The Role of Cortical Spreading Depolarizations in Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage

Depressão alastrante cortical e seu possível papel na lesão neuronal subsequente à hemorragia subaracnóide aneurismática

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ABSTRACT

Delayed cerebral ischemia (DCI) is the leading potentially treatable cause of mortality and disability in patients with aneurysmal subarachnoid hemorrhage (SAH). However, to date there is no effective treatment for this entity. The recently demonstrated lack of clinical response to pharmacologic reversal of arterial spasm as a result of SAH has spurred a reassessment of the pathophysiological concepts on DCI that follows SAH. DCI was long believed the consequence of the angiographically visible arterial spasm observed in patients with SAH. Since the measurement of cortical spreading depolarizations (CSD) in patients with SAH, increasing evidence has suggested a role for these phenomena in the pathophysiology of DCI. When induced in a healthy brain, CSDs are associated with an increase in regional cerebral blood flow that facilitates the delivery of the necessary energy substrates for cellular repolarization. In a brain that has been injured, however, CSDs can induce microvascular constriction, or cortical spreading ischemia. This inverse hemodynamic response to CSD was first discovered in an animal model replicating the conditions following SAH, and later demonstrated in patients with SAH. The spreading ischemia leads to energy substrates shortage and hypoxia, resulting in cortical lesions, and may explain similar lesion patterns which occur in SAH patients. This review describes the salient characteristics of CSD and its potential relevance in the pathophysiology, monitoring, and treatment of ischemic complications following SAH.

Keywords: cerebral vasospasm, cortical spreading depression, subarachnoid hemorrhage, delayed ischemic neurologic deficit.

SINOPSE

Isquemia cerebral tardia (delayed cerebral ischemia; DCI) é a principal causa potencialmente tratável de mortalidade e incapacidade em pacientes com hemorragia subaracnóide aneurismática (HSA). No entanto, não existe tratamento eficaz para esta condição até o momento. A recente demonstração da falta de resposta clínica à reversão farmacológica do espasmo arterial após HSA estimulou uma reavaliação dos conceitos fisiopatológicos na DCI que segue a HSA, que foram por muito tempo creditados ao espasmo arterial observado em doentes com HSA. Desde a demonstração de resultados electrocorticográficos de depressão cortical generalizada (“cortical spreading depressions”, CSD) em pacientes com HSA, um crescente interesse foi despertado sobre o papel destes fenômenos na fisiopatologia da DCI observados em pacientes com HSA. Quando induzida em um cérebro saudável, a CSD está associada com aumento do fluxo sanguíneo cerebral, facilitando a distribuição de substratos de energia necessários para repolarização celular cerebral. Em um cérebro lesado, no entanto, CSDs estão associados a uma redução do fluxo sanguíneo cerebral, que, no contexto de aumento das necessidades da energia, leva à falha de energia e hipóxia, acentuando a gravidade da lesão cerebral. Esta resposta inversa hemodinâmica à CSD foi descoberta pela primeira vez em um modelo animal, replicando as condições de HSA e, posteriormente, demonstrado em pacientes com HSA. A isquemia leva à escassez de substratos energéticos e propagação da hipóxia, resultando em lesões corticais, e podem explicar os padrões de lesão, semelhantemente ao que ocorre em pacientes com HSA. Estas observações sugerem que o déficit de energia produzido por CSD é um fator chave na patogênese dos DCI observados como resultado da HSA.

Este artigo detalha as principais características de CSDs e sua potencial relevância na fisiopatologia das complicações isquêmicas da HSA.

Palavras-chave: vasoespasmo cerebral, depressão cortical generalizada, hemorragia subaracnóide, déficit neurológico isquêmico tardio.
A little bit of history

