DOI: 10.53469/jcmp.2025.07(02).34

The Research Progress on the Role of Adenosine A1 Receptors in Acupuncture Analgesia Mechanism

Hanbo Xu[1], Ani Zheng[1], Chunyan Zhang[1], Xintong Wu[2], Jiming Jin[1], Tong Ke[1], Wan Wei[1,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Shaanxi Nuclear Industry 215 Hospital, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Acupuncture analgesia has become a key focus of acupuncture research in recent years, and the role of adenosine receptors in acupuncture-induced analgesia requires further investigation. Adenosine (ADO) is an important neurotransmitter in the central nervous system, which exerts different physiological effects by binding to various adenosine receptor subtypes (A1, A2A, A2B, A3), playing a particularly significant role in pain regulation and acupuncture analgesia. Among these, adenosine has the highest affinity for the A1 receptor (A1R), and the binding of adenosine to A1R plays a crucial role in the transmission and modulation of pain signals. Previous studies have shown that acupuncture analgesia is associated with the adenosine A1 receptor. This study briefly introduces the distribution and functions of adenosine and adenosine A1 receptors, with a focus on the involvement of adenosine A1 receptors in pain modulation at both the central and peripheral levels. It aims to provide insights into the further exploration of the pain mechanisms of adenosine A1 receptors in both the peripheral and central systems and their role in acupuncture-induced analgesia.***

Keywords: Adenosine, Adenosine A1 Receptor, Central, Peripheral, Acupuncture Analgesia**.**

1. Introduction

Acupuncture, as an important component of traditional medicine, has widely been used in clinical practice for its analgesic effects [1, 2]. However, the molecular mechanisms underlying acupuncture-induced analgesia remain a hot topic of research. Studies have shown that the peripheral injection of the adenosine A1 receptor agonist CCPA has significant effects in inflammatory pain and neuropathic pain. Moreover, the analgesic effects mediated by acupuncture also require the expression of A1 receptors, indicating that the involvement of adenosine A1 receptors is essential for the analgesic effects of acupuncture. Previous studcies have demonstrated that adenosine can inhibit the release of various neurotransmitters and plays a crucial role at the presynaptic terminals of nerve endings. By activating presynaptic adenosine A1 receptors or A2AR, adenosine inhibits the activity of adenylate cyclase, promotes the opening of potassium channels, and inhibits calcium ion influx, thereby exerting neuroprotective and inhibitory effects [3]. This study aims to elucidate the role and relationship of adenosine and adenosine A1 receptors in pain signal transmission and acupuncture-induced analgesia.

2. Distribution and Function of Adenosine and Adenosine Receptors

2.1 Adenosine Release in the Periphery

Upon receiving signals of tissue damage or inflammatory responses, primary nociceptive afferent nerve fibers are capable of releasing adenosine at their nerve endings. In the acute pain model where formalin is injected into the plantar region, a dose-dependent release of local adenosine is observed in the periphery. At low doses of formalin, adenosine release originates from unmyelinated sensory afferent nerve endings, while at higher concentrations of formalin, the early stage of adenosine release comes from unmyelinated afferent nerve endings, and in the second stage, it is derived from postganglionic sympathetic nerve endings [4]. Electrophysiological studies have shown that during the first stage of acute pain, Aβ, Aδ, and C fibers are primarily activated, while in the second stage, Aδ and C fibers are mainly activated. Studies suggest that adenosine A1 and A2A receptors in the spinal cord may be involved in the regulation of early and late responses in the formalin test.

Additionally, immune cells such as endothelial cells, neutrophils, mast cells, and fibroblasts can also release adenosine following inflammation or tissue damage. Furthermore, ATP is released from both the central nervous system, spinal cord, and periphery, where it is converted to adenosine by 5'-nucleotidase, thus increasing its local concentration. Adenosine receptors are present on certain blood vessels and immune cells, and activation of these receptors can contribute to the inflammatory response. For instance, the activation of adenosine A1 receptors can induce adhesion, migration, and phagocytosis of neutrophils, monocytes, or macrophages, thereby mediating the inflammatory response. Therefore, the release of adenosine in peripheral tissues can modulate pain signal transduction by activating different target cells and receptors.

