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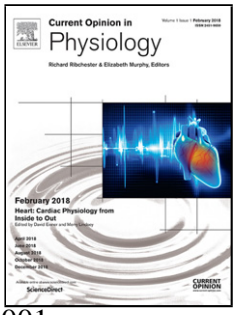

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Ion channels in migraine disorders

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Abstract

Migraine is a complex brain disorder characterized by recurrent attacks of unilateral headache and a global dysfunction in multisensory information processing. Genetic studies implicate several ion channel genes in migraine, ether as causative of a monogenic subtype (FHM) or possible contributors. Here we mainly discuss functional studies in transgenic mice carrying a $Ca_V2.1$ mutation causing FHM, and the insights they provide into the disease mechanisms, in particular regarding susceptibility to cortical spreading depression (CSD), the phenomenon that underlies migraine aura and can trigger the headache mechanisms. We also discuss recent findings implicating the ATP-gated P2X7 receptor in initiation of experimental CSD, and review some properties of the channels identified by genome-wide association studies as having a potential role in migraine.

Introduction

Migraine is a common, complex brain disorder primarily affecting the sensory nervous system; it is characterized by recurrent attacks of severe, unilateral, throbbing headache and by a global dysfunction in multisensory information processing, whose principal manifestations are amplification of percepts from multiple senses during the headache attack and impaired adaptation of sensory and cognitive event-related potentials resulting in heightened cortical responses and hypersensitivity to sensory stimuli in the period between attacks [1-3]. In a third of migraineurs the headache is preceded by transient sensory (most frequently visual) disturbances, the so called migraine aura, whose neurophysiological correlate is cortical spreading depression (CSD) [4, 5]. CSD is a self-sustaining, slowly propagating wave of nearly complete depolarization of brain cells that lasts about one minute and silences brain electrical activity for several minutes. CSD can be induced in healthy brain tissue by intense depolarizing stimuli that increase the extracellular concentration of K^+ ions, $[K]_e$, above a critical threshold [4].

The migraine pain is caused by activation and sensitization of the trigeminovascular pain network, beginning with the activation and sensitization of trigeminal sensory afferents, that innervate cranial tissues, in particular the meninges, and second order neurons in the trigeminal nucleus caudalis (TNC); the TNC projects directly or indirectly to different areas of the brainstem and forebrain that are involved in different aspects of pain and other aspects of the complex migraine symptomatology (Figure 1)[1-3]. Whereas the properties of pial afferents remain largely unknown, the dural afferents have properties typical of nociceptors in other tissues [1, 6]. A sterile meningeal inflammation is considered to be a key mechanism that may underlie the sustained activation and sensitization of meningeal nociceptors during migraine attacks [1, 6].

However, the endogenous processes that activate meningeal nociceptors and promote meningeal inflammation during a migraine attack remain incompletely understood. While most migraine attacks start in the brain, the mechanisms of the primary brain dysfunction that causes migraine and leads to episodic activation-sensitization of the trigeminovascular network remain largely unknown.

Key insights into these questions were provided by evidence that a single experimental CSD leads to delayed sustained increases in dural blood flow and in ongoing activity of rat

dural nociceptors and TNC trigeminovascular neurons as well as delayed sensitization of the TNC neurons [7-10]. According to an interesting study, the delayed trigeminal activation results from a cascade in which CSD induces opening of neuronal pannexin1 (panx1) channels and inflammasome activation, which initiate a parenchimal inflammatory response leading to dural mast cell degranulation, possibly consequent to release of proinflammatory molecules in the meninges via glia limitans [11]. Neuronal panx1 are large-pore channels permeable to high-molecular weight molecules like ATP; their opening is promoted by conditions occurring during CSD, such as high $[K]_e$, increase of intracellular calcium, $[Ca]_{in}$, NMDAR activation [4, 12, 13] (section 3). Since activation of meningeal nociceptors *in vivo* leads to release of vasoactive proinflammatory peptides from their peripheral nerve endings, that produce vasodilation of meningeal blood vessels (mainly due to CGRP), plasma extravasation and local activation of dural mast cells [1, 6], the algesic signals arising from the parenchimal inflammatory cascade might be amplified by the neurogenic inflammation; this CSD-induced inflammatory cascade may provide the sustained stimulus required for senzitization of trigeminal nociceptors and lasting pain [11] (Figure 1).

Several findings support a pivotal role of CGRP in migraine, including the efficacy of CGRP receptor antagonists in migraine treatment and the induction of delayed migraine-like headache in a large fraction of migraineurs, but not in controls, suggesting that many migraineurs are hypersensitive to CGRP-mediated modulation of nociceptive pathways. The mechanisms underlying this hypersensitivity and the mechanisms of action of CGRP during a migraine attack remain unclear, although the therapeutic efficacy of monoclonal antibodies against CGRP (CGRP-mAb) point to peripheral mechanisms [1, 14]. Notably, CGRP-mAb treatment inhibited the CSD-induced activation of Aδ nociceptors the activation-sensitization of high-threshold TNC neurons [15, 16].

The findings just reviewed support the idea that CSD not only causes migraine aura but may also trigger migraine headache. However, the mechanisms underlying susceptibility to “spontaneous” CSDs in migraine remain largely unknown.

