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# Cortical Spreading Depression and Migraine

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**Abstract** Cortical spreading depression, a slowly propagating wave of transient neuronal and glial depolarization, is widely accepted as the electrophysiologic substrate of migraine aura and a trigger for headache. Recent clinical and experimental evidence reinforces the putative role of cortical spreading depression in migraine pathophysiology. Imaging studies in migraineurs demonstrated hemodynamic changes consistent with cortical spreading depression during aura, whereas recent animal studies helped unravel pathophysiologic aspects such as the triggering mechanisms, genetic and hormonal modulation, and potential therapeutic targets. Here, we provide an overview of recent advances in our understanding of migraine pathophysiology and treatment.

**Keywords** Cortical spreading depression (CSD) · Migraine · Familial hemiplegic migraine (FHM) · Hormones · Aura · Trigger

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## Introduction

There is growing evidence that cortical spreading depression (CSD) underlies migraine aura [1] and possibly acts as a trigger for headache as well [2, 3]. CSD is a slowly propagating depolarization of neuronal and glial membranes evoked when extracellular $K^+$ concentrations ($[K^+]_e$) increase above a genetically determined threshold, for example, by transient ischemia [4]. The threshold for initiation of CSD presumably is lower in migraineurs than in the normal population and possibly is linked to overall cerebral hyperexcitability. Indeed, interictal cortical excitability is increased in migraineurs [5], and there is a clinical association between migraine and epilepsy [6]. The genetically determined CSD threshold is modulated further by endogenous (eg, gonadal hormones) and exogenous factors (eg, migraine prophylactic drugs) [7•, 8, 9, 10••]. Hence, the susceptibility of brain tissue to CSD (and thus migraine) is governed by complex interactions among multiple independent triggers, risk factors, and modulators, some of which are reviewed in the following text.

## Basic Features of CSD

CSD, originally described by Leão [11], is an intense depolarization of neuronal and glial membranes due to a sudden loss of membrane resistance and ionic gradients. It is characterized by cessation of all spontaneous or evoked synaptic activity and massive $K^+$ efflux causing $[K^+]_e$ to rise above 40–50 mM, exacerbated by cell swelling and shrinkage in extracellular space as a result of water entering the cells coupled to $Na^+$ influx. High $[K^+]_e$ in the tissue undergoing CSD is believed to depolarize adjacent brain tissue, and in this way, the CSD wave propagates into

contiguous gray matter at an average speed of 3 mm/min, regardless of functional divisions or arterial territories [12]. Large $Ca^{2+}$ influx and glutamate efflux add momentum to the spreading wave of depolarization [13].

Although little is known about the triggers of migraine attacks in humans, CSD is initiated when local $[K^+]_e$ exceeds a threshold of approximately 10–12 mM in a minimum critical volume of brain tissue (~1 $mm^3$ in rodents). This can be achieved by cerebral ischemia and trauma or direct cortical application of excitatory amino acids, $Na^+/K^+$-pump inhibitors, or concentrated $K^+$ solutions in both lissencephalic [11] and gyrencephalic animals [14], as well as in humans [15, 16, 17•]. Triggering CSD often requires activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors [18, 19], which, as noted earlier, adds momentum to the depolarization wave facilitating its spread. Direct intercellular transfer of ions and small molecules through gap junctions also may facilitate the spread.

CSD is associated with characteristic cerebral blood flow (CBF) changes: an initial, species-dependent reduction in CBF is followed by hyperemia, reaching up to 200% of baseline in some species, and then by oligemia (40–90% of baseline), which usually lasts up to an hour. During this post-CSD oligemic phase, neurovascular coupling and hypercapnic hyperemia are impaired [20]. Both the CSD and the post-CSD oligemia may cause relative tissue hypoxia [21]. Beyond the vasomotor effects, CSD affects neurotransmitter and neuromodulatory systems, second messenger cascades, immediate early genes, and growth factors, as well as inflammatory mediators such as interleukin-1β and tumor necrosis factor-α [22, 23].

