Magnetic and Impedance Measurements for the Detection of Spreading Depression at a Distance

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SUMMARY

1. Two distinct reasons are set out for attempting to detect Spreading Depression from a distance (i.e. through measurements at remote sites): (1) the need for additional evidence relevant to the possible occurrence of Spreading Depression in migraine, and (2) the advisability of monitoring for the occurrence of Spreading Depression and allied phenomena during surgery.

2. Biomagnetic measurements may be capable of detecting SD non-invasively in man, but the nature of the signals obtained from anesthetised rabbits during propagating SD suggests that DC recording may be required, with highly stable baselines.

3. With neurosurgical exposure of vulnerable brain tissue, the monitoring of disturbances such as SD beneath the surface, causing local changes of electrical impedance, may be carried out through the application of current and the measurement of voltage changes restricted to the tissue surface. 4. In neurosurgical monitoring an important distinction must be made between mild superficial disturbances and deeper profound disturbances, which in some respects produce similar signals at the surface. Information about the depth of the disturbance can be extracted from multiple surface impedance measurements, and may assist in making this distinction.

Introduction

This paper considers two clinical situations where it would be useful to be able to monitor the occurrence of Spreading Depression (SD) in brain tissue without the use of invasive electrodes or other probes. Study of SD in the retina has the great advantage over studies in the brain that the disturbance is clearly visible as a result of the associated changes of light scattering (Martins-Ferreira & Oliveira-Castro, 1966). This has made it possible to identify the initiation, propagation and failure of SD throughout the whole of the retinal tissue in a manner that otherwise would have required complex, multiple, and potentially traumatic recording probes. The result has been a better understanding of the conditions for propagation (Martins-Ferreira, 1983). Nevertheless, the most important advances in the understanding of SD both in the brain and in the retina (see Bures et al., 1974; Nicholson & Kraig, 1981; Do Carmo & Martins-Ferreira, 1984, for reviews) have been made through microelectrode and chemical studies. Why, then, do we need remote techniques for studying SD in the brain?

The two clinical problems

The two situations in which such techniques are needed both relate to the clinical study of SD in man. The rationale and the technical requirements are very different. The first is for the study of migraine. It has long been thought possible (Leão & Morrison, 1945) that SD occurs in classic migraine, i.e. the form of migraine in which there are acute symptoms of neurological dysfunction preceding the headache (for reviews, see Gardner-Medwin, 1981). Studies on migraine sufferers require totally non-traumatic and preferably non-invasive techniques.

One such technique for the study of migraine has existed for a number of years: the measurement of regional cerebral blood flow (rCBF). This has contributed greatly to the characterisation of migraine attacks (Olesen, Larsen & Lauritzen, 1981), and in many respects supports the possible involvement of SD in classic migraine (see Hansen & Lauritzen, 1984 for review). Unfortunately however, the circulatory changes are only indirect consequences of SD, and might plausibly result from any other mechanism causing the migraine aura. It is possible (Olsen et al., 1987), though controversial (Kronborg et al., 1990), that blood flow may fall low enough in some patients directly to cause neurological dysfunction. This could be true, however, whether SD occurs or not to trigger the blood flow changes. More direct techniques are required, if the occurrence of SD is to be clearly established or refuted. Meanwhile, the evidence that is hardest to explain on any hypothesis other than the SD hypothesis would appear to remain the remarkable quantitative and qualitative similarity that SD bears to the aura in classic visual migraine (Milner, 1958).

