The K_{ATP} channel in migraine pathophysiology: a novel therapeutic target for migraine

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Abstract

Background: To review the distribution and function of K_{ATP} channels, describe the use of K_{ATP} channels openers in clinical trials and make the case that these channels may play a role in headache and migraine.

Discussion: KATP channels are widely present in the trigeminovascular system and play an important role in the regulation of tone in cerebral and meningeal arteries. Clinical trials using synthetic K_{ATP} channel openers report headache as a prevalent-side effect in non-migraine sufferers, indicating that K ATP channel opening may cause headache, possibly due to vascular mechanisms. Whether K_{ATP} channel openers can provoke migraine in migraine sufferers is not known.

Conclusion: We suggest that K_{ATP} channels may play an important role in migraine pathogenesis and could be a potential novel therapeutic anti-migraine target.

Keywords: Migraine, K_{ATP} channel, K_{ATP} channels, Headache, Levcromakalim, Cromakalim

Introduction

Adenosine 5'-triphosphate-sensitive K⁺ (K_{ATP}) channel openers have been used in clinical trials for the treatment of hypertension and asthma. The most common side effect mentioned during treatment with K_{ATP} channel openers was headache [62, 64, 66–79] (Tables 2 and 3). However, only little attention has been focused on the role of K_{ATP} channels in migraine pathophysiology.

K_{ATP} channels were originally identified in cardiomyocytes [1], but have also been found in several tissues, including pancreatic α- and β-cells, smooth muscle, skeletal muscle and central neurons [2, 3]. The channels belong to the family of inwardly rectifying K⁺ channels that are inhibited at physiological intracellular levels ATP/ADP ratio. When intracellular ATP is reduced under conditions of metabolic challenges they open. K_{ATP} channels are critical in regulating insulin secretion, controlling vascular tone, and protecting cells against metabolic stress [2, 4, 5].

Over the past three decades, some preclinical evidence has emerged indicating that K_{ATP} channels may play an important role in migraine pathophysiology. In particular, the vasodilation effect of K_{ATP} channels is relevant, since it is has been established that endogenous neurotransmitters that trigger migraine attacks are often associated with dilation of cranial arteries [6].

Here we review preclinical and clinical studies on K_{ATP} channels and discuss the K_{ATP} channel as a novel therapeutic target for migraine treatment.

Molecular structure and isoforms

The K_{ATP} channel is a hetero-octameric complex that consists of four pore-forming K⁺ inwardly rectifying (Kir) subunits and four regulatory sulfonylurea receptor (SUR) subunits [7].

The Kir6.x subunit exists in two isoforms, Kir6.1 and Kir6.2. The SUR subunit belongs to the ATP-binding cassette (ABC) transporter family, regulated by...
sulfonylurea, with three isoforms, SUR1, SUR2A, and SUR2B [7, 8].

K\textsubscript{ATP} channels have specific tissue expression with different compositions of Kir\textsubscript{6.x} and SUR subunits which lead to distinct functional properties (Figs. 1 and 2 and Table 1).

**Channel function**

K\textsubscript{ATP} channel activity is controlled by changes in concentrations of intracellular ATP and magnesium adenosine diphosphate (Mg-ADP). K\textsubscript{ATP} channels couple the metabolic state of the cell to the membrane potential and thus play a crucial role in many tissues under both

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**Fig. 1** Molecular structure and isoforms. **a** Two major Kir\textsubscript{6.x} isoforms (Kir6.1 and Kir 6.2) and three major SUR isoforms (SUR1, SUR2A and SUR 2B) have been identified. **b** Kir\textsubscript{x} subunits combine tissue-specifically with different SUR subunits to form various native K\textsubscript{ATP} channels. Pancreatic, cardiac and smooth muscle K\textsubscript{ATP} channels are made up of Kir6.2/SUR1, Kir6.2/SUR2A and Kir6.1 (or Kir6.2)/SUR2B, respectively [2]. Kir, inwardly rectifying K\textsuperscript{+} channels; SUR, sulfonylurea receptor.
physiological and pathological conditions [9]. K⁺ channels participate in the regulation of vascular tone, including cerebral arteries [10]. When intracellular ATP is reduced, K<sub>ATP</sub> channels become activated; K⁺ efflux hyperpolarize the membrane and close voltage-operated Ca<sup>2⁺</sup>-channels (VOCC). The result is a decrease in cytosolic Ca<sup>2⁺</sup> concentration followed by relaxation of vascular smooth muscle cells and an increase in blood flow [11]. The same applies if cells are exposed to metabolic stress such as ischemia or hypoglycemia [12]. Closure of K⁺ channels leads to membrane depolarization and constriction of the vessels [11]. In addition an increase in intracellular cAMP and cGMP levels activate K<sub>ATP</sub> channels to produce vasodilation [11]. Synthetic K<sub>ATP</sub> channel openers (like levcromakalim and cromakalim) and blockers (like glibenclamide, second generation of sulfonylurea and PNU37883A) directly activate or inhibit the vascular K<sub>ATP</sub> channels, respectively [9] (Fig. 3).

