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Review

Subverting the hegemony of the synapse: Complicity of neurons, astrocytes, and vasculature in spreading depression and pathology of the cerebral cortex

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ABSTRACT

Contrary to Golgi's "reticular" theory of nervous structure, it is clear that the synapse rules over communication among nerve cells. Spreading depression, however, does not follow synaptic pathways. It sweeps across gray matter like a political revolution, ignoring structural boundaries and carefully established regulatory mechanisms. Neurons form alliances with their usually subordinate partners, the astrocytes, to cause a perturbation of function that strains resources necessary for recovery. Innocent bystanders, the blood vessels, are obliged to try to ameliorate the disturbance but may not be able to respond optimally in the chaotic environment. Under extreme circumstances, a purge of some of the instigators may ensue. This anarchic picture of interactions among the elements of nervous tissue does little to rescue the reticular theory that was one of Golgi's most important intellectual offerings. Nevertheless, it reminds us that the behavior of populations of nerve cells need not necessarily be limited by the pathways dictated by synaptic junctions. Spreading depression is a multifactorial phenomenon, in which intense depolarization of neurons and/or astrocytes leads to perturbations that include release of K^+, release of glutamate, increase in intracellular Ca^{++}, release of ATP and local anoxia, as well as vascular changes. This process plays a role in migraine and contributes to the damage produced by brain anoxia, trauma, stroke, and subarachnoid hemorrhage. It may provide clues to new treatments for the damaged brain.

Contents

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When Camillo Golgi was awarded the Nobel prize in 1910 together with Santiago Ramón y Cajal, they were cited for their contributions to the structure of the nervous system. The practical techniques that Golgi developed were important resources, even for Cajal. By the time of the Nobel award, however, it was probably already clear that Golgi's adherence to the "reticular" theory of nervous structure, in which the nerve cells were believed to form an interconnected network, was ill-advised and possibly, to forward thinkers, even an embarrassment. Instead it was Cajal's idea of a system of discrete nerve cells, separated by contacts now identified as synaptic junctions, that had carried the day (Jones, 1999). Thus in 1944, when Aristide A.P. Leão began to present his studies of spreading cortical depression, which manifested itself as a wave of decreased electrical activity moving slowly over the cortex (Fig. 1), this phenomenon was inevitably interpreted in terms of the activity of individual nerve cells that acted on one another by volleys of action potentials (Leão, 1944a).

In particular, Leão's views were influenced by studies of the electrical activity displayed in the electroencephalogram (EEG), which was actively being recorded and analyzed at that time in the Department of Physiology at Harvard Medical School, where Leão was taking his PhD degree. Because of the importance of the EEG in the diagnosis of epilepsy, Leão was especially interested in the relationship between spreading depression (SD) and "experimental epilepsy", since "tonic–clonic discharges" resembling epileptic activity could be initiated, like SD, by strong electrical stimulation of the cerebral cortex, and the onset of depression was sometimes accompanied by similar discharges. From the time SD was first recognized, therefore, it was clearly linked to clinically important pathological phenomena in the cerebral cortex, and it has subsequently been shown to play a role in migraine as well as in determining the consequences of brain anoxia, trauma, stroke, and subarachnoid hemorrhage.

Although the phenomenon was already identified nearly 70 years ago, our understanding of SD has developed slowly and, in doing so, has provided new insights into the cellular organization of the brain. It has become evident that it comprises a multiplicity of events, each contributing to the final silencing of the nervous tissue. This has led to the perception of the ecology of that tissue as a community of cells

