Review Article

The research progress on the mechanism of adenosine A1 receptor-mediated calcitonin gene-related peptide to relieve migraine

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ABSTRACT

Currently, the pathogenesis of migraine is unclear. The trigeminal vascular reflex theory is the dominant pathogenesis theory, and its core parts are neurogenic inflammation and pain sensitisation. Calcitonin gene related peptide (CGRP) is the most powerful vasodilating peptide in brain circulation. It is also a marker of trigeminal nerve microvascular activation that plays a synergistic role in the pathogenesis of migraine. Adenosine A1 receptor (A1R) can inhibit the release of CGRP in the trigeminal nerve vascular system to alleviate migraine by mediating adenosine. This review summarises the progress of research on the alleviation of migraine by using A1R-mediated CGRP.

Keywords: Adenosine A1 receptor, Analgesia, Calcitonin gene-related peptide, Migraine

INTRODUCTION

Migraine is a unilateral attack, and its characteristics are paroxysmal, medium severe and pulsatile. Migraine is accompanied by nausea, vomiting, photophobia and phonophobia. It generally lasts for 4-72 hours. According to American epidemiological statistics, migraine is one of the seven most serious causes of disability in the world and seriously affects the quality of human life. Its incidence is 18% in women and 6% in men.1

At present, the drugs that can relieve pain caused by an acute attack of migraine are ergotamine, triptan and non-steroidal anti-inflammatory drugs. However, most of these drugs have adverse reactions. A1R can alleviate pain from acute migraine attack by inhibiting the release of CGRP. Its analgesic effect is significant, and it has relatively few adverse reactions.2 At present, CGRP has become a hot topic in the research field of migraine in the country and in other countries. Therefore, it is particularly important to study A1R-mediated CGRP for the relief and treatment of migraine.

CGRP and migraine

Migraine

The pathogenesis of migraine is unclear. At present, the more recognized theories on the pathogenesis of migraine are the cortical spreading depressing (CSD) and the trigeminal vascular reflex theories. The trigeminal vascular reflex theory combines nerves, blood vessels and transmitters, and it can explain the mechanism of migraine.3 This theory shows that the pathogenesis of migraine mainly involves three mechanisms, namely, dilatation of intracranial and extracranial blood vessels, the neurogenic inflammation caused by vasoactive intestinal peptide (VIP) from peripheral nerves and the sensitization of pain centers. The nociceptive stimuli are carried along pain transduction system to the pain centers, thereby resulting in headaches. The trigeminal vascular reflex theory is characterized by meningovascular dilatation, exudation of plasma protein and mast cells degranulation, and it is based on the release of neuropeptides such as CGRP, substance P (SP)
and neurokinin A and their neuro-inflammatory responses.\textsuperscript{4}

### CGRP

CGRP is the most powerful endogenous vasodilating substance among many vasoactive substances released by the trigeminal sensory nerve endings. The trigeminal ganglia (TG) and the trigeminal nucleus caudalis (TNC) are important components of the trigeminal vascular system (TVS).\textsuperscript{3} CGRP is widely expressed in nerve tissues, including TG and TNC.\textsuperscript{4} CGRP and its receptors are widely found in the central and peripheral nervous systems.\textsuperscript{5}

### CGRP and migraine

According to domestic and foreign studies, CGRP has become a hot topic in migraine research. Studies have found that CGRP’s expression in the trigeminal nerve is a key factor in the pathogenesis of migraine. During a migraine attack, the activated trigeminal sensory nerve endings can release CGRP, which cause the increase of vascular permeability and exudation of plasma protein. The release and aggregation of various inflammatory response mediators are stimulated. The degranulation of mast cells and the release of histamine are prompted. The last effect of CGRP may be related to its involvement in neurogenic inflammation by promoting meningeal vascular leakage. This causes migraines, because the trigemino-cervical complex is stimulated, thereby sending the abovementioned information to the thalamus and cortex.\textsuperscript{7} The release of CGRP and its neurogenic inflammation is considered to be the pathophysiological basis of migraine.