**Table 1** Distribution of K<sub>ATP</sub> channels

| Subtypes of K<sub>ATP</sub> channels | Tissue expression | Migraine related structures |
|-------------------------------------|------------------|-----------------------------|
| Kir6.2/SUR1 Pancreas and brain      | DRG, TG and TNC from rats (20–24, 26). |
| Kir6.2/SUR2A Cardiac and skeletal muscle |                   |
| Kir6.2/SUR2B Smooth muscle          | DRG, TG, TNC, BA and MCA from rats (20–24, 26). |
| Kir6.1/SUR2B Smooth muscle          | MMA from rats, pigs and human; MCA from rats and pigs; BA, DRG, TG and TNC from rats (20–24, 26). |

DRG Dorsal root ganglia, TG trigeminal ganglion, TNC trigeminal nucleus caudatus, BA basilar artery, MMA middle meningeal artery, MCA middle cerebral artery

**Distribution of K<sub>ATP</sub> channels in migraine related structures**

**Intracranial arteries**
K<sub>ATP</sub> channels are present and functional in intracranial arteries [13–15]. They are found in vascular smooth muscle cells and vascular endothelial cells [16, 17]. In rat cerebral arteries, the distribution of K<sub>ATP</sub> channels varies with vessel size and brain region [18]. Real time polymerase chain reaction (RT-PCR) analysis revealed Kir6.1 and SUR2B subunits in middle meningeal artery (MMA) and middle cerebral artery (MCA) in rats and pigs [19, 20]. This profile of K<sub>ATP</sub> channels is also identified in human MMA [21] (Table 1).

**Trigeminal ganglion and trigeminal nucleus caudalis**
Kir6.1, Kir6.2, SUR1 and SUR2 are expressed in the trigeminal ganglion and trigeminal nucleus caudalis [22] (Table 1). In trigeminal neurons Kir 6.1 and Kir 6.2 immunoreactivity were expressed in cells with all soma sizes in all three divisions of the trigeminal ganglion [23].

**K<sub>ATP</sub> channels openers and migraine signaling pathways**
A number of endogenous vasoactive signaling molecules have been implicated in migraine [6], and K<sub>ATP</sub> channels may interact with these molecules.
Nitric oxide (NO)

In humans, infusion of the NO donor, glyceryl trinitrate, and inhibition of the breakdown of cGMP by sildenafil [24] provoke migraine attacks in migraineurs [25–27]. The NO-cGMP signaling pathway is involved in the relaxation of vascular smooth muscle [28]. In vitro studies with cerebral arteries isolated from rat and piglet and extra-cerebral arteries from rabbit reported that activation (opening) of K_ATP channels contributed to both cAMP- and cGMP-mediated vasodilation [29–31]. Yuan et al. [32] reported that sildenafil-induced vasodilation in porcine retinal arterioles was significantly inhibited by glibenclamide and suggested that cGMP signaling triggers opening of K_ATP channels. In contrast, NO-induced dural and pial artery dilation in rats was not attenuated by the K_ATP channel blocker, glibenclamide [33]. Together, these data suggest that interspecies differences are likely to explain the discrepancy in findings of the role of K_ATP channels in NO-induced vasodilation.

