Analysis of Pharmaceutical Therapies for Primary Headache

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Abstract. Primary headaches, secondary headaches, neuropathies and facial pains, and other headaches are the four types of headache disorders, in which primary headache disorder includes migraine, cluster headache, tension-type headache, and new daily persistent headache. Pathologies of migraine and cluster headaches are still unclear but possible explanations are proved to be related to trigeminal neurons, calcitonin gene-related peptide (CGRP) release, and neuroinflammation. This research listed these possible explanations and summarized the basic factors of migraine and cluster headache attacks. Based on the pathologies, various choices of therapies were introduced. This research mentioned typical pharmaceutical therapies for headaches, including nonsteroidal anti-inflammatory drugs, paracetamol, 5-HT1 receptor agonists involving triptan and dihydroergotamine mesylate, opioids, caffeine, and botulinum toxin. Furthermore, new medications in recent studies, including CGRP antagonists and caffeine were noticed as well. Related reliable mechanisms and side effects of all these drugs were highlighted in this review. Realizing the pros and cons of current treating medications is significant for better understanding on mechanism of headaches and designing more effective drugs in order to offer better promise on treating therapies.

Keywords: Primary headache therapies, Migraine pathology, Pharmacology.

1. Introduction

The prevalence of headache disorders means that they have a persistent impact on people's health. There are many people who are suffering from headaches. There may be a gender and age preference for headaches. 52.0% of people, including 44.4% of men and 57.8% of women, suffer active headaches of some kind, according to statistics. Both migraines (14%; males 8.6%; females 17.0%) and tension-type headaches (TTHs; 26.0%; males 23.4%; females 27.1%) are common. The top ten causes of disability-adjusted life years (DALYs) among persons aged 10-49 are headache disorders, according to the Global Burden of Disease (GBD) 2019 report [1].

There is great room for studies on the classification and different treatments of headache disorders. On PubMed, in the five years from 2019 to 2023, there are close to 30,000 related articles. Anxiety, depression, sleep deprivation, tiredness, and menstruation in women are common causes of headaches that may lead to different types of headaches. Headaches can be broadly categorized into four types, which are primary headaches, secondary headaches, neuropathies and facial pains, and other headaches. Primary headaches are not caused by other diseases, which can be treated by drugs. Migraines, cluster headaches (CHs), tension-type headaches (TTHs), and new daily persistent headaches (NDPHs) are typical kinds of primary headaches. Among the world's causes of disability, migraine is the second and the first among young women. Migraines are the most common type of primary headache clinically, generally lasting for 4-72 hours, with symptoms involving nausea and vomiting. Cluster headaches are divided into episodic and chronic types, the former have intervals of less than 3 months and the latter may have intervals longer than 1 year. The severity and frequency of headaches have an impact on TTHs and TTHs worsen with genuine headaches. They are typically related to increased pericranial tenderness. NDPHs begin as daily symptoms and soon become unrelenting. In contrast, secondary headaches are associated with other diseases. By treating the primary diseases, the symptoms of headaches can be reduced.

To deal with primary headaches, several treatments are used. Study shows that non-pharmacological treatments including acupuncture and manual therapy are effective for TTH. A hot and cold compress may take effect toward light headaches as well. Moreover, a low glycemic diet may play a role in controlling headaches by attenuating the inflammatory state. However,

pharmacological treatments are more valid and efficient. Analgesic that are widely used to treat headache has various types. Nonsteroidal anti-inflammatory drugs (NSAIDs) involving aspirin, indomethacin, rofecoxib, and ibuprofen can reduce inflammation, blood clots, and pains. They are potent for most types of headaches. Paracetamol (acetaminophen) is also one of the common analgesics. Furthermore, the advance in the development of 5-hydroxytryptamine $(5\text{-HT})_1$ receptor agonist for migraine may lead to better treatment of migraine. For instance, triptans including sumatriptan, zolmitriptan, naratriptan, and florotriptan are specially designed to treat migraines, these drugs have a promising future due to their great efficacy. Dihydroergotamine (DHE) is also one of the available therapies for acute migraine as well. Opioids, in particular morphine, are some of the most useful medications for managing severe headaches. However, the adverse effects, such as toleration and respiratory depression, cannot be neglected. In addition, recent studies have found more possibilities for treating headaches. Based on the migraine pathology, calcitonin gene-related peptide (CGRP) has become a main target of migraine therapeutics, therefore CGRP antagonists are found to play a role in treating migraines. Additionally, caffeine is a useful component of several analgesics since it has the potential to modulate pain by acting on adenosine receptors. Furthermore, Botulinum toxin type A has also become an option for treating migraine.