The study found that the release of CGRP can result in migraine. In addition, exogenous CGRP can also induce a series of pathophysiological reactions, such as cerebral artery dilation, the degranulation of mast cells, the release of histamine, meningeal vascular leakage and neurogenic inflammation. All these cause migraines. CGRP receptor antagonists can relieve migraine attacks.\textsuperscript{8} In addition, during the onset of migraine, the plasma CGRP level will increase, and the intensity and duration of migraine are positively correlated with the plasma CGRP level.\textsuperscript{9}

### A1R and CGRP

#### Expression and distribution of A1R

A1R is a member of the adenosine receptors (ARS) family. ARS is a class of G-protein-coupled receptor (GPCR), which includes four subfamilies, namely, A1, A2a, A2b and A3.\textsuperscript{10} A1R is the most abundant adenosine receptor in the brain and has the highest affinity with adenosine. Their combination plays an important role in the transmission and regulation of nociceptive information and inflammatory response.\textsuperscript{11}

A1Rs are widely distributed in various systems of the body. However, it is most widespread in the nervous system. Moreover, it is associated with pain. In the peripheral nervous system, A1R is mainly distributed in dorsal root ganglion (DRG) neurons and primary afferent neurons. The density of A1R in the dorsal side of the spinal cord is significantly higher than in the ventral side. In the central nervous system (CNS), A1R is mainly distributed in the spinal cord, hippocampus, cortex, cerebellum and striatum, and opioid receptors also have a high level of expression in the above areas.\textsuperscript{12} The similarity between A1R and opioid receptor in distribution may determine their regulatory role in analgesia. The study found that A1R is widely distributed in the TG, which may be the basis for TVS to play a role in migraine (Schindler, 2001).\textsuperscript{13}

#### Possible analgesic mechanisms involving A1R

Adenosine, a purine nucleoside, can act as a nerve regulator that participates in the transmission and sensitization of pain.\textsuperscript{11} Studies have shown that adenosine has analgesic effect when administered via veins, reticular structure of brain stem and lateral ventricle.\textsuperscript{14} Due to the high affinity between adenosine and A1R, adenosine’s analgesic effect may be mainly mediated by A1R. Current studies have shown that A1R can produce analgesic effects through a variety of signaling pathways, which are an important endogenous signal transduction molecule.\textsuperscript{15} The analgesic mechanisms involving A1R may include the following.

- **Analgesic effect is generated by inhibiting cyclic adenosine monophosphate (cAMP), protein kinase A (PKA) and the interaction between Ca\textsubscript{2+} and K\textsuperscript{+} channels.** In the process of pain regulation, after the activation of A1R on peripheral sensory terminals, the signal pathway of A1R may inhibit AMP, PKA and the interaction between Ca\textsubscript{2+} and K\textsuperscript{+} channels through Gai, thereby producing the analgesic effect.\textsuperscript{2,16} The A1R is injected into the rat brain stem reticular structure to induce its analgesic effect, which is dose-dependent and could be completely blocked by A1R antagonist (Feng et al. 2006).\textsuperscript{2} Scholars speculated that activated A1R has analgesic effect. The combination of adenosine and A1R can inhibit the activity of adenylate cyclase (AC), reduce the generation of cAMP and activate G protein-dependent K\textsuperscript{+} channels by acting on the cell surface of G protein. This combination increases the outflow of K\textsuperscript{+} and generates nerve cell membrane hyperpolarization that inhibits N-type Ca\textsubscript{2+} channel and reduces the internal flow of Ca\textsubscript{2+}. The analgesic effect is produced by inhibiting the excitability of neurons and reducing synaptic transmission.\textsuperscript{17}

- **γ-Aminobutyric acid (GABA) is inhibited via the intracellular protein kinase C (PKC) signaling pathway.** By studying the regulation of adenosine on the GABA signal in the superficial neurons of the...
spinal dorsal horn of an acute isolated rat, Wu et al. found that adenosine exerts an inhibitory effect on GABA current by activating A1R. Moreover, a certain analgesic effect is produced through the intracellular Ca\(^{2+}\) non-dependent PKC signal pathway.\(^{18}\)