Despite extensive investigation of CSD in experimental animals in vivo and in vitro [11, 12, 24, 25] and in human neocortical and hippocampal tissues in vitro [26, 27], evidence supporting CSD in human brain in situ was obtained only recently, using functional MRI during migraine [28] and epidural and intracortical recordings in injured brain [29–32].

## CSD and Aura

Leão [33] and Milner [34] both pointed out the similarity between the velocity of CSD propagation and the march of visual aura reported by Lashley [35]. As with CSD in mammalian cortex, the speed of spread of migraine aura is approximately 3 mm/min. Aura is characterized by negative symptoms (eg, loss of sensation, visual scotoma) often preceded by positive symptoms (eg, paresthesias, visual scintillations), reminiscent of the cessation of cortical neuronal activity preceded by a brief burst of action potentials at the CSD wavefront. The first compelling evidence for the CSD theory of migraine in human brain was obtained using intra-arterial $^{133}Xe$ tomography during aura. A slowly spreading oligemia (25–35% below baseline) was found propagating anteriorly from the occipital cortex with a speed similar to that of CSD [36, 37]. In some cases, the oligemia was preceded by focal hyperemia resembling the hemodynamic effects of experimental CSD summarized earlier. The temporal association between cerebral hemodynamic changes and migraine symptoms suggested that oligemia was probably not the cause, but rather a consequence of a primary upstream event, presumably CSD. These findings subsequently were corroborated by positron emission tomography [38] and magnetoencephalography [39]. However, the strongest piece of evidence emerged from high-field strength functional MRI (fMRI) studies during aura. Brain oxygen level-dependent (BOLD) imaging, which detects the ratio of non-paramagnetic oxygenated hemoglobin to paramagnetic deoxyhemoglobin as a rough measure of the difference between oxygen delivery and consumption, forms the basis for fMRI [40, 41]. A focal increase in BOLD signal was detected during visual aura, spreading within occipital cortex at a rate of 3.5 mm/min in a fashion that was retinotopically congruent with the patient's aura symptoms. This initial BOLD increase was followed minutes later by a decrease, suggesting a rise and then a fall in CBF [28]. These and other lines of evidence [8] strongly suggest that CSD is the electrophysiologic substrate of migraine aura.

## Evidence for an Enhanced Cortical Excitability in Migraineurs

It is not clear how CSD is triggered in migraineurs. However, because most factors that facilitate CSD occurrence are excitatory, depolarizing events (eg, NMDA receptor activation, intense neuronal activity such as seizures), it is plausible to hypothesize that migraineurs have enhanced cerebral excitability. In support of this hypothesis, migraineurs exhibit a reduced threshold to evoked phosphenes (bright scintillations) after transcranial magnetic stimulation. Patients with probable chronic migraine reportedly show increased transcranial magnetic stimulation-induced excitability, which may correlate with the frequency of their migraine attacks [42].

Mutations in genes encoding ion channels and pumps expressed by neurons or glia have implicated glutamatergic neurotransmission as a critical modulator of CSD threshold and cortical hyperexcitability in the pathophysiology of migraine. Familial hemiplegic migraine (FHM) is an autosomal dominant migraine syndrome characterized by severe and prolonged auras (eg, unilateral motor deficits,

coma); more than 60% of FHM patients also suffer from migraine attacks with typical aura or without aura, making FHM a useful genetic model to explore the mechanisms of more common types of migraine as well. Numerous FHM mutations in three different genes have been identified, all of which appear to enhance cerebral excitability via different mechanisms (Table 1).

FHM type 1 is caused by gain-of-function mutations in the *CACNA1A* gene on chromosome 19p13 encoding the $\alpha_1$ pore-forming subunit of $Ca_v2.1$ voltage-gated $Ca^{2+}$ channels (P/Q type) expressed on both presynaptic terminals and somatodendritic membranes. Mutant channels open at lower depolarizing voltages so that $Ca^{2+}$ influx is enhanced through single $Ca_v2.1$ channels under depolarizing conditions, and neurotransmitter release presumably is increased [43]. The control of transmitter release by $Ca_v2.1$ channels is much more prevalent in excitatory (eg, glutamate) than inhibitory (eg, γ-aminobutyric acid) synapses [44, 45], and an enhanced probability of glutamate release has been demonstrated in cortical pyramidal cell synapses of FHM1 mutant mice [46••]. Therefore, FHM type 1 mutations are believed to enhance cerebral excitability by both increasing glutamate release and amplifying the postsynaptic depolarization [46••, 47, 48]. FHM type 1 accounts for 50% of all FHM families [49].

