

Spreading Depolarisations: Tsunamis in the Injured Brain



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Acknowledgements:

This review summarises results of work by many immediate colleagues, and by members of COSBID (www.cosbid.org), and their contributions are warmly acknowledged, with thanks. The author's earlier clinical and experimental work was supported by The Wellcome Trust. Current work is funded by HeadFirst.

Glossary:

COSBID: Co-Operative Study of Brain Injury Depolarisations (www.cosbid.org)

CSD or SD: cortical spreading depolarisation (usually implies that the vascular response is vasodilator)

PID: peri-infarct depolarisation (usually quickly followed by vasoconstriction of varying duration)

DC: direct current

ECoG: electrocorticogram

Ke: extracellular potassium ion concentration

NADH: nicotinamide adenine dinucleotide (reduced state)

TBI: traumatic brain injury

History and basic neurophysiology

"Spreading depression of activity in the cerebral cortex" is the title of a paper by Aristides Leão that reported his finding of an apparent wave of silence in the electrocorticogram (ECoG) that spread backwards from a site of electrical stimulation on the frontal lobe of rabbits at a rate of some 3mm/minute.¹ Leão's aim had been to establish a model of Jacksonian epilepsy, and the unexpected result stimulated him to further work. The title has stood the test of time, and the phenomenon has been the subject of many papers from basic neuroscientists, but as he himself established, its essence is mass depolarisation of cellular elements in the cortex, with the spreading depression of the ECoG that he first observed being an effect of this: the term "spreading depolarisation" (SD) best identifies the fundamental event. Leão thought that his phenomenon might be the basis of the visual aura of migraine, and recent imaging work (see below) confirms directly the longstanding and universally held concept of spatial spread of the phenomenon in the cerebral cortex being analogous with the first ripple that spreads from a stone thrown into a pond (see video 1). That SD is the basis of the visual aura of migraine has also been confirmed.² As Leão recognised, in healthy cortex spreading depolarisation needs to be deliberately induced with some form of mild insult to the cortex, but experimental work over the past 30 years, and especially recently, has emphasised the profound pathogenic potential of many spreading depolarisation events that occur spontaneously, and we shall see below that the analogy of a "tsunami" is very appropriate.

Leão established some important fundamental features of SD. There is marked but transient vasodilation in the pial circulation,³ and surface cortical veins are briefly arterialised. He also found that carotid occlusion delayed recovery of the surface DC potential, indicating the dependence of recovery on energy supply. Grafstein isolated slabs of cortex in situ in rabbits, using subpial transections, and with microelectrodes was able to show a transient phase of mass, uncoordinated neuronal firing that coincided with the onset of the depolarisation.⁴ This is marked by an abrupt negative change in the surface cortical DC potential by some 15 mV, and this rather than ECoG amplitude suppression is the principal marker of a depolarisation, since it can still occur when the ECoG is already flat (see below). Grafstein also proposed that release of potassium

ions into the extracellular space is an important and possibly critical element supporting the spread of depolarisation, and this is closely coupled with glutamate release.⁵ In broad summary, the mechanism of spread of a depolarisation is thought to centre on a massive focal release of potassium in a small focus, in sufficient concentration in the extracellular space of grey matter to depolarise neighbouring neurones (and probably astrocytes), leading to further, "regenerative" depolarisation of adjacent tissue, thus spreading the depolarisation throughout tissue that is susceptible. Multiple areas of grey matter in addition to neocortex have been reported to support spreading depolarisation – hippocampus, basal ganglia, spinal cord, and, if heavily pre-treated, brain stem nuclei. The early 1970s saw the arrival of ion-selective microelectrode technology, bringing support for Grafstein's concept from the use of potassium sensitive electrodes. Soon afterwards, a paper from Branston et al was the first to report spontaneously occurring, transient increases in extracellular potassium (Ke) in the periphery of an ischaemic territory in the primate cerebral cortex.⁶ These transient events were thought by these authors to "resemble spreading depression", and came to be widely recognised as a prominent feature of the ischaemic penumbra in experimental stroke models: peri-infarct depolarisations, PIDs.⁷

"Cortical spreading depression" (SD) versus "peri-infarct depolarisations" (PID): critical differences