Migraine is a complex polygenic genetic disorder, with heritability estimates as high as 50 % [17, 18]. The largest genome-wide association study (GWAS) of migraine so far led to the identification 38 genomic loci as likely susceptibility genes, three of which contain ion

channel genes: TRPM8, KCNK5, GJA1; these genes encode the non-selective cation channel TRPM8, a member of the family of transient receptor potential channels, the TASK2 (TWIK-related acid sensing K) channel, a member of the family of K^+ channels with two pore-forming domains (K2P) giving rise to "leak" currents, and Cx43, a member of the connexins family, respectively [19]. However, most of our current molecular understanding of migraine comes from studies of familial hemiplegic migraine (FHM), a rare monogenic subtype of migraine with aura (MA) [17, 18], with three causative genes: CACNA1A (FHM1), ATP1A2 (FHM2) and SCNA1A (FHM3) [20-22]. CACNA1A and SCNA1A encode the pore-forming subunits of the voltage-gated ion channels $Ca_V2.1$ and $Na_V1.1$, while ATP1A2 encodes the alpha2 Na, K ATPase. Apart from the motor aura and the possible longer aura duration, typical FHM attacks resemble common MA attacks, but some patients can also have atypical severe attacks and/or permanent cerebellar symptoms [18]. The generation of four FHM knockin (KI) mice, carrying the FHM1 R192Q or S218L and the FHM2 W887R or G301R mutations in the orthologous genes, provided the unique opportunity to study the primary brain dysfunctions of a migraine disorder [23-26].

Here, we will focus on the functional studies in FHM1 KI mice carrying the $Ca_V2.1$ channel mutation R192Q, which causes typical FHM attacks in humans [20], and on the insights into migraine pathophysiology and the mechanisms underlying the susceptibility to CSD obtained from these studies. We will only briefly discuss the different findings in the S218L FHM1 mouse model, that may give insights into the additional clinical features of the severe syndrome caused by the S218L mutation [24]. We will also discuss recent findings implicating novel ion channels in the induction of experimental CSD, besides the established glutamate NMDA receptors (NMDARs) [4]. Finally, we will briefly discuss the properties of the channels whose potential role in migraine was indicated by the recent GWAS [19].

1. $Ca_V2.1$ channels and FHM1

$Ca_V2.1$ channels are widely expressed in the nervous system, including all structures implicated in the pathogenesis of migraine, and play a dominant role in controlling neurotransmitter release, particularly at central synapse; their somatodendritic localization points to additional postsynaptic roles ([27] and references therein) (Figure 2). Analysis of the single channel properties of mutant recombinant human $Ca_V2.1$ channels and of the $Ca_V2.1$ current in neurons of FHM1 KI mice revealed that the mutations produce gain of function, mainly due to increased channel open probability and channel activation at lower

voltages; the gain-of-function effect may be dependent on the specific $Ca_V2.1$ splice variant and/or auxiliary subunit ([27] and references therein). Indeed, neuron-specific effects have been uncovered in FHM1 mice, likely due to expression of specific $Ca_V2.1$ splice variants and/or auxiliary subunits [28, 29], which may help to explain why a mutation in a channel widely expressed in the nervous system produces the specific neuronal dysfunctions leading to migraine (see below).

A key migraine-relevant consequence of gain-of-function of mutant brain $Ca_V2.1$ channels is increased susceptibility to experimentally induced CSD, as revealed by a lower threshold for CSD induction and an increased rate of CSD propagation in FHM1 KI mice *in vivo* [23, 24]. During CSD, the increase of $[Ca]_{in}$ in neurons, axons and dendrites and the decrease of tissue oxygenation were both larger in FHM1 compared to wild-type (WT) mice; after CSD, the reduction of cerebral blood flow was more prolonged [30, 31]. CSD more readily propagated into the striatum and produced more severe and prolonged motor deficits (including hemiplegia) in FHM1 mice [32-34]. In good correlation with the larger $Ca_V2.1$ gain-of-function produced by the S218L compared to the R192Q mutation [23, 24, 35, 36], the strength of CSD facilitation as well as the severity of the post-CSD neurological motor deficits and the propensity of CSD to propagate into subcortical structures were larger in S218L compared to R192Q KI mice [23, 24, 32-34].

The study of cortical synaptic transmission in R192Q mice revealed enhanced excitatory neurotransmission, due to enhanced action-potential (AP) evoked Ca^{2+} influx through mutant presynaptic $Ca_V2.1$ channels and enhanced probability of glutamate release at cortical pyramidal cell synapses [37]. Congruently, short-term synaptic depression during trains of APs was also enhanced. In vivo evidence of enhanced glutamatergic neurotransmission in R192Q mice was recently obtained from measurements of CA1 field potentials in response to stimulation of anterior hippocampal commissure. Interestingly, LTP at these synapses was also stronger in R192Q mutants, although paradoxically learning and memory were impaired [38]. Although indirect, evidence for gain-of-function of excitatory neurotransmission was also obtained at parallel fibers-Purkinje cell synapses in cerebellar slices [39] and at excitatory synapses onto dorsal suprachiamastic nucleus neurons of R192Q mice [40].

In striking contrast with the enhanced glutamatergic transmission, inhibitory GABAergic transmission at cortical fast-spiking (and other multipolar) interneuron synapses was unaltered in R192Q mice, despite being initiated by $Ca_V2.1$ channels [29, 37]. This is likely due to the expression of interneuron-specific $Ca_V2.1$ channels whose gating properties are barely affected by the FHM1 mutation [29].

As a consequence of the differential effect of FHM1 mutations on excitatory and inhibitory synaptic transmission, one predicts functional alterations of the highly interconnected cortical microcircuits, in which three main microcircuits core motifs composed of excitatory and inhibitory neurons can be recognized [41] (Figure 3). Although functional alterations in these microcircuits are expected to result in dysfunctional regulation of the cortical excitatory/inhibitory (E/I) balance and altered processing of sensory information, it is not straightforward to predict the effect of FHM1 mutations on microcircuit and network function, because in the cortex excitation and inhibition are inseparable events. Indeed, an enhanced excitatory transmission at the synapses onto inhibitory interneurons may lead to increased inhibition due to increased interneurons recruitment, and the net effect may be inhibitory in certain conditions. This might possibly explain the reduced neuronal calcium responses to repeated whisker stimulation in anesthetized R192Q mice in [31].

