Received: 18 May 2022 | Revised: 17 July 2022 | Accepted: 25 August 2022

DOI: 10.1111/bcpt.13787

MINIREVIEW

BCPT Basic & Clinical Pharmacology & Toxicology

The role of high-conductance calcium-activated potassium channel in headache and migraine pathophysiology

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Funding information
The Research Fund of Rigshospitalet (E-23327-04). The Novartis Pharma AG. The Lundbeck Foundation for supporting the study through the Professor Grant (R310-2018-3711).

Abstract

Migraine is a common, neurovascular headache disorder with a complex molecular interplay. The involvement of ion channels in the pathogenesis of migraine gathered considerable attention with the findings that different ion channels subfamilies are expressed in trigeminovascular system, the physiological substrate of migraine pain, and several ion channel openers investigated in clinical trials with diverse primary endpoints caused headache as a frequent side effect. High-conductance (big) calcium-activated potassium (BK_{Ca}) channel is expressed in the cranial arteries and the trigeminal pain pathway. Recent clinical research revealed that infusion of BK_{Ca} channel opener MaxiPost caused vasodilation, headache and migraine attack. Thus, BK_{Ca} channel is involved in pathophysiological mechanisms underlying headache and migraine, and targeting BK_{Ca} channel presents a new potential strategy for migraine treatment.

KEYWORDS
human, ion channels as drug targets, migraine, pain, pain models, potassium channels

1 | INTRODUCTION

Migraine is a primary headache disorder,[1] affecting more than 15% of the global adult population in their most productive years of life[2] with a health and economic burden of billions of dollars globally.[3,4] The clinical manifestation of migraine is recurrent attacks with severe and usually unilateral and throbbing headache, lasting 4–72 h and associated with nausea and/or photophobia and phonophobia.[5] Approximately, one third of individuals with migraine report that the headache is preceded by an aura, which is characterized by reversible focal neurologic symptoms, typically comprising visual or hemisensory disturbances.[6] Despite advances in migraine research and novel emerging therapies, signalling pathways initiating migraine attacks remain a conundrum, and mechanism-based pharmacological treatments are warranted.[7] Trigeminovascular system consisting of trigeminal afferents innervating the meninges and its vessels are thought to be the biological underpinnings of migraine headache. In 1940, Ray and Wolff showed that alteration of vascular tone by distension of dural arteries and/or large cerebral (pial) caused a throbbing, unilateral migraine headache.[8]

Interplay between several ion channel subfamilies regulates vascular tone and nociceptive threshold. Ion channel involvement in migraine genesis is further strengthened by the observation that migraine is more prevalent in patients with channelopathies including epilepsy and episodic ataxia,[9] and inherited dysfunction of voltage-gated Ca^{2+} channels in the pathophysiological

cause of familial hemiplegic migraine (FHM), a small portion of the migraine spectrum. Whether ion channels initiate or contribute to migraine headache is yet to be elucidated.

High-conductance (big) calcium-activated potassium (BK_{Ca}) channel is expressed in the cranial arteries and the trigeminal pain pathway.[10–12] Here, we review data implicating BK_{Ca} channel in headache and migraine and discuss targeting BK_{Ca} channel as a new potential strategy for migraine treatment.