Cortical spreading depolarizations (CSDs) are a class of waves originally described in 1944 by Dr. Aristides Azevedo Pacheco Leão, a Brazilian neurophysiologist, while working on his doctoral thesis at Harvard University. His discovery was a classic case in which the observation of an unexplained and seemingly irrelevant artifact by an alert researcher initiated a new, unexpected field of study. Leão intended to study the propagation of epileptic discharges induced by electrical stimulation of the rabbit cerebral cortex. To his surprise, instead of epileptic discharges, he observed on some trials an electrocorticographic silencing at the recording electrodes adjacent to the stimulated cortex. This depression of spontaneous activity spread in an orderly sequence to cover the entire ipsilateral cerebral cortex, followed by recovery of activity in the same sequence as the depression. In Leão’s continued study of this phenomenon, he termed ‘spreading depression’, he described the essential elements that characterize CSD, namely: 1) depression of spontaneous electrocorticographic activity that lasts a few minutes, 2) spread across contiguous cortex at a propagation rate of 2-5 mm/min, 3) functional inactivation of affected cortex, evidenced by the failure to elicit evoked potential waves by either sensory or direct cortical stimulation, 4) induced epileptic discharges are suppressed by the CSD, although sometimes the CSD can be preceded or followed by tonic-clonic activity.

Later, once re-established in Brazil, Leão described what would prove to be the hallmark characteristic of CSD: a negative slow voltage change lasting 1-2 min that accompanied the depression period. He concluded that “the voltages recorded are the expression of the depolarization of the normally polarized membrane of the neurons.” Subsequent work confirmed that this negative shift of extracellular potential reflects the mass, sustained depolarization of neurons/astrocytes that defines CSD. The negative shift closely relates to the breakdown of electrochemical gradients across cellular membranes and therefore roughly mirrors the rise of extracellular K+ and decline of Na+ and Ca2+. In this state, action potential generation is no longer possible due to the persistent inactivation of voltage-gated Na+ channels. This explains the depression of spontaneous activity, the lack of evoked potentials, and the ability of CSD to abort seizures.

Leão further observed that recovery of spontaneous cortical activity could be delayed by interruption of the cerebral circulation, suggesting that repolarization is an energy-dependent process. Thus, under physiologic conditions with circulation intact, he found that “vasodilation with increased blood flow in the pial vessels occurred concomitantly with CSD.” This regional surge in cerebral blood flow propagates along with the

Introduction

Delayed cerebral ischemia (DCI) is the leading potentially treatable cause of mortality and disability in patients with aneurysmal subarachnoid hemorrhage (SAH). The occurrence of cerebral vasospasm, however, does not necessarily lead to clinical consequences: radiographic vasospasm may occur in up to 70% of patients with SAH, while clinical deterioration caused by DCI is observed in 20-30% of them. Of those patients who develop delayed clinical deterioration, approximately 50% will develop stroke, and between 15 and 20% will die as a result of cerebral ischemia, even despite intensive treatment.

Since the description of the association between angiographic arterial narrowing with the clinical syndrome of DCI in 1951, most research on delayed neurological deterioration as a result of SAH was based on this axiom with vasospasm as the presumptive cause. However, a series of disappointing failures in clinical trials targeting this pathophysiological model in the last 50 years suggest that DCI, as a clinical phenomenon, cannot be explained only as the direct result of arterial narrowing caused by extravasation of blood and their toxic by-products. In the most emphatic and eloquent case and failure, the CONSCIOUS-1 trial, it was clearly demonstrated that the reduction in the incidence of angiographic vasospasm with the use of clazosentan, a selective inhibitor of the endothelin-1 receptor, did not result in a reduction of cerebral ischemia and mortality. Conversely, previous trials with the Ca2+ antagonist nimodipine showed improved patient outcome and a significant reduction in delayed cerebral ischemia, but without effect on angiographic vasospasm. These results have forced the scientific and medical communities to re-examine assumptions about the pathophysiology underlying ‘symptomatic or clinical vasospasm’, terms which themselves are at best presumptuous or at worst misleading. The dogma of vasospasm as the presumptive, prime mechanism of DCI has been refuted, at least to the initial injury. Indeed, initial studies have suggested that depolarizations are associated with, and possibly cause, DCI after SAH. Here, we will review this translational research along with the patho-mechanisms and potential therapies.
electrochemical wave as a spreading hyperemia (Figure 1). The very significant hyperemia accompanying depolarization is the physiologic mechanism to increase the supply of glucose and oxygen to meet the metabolic demands of repolarizing neurons and astrocytes to terminate the CSD wave. For the first time, Lashley had mapped the rate of propagation of the visual field scotoma (his own) that often occurs in the aura prodrome of migraine headache. Translating visual field coordinates to those of cerebral cortex, he concluded that the cortex must support a pathologic activity travelling at 3 mm/min. Thus, Léão’s work had an immediate relevance to human disease, and to this day CSD remains a central mechanism in the theory of migraine pathophysiology. However, despite occasional speculation that CSD was involved in other human conditions for decades it was considered largely an experimental curiosity, unproven in the gyrencephalic human cortex. This tide began to change in the 1980’s, as a growing body of experimental work in focal cerebral ischemia suggested an important endogenous role of CSD in cortical lesion development.

