**REVIEW ARTICLE**

Pathophysiology of the migraine aura
The spreading depression theory

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**Summary**

The characteristic form and development of sensory disturbances during migraine auras suggests that the underlying mechanism is a disturbance of the cerebral cortex, probably the cortical spreading depression (CSD) of Leão. The demonstration of unique changes of brain blood flow during attacks of migraine with aura, which have been replicated in animal experiments during CSD, constitutes another important line of support for the 'spreading depression' theory, which may be a key to an understanding of the migraine attack. Cortical spreading depression is a short-lasting depolarization wave that moves across the cortex at a rate of 3–5 mm/min. A brief phase of excitation heralds the reaction which is immediately followed by prolonged nerve cell depression synchronously with a dramatic failure of brain ion homeostasis, efflux of excitatory amino acids from nerve cells and enhanced energy metabolism. Recent experimental work has shown that CSD in the neocortex of a variety of species including man is dependent on activation of a single receptor, the N-methyl-D-aspartate receptor, one of the three subtypes of glutamate receptors. The combined experimental and clinical studies point to fruitful areas in which to look for migraine treatments of the future and provide a framework within which important aspects of the migraine attack can be modelled.

**Key words:** migraine; cerebral blood flow; spreading cortical depression; glutamate; nitric oxide

**The theories**

The migraine aura may be defined as any neurological disturbance that appears shortly before or during the development of a migraine headache. Seemingly similar migraine auras may have different features, suggesting involvement of different brain regions. The headache is most often throbbing and unilateral, on the side of the head relevant for the focal symptoms (Wolff, 1963; Olesen et al., 1990).

To explain this sequence of events Wolff (1963) suggested that the focal symptoms were due to transient constriction of a cerebral artery and the headache to a sterile inflammatory reaction around the walls of dilated cephalic vessels.

Several clinical arguments were in favour of the vascular concept. First, the pulsating quality of the pain in migraine and the existence of many other headache syndromes secondary to vascular disease such as stroke, subarachnoid haemorrhage, arterial hypertension and temporal arteritis indicated a vascular mechanism. Secondly, vascular headaches were effectively treated with ergotamine which constricts cerebral arteries without decreasing cerebral blood flow (Tfelt-Hansen et al., 1991). Thirdly, extensive work on the localization of intracranial pain sources pointed towards the blood vessels and associated structures at the ventral surface of the brain as most pain-sensitive, while the brain parenchyma itself was insensitive to noxious stimuli. Finally, inhalation of gas mixtures containing 10% carbon dioxide and 90% oxygen prevented headache and aborted the aura, supposedly due to vasodilatation and increased oxygen supply to the region suffering from vasospasm. The functional anatomical basis of vascular headaches is most likely the trigeminovascular system and there is little doubt that the source of pain in migraine resides within the blood vessels (Moskowitz, 1992; Goadsby and Edvinsson, 1993).

The vascular theory has much merit with respect to the headache, but cannot explain all the phenomena which are associated with the migraine aura. In particular, the stereotyped recurrence of an unprovoked, transient disturbance of brain function is reminiscent of epilepsy more than of any known
disorder of the peripheral vasculature (Gowers, 1907). The focal symptoms in migraine develop in a characteristic 'creeping' fashion, commonly used to differentiate migraine from epilepsy. Several investigators have described their own migraine aura. Lashley's scintillation-scotomas developed symmetrically in the visual fields, suggesting a cortical localization of the symptoms (Lashley, 1941). The disturbance started at the visual field centre and propagated to the peripheral (temporal) parts within ~10-15 min, while function returned to normal within another 10-15 min. The aura symptoms indicated a wave of intense excitation in the primary visual cortex that moved at the speed of 3 mm/min, followed by a longer period of inhibition (Lashley, 1941) (Fig. 1). Similar calculations can be made with respect to somatosensory symptoms developing along the sensory homunculus (Lord, 1986). The very orderly development of the aura makes a vascular origin a remote possibility, while a primary disturbance of cortical nerve cell function, probably cortical spreading depression (CSD) is a more attractive explanation (Leão and Morison, 1945; Milner, 1958).

