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(REVIEW ARTICLE)

Research progress on studies on the vlPAG in pain modulation and electroacupuncture analgesia

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Abstract

The ventrolateral periaqueductal gray , located within the midbrain, is a brain region implicated in various physiological and pathological processes, including pain modulation. This area integrates nociceptive signals from multiple brain regions such as the prefrontal cortex, amygdala, and hypothalamus, and inhibits nociceptive input through descending pathways. It is also involved in the analgesic effects of electroacupuncture. This review summarizes and analyzes the role of this area in pain modulation and electroacupuncture-induced analgesia, offering insights into the central mechanisms underlying pain and electroacupuncture analgesia, as well as providing recommendations for future basic and clinical research.

Keywords: Ventrolateral periaqueductal gray; Pain; Electroacupuncture; Literature review

1. Introduction

Pain is a complex somatic and emotional experience involving not only sensory responses to actual or potential tissue damage, but also multidimensional components, including emotional, cognitive, and behavioral responses [1–3]. Owing to its critical role in disease diagnosis, clinical evaluation, therapeutic decision-making, and treatment monitoring, pain has long attracted extensive attention and is widely regarded as the “fifth vital sign” [4].

In traditional Chinese medicine (TCM), pain is generally classified under the category of “Bi syndrome.” Bi syndrome is thought to result from impaired circulation of qi and blood, obstruction of the meridians, deficiency of qi, blood, yin, and yang, and insufficient nourishment of the tendons and vessels. These pathological changes may be induced by external pathogenic factors, emotional disturbances, dietary imbalance, physical exhaustion, or traumatic injury [5]. Because of differences in etiology and pathogenesis, pain may present with diverse clinical manifestations, such as distending pain, stabbing pain, migratory pain, or dull pain. These symptoms may be accompanied by either moving or fixed pain and may be characterized by tenderness or resistance to pressure. In many cases, pain is aggravated by cold and relieved by warmth.

Electroacupuncture (EA), which combines traditional acupuncture with electrical stimulation, has been demonstrated to exert beneficial multidimensional effects on pain perception as well as pain-related emotion and cognition. Among the central mechanisms underlying pain modulation and EA-induced analgesia, the ventrolateral periaqueductal gray (vlPAG) has been shown to play a crucial role [6–9]. Therefore, this paper reviews recent advances in understanding the involvement of the vlPAG in pain regulation and electroacupuncture analgesia, with the aim of providing a reference for future basic and clinical studies on pain and EA-mediated analgesia.

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2. Anatomy and function of the vlPAG

Located in the mesencephalic tegmentum and surrounding the cerebral aqueduct, the periaqueductal gray (PAG) serves as an anatomical and functional interface between the forebrain and the lower brainstem. Functionally, the PAG is thought to integrate nociceptive information from the soma and visceral autonomic nerves with emotional and cognitive signals from the forebrain [10]. Animal studies have demonstrated that the PAG plays a central role in the homeostatic regulation of pain, anxiety, and autonomic function. Consistent with these findings, human imaging studies using structural and functional magnetic resonance imaging, functional connectivity analysis, diffusion-weighted imaging, and positron-emission tomography have largely confirmed the involvement of the PAG in pain modulation, anxiety-related behaviors, regulation of urinary and gastrointestinal functions, and autonomic nervous system control [11].

The ventrolateral PAG (vlPAG), located in the ventrolateral column of the PAG, is a key component of its longitudinal functional organization. Anatomically, the vlPAG receives descending projections from cortical regions such as the medial prefrontal cortex [12], as well as inputs from the amygdala and hypothalamus [13,14]. Its major descending targets include the rostral ventromedial medulla (RVM) [15], dorsal raphe (DR) [16], and dorsolateral pons [17]. Functionally, one of the best-established roles of the vlPAG is its participation in the descending pain modulatory pathway, namely the PAG–RVM–spinal dorsal horn circuit [18]. In addition, the vlPAG is critically involved in passive defensive behaviors, such as freezing, and also contributes to sleep regulation [19,20]. Taken together, the vlPAG may be regarded as a crucial hub linking pain modulation, emotion, defensive behavior, autonomic regulation, and sleep.

3. The role of vlPAG in pain regulation

3.1. Descending analgesic system

The vlPAG is a crucial relay region in the descending pain modulatory system and regulates nociceptive transmission primarily through the PAG–RVM–spinal cord pathway. Early evidence for this role came from the classic study by Osborne et al. [21], in which retrograde tracers were injected into the RVM and patch-clamp recordings were performed on PAG–RVM projection neurons in normal rats. Their results showed that the effects of opioids on these descending output neurons were broadly consistent with a disinhibition mechanism. Based on these findings, opioid-induced analgesia is considered to depend largely on vlPAG neurons projecting to the RVM. Subsequent studies further refined the anatomical basis of this pathway. By subdividing the PAG into four regions—the dorsomedial PAG , dorsolateral PAG , lateral PAG , and vlPAG—and combining this with retrograde tracing from the RVM, Yin et al. [22] demonstrated that the vlPAG contained the greatest number of RVM-projecting neurons and exhibited the strongest activation in a formalin-induced acute pain model. Together, these findings indicate that the vlPAG is the principal upstream subregion of the PAG–RVM descending pain regulatory pathway.