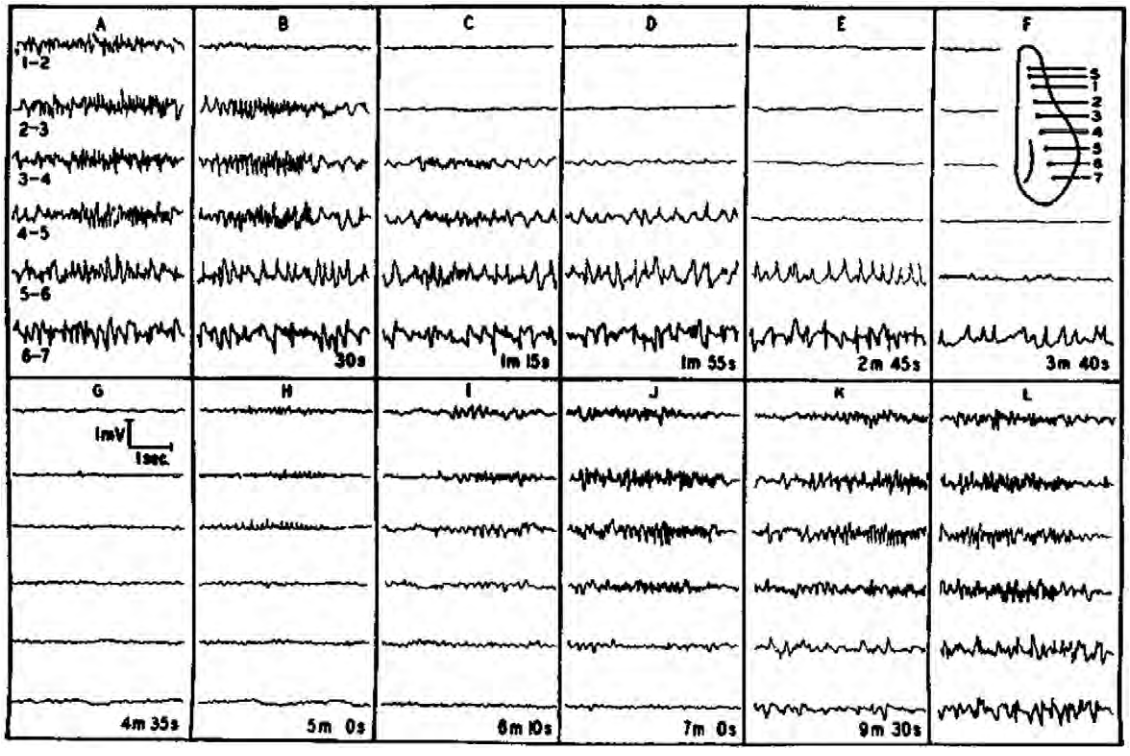

Fig. 1 – Spreading depression of activity in rabbit cortex. (A) Electrical activity before stimulation, bipolar recording with electrodes arranged as shown at the upper right. (B–K) Electrical activity after repetitive stimulation at site S, recorded at the times indicated in each panel. (L) Recorded 7 min after panel K. Upward excursions indicate negativity at the more anterior electrode. Reproduced from Leão (1944a) with permission of the American Physiological Society.

with many mechanisms of interaction that may eschew the circumscribed paths dictated by groups of neurons bound by their synaptic connections. Our recognition of the movement of chemical agents in the extracellular space, the existence of gap junctions that potentiate the liberation of such agents, and the widespread distribution of numerous receptors for such agents on all cellular elements of the nervous tissue has led to a more pantheistic view of possible functional relationships among these elements. This has had special significance for the understanding of pathological brain mechanisms.

1. Characteristics of cortical spreading depression

SD is not only characteristic of the mammalian cerebral cortex but has been observed in the retina, hippocampus, and cerebellum of various vertebrates, as well as the forebrain of birds. It is a self-maintained change that travels over the cerebral cortex at a rate of a few millimeters per minute, accompanied by intense neuronal depolarization, generating a negative shift of up to 15–20 mV in the cortical surface potential. Once initiated by electrical or mechanical stimulation, neither spontaneous electrical activity nor physiologically evoked responses survive its inexorable advance, requiring many minutes for recovery. Its slow rate of advance and long persistence, together with the fact that it resisted anoxia and anesthesia, soon made it clear to early investigators that it was unlikely to be due to neurons acting on one another through synaptically mediated volleys of action potentials (Leão and Morison, 1945). The advance of the depression wave is usually accompanied by significant changes in the pial circulation. Leão first described a dramatic vasodilatation in rabbit cortex (Leão, 1944b), but depending on the species, the anesthetic, and the underlying condition of the cortex, a variety of sequential changes may be observed (Busija et al., 2008). An increase in electrical impedance that occurs in the course of SD makes it possible to visualize the course of the depression wave in the form of an increase in light scattering in transparent tissue such as the isolated chick retina (Fig. 2).