All these types of medications applied clinically especially drugs for treating primary headaches have different mechanisms and they target different symptoms. Therefore, a systematic summary and review is needed.

2. Possible Mechanisms

2.1. Migraine

The second most common cause of disability worldwide is migraines. Migraines are the most frequent type of primary headache from a clinical perspective, generally lasting for 4-72 hours, with symptoms involving nausea and vomiting. The mechanism of migraines is complex and hasn't been fully identified by researchers, but there are some possible theories. Many factors of mechanisms of migraine are shown in Fig. 1.

First, the occurrence of cortical spreading depression (CSD) is one of the possible mechanisms of migraines. After electrical or chemical stimuli, CSD will be initiated by efflux of K^+. Accumulated K^+ can cause further neuronal depolarization, then astrocyte interconnections can open K^+ channels which lead CSD to produce propagating waves of transient neuronal hyperexcitability followed by depression. In the visual cortex, there is a correlation between the temporal spreads of CSD and the precursor to migraine spreads. This asserted that CSD is possible to be the source of migraines' visual aura. Additionally, as materials are transferred from the cerebral cortex to the meninges during CSD, C-fiber nociceptors in the dura will be activated. The subsequent release of CGRP will further sensitize C-fiber nociceptors and may also help to activate A-delta pain fibers beside. However, the specific relationship between CSD and migraines is still unclear.

Another hypothesis asserted that migraines are greatly impacted by the release of neuropeptides from the trigeminal nerve, particularly calcitonin gene-related peptide (CGRP), as well as the innervation of the meninges and meningeal blood vessels. CGRP can widen blood vessels by interacting with the receptors on the smooth muscle of dural blood vessels. Through the activation of adenyl cyclase and an increase in the concentration of cyclic adenosine monophosphate (cAMP), CGRP causes blood vessels to dilate at the intercellular level. Additionally, CGRP can increase the sensitivity of meningeal nociceptors and cause mast cells to degranulate through its special receptors, which raises the possibility that migraines may be caused by neuroinflammation. Recently, based on the mechanism, CGRP antagonists have shown great efficacy in treating migraine.

Furthermore, migraines are also associated with abnormal activation of brain regions, including periaqueductal grey matter (PAG). Trigeminal neurons may become more sensitive as a result of abnormal brainstem activation, which then sends signals of pain to the sensory cortex. The midbrain and pons, even the hypothalamus is activated during migraines. Moreover, paraventricular

hypothalamic neurons (PVN) can mediate the spontaneous and induced activities of Sp5C neurons. It can inhibit or promote meningeal-evoked activity after exogenous stimulation of nociceptors, and regulate migraine through direct control of the spinal trigeminal nucleus.