Although the basic neurophysiological mechanisms of depolarisation and its spread appear similar in SD and PID,⁸ there are critical differences that are potentially highly relevant to clinical management, now that both phenomena are known to be common events in the injured human brain (see below). SD is associated with profound hyperaemia – up to 400% - that lasts for approximately 1 minute, and is followed by mild oligoemia to some 80-90% of baseline,⁹ and it now seems clear that hyperaemia is what ensures that SD is not associated with tissue damage. That restoration of resting membrane potential following SD imposes a large metabolic load on grey matter was shown by Shinohara and colleagues, who found that local cerebral glucose utilisation was doubled during recovery from SD.¹⁰ It is possible that the hyperaemia is not sufficient to meet the demand, even with full, aerobic oxidation of glucose, since it has been shown that tissue extracellular glucose is

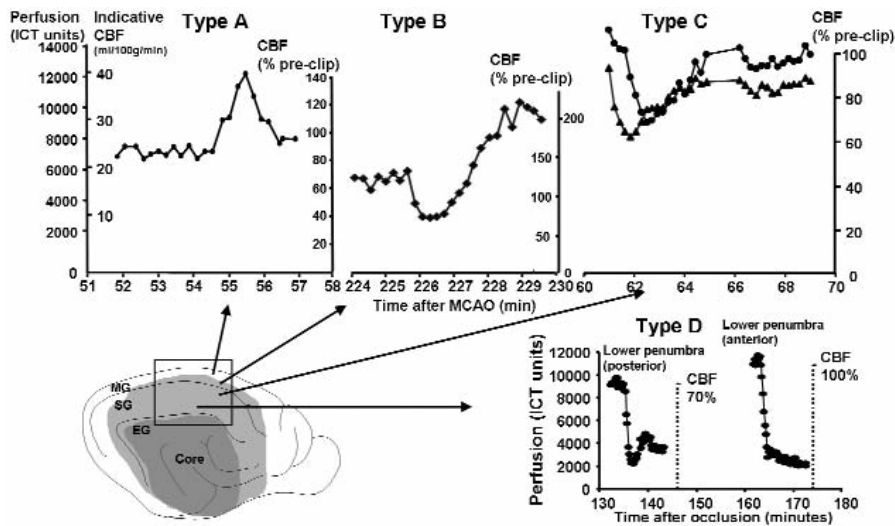


Figure 1: (Figure and legend based on (Open Access) Strong et al. 2007.¹⁹ Brain 130(4):995-1008)

Examples of four different patterns of transient (A, B, C) and sustained (D) changes in perfusion that propagate in penumbral or near-normal gyri linked to depolarisations following experimental middle cerebral artery occlusion in the cat. For upper three panels, speckle contrast and indicative CBF scales are shown to the left, and individual reactivity scales to the right of each figure. Type A: monophasic transient increase in perfusion, typical of near-normal/normal cortex (unshaded, medial ribbon of MG (marginal gyrus) uppermost in diagram, perfused largely by the anterior cerebral artery). Type B: biphasic, consisting of a transient fall in perfusion (approximate half-time for recovery to baseline 0.5-1.5min), followed by hyperaemia, typically lasting 5-10min,

typical of upper penumbra (shaded portion of MG in diagram). Type C: monophasic transient decrease in perfusion, with varying rate of recovery, which was sometimes incomplete, approximate half-time 2-30min. The panel illustrates effects on perfusion of a single Type C event propagating forward through two ROIs, here in upper penumbra (lateral MG). Type C events were more typical of intermediate penumbra, as illustrated by arrow. Type D: examples of abrupt, marked falls in perfusion, with no or minimal recovery, associated here with two separate spreading events, some 40min apart, on lower penumbra; indicative CBF fell to $<10\text{ mL}/100\text{ g}/\text{min}$, i.e. core conditions. Dotted calibration bars indicate CBF change as percentage pre-occlusion.

reduced for up to 30 minutes after SD.¹¹

In contrast, the number of PIDs is closely related to infarct size in stroke models,¹² and has been shown to be the determining variable, rather than simply a marker, of infarct size.¹³ Additional work has suggested that aggregate duration of depolarisations rather than simply their number is the critical factor.¹⁴ As well as the large increase in K⁺ with depolarisation, there is also a large inward calcium ion movement which, if at all sustained, initiates both necrotic and apoptotic cascades. The role of PIDs in ischaemia was attributed until recently to energy metabolite depletion and failure of the cortical surface collateral circulation in the penumbra to deliver the increments in perfusion required to achieve repolarisation. This would lead to sustained depolarisation and hence to infarction in the affected area of penumbra, resulting in the stepwise recruitment of penumbra into the expanding core.