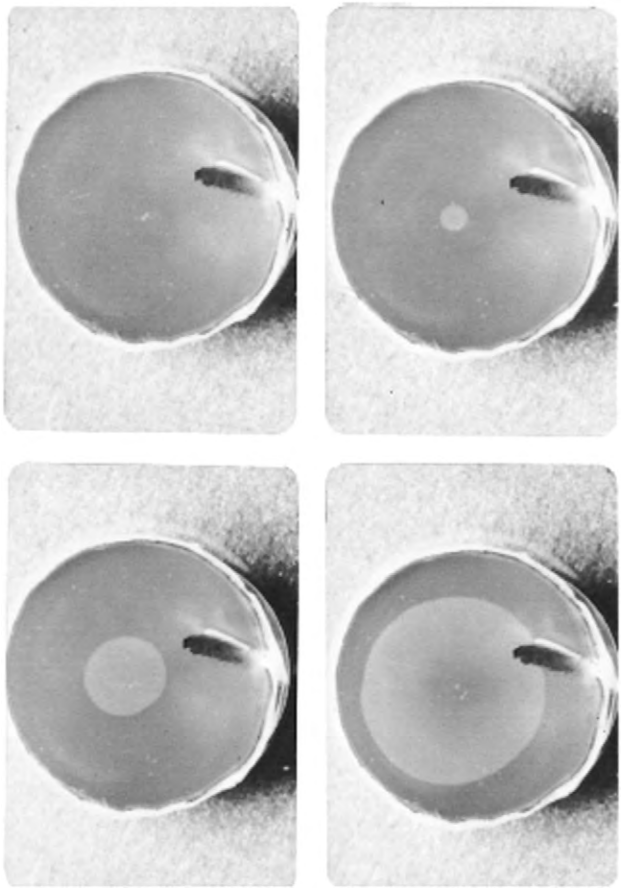

Fig. 2 – Progression of spreading depression in chick retina ex vivo, viewed as an increase in light scattering. Upper left, before stimulation; subsequent images taken 17, 40, and 100 s after mechanical stimulation at the point corresponding to the center of the expanding circle. Reproduced from Martins-Ferreira et al., (2000) with permission from Elsevier Press.

2. The role of K^+ and other cations

The changes in the pial vessels led to the suggestion that their innervation might play an active role in the propagation of SD. As early as 1945, Leão and Morison suggested that neuronal activity produced by the strong stimulation required to initiate SD caused the liberation of some "depressing substance" that would "stimulate endings of nerves in the pial membrane" to bring about the reflex release of that same substance in neighboring cortical regions. Subsequently, in view of the intense neuronal excitation observed at the onset of the slow negative wave (Fig. 3), Grafstein (1956) proposed that the propagation of SD involved an initial phase of intense neuronal activity that "caused the liberation of K^+ into the interstitial spaces [of the cortex] in sufficient quantity to depolarize adjacent cells" and thereby caused their excitation, so that the process repeated itself. The slow progress of the depression wave was therefore attributed to a combination of excitatory release of K^+ and its diffusion through the extracellular space (Grafstein, 1963). The prominent role of K^+ was supported by the demonstration of SD-associated release of radioactively labeled K^+ from the brain surface (Brinley et al., 1960) and by studies on the movement of K^+ in the extracellular space (Martins-Ferreira et al., 2000). Extracellular K^+ levels have been found to reach close to 50 mM at the peak of the negative wave, and even when conducted neuronal action potentials have been abolished by tetrodotoxin, this rise in extracellular K^+ persists, and the magnitude and rate of advance of the slow wave are unchanged (Sugaya et al., 1975). The importance of the contribution of K^+ in spreading depression therefore remains certain, even though the phase of neuronal hyperexcitability may not always be essential for propagation.

Although the earliest extracellular ionic change is the increase in K^+ (Kraig and Nicholson, 1978), other ionic changes soon follow. First observed by Van Harreveld in the late 1950s is the massive entry into the cells of Na^+, accompanied by Cl^- and water, resulting in a decrease of the extracellular space and the consequent increase in electrical impedance (Kraig

