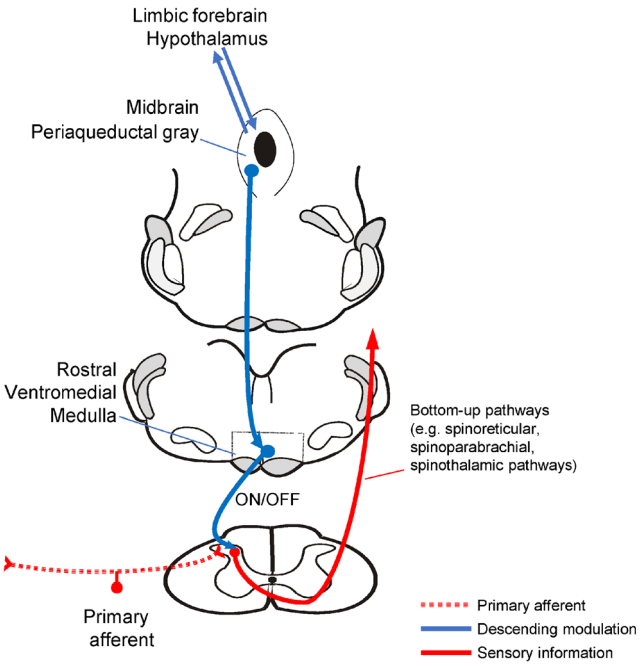

Fig. 1 The PAG-RVM descending pain-modulating pathway exerts facilitatory and inhibitory drive on dorsal horn neurons. The output of this pathway can be influenced by higher structures, such as hypothalamus and limbic forebrain

Physiology of Brainstem Circuits Mediating Descending Control

Extensive work from numerous laboratories has gone into characterizing the connectivity, physiology, and function of descending pain control circuitry over the last 30 years. (See Heinricher and Fields [2] for an overview of this circuitry.) It was recognized as early as 1969 that electrical stimulation of specific brainstem structures, such as the midbrain periaqueductal gray (PAG), produces analgesia and inhibits nociceptive neurons in the dorsal horn. This analgesic influence of the PAG is not mediated by a direct projection from PAG to the dorsal horn, but through a relay referred to as the "rostral ventromedial medulla" (RVM). The RVM, encompassing the area of the raphe magus and surrounding reticular region at the level of the facial nucleus, has been established as the major output node in descending modulation of nociception. As with the PAG, electrical stimulation of the RVM produces potent analgesia. The RVM receives a dense input from the PAG, and sends diffuse bilateral projections to the dorsal horn with terminations at multiple levels. The PAG-RVM system remains the best-studied circuit for descending pain modulation, and there is every reason to think that it is functionally the most significant.

Based on the early studies demonstrating the analgesic effects of electrical stimulation in both PAG and RVM, the PAG-RVM circuit was initially viewed as an "analgesia system" [16–18]. However, subsequent studies revealed that RVM modulates nociception in a bidirectional manner, and that it can facilitate as well as inhibit pain [19, 20]. The capacity for bidirectional control derives from two classes of RVM neurons referred to as "OFF-cells" and "ON-cells" [2], which are described in more detail below. Overwhelming evidence has demonstrated that OFF-cells exert a net inhibitory effect on nociceptive transmission, whilst ON-cells have a net pronociceptive action [3, 21].

The OFF- and ON-cell designations arise from the fact that OFF-cells cease firing, or "turn off" when an animal responds to a noxious stimulus, whereas ON-cells are activated or "turn on" in association with responses to noxious stimuli. Although non-selective activation of all RVM neurons produces analgesia, selective activation of ON-cells results in hyperalgesia [22]. Exogenous activation of OFF-cells or elimination of the OFF-cell pause is sufficient to produce antinociception, and it has been estimated that activation of as few as 30 OFF-cells produces behaviorally measurable analgesia [23, 24]. ON- and OFF-cell activity is usually antiphase-synchronized under unstimulated conditions, having alternating periods of silence and activity [25]. The nocifensor withdrawal–related ON-cell burst of activity and OFF-cell pause in firing are also antiphase-synchronized [26]. Thus, output from the two cell classes modulates nociceptive transmission at the level of spinal dorsal horn in a parallel fashion, where the withdrawal threshold for the

organism is in part determined by collective activity across the two cell populations.