2.2 Adenosine Release in the Central Nervous System

The release of adenosine in the central nervous system or spinal cord is mainly due to neuronal depolarization, and the increase of potassium concentration in cells can lead to the release of adenosine in the dorsal horn of the spinal cord, which is derived from the N-type calcium ion channel of the capsaicin-sensitive neurons. Primary sensory afferent neurons accept nociceptive stimuli, which can lead to neuronal depolarization and activate pain afferents causing the release of nociceptive neurotransmitters such as substance P, glycine

and glutamate from the terminals of afferent neurons in the periphery or spinal [5-7]. At the same time, substance P can also lead to the release of adenosine from the synaptic boutons of capsaicin-sensitive in the dorsal horn of the spinal cord through Ca2 -dependent mechanisms. Opioid receptors can also cause the release of adenosine in the spinal cord and this release is mediated by u opioid receptors [8].

2.3 Adenosine Receptor Distribution and Its Effects

Adenosine, as an excitatory neurotransmitter, is distributed in various parts of the body, especially in the central system. Under physiological and pathological conditions, it plays a dual role in neuromodulation and homeostatic regulation by binding to different receptors. Adenosine receptors members of the G protein-coupled receptor family [9, 10]. Adenosine has a high affinity for A1, A2A, and A2B, and a affinity for A3 receptors. A1 receptors are widely distributed in peripheral sensory nerve endings, the dorsal horn of the spinal cord, and the central system, and are in the regulation of acute pain, inflammatory pain, neuropathic pain, and migraine. Activation of spinal or central adenosine A1 receptors can reduce nocice. In addition, adenosine A1 receptors can synergistically regulate analgesia with opioid receptors. Studies have shown that the analgesic effect of adenos A1 receptor agonist N6-cyclopentyladenosine (CPA) in the spinal cord is related to the activation of κ-opioid, and the use of CPA and κ-opioid receptor agonists can significantly prolong the analgesic time, providing ideas for the treatment of chronic inflammatory pain. In addition, A1 receptors are also located on spinal astrocytes, and play an analgesic role by inhibiting the activation of glial cells. A2A receptors are mainly expressed on peripheral inflammatory cells or immune cells, and are mainly selectively expressed in some brain regions related to pain in the central system, such as presynaptic and postsynaptic neurons and microglia. In primary afferent nociceptors, peripheral sensitization mediated by c can be reduced or increased by activating A1 or A2AR receptors on nociceptive afferent fibers; it can produce analgesia or nociceptiveization. A2B receptors are mainly expressed in peripheral immune cells and inflammatory cells, and are expressed in small amounts in astrocytes in the central nervous system or cord, and participate in pro-inflammatory effects. A3 receptors are expressed less in the central nervous system, and injecting A3 receptor agonists into the neuropathic model can produce a certain analgesic effect.