Cortical spreading depression in animals, including monkeys, gives rise to specific changes of behaviour which mimic important features of the migraine aura (Bureš et al., 1974, 1984). The rat is the most popular animal for studies of behaviour in which single unilateral waves of CSD induce contralateral sensory neglect and motor impairment of the forepaw lasting for 15-30 min, i.e. much shorter than the blood flow reduction (Bureš et al., 1984; Lauritzen, 1987a). Rats do not experience hippocampal or CSD as aversive (Koroleva and Bures, 1993). The analogy can hardly be taken further due to the obvious differences between rat and human brains, but it is important that the behavioural changes caused by CSD in animals are consistent with the transient neurological deficits recorded during the migraine aura.

This review summarizes clinical and experimental data which suggest that the development of a CSD in migraine patients triggers the aura, the changes of cerebral blood flow and possibly migraine headaches. The key to this theory of migraine is an understanding of the mechanisms of brain blood flow changes during attacks of migraine as summarized in the following.

The 'spreading oligaemia': arterial or arteriolar vasospasm?
Methods for the measurement of regional cerebral blood flow (rCBF) in man with a high spatial resolution are well-established (Sveinsdottir et al., 1977; Celsis et al., 1981; Lauritzen, 1987a). Studies during acute migraine attacks, provoked by angiography or occurring spontaneously, have revealed unique changes of rCBF which were not observed in >1,000 patients with other categories of neurological disorders examined with the same types of equipment (Olesen et al., 1981; Lauritzen, 1987a; Olesen, 1991). The migraine symptoms which developed during the provoked attacks were similar, but not identical to the symptoms which developed during spontaneous attacks.

![Fig. 1 Successive maps of a scintillation-scotoma to show characteristic distribution of the fortification figures. In each case the asterisk indicates the fixation point. Knowledge of the retinotopic organization of the visual cortex allowed Lashley (1941) to calculate the speed of propagation of the excitation-depression wave as ~3 mm/min. Reproduced with permission from K. M. Lashley (published in Archives of Neurology and Psychiatry; 46: 331-9; © American Medical Association 1941)](http://brain.oxfordjournals.org/)

Therefore, the pathophysiology of induced and spontaneous attacks may be different. On the other hand, the disparities of symptoms between the two types of attacks were felt to be minor and it was therefore assumed that the changes of rCBF during provoked and spontaneous attacks of migraine were similar. The data from the studies in Copenhagen including both patients with induced and spontaneous attacks of migraine are summarized in the following, while the results of earlier studies have been reviewed in detail in other recent publications (Olesen et al., 1981, 1990; Lauritzen, 1987a,b; Olesen, 1991).

At the very beginning of migraine attacks rCBF decreases in the posterior part of the brain. Subsequently, the low flow region spreads into the parietal and temporal lobes at rate of 2-3 mm/min for the next 30-60 min to various extent in individual patients, the so-called 'spreading oligaemia' (Olesen et al., 1981). The spread of reduced rCBF does not match the territories of supply of large arteries, but follows the cortical surface. Arterial vasospasm is therefore not the mechanism of reduced flow in migraine, which appears to be due to arteriolar vasoconstriction. The rCBF remains constant in hypo- as well as normoperfused brain regions despite variations of the mean arterial blood pressure, i.e. autoregulation is preserved. This is another strong argument against arterial vasospasm as the mechanism of reduced flow, and an equally strong argument for cortical arterioles as the site of increased resistance. Vasoconstriction of a large artery would cause compensatory dilatation of the arterioles if severe enough to reduce rCBF. In this situation, increased blood pressure would lead to an increase of rCBF in the oligemic region because of autoregulatory dilatation of the cortical arterioles, but in migraine rCBF remained constant. Therefore, the reduced rCBF in migraine is probably due to arteriolar, not arterial vasoconstriction.
Vascular reactivity to mental tasks and changes of arterial CO₂ is impaired in the hypoperfused parts of the brain, but normal in neighbouring non-invaded regions. Thus, there is no evidence of vascular dysfunction before the blood flow decreases. The effects of hypercapnic hyperoxia on migraine symptoms (Wolff, 1963) are not explained by dilatation of resistance vessels, since rCBF in hypoperfused regions is insensitive to changes of PaCO₂ during migraine attacks. The rCBF changes are consistent with a process propagating at a rate of 2–3 mm/min, while constricting pial and cortical arterioles, i.e., the vessels which are imbedded in and strongly influenced by changes of the local neuronal microenvironment (Lauritzen, 1987a).