CSD rescue experiments support a causative link between increased glutamatergic transmission at cortical synapses and facilitation of initiation and propagation of experimental CSD in R192Q KI mice. In fact, when AP-evoked glutamate release at pyramidal cell synapses was brought back to WT values by partially inhibiting the $Ca_V2.1$ channels, the facilitation of CSD in R192Q cortical slices was completely eliminated [37]. The finding that propagation of CSD to striatum and hippocampus in R192Q mice is eliminated by systemic treatment with pregabalin, which reduces excitatory transmission in R192Q hippocampal slices [34], suggests that the increased propensity of CSD to propagate into subcortical structures is also linked to increased excitatory neurotransmission. The key role of excessive cortical glutammatergic transmission in CSD facilitation is further supported by the recent findings that heterozygous FHM2 KI mice, carrying a loss-of-function mutation in the astrocytic alpha2 Na,K ATPase that in humans cause typical FHM attacks [25], show reduced rate of glutamate clearance by cortical astrocytes during neuronal activity and reduced density of glutamate transporters GLT1 at perisynaptic astrocytic processes; notably, the defective glutamate clearance may largely

account for the lower threshold for CSD induction in the FHM2 mice [42]. A loss-of-function mutation in the glial glutamate transporter EAAT1 was recently identified in a man with MA including hemiplegia [43].

Gain-of-function of additional $Ca_V2.1$-dependent processes, besides enhanced glutamatergic synaptic transmission, likely underlie the particularly high susceptibility to CSD and the unique propensity of CSD to spread into subcortical structures in S218L KI mice [30, 34, 44]. A specific feature of cortical excitatory synapses in (even heterozygous) S218L KI mice not observed in homozygous R192Q KI mice is the presence of a fraction of mutant $Ca_V2.1$ channels that is open at resting potential; this was revealed in cortical slices by sensitivity of miniature excitatory postsynaptic currents (mEPSCs) to $Ca_V2.1$ block [44], and, in vivo, by increased baseline $[Ca^{2+}]_{in}$ in layer 2/3 axonal boutons and shafts [30](cf also [45] for similar findings at Calyx of Held synapses). In contrast, the mEPSCs frequency was not altered in R192Q KI mice, indicating that presynaptic $Ca_V2.1$ channels carrying the R192Q mutation are closed at resting potential [37, 46].

Overall, the findings in FHM1 (and FHM2) KI mice support i) a model of initiation of experimental CSD in which excessive glutamatergic transmission and activation of NMDA receptors are key elements in the positive feedback cycle that ignites CSD, with glutamate and K^+ clearance by astrocytes exerting a dampening role [4] (section 3); ii) the view of migraine as a disorder of brain excitability characterized by dysfunctional regulation of the E/I balance in specific neural networks [42, 47], which likely underlies the typical alterations in multisensory information processing. To explain the ignition of “spontaneous” CSDs, it seems plausible to hypothesize that dysfunctional regulation of the cortical E/I balance may, in certain conditions, lead to overexcitation and network hyperactivity, with consequent excessive K^+ increase and NMDAR activation, thus creating the conditions for initiation of the positive feedback cycle that ignites CSD [4] (section 3) (Figure 3).

R192Q KI mice do not show an overt phenotype [23], but when subjected to novelty or restrain stress show behavioral changes suggestive of unilateral head pain [48]. Relatively few studies investigated whether and how the trigeminovascular pain network is altered in FHM1 KI mice. Given the evidence that $Ca_V2.1$ channels are involved in controlling CGRP release from capsaicin-sensitive perivascular terminals of meningeal nociceptors, in tonic inhibition of TNC neurons with input from the dura, and in descending inhibitory and facilitatory pathways that regulate pain transmission ([27] and references therein), one

may expect alterations at different levels of the trigeminovascular system in FHM1 mutants.

However, measurements of CGRP release from dura mater in fluid-filled hemisected skulls revealed that neither basal nor K^+-evoked CGRP release were significantly different in adult R192Q KI compared to WT mice [49, 50]. This findings is consistent with lack of effect of the FHM1 mutation on $Ca_V2.1$ channels at the peripheral terminals of CGRP-expressing dural afferents. Indeed, the $Ca_V2.1$ current in small capsaicin-sensitive TG neurons dissociated from adult R192Q KI mice, which constitute the majority of small dural afferents, was not affected by the FHM1 mutation [49]; likely, most of these neurons coexpress CGRP [1, 51]. Congruently, dural artery vasodilation induced in vivo by systemic capsaicin was not increased in R192Q KI mice; actually, vasodilation induced by both systemic CGRP and capsaicin was decreased [50], suggesting downregulation of blood vessels CGRP receptors, perhaps as a compensatory mechanism in response to frequent activation of meningeal nociceptors by CSD. A lower fraction of CGRP-expressing TG neurons and a less dense plexus of dura CGRP fibers may be additional compensatory mechanisms [52]. Although it remains unknown whether the FHM1 mutation enhances the $Ca_V2.1$ current in pial meningeal afferents (and in dural afferents of medium-large size), the findings in R192Q KI mice argue against the idea that facilitation of CGRP-dependent processes at the dura (e.g. vasodilation and mast cell degranulation) contribute to the generation of migraine pain in FHM1.

Depending on the study, K^+-evoked CGRP release from isolated trigeminal ganglia was either increased [49] or unaltered [50] in adult R192Q mice; in the latter study, also CGRP release from TNC was unaltered in the mutants (but note that, since the FHM1 mutations shift channel activation without affecting maximal open probability [53], the K^+ concentration in [50] was likely too high to be able to reveal increased CGRP release). Enhanced K^+-evoked CGRP release from R192Q trigeminal ganglia implies gain-of-function of $Ca_V2.1$ channels in some TG neurons; this was indeed shown in a subpopulation of small capsaicin-insensitive TG neurons, which do not innervate the dura [49]. Although one predicts enhanced transmitter release from these neurons upon activation (given the larger AP-evoked $Ca_V2.1$ current [49]), their function, transmitters and possible involvement in migraine pain remain unknown.

