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The Role of the Periaqueductal Gray in Pain Modulation and Electroacupuncture Analgesia: A Literature Review

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Abstract: *The article explores the complex role of the periaqueductal gray (PAG) in pain modulation mechanisms and its correlation with electroacupuncture (EA) analgesia. As a crucial relay station in the descending pain modulation system, the PAG can attenuate pain signals. The review discusses how PAG regulates various types of painful conditions and how PAG contributes to EA analgesia. Additionally, we explore the pivotal role of neurotransmitters and their receptors, such as GABA and GABA receptors, CB1 and OX1 receptors, TRPV1, nACh receptors, Toll-like receptor 4 (TLR4), and myeloid differentiation factor 2 (MD2), in orchestrating the PAG's analgesic effect， as well as EA analgesia. Finally, we investigated the role of PAG PAG-associated neural circuit for chronic pain. These therapeutic approaches harness the PAG's ability to regulate pain perception and EA analgesia. The purpose of this paper is to summarize the role and mechanism of PAG in pain regulation and EA analgesia in recent years, and propose prospects for follow-up research, with the aim of exploring new targets for PAG in pain regulation and tapping into the potential of EA intervention.*

Keywords: *periaqueductal gray (PAG); Pain modulation; electroacupuncture; GABA; CB*

1. Introduction

The periaqueductal gray matter (PAG) is the core structure of the midbrain, which is distributed around the brain aqueduct and can be divided into four subregions: medial, ventrolateral, dorsolateral, and dorsal. PAG receives input from multiple brain regions such as the anterior cingulate cortex, amygdala, and hypothalamus, and projects mainly to the ventromedial region of the medulla head and the dorsal horn of the spinal cord, forming the trunk pathway of the descending pain regulation system. In pain regulation, PAG bidirectional regulates the upward transmission of pain signals by releasing endogenous opioid peptides, GABA, and glutamate. In addition, PAG is also involved in the integration of autonomic function, emotional responses, and defensive behaviors, and is closely related to mood disorders such as anxiety and depression [1]. Electroacupuncture analgesia studies show that PAG is a key target for the action of electroacupuncture (EA). EA modulates various neurotransmitter systems and the receptor activity within the PAG. Recently, it was found that the regulation of PAG by EA involves multiple systems such as GABA energy, cannabinoid, and 5-HT, and can specifically activate neural loops [2] such as ARC-PAG. A deeper understanding of the mechanisms of PAG in pain and EA analgesia is important for the development of novel analgesic strategies.

2. The central role of the PAG in pain regulation

2.1. Regulation of different types of pain by the PAG

PAG is involved in the regulation of multiple pain through its heterogeneous neuronal populations and complex neural loops. Chen T[3] et al. found that glutamate/glutamine (Glx) levels in PAG were

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negatively correlated with pain scores in patients with new persistent daily headache (NDPH), suggesting the important role of excitatory neurotransmitters in pain regulation. Midbrain PAG (vlPAG) is a key downward pathway to regulate pain, fear, and anxiety. Assareh N[4] et al found that glycinergic neurons in the vlPAG were selectively regulated in GlyT 2: Cre mice, and that activation of these neurons increased cold and heat pain responses as well as motor activity, while inhibition of them reduced pain responses but did not affect movement. Yang L[5] In the diabetic neuropathic pain (DNP) model, et al. found that the activation state of vlPAG astrocytes was closely related to pain behavior, and that chemical genetic regulation of these cells could significantly improve hyperalgesia and anxiety-like behavior. In addition, PAG is also involved in the regulation of hormone-related pain. Geng X[6] et al. found that in the premenstrual anxiety disorder (PMDD) model, the Chinese medicine Shuyu capsule improved hyperalgesia and depressive behavior by regulating PAG neuronal activity and the expression of GABA A receptors.

