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Signal Transduction Pathways in Pathogenesis of Migraine

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Abstract

Migraine is one of the most common neurological diseases. However, the pathogenesis of migraine is not completely clear, and there is no specific cure. Most researches showed that the pathophysiology of migraine is related to abnormal pain regulation, central sensitization, increased cortical excitability and neurogenic inflammation. Although studies have found that the key signaling pathways in migraine are dysregulated, the research on signal transduction pathways is incomplete. The goal of this review will be to the signal transduction pathways may involve in the pathogenesis of migraine, and focused on the central sensitization, the sensitization of trigeminal vascular system and the role of microglia in migraine. In the end we proposed research direction of target-based drugs under migraine signaling transduction pathway. Migraine is a common multiple disease, accurate diagnosis and etiology research play an important role in the treatment of migraine. We review the signaling pathways involved in the pathogenesis of migraine. Further studies based on signal transduction pathways will help to have a deeper understanding of the pathogenesis of migraine to help aid better treatment to patients with migraine.

Keywords: Migraine; Signal transduction pathways; Trigeminal vascular system; Microglia

Introduction

Migraine, a common primary headache disorder, is currently ranked as the third most prevalent medical condition and the second most disabling neurological disorder in the world [1]. Unfortunately, the recent therapeutic options on the market have not progressed accordingly. In fact, 50% of patients reported they are dissatisfied with the pain recurrence and 80% of patients discontinue therapy due to supplementary dosing [2]. Migraine was primarily proposed to be a vascular disease caused by the abnormal vasodilation which is controlled by the trigeminal nerve [3,4]. Hence, triptans as a vasoconstrictive drug which mostly bind to 5-hydroxytryptamine receptor 1B (5-HT1B) and 5-hydroxytryptamine receptor 1D (5-HT1D) receptors within cerebral blood vessels appear. However, a lot of recent experimental evidences challenge this hypothesis [5,6]. Cerebral blood vessels vasodilation is not the primary cause but only an epiphenomenon in migraine pathophysiology [7-9]. In fact, migraine is a pathophysiologically complex disease. Although findings emphasise that vasodilation is not the cause of migraine, vascular mechanisms might nonetheless have an important role effect in the pathophysiology of migraine [5]. The pathophysiology of migraine now supposed to be a dysfunctional sensory modulatory network involves the activation and sensitization of the trigeminocervical complex nociceptors, Cortical Spreading Depression (CSD) as well as abnormal brainstem activity [10-12]. Sensory transmission of nociceptive signals from peripheral trigeminal nerve sensations, such as intracranial and extracranial structures for pain sensing, including the dura mater and peripheral blood vessels of the trigeminal nerve transmit to second order neurons. From here, the ascending projection of the secondary neurons of TNC terminates in brainstem, hypothalamic, and thalamic nuclei [13]. In the cascade of events regarding vascular function, second order neurons also involved in the release of several neurotransmitters [14]. For example, calcitonin gene-related peptide (CGRP), which is a well-known vasodilatator, leading to subsequent increase in vessel diameter and blood flow in the meninges and cortex, both of which could further activate vascular and meningeal nociceptors leading to migraine headache [13].

Signaling pathways in migraine

Many of molecular signaling pathways that neuron homeostasis is highly regulated are abnormally activated or repressed in human migraine and in experimental models of migraine. Such abnormalities are not prone the self-renewal, proliferative, survival, and differentiation. In general, these pathways are intricate, with extrinsic and intrinsic molecular signals and regulatory elements. Many of these "pathways" are not linear, but rather interwoven networks of signaling mediators that feed into one another, facilitating intrapathway cross talk. Thus, this review will highlight signaling pathways cascades in migraine pathology and introduce the activation of microglial intracellular cascades work to these pathways.