The second situation where the remote detection of SD would be valuable is in neurosurgery. It is plausible, but not certain, that SD occurs during neurosurgery in man (Gardner-Medwin & Mutch, 1984). If it does occur, then some of the particular conditions in surgery render it longer lasting (Mutch & Gardner-Medwin, 1987) and a potentially more damaging disturbance than it would be in a normal healthy individual. Levels of blood flow and metabolic provision that are adequate for the healthy survival of normal tissue may result in frank anoxia with the added metabolic load presented by SD (Haselgrove et al., 1990). The detection of SD and related phenomena (e.g. local anoxic depolarization) during surgery could represent a valuable clinical tool, both for the identification of possible causes of lesions due to surgery and for their alleviation if sufficiently rapid warning can be given of their incipient development. The prime requirements for a technique that could be useful in neurosurgery are (i) that it be compatible with practice in the operating theatre, and (ii) that it should not increase the risks of tissue trauma. For these reasons, any probe devices must not penetrate the tissue surface. We are again faced with the problem of detecting SD from a distance if sensitivity is to be maintained for more than purely superficial disturbances.

Nature of the disturbances during SD

In rat cortex, SD propagates at a uniform rate through fairly flat tissue. This means that a cross sectional map of the changes within a propagating SD wave can be inferred, at least approximately, from measurements at different depths on a single electrode track (Fig. 1). The zone of extracellular negativity and high extracelluar

potassium concentration ([K+]o) extends from the surface to a depth of 1-2mm, and is 1mm or more in width, varying with the ambient conditions, for example blood flow & PCO2. In the perpendicular direction (parallel to an advancing wavefront) the region of tissue affected at any one instant can be much more extensive, commonly forming a complete ring around a focus of initiation in the manner that is seen so clearly in the chick retina preparation (Martins-Ferreira, 1983).

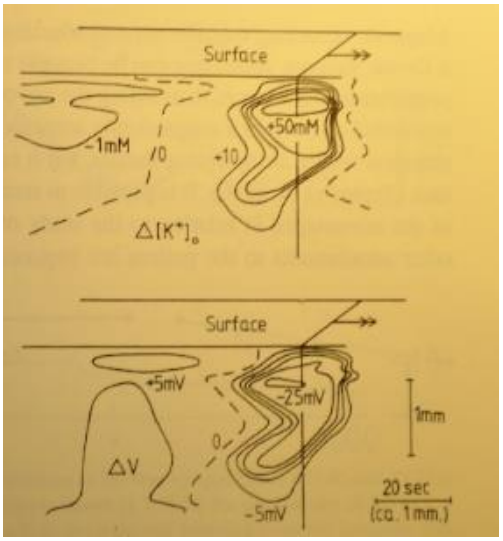

Fig. 1. Contour plots showing the region of tissue affected by extracellular K+ changes (above) and extracellular voltage changes (beneath) during Spreading Depression, in parietal cortex of a urethane-anesthetized rat. The plots were derived from K+ microelectrode recordings at different depths on a single electrode track, during 8 successive propagating waves of SD at 6min intervals. Records were aligned in time relative to the peak negativity recorded simultaneously from a fixed Ag/AgCl electrode at the surface (vertical line). The horizontal axis is strictly a time axis, but is equivalent to a horizontal spatial axis (with calibration matched to the vertical, depth axis) for propagation at 3mm/min (towards the right) through uniform flat tissue. Data obtained in collaboration with J.L. Skelton.

The physical changes that might be used to detect the occurrence of SD include those directly associated with the electrophysiological events: the changes of ionic and neurotransmitter concentrations, the prolonged voltage shifts and associated currents, the cessation of action potentials and the changes of cellular and extracellular volumes. There are also changes that arise in a secondary manner as physiological responses to the primary events of SD, in at least some circumstances: changes in active transport, metabolic biochemistry, blood flow, glucose uptake, oxygen availability, etc.. In very many of these respects, SD produces larger changes than are known to occur in the course of normal physiological activity.

Very many techniques have been used to observe these changes, either directly or indirectly. The list of possible physical techniques is essentially open-ended. No attempt will be made here to review these techniques. Instead, I shall examine the potential of two specific techniques for assisting with the specific clinical problems outlined above: magnetic field measurement in relation to the detection of SD in neurological disturbances such as migraine, and electrical impedance measurement in relation to the detection of SD and anoxic regions beneath the tissue surface in neurosurgery.