In cultured TG neurons from R192Q pups, also basal (besides K^+-evoked) CGRP release was increased, suggesting opening of mutant $Ca_V2.1$ channels at resting potential [54].

Indeed these cultured TG neurons show interesting $Ca_V2.1$-dependent alterations such as increased immunoreactivity for activated CaMKII and loss of constitutive inhibition of ATP-gated P2X3 receptors (P2X3Rs) by brain natriuretic peptide receptors, which leads to increased ATP-gated P2X3R current and enhanced excitability in response to ATP [55-57]. Blocking the CGRP receptors eliminated both the neuronal upregulation of the P2X3R function and the recently uncovered upregulation of P2X7Rs function in SGCs and macrophages, suggesting that the increased basal release of CGRP promotes sensitization of P2X3R-expressing TG neurons, cross-talk between neurons and SGCs and macrophages, resulting in a local persistent inflammatory environment [54, 58, 59]. However, basal release of CGRP was not increased in trigeminal ganglia from adult R192Q KI mice [28, 50], suggesting caution in drawing conclusions regarding migraine pain mechanisms from pups TG cultures findings. Whether the adult TG shows a constitutive inflammatory phenotype in R192Q mutants remains unclear, since in FHM1 ganglia the number of active macrophages was increased (in all divisions), but the protein level of the pro-inflammatory cytokines IL1beta, IL6 and TNFalpha was unaltered [60].

2. $Na_V1.1$ and FHM3

In several brain areas including the cerebral cortex, $Na_V.1.1$ channels are highly expressed in inhibitory interneurons, especially at the axon initial segment, and play a key role in interneurons (but not excitatory neurons) excitability, particularly in sustaining high-frequency firing [61-63] (Figure 2). Indeed loss-of-function mutations in $Na_V.1.1$ channels cause a spectrum of epilepsy syndromes [64]. Conflicting findings were obtained from the analysis of the functional consequences of FHM3 mutations on recombinant human $Na_V1.1$ channels expressed in non-neuronal cells, pointing to either gain- or loss-of-function effects depending on the mutation and/or the $Na_V1.1$ splice variant [65-68]. However, the L1649Q mutant Nav1.1, that was non-functional when expressed in a non neuronal cell line because of lack of plasma membrane delivery, showed an overall gain-of-function phenotype and could sustain high-frequency firing better than the WT channel when expressed in cortical interneurons [69]. Overall the data suggest that, most likely, FHM3 is associated with gain-of-function of $Na_V1.1$ channels and consequent selective hyperexcitability of cortical interneurons.

3. Ion channels in initiation of experimental CSD

Despite important progress, the mechanisms underlying the initiation of experimental CSD remain incompletely understood. However, the generation of a self-sustaining neuronal net inward current and regenerative local K^+ and glutamate release are considered essential components of the positive feedback cycle that confers to CSD its all-or-none characteristics and causes complete neuronal depolarization if the removal of K^+ and glutamate from the interstitium does not keep pace with release [4]. There is strong pharmacological evidence that the key ion channel involved in initiation of experimental CSD is the NMDAR (reviewed in [4]). The findings in FHM mouse models are consistent with a key role of both NMDARs and $Ca_V2.1$ channels in CSD initiation.

A recent study revealed that also the ATP-gated P2X7 receptors (P2X7Rs) play an important role in induction of CSD by electrical or KCl stimulation [70]. The unique C-terminal tail makes P2X7Rs able to form a large pore permeable to high-molecular weight molecules (including ATP and glutamate) upon prolonged exposure to ATP. Although it is still debated whether this is an intrinsic property of the P2X7R protein or whether a large-pore channel (in particular panx1) is associated with P2X7R, converging evidence suggests that it is an intrinsic property [12, 71, 72]. In any case, opening of the large pore associated with activation of P2X7Rs is critically involved in CSD initiation, as revealed but the much lower threshold for CSD induction in mice with a spontaneous P2X7R mutation, which partially impairs the large- pore formation [70]. The mechanism by which P2X7Rs affect induction of experimental CSD remains unclear, also because there is an ongoing discussion regarding the presence or absence of P2X7Rs in neurons [73] [74]. While it is clear that P2X7Rs are expressed in the major non-neuronal cell types in the brain, the neuronal mRNA expression seems to be restricted to CA3 hippocampal neurons [75]. On the other hand, it is unclear whether panx1 is expressed in adult astrocytes in vivo [13]. Specific inhibition of panx1 channels increased the electrical CSD threshold, although not to the same extent as P2X7R inhibition [70], but did not affect CSD induced by pinprick ([11]; cf also unaltered SDs induced by focal cerebral ischemia in [72]).

4. Ion channels implcated in migraine from GWAS

TRPM8. The TRPM8 channel is activated by chemical cooling agents and temperatures below 26 °C, and is essential for detection of cool to noxious cold temperatures [76]. In rodents, TRPM8 is primarily expressed in the sensory ganglia, in about 10% of small-diameter neurons, which do not express CGRP [77]. The abundance of TRPM8-

expressing neurons in the dural TG afferents is lower than in the total TG [78]. It is unknown whether the TRPM8-expressing dural afferents are nociceptors, and whether activation of TRPM8 in the meninges leads to an increase or decrease in pain, in that activation of TRPM8-expressing fibers may be pro- or anti-nociceptive depending on context, in particular on the absence or presence of inflammation [76, 79, 80]. The endogenous mechanisms that may activate TRPM8 in the meninges are unknown.