MAPK Pathway

Mitogen-activated protein kinases (MAPKs), which consists of c-Jun N-terminal kinase (JNK), p38 MAPK, and extracellular signal-regulated kinase (ERK), representing extracellular stimuli into intracellular posttranslation and transcription by phosphorylation [15-17]. MAPK signaling pathways can be triggered by several different stimulus, not only proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), substance P but also inflammatory proteins, such as Inducible Nitric Oxide (iNOS), cyclooxygenase-2 (COX-2), ionized calcium binding adapter 1 (IBA-1) as well as pathological conditions, including oxidative, genotoxic, and osmotic stress [18-21]. While the phosphorylation of MAPK also contributes to the transcription factors which may increase and sensitize proinflammatory cytokines and other pain mediators, leading to induce and maintain even exacerbate of neuropathic pain status [18,22-24]. The MAPK activates several downstream signaling pathways through nontranscriptional processing and increasing gene transcription to produce short-term functional changes and long-term adaptive changes [25]. For example, phosphorylated ERK translocates to the nucleus activates nuclear factor erythroid 2-related factor 2 (Nrf2), which is a protein can regulates the heme oxygenase-1 (HO-1) expression to against oxidation and inflammation [26-28]. In addition, previous studies have reported that activated ERK may induce the activation of ribosomal s6 kinase (Rsk2), which then phosphorylates the transcription factor cAMP response element-binding protein (CREB) on serine 133 [29], binding to the DNA promoter regions and initiating the genes transcription [30-33]. The role of MAPK signaling in migraine has been demonstrated in animal models of nitroglycerin (NTG) [34,35]. Both Sun et al. [28]and Lai et al. [36] have explored the anti-migraine function of rhynchophylline. They all reported that the protection effect of rhynchophylline revised the activity of MAPK/ Nuclear factor-KB (NF-κB) pathway by NTG. In the migraine model of electrical stimulation of the superior sagittal sinus, chronic administration of paroxetine suppresses activation of p38 MAPK in the TNC compared with in the model group [37]. In addition, p- ERK appears to be a better marker in the dura mater, trigeminal ganglion (TG), and TNC for central sensitization induced by NTG infusion [38]. On the one hand p- ERK increase recepter plasticity, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, on the other hand it can suppress the activity of potassium Kv4.2 channels, induce and maintain central sensitization [39]. Based on these studies, there is a close relationship between MAPK phosphorylation and NTG in contributing to the development and maintenance of migraine.

cAMP/PKA/CREB pathway

As one of the earliest identified and ubiquitous secondary messengers, cyclic adenosine 3',5'-monophosphate (cAMP), is generated from adenosine Triphosphate (ATP) via adenylyl cyclases (ACs) and degraded via phosphodiesterases (PDEs), which catabolizes 1cAMP into 5AMP [40,41]. The widely known downstream effector of cAMP signaling is protein kinase A (PKA). PKA is made of two regulatory subunits (PKA-R) and two catalytic subunits (PKA-C). It was reported that cAMP-PKA signaling cascades is closely related to an array of transcriptional cascades involved in immune response, cellular metabolism promotes the synthesis of presynaptic neurotransmitters and synaptic plasticity, which is a prime mechanism underlying chronic pain, such as migraine [42,43]. Previous studies have demonstrated the involvement of cAMP-PKA pathway in inflammatory pain [44], neuropathic pain [45]and bone cancer pain [46]. Activated PKA phosphorylates and catalyzes phosphorylation of regulatory proteins causing a series of downstream changes. Not only including CREB phosphorylation, a key transcriptional co-factor that initiates biological processes, but also the activity of ion channels, cellular motor proteins and many enzymes involved in intermediate metabolism [47,48]. These phosphorylation events intertwine cAMP-PKA signaling with other cellular messengers and signaling cascades, providing multiple feedback loops and further modulating cAMP signaling, which indicates the crucial role of the cAMP-PKA pathway in the induction and maintenance of synapse plasticity in the nervous system [49,50].