Vasoconstriction and spasm associated with focal ischaemia

However, in vivo experimental stroke work from several laboratories has now shown that the vascular response to depolarisation in ischaemic boundary zones is – in terms of pathogenesis – much more aggressive than previously thought. Rather than simply a failure to dilate in response to depolarisation, there is active vasoconstriction that is frequently sustained for long periods. In chronological order, Waltz and Sundt published an elegant description of episodic vasoconstriction of surface vessels in the primate cortex following occlusion

of the middle cerebral artery.¹⁵ They attributed this to a process of active vasoconstriction but did not seek or detect evidence of depolarisation events. Dreier and colleagues showed in a series of experimental papers that if the cerebral cortex of rats is superfused with artificial CSF containing haemoglobin and potassium ion, the hyperaemia that spreads in response to a SD (the most extreme challenge to the normal coupling of cerebral blood flow with function and metabolism) is converted to spreading ischaemia,¹⁶ and indeed leads to cortical infarction that closely resembles what is seen in patients who have suffered a fatal aneurysmal subarachnoid haemorrhage.¹⁷ They designated their observation “inverse coupling” of blood flow. Later, using laser speckle imaging of the exposed mouse cortex to map perfusion quantitatively as a marker of depolarisation, Shin and colleagues were able to document recruitment of additional peri-infarct tissue into the area where perfusion was less than 20% of pre-occlusion, in step with each repeated depolarisation event. Importantly, they also showed that the timing of each perfusion event that resulted in a sustained fall followed – rather than led to or caused – the electrophysiological depolarisation.¹⁸ Most recently, Strong et al, also studying the effects of middle cerebral artery occlusion with laser speckle imaging, but now in the gyrencephalic brain (cats), found that the transient perfusion response to a depolarisation could be assigned qualitatively to one of four categories, ranging from sustained (and sometimes profound) reduction in perfusion to normal hyperaemia, depending on proximity of the

focus being assessed to the infarct core (see figure 1 and video 2).¹⁹ This pattern of response is radically different from that of the normally perfused brain, where a wave of hyperaemia spreads as a concentric wave from a point of disturbance, such as Leão envisaged (Video 1). The mechanism of vasoconstriction in ischaemia clearly needs to be understood, and therapies to reverse it devised: activity of, and substrate availability to, endothelial nitric oxide synthase is one possible candidate.²⁰

Other adverse effects of depolarisations

Brain glucose. Technology to sample glucose and lactate in brain microdialysate at high frequency (30 seconds) has detected time signatures typical of peri-infarct depolarisations – a transient or more sustained fall in tissue glucose, accompanied by a rise in lactate,²¹ and it is now clear that even a “normal”, hyperaemic depolarisation is accompanied by a fall in tissue glucose that may last up to 30 minutes.¹¹ Such falls can be cumulative,²² and low levels of brain dialysate glucose are associated with poor outcome in patients with traumatic brain injury (TBI).²³

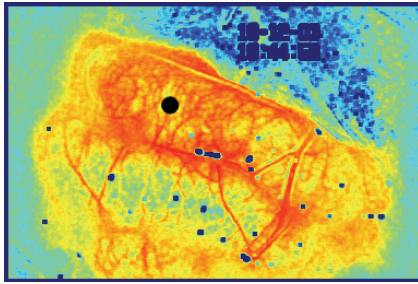
Inflammation. Depolarisations, even in the normally perfused brain, lead to increased levels of matrix metalloproteinase-9, which greatly increases blood brain barrier permeability²⁴; the inflammatory cytokines IL-1 β and TNF α are also upregulated.²⁵ Cyclooxygenase-2 and c-fos and jun-B are also induced by CSD.^{26,27} In some cases, the association is relatively specific: for example, the degree of induction of the mRNAs encoding brain-derived neurotrophic factor and heat-shock protein-72 in response to CSD induced in the rat is dependent on the number of CSDs.²⁸

Are depolarisations ever beneficial?