The ‘spreading oligoemia’: relation to symptoms

During migraine attacks provoked by angiography, the aura symptoms usually appeared at some time point during the early phase of spread of the oligoemia, lasted for 15–30 min and then ceased while the hypoperfusion continued to spread while the patients developed migraine headaches (Olesen et al., 1981, 1990; Lauritzen, 1987a).

The studies of spontaneous attacks confirmed that cortical blood flow was reduced during the initial part of the headache period after the aura symptoms had altogether vanished. Eventually, after about 2–6 h, patchy regions of increased flow sometimes developed in cortical regions which were previously hypoperfused (Lauritzen, 1987a; Andersen et al., 1988). Interestingly, the side of the headache usually corresponded to the side of the vascular changes (Olesen et al., 1990) suggesting that the process which triggered the changes of rCBF also stimulated the vascular nociceptors. The average rCBF reduction amounts to 20–25%, with only small areas of ischaemia in the apparently homogeneously perfused oligoemic region, suggesting that ischaemia is not of primary importance in the development of focal migraine symptoms. In conclusion, the time base of the focal symptoms and the reduced rCBF are clearly different. This is a strong argument against a simple version of the ‘vascular’ theory of migraine. The focal neurological symptoms develop while the ‘spreading oligoemia’ expands, but the flow reduction is usually moderate and does not explain the focal symptoms. On the other hand, the data do not exclude that a critically low rCBF, under certain conditions, may contribute to a persistent neurological deficit. The headache in turn is associated with decreased, normal or increased rCBF and slightly dilated cerebral arteries, which may constrict in response to anti-migraine medication (Olesen et al., 1990; Friberg et al., 1991).

Compton scatter and rCBF during migraine attacks

It has been claimed that brain ischaemia is the primary cause of neurological deficits during classic migraine attacks, and that rCBF in the hypoperfused regions is overestimated due to Compton scattered radiation from 133Xe in the neighbouring normoperfused regions (Skyhøj Olsen et al., 1987; Skyhøj Olsen and Lassen, 1989). Dissipation of energy from 133Xe in organic tissue occurs particularly from Compton scatter, causing change of the direction and energy of the emitted photon. The Compton scatter has almost the same energy as the primary radiation. Therefore, it is not possible to discriminate accurately the primary radiation from Compton scatter, and the radiation from every tissue element is influenced by its surroundings. This source of error is specially important in regions with low isotope distribution (low flow) since scatter from adjacent normally perfused tissue influences the radiation and accordingly the steepness of the clearance curves, leading to an overestimation of rCBF. The controversy of the importance of Compton scatter for rCBF measurements with 133Xe has been a major issue in the ongoing discussion of migraine pathophysiology and will be discussed here in some detail.

Skyhøj Olsen et al. (1987, 1989) reanalysed the rCBF data from all the migraine patients who had been investigated with the 133Xe intracarotid technique. The purpose was to estimate the degree of rCBF reduction when taking Compton scatter into consideration. They selected three rCBF values each representing a value of one of the 254 channels: the highest rCBF value ‘closest to’ the non-affected region, the lowest rCBF value ‘furthest away’ from the non-affected region and the rCBF in the ‘centre’ of the low-flow region. The correlations between each of the three sets of rCBF values and the mean rCBF of the non-affected region were then calculated. The correlation coefficients were significantly different from zero and apparently growing with increasing distance from the non-affected region. This led the authors to conclude that the lowest value of rCBF in the low-flow region represented the ‘true value’ of rCBF, as the values closer to the non-affected region were more influenced by Compton scatter as indicated by a higher correlation coefficient.