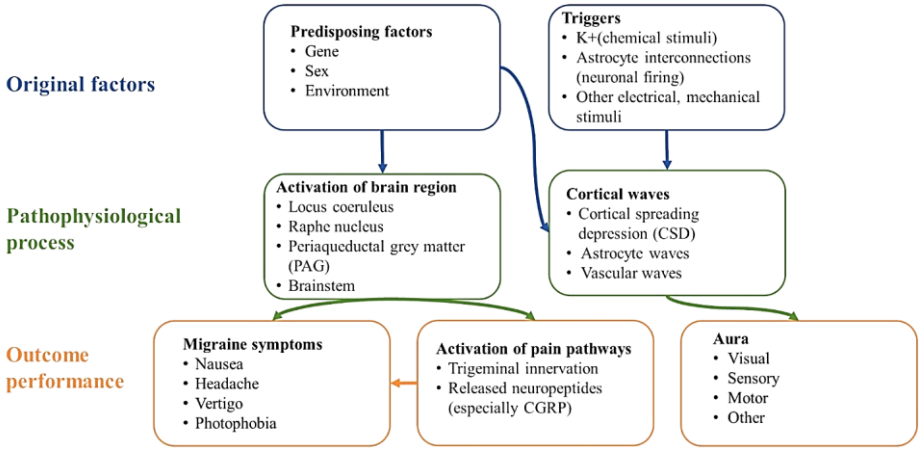


Figure 1. Basic mechanism of migraine. Neuronal firing or electrical, mechanical, and chemical stimuli would trigger abnormal activation in brain regions, as a result, the sensitization of trigeminal neurons and release of nociceptors and other possible symptoms will occur, thus leading to activation of pain pathways followed by migraine symptoms (Picture credit: Original)

2.2. Cluster Headache

Cluster headaches are typical types of trigeminal automatic cephalgia, which have intervals from fewer than 3 months to over 1 year. The following symptoms involve nasal congestion and eyelid oedem. Initially, it was believed that cluster headaches were associated with narrow cavernous sinuses, but magnetic resonance imaging (MRI) from neuroimaging studies reveals that there are no appreciable size differences between CH patients and normal people in the cavernous sinuses (although CH patients have broader skulls) [2]. In the past several years, researchers have greater understanding of the pathophysiology of CH. CGRP and trigeminal vascular are hypothesized to take part in the occurrence of CH. The meningeal vessels may vasodilate as a result of the trigeminal nerve's first branch being activated, triggering the meningeal nociceptors and producing pain. Moreover, through the specific regions of the brain that mediate spontaneous symptoms, this activation can elicit the trigeminal parasympathetic response. The activation can inhibit the cranial sympathetic system as well. Furthermore, during CH attacks, CGRP will cause vessel vasodilation, and modulate nociceptive trigeminal neural transmission. CGRP antagonist has succeeded in inhibiting nociceptive trigeminal neural transmission in the trigeminal cervical complex of cats.

According to irregularities in melatonin and growth hormone, cluster headaches may potentially be related to hypothalamic activity. According to theory, the hypothalamus modulates pain and predominantly affects descending pain modulation while acting as an antinociceptor. The anterior cingulate cortex was activated, as did the hypothalamus. Particularly, the hypothalamus is only activated during headache attacks. According to MRI results, people with CH have a larger hypothalamus than people with migraines, and those with chronic CH have more anterior hypothalamic gray matter (GM) than people without CH [3]. This also supported the role of the hypothalamus in CH attacks. However, the question of how hypothalamic activation affects CH is still unsolved.

3. Pharmaceutical Therapies

3.1. Nonsteroidal Anti-inflammatory Drugs (NSAID)

Since the discovery of aspirin by Felix Hoffman of Bayer industry, Germany, in 1897, NSAIDs were started to be seen as potential drugs in the pharmaceutical industry. Because of their structural

and functional diversity, NSAIDs can be classified in different ways, including classification based on structures, classification based on the type of COX interaction and selectivity, and classification based on the plasma half-life. At present, NSAIDs are one of the most popular worldwide drugs. They are widely used in treating pain, inflammation, and fever. A great range of headaches can be treated or released by taking NSAIDs, which almost take effect each time. However, multiple side effects of NSAIDs, including gastrointestinal toxicities and renal injuries, were discovered.