3. The Mechanism of Action of Adenosine A1 Receptors in Central Analgesia

At the spinal cord level, A1 receptors can inhibit pain responses through both presynaptic and postsynaptic mechanisms in nocptive afferent neurons. Adenosine A1 receptors can mediate spinal analgesia by coupling with Gi/o proteins, where Gi proteins are with adenylyl cyclase and G0 proteins are coupled with ion channels. The analgesic effect of adenosine in the spinal cord is achieved byiting adenylyl cyclase through Gi proteins, reducing the production of PKA, and by activating purinergic receptors through G0 proteins to inhibit calcium ion into the cell and alter potassium ion conductance in the spinal cord. In cultured dorsal root ganglion cells, adenosine can inhibit calcium-dependent action potentials, indicating it can inhibit neurotransmitter release at the presynaptic terminals of primary afferent neurons and hyperpolarize neurons by increasing potassium conductance in the postsyn membrane. The participation of adenosine A1 receptors in central analgesic mechanisms can be summarized in two aspects. First, A1 receptors reduce excitability by inhibiting the release of the excitatory neurotransmitter glutamate. Excitatory neurotransmitters activate NMDA receptors on the postsynaptic membrane, a large amount of adenosine, which, through high local concentrations, inhibits N-type calcium channels via presynaptic A1 receptors, further inhibiting the of glutamate, thereby reducing the activation of NMDA receptors on the postsynaptic membrane, thus forming a negative feedback mechanism [11]. The use of1 receptor agonists can increase the expression of metabotropic glutamate receptors in the brain, inhibit glutamate release, and play a temporary protective role. On the other, the activation of A1 receptors on the postsynaptic membrane can increase potassium ion efflux from the cell to depolarization, reduce excitability, and thus neurons.

Acupuncture can release adenosine, a neuromodulator with antinociceptive properties, and the antociceptive effect of adenosine requires the expression of adenosine A1 receptors, and direct injection of adenosine A1 receptor agonists can reproduce the analgesic effect of acupuncture. Inhibition of the enzymes involved in the degradation of adenosine can enhance the concentration of adenosine and its antinocice effect after acupuncture, indicating that adenosine is a mediator of the effects of acupuncture, and interference with the metabolism of adenosine may prolong the clinical efficacy acupuncture [12]. The researchers observed that electroacupuncture at Zusanli in the CCI rat model may mediate the supraspinal analgesic effect the transcription factor GATA4 regulating the expression of A1 receptors [13, 14]. It has also been proven in animal models of migraine that the analgesic mechanism the liver-soothing and spirit-regulating acupuncture method also requires the participation of adenosine A1 receptors, and the liver-soothing and spirit-regulating method can increase the content of adenosine A1 receptors and vasoactive substances 5-HT, CGRP, SP in the rat's trigeminal spinal, and the analgesic effect is more obvious than that of ordinary acupuncture. Ectonucleotidase in skeletal muscle cells convert nucleotides into adenosine, increasing the source of adenosine [15]. Local injection of recombinant ectonucleotidase (such as P) at acupoints can produce a more sustained A1 receptor-dependent analgesic effect than acupuncture alone or direct use of A1 receptor agonists [16] The study observed that there was more ATP, ADP, AMP, and ADO in the local area of the acupoint after acupuncture, among which the content AMP was higher, because there is a rich substrate in the local area of the acupoint that can hydrolyze PAP to generate adenosine, andenosine binds to the A1 receptor to exert the analgesic effect of acupuncture. In the neuropathic pain model, electroacupuncture can simultaneously activate PX3R and A1 receptors, and may play a role by reducing the expression of P2X3 receptors and increasing the expression of A1 receptors, indicating A1 receptors and other receptors interact and jointly regulate the acupuncture analgesia process [17].

4. Summary

Acupuncture analgesia has a definite effect, but the mechanism affecting acupuncture analgesia is still not clear, andenosine and its receptors have always played an important role in acupuncture analgesia. Adenosine is a purine nucleoside that regulates various physiological and pathological by activating adenosine receptors, especially by binding to adenosine A1 receptors to exert acupuncture analgesia. Studies have shown that both in animal models of pain, neuropathic pain, or migraine, and in healthy subjects, electroacupuncture or manual acupuncture can increase interstitial adenosine, thereby reducing the severity chronic pain through adenosine A1 receptors, which indicates that adenosine and adenosine A1 receptor-mediated analgesia contribute to the clinical efficacy of. Caffeine is a non-specific adenosine receptor antagonist, and a high concentration of caffeine in the diet can weaken the effect of acupuncture analgesia. experimental design of caffeine on different adenosine receptors involved in acupuncture analgesia is not deep enough, and the parameter design needs to be further improved to explore the between caffeine and adenosine receptors. In addition, the expression of adenosine receptors is also related to the use of acupuncture techniques, and further research is needed the biological mechanism of adenosine A1 receptors involved in different acupuncture techniques or new sensory acupuncture in peripheral and central acupuncture analgesia, so as to provide theoretical for the clinical use of acupuncture to relieve pain and the development of new sensory acupuncture.