2 | BK_{CA} (SLO1) CHANNELS

The observed prominent outward K^+ current upon membrane depolarization and/or after influx of Ca^{2+} revealed the existence of BK_{Ca} channel. The channel is an octamer membrane protein complex consisting of four pore-forming subunits (α) associated with four accessory subunits (β) that regulate channel-gating behaviour (Figure 1).[13,14] The α-subunit encoded by a single gene (*Slowpoke* [*Slo*], *KCNMA1*)[15] has 10 segments divided into a *core region* (S0–S6) and an extensive carboxyl extension (S7–S10). The BK_{Ca} α-subunit has two or more high-affinity Ca^{2+} binding sites: regulators of conductance of K^+ domains (RCKs) within the extensive carboxyl extension and the calcium bowl within the *tail region* (S9–S10). Of all K^+ selective channels, BK_{Ca} channels have the largest single-pore conductance with a high kinetic energy for flow of K^+ current. The characteristic feature of BK_{Ca} channels is that they become activated (opened) by membrane depolarization alone, increasing intracellular Ca^{2+} alone or both. The β-subunits are non-covalently associated with α-subunit to form a BK_{Ca} channel complex. Four distinct β-subunits (β1–β4) have been discovered. The β2 and β3 subunits share sequence similarities with β1, but unlike β1 and β4 which favour the active conformation, β2 and β3 promote a fast-inactive conformation in BK_{Ca} channels. The β1-subunit is expressed primarily in smooth muscle and some neurons, while the β4-subunit is highly expressed in the brain.

3 | BK_{CA} CHANNEL OPENERS

Numerous BK_{Ca} channel openers have been developed including MaxiPost, andolast and cilostazol.[16] MaxiPost

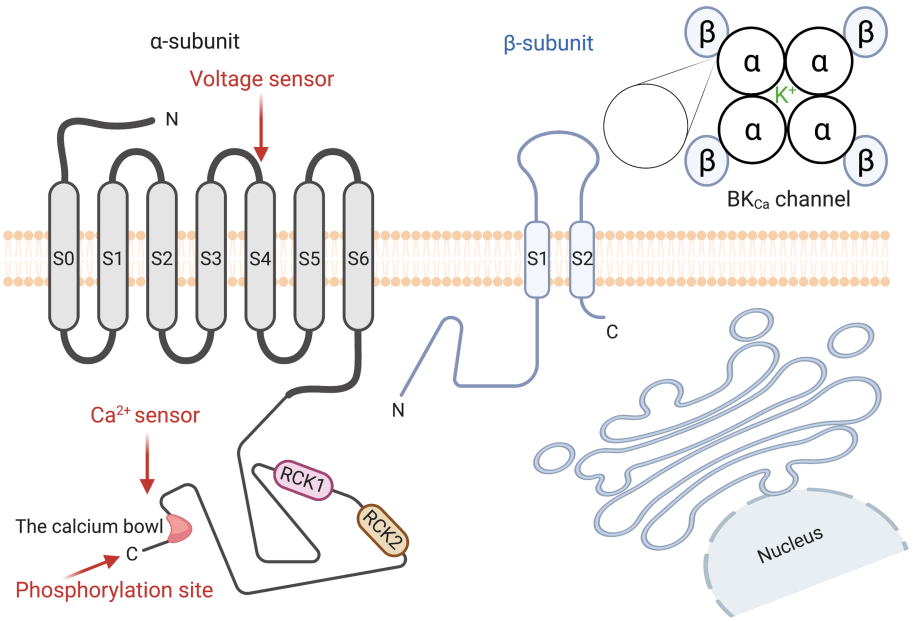

FIGURE 1 The structure of BK_{Ca} channels. BK_{Ca} channel is a hetero-octameric complex consisting of four pore-forming α-subunits and four regulatory β-subunits. The α-subunit has 10 segments divided into *core region* (S0–S6) and an extensive carboxyl extension (S7–S10) where the *tail region* (S9–S10) with the calcium bowl is located. regulators of conductance of K^+ domains (RCK) within the α-subunit form an intracellular gating involved in ligand-gating mechanism. The β-subunits are non-covalently associated with α-subunit to form a BK_{Ca} channel complex. the BK_{Ca} α-subunit includes several high-affinity Ca^{2+} binding sites such as the calcium bowl and RCK domains. Membrane depolarization registered by voltage sensors (S4) and/or binding of Ca^{2+} within the normal physiological range to the gating ring result in opening of the BK_{Ca} channel. cellular kinase and phosphatase directly regulate BK_{Ca} channel activity by phosphorylation and dephosphorylation. Phosphorylation occurs near to the C-terminal edge of the calcium bowl sequence, and the open-channel probability increases when all four subunits of a homomeric BK_{Ca} channel are phosphorylated.

