

Spreading Cortical Depression (SCD) from Pathophysiology: Can We Detect Signals Non-invasively Using DC-MEG?

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ABSTRACT

SCD is a non-specific, transient, disturbance of the function of neurons in the cortical environment. First observed in 1944 by Leão, SCD has been linked to migraine, epilepsy, anoxia, cerebral ischemia, and head trauma. The tissue undergoing SCD exhibits vigorous discharges and then becomes electrically inactive for several minutes. This wave of hyper-excited neurons spreads across the cortex at a rate of 2-5mm/minute, creating large direct current (DC) changes. Detection of brain activity during SCD-like events has uses in the clinical evaluation of a number of neurological disorders. Microsquad MEG systems have been used to characterize the DC-MEG signals from a gyrencephalic and a lissencephalic brain in animal models of SCD. DC-MEG signals of SCD-like events during ischemia, anoxia, and epilepsy in animal models have also been studied. We have recorded DC-MEG signals of cortical activity in migraine patients. During migraine aura large amplitude, slowly shifting, DC-MEG waveforms, are associated with a simultaneous reduction of spontaneous EEG and MEG, reminiscent of what is seen during SCD in animals.

In 1943 A. A. P. Leão, a graduate student, from Harvard Medical School, wrote a paper, as part of his thesis, entitled Spreading Depression of Activity in the Cerebral Cortex. This paper described the phenomenon of a slow, spreading wave of suppressed neuronal activity across the cortex of rabbits. SCD is a non-specific, transient disturbance of the function of neurons in the cortical environment. SCD has been studied extensively *in vivo* and *in vitro* in experimental animals (Bures, 1974; de Carmo, 1992). SCD had been seen in human hippocampus and striatum (Sramka, 1978). SCD is a disturbance of the cortical environment that has been linked to migraine (Lauritzen, 1994), epilepsy (Marshall, 1959), anoxia (Hansen, 1985), cerebral ischemia (Hansen et al., 1981) and head trauma (Oka et al., 1977). SCD can be initiated by using electrical stimulation of a few microamps, mechanical stimulation with a pinprick, and chemical stimuli such as KCl, or glutamate (an excitatory amino acid). During SCD a wave of hyperexcited neurons followed by functionally depressed neurons propagates outward in an annular fashion from a focal point. SCD propagates slowly along the cortex at a rate of a 2-5 mm/minute. SCD wave will not propagate through a cut made in the cortical surface, extending into the white matter, nor will SCD propagate across the midline to the opposite hemisphere (Ochs, 1962). The tissue undergoing SCD exhibits vigorous discharges and then becomes electrically inactive for a few minutes (Herreras et al., 1994). This hyperexcited wave of SCD can be detected by MEG (Okada, 1987; Bowyer, 1999). DC-shifts of approximately 5mV may be seen in DC-electrocorticogram (DC-ECOG). During SCD, membrane resistance of the neurons is reduced, and ion concentrations across the cell membrane are grossly altered (Nicholson, 1981).

Hansen and Zeuthen (1981) and Lauritzen et al. (1988), investigated the homeostasis of ion changes between intra and extra cellular space during SCD. They found potassium (K) flowing out of a cell and sodium (Na), calcium (Ca), chloride (Cl) and water (H₂O) flowing into it. These ionic movements caused a depolarization of the neurons. The depression was preceded by a brief hyperexcited phase and was followed by a depolarization of neurons lasting for 30-60 seconds. In the extracellular space $[K^+]_o$ increased by 10 times its normal amount (3mM to 30 mM), $[Na^+]_o$ decreased by 1/3 of its normal amount (150mM to 50mM), and $[Ca^{2+}]_o$ decreased by 1/10 its normal amount (1.2mM to 0.1mM). PH levels decreased from 7.3 to approximately 6.9. $[Cl^-]_o$ decreased by 1/2 of its normal amount (120mM to 60mM). H₂O entered the cell and caused a reduction in extracellular space due to cell swelling (Hansen, 1981).

Lauritzen et al. (1987), and Shibata et al. (1990) using animal models, studied cerebral blood flow during SCD. They found that the main wave of SCD was accompanied by dilation of the blood vessels and a brief local increase of blood flow. This was followed by long-lasting vasoconstriction (hypoperfusion), which was followed by a hyperperfusion. This blood flow change is similar to the patterns found in migraine patients (Lauritzen, 1994; Olesen, 1981). Wadman et al. (1992), found that the extracellular current source was located in the cell body and the corresponding sink located in the apical dendrite of the hippocampal CA1 pyramidal cells during SCD. Thus, the currents were oriented along the longitudinal axis of the pyramidal cells and were directed from the apical dendrites toward the soma. Sloan and Jasper (1950) used cat and monkey to study propagation of SCD in a convoluted brain. Using ECOG they found that SCD in cat and monkey were more difficult to initiate than in the lower species such as rat and rabbit. They also found that SCD appeared to propagate along the sulcal wall.