Previous studies have revealed that the cAMP-PKA-CREB signaling is involved in migraine associated behaviors in animals. Consistently, migraineurs have an increased in plasma cAMP and CGRP levels during migraine attacks [51]. Moreover, elevated levels of cyclic AMP can active trigeminal neurons, leading to central sensitization [52]. Furthermore, previous study showed cilostazol, a selective inhibitor of phosphodiesterase 3(PDE3), increased intracellular levels of cyclic AMP inducing more migraine-like attacks [53]. The behavioral test of mechanical allodynia recovered with the inhibition of cAMP-PKA-CREB signaling by PKA inhibitor, suggesting that the effects of PKA inhibitor may be through regulation of the signaling pathway [54,55]. Interestingly, previous studies showed that both PKA inhibitors, H-89 and PKI (14-22) can block the regulation of CGRP release and regulate pain sensitization [56]. In all, these data suggests that the cAMP pathway offers an interesting exploration for initiating head pain and migraine, which deserves future focus.

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NF-κB pathway

NF-κB is a pleiotropic transcriptional factor which plays a pivotal role in transcription of the genes encoding the neuroinflammation, immune responses, cell cycle and survival as well as nociception [56]. In an inactive state NF-κB is sequestered within the cytoplasm by binding with IκBα (IκB family of inhibitory proteins). Once IκBα is phosphorylated and degradation, p-IκBα releasing NF-κB to enter the nucleus, resulting in initiating gene expression [57-59]. Under basal conditions, NF-κB is located within the cytoplasm, but following specific stimuli, its p65 subunit translocates into the nucleus, causing the initiation of transcriptional activity [60]. Various studies have showed that NF-κB and its downstream proinflammatory cytokines contribute to migraine. For example, studies have showed that parthenolide attenuated migraine via suppression of the NF-kB pathway after GTN triggered transcriptional events [61]. NF-kB, which controls iNOS expression following proinflammatory cytokine administration, was crucial to the transcription of iNOS following GTN infusion in rat meninges [57]. Besides, pretreatment of valproate (VPA), against migraine with mild side effects, could inhibit the activation of NF-κB [62]. The pathways involved in the induction of migraine by NTG actually initiates the activation of NF-kB [63]. To accomplish this, nitric oxide (NO) enhances IκBα degradate from the IκBα–NF-κB complex, then regulating the expression of inflammatory mediators, such as TNF-α, IL-1β and COX-2[64].

NO/ sGC/ cGMP pathway

During the past three decades multiple lines of evidence shows that NO is implicated in the migraine pathogenesis [65,66]. Once formed, NO binds with its high-affinity receptor, soluble guanylyl cyclase (sGC) resulting in enzyme activation [67]. The activated sGC converts guanosine triphosphate (GTP) into the second messenger guanosine3', 5'-cyclic monophosphate (cGMP). In addition, cGMP phosphorylates protein kinase G (PKG) [68], which phosphorylates ion channels eliciting decreased intracellular calcium. Upregulation of the NO/sGC/cGMP pathway has been implicated in migraine [69,70]. To support the role of the NO-sGC pathway in migraine, Manel Ben Aissa probed that the novel sGC stimulator, VL-102, stimulates cGMP production and induces migraine-associated hyperalgesia [71]. Furthermore, ODQ, sGC inhibitor effectively blocked chronic migraine-associated pain, which is produced by NTG experimental models of migraine [72]. Simplistically, cGMP is degradated to GMP by hosphodiesterase 5 (PDE5), acting as a negative regulator of this pathway. A PDE5 inhibitor sildenafil was found to evoke migraine-like pain in both migraineurs [73] and mice [74]. Taken together, these results strengthen the notion of increased NO as a hallmark of migraine-associated symptoms and establishes NTG as a useful translationally significant model of migraine.