(BMS-204352 or flindokalner) is a positive modulator of potassium channels with a high degree of potency and specificity at the BK_{Ca} channel.[12] The lipophilic property of MaxiPost facilitates its crossing the blood brain barrier (BBB) at high levels after intravenous administration. Preclinical stroke models revealed that MaxiPost was a promising neuroprotective agent in the treatment of acute stroke.[17–19] However, MaxiPost failed to show a significant effect in clinical trials. Andolast (CR-2039) succeeded to phase 3 trial and has proven to be significantly more effective than placebo in the treatment of bronchial asthma.[20] Besides being a BK_{Ca} channel opener, cilostazol (Pletal) inhibits phosphodiesterase 3 degradation and adenosine reuptake and is currently used in the treatment of intermittent claudication.[16] Clinical use of BK_{Ca} channel openers led to headache as a frequent adverse event.[21] Noteworthy, cilostazol is known to induce headache in healthy volunteers and migraine attack in migraine patients.[22] Yet, the several molecular targets of cilostazol hampered to implicate adequately BK_{Ca} channel in migraine pathophysiology. BK_{Ca} channel-induced headache has not been further investigated.

4 | BK_{CA} CHANNEL ACTIVATION CAUSED HEADACHE

To systemically explore headache induction upon BK_{Ca} channel activation, we recruited and allocated 20 healthy adults to receive a continuous intravenous of 0.05 mg/min MaxiPost (active drug) or placebo (isotonic saline) over 20 min on two study days separated by a washout period of at least 1 week (Figure 2).[23] The dose of MaxiPost was chosen based on previous human studies with MaxiPost.[17] Eighteen participants (90%) reported headache after the start of MaxiPost infusion compared with six (30%) after placebo. The median time to onset of headache was 40 min (range 10 min to 5 h) after MaxiPost. One participant reported a migraine-like attack. The headache localization was mostly in the frontal and temporal regions. The area under the curve (AUC) 0–12 h for headache intensity was significantly larger after MaxiPost compared with placebo.

5 | BK_{CA} CHANNEL ACTIVATION CAUSED MIGRAINE ATTACK

To explore whether BK_{Ca} channel activation induces migraine attack, we recruited and allocated 22 adults with migraine without aura to receive a continuous intravenous of 0.05 mg/min MaxiPost (active drug) or placebo (isotonic saline) over 20 min on two study days separated by a washout period of at least 1 week (Figure 3).[24] The incidence of headache over the 12-h reporting period was superior and significant after MaxiPost infusion ($n = 22$) (100%) compared with placebo. The AUC for headache intensity was larger after MaxiPost compared with placebo. The median time to onset of headache was 20 min (10–40 min). Twenty-one of 22 participants diagnosed with migraine without aura (95%) reported migraine attacks after MaxiPost infusion compared with none after placebo. The median time to onset of migraine attacks was 3 h (range 1–9 h). The head pain of the induced migraine attacks was mostly localized in the frontal and temporal regions. The