Magnetic fields due to SD

In some circumstances the current flow around a region of SD can produce distant voltage changes and magnetic fields. The voltage changes are restricted to the tissue, and are both attenuated and smoothed over a large area on the scalp by the combined effect of the high resistance of the meninges and skull and the relatively low resistance of the scalp. The magnetic fields extend into surrounding space and are not affected by the skull and the scalp. Magnetic recordings during SD were first

made by Okada et al. (1988), using an in vitro preparation from the turtle cerebellum. Recordings have also been made in vivo during SD in the cortex of intact anesthetised rabbits (Gardner-Medwin et al., 1990). The fields are small (a few pico Tesla (pT) at 20mm distance, cf. the Earth's magnetic field, ca. 50µT).

Magnetic recording requires superconducting sensor coils immersed in liquid helium within a Dewar vacuum vessel that can be brought close to the head (Fig. 2). The tissue and animal preparation require care in avoiding the use of magnetic materials, and the experiments must be carried out within a magnetically screened chamber. The technique is unlikely ever to be practical within an operating theatre, but it can be used with migraine subjects during an attack (Tepley et al. 1990). It is possible to record simultaneously from multiple coils, and one of the advantages in relation to the study of neurological patients is that no electrodes or other attachments to the patient are required, and hence there is very little delay in commencing a recording session. Against this must be set the need for careful control for sources of magnetic interference that can lead to artefacts due to magnetic contamination and patient movement. For example, dental materials and hair spray can both cause problems that can vary between sessions even with the same subject.

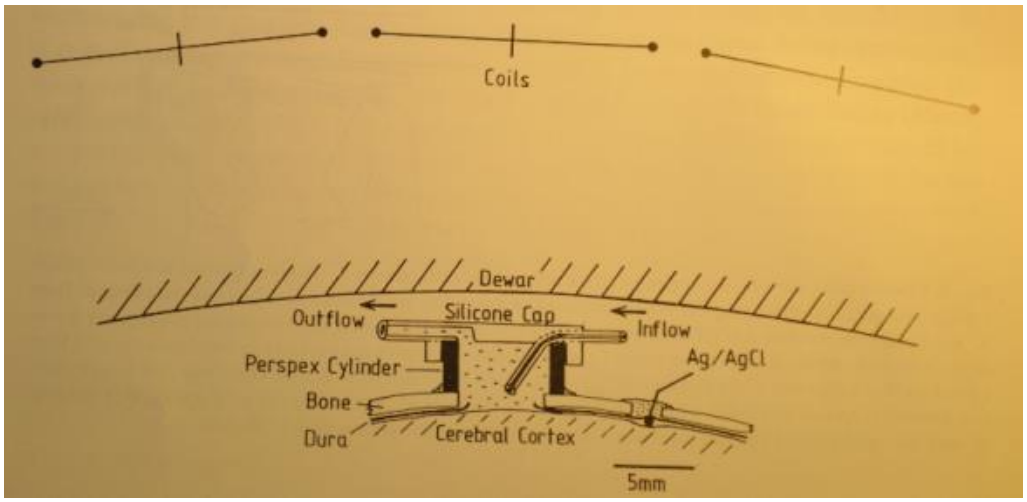

Fig. 2. Arrangement for magnetic recording during SD in anesthetized rabbits, used by Gardner-Medwin et al. (1990). A perspex (plexiglass) cylinder was cemented to the bone over the exposed pial surface. A transparent silicone rubber cap with silicone rubber inflow and outflow tubes allowed artificial csf over the cortical surface to be exchanged for KCl to initiate SD, under the control of a remote experimenter. The animal's head was supported on pillows, with careful exclusion of all magnetic materials, under the Dewar vessel of a BTI Model 607 SQUID Magnetometer containing liquid helium and seven superconducting pickup coils (six outer coils arranged around a central coil) about 25mm above the brain.