FHM type 2 mutations in the *ATP1A2* gene on chromosome 1q23 also might increase ambient $[K^+]_e$ and glutamate in the synaptic cleft as a result of a loss of function of the $\alpha_2$ $Na^+/K^+$ adenosine triphosphatase (ATPase), a P-type ion pump that uses adenosine triphosphate to actively countertransport $Na^+$ and $K^+$ ions. FHM type 2 point mutations produce substitutions of conserved amino acids in important functional regions, such as the intracellular four to five loop containing the nucleotide-binding domain and the extracellular seven to eight loop, which is responsible for β subunit binding [50]. The $Na^+/K^+$ ATPase generates the ion gradients that maintain resting membrane potential and cell volume, regulate resting and activity-induced $[K^+]_e$ levels, and provide the driving force for nutrient and neurotransmitter uptake [51].

The FHM type 3 missense mutation (Gln1489Lys) in the *SCN1A* gene on chromosome 2q24 encoding the $\alpha_1$ subunit of $Na_V1.1$ voltage-gated $Na^+$ channels [52] accelerates channel recovery from fast inactivation, an effect predicted to increase dendritic excitability and neuronal firing rates [53]. As a consequence, a relatively weak depolarizing stimulus (perhaps without consequences in healthy individuals) may cause excessive neuronal firing that increases $[K^+]_e$ above the critical value that triggers CSD. Therefore, elevated extracellular glutamate and $[K^+]_e$ may be a common mechanism of reduced CSD threshold in migraine [54].

## CSD Susceptibility as a Consequence of Enhanced Excitability in Migraine

Experiments on mutant mouse models provide mechanistic insight into modulation of CSD susceptibility as a relevant mechanism in migraine. Spontaneously occurring or engineered mutations within the *CACNA1A* gene modulate CSD threshold. For example, the tottering mutation (a proline-to-leucine substitution in the S5-S6 linker region of repeat domain II of the $\alpha_1$ subunit of the P/Q-type $Ca^{2+}$ channel) causes loss-of-channel function, impaired presynaptic $Ca^{2+}$ influx, and reduced neurotransmitter release, mainly inhibiting excitatory neurotransmission [45, 55–58]. Tottering mice show a 10-fold resistance to CSD, with a slower CSD propagation speed and a failure to sustain regenerative spread of the depolarization wave [44]. In contrast, mutant mice expressing human FHM type 1 mutations in the same gene (R192Q or S218L) show increased CSD susceptibility [7•, 59, 60]. In accordance with the more severe clinical phenotype associated with the S218L mutation, CSD susceptibility was even higher in S218L mutant mice than in R192Q mutants, and S218L mutant mice developed coma and seizures in addition to the transient hemiplegia observed in both mutants in response to CSD [7•]. Furthermore, FHM type 1 mutant mice showed a facilitated subcortical propagation of CSD [7•], providing a potential explanation for the hemiplegia, seizures, and coma in FHM patients [61, 62].