A NOTE ON TERMINOLOGY

Strictly speaking, the terms spreading depolarization and spreading depression should not be used synonymously since spreading depolarizations can occur in cortex that has no spontaneous electrocorticographic activity. In such cases, as occur in the ischemic penumbra or immediately following anoxia, depolarizations are observed by spreading negative slow voltage changes only and further depression of spontaneous activity is not possible. Therefore, spreading depolarization is nowadays used as the generic term for the whole class of spreading depolarization phenomena, while the term spreading depression just describes their effect to depress spontaneous cortical activity when it is present. This differentiation is in fact important for the diagnostic evaluation of human recordings where spreading depolarization with spreading depression of activity seems to indicate a better prognosis of the event than spreading depolarization in isoelectric (i.e. persistently depressed) cortex (Hartings et al., 2011).


CORTICAL SPREADING DEPOLARIZATIONS IN STROKE: ANIMAL STUDIES

It is widely accepted that, in the intact brain, hyperemic CSD does not cause persistent neurologic or histologic damage. In fact, the deliberate induction of CSD in rats confers a degree of protection against subsequent ischemic injury. Although these findings might suggest that hyperemic CSD may be harmless or beneficial, on the contrary, many experimental studies argue against this potential effect in the context of brain injury. Therefore, based on current evidence, the conclusion that CSD is usually a benign or protective phenomenon is not valid. Factors such as the total number of depolarizations and/or the plasma glucose concentration may be determinants of the net beneficial or detrimental effect of CSD under conditions of normal cerebral perfusion.

On the other hand, it is clear that pre-existing vascular pathology or other metabolic compromise endows CSDs with a greater cytotoxic potential. In animal models of ischemic stroke, usually induced by occlusion of the middle cerebral artery, CSDs arise spontaneously from the rim of the evolving core infarction, where sustained depolarization provides a constant stimulus for repetitive CSDs. Once evoked, CSDs propagate through the penumbra outward into intact cortex or may cycle through the penumbra around the infarct core. These penumbral CSDs, often called peri-infarct depolarizations (PIDs), are associated with infarct expansion, or recruitment of penumbral cortex into the ischemic core, and they have even been shown capable of causing such expansion.

Unlike CSDs in intact brain, PIDs can cause waves of microvascular constriction, or cortical spreading ischemia, which may in part underlie their deleterious effects. Under conditions of ischemic penumbra, it has been demonstrated that vascular reactivity to stimulation of the cerebral cortex is reduced. Thus, cerebral perfusion studies in mice have shown that as PIDs spread through the penumbra, they are associated with a profound reduction, rather than increase, of cortical perfusion, and that perfusion recovery becomes less complete with each recurring depolarization. Recovery of glucose levels in the tissue after PIDs is similarly incomplete. Thus, widespread and recurrent cortical depolarizations engender a widespread developing ischemia.
Cortical spreading ischemia was originally discovered in an animal model replicating the conditions present following SAH. In this rat model, erythrocyte degradation products caused the normal hemodynamic response to CSD, hyperemia, to change to the inverse hemodynamic responses, a cortical spreading ischemia, in the absence of any preceding vascular occlusion. The occurrence of spreading ischemia, as opposed to hyperemia, was dependent on elevated K+ and the effect of hemoglobin to scavenge the vasodilator nitric oxide; nitric oxide inhibition had effects similar to application of hemoglobin. This uncoupling of metabolism and cerebral blood flow resulted in a profound prolongation of the depolarization. Critically, it was found that the CSD-triggered perfusion deficit was sufficient to induce widespread focal cortical necrosis. Spreading ischemia is contrasted with hyperemic CSD in Figure 1. Based on these animal experiments, it was hypothesized that CSD with spreading ischemia might be an important mechanism of DCI.