It was first suggested that the mechanism of NSAIDs was to block prostaglandin synthesis. Then, in 1996, the two isoforms of cyclooxygenase-2 (COX or PGH_2), COX-1 and COX-2, were discovered as the targets of NSAIDs. COX can oxidize arachidonic acid (AA) to prostaglandin G2 (PGG_2) and then hydroperoxidase (POX) peroxidize PGG_2 to PGH_2. Therefore, NSAIDs can work as an analgesic, by inhibiting the COX in order to inhibit the conversion of AA into PGH_2, thus reducing the prostaglandin mediators of pain. Excepting COX-1 and COX-2, COX-3 was identified in the brain tissue of dogs. This enzyme was inhibited by some of the NSAIDs such as phenacetin, antipyrine, and dipyrone. A new concept that appeared in 1996, suggested that COX-2 inhibition was responsible for the therapeutic outcomes, such as the anti-inflammatory effect, while COX-1 inhibition was responsible for the negative effects. Therefore, the direction of research has transformed to the study of specific COX-2 inhibitors, for example, celecoxib and etoricoxib, in order to avoid the risk of gastrointestinal injuries. However, COX-2 inhibitors were not safe enough as the previous thought, they will increase the risk of serious cardiovascular events. In recent studies, researchers started to focus on exploring other potential effects of NSAIDs. NSAIDs such as aspirin and ibuprofen are still popular among patients, but their adverse effects will be taken more seriously.

3.2. Paracetamol

Paracetamol, pharmaceutically known as acetaminophen and chemically known as N-acetyl-para-aminophenol, was introduced in the nineteenth century and was widely used in prescription in the UK in 1956. Paracetamols are widely used for treating pain including headaches due to their high efficacy and toleration. Paracetamol is also used in combination therapies. It was found that other medications combined with paracetamol are effective therapies and have a high safety profile. The flunarizine-paracetamol group had a lower frequency of attack and shorter duration compared to the control group. Because paracetamols don't have anti-inflammatory effects, they are not considered to belong to the NSAIDs.

The mechanism of paracetamols is complex, which is still unclear. One of the theories suggested that paracetamols may act as selective COX-2 inhibitors, especially the preferential inhibitors of COX-2 isoenzyme, but environmental redox is a key effect. Another theory was related to the formation of ferryl protoporphyrin IX radical cation (Fe^{4+}=OPP^{*+}), which was essential for the formation of tyrosine radicals [4]. These tyrosine radicals played a significant role in the conversion of AA to PGG2 (Fig. 2). First, the tyrosine radical (Tyr385*) in the COX site is required for the oxidation of AA to PGG2. Second, at the POX site, PGG_2 is converted to PGH_2. Following the formation of Fe^{4+}=OPP^{*+}, Tyr385* radicals are produced. The POX site Fe^{4+}=OPP^{*+} can be reduced by paracetamol, which results in less Tyr385* radical production and less Fe^{4+}=OPP^{*+} formation. Paracetamols were associated with the decrease of Fe^{4+}=OPP^{*+} at the peroxidase site of prostaglandin H synthase (PGHS) enzymes. Therefore, paracetamol can inhibit the prostaglandin production. Moreover, hydroperoxides of fatty acids, including PGG_2, can oxidize porphyrin at the POX site. In an environment with high peroxide levels, it was difficult for paracetamol to block the COX. This also explains why the mechanisms of paracetamols and NSAIDs are different. Furthermore, the central action of paracetamols involving the inducing effect on reducing serotoninergic pathways takes part in the blockage of pain sensation. One of the mechanisms of paracetamol related to the 5-HT3 subtype of serotonin receptors was determined. A double-blind, and cross-over study by Pickering et al., found that the antinociceptive action of paracetamols was totally inhibited in the group of volunteers treated with paracetamols and trpisetrons, which are 5-HT3 antagonists [4]. Furthermore, paracetamols can be deacetylated to p-aminophenol, thus reacting with AA through the

catalyzation of fatty acid amide hydrolase (FAAH). On the one hand, the result of this reaction, the fatty acid amide N-arachidonoylphenolamine (AM404), can directly activate the transient receptor potential cation channel subfamily V member (TRPV1) receptors, which are found in pain and thermoregulatory pathways, and indirectly activate CB1 receptors. On the other hand, AM404 can prevent cellular anandamide from being taken up, which results in higher levels of endogenous cannabinoids. Endogenous cannabinoids have antinociceptive effects on the spinal cord and the brain [4]. Moreover, cannabinoids can lower body temperature via stimulating CB1 receptors in the pre-optic region. Long-term use of paracetamols may cause liver damage and high blood pressure [4]. However, the fact that paracetamols have fewer gastrointestinal adverse effects than NSAIDs is one of its benefits.