2.2. The PAG contributes to EA analgesia

EA exerts analgesic effects by activating NMDA receptors and increasing the unit firing frequency, which may be related to the endogenous opioid substances released within the PAG. In addition, oxytocin (OT) in the PAG plays an important role in electroacupuncture analgesia, and its injection enhances the analgesic effect of electroacupuncture, which is blocked by anti-OT serum. Guo P [7] et al found that EA can alleviate VH symptoms by regulating PAR 2 and PAR 4 expression in the pain pathway, providing new insights into understanding the analgesic mechanisms of EA and providing potential targets for the development of new therapeutic approaches.

3. Role of PAG-related neurotransmitters and receptors in pain regulation and EA analgesia

3.1. GABA

Multiple neurotransmitter systems within the PAG together constitute a fine pain regulatory network. As the main inhibitory transmitter, GABA and its receptor activation can inhibit PAG output neurons, relieve the inhibition of RVM, and produce an analgesic effect. Manning CE[8] et al. showed that acute inflammation mainly affects the synaptic plasticity of GABA neurons in the ventral tegmental area (VTA), which in turn indirectly affects the activity of dopamine (DA) neurons. Wang W[9] et al. found that the neurochemical levels were altered in the PAG and dentate nucleus (DN) in chronic migraine patients, suggesting that the neurotransmitter changes in these areas may be related to the chronicity of migraine. Pati D[10] et al revealed a differential modulation of TNF-α on GABA and DA neurons in vlPAG, possibly affecting pain processing. Zhang W[11] et al. pointed out that the activation of NOX 4 in PAG in the rat model of Parkinson's disease (PD) leads to oxidative stress, which damages the GABA downward inhibition pathway and causes high pain sensitivity, while the inhibition of NOX 4 can relieve pain. De Andrade EM[12] et al. show that motor cortex stimulation (MCS) exerts analgesic effects by increasing glycine and GABA levels in PAG and that these neurotransmitters play a key role in PAG. Huang CP[13] et al found that EA increases GABA and GABA A receptors in PAG and decreases glutamate in the hippocampus, thereby relieving neuropathic pain. Winters[1] et al showed that opioids and cannabinoids regulate GABAergic synapses in the PAG through different mechanisms, providing a flexible way to control the descending analgesic pathway. Together, these studies highlight the important role of the GABAergic system in PAG in pain modulation and EA analgesic therapy.

3.2. Cannabinoid receptor 1 (CB1R)

The cannabinoid system has important physiological implications in PAG, especially in analgesia. Pereira AF[14] et al found that CB1R activation can reduce pain in oxaliplatin-induced peripheral sensory neuropathy, suggesting the endocannabinoid system as a therapeutic target for neuropathy. Llorente-Berzal A[15] et al revealed that there were sex differences in the PAG endocannabinoid system in fear-conditioned analgesia and even more pronounced analgesia in male rats. Wilson-Poe AR[16] et al found that inflammatory pain upregulates synaptic CB1R expression in PAG and enhances CB1R activity in ventrolateral PAG. Binda KH[17] et al noted that exercise can relieve pain symptoms in a rat model of Parkinson's disease by regulating cannabinoid receptors. Roberts CJ[18] et al. found that AEA microinjection into PAG in the dorsal midbrain reduced DHN activity and triggered sympathetic excitation, and this effect was mediated by CB1R to provide analgesia. Zeng X[19] et al

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showed that CB1R has potential value in preventing chronic migraine by alleviating central sensitization by regulating HCN2-pNR2B signaling in a rat model of chronic migraine. MaNQ [20] et al found that EA, the analgesic effect of the OX 1 R-CB1R pathway and was independent of opioids. Yuan X[21] et al showed that EA increased the expression of hemoglobin α chain and haemoglobin ocrit levels, and that microinjection of a related peptide in the ventrolateral PAG mimicked the analgesic effect of EA. Together, these studies highlight the important role of the cannabinoid system in PAG in pain modulation and EA analgesic therapy.