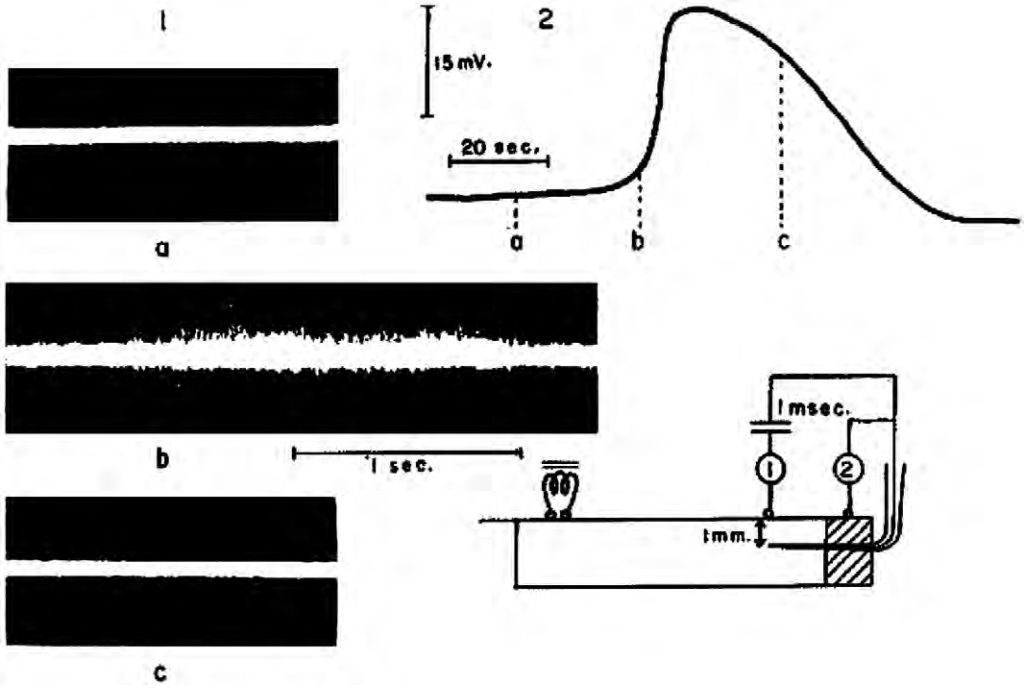

Fig. 3 – Spreading depression in a surgically isolated slab of cat cortex in vivo (from Grafstein, 1956). Simultaneous recording of unit activity at 1-mm depth in the cortex (1) and slow potential change during SD recorded at corresponding point on the cortical surface (2), with upward deflection indicating negativity of the cortical surface relative to an indifferent electrode. (a) Before onset of the slow potential change; (b) during initiation of the slow potential change; (c) during declining phase of the slow potential. Electrodes arranged as shown, with stimulating electrodes at left in the diagram. Reproduced from Grafstein (1956) with permission from the American Physiological Society.

and Nicholson, 1978; reviewed by Somjen, 2001). Na^+ carries the bulk of the charge leading to depolarization in SD and, in its absence, SD is suppressed (Somjen, 2001). Since the propagation of SD is insensitive to tetrodotoxin, the entry of Na^+ through voltage-gated channels has been ruled out (Tobias and Nicholson, 1982). The mechanism propelling the Na^+ movement has not been ascertained. An important role for Cl^- has been proposed (Martins-Ferreira, 2000; Rothman and Olney, 1987).

Although activity involving Na^+-mediated action potentials is not necessary for the propagation, Ca^{++}-mediated action potentials of the kind that occur in dendrites have not been ruled out. It is significant that Ca^{++} moves from the extracellular to the intracellular compartment during SD, beginning about 20–40 s after the K^+ begins to rise ((Kraig and Nicholson, 1978; Martins-Ferreira et al., 2000). There is some disagreement about whether removing extracellular Ca^{++} interferes with the propagation of depression (Nedergaard et al., 1995; Somjen, 2001).

3. The role of glutamate

The early students of SD could not be faulted for failing to consider the possible role of synaptic transmitters, since their studies were made at a time when the electrical/chemical debate about the nature of synaptic function was still being resolved (Eccles, 1982). Van Harreveld (1959) first recognized the participation of glutamate at a time when it was beginning to emerge as a bona fide synaptic transmitter. Subsequently, it was shown that glutamate is released in the course of SD (Van Harreveld and Fifková, 1970) and that blockade of NMDA receptors for glutamate attenuates the spread (Lauritzen and Hansen, 1992). This involvement in SD reveals the role of glutamate as a double agent, causing excitation in functioning as synaptic transmitter, but then eliciting SD and ultimately neuronal injury, a process characterized as "excitotoxicity" (Rothman and Olney, 1987). However, the crucial aspect of the role of glutamate in SD is not necessarily (or not solely) to evoke synaptically mediated neuronal excitation: its role is to cause Ca^{++} influx when the NMDA receptors are activated, which is a condition that is necessary but not sufficient for SD (Nedergaard et al., 1995). The consensus is that both glutamate and K^+ have essential roles to play (Somjen, 2001).

The flooding of K^+ and glutamate into the extracellular space to act on neighboring cells recalls the process of "volume transmission" (Fuxe et al., 2010, cogently summarized by Ridet and Privat, 1999), in which synaptic transmitters and neuropeptides may access receptors at some distance from the sites of release, presumably undergoing distribution by diffusion as well as by pressure and temperature gradients and electrical field potentials (Agnati et al., 2005). While these mechanisms may also apply to the agents of spreading depression, the distribution mechanism would be greatly enhanced by the self-propagating nature of the depression wave and the shrinkage of the extracellular space in the course of SD.

4. The role of astrocytes

Beginning with observations of SD in isolated retina (Martins-Ferreira et al., 2000), there emerged an interest in the comparison between SD and traveling waves of increased intracellular Ca^{++} concentration in astrocytes (Martins-Ferreira and Ribeiro, 1995; Nedergaard et al., 1995). These waves have the same velocity as SD and are initiated by the same kinds of stimuli. Moreover, similar waves can be evoked in pure cultures of astrocytes (although they do not travel as far), indicating that the manifestation of at least some aspects of SD can occur independently of neurons. The propagation of the Ca^{++} waves can be prevented by purinergic receptor antagonists (Cotrina et al., 1998), indicating that the waves are mediated by the release of ATP into the extracellular space. Since the waves are also attenuated by gap junction blockers (Finkbeiner 1992), it appears that gap junctions are also involved, apparently by facilitating the release of ATP (Cotrina et al., 1998). SD is likewise affected by gap junction blockers (Martins-Ferreira, 1995; Nedergaard et al., 1995), leading to the view that astrocytic Ca^{++} waves are an important mechanism in the propagation of SD. This is supported by the observation that the neuronal depolarization at the onset of the slow negative wave is preceded by depolarization of the astrocytes and increase in their intracellular Ca^{++} (Sugaya, 1975; Kunkler and Kraig, 1998), so that the astrocytic Ca^{++} wave may constitute the leading edge of the SD wave.