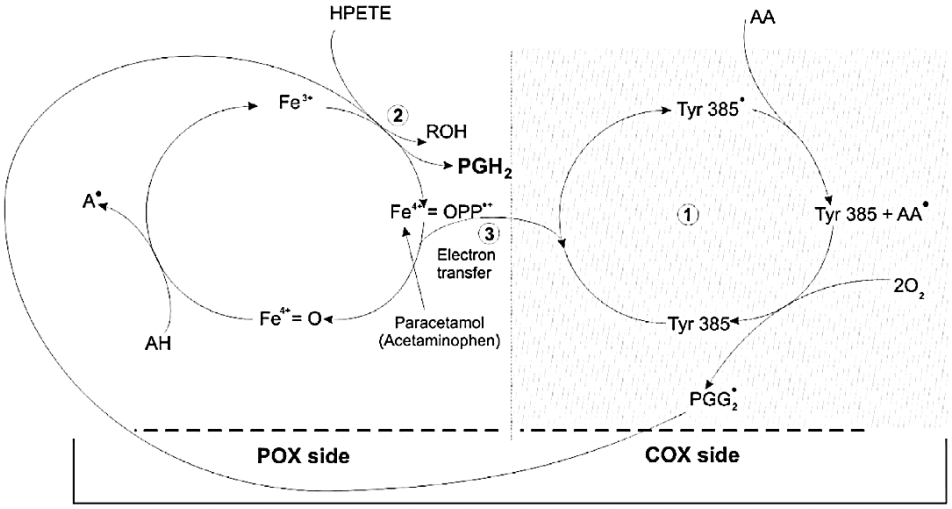


Figure 2. Two components of PGHS: COX and POX, which convert AA to prostaglandin PGH_2 [4, https://europepmc.org/article/med/24779190?utm_medium=email&utm_source=transaction&client=bot&client=bot&client=bot]

3.3. 5-HT_1 Receptor Agonist

3.3.1 Triptan

As the 5-HT_1 as a possible treatment target was discovered, triptans, which are 5-HT_1 receptor agonists, were found to be available for migraine treatment. Triptans have two routes of administration, one is oral and the other is subcutaneous injection, which has bioavailability approaching 100% [5]. Around 1990, studies on 5-HT_1 receptor agonists have further developed. The first triptans are sumatriptans, which are serotonergic agonists with selective activity on 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors. Numerous studies have shown that sumatriptan stood out in the rate of response over 70% of the patients responded to sumatriptan within 2 hours [6]. After sumatriptan was introduced as the migraine treatment, the second-generation triptans including zolmitriptan, rizatriptan, and naratriptan occurred, which have higher bioavailability and longer plasma half-life than sumatriptan. The pharmacokinetics of triptans are different between individuals. In general, triptans can be divided into two groups, one includes sumatriptans and second-generation triptans due to their fast onset but high tendency of recurrence, and another includes naratriptans and frovatriptans due to their high tolerability.

The specific mechanism of triptans is still unclear, but there are reliable theories. At first, triptans were thought to bind with 5-HT1B receptors, which leads to the vasoconstriction of the cranial arteries in order to go against the dilatation of intracranial extracerebral arteries during a migraine attack. Trials with canines and rabbits have clearly proved their effect on promoting vasoconstriction, which strongly supports the vascular theory [7]. In recent studies, the realization of the mechanism of the triptans has developed. Triptans can limit the production of proinflammatory neuropeptides and the neurogenic dural vasodilation through the neurological mechanism of peripheral trigeminal nerve terminals, preventing the pain signals from being sent to the brain. However, the limitations of triptans

cannot be neglected. Triptans are contraindicated in patients with cardiovascular or cerebrovascular illnesses, hemiplegic migraines, and uncontrolled hypertension due to their impact on the vasoconstriction of blood vessels.