Calcitonin gene-related peptide (CGRP)

CGRP is one of the most potent endogenous vasodilators and major arteries in the intracranial circulation of man and animals are innervated by CGRP-containing nerve fibers [34–36]. Efficacy of CGRP antagonism is established in acute [37, 38] and preventive treatment of migraine [39]. CGRP activates vascular smooth muscle K_ATP channels indirectly through adenylate cyclase and protein kinase A (PKA) phosphorylation (Fig. 4) [40–43]. In rats, CGRP-induced dilation of the dural and pial arteries in vivo was shown to be inhibited by glibenclamide [33], but K_ATP channel openers do not interact with CGRP release in trigeminal ganglion and trigeminal nucleus caudalis [22]. This suggests that K_ATP channels are involved in CGRP-induced intracranial vasodilation.

Pituitary adenylate cyclase activating polypeptide (PACAP)

Pituitary adenylate cyclase activating polypeptide (PACAP) is a potent endothelium independent vasodilator of various vascular beds, including cerebral arteries [44, 45]. In vivo and in vitro studies have demonstrated that PACAP dilates cranial arteries in different species, e.g. human cerebral arteries [34, 46, 47], pig pia artery, canine basilar artery, cat cerebral arteries, rabbit posterior cerebral arteries and rat middle cerebral arteries [48–52]. Emerging
data suggest that PACAP or its receptors are a promising target for migraine therapeutics [53]. PACAP has three types of receptors; pituitary adenylate cyclase PAC1 (pituitary adenylate cyclase receptor 1), VPAC1 (vasoactive intestinal peptide and pituitary adenylate cyclase receptor 1) and VPAC2 (vasoactive intestinal peptide and pituitary adenylate cyclase receptor 2) [54] the two latter ones are also activated by vasoactive intestinal peptide and all three receptors are found in cerebral artery smooth muscle cells [55]. Through these receptors, PACAP leads to an increase in intracellular cAMP, which activates PKA and produces vasodilation by several mechanisms including activation of K<sub>ATP</sub> channels (Fig. 4) [45]. Interestingly, glibenclamide could partially inhibit PACAP induced vasodilation in cerebral, coronary and pulmonary arteries, suggesting that PACAP may also activate K<sub>ATP</sub> channels [44, 45].

### Prostaglandins

Prostacyclin (PGI<sub>2</sub>) activates and sensitizes meningeal sensory afferents, and provokes immediate migraine-like attacks in migraine sufferers [56]. PGI<sub>2</sub> also increases K<sub>ATP</sub> channel activity in vascular smooth muscle preparations by cAMP-dependent PKA activation [57] (Fig. 4).

#### Headache induced by K<sub>ATP</sub> channels openers

In the late 80’s there was a tremendous interest in developing novel K<sub>ATP</sub> channel openers for hypertension, angina pectoris and asthma. Three pharmacological drugs were developed, pinacidil, nicorandil and levcromakalim. One of most common adverse events after treatment reported in these studies was headache [58–63].

Six clinical trials with pinacidil have been published for treatment of essential hypertension. Between 7% and 21% of the patients reported headache as an adverse effect (Table 2).

Noricandil was tested for the treatment of angina pectoris and ischemic heart disease. 23% to 88% of the patients reported headache as an adverse event (Table 3). The high incidence of headache is likely due to the mixed K<sub>ATP</sub> channel opener and NO donor properties of nicorandil which thus cause vasodilation via two separate mechanisms.

Levcromakalim was investigated for the treatment of asthma and essential hypertension. In these studies

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**Table 2** Headache incidences registered during randomized controlled trials (RCT) and open label clinical trials with pinacidil

| Paper                     | Study design | Dose (daily) | Indication              | No. of patients | Headache No. |
|---------------------------|--------------|--------------|-------------------------|----------------|--------------|
| Muiesan et al. 1985, Eur. J. Clin. Pharmacol [86]. | RCT          | 30–75 mg     | Essential hypertension | 30             | 2 (7%)       |
| Laher & Hickey 1985, J. Int. Med. Res [87].      | Open label   | 12.5 mg      | Healthy volunteers      | 12             | 1 (8%)       |
| D’Arcy et al. 1985, Eur. J. Clin. Pharmacol [88]. | Open label   | 20–100 mg    | Essential hypertension  | 23             | 4 (17%)      |
| Zachariah et al. 1986, Eur. J. Clin. Pharmacol [89]. | RCT          | 62 mg (mean) | Essential hypertension  | 23             | ———         |
| Sterndorff & Johansen 1988, Acta Med. Scand [90]. | RCT          | 25–100 mg    | Essential hypertension  | 71             | 7 (10%)      |
| Goldberg 1988, J. Cardiovasc. Pharmacol [91].    | RCT          | 25–100 mg    | Essential hypertension  | 145            | 31 (21%)     |
between 29% and 76% of the patients reported headache as an adverse event (Table 4).

