RVM Modulates a Variety of Painful Conditions and Therapeutic Approaches

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Abstract. The article explores the complex role of the rostral ventromedial medulla (RVM) in pain modulation mechanisms and its correlation with neural activity and pain behavior. As a crucial relay station in the descending pain modulation system, the RVM can both amplify and attenuate pain signals. The review discusses how RVM regulate various types of painful conditions. Specifically, it examines RVM involvement in regulating neuropathic pain induced by chemotherapy, migraine, temporomandibular joint syndrome (TMJ), stress-induced pain, sickle cell disease (SCD) pain and stomofacial pain. Additionally, we explores which treatments can activate RVM and related neural circuit to modulate pain perception, such as exercise analgesia, transcutaneous electrical nerve stimulation (TENS), electroacupuncture, transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS). These therapeutic approaches harness the RVM's ability to regulate pain perception and improve pain-related behaviors.

Keywords: Rostral ventromedial medulla (RVM); Pain modulation; Chemogenetics; Neuropathic pain; Deep brain stimulation (DBS).

1 Introduction

The rostral ventromedial medulla(RVM) plays a crucial role in pain modulation, serving as a pivotal relay for both amplifying and attenuating pain signals[1]. RVM is an essential component of the pain controlling pathway, functioning as a key output element[2]. RVM alleviates pain by impeding the transmission of noxious stimuli. We examined the regulatory role of RVM in various pain conditions and investigated treatments that can activate RVM and its associated neural circuits to modulate pain perception[3].

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2 RVM Regulates Various Types of Pain

2.1 RVM Regulates Chemotherapy-Induced Neuropathic Pain

Chemotherapy-induced neuropathic pain refers to the pain that arises as a consequence of chemotherapy treatment. It typically presents as a burning, tingling, or stabbing sensation and is attributed to damage to peripheral nerves caused by chemotherapy drugs.

Costa-Pereira et al. investigated the serotonergic pain modulation mechanism in chemotherapy-induced neuropathy (CIN), with a focus on the RVM and spinal 5-HT3 receptors (5-HT3R). Male Wistar rats were divided into two groups and administered paclitaxel or vehicle. One month later, the activation of RVM neurons and serotonergic activity was examined. Immunohistochemical detection revealed higher levels of pERK activation in rats treated with paclitaxel. Dual immunohistochemistry showed elevated TpH levels in these animals, co-localized with pERK, indicating increased serotonergic activation of RVM neurons. HPLC measurements indicated higher levels of 5-HT in the spinal dorsal horn of rats treated with paclitaxel, and immunohistochemistry demonstrated an increase in 5-HT content in I-II layers. Additionally, elevated 5-HT3R levels were observed in the I-II layers. The use of the 5-HT3R antagonist oxytocin reversed mechanical and cold hypersensitivity as confirmed by von Frey and cold plate tests, supporting that CIN involves enhanced RVM downward regulation affecting the serotonergic system of the spinal cord; among which, involvement of 5-HT3R in pain hypersensitivity was noted[4].

2.2 RVM Regulates Migraine

Migraine is a neurological disorder characterized by recurrent, severe headaches that occur in cycles and are often accompanied by symptoms such as nausea, vomiting, sensitivity to light and sound[5].

Recent neuroimaging studies, particularly those using functional MRI (fMRI), have provided insights into how acupuncture may help prevent migraines. Chang CM et al.'s review suggests that verum acupuncture normalizes the connectivity of several brain networks that are typically disrupted in migraine sufferers. This includes the frontal-parietal network, RVM-trigeminocervical complex (RVM/TCC), and others, which are all linked to the pain matrix. Verum acupuncture's ability to restore this connectivity is more pronounced than that of sham acupuncture, offering a potential mechanism for its prophylactic effects in migraine treatment. These findings underscore the therapeutic potential of acupuncture and its role in modulating central nervous system activity in migraine prevention[5].

2.3 RVM Regulates the Temporomandibular Joint Syndrome (TMJ)

Temporomandibular Joint Syndrome (TMJ) encompasses a range of conditions impacting the temporomandibular joint (TMJ) and its surrounding musculature. This condition

commonly presents with pain in the jaw, face, and neck, along with challenges in chewing and mouth opening. Symptoms may include audible clicking or popping from the jaw joint, headaches, and muscle rigidity.