Typical signals recorded during SD propagation in the rabbit cortex are shown in Fig. 3 (see also Barkley et al. 1989, Gardner-Medwin et al. 1990). SD was initiated with 150mM KCl in the left parietal cortex, and the trace shows the mean changes of vertical magnetic field for up to 15min after SD initiation, recorded from coils in one of the sites (posterior and right from the KCl chamber) that gave the largest changes. The consistent component of the magnetic response was a slowly developing upward deflection (upward field through the coil) between about 200s and 600s after KCl application, with a peak at about 350s. In addition there were transient downward shifts at the times of KCl application and washout, consistently present in

some preparations and absent in others and are not statistically significant overall: their origin is not known, but may have been connected with the mode of perfusion of the cortical chamber.

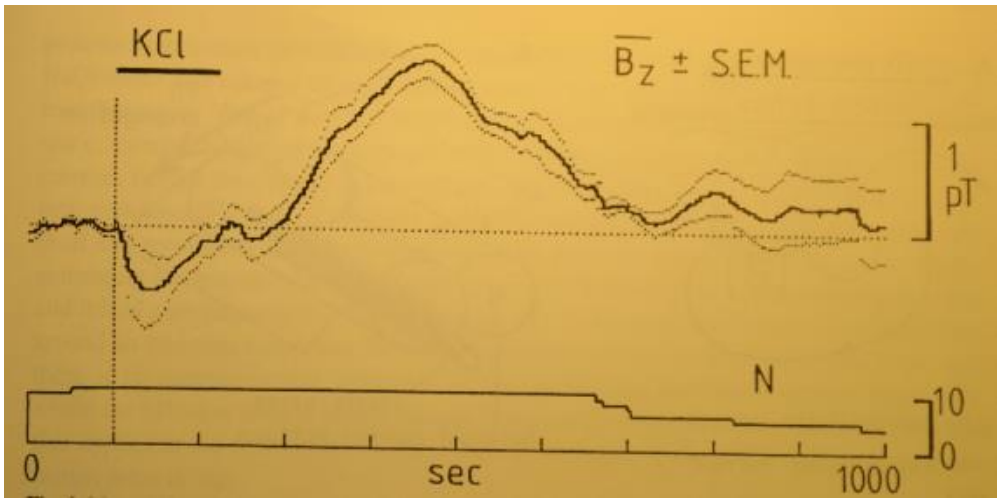

Fig. 3. Mean shifts of magnetic field associated with SD. Initiation of SD was by application of 150mM KCl for 120s over the left parietal cortex. The mean vertical field (Bz) is shown (± 1 s.e.m.) for 10 episodes of SD in 5 animals, for the coil in each recording session that was both to the right and posterior from the initiation site. Records were aligned relative to the start of KCl application. Since different records extended for different lengths of time, the number (N) for each part of the trace is plotted beneath. Data from the study by Gardner-Medwin et al. (1990).

In addition to these changes in the DC magnetic recordings, clear changes in the level of magnetic fluctuations in the 1-50Hz bandwidth were occasionally seen (Gardner-Medwin et al., 1990). For technical reasons, these only became evident in analysis of the recorded data after the end of the study, and the conditions for their generation were not investigated. Drops in the level of fluctuations of up to 70% occurred sometimes over a few seconds, sometimes at the time of KCl application and sometimes at other times without any evident precipitating stimulus. It seems more likely that this was related to changes of diffuse activating influences within the nervous system than to the generation of SD.

Mechanisms of generation of magnetic fields in SD

The relations between observed magnetic signals and the particular details of SD propagation in rabbit cortex are discussed elsewhere (Gardner-Medwin et al., ms submitted). Only the general mechanisms by which SD can generate magnetic fields are described here (Fig. 4). The relationship between currents in neural tissue and the magnetic fields they generate is fairly complex (Williamson & Kaufman, 1987). There are many patterns of current that lead to electric fields but no magnetic fields at all, for example (in a simple spherical model of the brain and skull) sources of inward and outward membrane current that lie on a line perpendicular to the skull. In general it is necessary for there to be some break in the symmetry of current patterns about a line or a plane perpendicular to the skull, if magnetic fields are to be generated.