The selective synthetic K\textsubscript{ATP} channel openers levcromakalim and pinacidil have been shown to induce dilation in rat cranial arteries [13, 15, 19] and in isolated human cerebral arteries [64]. Moreover, the arterial dilation can be inhibited by synthetic K\textsubscript{ATP} channel blockers like glibenclamide [10, 33] and PNU37883A [21, 65] (Fig. 3). These findings suggest that high incidences of headache could be due to vasoactive effect of the K\textsubscript{ATP} channel openers in pain-sensitive extra- and/or intracerebral arteries.

**Discussion and future perspectives**

K\textsubscript{ATP} channels are expressed in migraine-related structures such as the cranial arteries, TG and TNC [18–22, 66]. K\textsubscript{ATP} channels are also connected to a number of key molecules in migraine pathogenesis, particularly nitric oxide, CGRP, PACAP and PGI\textsubscript{2} known to provoke migraine attacks [56, 67–71]. Therefore, the K\textsubscript{ATP} channels are interesting in migraine context.

Human experimental models have demonstrated that the activation of the cAMP and cGMP pathways can trigger headache in healthy volunteers and migraine attacks in migraine sufferers [6, 71, 72]. The cAMP and cGMP signaling pathways are crucial in the activation of K\textsubscript{ATP} channels, which result in the relaxation of smooth muscle [29–31]. Furthermore, synthetic K\textsubscript{ATP} channel openers like levcromakalim and pinacidil trigger headache in non-migraine patients [58–63]. Although a detailed description of levcromakalim- and pinacidil-induced headache and accompanying symptoms are lacking, these data support a role of K\textsubscript{ATP} channels in migraine headache. Because K\textsubscript{ATP} channel openers were tested for other indications, there are no available data on the potential migraine-inducing effects of pinacidil and levcromakalim in migraine patients. It is conceivable that both headache and migraine are underreported as adverse events, as was found for the phosphodiesterase inhibitors, cilostazol and sildenafil [73, 74].

In addition to the vasoactive effects, the K\textsubscript{ATP} channels might also tap into other parts of the migraine cascade. For a number of patients, migraine attacks are associated with transient focal neurological symptoms called the aura [75], possibly caused by cortical spread depression (CSD) [76]. During CSD K\textsuperscript{+} conductance is increased, and CSD may be inhibited by Kir antagonist [77]. The fact that K\textsubscript{ATP} channels open under cellular stress, as seen during long lasting depolarizations, could provide a link between K\textsubscript{ATP} channels, CSD and migraine aura.

With regard to the migraine pain, it is worth noting that K\textsubscript{ATP} channels are also found in peripheral nociceptive fibers [78] and activation of these channels play a crucial role in anti-nociception at both spinal and supra-spinal levels [23, 79]. The exact role of these findings in the headache induced by K\textsubscript{ATP} channel openers is unknown.

If K\textsubscript{ATP} channel openers are in fact able to trigger migraine, the next step to consider is whether K\textsubscript{ATP} channel antagonists can relieve migraine. K\textsubscript{ATP} blockers for the treatment of migraine should be selective for the Kir6.1/SUR2B subtype because of its dominant presence in vascular tissue (Table 1). The necessity of a subtype

| Table 3 | Headache incidences registered during randomized controlled trials (RCT) and open label clinical trials with nicorandil |
|---------|-------------------------------------------------------------------------------------------------------------|
| Paper   | Study design | Dose (daily) | Indication | No. of patients | Headache No. |
| Camm & Maltz, 1989, Am. J. Cardiol [92]. | RCT | 20–60 mg | Angina pectoris | 8 | 20 mg 50% 40 mg 88% 60 mg 67% |
| Raftery et al. 1993, Eur. Heart Journal [93]. | RCT | 20 mg and 40 mg | Angina pectoris | 18 | 11 (61%) |
| Roland 1993, Eur. Heart Journal [94]. | Review | 10–80 mg | Angina pectoris | 1680 | 36% |
| Wolf et al. 1993, Eur.J.Clin.Pharmacol [95]. | RCT | 20–200 μg i.v. | Healthy volunteers | 48 | 19 (40%) |
| Witchitz & Darmaon, 1995, Cardiovasc. Drugs & Therap [96]. | Open label | 20–40 mg | Angina pectoris | 197 | 45 (23%) |
| Dunn et al. 1999, Pharmacoepidemiology and Drug safety [97]. | Prescription-event monitoring (PEM) study | Varying | Angina pectoris & ischemic heart disease | 13,260 | 477 (4%) |