One recurring question that has arisen in the study of the PAG-RVM system is whether this system truly modulates pain, or whether it is instead simply controlling output of nocifensor reflex circuits. Multiple lines of evidence argue against this latter view. First, although RVM terminals are not limited to the dorsal horn, projections of OFF- and ON-cells to the dorsal horn have been identified, including interactions with primary afferent terminals [27, 28••]. Second, activity of RVM neurons is well correlated with activity of dorsal horn nociceptive neurons, and less strongly linked to motor output [29, 30]. Third, manipulations of RVM can be demonstrated to modulate the affective dimension of pain, and not simply spinal reflexes [31••, 32]. Finally, stimulation of the PAG in humans produces subjective reports of analgesia, not simple motor inhibition [33]. Viewed as a whole, these data strongly support the idea that the brainstem descending control system modulates nociception *as a sensory system*.

An important challenge to analysis of RVM circuitry has been the difficulty of applying genetic tools to the two cell classes, since neither OFF-cells nor ON-cells, as a class, express a specific neurotransmitter. Over half of both the OFF- and ON-cell classes are GABAergic, implying that function derives from connectivity rather than cell "type" [34]. Indeed, it is likely that GABAergic ON-cells facilitate nociception by inhibiting GABA-mediated circuits at the level of the dorsal horn [35••]. There is also recent evidence suggesting that co-localization of enkephalin with GABA might be a marker for OFF-cells, since specific activation of RVM GABA+enkephalin neurons produced antinociception [28••]. Verifying this possibility will require significant additional analysis. This is because, as already noted, co-activation of ON-cells and OFF-cells produces antinociception, thus the possibility that some GABA+enkephalin neurons are ON-cells cannot be ruled out. In addition, a subset of ON-cells may be serotonergic, although not all serotonergic neurons in RVM are ON-cells [36, 37].

Plasticity in RVM Descending Control and Persistent Pain States

The last decade has seen increasing evidence that plasticity in RVM pain-modulating circuits contributes to persistent pain. Understanding the role of the RVM in persistent pain has necessarily been complicated by the fact that increased pain or lowered pain threshold could reflect an increase in ON-cell activity, a decrease in OFF-cell output, or, and most likely, a combination of these two factors.

Increased ON-cell ongoing activity has been associated with hyperalgesia in a number of *acute* inflammatory pain models. Localized hindpaw injection of inflammatory agents results in immediate hyperalgesia with increased ON-cell and decreased OFF-cell activity. Blocking ON-cell activation reduces hyperalgesia under these conditions [38–40]. Similarly, visceral acute inflammation induced by application of capsaicin increases ON-cell ongoing activity, and decreases the threshold for nociception-evoked hindpaw withdrawal [41]. Taken together, these results demonstrate the contribution of descending facilitation mediated by RVM ON-cells to *acute* inflammatory pain.

The situation becomes more complex as inflammation persists beyond a few hours. Hypersensitivity to non-noxious tactile stimulation ("mechanical allodynia") is maintained, but animals show fewer behaviors indicating ongoing spontaneous pain [42–45]. The timing of this change in the nature of behavioral hypersensitivity correlates with plasticity in RVM. Beginning 1 day after CFA injection, there is an upregulation of AMPA receptors, and activating these receptors enhances descending inhibition and attenuates hyperalgesia [46]. RVM κ- and μ-opioid receptor-mediated descending inhibition is also enhanced [47–49], whereas GABA inhibition may be reduced [50].

In parallel with these molecular changes, there is a restoration of normal levels of ongoing OFF- and ON-cell activity. Blocking RVM once inflammation is established potentiates, rather than blocks hyperalgesia, as in acute inflammation. The increased hyperalgesia with RVM block in persistent inflammation suggests that the restoration of OFF-cell ongoing output serves as a compensatory adaptation that limits hyperalgesia in persistent inflammation [39].

The idea that RVM limits hyperalgesia is important, and consistent with the notion that dysfunction in descending control contributes to significant chronic pain in both animal models [51] and patients with chronic pain [5]. Indeed, functional imaging studies are providing increasing evidence that functional connectivity with descending control systems, most notably the PAG, is depressed in chronic pain states [52, 53•, 54].

How Is Descending Control Engaged by "Bottom-Up" and "Top-Down" Processes?