3.3.2 Ergot alkaloid: dihydroergotamine mesylate (DHE)

Ergot alkaloids, which are isolated from ergot, are derivatives of ergot acids. Ergotamine has been used pharmaceutically to treat migraines since 1926, and in 1943, Stoll and Hofmann became the first scientists to synthesize dihydroergotamine mesylate. The main route of administration of DHE is the intravenous injection administration, because of the low bioavailability of DHE and the big difference in bioavailability between individuals. As same as the triptan, DHEs are also 5-HT1 receptor agonists, especially the 5-$HT_{1B/1D}$ receptor agonists. Other receptors, including 5-HT_{1A}, 5-HT_{2A}, 5-HT_{1F}, 5-HT_{2C}, 5-HT_3, and dopamine D1/D2 receptor subtypes can also be activated by DHEs. The great efficacy of DHE has been proved by some studies. In a placebo-controlled study with 902 patients, MAP0004, a DHE, was much more effective than placebo, even 8 hours after the start of the attack of migraine, which means MAP0004 was independent of the time of treatment [8]. Additionally, repetitive IV of DHE showed a great trend in helping to terminate cycles of intractable migraines.

As the 5-$HT_{1B/1D}$ receptor agonists, the mechanism of DHEs is similar to the mechanism of triptans. Through binding with 5-HT_{1B} receptors, DHE can reduce activation of the trigeminal neuron and induce vasoconstriction of vessels in the meningeal. However, another novel theory suggested that first, results show that the P2X3 antagonists can inhibit the sensitization of ATP, which means the process of ATP mediating sensitization of trigeminal neurons, involves the activation of P2X3 receptors [9]. Then, cells exposed to α, β-methyl ATP 15 minutes before the potassium chloride (KCl) was added, had a comparable four times augment in CGRP levels in comparison to controls, indicating that the combined effects of KCl and ATP can promote CGRP release. Furthermore, through α_2a and/or α_2c-adrenergic receptors, but not 5-HT1B/1D receptors, ATP and KCl-induced CGRP release can be inhibited by DHE. In order to prevent the sensitization of trigeminal neurons caused by ATP, the mechanism of DHE entails preventing the release of CGRP and reducing P2X3 membrane expression through activation of α_2-adrenoceptors. The disadvantages of DHE include nausea and vomiting. Bilateral lower limb cramps, chest discomfort, and abdominal cramps may also occur after the administration of DHE.

3.4. CGRP Antagonists

CGRP is a 37 amino acid peptide, produced through alternative splicing of the calcitonin gene (CALCA). CGRP was mainly synthesized in the hypothalamus. One year later, the function of CGRP in pain perception and the regulation of the autonomic and endocrine systems was found. They found the potential role of CGRP as a vessel vasodilator in the peripheral and central nervous systems. In later studies, its role in promoting vasodilation and its relationship with trigeminal neurons was further identified (see above). CGRP has also become a key molecule in migraine pathogenesis. Moreover, Wang et al. adapted an optogenetic strategy and studied $Calca^{cre/+}$ mice [10]. They discovered that MN neurons (MNCGRP) that express CGRP may have a role in migraine-like sensitivity to light and touch. Based on former studies, CGRP antagonists started to be used in treating migraines. Through blocking the release of CGRP, CGRP antagonists can inhibit vasodilation and neuroinflammation.

CGRP antagonists are antagonists of the receptor or ligand of CGRP. CGRP antagonists include monoclonal antibodies, involving erenumab, fremanezumab, and galcanezumab, and non-peptide small molecules (gepant), which includes rimegepant, ubrogepant, and atogepant. In 2023, a long-term, open-label research of lasmiditan, rimegepant, and ubrogepant in the treatment of migraines found that rimegepant was well tolerated, safe, and had no substantial cardiovascular disease risk or side effects [11]. Its main side effects are upper respiratory tract infections (8.5%), nasopharyngitis (6.4%), and sinusitis (4.8%). Moreover, ubrogepant was well tolerated, with the most typical adverse effects including dry mouth (7.5%), fatigue (27.4%), and nausea/vomiting (6.6%). As a developing

medication for the therapy of migraine, CGRP antagonists have a bright future. They require further study on their side effects and pharmaceutical values.