There are serious problems with this type of analysis, in particular with respect to the method of data selection (Kronborg et al., 1990). The rCBF value of the region ‘closest to’ the non-affected region was selected as the highest value in one single channel of the low-flow region and represents neither a typical rCBF value nor the median or mean value of a group of ror of detectors aligned in the border zone between ‘non-affected’ and ‘affected’ regions. Similarly, the lowest rCBF of the low-flow region was selected as the lowest value in one single channel of the low-flow region ‘furthest away’ from the non-affected region. Clearly, the selection procedure was the basis for the variations of correlation coefficients observed, which could not be used as arguments for uniformity of rCBF in the low-flow region. In addition, there were geometrical problems related to defining areas such as ‘closest to’, ‘centre of’ and ‘furthest away’ from the boundary of a ‘non-affected’ region of a three-dimensional structure, the brain, with equipment that measures rCBF along two axes only. First, the distance from the low-flow region to the non-affected region was not the same in all patients, since the size of the low-flow region varied.
between 9 and 84 cm². Secondly, it is also important that the low-flow region only exceptionally conformed to any well-defined geometrical figure and that the form of the low-flow region varied between measurements. Thus, the metaspatial scale ‘closest to’, ‘centre’ and ‘furthest away’ had to be regarded with the highest degree of scepticism. Thirdly, the strong positive correlation between rCBF in the low-flow regions and rCBF in the ‘non-affected’ regions were partly due to individual rCBF levels for the patients. The correlation coefficients decreased considerably when this was taken into account and huge variations of the correlation pattern were observed between patients. This made the interpretation of the calculated population correlations very difficult (Kronborg et al., 1990). Fourthly, an examination of the original data of six of the 11 patients revealed no anterior-to-posterior gradient of rCBF values as expected from the papers by Skyhøj Olsen et al. (1987, 1989). Therefore, it was doubted that this kind of statistical analysis had any prospect of contributing to our understanding of the role of Compton scatter when using 133Xe for measurements of rCBF (Kronborg et al., 1990).

In a subsequent paper, a mathematical model was suggested to explain the impact of Compton scattered radiation for the measured rCBF (Skyhøj Olsen and Lassen, 1989). The main conclusion of the paper was that the ‘spreading oligaemia’ resulted from Compton scatter radiating from a normally perfused region to a region of increasingly reduced rCBF, i.e. the spread of the ‘spreading oligaemia’ was apparent, not real. The basis for the choice of equation was, however, difficult to define and very different conclusions could be reached by small alterations of the (arbitrary) constants used in the equations (Dalggaard et al., 1991). Alternative mathematical models gave different results suggesting that this approach was of very limited utility for the interpretation of the migraine data (Dalggaard et al., 1991). Taken together, there is no doubt that Compton scatter leads to an overestimation of rCBF in low-flow regions, in migraine patients and in patients with other neurological diseases. We are, however, ignorant of the magnitude of the correction factor and it is not possible at the moment to make any categorical conclusion with respect to the importance of ischaemia for migraine. However, it should be clear that ischaemia during migraine attacks is the exception, not the rule, and in most migraine patients the benign nature of the disease is reflected in a mild blood flow reduction (Kronborg et al., 1990; Dalggaard et al., 1991).

At this point I will return to discuss the physiological basis of the ‘spreading oligaemia’ which has a number of important features in common with Leão’s CSD.

### Cortical spreading depression: basic features

The literature concerning CSD is overwhelming, but a number of reviews cover all but the most recent studies (Bureš et al., 1974; Somjen, 1979; Nicholson and Kraig, 1981; Martins-Ferreira, 1984; Do Carmo, 1992; Somjen et al., 1992; Lehmenkühler et al., 1993). The reaction was first identified in rabbit cerebral cortex (Leão, 1944a, b). The basic observation was that the EEG following mild noxious stimuli would become completely extinguished for a minute or so and that the depression would propagate very slowly across a wide cortical region.

Cortical spreading depression has been induced in most grey matter regions studied so far, e.g. in the cortex, the hippocampus and the cerebellum of a variety of species (Bureš et al., 1974). It has been observed in human cortical tissue in vitro (Avoli et al., 1991), and in human hippocampus and striatum in vivo (Sramka et al., 1977/8). Thus, human cortical tissues do support the development of CSD, but a recording of CSD from the human neocortex in vivo is still missing (Gloor, 1986).

Successful elicitation of CSD in experiments depends on the susceptibility of the tissue and the trigger factor involved. Hypoglycaemia and hypoxia lower the threshold (Bureš et al., 1974). Common methods of triggering CSD include local electrical or mechanical stimulation or injections of high concentrations of KCl. Potassium plays a central role for CSD and it is reasonable to assume that any disturbance of K+ homeostasis would predispose the brain region to CSD (Grafstein, 1963). Brain K+ clearance systems are heavily dependent on the capacity of glial cells (Nicholson and Kraig, 1981). In humans the lowest glial–neuronal cell ratio is in the primary visual cortex (Bailey and von Bonin, 1951). Therefore, one would expect human CSD to be initiated occipitally. As is well known, visual auras are indeed very frequent in migraine (Olesen et al., 1990).