Given the evidence outlined above for the importance of brainstem descending control processes in both normal and pathological pain processing, and the now clear role of RVM OFF- and ON-cells in suppressing and enhancing pain, the key question to be answered now is how these systems are engaged to modulate pain in response to different challenges.

"Bottom-Up" Modulation of Descending Control by Sensory Input

It has long been recognized that RVM neurons both *modulate* and *respond* to noxious stimuli. Indeed, as described above, OFF- and ON-cells are defined by their nociception-related responses: ON-cells increase firing, creating a "burst" of

activity, while OFF-cells abruptly "pause" firing in a reciprocal manner [55]. The pathway through which nociceptive information gains access to OFF- and ON-cells was recently identified, with the demonstration that the parabrachial complex (PB) is the primary relay of acute noxious stimuli to the RVM [56, 57] (Fig. 2. Interestingly, the PB projection to RVM is distinct from the projection to the central nucleus of amygdala, which is thought to be important in the affective dimension of pain [57, 58]. OFF- and ON-cells are thus part of a recurrent circuit, with inputs from, as well as projections to, the dorsal horn. However, whether spinoparabrachial neurons that send information to RVM via PB are themselves directly modulated by RVM descending projections has not been investigated.

Plasticity in Parabrachial Relay to the RVM in Persistent Inflammation

The PB input to RVM may play an important role in the transition from acute to persistent pain. Under basal conditions or in acute inflammation, blocking PB contralateral to a stimulated paw interferes with the OFF-cell pause and ON-cell burst evoked by that stimulation, and has a hypoalgesic effect. At later time points, blocking PB *contralateral* to an inflamed paw does not reliably interfere with OFF- and ON-cell responses, and has no effect on nociceptive behavior. Instead, blocking PB *ipsilateral* to the site of inflammation prevents the OFF-cell pause and ON-cell burst evoked by stimulation of the inflamed paw, and reverses hyperalgesia [59••]. PB *ipsilateral* to the inflamed paw thus conveys nociceptive information to RVM during persistent inflammation, maintaining the hypersensitivity of ON- and OFF-cells to innocuous stimuli. These findings indicate that the PB ipsilateral to an inflamed site has the capacity to provide nociception-related input to RVM ON- and OFF-cells, but that this input is only recruited or unmasked in persistent inflammation [59••] (Fig. 2).

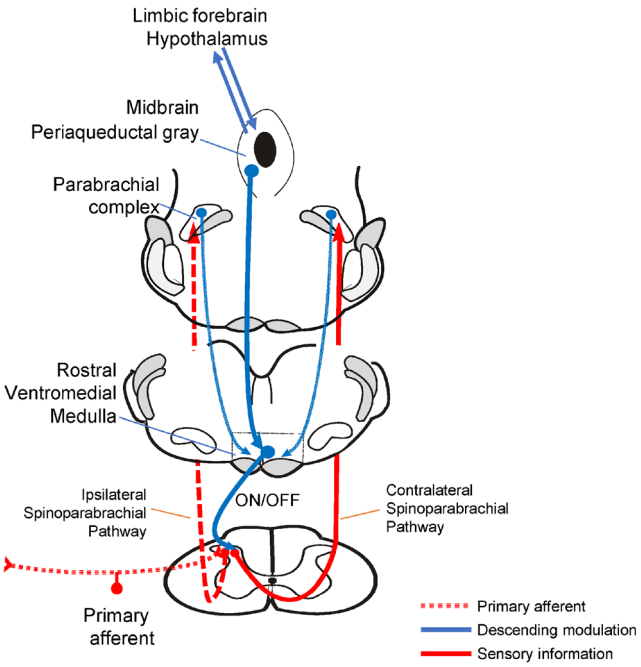

Fig. 2 The RVM, the output node of the descending modulatory pathway, can also be modulated by ascending sensory input, specifically that relayed through the parabrachial complex (PB). The contralateral PB relays information related to in acute pain to RVM, whereas the ipsilateral PB is recruited in chronic pain

"Top-Down" Modulation of Descending Control

A key advance over the past decade has been increasing recognition and acceptance of "top-down" mechanisms for pain modulation. These mechanisms have the potential to give us a rational neural basis for cognitive and emotional modulation of pain. The placebo response, for example, has sometimes been viewed as undermining the reality of pain as mere "subjective" experience. However, an important line of research that has emerged in recent years combines sophisticated psychophysical analysis with imaging to implicate altered functional connectivity of prefrontal and insular cortex with descending control circuits as the underlying mechanism for both placebo and nocebo responses [8, 60–62].