3.3. Serotonin (5-HT)

5-HT is a key neurotransmitter involved in the regulation of physiological processes and psychiatric disorders. Zhao YL[22] et al. found that 5-HT 5A receptors activated in the ventrolateral orbitofrontal cortex (VLO) could activate the descending inhibitory system of the brainstem through the inhibitory effect of GABAergic interneurons, thus inhibiting pain conduction at the spinal cord level of projection neurons. Hiroki T[23] et al showed that the reduction of morphine efficacy in neuropathic pain may be related to the activation of the descending serotonergic system and spinal 5-HT 3 receptors, which increases GABA levels and changes GABA A receptor function, thereby weakening the analgesic effect.

3.4. Opioid receptor (MOR) and cannabinoid receptor 1 (CB1R)

The PAG is the central hub for analgesia, in which serotonergic activity is influenced by other brain regions such as the paraventricular nucleus, amygdala, dorsal suture nucleus, and ventrolateral orbitofrontal cortex. Furthermore, activation of receptors within the PAG promotes the release of serotonin [24]. Datta U[25] et al found that CB1R PAMs may antagonize the effects of opioids in pain management, highlighting the complex interaction between opioid and cannabinoid systems within the PAG.de Oliveira HU[26] et al showed that the endocannabinoid system plays a role at both the peripheral and central level in TENS-induced anti-nociceptive properties. Barriere DA [27] et al found that acetaminophen exerts its analgesic effects by regulating neurotransmitter release in PAG and activating specific signaling pathways. DuY [28] et al showed that MOR in stress-induced analgesia functions in glutamatergic (MORGlut) ergic and GABAergic (MORGABA) neurons, in which MORGABA promotes analgesia, while MORGlut opposes analgesia, and stress intensity shifts the balance to a MORGABA-mediated process.

3.5. Nicotinic acetylcholine receptor (nACh)

The nACh is a class of membrane-spanning ligand-gated ion channels composed mainly of subunits including α, β, γ, δ, and ε. These receptors are expressed in the neuromuscular junction, in the central nervous system, as well as in the peripheral nervous system. The expression of nACh in regions such as the dorsal horn and thalamus is closely related to the transmission of pain signals. Alfonso-Rodriguez J[29] et al. found that EA exerts analgesic effects by increasing the expression of nicotinic acetylcholine receptors (nAChR α7 and β 2 isoforms) in the spinal cord and PAG, while reducing the levels of COX 2 and Iba 1 in the spinal cord. This finding provides new insight into understanding the role of EA in pain management.

3.6. Multi-target regulatory mechanism of the PAG-related receptor system in electroacupuncture analgesia

As an important component of the innate immune system, myeloid differentiation factor 2 (MD2) plays a unique role in EA analgesia. LiWR [30] et al. found that EA intervention could not only increase the number of MD2 + / c-fos + neurons in the superficial layer of the dorsal horn (layer I-IIo) of the spinal cord, but also bidirectional regulate the expression level of MD2 expression in different regions of the center. In the treatment of high visceral sensitivity, EA demonstrates the ability to accurately regulate the protease-activated receptor (PAR) subtype. The study of GeoP [7] et al revealed that EA re-established the physiological balance between both by simultaneously upregulating PAR 4 by downregulating PAR 2 expression in the PAG and RVM. Fibromyalgia (FM) is a complex, painful condition that can lead to depression and sleep problems. LeiP [31] et al found that EA reduced mechanical and thermal hyperalgesia in FM mice by reducing the Toll-like receptor 4 (TLR 4) and related molecules in the hypothalamus, PAG, and cerebellum, indicating that the analgesic effect of EA is related to the TLR 4 pathway. PeiP [32] et al. Research on purinergic 2X7 receptor (P2X7R) found

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that EA treatment caused significant activation of microglia in the PAG region, increased expression levels of Iba-1, IL-1 β, and P2X7R proteins, and improved symptoms in migraine rats. Lin YW [33] et al and Liao HY[34,35] et al found that knockdown of EA on transient receptor potential vanilloid subtype 1 (TRPV 1) treated chronic pain and depression, respectively. Together, these studies revealed the mechanisms of multiple neurotransmitters and receptors in EA analgesia.