3.2. Opioid analgesia system

The vlPAG regulates pain perception by participating in the endogenous opioid analgesia system. In mouse models of morphine analgesia and morphine-conditioned placebo analgesia, Livrizzi et al.[12] reported that chemogenetic inactivation of a subset of excitatory neurons within the vlPAG abolished both morphine-induced analgesia and morphine-conditioned placebo analgesia. This finding indicates that excitatory neurons in the vlPAG represent a key cellular population required for the expression of opioid analgesia.Consistent with this view, the vlPAG also functions as an important hub for transmitting endogenous opioid analgesic signals. Using circuit tracing, fiber photometry, and pathway-specific manipulations in mouse models, Lubejko et al.[17] demonstrated that robust opioid analgesia critically depends on excitatory projections from the vlPAG to the locus coeruleus. Their results further support the notion that the vlPAG serves as a central node through which opioid analgesic effects are propagated to downstream brain regions.

3.3. Central sensitization of chronic pain

The vlPAG is not only a key component of the descending analgesia system but also contributes to central sensitization associated with chronic pain. In a rat model of persistent inflammatory pain, McPherson et al.[23] used ex vivo patch-clamp recordings combined with physiological classification of vlPAG neuronal subtypes and found that persistent inflammation selectively activated opioid-sensitive phasic vlPAG neurons, whereas acute inflammation did not produce the same effect. These findings suggest that chronic inflammation induces excitatory remodeling within specific neuronal subpopulations in the vlPAG, thereby implicating the vlPAG in chronic pain–related central sensitization. Supporting this conclusion, Lee et al.[24] performed morphological analyses, glial cell manipulation, and functional behavioral experiments in a rat model of diabetic neuropathic pain. They found that selective activation of astrocytes in

the vlPAG was associated with heightened pain sensitivity, whereas inhibition of astrocytic activation alleviated pain behaviors. These results indicate that, in addition to neurons, glial cells within the vlPAG also participate in the central sensitization processes underlying chronic pain.

3.4. Integration of cognitive, emotional and expectation signals

The vlPAG integrates cognitive, emotional, and expectation-related signals from other brain regions and thereby participates in the regulation of pain. In a mouse model of chronic pain, Yin et al.[25] used multiple tracing techniques, rabies virus–based trans-synaptic labeling, and optogenetic manipulation to identify an excitatory descending pathway from the dmPFC to the vlPAG. Selective activation of this pathway increased pain thresholds and reduced anxiety-like behaviors. These findings indicate that the vlPAG receives cognitive and emotional inputs from the prefrontal cortex and contributes to top-down modulation of pain. In a separate mouse model of chronic pain accompanied by anxiety-like behavior, Zhu et al.[26] selectively activated the glutamatergic projection from the rACC to the vlPAG and found that stimulation of this pathway induced both heightened pain sensitivity and anxiety-like behavior. These results suggest that the vlPAG not only integrates cortical inputs related to analgesia but also processes ascending cognitive and emotional signals that promote pain and negative affect.

4. Role of vlPAG in electroacupuncture analgesia

4.1. The vlPAG is recruited for EA analgesia

The vlPAG is an important brain region involved in the analgesic effects of electroacupuncture (EA). In physiologically normal rats, de Medeiros et al.[27] applied EA at Zusanli (ST36) and conducted pain-threshold behavioral tests along with c-Fos immunohistochemical staining in the PAG. They found that EA produced a significant analgesic effect accompanied by elevated c-Fos expression in the PAG, indicating neuronal activation. In a spared nerve injury (SNI) model of neuropathic pain, Zhu et al.[28] further demonstrated that reduced excitability of CamKIIα$^+$ neurons in the vlPAG contributed to pain maintenance, and EA treatment restored the excitability of these neurons. Moreover, inhibition of CamKIIα$^+$ neurons in the vlPAG abolished EA-induced analgesia, whereas activation of the same neuronal population partially reproduced the analgesic effect of EA. These findings suggest that CamKIIα$^+$ neurons in the vlPAG constitute a key effector cell population mediating EA-induced modulation of neuropathic pain.