Interaction between signaling pathways

As mentioned previously, these complex signal transduction pathways are not linear and, in some cases, cross-talk between and among various pathways occurs in the migraine. Some examples of convergence between pathways were discussed earlier. For example, in Lai et al. [36] studies, the function of rhynchophylline on migraine was exerted by inhibiting MAPK/NF-κB pathway. The results show that cooperation between the MAPK and NF-kB signaling pathways contribute to understanding the pathogenesis of migraine and mechanisms by which NTG contributes to migraine [66,75]. Furthermore, the converge of cAMP and cGMP pathways, leading to initiation of the same migraine attacks, which is demonstrated in attacks induced by CGRP and sildenafil [76]. In other cases, show that female ovariectomized rats significantly reduce the expression of brain derived neurotrophic factor (BDNF), TrkB, p-CREB and p-ERK in NTG-induced migraine model [77]. In contrast, giving estrogen is also able to reverse the suppression in BDNF, TrkB, p-CREB and p-ERK These data suggest that BDNF/TrkB and ERK/CREB axes are important for the induction or development of estrogen signals in the migraine [78].

Neuron–Glia Signaling in Trigeminal Ganglion

Increasing evidence suggests that neuronal–glia cell interactions are likely to play an important role in migraine pathophysiology, such as central sensitization and peripheral sensitization [79,80]. Activated microglia can communicate with neurons through chemotaxis and produce various pro-inflammatory cytokines leading to amplify nociceptive signals. Previous studies demonstrated that microglia- derived IL-18 is involved in migraine signaling pathway [82,83]. In inflammatory soup (IS) dural infusions mouse models of migraine, activated microglia synthesize and release IL-18, then, promoting NF-kB phosphorylation [84]. And resulting in gene expression, such as BDNF, which is a key molecule for maintaining migraine hypersensitivity. Furthermore, suppression of IL-18 attenuated nociceptive behavior and significantly inhibited the activation of NF-kB phosphorylation [85]. LPS-activated microglia increase the level of TNF-α, which is involved in various diseases, such as migraine [86]. Inflammatory mediators like TNF-α, acts on TLR4, and involves MAPK family member (P38, ERK, and JNK) signaling, resulting in NF-kB-mediated transcription [87,88]. Lalita Subedi [89] confirmed that regulation of JNK/NF-kB/TNF-αsignaling contribute to migraine. Therefore, neuron–glia interactions have been shown in stages of the TNF-αthey secrete, mediating the regulation of NF-κB and JNK signaling cascades. In Long at al. [39] study, enhancement of P2X4R expression in the TNC was found in chronic migraine mice. Extensive evidences have shown that P2X4Rs are mainly expressed in microglia, contributing to inflammatory pain, neuropathic pain, and migraine [90-93]. Activated P2X4Rs evoke p38-MAPK phosphorylation, resulting in MAPK signaling downstream [94]. Furthermore, 5-BDBD, The P2X4R inhibitor, prevents mechanical hyperalgesia [95]. Hence, it is inferred that a certain microglia-regulated P2X4R expression may be regulating migraine occurrence. On the other hand, Cortical spreading depression (CSD) is a phenomenon that

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results in prolonged suppression of electrical activity [96]. This slowly propagating wave seems to be involved in stroke, head trauma, migraine and epilepsy [97,98]. Neuron-glial interactions is thought to play a role in CSD occurrence. Microglia express voltage-sensitive ion channels, including Nav1.1, Kv1.3, and Kv1.5, and are thought to sense electrical activity pertaining to CSD [99-101].

Conclusion

Migraine is a common multiple disease, accurate diagnosis and etiology research play an important role in the treatment of migraine. Although no animal model of migraine is sufficient to explain how pain develops, what these hypothesized models have in common is the dysregulation of key signaling pathways. We review the signaling pathways involved in the pathogenesis of migraine, including migraine-related pathological processes, such as inflammatory response, synaptic remodeling, and central sensitization. At present, there are still a lot of deficiencies in the pathogenesis of migraine. Further research based on signal transduction pathways will help to have a deeper understanding of the occurrence, development and pathogenesis of migraine.

Authors' contribution

All authors read and approved the final manuscript. Qingling Zhai and Xiaowen Song edited the manuscript. Danna Xie collected the literatures. Jinbo Chen designed and monitored this manuscript. Qingling Zhai and Xiaowen Song contributed equally to this paper.

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