References

[1] Liu, Y., et al., Comparison of femoral mechanics before and after internal fixation removal and the effect of sclerosis on femoral stress: a finite element analysis. BMC Musculoskeletal Disorders, 2022. 23(1).

[2] Li, Z., et al., Global trends of acupuncture clinical research on analgesia from 2010 to 2023: a bibliometric and visualization analysis. Front Neurol, 2024. 15: p. 1368988.

[3] Sawynok, J., Adenosine receptor targets for pain. Neuroscience, 2016. 338: p. 1-18.

[4] Yoon, M.H., H.B. Bae and J.I. Choi, Antinociception of intrathecal adenosine receptor subtype agonists in rat formalin test. Anesth Analg, 2005. 101(5): p. 1417-1421.

[5] Bai, H., et al., Adenosine A1 receptor potentiated glycinergic transmission in spinal cord dorsal horn of rats after peripheral inflammation. Neuropharmacology, 2017. 126: p. 158-167.

[6] Diao, X., et al., Analgesic action of adenosine A1 receptor involves the dephosphorylation of glycine receptor alpha1(ins) subunit in spinal dorsal horn of mice. Neuropharmacology, 2020. 176: p. 108219.

[7] Macedo-Junior, S.J., et al., The role of peripheral adenosine receptors in glutamate-induced pain nociceptive behavior. Purinergic Signal, 2021. 17(2): p. 303-312.

[8] Weizmann, T., et al., Mechanistic Insights into the Adenosine A1 Receptor's Positive Allosteric Modulation for Non-Opioid Analgesics. Cells, 2024. 13(24).

[9] Ramos-Zepeda, G. and J.F. Herrero, Interaction of the adenosine A1 receptor agonist N6-cyclopentyladenosine (CPA) and opioid receptors in spinal cord nociceptive reflexes. Life Sci, 2013. 93(5-6): p. 233-9.

[10] Ramos-Zepeda, G.A., C. Herrero-Zorita and J.F. Herrero, Interaction of the adenosine A1 receptor agonist N6-cyclopentyladenosine and kappa-opioid receptors in rat spinal cord nociceptive reflexes. Behav Pharmacol, 2014. 25(8): p. 741-9.

[11] Constantino, L.C., et al., Adenosine A1 receptor activation modulates N-methyl-d-aspartate (NMDA) preconditioning phenotype in the brain. Behav Brain Res, 2015. 282: p. 103-10.

[12] Kiani, F.A., et al., Electroacupuncture Relieves Neuropathic Pain via Adenosine 3 Receptor Activation in the Spinal Cord Dorsal Horn of Mice. Int J Mol Sci, 2024. 25(19).

[13] Li, S., et al., [Effects of electroacupuncture on activation of microglia cells in spinal cord in rats with neuropathic pain]. Zhongguo Zhen Jiu, 2017. 37(4): p. 411-416.

[14] Gao, Y., et al., [kappa-opioid receptor is involved in electroacupuncture analgesia via inhibition of spinal microglial Toll-like receptor 4 in neuropathic pain rats]. Zhen Ci Yan Jiu, 2022. 47(2): p. 95-100.

[15] Ma, X., et al., Potential mechanisms of acupuncture for neuropathic pain based on somatosensory system. Front Neurosci, 2022. 16: p. 940343.

[16] Hurt, J.K. and M.J. Zylka, PAPupuncture has localized and long-lasting antinociceptive effects in mouse models of acute and chronic pain. Mol Pain, 2012. 8: p. 28.

[17] Huerta, M.A., et al., P2X3 and P2X2/3 receptors inhibition produces a consistent analgesic efficacy: A systematic review and meta-analysis of preclinical studies. Eur J Pharmacol, 2024. 984: p. 177052.