Since the spread of the astrocytic Ca^{++} waves is limited to a few hundred micrometers (Nedergaard et al., 2003), it is unlikely that they are in themselves sufficient to explain the much longer distances traversed by SD. The necessary amplification of the Ca^{++} waves would be provided by the neuronal activation that occurs in the course of astrocyte wave propagation (Nedergaard, 1994). The resulting release of K^+ and glutamate from neurons would activate not only adjacent neurons but also nearby astrocytes (Wang et al., 2009). Thus, the propagation of SD involves the communal activity of both neurons and astrocytes.

Critical to the interaction between neurons and astrocytes in SD is that both are depolarized by elevated extracellular K^+, both can release glutamate and ATP when depolarized, and both have glutamate receptors as well as purinergic receptors for ATP (Fields and Stevens, 2000). To some extent, the interaction would involve modification of synaptic activity by glutamate and ATP, but non-vesicular release and actions on extrasynaptic targets by the transmitters, as well as the generalized depolarizing effect of the increased extracellular K^+, would enable signaling between neurons and astrocytes that would bypass the synapses.

5. The role of neurovascular changes

Leão's (1944b) emphasis on the dilation of the pial blood vessels accompanying SD has been superseded by a much more nuanced view of the kinds of changes that may occur in the cortical circulation. For example, a study with high spatial resolution in the brains of normal mice (Takano et al., 2007) has shown a brief phase of vasoconstriction preceding the vasodilation and then a period of intense vasoconstriction lasting several minutes, i.e., extending well into the period of recovery from depression. An important consideration is whether the observed changes are the result of events in the pial capillaries, cortical arterioles, or pial arteries, each of which is subject to different regulatory factors (Iadecola and Nedergaard, 2007).

An obvious modulator of neurovascular tone is neuronal activity (Drake and Iadecola, 2007). Elevated neuronal activity during SD would result in local hypercapnia and hypoxia, and discharge of H^+ and K^+, but these would likely produce relatively brief vascular changes (Filosa et al., 2006). On the other hand, the release of glutamate (as well as other neurotransmitters and neuromodulators) would have a potent vascular effect (Drake and Iadecola, 2007). Moreover, increased utilization of ATP during activity would result in the production of adenosine, which is an effective vasodilator (Xu and Pelligrino, 2007). To some extent, these neuronal factors would act directly on the blood vessels (Drake and Iadecola, 2007), but a major influence would be activation of the astrocytes (Wang et al., 2009). These provide a channel for conveying the products that arise from synaptic activity to blood vessels, by virtue of the dual distribution of their end-feet: they cover neuronal synapses and they have intimate contact with the brain's arterioles and capillaries [as Golgi already observed in the late 19th century (Jones, 1999)]. The increased intracellular Ca^{++} in astrocytes that accompanies SD would result in the intraparenchymal release from the astrocytes of the vasodilators ATP and nitric oxide (NO), but also prostaglandins and other cyclooxygenase products, some of which have a powerful constrictor effect (Busija et al., 2008). An example of the complexity of these mechanisms is seen in the case of SD in rat cortex, where pharmacological blockade of NO activity results in reversal of the depression-associated changes from hyperemia to ischemia (Busija et al., 2008).

The intimate interaction between neurons, astrocytes, and blood vessels has given rise to the concept that these three elements constitute a "neurovascular unit" (Xu et al., 2004), a dynamic entity that adjusts the cerebral microcirculation to neuronal activity. An interesting question is how information from the neurovascular unit might be conveyed "upstream" to the arterioles of the pia-arachnoid, which are critical in determining the delivery of blood to the parenchymal circulation and which are the site of the changes detectable in SD. These vessels are physically separated from the elements of the neurovascular unit by the glia limitans, consisting of a dense layer of astrocytic end-feet overlaid by basal membrane. The pial vessels are innervated by extracerebral sensory and autonomic nerves, which are likely to produce widespread changes in cerebral blood flow (Iadecola and Nedergaard, 2007) rather than the site-specific changes characteristic of SD. However, like the astrocytes, the cells of the pia-arachnoid have gap junctions and can give rise to ATP-mediated Ca^{++} waves, which can spread from pia-arachnoid cells to astrocytes and vice versa (Grafstein et al., 2000). Thus during astrocyte activation, diffusion across the glia limitans of ATP from astrocytic end-feet could initiate meningeal Ca^{++} waves that would lead to dilation of the pial arterioles in association with events in the parenchyma.