Neurons and glial cells depolarize during CSD, giving rise to an intense, but transient spike activity (seconds) when the reaction enters the tissue (Sugaya et al., 1975). Neuronal silence immediately follows, lasting for a few minutes, but evoked potentials usually take a longer time to recover, 15–30 min (Bureš et al., 1974). This sequence of brief excitation followed by a short-lasting depression is supposed to be the neurophysiological basis of the sensory symptoms during migraine auras (Leão and Morison, 1945; Milner, 1958; Gardner-Medwin, 1981; Lord, 1986; Lauritzen, 1987a, b).

The depolarization is associated with dramatic changes in the distribution of ions between the intra- and extracellular compartments: K+ and hydrogen ions leave the cells, while Na+, Ca2+ and Cl− enters together with water, as the size of the extracellular space decreases to approximately half of the control values (Fig. 2) (Nicholson and Kraig, 1981; Hansen, 1985). A return to normal of most ion concentrations and of the size of the extracellular space occur spontaneously after 30–60 s, whereas Ca2+ and pH usually take a few more minutes to recover. There is, at the moment, no satisfactory explanation of the spreading mechanism of CSD, but the spread probably involves the diffusion of one or more chemical mediators, most likely K+ and glutamate, into the extracellular compartment (Nicholson, 1993). It has been suggested that a calcium wave in glial cells underlies CSD, but this still remains to be proven (Leibowitz, 1992). A simplistic scheme of the mechanism of
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Fig. 2 Electrophysiological changes accompanying cortical spreading depression in rat brain. Interstitial ion concentrations of sodium, potassium, calcium and hydrogen were measured by ion-selective electrodes. The extracellular potential ($V_e$) and the single unit activity were measured by single-barreled potential electrodes. Cortical spreading depression was elicited in frontal cortex and the electrophysiological changes were recorded in the parietal cortex.

spread of CSD is given in Fig. 3, while regenerative processes are depicted in Fig. 4. It is important to appreciate the transient nature of CSD. If the electrophysiological changes are sustained and propagation is absent, then the phenomenon is usually anoxia or hypoglycaemia rather than CSD. Repeated episodes of CSD increases the immunohistochemical staining of glial fibrillary acidic protein in the rat cortex that is associated with activation of this cell type (Kraig et al., 1991) and a prolonged period (24 h) of expression of the c-fos proto-oncogene (Herrera et al., 1993) and inhibition of protein synthesis (Mies, 1993).

Cortical spreading depression phenomena occur in experimental animals in the penumbra zone, immediately adjacent to a cortical infarct, where nerve cells are viable but electrically silent (Nedergaard and Astrup, 1986; Gill et al., 1992; Iijima et al., 1992). In many respects, the ionic

**Reaction-diffusion model of cortical spreading depression**

![Diagram of reaction-diffusion model](image)

Fig. 3 Simplistic scheme of autocatalytic cycle possibly occurring during CSD.
disequilibria during CSD resemble transient ischaemia, but there is usually no shortage of energy supply during CSD (Lauritzen et al., 1990). These dramatic changes of neuronal function and ion homeostasis are associated with profound changes of the local circulation.

**Brain blood flow during CSD and migraine: precise communication**

Cortical blood flow may decrease before CSD or during the onset of depolarization, but the vasoconstriction is variable and usually brief (Lauritzen, 1987a). Propagation of CSD is totally independent of the vascular reaction: cortical, hippocampal, cerebellar and retinal nervous tissue support CSD perfectly well in vitro (Bureš et al., 1974; Martins-Ferreira, 1984; Do Carmo, 1992). Therefore, it is questionable whether or not CSD sets up a cycle of potassium-induced vasoconstriction of importance for its propagation (Young and Van Vliet, 1992).

During return to normal of ionic changes, rCBF increases by ~100% in anaesthetized animals (Leão, 1944b; Lauritzen, 1987a), simultaneously with the release of lactate to the brain interstitial fluid (Scheller et al., 1992). The flow rise lasts for 1–2 min, being rapidly succeeded by a 20–30% reduction due to cortical arteriolar vasoconstriction, while rCBF in non-invaded regions remains constant (Mies and Paschen, 1984; Lauritzen, 1987a; Kocher, 1990; Shibata et al., 1990; Duckrow, 1991; Piper et al., 1991; LaCombe et al., 1992). The hyperperfusion in rats persists for ~1 h. Blood pressure autoregulation of rCBF is preserved in the entire brain. In contrast, the responsiveness to changes of PaCO₂ (Lauritzen, 1987a; Piper et al., 1991; Lacombe et al., 1992), basal forebrain stimulation (Lacombe, 1992) and vasoactive substances applied directly to the pial arterioles are markedly impaired in the CSD cortex (Wahl et al., 1987). At 90 min after CSD, cortical rCBF increases transiently (Fig. 5) (Fabricius and Lauritzen, 1992).