After 60 years of studying SCD the biophysics are still incomplete (Kager, 2002). What is known is that SCD is an all-or-none process and that rising extracellular potassium concentrations $[K^+]_o$ and/or the overflow of glutamate can initiate SCD. SCD does not require working synapses nor does it need calcium ions or calcium channels. We also know that ion channels in neuron membranes can mediate the SCD-like depolarizations.

***In-vitro* studies of SCD using MEG** Okada et al. (1988) were the first investigators to record magnetic signals arising from SCD. They measured the signal in the isolated turtle cerebellum during SCD. The turtle cerebellar slice was oriented perpendicular to a single channel magnetometer. The neurons in the slice were aligned tangential to the pick up coils. Five different locations were monitored with a single channel sensor during electrically stimulated SCD. The waveforms, acquired from this system, indicated that MEG deflections occurred from fields produced by neurons oriented perpendicular to the cerebellar surface.

Four years later using a 4 channel μ SQUID system, Okada et al. (1992) detected magnetic fields from the isolated chick retina during SCD. In the chick retina, SCD was initiated by mechanical stimulation. The propagation was seen visually as changes in color of the tissue, due to alterations in light-scattering. Retinal activity was recorded with surface electrodes. Magnetic fields were seen as SCD propagated under the pickup coils. The spatial pattern of the magnetic signal indicated that the signals were coming from currents perpendicular to the retinal surface. A dipole fit of the data was used to find the propagation rate of approximately 1 mm/minute, slow presumably due to the cool temperature of the Ringer bath used. Based on these two studies it was concluded that MEG could be used to detect SCD.

***In vivo* studies** Welch et al. (1987) predicted that SCD should be detectable by MEG during migraine. From 1988 to 1998, the MEG lab at Henry Ford Hospital has used a 7-channel and, since 1998, a 148-channel system, to conduct MEG and EEG studies on migraine and epilepsy patients. Initially animal studies were performed to understand the MEG waveforms arising during migraine in humans.

Several *in vivo* studies showed MEG signals from SCD induced by an application of KCl to the cortex, could be monitored outside animal heads. Gardner-Medwin and the Henry Ford Hospital Group used MEG to measure magnetic fields from the rabbit cortex *in vivo* during SCD, in order to better understand MEG signals of SCD *in vitro* (Barkley et al., 1989, Gardner-Medwin, et al., 1991). This study found large DC-MEG shifts after initiation of SCD by KCl application. Takinashi et al. (1992), also with the Henry Ford Hospital Group, used a 7 channel MEG system to

monitor SCD arising from a rat model during KCl induced SCD. This study found DC MEG signals similar to those from the Gardner-Medwin study. These animal model studies have shown that DC MEG signals are correlated with both AC and DC changes in ECoGs.

A four channel micro squid was used to characterize the MEG signal expected to arise during SCD in a convoluted cortex initiated by electrical stimulation in a swine and rabbit model (Bowyer 1999a,b). We found that the hyperexcited wave can be detected as it turns into a sulcus or the midline of the brain. These findings were the basis for the interpretation of the MEG waveforms detected during migraine aura in humans.

We found that the human data revealed a reduction of spontaneous EEG and MEG activity during migraine with aura (Barkley, 1990). DC studies (0-50Hz filters) were also conducted on migraine patients. There were many long, large, slow DC shifts during the actual migraine aura compared to control subjects where no DC shifts occurred (Bowyer, 2001). In humans, DC-MEG has been used to demonstrate similar findings in familial hemiplegic migraine (Gutschalk, 2002).

In epilepsy slow DC-shifts are expected during seizures (Marshall, 1959; Leao, 1944) and probably the postictal state. DC shifts during ECoG recordings in patients with epilepsy have provided DC recordings just prior to seizure onset (Ikeda, 1997). Conventional surface EEG cannot be used to record near DC activity because of baseline drift that occurs at the scalp-electrolyte-electrode interface. Though a study has been performed recently using a new technique of gel filled EEG electrodes in which DC shifts were seen at onset of seizure (Vanhatalo, 2003). Since MEG can record cortical DC shifts and, with care, DC MEG recordings can be routinely performed (Barkley, 1991), we now record all patients undergoing MEG evaluations for interictal spike analysis with a DC high pass filter.

Further studies on SCD may render a deeper understanding of the biophysics occurring during the initiation of SCD. This may also lead to a more complete understanding of the neurological disturbances linked to SCD.

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