Mills EP et al. investigated the brainstem pain regulation circuitry in chronic non-neuropathic pain, focusing on temporomandibular joint (TMJ) disorders. Their findings revealed that compared to the control group, TMJ patients exhibited significantly increased static functional connectivity between the RVM and SRD/SpV. No disparities were observed in other brainstem regions, such as the midbrain tegmentum and locus coeruleus. Furthermore, TMJ patients displayed greater variability in dynamic functional connectivity between the RVM and SRD/SpV. These alterations may potentiate the downward facilitating effect and exacerbate ongoing pain transmission[6].

2.4 RVM Regulates Painful Trigeminal Neuropathy

Chronic pain, particularly following nerve injury, can persist in the absence of an external trigger. Although the pain may endure, its intensity typically fluctuates. Animal studies indicate that brainstem circuits modulating pain signal synapses may perpetuate abnormal persistent pain in the nervous system.

Mills EP et al. conducted an fMRI study on 19 patients with trigeminal neuralgia pain to investigate whether changes in spontaneous pain intensity impact the regulation of pain circuits in the brainstem. They observed that high-intensity pain was linked to increased connectivity between the midbrain PAG, RVM, and the spinal trigeminal nucleus (SpV), while low-intensity pain showed decreased connectivity. Sliding window analysis revealed that during the 12-minute scan period, sustained high-intensity pain exhibited a positive correlation with RVM-SpV connectivity. These findings suggest that dynamic changes in the brainstem lead to fluctuations in chronic neuropathic pain intensity[7].

2.5 RVM Modulates Stress Induced Pain

Modulating the RVM has been demonstrated to alleviate pain and depression-related behaviors induced by stress. During chronic social defeat stress (CSDS), chemogenetic activation of the RVM can mitigate symptoms. Conversely, chemical genetic inhibition of the RVM heightens susceptibility to these stress-induced symptoms. Prolonged suppression of the RVM may lead to chronic pain without depressive-like behaviors. These findings underscore the significance of the RVM in the comorbidity of chronic pain and depression and its association with behavioral responses elicited by social stress.[8].

Repetitive psychological and physiological stress often results in stress-induced hyperalgesia (SIH), which increases pain sensitivity. Imbe H conducted a study on the neural mechanisms of SIH by examining the expression of MOR mRNA, MeCP2, and global DNA methylation in the dorsal raphe nucleus (RVM) following repeated restraint stress. Dermorphin-SAP neurotoxin was administered into the RVM. The findings indicated that repeated restraint stress caused mechanical hypersensitivity and elevated expression of MOR mRNA and MeCP2 in the RVM, while reducing global DNA methylation levels. In stressed rats, there was a decrease in MeCP2 binding to the

MOR gene promoter. However, injecting dermorphin-SAP into the RVM prevented stress-induced mechanical hypersensitivity, suggesting that MOR-expressing neurons in the RVM are involved in SIH[2].It was also found that the activation of RVM by PAG-derived nerve fibers has a suppressive effect on CRS-induced hyperalgesia [9].

2.6 RVM Regulates Sickle Cell Disease (SCD) Induced Pain

Sickle cell disease (SCD) is associated with acute and chronic pain. Rogers VM et al. [10] conducted a study on the role of RVM in SCD-related hypersensitivity pain using mice. They found that injecting lidocaine into RVMs in mice with the disease-like state eliminated their mechanical and thermal hypersensitivity, but was ineffective in normal C57BL6 mice, indicating that RVMs play an important role in maintaining SCD-related pain. By conducting electrophysiological analysis on ON, OFF, and Neutral cells in RVMs, they found that the proportion and spontaneous activity of these cells were not significantly different between mice with the abnormal state and the control group. However, ON cells in mice with the abnormal state responded to temperature and mechanical stimuli approximately three times more than normal mice, indicating that RVMs enhance SCD-related hypersensitivity by increasing ON cell-dependent conduction[11].