TASK2. The TASK2 K^+ channel is prominently expressed in the kidney and is not, or only weakly expressed in the brain, where its expression is restricted to a few brainstem areas, including the dorsal raphae nucleus and the retrotrapezoid nucleus, where TASK2 plays a role in O_2 chemoreception [81, 82]. TASK2 is also expressed in the dorsal root ganglion, particularly in small neurons [83]. It is unknown whether these neurons are nociceptors and whether TASK2 is expressed in TG meningeal afferents. TASK2 is highly sensitive to external pH in the physiological range, its open probability increasing with increasing pH [81]. Notably, a loss-of-function mutation in the gene encoding the TRESK channel, a member of the K2P family highly expressed in TG, cosegregated with MA in a large family [84]. Expression of mutant TRESK in TG neurons resulted in a decrease of the endogenous TRESK current and in hyperexcitability of TG neurons [85]. However, another TRESK loss-of-function mutation was found in both migraineurs and controls, suggesting that a single non-functional TRESK variant may be not sufficient to cause migraine ([86]; but cf [87]).

Cx43. Cx43 forms two types of channels: gap junction channels (GJCs) allowing direct cytoplasm-to-cytoplasm communication and hemichannels (HCs) that, like pannexins, mediate release and uptake of ions and small molecules. Because of this double function CX43 has many physiological roles in the brain, where it is not expressed in neurons but highly expressed in astrocytes [88]. In its GJC function, CX43 is involved in e.g. propagation of Ca^{2+} waves between astrocytes and K^+ spatial buffering by astrocytes [88, 89]. Notably, probably as a consequence of impairment of the latter, astrocyte-directed inactivation of Cx43 facilitates CSD induction and increases the velocity of CSD propagation [90]. Cx43 HC activity in astrocytes is associated with release of gliotransmitters such as ATP, glutamate and D-serine, and hence with modulation of basal synaptic transmission and plasticity [88, 91-93]. Cx43 HC activity increases in pathological conditions, such as inflammation, possibly contributing to the activation of the inflammasome pathway [88, 92]. Cx43 is also expressed in SGCs in the trigeminal ganglion, where its expression increases after nerve injury; knockdown of CX43

expression reduced pain behaviour in the neuropatic rats, but increased pain behaviour in control rats [94]. Increasing coupling among SCGs is a consistent feature of different pain models, which might contribute to peripheral sensitization [95].

Although the functional consequences of the migraine-associated variants remain unknown, it seems plausible that alterations in TRPM8 and TASK2 might contribute to migraine by making the meningeal afferents hyperexcitable, while those in Cx43 might contribute by altering brain synaptic transmission and plasticity and by increasing CSD susceptibiliy besides facilitating pain mechanisms.

Figure legends

Figure 1
From cortical spreading depression (CSD) to trigeminovascular nociception and migraine pain. The right panel illustrates the changes in extracellular potential (Vo) and extracellular concentrations of K^+, Na^+, Ca^{2+} and glutamate during the CSD depolarization, which propagates from right to left; the red dashed line represents the CSD wavefront. CSD underlies migraine aura. CSD induces a pannexin1-dependent parenchimal inflammatory cascade, dural mast cell degranulation and neurogenic inflammation, which lead to activation and sensitization of meningeal trigeminovascular afferents (left panel) and of central trigeminovascular neurons in the trigeminal nucleus caudalis (TNC) and C1/C2 dorsal horns; these neurons make direct ascending connection with thalamic nuclei and different areas in the brainstem (including the superior salivatory nucleus, SSN, the locus ceruleus (LC), the periaqueductal grey (PAG)) and hypothalamus); the third order thalamocortical neurons project to several cortical regions, including somatosensory (S1, S2), insula, and visual (V1, V2) (central panel). Activation and sensitization of this trigeminovascular network underlies migraine pain.

Figure 2
Ion channels implicated in migraine pathophysiology. A. Cellular and subcellular localization of ion channels implicated in migraine in the cerebral cortex. B. ion channels implicated in migraine in the trigeminal ganglion and in dural afferents.
Only channels implicated by human genetic studies are considered, with the exception of channels involved in initiation of experimental CSD. Mutations in the neuronal $Ca_V2.1$ and

$Na_V1.1$ channels cause FHM1 and FHM2, respectively; mutant astrocytic α_2 Na, K ATPases (α_2 NKA) cause FHM2. $Ca_V2.1$ are localized at synaptic terminals, but also in the somatodendritic compartment, while Nav.1.1 are mainly localized at the axon initial segment of inhibitory neurons. GWAS indicate that alterations in neuronal TRPM8 and TASK2 channels and glial Cx43 channels are possibly implicated in migraine. NMDA and P2X7 receptors and possibly pannexin1 (panx1) are involved in initiation of experimental CSD. Panx1 is involved in the CSD-induced parenchimal inflammatory cascade.

Figure 3

Functional consequences of FHM1 mutations in the cerebral cortex. Analysis at the cellular and synaptic level in a FHM1 mouse model revealed differential effects on $Ca_V2.1$ channel function in excitatory and inhibitory interneurons and on excitatory and inhibitory synaptic transmission. One predicts altered function, that remains to be investigated, of the cortical microcircuit motifs composed of excitatory and inhibitory neurons, which mediate feedback recurrent and lateral inhibition, feedforward inhibition and dishinibition; these microcircuits are essential for gain control and correct processing of sensory information and to dynamically maintain the excitatory-inhibitory (E/I) balance necessary for the transfer of information while preventing runaway excitation [ ]. Analysis of experimental CSD revealed a lower threshold for CSD induction and enhanced rate of CSD propagation due to excessive glutamatergic transmission. It remains to be investigated whether, in certain conditions, the dysfunctional regulation of E/I balance may lead to overexcitation and network hyperactivity creating the conditions for ignition of “spontaneous” CSD, as hypothesized.