**Table 1** Familial hemiplegic migraine syndromes

| FHM type | Gene | Protein | Cell type | Functional change | CSD susceptibility |
|---|---|---|---|---|---|
| 1 | *CACNA1A* | $Ca_v2.1$ | Neurons | Gain of function | ↑ |
| 2 | *ATP1A2* | $Na^+,K^+$-ATPase | Astrocytes | Loss of function | ? |
| 3 | *SCN1A* | $Na_v1.1$ | Neurons | Gain of function | ? |

Three familial hemiplegic migraine (FHM) syndromes have been identified, associated with pathogenic mutations in genes encoding neuronal or astrocytic ion channels or pumps. The functional consequences of mutations associated with all three syndromes are predicted to augment excitability and cortical spreading depression susceptibility, although this has been demonstrated only for FHM1 thus far

*ATPase* adenosine triphosphatase

Consistent with the female preponderance of nonhemiplegic migraine with aura and familial as well as sporadic hemiplegic migraine [63, 64], female mice expressing the R192Q or S218L mutation exhibited a significantly higher susceptibility than male mice toward CSD [7•]; this sex-related difference was completely abrogated by ovariectomy and "postmenopausal" age. Estrogen augments the effect of glutamate on Purkinje cells and the sensorimotor system [65], and estrogen and progesterone reportedly evoke changes in excitability during transcranial magnetic stimulation [66]. Interestingly, androgens appear to influence CSD in the opposite direction in FHM type 1 mutant mice: castration increased KCl-induced CSD frequency and propagation speed, and this was prevented by testosterone replacement in an androgen receptor-dependent manner [9]. Although the mechanisms linking sex steroids to migraine remain poorly understood, these data suggest that genetic and hormonal factors modulate both CSD and migraine susceptibility (Fig. 1).

## Microembolism as a Possible Endogenous Trigger for CSD

Migraine is associated with an increased risk of stroke, especially in younger women suffering from migraine with aura [67–69]. Patent foramen ovale is more common in migraineurs with aura, and vice versa [70]. Cardiac or pulmonary arterial defects (eg, patent foramen ovale, pulmonary arteriovenous malformations) with right-to-left shunts that increase the risk of cryptogenic stroke also are associated with a higher incidence of migraine [71]. Closure of such defects may reduce or abolish migraine attacks [72]. These findings imply that subclinical cerebral ischemia due to paradoxic embolism may trigger a migraine attack [73]. Indeed, cerebral ischemia is a well-known experimental trigger of CSD. Recent experimental data clearly demonstrate that cerebral microembolism can initiate CSD without causing lasting tissue injury [4]. Therefore, in susceptible brains, CSD may be triggered by transient mild hypoperfusion events, and less frequently, such events may lead to microinfarcts, placing migraine and stroke on a spectrum of vascular complications. If true in humans, vascular and hematologic disorders may act as migraine triggers.

## CSD as a Headache Trigger

Besides causing the aura, CSD also has been proposed as a trigger of headache [74]. CSD can activate the meningeal trigeminovascular system and downstream pain pathways in rodents and lead to meningeal inflammation and plasma extravasation [2, 3, 75]. Although the mechanism of activation remains unknown, it has been assumed that $H^+$, $K^+$, NO, and other agents released into the extracellular space during CSD depolarize or otherwise activate adjacent perivascular trigeminal nerve endings surrounding local blood vessels. These changes may be facilitated by CSD-induced activation of matrix metalloproteinases and mild disruption of the blood–brain barrier [76]. CSD as a headache trigger is supported further by data showing that migraine prophylactic drugs, which are efficacious in preventing migraine attacks with or without a perceived aura, decreased CSD susceptibility [10••]. Reminiscent of the gradual buildup of their clinical efficacy over weeks to