A NOVEL HYPOTHESIS: CORtical SPREADING DEPOLARIZATIONS IN SUBARACHNOID HEMORRHAGE

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A further stimulus for this idea was the inadequacy of proximal vasospasm to explain the occurrence of delayed cortical lesions after SAH (e.g. Figure 2D). Cortical lesions represented by far the most abundant patho-morphological finding in a number of autopsy studies of DCI after SAH. Such lesions were found in over 70% of the autopsy cases. In particular, the cortical lesions were much more frequent than territorial infarcts in those patients where the surgical treatment of the aneurysm was excluded as a confounding cause. Clinical studies on the cortical lesions after SAH have only gained momentum with the improvement of imaging technology, since they are often not visible in computed tomography scans. The lesions can occur outside the territory of the vessels affected by proximal vasospasm, and reduction in blood flow due to vasospasm seems not sufficient to cause this ischemic injury. Furthermore, only half of patients with angiographic evidence of vasospasm develop delayed ischemic lesions. Rather, cortical lesions evolve more often in the vicinity of subarachnoid blood, suggesting that the clots may directly cause lesions through induction of microvascular spasm or through toxic effects on the underlying cortex. Indeed, in a non-human primate clot model of SAH, cortical infarcts developed exclusively in areas with subarachnoid blood and did not correlate with the degree of vasospasm in the middle cerebral artery.

TRANSLATIONAL STUDIES: A REBIRTH FOR LEÃO

Despite the accumulating experimental data, without evidence from the human brain, at the turn of the century CSD remained little more than a fashionable hypothesis for clinical neurologic disorders. In 1996, M eyevsky et al. had looked for evidence of CSD in a series of 14 patients suffering from severe traumatic brain injury by using ECoG as part of an invasive multimodal research monitor. Although they impressively documented a series of repetitive CSDs in one patient, including the extracellular K+ and cerebral blood flow transients accompanying the ECoG depressions, the negative results from the remaining 13 patients and the specialized nature of their monitor forestalled a broader exploration of the clinical relevance of CSD. Other efforts to study CSD in humans were similarly limiting in the technique or produced negative results.

The story of Leão’s spreading depression took a dramatic turn in 2002, however, when Strong and colleagues published ‘‘Spreading and synchronous depressions of cortical activity in acutely injured human brain’’. Anthony Strong, a neurosurgeon who had contributed to the new concept of the ischemic penumbra in the lab of Lindsay Symon in the late 1970’s, recognized the opportunity to monitor CSD in patients who required craniotomies for cerebral decompression or lesion evacuation after cerebral hemorrhage or trauma. By placing electrode strips in the subdural space during surgery, patients could then be monitored for several days during intensive care using ECoG techniques that are standard practice in epilepsy patients (Figure 2). They found evidence for CSD in 8 of 14 patients, and, as important, introduced a technique that could be widely adopted by others.

Subsequently, an international research consortium, the Cooperative Study on Brain Injury Depolarizations (COSBID), was established to study depolarizations occurring in the context of brain injury, including malignant stroke, brain trauma, and intracerebral and subarachnoid hemorrhage. To date, more than 250 patients in Europe and the U.S. have been enrolled in these studies which have unequivocally demonstrated a high incidence of CSDs. For instance, almost all patients with malignant hemispheric stroke (10) and 55-60% of patients with severe brain trauma experience CSD. The translational findings and clinical relevance of CSDs for these diseases were recently reviewed.