Thus, CSD in rats may be associated with a brief initial flow rise succeeded by a moderate but prolonged decrease of rCBF due to pial arteriolar vasoconstriction. The reduced rCBF is associated with preserved autoregulation and decreased vascular reactivity to chemical stimuli including CO₂. A brief, small hyperperfusion follows. This pattern of rCBF changes compares favourably with the rCBF changes associated with attacks of migraine (Lauritzen, 1987a; Olesen, 1991).

**Energy metabolism in migraine and spreading depression**

Our knowledge of the changes of energy rich phosphate compounds and oxygen and glucose metabolism during migraine attacks is minimal. This is due to the inherent difficulties in investigating short-lasting paroxysmal disorders like migraine, in which the disturbed metabolic function may have disappeared at the time the patient is referred to, or appears at the clinic. A PET study has shown normal cerebral oxygen metabolism in the hypoperfused regions of a patient with migraine aura at the time of neurological deficits (Herold et al., 1985). The data suggest that ischaemia is not the cause of the focal deficits in migraine. Following the first minutes of CSD in rats, the cerebral metabolic rate of glucose remains normal despite the low cerebral blood flow (Lauritzen, 1987a). By analogy, the behavioural changes at this time point after CSD are also not caused by impaired glucose metabolism.

Magnetic resonance spectroscopy applied to migraine patients at 3–48 h after the beginning of the attack showed a decrease of the phosphocreatine (PC) concentration, an increase of inorganic phosphate, while ATP and intracellular pH remained constant (Welch et al., 1989). The absence of pH changes was taken as argument against the 'vascular' theory since pH was found to be reduced in the affected region in almost all patients with a stroke or a transient ischaemic attack (Welch et al., 1989). Intracellular pH during and following CSD is unknown, but PC decreases by ~38% while ATP remains constant at the CSD wave front (Lauritzen et al., 1990), concomitantly with an increase of cortical oxygen consumption which is matched by a rise in blood flow (Mayevsky and Weiss, 1991). Thus, there are similar changes of PC and ATP during CSD and migraine attacks, suggesting an increased turnover rate of these compounds, but no evidence of ischaemia.

**The magnetoencephalographic experience**

Magnetoecephalography is a technique by which the brain’s electrical activity is recorded by sensors of magnetic fields and not by electrodes as the conventional EEG (Cohen and Cuffin, 1983). Magnetoecephalography measures slow changes of brain electrical activity accurately, which is not possible by EEG (Okada et al., 1988). Cerebral spreading depression depolarizes the cortex for ~1 min and changes the brains DC potential, the steady potential around which the EEG oscillates (Leão, 1951). The major purpose of the ongoing magnetoencephalographic research in migraine has been to record a slow change
of the cortical magnetic field corresponding to the DC potential change in CSD (Okada et al., 1987, 1988; Gardner-Medwin et al., 1991; Barkley et al., 1991).

The magnetoencephalographic signal associated with CSD in vitro is in the picotesla range (Okada et al., 1987). This raises the possibility of non-invasively detecting CSD in human cerebral cortex in association with migraine attacks, but the studies are extremely difficult to perform. Preliminary results obtained with a seven-channel AC-coupled magnetoencephalographic system in a group of migraine patients are not unambiguous (Barkley et al., 1990, 1991). The magnetoencephalographic signals share important features with signals recorded with the same equipment during CSD in rabbits (Gardner-Medwin et al., 1991). However, the specificity of the signals remains to be defined, and further confirmation of the results is needed.

Cortical spreading depression as a migraine mechanism: the theory
The theory now is that migraine attacks are initiated by a CSD originating in the posterior part of the brain. The CSD...
The generation of headache from intracranial sources requires activation of pain-sensitive fibres that are located at the ventral surface of the brain. Recent data suggest that CSD activates nociceptive fibres in rats (Moskowitz et al., 1993), but conscious rats do not experience CSD as an aversive stimulus (Koroleva and Bures, 1993). The latency period between onset of aura and headache may reflect the time it takes for the CSD to propagate from the occipital cortex to the pain triggering zone (Moskowitz, 1984), but the mechanism by which CSD may inflict pain is still far from understood.