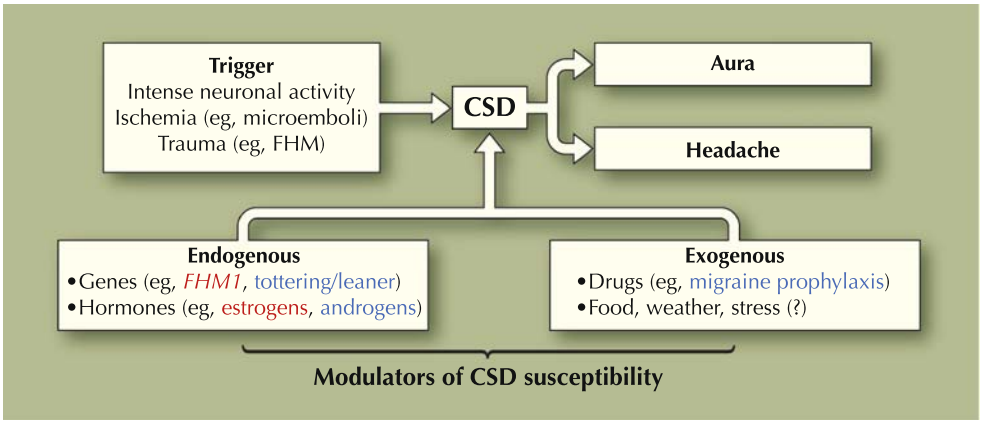


**Fig. 1** A simplified scheme for the cortical spreading depression (CSD) theory of migraine. In susceptible brains, diverse triggers, such as intravascular microemboli and head trauma, can evoke CSD and lead to migraine aura and headache. The overall CSD susceptibility—that is, the likelihood of triggering CSD upon a given stimulus type and intensity—is enhanced (*red*) or suppressed (*blue*) by endogenous factors, such as monogenic or polygenic determinants and sex hormones, and exogenous factors known to influence migraine susceptibility, such as weather, fasting, specific types of food, sleep deprivation, stress, and drugs. Thus far, only the last item (ie, migraine prophylaxis) has been shown to affect CSD susceptibility; the others remain to be tested. FHM—familial hemiplegic migraine

months, these drugs required chronic treatment to suppress CSD in experimental animals and did not show efficacy when tested acutely after a single dose.

## Conclusions

A large body of clinical and experimental evidence implicates CSD as the electrophysiologic event underlying migraine aura and possibly the headache. Enhanced excitability appears to be a common theme in brains susceptible to migraine, which may translate into enhanced CSD susceptibility. Animal studies point toward genetic and hormonal factors modulating CSD susceptibility and suggest that transient mild ischemic events may trigger CSD without residual tissue damage. Improved understanding of the clinically relevant triggers and modulators of CSD will help researchers design targeted therapies for migraine.

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## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


