Opinion

Cortical spreading depression and migraine: new insights from imaging?

Michael F. James, Justin M. Smith, Simon J. Boniface, Christopher L-H. Huang and Ronald A. Leslie

The possibility that spreading depression (SD) of cortical activity, a phenomenon observed in all vertebrates, causes the aura of migraine remains an open question in spite of nearly half a century of investigation. SD is also thought to be associated with the progressive neuronal injury observed during cerebral ischaemia. Thus, the ability to detect and investigate SD in humans might prove clinically significant. Animal studies of cortical spreading depression (CSD) have benefited greatly from the advent of relatively non-invasive imaging techniques. The use of these new imaging techniques for clinical studies will accelerate progress in this area of neurobiology.

Migraine is a debilitating condition affecting 10–15% of the population\textsuperscript{1,2}, and is characterized by episodic attacks of severe headache that are often unilateral, pulsating and aggravated by movement. It is associated with nausea, vomiting, photophobia or phonophobia. Accordingly, migraineurs have a large economic cost\textsuperscript{3}. The cerebral cortex of migraineurs is thought to be abnormally responsive to repeated stimuli\textsuperscript{4}, so that a wide variety of stimuli (flickering light\textsuperscript{5}, noise, even the smell of strong perfume\textsuperscript{6}) might act as triggers for a migraine attack by many hours. A possibly related premonitory symptom (e.g. repetitive yawning, fatigue, stiff neck, photophobia or phonophobia) might precede a migraine attack by many hours. A possibly related phenomenon called migraine ‘aura’ occurs in about one-third of sufferers. Aura precedes the headache phase, and commonly includes visual disturbances, but other sensory, motor or speech disturbances can be involved. Aura has a slow, progressive onset and can be associated with movements of scintillations or fortification illusions, followed by a ‘scotoma’ or blind spot, across the visual field. In a classic reference, 'Forty years ago the progression of visual symptoms during aura was noticed to have remarkable similarities with the spreading depression of cortical electro-encephalographic (EEG) activity…’
Lashley mapped the progression of his own visual aura, calculating that cortical function was affected at a rate of ~3 mm.min⁻¹. Forty years ago the progression of visual symptoms during aura was noticed to have remarkable similarities with the spreading depression of cortical electroencephalographic (EEG) activity described by Leão. Although CSD is relatively easy to observe in animal brains, technical challenges probably account for the dearth of human CSD studies. Nevertheless, some reports do indicate the occurrence of CSD in humans.

Here we consider the evidence linking CSD with migraine and its aura, and show how modern in vivo techniques are unlocking its secrets.

### Box 1. Ionic and cellular components of cortical spreading depression

Cortical spreading depression (CSD) involves a temporary, but major, localized redistribution of ions between intracellular and extracellular compartments. This ion redistribution is energy dependent, becoming clinically significant in ischaemia when brain metabolism is impaired. During CSD initiation the concentration of extracellular K⁺, [K⁺], rapidly rises, causing brief neuronal excitation then depolarization and a period of electrical silence during which the direct current (DC) potential at the brain surface falls. In tandem, [Na⁺], and [Cl⁻], levels decrease as these ions enter cells. Consequently, water enters cells, the extracellular space is reduced, and cells swell. Ca²⁺ ions also move inwards, but slightly later than the outward movement of K⁺, suggesting that Ca²⁺ movements follow K⁺ fluxes. Additional negative ion species move outwards to maintain electrical balance, the excitatory neurotransmitter glutamate probably being the most important.

In the isolated chick retina, human neocortical tissue and cat brain, NMDA receptor antagonists block SD completely. By contrast, in rat hippocampus, glutamate (and Ca²⁺) facilitates SD initiation, whereas NMDA antagonists (and low [Ca²⁺]) delay its onset but fail to block SD completely.

Both volume-activated ion channels and glial cells probably play important roles in the restoration of normal cellular homeostasis. The former are stimulated during cell swelling, and the latter provide spatial buffering that prevents increased levels of K⁺ and Glu⁻ during normal neuronal activity. However, they might also prolong CSD: volume-activated ion channels release glutamate during CSD (Ref. 1); and although gliotoxins prolong CSD (Ref. m), they also reduce glutamate efflux from glial cells. CSD and PID appear more difficult to evoke in brains of larger animals in which the ratio of glia to neurones tends to be higher, suggesting that glial cells are important for limiting CSD activity. Such limiting forces might be greater in the more complexly folded human brain, and could explain the paucity of literature accounts of CSD during neurosurgery.

Cooperation between glia and neurones maintains normal ion and transmitter levels during neuronal activity. During CSD the magnitude of the ion movements and the synchrony of these fluxes might be abnormal. A possible mechanism for such a greatly enhanced, but transient, synchrony might involve changes in the permeability of gap junctions, because the gap junction blockers octanol and halothane prevent CSD propagation, especially in gyrencephalic species.