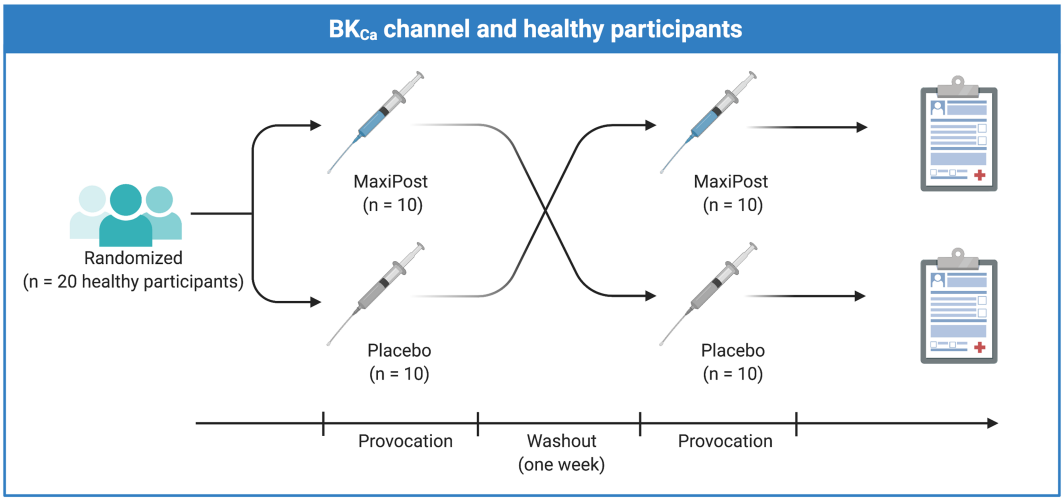

FIGURE 2 Study design with healthy adults. In a crossover, double-blind, placebo-controlled and randomized design, we randomly allocated 20 healthy participants to receive an intravenous infusion MaxiPost or placebo. To avoid accumulative physiological effect of MaxiPost, we had a washout period of at least 1 week between the two study days.

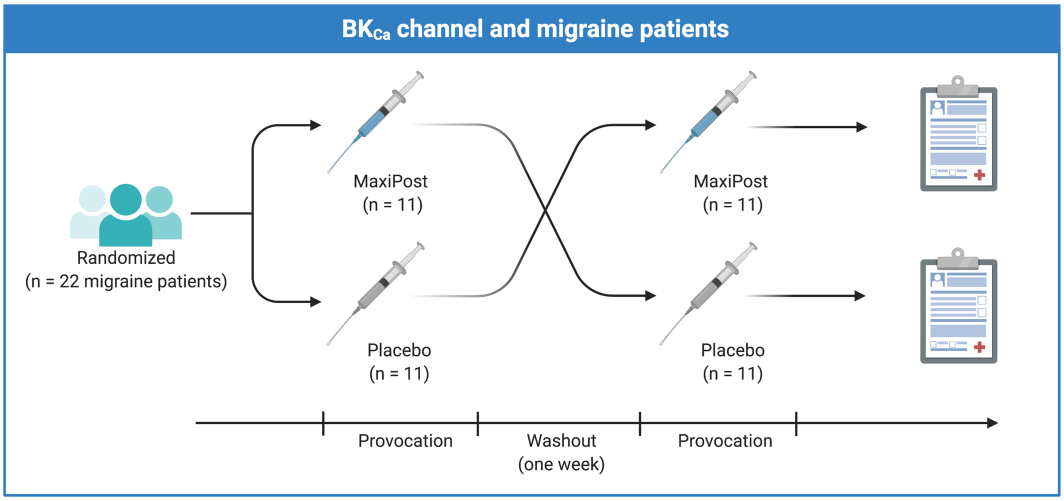

FIGURE 3 Study design with adults diagnosed with migraine. In a crossover, double-blind, placebo-controlled and randomized design, we randomly allocated 22 migraine patients to receive an intravenous infusion MaxiPost or placebo. To avoid accumulative physiological effect of MaxiPost, we had a washout period of at least 1 week between the two study days.

incidence of nausea, photophobia and phonophobia was higher after MaxiPost compared with placebo.

6 | VASCULAR EFFECTS AND ADVERSE EVENTS

In both experiments, we measured heart rate (HR), mean arterial blood pressure (MAP), velocity of middle cerebral artery (V_{MCA}) bilaterally using transcranial Doppler, diameter of the left radial artery (RA) and left frontal branch of the superficial temporal artery (STA) using high-resolution ultrasonography and facial blood flow using speckle technique. We found that MaxiPost decreased V_{MCA} and increased HR, STA diameter, RA diameter and facial blood flow during the in-hospital phase (=2 h). While MAP remained largely unchanged. Infusion of MaxiPost caused no serious adverse events and was well-tolerated by healthy participants and participants diagnosed with migraine. Adverse events observed and reported after MaxiPost were flushing, palpitations, unusual tiredness and warm sensation.