Fig. 4A shows the principal intracellular current flow associated with SD (hollow arrows). This is probably largely glial current associated with K+ clearance (Gardner-

Medwin, 1981). These arrows correspond to current dipoles, with outward membrane current at their heads and inward current at their tails. The magnetic effect of the dipoles can be calculated within uniformly resistive tissue without regard for the return extracellular current paths, since by symmetry the effect of these return paths can be shown to be zero. Since the forward and backward dipoles associated with SD are similar and largely cancel in their magnetic effects, the principal magnetically effective intracellular dipole is away from the adjacent tissue surface (Okada et al., 1988). Thus one of the principal ways in which SD can generate a magnetic field is through an array of dipoles pointing away from the cortical surface throughout the zone of depolarisation (Fig. 4B). A field is only generated by this mechanism, however, where these dipoles are not perpendicular to the skull, i.e. where SD propagates in cortex facing a sulcus such as the sagittal sulcus in the rabbit, or the numerous sulci in the convoluted cortex of man.

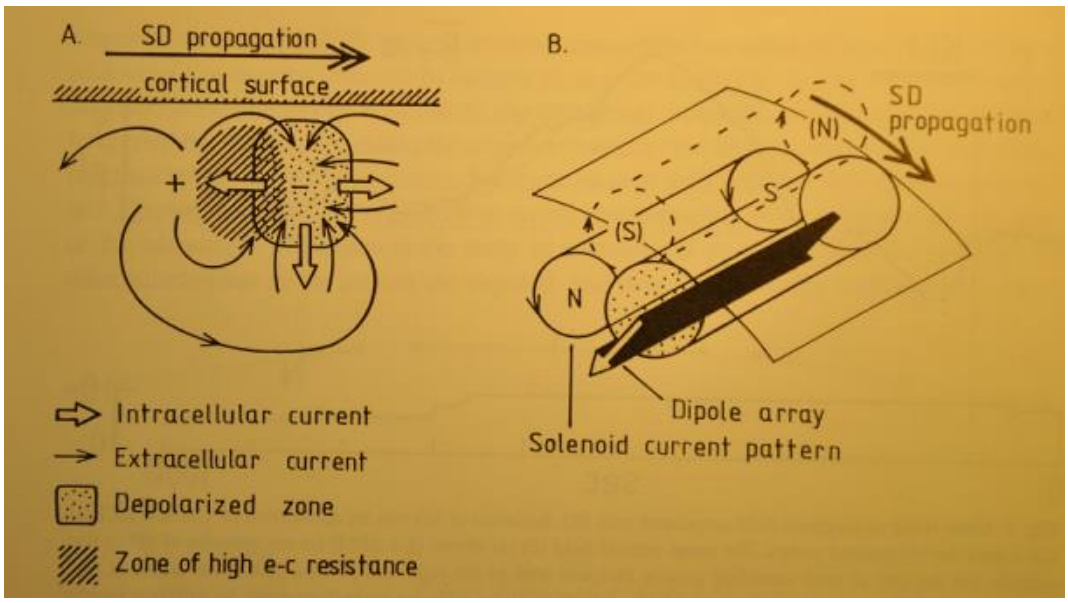

Fig. 4. Diagram of currents (A) and principal magnetic generators (B) around a region of SD propagating to the right. The depolarized region is shown stippled (cf. the zone of extracellular negativity and high [K+]o in Fig.1). The principal intracellular currents (A) are away from this region: forward, backward and towards deeper tissue. The relatively small distance over which intracellular currents can flow towards the surface leads to a net intracellular dipole array towards deeper tissue (B). In addition, there is asymmetry between the extracellular resistance around the zones of forward and backward currents, due to the high extracellular resistance caused by SD (hatched zone). This leads to more of the backward current returning via long distance extracellular current loops, rather than through the local extracellular space. If the cortical surface lies against high resistance tissue such as dura and bone, these loops are predominantly in the deep tissue and have a magnetic effect similar to that of a solenoid (B), with a North pole (N) to the right of a restricted zone of propagation and a South pole (S) to the left. The solenoidal currents have no magnetic effect if the SD wave forms a complete ring around a point of initiation.