2.7 RVM Regulates Dental Pain and Facial Discomfort

Piraiprasart K et al. investigated how stress contagion influences pain perception within mouse masseter muscles. Following a period of ten days cohabitating with conspecifics exhibiting stress-related behavior, observers displayed heightened anxiety and behaviors resembling oral inflammation on day 11. Stimulation of the masseter muscles resulted in augmented immune responses involving c-Fos and FosB within the upper cervical spinal cord region. In mice experiencing stress contagion, there was an elevation of c-Fos expression specifically within regions such as RVM (medial prefrontal nucleus), notably within lateral prefrontal nucleus as well as raphe magnus nuclei areas; accompanied by elevated levels of serotonin (5-hydroxytryptamine) along with an increase in serotonin-positive cell count observed within these regions too - indicating potential involvement therein related to social defeat-induced hyperalgesia mechanisms[10]. As show in Table 1.

Table 1. RVM regulates various types of pain.

Pain types	RVM and related structure	Changed	RF
Chemotherapy-induced neuropathy	RVM -spinal cord	Activity- 5-HT↑ 5-HT3R↑	[4]
Migraine	RVM-TCC	FC ↓	[12]
TMJ	RVM-SRD RVM-SpV	FC↑	[6]

Painful trigeminal neuropathy	RVM-SpV	FC↑	[7]
Stress induced pain	RVM	Activity-	[8]
	RVM	MOR mRNA↑ MeCP2 ↑ DNA methylation↓	[2]
	PAG-RVM	Activity-	[9]
SCD induced pain	RVM	ON cell↑	[11]

Notes: (+) indicates activation, (-) indicates inhibition; (↑) represents increase, (↓) represents decrease; RVM: rostral ventromedial medulla; TCC: trigeminocervical complex; TMJ: temporomandibular joint syndrome; FC: functional connectivity; SRD: subnucleus reticularis dorsalis; SpV: the spinal trigeminal nucleus; SCD: sickle cell disease; RF: Reference

3 RVM Addresses a Wide Range of Pain Conditions

3.1 Exercise Analgesia

Regular physical exercise or activity can effectively alleviate chronic pain, and this relief is non-pharmacological. Central inhibitory mechanisms, including serotonin and opioid substances, play a crucial role in the pain-relieving process induced by exercise, as the RVM projects to the spinal cord and regulates pain neurons.

Sluka KA et al. investigated the impact of regular physical activity on the RVM-spinal cord circuit. Their findings indicate that, in comparison to sedentary animals, exercised animals exhibited a reduced number of mu-opioid receptor-positive neurons projecting from the RVM to the spinal cord, while there was no change in the number of neurons in the raphe obscurus/raphe pallidus and TPH. These results suggest that regular exercise has the potential to modify central facilitation, decrease downward facilitation, and enhance inhibition[13].

3.2 Transcutaneous Electrical Nerve Stimulation (TENS)

Although both traditional high-frequency low-intensity transcutaneous electrical stimulation (TES) and low-frequency high-intensity acupuncture-like TES have demonstrated pain-relieving effects, controversies persist regarding their neural mechanisms within human physiology. In a controlled study involving 60 healthy volunteers led by Bi Yu et al., functional magnetic resonance imaging (fMRI) was employed to assess alterations in pain perception, brainstem activity measured by low-frequency amplitude fraction (fALFF), as well as changes in resting-state functional connectivity (RSFC). Conventional TES solely alleviated forearm pain while reducing brainstem activity alongside RSFC with contralateral primary somatosensory cortex. Conversely, acupuncture-like TES induced broad analgesic effects along with heightened activity

within superior longitudinal fasciculus and retrosplenial complex regions; it also decreased RSFC between superior temporal gyrus & inferior frontal gyrus as well as between superior temporal gyrus & lingual gyrus. These findings elucidate distinct analgesic pathways for conventional TES versus acupuncture-like TES beyond spinal cord levels[14].

3.3 Electroacupuncture (EA)

Guo P et al. discovered in their research that EA is significantly effective in the treatment of visceral hypersensitivity (VH). They observed the effects of EA on Housanli, evaluated its impact on the expression of PPAR2 and PPAR4 in the PAG, RVM, and SDH, as well as its effects on pro-inflammatory cytokines IL-1β and TNF-α, COX-2 enzyme, c-Fos, neuropeptide CGRP, and SP in the descending pain regulation system.

In this research, the investigators induced heightened sensitivity in the goat ileum walls by administering a TNBS-ethanol solution. They observed significantly elevated visceral motor response (VMR) and pain response scores in the TNBS group. Furthermore, compared to the control group, there was a significant increase in protein and mRNA levels of PAR2 and PAR4 in the downstream pain regulation system in the TNBS group.