7 | DISCUSSION

Experimental studies demonstrated that BK_{Ca} channel is a crucial molecule in signalling pathways underlying the pathogenesis of headache and migraine. Infusion of BK_{Ca} channel opener MaxiPost caused headache in healthy participants and migraine attacks in adults diagnosed with migraine without aura. The features of reported migraine attacks including the intensity and localization of headache and associated symptoms mimicked patients' spontaneous migraine attacks. The observed vascular effects reflect the universal and long-lasting (>2 h) vasodilatory properties of MaxiPost (Figure 4). Thus, BK_{Ca} channels are widely expressed in cephalic and non-cephalic regions, and activation (opening) of these channels causes vasodilation, headache and migraine attack but no extracephalic pain.

Hitherto, the exact and the order of molecular cascades underlying headache and migraine are not fully clarified; previous pharmacological human models of migraine[27] revealed two intracellular signalling pathways to be involved in headache and migraine: stimulatory alpha (α_s) subunit associated with guanine nucleotide binding protein (G-protein)-coupled receptors—cyclic adenosine monophosphate (cAMP)—protein kinase A (PKA), *$G\alpha_s$-cAMP-PKA* and nitric oxide (NO)—cyclic guanosine monophosphate (cGMP)—protein kinase G (PKG), *NO-cGMP-PKG*. Since BK_{Ca} channels are directly regulated by a shifting balance between cellular kinase and phosphatase activities and become activated upon phosphorylation by PKA and PKG, it is possible that different intracellular signalling cascades converge in potassium channels including BK_{Ca} channel as a common downstream pathway.

Migraine pain involves both vascular components (dilation of cephalic arteries during a migraine attack) and neuronal pathways (hyperexcitable sensory neurons causing sensitization).[28] Whether neuronal activation is the primary cause of migraine pain and the vascular component is secondary to neuronal dysfunction is yet to be clarified. Migraine pain is believed to be initiated when trigeminal perivascular nociceptors are sensitized and

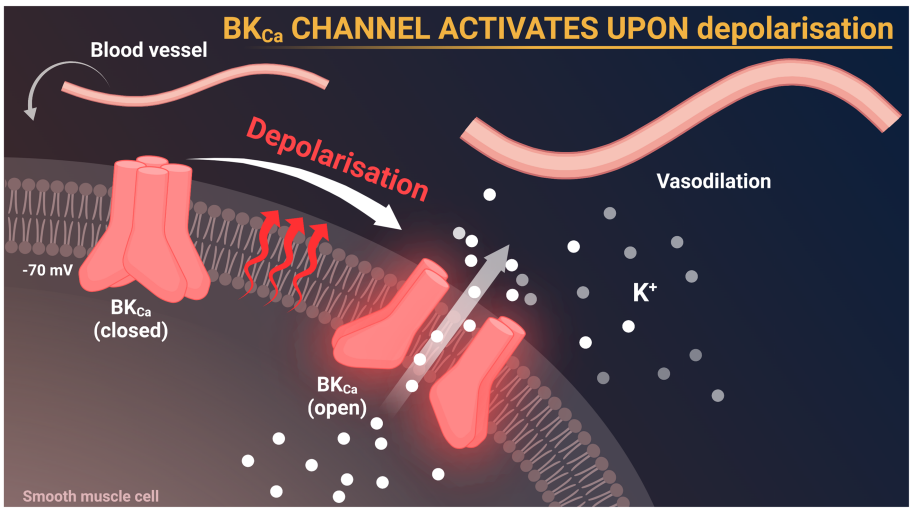

FIGURE 4 BK_{Ca} channels in vascular smooth muscle cells. BK_{Ca} channels are found in vascular smooth muscle cells (VSMCs) in cranial arteries and the trigeminal pain pathway including afferent fibres, trigeminal ganglion (TG) and trigeminal nucleus caudalis (TNC).[10,25,26] Membrane depolarization alone and/or Ca^{2+} influx through voltage-dependent Ca^{2+} channel (VDCCs) activate BK_{Ca} channels. In VSMCs, BK_{Ca} channel activity regulates myogenic tone and vessel contractibility, and BK_{Ca} channel activation (opening) causes K^+ outflow from VSMCs and subsequent vasodilation.