Recent observations have shown that dilation of arterioles on the cortical surface may propagate at a greater velocity

than the underlying SD wave and may spread into areas not reached by the SD wave (Brennan et al., 2007). This suggests that although it may be triggered by the wave of SD, the vascular response may proceed independently within the pia-arachnoid, possibly by direct vascular conduction. However, since SD can proceed without obvious alteration in the absence of the vascular response, this response is apparently not essential for the depression process.

6. The role of anoxia

Regardless of the particular sequence of vascular changes, it is most significant that they are superimposed on a prolonged period of greatly increased O_2 utilization. This may cause anoxia sufficient not only to abolish neuronal activity but also to produce detectable neuronal injury. In at least some cases, this includes dendritic swelling and loss of dendritic spines beginning within seconds of the onset of depolarization (Takano et al., 2007). The similarity between the effects of anoxia and SD was already observed by Leão (1947), who found that SD can be initiated by anoxia and is prolonged by anoxia and, moreover, that the large negative potential shift of the cortical surface that is characteristic of SD is also reproduced by anoxia. In view of the occurrence of pial vasodilation during the active phase of the depression process, O_2 tension may not be a limiting factor (Lauritzen, 1994; Somjen, 2001). Nevertheless, observations of the oxidative state of the cortical tissue and direct O_2 measurements have shown that even under conditions of pial vasodilation, the vascular delivery of O_2 may be greatly exceeded by O_2 demand (Takano et al., 2007). The increased O_2 utilization is required to reverse the effects of the depression process and is at least partly attributable to the elevation in activity of ATPases required to restore ion concentrations. Not only the neurons but also the astrocytes would be involved to a significant degree. Thus, tissue anoxia may be a component in the rate of propagation and duration of SD, and the determining factor in whether recovery or cell death would result. Even repeated waves of SD may not produce overt neuronal injury in normal brain (Nedergaard and Hansen, 1988)), but SD in injured brain can have very deleterious consequences (see below).

7. The migraine connection

Already in 1945 Leão and Morison had suggested a link between SD and migraine. This was based on the vascular changes they observed during SD, relating them to the then current vascular hypothesis about the mechanism of migraine (summarized by Lauritzen, 1994). However, it was not until 1958 that Milner remarked on the similarity between the rate of advance of spreading depression and the rate calculated by Lashley (1941) for the progress of activity in the visual cortex that he assumed gave rise to the visual aura he experienced during his own migraine attacks. Milner (1958) was particularly struck by the correspondence between Lashley's description of his "scintillating scotoma", which appears as a band of intense excitation bordering the advancing edge of a region of complete inhibition of activity and Grafstein's (1956) observation of the intense activity at the leading edge of the electrical silence in SD.

This idea was met with considerable skepticism because of the apparent lack of congruity between some features of migraine and SD, including the difference between the transient nature of SD and the long duration of the migraine headache, as well as the fact that the headache and the migraine aura did not necessarily occur together. However, careful studies in migraineurs have revealed cerebrovascular changes and electromagnetic fluxes during migraine aura that correspond to the advance of a wave of SD through the cortex (reviewed by Lauritzen, 1994; Pietrobon and Striessnig, 2003). This has unequivocally established SD as an essential factor in migraine aura and possibly a participant in most types of migraine. Although the characteristic sign of SD in migraine has usually been considered to be a spreading wave of oligemia (Lauritzen, 1994), an increase in blood flow may be detected for a few minutes before that (Hadjikhani et al., 2001), a pattern more closely resembling the changes with experimental SD, for example, in the rat cortex (Takano et al., 2007). In any case, it appears that in spite of the prominent oligemia, lack of O_2 is not the critical factor in generating migraine symptoms, but that the clinical symptomatology and the vascular changes are both triggered by spreading depression (Lauritzen, 1994). Typically, the migraine aura appears early in the oligemic period, and oligemia is still present at the onset of the headache, but the oligemia is followed by a prolonged period of hyperemia that may or may not outlast the headache (Fig. 4), and hence is unlikely to be the cause of the headache (Olesen et al., 1990).

A clue to the nature of the underlying pathology in migraine is provided by observations in patients with familial hemiplegic migraine, linking the tendency to migraine attacks with a decreased threshold for SD. Many patients with this genetic disease, who display an aura consisting of weakness or

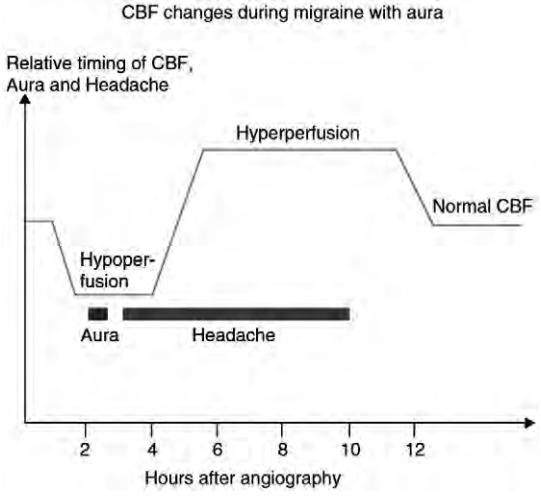

Fig. 4 – Schematic drawing based on information from many patients showing typical temporal relationship between migraine symptoms and blood flow changes. Reproduced from Tfelt-Hansen, 2010 (modified from original by Olesen et al., 1990). Used with permission from Sage Publications copyright 2010.