3.5. Opioid

Opioids often act as effective analgesic for treating severe pains, but due to their tolerant effect, their use is controversial. Opioids have four main types of receptors however the mu-opioid receptor (MOPr) is the main target of most of the medications. Microinjection of morphine into the ventrolateral periaqueductal gray (vlPAG) ignites an antinociceptive effect, which can be blocked by the injection of naloxone or naltrexone hydrochloride (opioid antagonists) into vlPAG. These studies indicated the significant role of PAG in the pathology of opioids. Moreover, the PAG's GABAergic neurons are crucial opioid action sites. When MOPr is produced at presynaptic locations in conjunction with opioids, this blockage of voltage-gated calcium and potassium channels reduces GABAergic neuron activity. When MOPr is expressed at postsynaptic sites, MOPr can cause a decrease in GABAergic neuron activity. GABAergic neurons are hyperpolarized as a result of the activation of G-protein inwardly rectifying potassium channels (GIRK). Whether MOPr is expressed presynaptic or postsynaptic, MOPr can lead to a decrease in GABAergic neuron activity, which in turn increases the output from PAG to the rostral ventromedial medulla (RVM).

However, the side effects of opioids cannot be neglected, especially their tolerability. One of the theories indicated that opioid tolerability may associated with changes in glutamatergic signaling. It has been demonstrated that the cerebrospinal fluid of opiate-tolerant people contains noticeably increased quantities of glutamate and aspartate. Another theory suggests that the mechanism of opioid tolerability involves the activation of adenylyl cyclase activity. Increased adenylyl cyclase activity can increase opioid tolerability but not antinociceptive effect, which is not considerably modulated by a single injection of opioids. Furthermore, activation of adenylyl cyclase can regulate both presynaptic and postsynaptic GABA neurotransmission, which also illustrates the possible relationship of GABA to opioid tolerability. Moreover, increased nerve excitability can reduce the ability of hyperpolarizing neurons of opioids, thus contributing to opioid tolerability. As controversial drugs, the use of opioids should be taken more seriously. Opioids can be therapies for moderate to severe pain, but given their tolerability, they need to be prevented from being abused.

3.6. Caffeine

Caffeine (C8H10N4O2), or “3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione” is a kind of alkaloid. At first, caffeine was discovered to be a component of daily drinks such as coffee and tea. However, its pharmaceutical effects have been noticed later. Not only act as a stimulant or energy and cognitive activities enhancer, but caffeine also acts as a short-term memory improver. However, the role of caffeine that will be discussed in this paper is its role in regulating pain, which is closely related to a caffeine structure-like material called adenosine. Adenosine receptors have four different types, including A_1, A_{2A}, A_{2B}, and A_3 in which A1 and A_{2A} are hypothesized to be activated to lead to antinociceptive effects. Because of the similarity between caffeine and adenosine, adenosine and caffeine may compete for binding to A_{2A} receptors, thus activating A_{2A} receptors. At the same time, adenosine failed in the competition and was unable to suppress the central nervous system (CNS) and peripheral nervous system (PNS). In a nutshell, caffeine expresses its analgesic effect through binding with adenosine receptors that are related to antinociception and blocking the action from adenosine.