A second break in the symmetry of current flow, capable of generating magnetic fields, applies also to SD propagating parallel to the skull. This results from the increase of extracellular impedance that is more pronounced in the wake of SD (Hoffman et al. , 1973), due to NaCl influx and reduced extracellular ion content (Fig. 4A). Much of the intracellular current flowing in front of the zone of SD depolarisation returns via the adjacent extracellular space, thereby diminishing its magnetic effect. This return pathway is partially occluded for currents behind the zone of

depolarisation, which therefore follow long extracellular pathways. If the tissue surface lies against a zone of high resistance (e.g. the skull and meninges), then the long extracellular paths are predominantly in deeper tissue, generating a solenoidal pattern of current flow with N and S poles respectively on the right and left of a propagating SD wavefront (Fig. 4B). If the wave of SD forms a complete ring around an initiating focus, then the solenoidal current pattern is closed in a torus shape, and there is no magnetic effect. Thus this second mechanism generates magnetic fields only where the SD wavefront is broken through failure of propagation at some point: a condition that applies in the retrosplenial cortical area in the rabbit (Leão, 1944) and presumably in certain areas in man.

Implications for magnetic studies in migraine

Various lessons can be learned relevant to the potential use of magnetoencephalography for characterising neurological disturbances in migraine or other disorders. The signals measured during SD in the rabbit were very slowly changing (Fig. 3), close to the limits of baseline stability for their detection in individual records and requiring DC recording conditions. Most prior records made with migraine patients had been carried out with AC recording (Tepley et al., 1990).

The signals from the rabbits were smaller and slower to change than those previously observed with SD in vitro (Okada et al. 1988). The conditions in vitro were especially favourable for magnetic recording in two respects: the tissue was surrounded by a saline solution with a substantially higher conductivity than the brain tissue around a zone of SD in vivo, and SD was initiated with electrical stimulation, which may have led to synchronous initiation over a relatively large area. The likely extent of tissue that might be synchronously involved in the initiation of SD in migraine is unknown.

Even the type of signals detected in the rabbit could in principle be identified if they occur in man associated with migraine attacks. It is also possible that larger signals than those seen in the rabbit might be recorded if SD does occur in migraine. The large amount of tissue that could become involved and the substantial fraction of this that could lie at optimal orientations both argue in favour of this. Such signals appear well worth seeking. The magnetic signals are likely to be highly dependent on the shape and orientation of the zones affected by SD, however. It is clear therefore that even large signals may be difficult to characterise as definitely due to SD rather than to zones of ischemia or to any other disturbance that one might postulate to account for the symptoms of migraine.

Use of impedance techniques for detecting deep tissue disturbances

The problem of detecting SD during neurosurgery is twofold: that of getting adequate sensitivity to disturbances beneath the tissue surface, with techniques limited to surface access, and that of distinguishing signals arising from deep disturbances from those arising nearer the surface. Impedance measurements offer a good prospect of achieving these goals, within limits that have yet to be determined.

It might be asked why it is necessary to distinguish surface disturbances from deep disturbances if both can be detected and both are known to be undesirable. The

problem is that most techniques based on measurements at the surface will be more sensitive to superficial than to deep disturbances. Thus the source of a given signal may in general be either a mild superficial disturbance or a more severe deep disturbance, with possibly quite distinct clinical implications.