paralysis usually of one side of the body, have a mutation in P/Q calcium channels that results in increased Ca^{++} entry intro presynaptic endings and hence increased excitatory neurotransmitter release (Pietrobon and Striessnig, 2003). Such mutations have been found to increase susceptibility to SD (van den Maagdenberg et al., 2004).

Nevertheless, the linkage between the intracortical events of SD and the pain experienced in migraine would still need explanation. In general, it is agreed that the pain experience is initiated by the stimulation of trigeminal afferents in the meninges, possibly as a direct effect of agents released during SD, such as K^+, H^+, and NO (Bolay et al., 2002), or as suggested above, by ATP liberated during meningeal calcium waves. The trigeminal afferent activity would be relayed via the trigeminal centers in the midbrain to give rise to pain sensation. Moreover, activation of the trigeminal afferents might have further consequences in producing changes in the dura mater (Moskowitz, 2007). Thus, trigeminal afferent input into brainstem centers would result in activation of postganglionic parasympathetic efferents, causing an increase of blood flow in the middle meningeal artery far outlasting the changes in the pial vessels during SD. This reflex vasodilation may be accompanied by extravasation of plasma proteins in the dura due to disruption of the blood–brain barrier by metalloproteinases. Vasoactive peptides released in the meninges by axon reflexes in the trigeminal afferents, including CGRP, substance P, and neurokinin A, would also play an important role in these events (Moskowitz, 2007).

8. The relationship with epilepsy

Leão's (1944a) original observations already emphasized a link between SD and epilepsy. Both SD and epileptiform activity were elicited by strong stimulation, and the advance of SD was often seen to be accompanied by epileptiform activity, although the epileptiform activity itself did not spread in the same systematic way. If SD is evoked repeatedly at short intervals, it can evolve into spreading convulsive activity (Whieldon and van Harreveld, 1950). Although they are independent to the degree that the stimulation threshold for SD under optimal conditions is lower than for epileptiform activity and each is independently self-propagating (Leão, 1944a), each appears to be capable of triggering the other, and each can limit the duration of the other.

Clinically, epilepsy and migraine (presumably involving SD) may sometimes occur in the same patient, and mutations in the same genes may give rise to either or rarely even both (Rogawski, 2008). Both entities involve neuronal hyperexcitability and an important role for ionotropic glutamate (NMDA) receptors. While seizures may increase the likelihood of SD, they are not necessary for its initiation (Fabricius et al., 2008). However, the circumstances for the differential elicitation of these two phenomena have not been defined. It is possible that, depending on local conditions, repetitive activation might have different effects whether in generating surround-inhibition around the active focus or releasing different amounts of glutamate (Obrenovitch and Urenjak, 1997) or producing ionic changes that would determine whether Cl^--mediated synaptic potentials were inhibitory or excitatory (Martins-Ferreira et al., 2000).

9. The relationship with brain lesions

Although the human cerebral cortex is resistant to the initiation of SD by electrical stimulation (McLachlan and Girvin, 1994), even relatively mild head injury may initiate SD (Gorji, 2001), making it a likely contributing factor in the development of chronic traumatic encephalopathy. In head-injured or stroke patients, localized or propagating episodes of depressed electrical activity have been frequently observed and have been recognized as manifestations of SD (Strong et al., 2002). These corresponded to experimentally observed "peri-infarct depolarizations" that had been found to cause the infarcts to enlarge because of impaired O_2 supply to the penumbral region (Back et al., 1994). The waves of depolarization usually arise spontaneously from the boundary zone adjacent to the lesion and are characterized not only by the decrease in neuronal activity but by the signature surface negativity (Fabricius et al., 2006). In cases of contusional head injury or subarachnoid hemorrhage, recurring waves of what are essentially a series of SDs may continue for hours after the injury and may even invade adjacent normal regions of the cortex (Strong et al., 2002; Dreier et al., 2009). Although it is expected that SDs in normal cortex would be accompanied by vasodilation in response to the increased O_2 demand, the peri-infarct depolarizations are often characterized by a reduction