- **Analgesic effect is produced when AIR competes with harmful stimuli and blocks pain signaling.** In the rat hot-plate test and the spinal cord injury model, Zhao et al. confirmed that the activated A1R competes with adenosine and reactive oxygen species, leading to the inhibition of extracellular signal-regulated protein kinase (ERK) phosphorylation and blocking pain signal transduction through mitogen-activated protein kinases (MAPK)/ERK pathway to achieve a central analgesic effect.\(^{19}\)

- **A1R inhibits pain sensitivity.** The activated A1R inhibits pain sensitization by reducing phosphatidylinositol-bisphosphate, thereby producing the analgesic effect.\(^{20}\)

In summary, A1R can produce the analgesic effect through a variety of signaling pathways, thereby suggesting that drugs that act on A1R levels may have the potential to relieve pain.

**The mechanism of AIR in migraine**

The analgesic effect of adenosine on inflammatory and neuropathic pain is mainly achieved by A1R, which regulates the transmembrane flow of intracellular cations by activating GPCR. A1R affects the excitability of neurons and the release of neurotransmitters and exerts analgesic and anti-inflammatory effects.\(^{21}\)

A1R is expressed in both presynaptic and postsynaptic membranes, and its mechanisms in migraine mainly include presynaptic and postsynaptic mechanisms, as follows.\(^{22}\)

- **The mechanism of presynaptic analgesia:** Activated A1R in the central process of primary afferent neurons inhibits Ca\(^{2+}\) influx and the release of presynaptic excitatory amino acids and SP.

- **The mechanism of postsynaptic analgesia:** Activated A1R acts on the ATP-sensitive K\(^{+}\) channel, thereby causing hyperpolarization of spinal dorsal horn neurons and inhibiting the conduction of nociceptive stimulation, the release of CGRP from nerve fibers and CNS sensitization.

**Presynaptic analgesia:** This mechanism is mainly manifested in the inhibition of glial cell activation. The activated microglia and astrocytes can cause migraine by releasing neuronal excitability material associated with migraine and neurogenic inflammatory medium or by enhancing the glutamate signal in brain stem tissue. However, activated A1R can alleviate migraine by inhibiting the activation of glial cells.\(^{11}\)

**Postsynaptic analgesia:**

- **Inhibition of the electrical induction response of intrinsically photosensitive retinal ganglion cell (iPnG):** Adenosine signaling plays an important role in auditory and visual conduction. Activated A1R inhibits the electrical induction response of iPnG and relieves the visual symptoms of migraine with visual aura.\(^{17,23}\)

- **Inhibition of excitatory postsynaptic potentials:** CGRP cannot affect the synaptic transmission of neurons in the brain, but it can enhance the excitatory postsynaptic potential of neurons by inhibiting AIR or activating adenosine A2α receptor (A2αR), which causes migraine.\(^{24,25}\) A1R agonists and A2αR inhibitors can play an important role in migraine by inhibiting the sensory neurogenic vasodilation of the CNS, the release of CGRP and the activation of the second order neurons of TNC via inhibition of the excitatory postsynaptic potential of neurons. The expression of A1R in TG and TNC of rats with migraine was negatively correlated with the level of CGRP in plasma. Its increase may reduce migraine attacks and ease the pain.\(^{15-24}\)

- **Inhibition of neurogenic inflammation and pain conductivity:** By inhibiting the release of Ca\(^{2+}\)-dependent synaptic transmitters, the activated A1R accelerates the opening of K\(^{+}\) channels in the postsynaptic membrane and leads to the hyperpolarization of the postsynaptic membrane, thereby inhibiting the neurogenic inflammation and pain conductivity and exerting analgesic effects on migraine.\(^{25}\) The A1R agonist can inhibit the neurogenic inflammation and pain sensitization of TVS and the release of CGRP in the vascular system without vasoconstriction, thereby suggesting that A1R has the advantage of non-vasoconstriction in the treatment of migraine. Thus, a new approach for the treatment of migraine is suggested.\(^{24}\)

**DISCUSSION**

A1R is widely distributed in the CNS. It plays an important role in migraine when activated. The inhibitory effect of A1R on CGRP in the trigeminal nervous vascular system without vascular contraction is significant.

Therefore, the study on A1R-mediated CGRP is beneficial to the determination of the pathophysiological process of migraine and provides new ideas for its prevention and treatment.
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