Through the above process, caffeine is used both as a direct analgesic and as an adjuvant component in other analgesics. The first case of hypnic headache (HH), a headache associated with sleep, was recorded in 1988. Based on numerous studies, caffeine is the most effective therapy for acute HH. Furthermore, caffeine is considered to be a treatment for post-dural puncture headache (PDPH), which is a typical complication of lumber puncture and spinal anesthesia. Possible explanations for the occurrence of PDPH are the leakage of cerebrospinal fluid into the epidural space and increased vasodilatation of intracranial and epidural veins. By inhibiting adenosine, caffeine can increase vasoconstriction of cerebral arterial and the formation of cerebrospinal fluid, which is caused

by stimulation of Na-K pumps. IV of caffeine sodium benzoate during spinal anesthesia can reduce PDHD safely. Differently, being an adjuvant component, caffeine is added to NSAIDs and paracetamols to enhance the efficacy. Caffeine added to common analgesics leads to better pain relief compared with analgesics alone.

Caffeine has shown good treatment trends in treating both HH and PDHD, and as an adjuvant component, caffeine has also shown considerable advantages, moreover, caffeine has no obvious side effects, so the ability of caffeine to regulate pain should be further studied and taken concerns.

3.7. Botulinum Toxin

Botulism has been first discovered by Justinus Kener and then has been named Clostridium botulinum. The pharmaceutical use of botulism toxin has been found by Alan Scott in 1977 as therapy for strabismus and recently. Over ten years ago, the botulinum toxin type A (OBTA) was first utilized to treat migraines. In a placebo-controlled randomized trial, Mathew et al. proposed that chronic daily headache patients treated with OBTA for 11 months, showed a significant decrease of 50% or greater in headache frequency compared to baseline at day 180 [12]. Also, OBTA treatment contributed to a 1.5 intergroup difference compared to placebo. Overall, OBTA is a safe and well-tolerated therapy for headaches.

Once the OBTA gets into extracellular space after IV, the heavy chain of the OBTA is combined with the receptors on terminals of the C-fiber nerve. when OBTA reaches the nerve terminal after being endocytosed, the heavy chain is separated with a light chain, which then reaches the cell cytoplasm. The synaptosomal-associated protein (SNAP-25), which is necessary for the fusion of vesicles that contain neuropeptide and the nerve terminal membrane, can be deactivated by the light chain in the cell plasma. This will prevent the release of neuropeptides, particularly CGRP. Additionally, OBTA can lessen the insertion of TRPV1 and TRPA1 into the membranes of nociceptive neurons, two examples of big dense-core vesicle cargo. Vesicles can be mediated by the SNARE protein receptor, which controls exocytosis, or they can fuse with the nerve terminal membrane through constitutive exocytosis. At the same time, OBTA may block the sensitization of C-fiber nociceptors and the activation of A-delta fibers can be prevented by CGRP that release from the terminals of the C-fiber nerve. There is a decrease in the concentration of CGRP in the plasma of patients during chronic migraine attacks through the treatment of OBTA. OBTA may decrease migraine attacks by stopping the CGRP from nociceptive C-fiber from getting released. More possibilities of OBTA have been discovered in recent years, the combination therapy with CGRP-A and OBTA has shown greater effect compared to either therapy alone. A limitation in the effect of OBTA is that toxins can only be delivered to C-fibers with lateral axons of extracranial tissue. Moreover, the combination therapy with erenumab and OBTA had an enhanced effect on headache treatments. Overall, more research should be done on both independent and combination therapy for botulinum toxin.

4. Conclusion

The pathology of headache was quite complex, and the theory involved the trigeminal nerve and CGRP. Understanding different pathways of pain management can help to understand the mechanisms of headache disorders. However, more evidence found in recent studies also indicated other possible theories. Current pharmaceutical therapies for headaches have shown a great trend in reducing headache attacks and have shown fewer adverse effects during treatments. Most of the adverse effects occur hardly or they are easy to avoid. Although the exact mechanism of many drugs is unclear, it is known that different drugs have certain differences in mechanism, so headache patients can have different drug options according to their own body conditions and history of illness. Recent studies have seen an increase in the variety of drugs, offering more possibilities for designing better headache medications. Furthermore, non-pharmaceutical treatments such as acupuncture and manual therapy, and low glycemic diet also produce promising futures. To find the pathology of headache,

all patients-benefited medications, and other effective therapies, future research, and more evidence is needed.

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