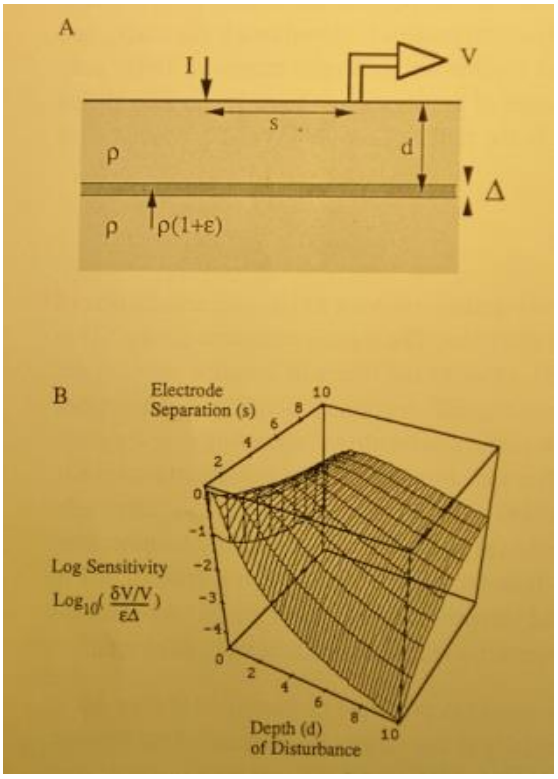

Fig. 5. The detection of impedance disturbances under the tissue surface with surface current application and voltage measurements. A. A zone of tissue of thickness Δ at depth *d* has its resistivity (ρ) raised by a fraction ε. Current is applied at a point on the surface (I), with a remote return electrode. The voltage gradient at the surface (V) is measured with a pair of electrodes at a distance *s* from the current injection site. The increase of ρ leads to a fractional increase δV/V, proportional (for relatively small changes) to εΔ. The sensitivity (B) is defined as the ratio of these quantities and is plotted on a logarithmic scale as a function of both *d* and *s*. At short *s* it falls rapidly with depth *d*, while with large *s* the sensitivity increases with depth (up to $d=s/\sqrt{6}$) and then falls more slowly.

In principle impedance measurements, or 'applied potential tomography' (Brown et al., 1985) can generate enough information to produce a complete image of disturbances of impedance within a tissue from just surface measurements, provided there are no zones surrounded by complete insulators. The present requirements fall far short of the need for images, and may perhaps be realised with much less than the optimal conditions.

One situation in which surface measurements can yield the necessary information about the depth of an impedance disturbance is illustrated in Fig.5A. Current (I) is passed from a surface electrode over the tissue of interest to a remote return electrode. The resulting voltage gradient (V) is measured with a pair of surface electrodes at a distance s. The sensitivity of V to a widespread change of impedance at a specific depth d is plotted in Fig. 5B. With a small electrode separation s the sensitivity to impedance changes falls rapidly with depth. An increase of the electrode separation lowers the sensitivity to superficial disturbances but raises the sensitivity to deep disturbances. Thus by observing the ratio of changes measured with different separations it is possible to deduce the depth of a disturbance.

This example illustrates the general principle of inferring the depth of a disturbance. Of course disturbances in general are not uniform at a constant depth in the simple manner assumed for these calculations. However, by adding measurements made with many current injection sites as well as many sites of recording, it is possible to

deduce the full pattern of impedance changes in both depth and horizontal position: the principle of applied potential tomography. The depth and resolution to which such information can be obtained depends on the number of measurement sites, their separation and the noise level of the measurements.

Impedance measurements during SD

SD has long been known to be associated with impedance increases detectable from surface measurements (Leão & Martins-Ferreira, 1953). The local increases beneath the surface are as great as a factor of 2-3 (Hoffman et al., 1973). Holder & Gardner-Medwin (1988) have made surface measurements under conditions that permit a comparison of the signals with those expected for disturbances at specific depths (Fig. 6). Alternating current (50kHz) was passed between the first and last of an array of 9 electrodes (Fig. 6A). The in phase amplitude of the resulting 50kHz potential changes was measured at each of the intermediate electrode sites during passage of a SD wave under the electrode array. In Fig. 6A the changes of this signal from baseline values are plotted against time for each electrode site.