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Declarations of interest: none.

Annotated references:

[19] Gormley et al, Nat Genet 2016**
This is the largest genetic study of migraine so far, involving 60000 migraineurs and 300000 controls; it identifies 44 disease-associated single nucleotide polymorphisms that implicate 38 genomic loci as the likely susceptibility genes (28 of which were not reported before), including 3 genes encoding ion channels only one of which was reported before. Several of the 38 genes are expressed and specifically active in the brain while many others are involved in arterial and smooth muscle function.

[30] Eikermann-Haerter et al, Ann Neurol 2015*
In this elegant *in vivo* study, multiphoton Ca imaging of layer 5 pyamidal cell dendrites and contralateral hemisphere axons, using a genetically encoded Ca^{2+}-indicator, reveals increased resting $[Ca]_{in}$ in layer 2/3 boutons, loss of $[Ca]_{in}$ compartmentalization, and altered synaptic morphology in heterozygous S218L FHM1 KI mice. If these changes will turn out to be specific for the S218L mutation, they might contribute to the severe clinical syndrome caused by the mutation. This study also shows a faster and larger neuronal $[Ca]_{in}$ surge during CSD and a more severe post-CSD oligemia and hemoglobin desaturation in the S218L FHM1 brain.

Cain et al, PNAS 2017*
Using a customized diffusion-weighted DW-MRI methodology to measure the spread of CSD through the brain with spatiotemporal accuracy, this study shows propagation of CSD to striatum and hippocampus with a significant delay after passage through the cortex in FHM1 mice with the mild R192Q mutation, but almost simultaneous propagation in the mutants with the severe S218L mutation. Pregabalin inhibits excitatory transmission at hippocampal CA3-CA1 synapses and propagation of CSD to subcortical structures in R192Q mutants, but not S218L mutants. These data confirm the importance of the gain-of-function of excitatory neurotransmission for CSD facilitation in R192Q KI mice and point to additional effects of the S218L mutation that remain to be clarified.

Dilekoz et al, J Neurosci 2015**
First in vivo evidence of enhanced hippocampal excitatory synaptic transmission and enhanced hippocampal LTP (with unaltered LTD) in a FHM1 mouse model. Paradoxically learning and memory were impaired in hippocampus-dependent fear conditioning and water maze tests, but unaltered in novel object recognition tests, which rely on a more distributed network. These findings might provide a possible explanation for cognitive changes detected in FHM.

Capuani et al, EMBO Mol Med 2016*
This study combines patch-clamp recordings from astrocytes in acute cortical slices and immunogold electron microscopy to show, for the first time, that reduced expression of the α_2 Na,K ATPase in heterozygous FHM2 knockin mice leads to reduced rates of glutamate and K+ clearance by cortical astrocytes during neuronal activity and reduced density of

GLT-1 glutamate transporters in perisynaptic astrocytic processes. Using ceftriaxone treatment of FHM2 mutants and partial inhibition of glutamate transporters in wild-type mice, the study provides evidence that defective glutamate clearance can account for most of the facilitation of CSD initiation in FHM2 knockin mice, pointing to excessive glutamatergic transmission as a common feature of FHM1 and FHM2.

Chen et al, Brain 2017**
This study reveals for the first time an important role of the ATP-gated P2X7 receptors in initiation of experimental CSD in wild-type mice *in vivo* and shows that opening of the large pore associated with activation of P2X7Rs is critical (although, as a consequence of the complex P2X7Rs pharmacology, the study does not fully clarify whether the large pore is an intrinsic property of P2X7Rs or it involves panx1, as proposed). The study also shows the critical involvement of P2X7Rs in downstream consequences of repeated CSDs such as upregulation of interleukin-1 beta, inducible nitric oxide synthase and cyclooxygenase-2 in the cortex.

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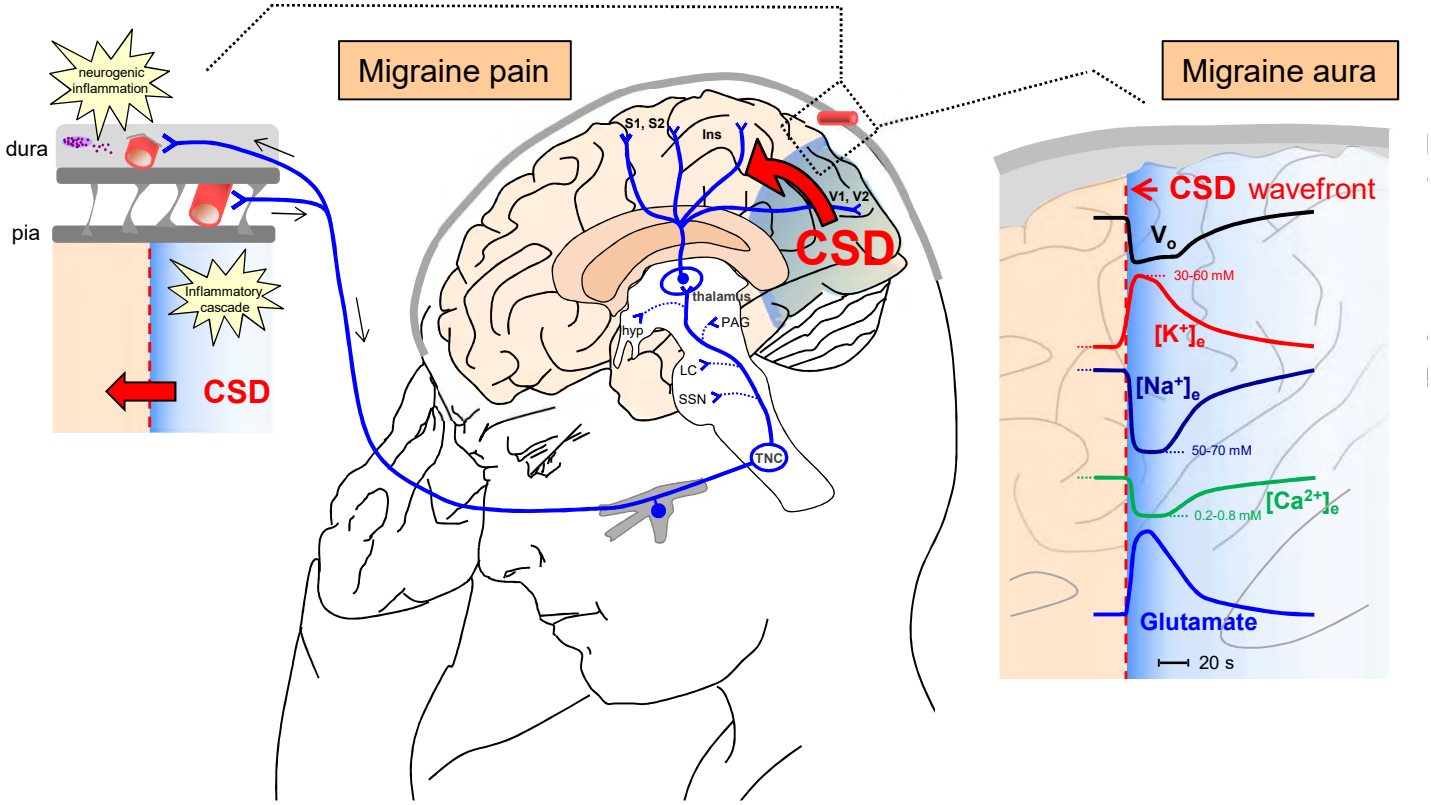