References


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Cortical spreading depression (CSD) in animal models (mainly rabbit and rat) affects single neurone spike activity, synchronization of synaptic potentials and steady membrane potentials produced by neurones or glia. Together these are recorded as a flattening of the EEG and a reduction in the cortical direct current (DC) potential. Although depression of the EEG is rarely complete, CSD changes its amplitude, shape and frequency when recorded from the exposed pia-arachnoid surface, with frequency changes sometimes occurring in advance of the main changes. Reduction or abolition of somatosensory evoked potentials also occurs.

The characteristic surface-negative, DC slow-potential change of CSD advances via all cortical layers, arriving earliest via the superficial ones in which ion movements are greatest. Single neurones discharge briefly at the onset of the EEG depression and are then suppressed, followed by a slow recovery of spontaneous activity. Average cell membrane potentials are reduced during the negative phase of CSD, during which the passive electrical properties of depressed neural tissue are reflected by changes in overall resistive and capacitive components of cortical impedance. Currents that are tangential to the skull arising from CSD alter the magnetic fields external to the skull. Such changes are detected by magnetoencephalography (MEG), but poor spatial resolution requires the locations of the current sources to be interpreted using computer modelling.

Most migraine studies have been largely interictal, with changes noted in evoked potentials and on transcranial magnetic stimulation (TMS) (Refs a,b). These changes are thought to reflect an abnormal excitability of cortical neurones. This altered excitability might enhance interictal visual acuity in migraineurs, but perhaps leads to a situation in which cortical activity is insufficiently damped and therefore CSD can ‘break through’ when the level of afferent input to the brain breaches some threshold. TMS studies, comparing migraineurs with and without aura and controls, showed that cortical responsiveness is altered in at least two respects: (1) TMS of the occipital cortex produces brief scintillations (phosphenes) in the visual field: in migraineurs with aura a lower phosphene threshold was detected compared with other subjects. (2) TMS of the motor cortex evokes a muscle contraction response: in migraineurs, an increase in the excitability threshold for muscle contraction has been reported. Such studies, however, produce mixed results from different protocols and study groups. Nevertheless these results imply that ictal studies of migraine should be investigated by a combination of MRI and simultaneous region-specific TMS, or by TMS assessments before and after ictal MEG. Acquisition of EEG or MEG during MRI is also likely to be fruitful. These approaches would also be compatible with an acute experimental pharmacotherapeutic intervention.

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occipital cortex and to persist into the headache phase. However, spreading cerebral perfusion changes have also been reported in migraine without aura, perhaps because SD occurs in brain regions subserving functions other than vision (including subcortical regions). This idea could explain some of the spreading physical symptoms that occur in some migraineurs. These perfusion changes spread at a rate that is consistent with the propagation of CSD (Refs 25, 27, 28).

CSD, migraine and EEG changes
In animals CSD ‘flattens’ the EEG response and decreases the direct current (DC) potential on the brain surface. This suggests that EEG and similar non-invasive electrophysiological techniques, such as magnetoencephalography (MEG), might be valuable for investigating CSD in humans (Box 2). The rapidly fluctuating voltages of EEG waveforms do not lend themselves to the detection of CSD because of the high-pass filtering normally used to process EEG signals. Changes in DC potential have been difficult to detect during neurosurgery, but have been shown

Fig. 1. Cortical spreading depression (CSD) propagating across the surface of the cat brain in vivo. Images were obtained at 10 s intervals starting ~50 s after KCl application; the coloured overlays represent decreased cerebral water diffusion caused by water movement into cells during the passage of the CSD; overlays are superimposed on an anatomical image of the brain surface. In frames (a–k), the elliptical wave front travels both anteriorly and posteriorly along the suprasylvian and suprasylvian sulci, out of the image plane, to reappear on the ectosylvian gyrus (frames r–v), and then on the marginal gyrus (frames t–w). Abbreviations: A, anterior; P, posterior; L, left; R, right. The event propagated with velocity 3.2 ± 0.1 mm min⁻¹; the field of view is 5 cm. Modified, with permission, from Ref. 34.