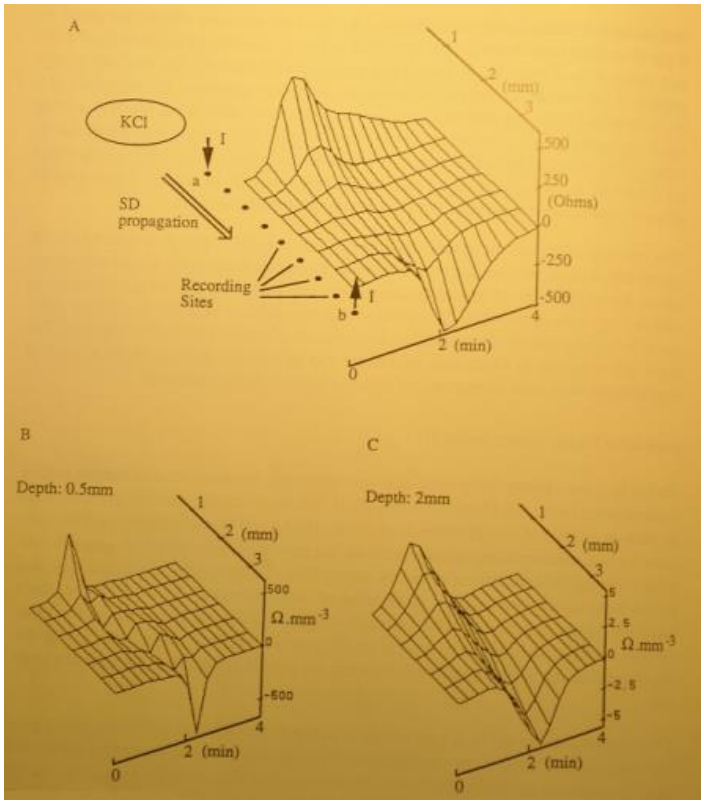

Fig. 6. Impedance measurements during SD in the cortex of an anesthetised rat. A. SD was initiated with 150mM KCl in a cup (marked KCl) and propagated along a row of 9 surface electrodes (a-b) at 0.5mm spacing. Alternating current was passed between the first and the last electrodes (I: ca. 20µA p/p, 50kHz). The voltage changes at 50kHz (relative to a remote earth) were selectively filtered and their in phase components measured with a phase locked detector during successive SD waves at each of the intermediate electrodes. The changes during SD are plotted as functions of time adjacent to each recording site. They are expressed in ohms, as the voltage change divided by the applied current. B,C show the calculated signals expected for small zones of impedance increase propagating at depths of 0.5mm (B) and 2mm (C) beneath the electrodes. These are plotted in the same way as (A), and expressed per mm3 of tissue rendered non-conductive. Baseline resistivity =420Ω. Data and calculations redrawn from Holder & Gardner-Medwin, 1988.

The recorded changes in Fig. 6A are largest at the electrodes adjacent to the two current passage sites, and are opposite in sign because of the opposite phase of the current at the two sites. The signal at the far end (b) is also displaced in time because of the propagation delay for the SD travelling between the two sites. The peak changes at the two ends were respectively 46% and 47% of the baseline 50kHz signals. The depth information can be seen by comparing the signals in Fig. 6A with those calculated for small propagating disturbances at depths of 0.5mm (Fig. 6B) and 2mm (Fig. 6C). The changes associated with the smaller depth would fall off more rapidly with distance between recording and current passage, while for the

greater depth the signals would fall off less rapidly than the observed data. This is consistent with the range of depths of the SD disturbance in the rat (Fig. 1).

The recordings made from the different electrodes for Fig. 6A were made sequentially during repeated SD episodes. It is possible, however, to multiplex signals from such electrodes with a single detector circuit (Brown et al. 1985) so that all the necessary measurements could be carried out essentially simultaneously on a single run. It is evident that the same principle explained above for widespread disturbances (Fig. 5), whereby the recorded signals are more strongly dependent on electrode separation for superficial than for deep disturbances, applies also for small zones of disturbance (Fig. 6B,C).

The optimal electrode configurations and separations for impedance monitoring during surgery would need to be tailored to specific applications, for example tissue particularly at risk beneath retractors (Gardner-Medwin & Mutch, 1984). The practical limits of resolution have yet to be determined.

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KEYWORDS

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