1. Lauritzen M: Pathophysiology of the migraine aura. The spreading depression theory. Brain 1994, 117(Pt 1):199–210.
2. Bolay H, Reuter U, Dunn AK, et al.: Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 2002, 8(2):136–142.
3. Moskowitz MA, Nozaki K, Kraig RP: Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. J Neurosci 1993, 13(3):1167–1177.
4. Nozari A, Dilekoz E, Sukhotinsky I, et al.: Microemboli may link spreading depression migraine aura and patent foramen ovale (p NA). Ann Neurol 2009 (In press).
5. Welch KM: Brain hyperexcitability: the basis for antiepileptic drugs in migraine prevention. Headache 2005, 45(Suppl 1):S25–S32.
6. Haut SR, Bigal ME, Lipton RB: Chronic disorders with episodic manifestations: focus on epilepsy and migraine. Lancet Neurol 2006, 5(2):148–157.
7. • Eikermann-Haerter K, Dilekoz E, Kudo C, et al.: Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. J Clin Invest 2009, 119(1):99–109. *The authors provide experimental evidence showing enhanced CSD susceptibility and post-CSD neurologic deficits in mutant mice expressing FHM1 mutations, as well as their modulation by gene-dosage and female hormones*.
8. Ayata C: Spreading depression: from serendipity to targeted therapy in migraine prophylaxis. Cephalalgia 2009, 29(10):1095–1114.
9. Eikermann-Haerter K, Baum MJ, Ferrari MD, et al.: Androgenic suppression of spreading depression in familial hemiplegic migraine type 1 mutant mice. Ann Neurol 2009, 66(4):564–568.
10. •• Ayata C, Jin H, Kudo C, et al.: Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol 2006, 59(4):652–661. *This was the first demonstration of CSD suppression by chronic treatment with migraine prophylactic drugs as a probable shared mechanism of action*.
11. Leão AAP: Spreading depression of activity in cerebral cortex. J Neurophysiol 1944, 7:359–390.
12. Somjen GG: Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. Physiol Rev 2001, 81(3):1065–1096.
13. Van Harreveld A: Compounds in brain extracts causing spreading depression of cerebral cortical activity and contraction of crustacean muscle. J Neurochem 1959, 3:300–315.
14. James MF, Smith MI, Bockhorst KH, et al.: Cortical spreading depression in the gyrencephalic feline brain studied by magnetic resonance imaging. J Physiol 1999, 519(Pt 2):415–425.
15. Hartings J, Strong AJ, Fabricius M, et al.: Spreading depolarizations and late secondary insults after traumatic brain injury. J Neurotrauma 2009, 26(11):1857–1866.
16. Dohmen C, Sakowitz OW, Fabricius M, et al.: Spreading depolarizations occur in human ischemic stroke with high incidence. Ann Neurol 2008, 63(6):720–728.
17. • Dreier JP, Woitzik J, Fabricius M, et al.: Delayed ischaemic neurological deficits after subarachnoid haemorrhage are associated with clusters of spreading depolarizations. Brain 2006, 129(Pt 12):3224–3237. *This prospective multicenter study demonstrated that ischemic depolarizations occur after subarachnoid hemorrhage and ischemic stroke in humans and may be an early indicator of delayed ischemic brain damage*.
18. Gorelova NA, Koroleva VI, Amemori T, et al.: Ketamine blockade of cortical spreading depression in rats. Electroencephalogr Clin Neurophysiol 1987, 66(4):440–447.
19. Gorji A, Scheller D, Straub H, et al.: Spreading depression in human neocortical slices. Brain Res 2001, 906(1–2):74–83.
20. Piilgaard H, Lauritzen M: Persistent increase in oxygen consumption and impaired neurovascular coupling after spreading depression in rat neocortex. J Cereb Blood Flow Metab 2009, 29(9):1517–1527.
21. Takano T, Tian GF, Peng W, et al.: Cortical spreading depression causes and coincides with tissue hypoxia. Nat Neurosci 2007, 10(6):754–762.
22. Kunkler PE, Kraig RP: Calcium waves precede electrophysiological changes of spreading depression in hippocampal organ cultures. J Neurosci 1998, 18(9):3416–3425.
23. Read SJ, Hirst WD, Upton N, Parsons AA: Cortical spreading depression produces increased cGMP levels in cortex and brain stem that is inhibited by tonabersat (SB-220453) but not sumatriptan. Brain Res 2001, 891(1–2):69–77.
24. Bures J, Buresova O, Krivanek J: The mechanism and applications of Leao's spreading depression of electroencephalographic activity. New York: Academic Press; 1974.
25. Kruger H, Heinemann U, Luhmann HJ: Effects of ionotropic glutamate receptor blockade and 5-HT1A receptor activation on spreading depression in rat neocortical slices. Neuroreport 1999, 10(12):2651–2656.
26. Avoli M, Drapeau C, Louvel J, et al.: Epileptiform activity induced by low extracellular magnesium in the human cortex maintained in vitro. Ann Neurol 1991, 30(4):589–596.