Fig. 2. Blood oxygen level-dependent (BOLD)-fMRI of the occipital cortex during a migraine attack. A migraine attack was provoked using an alternating red–green checkerboard pattern projected to the patient in the magnet. The pattern alternated at 9 Hz and was on or off every 14 s. The patient experienced visual symptoms that appeared at the onset of a severe headache 6.1 min after the start of the visual stimulus (~image 104). The visual changes reported were different to the patient’s usual aura. (a) (Upper trace): in normal subjects, no migraine attack was provoked and the visual cortex responded to the on-off visual stimulus with corresponding changes in BOLD signal for 12.4 min (224 images). (Lower trace): in the patient, cortical responsiveness was inhibited during the migraine attack and the BOLD signal intensity was decreased (blue) BOLD signal changes occurred before symptom onset; these changes were observed only in patients who reported visual symptoms. (c) Significant increases in BOLD signal (red) that coincided with the suppression of cortical responsiveness were also observed during this time period, especially in the left visual cortex (i.e. right of the image). The authors suggest that the BOLD intensity increase that coincided with the suppression of visual activation might reflect vasodilation similar to that observed during the earliest phase of cortical spreading depression (CSD). They also indicate that the waves of suppression of visual activation or neurologic symptoms of their patients. Modified, with permission, from Ref. 28. See also Ref. 38 which amplifies these findings and provides further strong evidence that CSD underlies migraine aura.

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with intracranial electrocorticography for head injury. Focal DC potential shifts propagating across the cortex should give rise to changes in the magnetic field outside the head. Thus MEG has been used in animals to detect CSD (Refs 30,31). Furthermore, DC potential shifts have been detected with MEG during migraine aura and headache. Nevertheless, reliable detection of small signal changes, perhaps as a result of CSD, during migraine remains a difficult task. These techniques will probably be combined with other non-invasive techniques, such as transcranial magnetic stimulation and in vivo imaging.

CSD, migraine and imaging

Both CSD and PID have been imaged in animal brains using MRI. Transient, localized changes in cerebral water diffusibility, arising from altered tissue water compartmentalization (Box 1), can be detected during CSD with diffusion-weighted MRI. Both CSD and PID, in normal and ischaemic brain, respectively, have been detected in animals in this way (Fig. 1). CSD has also been detected with MRI techniques that are sensitive to transient hyperemic changes. There are, however, some technical impediments to imaging CSD in humans.

- Migraine attacks usually occur unpredictably, often without prior warning, and volunteers are rarely available for imaging at the start of an attack.
- In animals, CSD wavefronts occupy very small brain areas (Fig. 1); if this is also true in humans, such small regions might not be easily detectable.
- Cortical folding could limit the spread of CSD in the human brain, further increasing the difficulty of detection.
- The clinical timing of CSD or PID events is uncertain, so that continuous imaging would be necessary to maximize their detection.

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The endoplasmic reticulum: one continuous or several separate Ca$^{2+}$ stores?

Ole Holger Petersen, Alexei Tepikin and Myoung Kyu Park

The Ca$^{2+}$ store and sink in the endoplasmic reticulum (ER) is important for Ca$^{2+}$ signal integration and for conveyance of information in spatial and temporal domains. Textbooks regard the ER as one continuous network, but biochemical and biophysical studies revealed apparently discrete ER Ca$^{2+}$ stores. Recent direct studies of ER luminal Ca$^{2+}$ movements show that this organelle system is one continuous Ca$^{2+}$ store, which can function as a Ca$^{2+}$ tunnel. The concept of a fully connected ER network is entirely compatible with evidence indicating that the distribution of Ca$^{2+}$-release channels in the ER membrane is discontinuous with clustering in certain localities.

The ER is crucial for Ca$^{2+}$ signalling. The ER can act as a sink for Ca$^{2+}$ that enters the cell through channels in the plasma membrane, but can also be a source for Ca$^{2+}$ release into the cytosol in response to intracellular messengers, such as inositol 1,4,5-trisphosphate [Ins(1,4,5)P$_3$] (Refs 1,2); cyclic ADP-ribose or nicotinic acid adenine dinucleotide phosphate, generated following activation by neurotransmitters. Because Ca$^{2+}$ can interact with many different molecular targets, signal specificity requires subcellular localization of the cytosolic Ca$^{2+}$ signal and/or special oscillation and spiking patterns. The ER is essential in this respect, because clustering and mixing of various Ca$^{2+}$-release channel types in specific regions can focus Ca$^{2+}$ signals in space and time. Failure of these processes can lead to serious pathological conditions. Changes in ER Ca$^{2+}$ storage and release might also be important in neuronal ageing.

Here we discuss whether the ER consists of one continuous vesiculo-tubular system or of separate isolated compartments. This issue is separate from, but relevant to, the discussion concerning ER heterogeneity. The question about the continuity and discontinuity of the ER lumen has consequences for cytosolic Ca$^{2+}$ signal generation and is related to the discussion about the quantal Ca$^{2+}$ release phenomenon: a sustained elevation of the cytosolic Ins(1,4,5)P$_3$ concentration to a submaximal level causes only a transient and partial liberation of Ca$^{2+}$ from the ER and further increments in the Ins(1,4,5)P$_3$ concentration elicit additional pulses of Ca$^{2+}$ release. This could be explained by subdivision of the ER into separate compartments.