The aura and headache may represent separate effects of CSD on different brain structures—the cortex and the nociceptive vascular afferents. This may explain the variations of migraine symptoms observed in the same patient and also in different patients. As is well known, headaches are observed quite frequently following epileptic attacks (Schon and Blau, 1987), which are associated with marked changes of the neuronal microenvironment similar to, but less profound than those found during CSD (Somjen, 1979; Avoli et al., 1991).

Some research perspectives in experimental migraine research

It appears that CSD displays sufficiently important similarities to the migraine attack that it can be considered as a disease model. The recent development of drugs directed against glutamate receptors have given us important clues to synaptic events which are clearly important for CSD.

Van Harreveld (1959) was the first to point out that glutamate triggered CSD. A few years later it was shown that an agonist of a glutamate subtype receptor, N-methyl-D-aspartate (NMDA), was 100 times more potent than glutamate in eliciting CSD (Curtis and Watkins, 1961). Indeed, the brain cortex releases excitatory amino acids, including glutamate and aspartate, to the interstitial fluid during CSD, but the increase is brief, lasting for only ~1 min (Fig. 7) (Van Harreveld and Kooiman, 1965; Fabricius et al., 1993).

Cortical spreading depression is blocked by various competitive and non-competitive NMDA antagonists (Van Harreveld, 1984; Gorelova et al., 1987; Hernandez-Caceres et al., 1987; Mody et al., 1987; Lauritzen et al., 1988; Marrannes et al., 1988; Avoli et al., 1991; Lauritzen and Hansen, 1992) but not by antagonists of non-NMDA glutamate subtype receptors (Lauritzen and Hansen, 1992). NMDA receptor activation in turn triggers the synthesis of nitric oxide, which is both an important vasodilator and a neurotransmitter (Garthwaite et al., 1988). This is of interest since nitroglycerin provokes headache in man (Iversen et al., 1989).

The fact that hypercapnic hypoxia aborted the migraine aura and prevented the headache could not be explained by vasodilatation as discussed in a preceding section, but CSD in rats is reliably inhibited by hypercapnic hypoxia (Gardner-Medwin, 1981) (Fig. 8). This result strengthens the case that CSD underlies the migraine aura (Gardner-Medwin, 1981). The mechanism of action of hypercapnia on CSD and the aura remains uncertain, but hypercapnia stimulates nitric oxide synthesis in the brain (Iadecola, 1992; Wang et al., 1992; Pelligrino et al., 1993; Fabricius and Lauritzen, 1994). Interestingly, amyl nitrite, a well-known donor of nitric oxide, curtails the migraine aura (Woff, 1963).

Magnetic resonance spectroscopy has revealed low brain
Migraine and spreading depression

Microdialysis, rat neocortex
Cortical Spreading Depression

Fig. 7 Maximal concentration in dialysate of glutamate (upper panel), and glycine (lower panel) during single episodes of cortical spreading depression of rat brain. Graphs represent mean values ± 1 SD of eight experiments at different time points during CSD. The CSD was elicited by needle stab in the frontal cortex while the dialysate was from the parietal cortex. Time zero corresponds to maximum of negative DC potential recorded with a single-barelled micro-electrode placed adjacent to the microdialysis probe. Amino acid concentrations were determined by HPLC (from Fabricius et al., 1993).

Fig. 8 Extracellular [K+]e in parietal cortex (upper trace) and DC potential change in the frontal cortex (lower trace) in rats exposed to CSD and cerebral ischaemia. After the fourth CSD MK801, a NMDA-antagonist, at 10 mg/kg was given intravenously (indicated by arrow). The drug blocked CSD completely, but did not delay or curtail the [K+]e changes during anoxic depolarization induced by intravenous injection of KCl (from Lauritzen and Hansen, 1992).

Drugs used for prophylactic migraine treatment including methysergide, propanolol, pizotifen, clonidine or flunarizine are ineffective as blockers of CSD (Hansen et al., 1984; Marranes et al., 1986). Probably these substances influence the sequence of events which cause pain (Moskowitz, 1992) rather than the CSD itself. Sumatriptan, the newly developed drug for treatment of migraine headaches, decreases the cortical input to the trigeminal nucleus caudalis of the brainstem without affecting the CSD itself (Moskowitz et al., 1993). Ergotamine on the other hand increases the threshold for CSD in rats (Marranes et al., 1986).

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