4.2. The neural circuit mechanism of EA analgesia

Several studies have identified vlPAG-related neural circuits that participate in EA analgesia. Using retrograde viral tracing, chemogenetic manipulation of the rACC glutamatergic projection to the vlPAG, EA intervention, and behavioral assays of mechanical pain threshold and anxiety-like behavior in an SNI mouse model, Zhu et al.[26] reported that activation of the rACC^{Glu}–vlPAG pathway induced hyperalgesia and anxiety-like behaviors in otherwise normal mice. Conversely, inhibition of this pathway alleviated SNI-induced mechanical hyperalgesia and anxiety-like behavior. Further experiments showed that activating the rACC–vlPAG pathway could counteract the analgesic benefits of EA on mechanical hyperalgesia, but did not significantly diminish EA's anxiolytic effect. These results suggest that the rACC–vlPAG circuit is a key ascending cortex–midbrain regulatory pathway through which EA alleviates neuropathic pain, and that this pathway is more specifically involved in mediating EA-induced analgesia rather than its broader mood-improving effects. In a rat model of SNI neuropathic pain, Zhang et al.[29] employed in vivo fiber calcium imaging to assess rACC CaMKII-positive neuronal activity, chemogenetic manipulation of the rACC–vlPAG CaMKII pathway, EA intervention, and behavioral testing of pain and cognition. They found that inhibition of the rACC^{CaMKII}–vlPAG pathway alleviated neuropathic pain and long-term cognitive impairment, whereas pathway activation reversed the therapeutic effects of 2-Hz EA. These findings indicate that the rACC–vlPAG pathway is involved not only in maintaining chronic pain but also in modulating EA's therapeutic impact on pain-associated cognitive deficits. This provides new evidence that upstream cortical regulation of the vlPAG plays a direct role in the analgesic mechanisms of EA[29].

4.3. The molecular mechanism of the vlPAG involved in EA analgesia

On the basis of mechanistic studies on neuronal activity, the molecular mechanisms by which the vlPAG participates in electroacupuncture (EA) analgesia have gradually become clearer. Accumulating evidence indicates that the vlPAG is a key brain region mediating EA analgesia, and that its effects depend on local circuits involving GABAergic/glutamatergic neurons and CB1 receptor signaling. Zhu et al. [30] combined EA intervention, cell type-specific manipulation of GABAergic and glutamatergic neurons in the vlPAG, and selective interference with CB1 receptor function in a mouse model of pain sensitization. They found that EA inhibited GABAergic neurons while exciting glutamatergic neurons in the vlPAG. Notably, deletion of CB1 receptors in vlPAG GABAergic neurons almost completely abolished the analgesic effect of EA, whereas deletion of CB1 receptors in glutamatergic neurons only partially reduced it. These findings

suggest that EA analgesia largely depends on CB1 receptor-mediated regulation of the local GABA/glutamate neuronal circuit in the vlPAG. Further evidence was provided by Yuan et al. [31] in a mouse model of monoiodoacetate (MIA)-induced knee osteoarthritis. Using EA with different stimulation parameters, microinjection of the CB1 receptor antagonist AM251 into the vlPAG, and selective knockdown of CB1 receptors in either GABAergic or glutamatergic neurons, they showed that EA reversed the chronic pain-induced reductions in CB1 receptor expression and 2-AG levels in the midbrain. Intra-vlPAG injection of AM251 abolished the beneficial effects of EA on pain hypersensitivity and diffuse noxious inhibitory controls (DNIC). Moreover, deletion of CB1 receptors in GABAergic neurons blocked the EA-induced enhancement of DNIC and 5-HT-related descending inhibition in the medulla oblongata. These results indicate that EA may exert analgesic effects by strengthening the descending inhibitory system through the "2-AG–CB1R–GABA–5-HT" signaling pathway in the vlPAG, with CB1 receptors on GABAergic neurons playing a particularly important role. In addition to endocannabinoid signaling, inflammatory signaling pathways in the vlPAG also appear to be involved in EA analgesia. In a TNBS-ethanol-induced model of visceral hypersensitivity, Wan et al. [32] found that model animals exhibited diarrhea, enhanced visceromotor responses (VMR), increased pain behaviors, and elevated levels of IL-6, pJAK2, and pSTAT3 in the vlPAG and related brain regions. EA treatment significantly reduced the abnormal upregulation of these molecules in the vlPAG and along the PAG–RVM–SCDH axis, while also alleviating visceral hypersensitivity. These findings suggest that EA may suppress central sensitization and produce analgesia by inhibiting the IL-6/JAK2/STAT3 signaling pathway within the vlPAG-dependent descending pain modulatory system.

5. Conclusion

In conclusion, as a key brain region involved in central pain regulation and EA-induced analgesia, the vlPAG plays an essential role in the descending pain inhibitory system, the integration of neural circuits, and the modulation of molecular signaling pathways. In this review, we summarized and analyzed current evidence regarding the role of the vlPAG in pain regulation and the analgesic mechanisms of electroacupuncture, with the aim of providing a basis for further understanding the central mechanisms underlying pain generation and progression, as well as the neurobiological basis of EA analgesia. Nevertheless, further studies using multidisciplinary approaches are still needed to clarify the specific roles of vlPAG-related cell populations, neural circuits, and molecular networks under different pain conditions and EA intervention paradigms. Such efforts will provide a stronger theoretical foundation for the precise prevention and treatment of pain and for the optimization of EA in clinical practice.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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