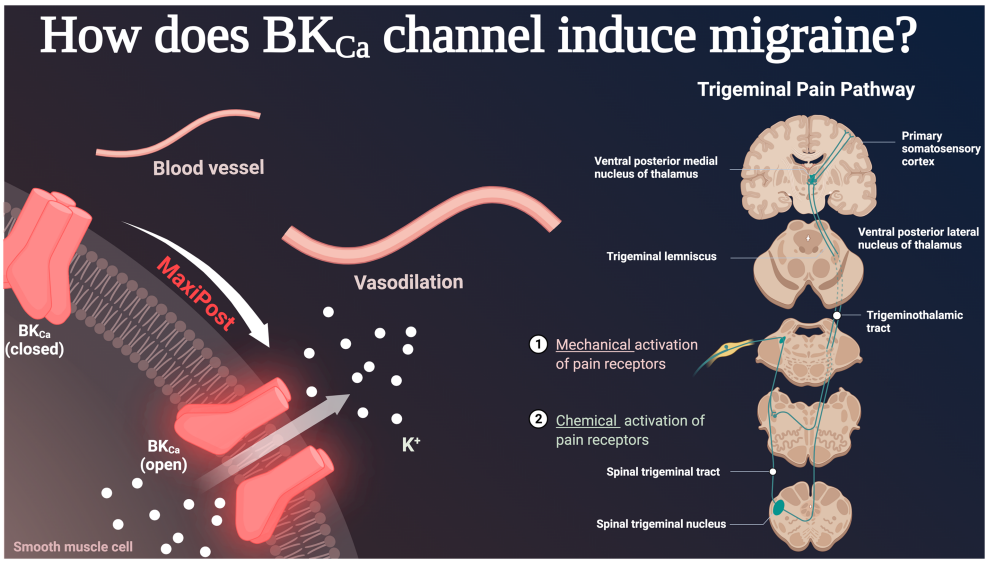

FIGURE 5 Mechanisms underlying migraine induction. BK_{Ca} channel activation causes long-lasting vasodilation resulting in mechanically induced sensitization of perivascular trigeminal afferents. Moreover, BK_{Ca} channel activation causes a substantial potassium (K^+) outflow and accumulation of extracellular positively charged ions resulting in chemically induced sensitization of perivascular trigeminal afferents. Mechanically and/or chemically induced activation of the trigeminal pain pathway causes headache and migraine.

activated mechanically or chemically.[7,29] Distension of cranial arteries is associated with head pain and prolonged, in contrast to short lasting, vasodilation induced migraine attacks in susceptible individuals.[30–33] Activation of BK_{Ca} channel expressed at vascular smooth muscle cells (VSMC)[34] causes efflux and accumulation of positively charged potassium in the extracellular space. This, in turn, creates an electrical gradient and influx of potassium and thus activation of trigeminal pain fibres[7] (Figure 5). This speculation lacks preclinical support including whether potassium ions from VSMC can reach and activate neighbouring nociceptors.