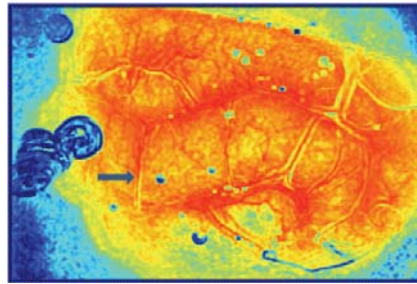
An inflammatory response should not necessarily be considered harmful, and it is easy to envisage that the inflammatory response evolved originally as a beneficial mechanism that only became potentially harmful in the context of cerebral ischaemia – thus largely after the reproductive phase of human life has closed and there is no evolutionary disadvantage from adverse effects of depolarisations. More specifically, experimental induction of depolarisations in rats confers protection from subsequent ischaemia,²⁹ and induces neurogenesis in the subependymal periventricular layer in rats.³⁰

Spontaneous depolarisations in the injured human brain

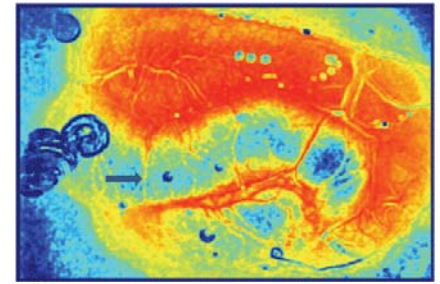
Mayevsky and colleagues used a multiparametric monitoring device located in the right frontal region in patients receiving intensive care following major head injury. They reported observation of linked potassium, perfusion and NADH transient events suggestive of transient depolarisation in one of 14 patients, but at the single observation site could not demonstrate spread of the event (Mayevsky et al. 1996).³¹ Later, Strong et al inserted linear 6- or 8-electrode subdural strips over pericontusional areas following evacuation of a traumatic



Interval image from video 1, indicating site of endothelin injection to initiate a typical hyperaemic depolarisation in the normally perfused brain.



Sample image from early in video 2, 170 minutes after experimental occlusion of the middle cerebral artery (MCAO), showing restricted area of ischaemia in proximal middle cerebral artery territory (lowermost in figure).



Final image in video 2, 180 minutes after MCAO, showing newly ischaemic territory following spread of a vasoconstrictor depolarisation. Note new spasm in a surface vessel (arrowed in centre and right panels).

LEGENDS TO VIDEOS

(Available for viewing with the online version of ACNR)

Video 1: Time-compressed sequence of pseudo-colour-mapped semiquantitative images of perfusion at the cortical surface (laser speckle method; (Dunn et al. 2001)¹⁹) following a microinjection of 10^{-7} M endothelin at the focus of initiation of the spreading hyperaemia. Animal experiment: chloralose anaesthesia; gyrencephalic brain. Images were acquired at 13-second intervals and illustrate concentric, radiating spread of hyperaemia (as a surrogate marker of depolarisation), at the rate characteristic of spreading depolarisation, approximately

3mm/minute. The wave is seen to disappear into sulci before re-emerging onto an adjacent gyrus.

Video 2: (Reproduced (Open Access) from Strong et al. 2007. Brain 130(4): 995-1008)¹⁹ Time-compressed sequence of pseudo-colour-mapped semiquantitative images of perfusion at the cortical surface (laser speckle method (Dunn et al. 2001)¹⁹; red = hyperaemia, blue = ischaemia). Animal experiment: chloralose anaesthesia; gyrencephalic brain, 3 hours following occlusion of the middle cerebral artery (MCA). Images of the ischaemic hemisphere were acquired at 13-second intervals. At the start of the sequence, which lasts some 10 minutes, perfusion in the