27. Sramka M, Brozek G, Bures J, Nadvornik P: Functional ablation by spreading depression: possible use in human stereotactic neurosurgery. Appl Neurophysiol 1977, 40(1):48–61.
28. Hadjikhani N, Sanchez Del Rio M, Wu O, et al.: Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A 2001, 98(8):4687–4692.
29. Mayevsky A, Doron A, Manor T, et al.: Cortical spreading depression recorded from the human brain using a multiparametric monitoring system. Brain Res 1996, 740(1–2):268–274.
30. Strong AJ: Detecting and characterizing spreading depression in the injured human brain. J Cereb Blood Flow Metab 2003, 23 (1):748.
31. Strong AJ, Fabricius M, Boutelle MG, et al.: Spreading and synchronous depressions of cortical activity in acutely injured human brain. Stroke 2002, 33(12):2738–2743.
32. Fabricius M, Fuhr S, Bhatia R, et al.: Cortical spreading depression and peri-infarct depolarization in acutely injured human cerebral cortex. Brain 2006, 129(Pt 3):778–790.
33. Leão AAP, Morison RS: Propagation of spreading cortical depression. J Neurophysiol 1945, 8:33–45.
34. Milner PM: Note on a possible correspondence between the scotomas of migraine and spreading depression of Leao. Electroencephalogr Clin Neurophysiol Suppl 1958, 10(4):705.
35. Lashley K: Patterns of cerebral integration indicated by the scotomas of migraine. Arch Neurol Psychiat 1941, 46:331–339.
36. Olesen J, Larsen B, Lauritzen M: Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981, 9(4):344–352.
37. Lauritzen M, Skyhoj Olsen T, Lassen NA, Paulson OB: Changes in regional cerebral blood flow during the course of classic migraine attacks. Ann Neurol 1983, 13(6):633–641.
38. Woods RP, Iacoboni M, Mazziotta JC: Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. N Engl J Med 1994, 331(25):1689–1692.
39. Bowyer SM, Aurora KS, Moran JE, et al.: Magnetoencephalographic fields from patients with spontaneous and induced migraine aura. Ann Neurol 2001, 50(5):582–587.
40. D'Esposito M, Deouell LY, Gazzaley A: Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nat Rev Neurosci 2003, 4(11):863–872.
41. Kim YR, van Meer MP, Mandeville JB, et al.: fMRI of delayed albumin treatment during stroke recovery in rats: implication for fast neuronal habituation in recovering brains. J Cereb Blood Flow Metab 2007, 27(1):142–153.
42. Aurora SK, Barrodale P, Chronicle EP, Mulleners WM: Cortical inhibition is reduced in chronic and episodic migraine and demonstrates a spectrum of illness. Headache 2005, 45(5):546–552.
43. Tottene A, Fellin T, Pagnutti S, et al.: Familial hemiplegic migraine mutations increase Ca(2+) influx through single human CaV2.1 channels and decrease maximal CaV2.1 current density in neurons. Proc Natl Acad Sci U S A 2002, 99(20):13284–13289.
44. Ayata C, Shimizu-Sasamata M, Lo EH, et al.: Impaired neurotransmitter release and elevated threshold for cortical spreading depression in mice with mutations in the alpha1A subunit of P/Q type calcium channels. Neuroscience 2000, 95(3):639–645.
45. Caddick SJ, Wang C, Fletcher CF, et al.: Excitatory but not inhibitory synaptic transmission is reduced in lethargic (Cacnb4 (lh)) and tottering (Cacna1atg) mouse thalami. J Neurophysiol 1999, 81(5):2066–2074.
46. •• Tottene A, Conti R, Fabbro A, et al.: Enhanced excitatory transmission at cortical synapses as the basis for facilitated spreading depression in Ca(v)2.1 knockin migraine mice. Neuron 2009, 61(5):762–773. *This in vitro study provided strong evidence for enhanced excitatory neurotransmission linked to increased glutamate release in FHM1 mutant mouse brain slices, supporting the notion that migraine is associated with increased cerebral excitability.*
47. Pietrobon D: Function and dysfunction of synaptic calcium channels: insights from mouse models. Curr Opin Neurobiol 2005, 15(3):257–265.
48. Pietrobon D, Striessnig J: Neurobiology of migraine. Nat Rev Neurosci 2003, 4(5):386–398.
49. Ophoff RA, Terwindt GM, Vergouwe MN, et al.: Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 1996, 87 (3):543–552.
50. Jorgensen PL, Hakansson KO, Karlish SJ: Structure and mechanism of Na,K-ATPase: functional sites and their interactions. Annu Rev Physiol 2003, 65:817–849.
51. D'Ambrosio R, Gordon DS, Winn HR: Differential role of KIR channel and Na(+)/K(+)-pump in the regulation of extracellular K (+) in rat hippocampus. J Neurophysiol 2002, 87(1):87–102.
52. Dichgans M, Freilinger T, Eckstein G, et al.: Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 2005, 366(9483):371–377.
53. Johnston D, Magee JC, Colbert CM, Cristie BR: Active properties of neuronal dendrites. Annu Rev Neurosci 1996, 19:165–186.
54. Moskowitz MA, Bolay H, Dalkara T: Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. Ann Neurol 2004, 55(2):276–280.
55. Qian J, Noebels JL: Presynaptic Ca(2+) influx at a mouse central synapse with Ca(2+) channel subunit mutations. J Neurosci 2000, 20(1):163–170.
56. Fletcher CF, Lutz CM, O'Sullivan TN, et al.: Absence epilepsy in tottering mutant mice is associated with calcium channel defects. Cell 1996, 87(4):607–617.
57. Doyle J, Ren X, Lennon G, Stubbs L: Mutations in the Cacnl1a4 calcium channel gene are associated with seizures, cerebellar degeneration, and ataxia in tottering and leaner mutant mice. Mamm Genome 1997, 8(2):113–120.
58. Plomp JJ, Vergouwe MN, Van den Maagdenberg AM, et al.: Abnormal transmitter release at neuromuscular junctions of mice carrying the tottering alpha(1A) Ca(2+) channel mutation. Brain 2000, 123(Pt 3):463–471.
59. van den Maagdenberg AM, Pietrobon D, Pizzorusso T, et al.: A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron 2004, 41(5):701–710.
60. van den Maagdenberg AMP, Kaja T, Terpolilli S, et al.: High CSD susceptibility and migraine-associated symptoms in Cav2.1 S218L mice (n NA). Neuron 2009 (In press).
61. Kors EE, Terwindt GM, Vermeulen FL, et al.: Delayed cerebral edema and fatal coma after minor head trauma: role of the CACNA1A calcium channel subunit gene and relationship with familial hemiplegic migraine. Ann Neurol 2001, 49(6):753–760.
62. Stam AH, Luijckx GJ, Poll-The BT, et al.: Early seizures and cerebral oedema after trivial head trauma associated with the CACNA1A S218L mutation. J Neurol Neurosurg Psychiatry 2009, 80(10):1125–1129.
63. Eriksen MK, Thomsen LL, Olesen J: Implications of clinical subtypes of migraine with aura. Headache 2006, 46(2):286–297.
64. Thomsen LL, Eriksen MK, Roemer SF, et al.: A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. Brain 2002, 125(Pt 6):1379–1391.
65. Smith SS: Female sex steroid hormones: from receptors to networks to performance—actions on the sensorimotor system. Prog Neurobiol 1994, 44(1):55–86.