EA decreased pain in the lumbar and sacral areas as well as visceral mechanical hyperalgesia responses, reduced PAR2 protein and mRNA levels, and elevated PAR4 levels. This impacted the pain regulation system situated in the lumbar and sacral regions, encompassing the SCDH, RVM, and PAG in the midbrain, thereby influencing mechanisms associated with visceral hypersensitivity[15].

3.4 Transcranial Direct Current Stimulation

Knee osteoarthritis (KOA) is a prevalent cause of persistent pain, associated with the descending pain modulation system. Ye et al. conducted a study on the application of transcranial direct current stimulation (tDCS) as a modality for managing KOA pain and its analgesic mechanism. They investigated the correlation between chronic KOA-induced pain and the BDNF/TrkB signaling pathway, while assessing the impact of tDCS on this pathway. The findings indicated that tDCS upregulated the expression of BDNF and TrkB along the PAG-RVM-SDH axis, suggesting that enhancing the BDNF/TrkB signaling pathway within this system could significantly alleviate chronic KOA-induced pain, with tDCS potentially mitigating associated discomfort by modulating the BDNF/TrkB signal in this pathway[16].

3.5 Deep Brain Stimulation (DBS)

In previous research, the impact of deep brain stimulation (DBS) in the ventrolateral parabrachial area (vlPAG) on a neuropathic pain model induced by nerve injury was assessed in male Sprague-Dawley rats. The findings revealed that 5 Hz DBS mitigated mechanical hyperalgesia and activated neurons in the RVM, facilitating recovery of the

impaired descending serotonin system. At the spinal level, glial cells remained activated, but only 5-HT1a receptors were stimulated, indicating their involvement in inhibiting mechanical hyperalgesia. This underscores the influence of neuropathic pain on the descending serotonin system in the RVM and suggests that long-term vlPAG stimulation may effectively modulate this pathway, potentially with fewer side effects than high-frequency stimulation or prolonged pharmacotherapy for targeted treatment[17]. As show in Table 2.

Table 2. RVM addresses a wide range of pain conditions

Treatment	RVM and related structure	Changes	RF
Regular physical activity	RVM-spinal projections	Mu-opioid receptor-expressing↓	[13]
Acupuncture-like TENS	SRD-RVM	Activity +	[14]
Electroacupuncture	RVM,PAG,SDH	PAR2↓ PAR4↑	[15]
Transcranial direct current stimulation	PAG-RVM-SDH	BDNF↑ TrkB↑	[16]
Deep brain stimulation	RVM	Activity +	[17]

Notes: (+) indicates activation, (-) indicates inhibition; (↑) represents increase, (↓) represents decrease; SRD: subnucleus reticularis dorsalis; RVM: rostral ventromedial medulla; PAG: periaqueductal gray; SDH: spinal dorsal horn; BDNF: Brain-Derived Neurotrophic Factor; TrkB: Tropomyosin receptor kinase B; RF: Reference.

4 Conclusion

RVM is a pivotal hub in pain modulation, with the unique ability to both enhance and diminish pain signals through descending pathways. The article highlights its crucial role in pain regulation, particularly its effectiveness in reducing tactile hypersensitivity via chemogenetics and its contribution to the management of neuropathic pain from diverse conditions, including chemotherapy-induced pain, migraines, TMJ, SCD, and orofacial pain.

The therapeutic potential of the RVM is further emphasized through the examination of various interventions, such as exercise-induced analgesia, TENS, EA, tDCS, and DBS. These methods demonstrate the RVM's capacity to alter pain perception and improve pain-related behaviors, paving the way for innovative pain management approaches.

Delving deeper into the neural circuits that govern pain offers a promising frontier in neuroscience. Gaining a more nuanced comprehension of RVM function within these circuits is pivotal for developing targeted approaches to pain relief. The advent of innovative modalities, such as optogenetics and chemogenetics, when applied to the RVM and its interconnected neural networks, introduces groundbreaking opportunities

for addressing specific pain conditions. These cutting-edge techniques have the potential to significantly augment our existing strategies for pain management, providing a richer and more effective toolkit for treating a diverse array of painful conditions.

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