Animal studies are now also beginning to elucidate the role of these higher structures in pain and descending control. A recent focus has been prefrontal areas including "medial prefrontal cortex" (mPFC) and anterior cingulate cortex (ACC) [63], and there is considerable evidence to support a role for these areas in pain processing, and specifically in engagement of descending control. As early as1985, electrical stimulation of the mPFC/ACC region was shown to have an analgesic effect, with inhibition of both the tail flick response (considered a spinal reflex) and the hot plate test (considered to be organized supraspinally) [64]. Consistent with the idea of mPFC exerting descending inhibitory control, Cheriyan and Sheets [65••] showed that mPFC neurons projecting to the PAG exhibited reduced excitability in an animal model of nerve injury pain. This finding could support the concept of dysfunction in descending control in pathological pain states, with reduced "top-down" recruitment of descending inhibition from the PAG. More recently, Zhuo and colleagues have focused on the ACC. Unlike the earlier report of antinociception with stimulation in mPFC/ACC, Zhuo and colleagues report *facilitation* of the tail flick reflex with stimulation in this area, albeit at high stimulus currents (100 μA). This pro-nociceptive effect was relayed through the RVM [66]. They also provide evidence for a facilitatory influence that is *not* mediated by the RVM, possibly involving a direct projection from ACC to the spinal cord. This RVM-independent facilitation produces an enhancement of synaptic transmission and increased expression of *c-fos* in laminae III

through V [67, 68]. However, the behavioral relevance of this projection has not yet been documented. It is also important to recognize that pain-related affect can be selectively modulated by manipulations of ACC through mechanisms that do not invoke descending control [31, 69–71]. These changes in pain affect presumably reflect alterations in pain transmission rather than engagement of pain-modulating circuits.

Conclusion: Descending Control and Chronic Pain

Acute pain has long been recognized as being adaptive, and appropriate responses to tissue-damaging inputs, including withdrawal from the immediate stimulus, are generally accorded high behavioral priority. However, typical responses to painful stimuli may sometimes be actively suppressed when other needs take precedence. The phenomenon of "stress-induced analgesia," in which a severe and immediate threat inhibits pain sensation despite significant injury has been well documented [72, 73]. Although stress-induced analgesia can take a number of forms, at least in some cases, it appears to be mediated through recruitment of RVM OFF-cells via opioid-dependent mechanisms in the basolateral amygdala [74, 75]. In contrast with intense stress and fear, mild stress can exacerbate pain. This "stress-induced hyperalgesia" is mediated by RVM ON-cells recruited via the dorsomedial nucleus of the hypothalamus, a structure known to engage autonomic and behavioral aspects of the response to mild stress [76–78].

As with intense stress, hunger can similarly inhibit pain behaviors [79, 80], and the interaction between hunger and pain depends on the palatability of the available food [81]. Alhadeff and colleagues [82•] recently provided a potential circuit-level explanation for this phenomenon, showing that activation of hypothalamic neurons expressing agouti-related peptide (AgRP) suppressed pain behaviors evoked by acute localized inflammation via a connection with the parabrachial complex. Interestingly, this antinociceptive effect was confined to pain evoked by an inflammatory stimulus, and behaviors evoked by an acute thermal stimulus were not inhibited by activation of the AgRP neurons. Instead, the opposite occurred such that activity of the AgRP neurons was suppressed by the noxious thermal stimulus.

Like the opposing effects of intense and mild stress, the balance between pain and hunger highlights the interesting challenge of how to tease out the mechanisms through which a particular behavioral context engages distinct circuits to enhance or suppress pain. The delineation of the PAG-RVM system and analysis of its outputs provides a firm foundation upon which to stand while we ask these key questions. While there can be no question that modulating pain processing based on other behavioral priorities can be adaptive [83], it is now clear that dysfunction of such a modulatory system can contribute to pathological pain conditions. A better understanding of the interface between pain transmission and pain modulation will be an essential element in elucidating the mechanisms of chronic pain.

Compliance with Ethical Standards

Conflict of Interest MMH is supported by grants from the National Institutes of Health (NS098660, DA042565, AA025024).

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