66. Smith MJ, Adams LF, Schmidt PJ, et al.: Effects of ovarian hormones on human cortical excitability. Ann Neurol 2002, 51(5):599–603.
67. Bousser MG, Welch KM: Relation between migraine and stroke. Lancet Neurol 2005, 4(9):533–542.
68. Kruit MC, van Buchem MA, Hofman PAM, et al.: Migraine as a risk factor for subclinical brain lesions. JAMA 2004, 291:427–434.
69. Kruit MC, Launer LJ, van Buchem MA, et al.: MRI findings in migraine. Rev Neurol (Paris) 2005, 161(6–7):661–665.
70. Schwedt TJ, Dodick DW: Patent foramen ovale and migraine—bringing closure to the subject. Headache 2006, 46(4):663–671.
71. Post MC, Letteboer TG, Mager JJ, et al.: A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005, 128(4):2485–2489.
72. Spies C, Schrader R: Transcatheter closure of patent foramen ovale in patients with migraine headache. J Interv Cardiol 2006, 19(6):552–557.
73. Azarbal B, Tobis J, Suh W, et al.: Association of interatrial shunts and migraine headaches: impact of transcatheter closure. J Am Coll Cardiol 2005, 45(4):489–492.
74. Moskowitz MA: The neurobiology of vascular head pain. Ann Neurol 1984, 16(2):157–168.
75. Kunkler PE, Kraig RP: Hippocampal spreading depression bilaterally activates the caudal trigeminal nucleus in rodents. Hippocampus 2003, 13(7):835–844.
76. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, et al.: Cortical spreading depression activates and upregulates MMP-9. J Clin Invest 2004, 113(10):1447–1455.