Preclinical investigations showed that application of BK_{Ca} channel opener NS1619 hyperpolarized the resting membrane potential and reduced the frequency of spontaneous action potentials in trigeminal nucleus caudalis

(TNC) neurons from rats, and these observations were reversed by the co-application of BK_{Ca} channel blocker iberiotoxin.[12] Of note, modulation of neuronal activity occurred presynaptically, on the primary sensory afferent emanating from the trigeminal ganglion (TG), and post-synaptically, on the second-order neuron within the TNC itself.[12,35] Moreover, activation of BK_{Ca} channel reduced neuronal firing and the release of neurotransmitters from trigeminal neurons that innervate the dural vasculature.[25] Interestingly, iberiotoxin increased the release of calcitonin gene-related peptide (a vasoactive molecule with a key role in migraine pathophysiology) from TNC neurons, and this was attenuated by activation of BK_{Ca} channel.[26] Thus, preclinical data failed to support clinical findings. This discrepancy can be explained by different models of migraine, including interspecies differences and various subunit expression.

Whether a direct activation of the BK_{Ca} channel in neurons causes headache and migraine is unknown. This, however, seems improbable since activation of BK_{Ca} channel hyperpolarizes the resting membrane potential in neurons and reduces the frequency of spontaneous action potentials.[36] Hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels are involved in pain sensation as modulation of HCN channels in afferents neurons causes spontaneous and persistent pain.[37–39] Whether activation of BK_{Ca} channel alters the threshold potential of HCN channels in the trigeminal afferents is yet to be elucidated. Additional imaginable rationalization is that inhibitory central neurons (either GABAergic and/or glycinergic) were hyperpolarized and inhibited upon Activation of BK_{Ca} channel. The result is disinhibition of excitatory neurons and hence augmented transmission of glutamatergic activity.

8 | FUTURE PERSPECTIVE TARGETING BK_{CA} CHANNEL

Current results raise the following substantial questions: (1) whether activation of BK_{Ca} channel causes migraine pain by activation of meningeal nociceptors and ascending trigeminal nociceptive pathways, as proposed during spontaneous migraine attacks; (2) whether activation of BK_{Ca} channel initiates cortical spreading depression and causes migraine aura in individuals diagnosed with migraine with aura; (3) whether activation of BK_{Ca} channel dilates meningeal arteries and alters cerebral blood flow; and (4) whether targeting BK_{Ca} channel relieves migraine pain. Several nonselective BK_{Ca} channel blockers such as iberiotoxin[12] and paxilline[40] have been developed, but these are not approved for clinical use. Since BK_{Ca} channels are diffusely expressed throughout the body, selective blockers against β1 or β4 subunits—because of its dominant presence in migraine-related structure[41]—are required to avoid unnecessary side effects. Besides being an inhibitor for ATP-sensitive potassium (K_{ATP}) channels,[42] the widely used antidiabetic drug glibenclamide was shown to attenuate activation of BK_{Ca} channel.[43] However, a series of clinical studies applying glibenclamide failed to affect activation of K_{ATP} channels.[44–47] Whether glibenclamide would affect activation of BK_{Ca} channel in a clinical setting is yet to be elucidated.

9 | CONCLUSION

A considerable proportion of individuals with migraine report a poor response and/or a lack of tolerability to available migraine drugs. BK_{Ca} channels are expressed in trigeminal pain pathway, and infusion of BK_{Ca} channel opener MaxiPost triggered headache in healthy volunteers and migraine attacks in individuals with migraine. Development of selective BK_{Ca} channel blockers would be beneficial as a candidate for future migraine therapies.

ACKNOWLEDGEMENTS

The authors thank the Research fund of Rigshospitalet, Novartis Pharma AG and Lundbeck Foundation for their collaboration.

CONFLICT OF INTEREST

MMK and CCH report no conflict of interest. MA has received consulting fees and honoraria for lectures/presentations from AbbVie, Allergan, Amgen, Eli Lily, Lundbeck, Novartis and Teva. MA has also received personal payments for participating on data Safety Monitoring Board or Advisory Board for AbbVie, Amgen, Eli Lily, Lundbeck and Novartis.

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How to cite this article: Al-Karagholi MA-M, Hakbilen CC, Ashina M. The role of high-conductance calcium-activated potassium channel in headache and migraine pathophysiology. *Basic Clin Pharmacol Toxicol*. 2022;131(5):347-354. doi:10.1111/bcpt.13787