"resting" state is normal in the majority of the exposed field, but reduced in the initial core area (lowermost). Sustained reduction in perfusion accompanies the depolarisation as it spreads outwards from the core infarct region, and there is a delay as the event traverses the lateral sulcus before emerging on the most medial gyrus. Here, in the outer penumbra (uppermost in image) the vasoconstriction is transient, and is followed by hyperaemia. Some constriction of a surface vessel is seen to the left of the newly ischaemic territory. The final image is at the conclusion of the sequence, and shows the ischaemic territory that has developed as the result of one vasoconstrictor depolarisation.

haematoma (the series –coincidentally also of 14 patients - included 2 patients with ruptured intracranial aneurysms and one with spontaneous hypertensive intracerebral haematoma) and recorded spreading waves of depression of ECoG amplitude, similar to Leão's original finding, in some 71% of patients overall.³² The much higher incidence of depolarisations that they reported (in comparison with Mayevsky et al) seems likely to result from placement of the electrode strips over peri-lesion cortex, and suggests in turn that a depolarisation in the injured human brain may not necessarily invade the whole hemisphere as widely as occurs in lissencephalic and smaller brains. Conversely, the possibility arises that in a patient with multiple areas of contusion, cortex around each contusion may be affected by depolarisations. These authors were subsequently joined by others to commence the CoOperative Study of Brain Injury Depolarisations ("COSBID", www.cosbid.org): the central goal of the study is to determine which, if any, patterns of depolarisation are independently associated with poor outcome in patients with TBI, higher grade aneurysmal subarachnoid haemorrhage (aSAH), malignant hemisphere occlusive stroke (MHS), or spontaneous intracerebral haematoma (ICH), and a strategy to address this issue is in place. High incidences of depolarisations have now been described by COSBID following aSAH³³ and ICH,³⁴ and in MHS the incidence is 100% if two cases are excluded in which the ECoG strip was placed over the infarct core (Dohmen et al. 2008).³⁵ Refinement of ECoG processing has made it possible to discriminate CSD from PID, on the basis that many depolarisations have been detected in the complete absence of ECoG activity.³⁶

Avoidable factors promoting depolarisations: plasma glucose reduction, pyrexia and arterial hypotension

Some factors have been identified which are likely to promote depolarisation activity and

which deserve attention in clinical management. In the laboratory, there is a robust association of increased frequency of spontaneous PIDs with even mild reduction in plasma glucose (5-6 mmol/L) following middle cerebral artery occlusion (cats)²¹; these data, coupled with much clinical evidence of an adverse effect of levels above 10 mmol/L, suggest that an optimal plasma glucose for a patient with acute brain injury might lie in the region of 7-9mmol/L. While there is evidence, heavily relied upon in general intensive care practice, of benefit from tight glycaemic control to 4-6 mmol/L with insulin in the general ICU population,³⁷ the potential risks of targeting the same levels in patients with acute brain injury have been highlighted.^{11,38,39,40} A high incidence of verified PIDs in association with low plasma glucose has now been reported in a patient with aSAH (Dreier, personal communication, 2008). Pyrexia appears to be associated with increased frequency of depolarisations,⁴¹ and there is emerging evidence to implicate arterial hypotension as a further cause.⁴²

Future clinical and experimental research

A curious feature of depolarisations, seen both in the laboratory and in patients, is a tendency for their occurrence to be grouped in temporal clusters, often with remarkably constant periodicity, usually in the range 20-40 minutes, depending on the precise setting. Since, as we have seen, depolarisations may induce both adverse and beneficial effects, repetition or clustering of depolarisations in the neighbourhood of a focal lesion probably constitutes a powerful mechanism serving to amplify its effects – either for better or for worse.

These uncertainties serve to emphasise the importance of detecting depolarisations in the injured human brain, and of determining whether their effects are likely to be beneficial or harmful in a given patient. At present, it seems that whether the cerebral circulation dilates normally or constricts in response to a

depolarisation event is likely to determine how an ischaemic or traumatic lesion evolves, and hence the clinical outcome. Thus the current challenge to clinical and basic researchers is to understand the nature of the abnormal vasoconstrictor response to depolarisation and how to characterise and reverse it in critically ill patients. In addition, since the need for subdural electrodes as a means of monitoring for depolarisations restricts the study population to patients requiring emergency craniotomy, a noninvasive method for detection of depolarisations would be valuable. ♦

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(The full list is available on the ACNR website, with the matching numbering)

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