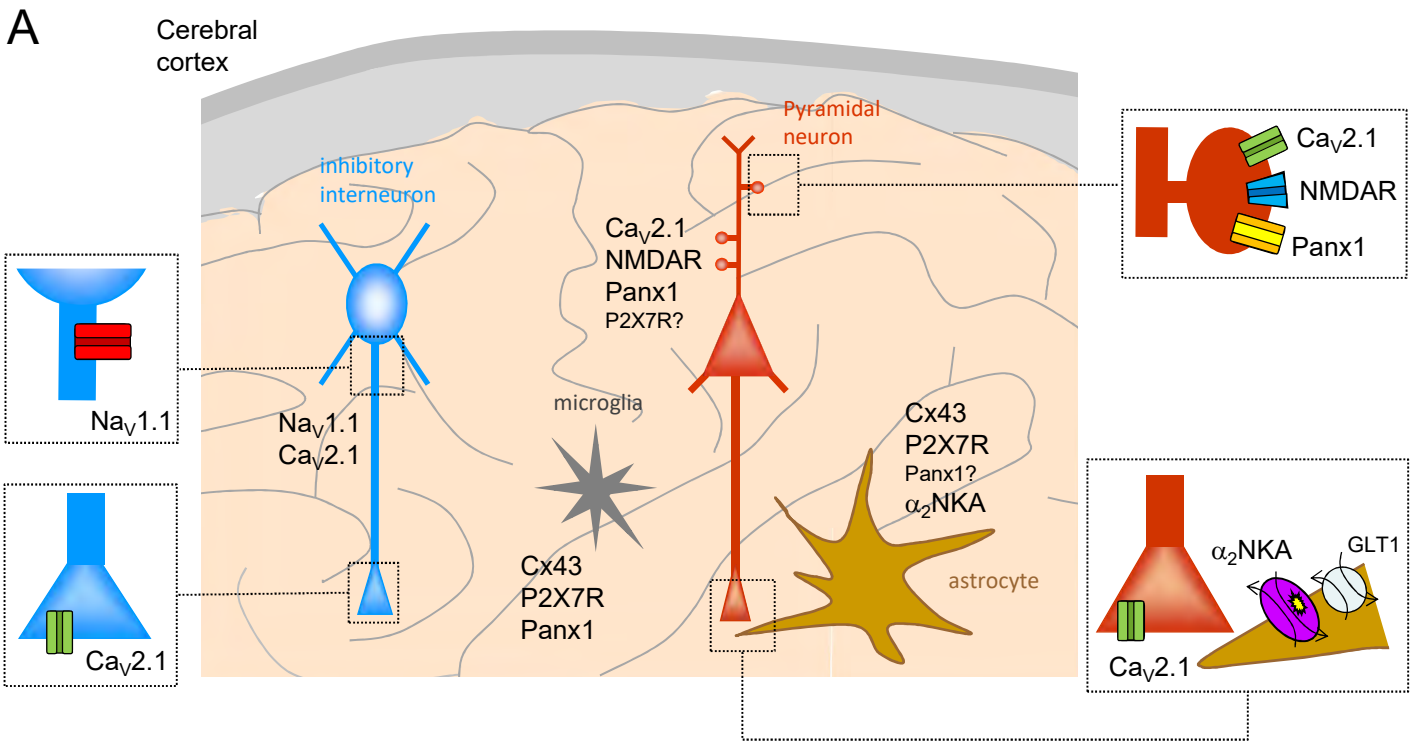

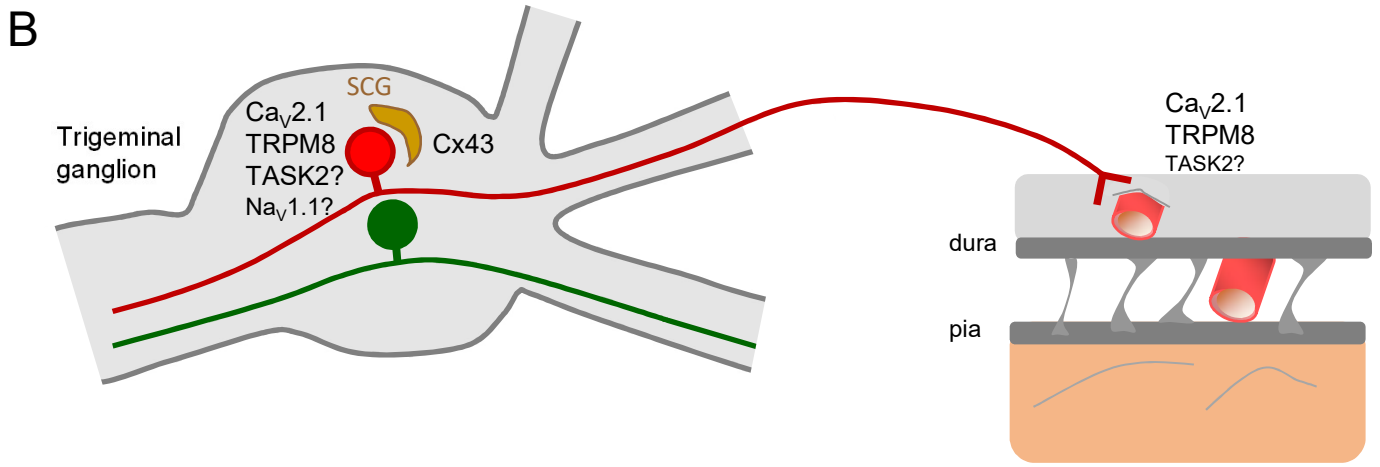

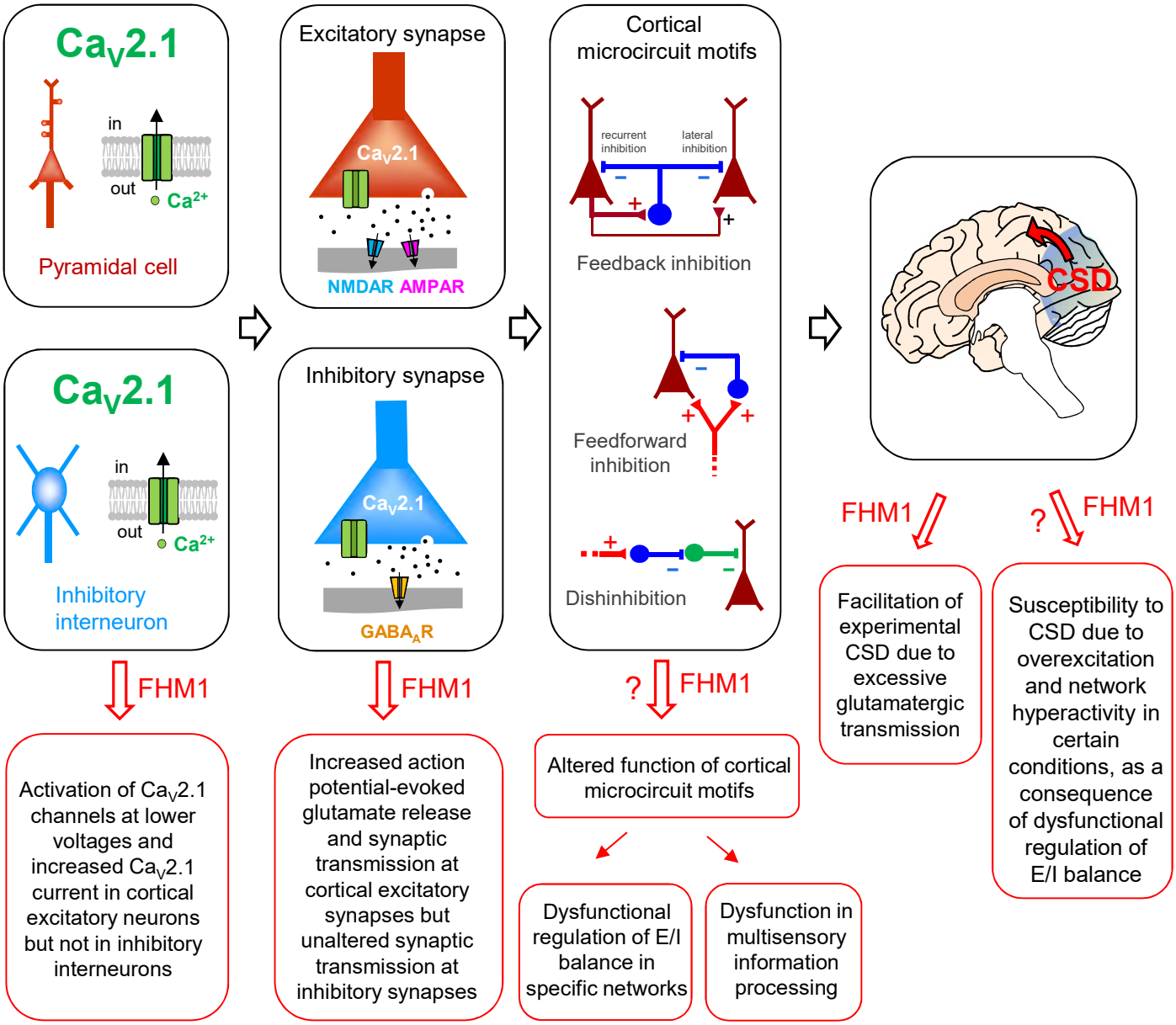

Highlights

We recapitulate current understanding of migraine pathophysiology.

We discuss how disease-causing $Ca_V2.1$ mutations affect cortical and trigeminal physiology

We discuss novel ion channel mechanisms in cortical spreading depression

We describe the ion channels in migraine genome-wide association studies

Declarations od interest: none