4. Role of PAG-related neural circuits in pain regulation and electroacupuncture analgesia

4.1. The role of neural circuits in pain regulation

The PAG integrates pain information through multi-dimensional neural loops. Lee JY[36] et al showed that excessive projection from the anterior cingulate cortex (ACC) to dorsolateral / Lateral PAG (dl / l PAG) has been demonstrated to be a key neural basis for fear avoidance behavior in chronic pain patients, and this loop mainly regulates sensorimotor integration rather than primary nociceptive processing.

Teuchmann HL[37] et al. show that PAG forms a bidirectional connection network with the lateral arm nucleus (LPBN), in which the glutamatergic and GABAergic projections of PAG to LPBN can be differentially modulated by opioids, benzodiazepines, and cannabinoids, providing a target for the precise intervention of pain-aversion.

Cheriyan J [38] et al. found that the basolateral amygdala (BLA) indirectly regulates PAG activity through the prefrontal cortex (prelimbic cortex), and nerve damage can specifically disrupt the excitatory/inhibitory balance of this circuit.

LinM [39] et al. showed that the μ opioid receptor (MORGABA) on GABA-ergic neurons in the mPFC activates the mPFC-PAG projections through a "disinhibitory" mechanism to mediate stress-induced analgesic effects.

DuY [40] et al revealed that PAG dopaminergic neurons activate the PAG-RVM pathway in a D2 receptor-dependent manner, constituting the analgesic basis for amphetamine drugs.

Ferrari LF [41] et al showed that PAG dopaminergic neurons mediate analgesia through a descending inhibitory pathway that projects to the RVM.

Jiang M [42] et al found that activation of GPR 30-PKA-GABAAα4β1δ signaling in the PAG of female rats promotes anxiety-related hyperalgesia. These findings provide a rationale for understanding the analgesic effects of electroacupuncture by modulation of specific neural loops.

4.2. The role of neural circuits in electroacupuncture analgesia

EA is widely known for its analgesic effect, which is achieved by the release of β -β-endorphin in the arcuate nucleus (ARC) of the hypothalamus. The PAG serves as an integration center, receiving projections from the ARC and other cortical regions. The study of Wang Q et al revealed that 2 Hz EA stimulation increased β -endorphin and POMC gene expression by activating cAMP-PKA-CREB signaling in ARC, and enhanced analgesia in turn. It was also found that EA promotes neural projections from ARC to PAG, and that the ARCPOMC-PAGGABA neural circuit plays a key role in EA analgesia. These findings provide a scientific basis for the clinical optimization of EA parameters.

5. Conclusion

As a key hub of the descending pain inhibition system, the PAG plays a central role in pain regulation and EA analgesia by integrating multiple neurotransmitter systems and neural loops. Studies have shown that PAG regulates different pain states through GABA energy, CB1R, 5-HT energy, and opioid system, and mediates the analgesic effects of EA. Among them, GABA A receptors, CB1R, TLR 4, TRPV 1, and other downstream signaling pathways are crucial in the nociception modulation of PAG. Moreover, the activation of PAG-related neural circuits (e.g., ARC-PAGGABA pathway) further revealed the neural mechanism of EA analgesia. This paper systematically summarizes the roles and mechanisms of PAG in pain regulation and EA analgesia, which provides a theoretical basis for the development of novel analgesic strategies.

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6. Outlook

Future studies should focus on exploring the fine mechanisms of PAG in pain regulation. It is suggested that multimodal imaging and single-cell sequencing techniques be used to systematically analyze the dynamic characteristics of neurons in each PAG subregion in different pain models. At the same time, the electrical regulation of the neurotransmitter networks (especially GABA, glutamate, and opioid systems) should be clarified in the PAG. Based on the plasticity of the PAG neural loop, developing precise analgesic strategies targeting specific pathways is of great clinical importance. In addition, multicenter clinical studies should be conducted to establish a prediction model of PAG function and electroacupuncture efficacy to provide a basis for individualized treatment. These studies will drive the deepening of the understanding of pain mechanisms and the development of novel analgesic techniques.

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