| Table 4 | Headache incidences registered during randomized controlled trials (RCT) and open label clinical trials with levcromakalim |
|---------|-------------------------------------------------------------------------------------------------------------|
| Paper   | Study design | Dose (daily) | Indication | No. of patients | Headache No. |
| Singer et al. 1989, J. Hypertens [98]. | RCT | 1.5 mg | Essential hypertension | 8 | 4 (50%) |
| Williams et al. 1990, Lancet [60]. | RCT | 1.5 mg | Asthma | 16 | 10 (62%) |
| Kidney et al. 1993, Thorax [62]. | RCT | 0.125–0.5 mg | Asthma | 25 | 19 (76%) |
| Suzuki et al. 1995, Arzneim.-Forsch./Drug Res [99]. | Open label | 0.5–1.0 mg | Essential hypertension | 14 | 4 (29%) |
specific blocker is unavoidable because of occurrence of different subtypes in different tissues. Glibenclamide cannot be used due to its high affinity to the Kir6.2/SUR1 subtype of K\textsubscript{ATP} channels present in the pancreas with hypoglycemia as a side effect [80]. PNU-37883A is a Kir6.1 selective K\textsubscript{ATP} channel blocker that was originally developed as a diuretic drug [81, 82]. The drug was not approved for human studies because of its cardiac depressant activity in animal studies [83]. This precludes further clinical development of PNU-37883A due to possible serious adverse events but may not exclude further investigations in other blockers against Kir6.1 subunit because it is not clear if all blockers against Kir6.1 subunit have non-favorable effects. These findings indicate that the SUR2B subunit and the Kir6.1 subunit should be a potential target for the treatment of migraine, but proof of concept studies are needed to examine this hypothesis.

**Conclusion**

Emerging evidence suggests that K\textsubscript{ATP} channels could be involved in the pathophysiology of migraine. K\textsubscript{ATP} channels exist in structures which are believed to be linked to the pathophysiology of migraine, including cerebral and meningeal arteries and the trigeminal system [19–22]. It is established that the cAMP signaling pathway and possibly cGMP signaling pathway are involved in the activation of K\textsubscript{ATP} channels [29–31]. This is interesting in migraine contexts, as the two signaling pathways are likely to be crucial in the development of a migraine attack. We suggest that the presented clinical and theoretical evidence support further studies of K\textsubscript{ATP} channel openers in migraine context. Future human studies will help clarify the role of K\textsubscript{ATP} channels in the pathophysiology of migraine.

**Abbreviations**

| Abbreviation                  | Definition                                                                 |
|-------------------------------|---------------------------------------------------------------------------|
| ABC transporter               | ATP-binding cassette transporter                                           |
| BA                            | Basilar artery                                                            |
| CGRP                          | Calcitonin gene-related peptide                                           |
| CSD                           | Cortical spread depression                                                |
| DRG                           | Dorsal root ganglia                                                       |
| K\textsubscript{ATP} channel  | Adenosine 5′-triphosphate-sensitive K\textsuperscript{+} channel           |
| Kir                           | K\textsuperscript{+} inwardly rectifying channel                           |
| MCA                           | Middle cerebral artery                                                    |
| Mg-ADP                        | Magnesium adenosine diphosphate                                           |
| MMA                           | Middle meningeal artery                                                   |
| NO                            | Nitric oxide                                                              |
| PACAP                         | Pituitary adenylate cyclase activating polypeptide                         |
| PGI                           | Prostacyclin                                                              |
| SUR                            | Sulfonylurea receptor                                                     |
| TG                             | Trigeminal ganglion                                                       |
| TNC                           | Trigeminal nucleus caudatus                                               |
| VOCC                          | Voltage-operated Ca\textsuperscript{2+} channels                          |

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**Competing interests**

The authors declare that they have no competing interests.

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