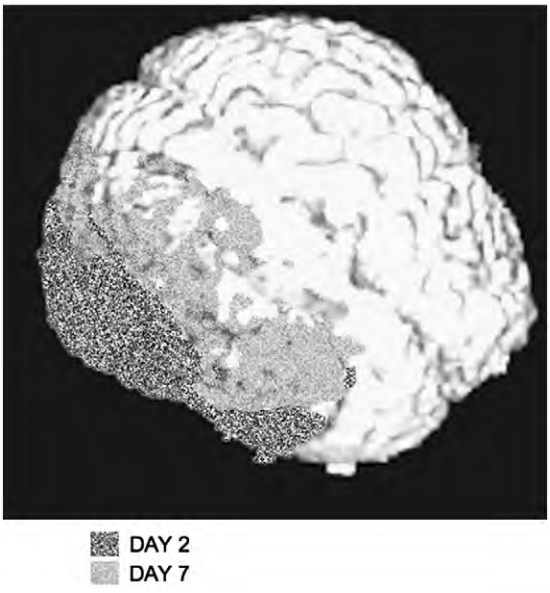

Fig. 5 – Increase in size of infarct from day 2 to day 7 in stroke patient undergoing repeated episodes of SD (modified from Nakamura et al., 2010). Figure is a reconstruction from MRI imaging. Dark shaded area indicates lesion at 2 days, total shaded area indicates lesion at 7 days. SD occurrence was detected by ECoG recording with subdurally implanted electrodes placed over the peri-infarct region. (Different colors in the original figures have been electronically replaced by differences in density of shading, and sketch overlay showing electrode placement has been removed.) Modified from Fig. 5 in Nakamura et al., 1994. Used with permission from Oxford Unversity Press.

in blood flow (Dreier et al., 2009), indicating an impaired vascular response or even frank vasoconstriction in at least some cases (Shin et al., 2006; Strong et al., 2007). This would have an important impact on the already energy-compromised regions adjacent to the lesion, increasing significantly the zone of irreversible neuronal damage (Fig. 5) (Mies et al., 1993; Nakamura et al., 2010). In cases of subarachnoid hemorrhage, lesions developing days after the initial event, which are a major cause of bad outcomes in this condition, are likely to be due to small initial ischemic lesions being enlarged by repeated depolarization events (Iadecola, 2009).

Another pathological event that has been related to SD is transient global amnesia. It is characterized by a sudden compete loss of memory and learning ability and has been attributed to SD originating in the hippocampus (Gorji, 2001). This is consistent with the finding that susceptibility to this condition is often associated with susceptibility to migraine and that SD in the hippocampus results in retrograde amnesia for learned tasks in experimental animals. One trigger for the clinical attacks is thought to be glutamate release provoked by excessive stress or emotion.

A paradoxical effect of SD that may be important in pathological conditions is its ability to increase the resistance of the brain to subsequent ischemic injury, thus protecting neurons from cell death. This effect can also be produced by other energy-depleting events, such as ischemia, hypoglycemia, and epileptic seizures and is dependent on a mechanism requiring release of glutamate (Kokaia et al., 1993). It has been at least partly attributed to the increased neuronal synthesis and release of BDNF (Kawahara et al., 1997). In the rat brain, where neurogenesis is ongoing, SD can increase the number of new neurons (Yanamoto et al., 2005). Moreover, SD can activate microglia, resulting in the expression of major histocompatibility antigens even in the absence of overt neuronal injury (Gehrmann et al., 1993), and many immediate early genes as well as genes associated with inflammation may show changes in expression (Sharp et al., 2000; Thompson and Hakim, 2005). The evocation of such events by SD can extend even to brain regions distant from the initial cortical locus (Sharp et al., 2000). This may represent a physiological stress response that could result in tolerance to subsequent injury and in neuronal plasticity, processes that may likewise be elicited in the penumbra of an ischemic lesion (Jander et al., 2001; Nakamura et al., 2010). Thus, SD has much to teach us about the balance between destructive and protective effects that are produced in the brain under pathological conditions, and it represents an important tool for investigating the conditions under which this balance might be tipped in the direction of better clinical outcomes.

10. Conclusions

We now know that looking for a single mechanism to explain SD, as the early investigators tended to do, has been a futile exercise. SD is a multifactorial phenomenon. Intense depolarization of neurons and/or astrocytes is essential, with release of K^+, release of glutamate, increase in intracellular Ca^{++}, release of ATP and local anoxia, each contributing to some degree. Both neurons and astrocytes release various vasoactive agents that can give rise to visible changes in the pial circulation, which are superimposed on a prolonged period of greatly increased O_2 utilization required for recovery. It is now acknowledged that SD is an essential factor in migraine aura and possibly in most types of migraine; it may be linked to some epileptic disorders; it may present as a series of "peri-infarct depolarizations" in traumatic injury, hemorrhage, or ischemic stroke; it may give rise to transient global amnesia; and it may play a role in the development of chronic traumatic encephalopathy. In the injured brain, SD may have an especially deleterious effect, enlarging the area of neuron loss, but paradoxically, it may evoke mechanisms that protect against subsequent insults. Addressing the mechanisms underlying SD in a clinical setting may make it possible to find new ways of healing the damaged brain.

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