CORTICAL SPREADING ISCHEMIA IN THE HUMAN BRAIN

The advent of clinical CSD monitoring and the COSBID consortium have enabled translational testing of the specific CSD/spreading ischemia hypothesis of Dreier and colleagues. In a work that may be recognized as a milestone in the study of SAH, the occurrence of CSDs was first documented in 13 of 18 patients (72%) with severe SAH (Fisher grade 3). In a total recording time of 2110 hours, 298 spreading depolarizations were observed by continuous ECoG using subdural electrode strips placed at the time of surgical aneurysm clipping. Consistent with the results of animal studies, the evolution of cerebrovascular ischemia was associated with clusters of CSD and increasingly prolonged periods of ECoG depression. In particular, the appearance of delayed infarcts, as demonstrated in consecutive evaluation by computed tomography and magnetic resonance, was associated with depression periods that evolved to 60 min or more, suggesting not only that CSD may contribute to lesion development, but also that ECoG monitoring of the progressive prolongation of depression periods could serve as early indicator of impending necrosis. In addition, the occurrence of a temporal cluster of repetitive CSDs had high positive (86%) and negative (100%) predictive values for the development of delayed ischemic neurologic deficits. Accordingly, patients with this clinical syndrome (interquartile range:
7.3-8.2 days after SAH) had significantly more CSDs on days 7-9 than patients without. CSDs with depression periods of 10 minutes or more were associated with poor outcomes. This initial study demonstrated an important association between CSD and delayed cerebral ischemia, but the question remained whether the causal mechanism of lesion development in animals - spreading ischemia - also existed in man. To address this, the authors used a novel technique of embedding fiber-optic probes for laser-Doppler flowmetry within the ECoG electrode strip. By this method, regional cerebral blood flow and cortical activity could be measured simultaneously at multiple locations. In a series of 13 SAH patients, they found that isolated CSDs predominantly induced a transient hyperemia, the physiological hemodynamic response. In 5 patients with temporal clusters of CSDs, however, the inverse response of spreading ischemia was observed, which persisted in some cases up to 144 min in duration. Tissue partial pressure of oxygen (PtiO2), as measured with an intraparenchymal brain tissue oxygen monitoring system probe (Licox®, Integra Neurosciences, Plainsboro, NJ), at the electrode strip increased during hyperemic CSDs, but decreased during spreading ischemia. Since the duration of the CSD-induced ischemia was correlated with the ECoG depression period, these results showed that spreading ischemia limits the critical delivery of oxygen that is necessary for recovery of cortical activity, resulting in prolonged depressions. As for prolonged depression periods, hypoxic PtiO2 responses to CSD occurred predominantly in patients with delayed ischemic neurological deficits.

### Implications of CSD for Potential Therapeutic Targets

In summary, when induced in a healthy brain, CSD induces a regional increase in cerebral blood flow, which facilitates the delivery of brain energy substrates needed to restore ionic gradients and repolarize neurons. In an injured brain, however, CSD can be associated with a reduction in cerebral blood flow, which in the context of increased energy needs, accelerates energy failure and tissue hypoxia, resulting in cortical lesions. These observations suggest that the energy deficit caused by CSD is a key factor in the pathogenesis of DCI observed as a result of SAH and place CSD as a potential target for therapeutic intervention.

Two possible strategies to mitigate against CSD-induced damage are to prevent the electrochemical wave of CSD itself, and secondly, to prevent the inverse hemodynamic response of spreading ischemia. N-Methyl-D-aspartic acid (NMDA) receptor antagonists are effective in preventing the spread of CSD through normally perfused tissue, but are less effective in blocking depolarizations in hypoxic or ischemic tissue where they cause the most damage. Preventing CSD-induced vasoconstriction may be a more effective approach, as several therapies with promising clinical efficacy have shown positive effects against CSD in animal studies. For instance, nimodipine, an L-type calcium channel antagonist, prevents spreading ischemia and thereby allows for more rapid repolarization of cells after CSD. Similar results are obtained by increasing nitric oxide concentration. Physiologic therapies such as hypertension-hypervolemia-hemodilution may also play a role. Moderate volume expansion/hemodilution can reduce the degree of CSD-induced hypoperfusion, and hypotension not only increases the risk of CSD, but also prolongs depolarization by abrogating the physiologic hyperemic response.

Many of these therapies have been tested or are used clinically and have limitations due to systemic side effects and inconsistent efficacy. Thus, the continued development of drugs and therapies more specifically targeted to pathophysiologic signaling pathways is necessary. A complementary approach, however, is to apply therapies more selectively to those patients who would benefit. For instance, if a candidate therapy’s principal mechanism of action is prevention of CSD, then only those patients exhibiting CSD, or particularly severe patterns of CSD, would be expected to benefit from treatment. By only including such patients, the chances of obtaining positive results in clinical trials would be improved. The discovery of CSD in SAH carries the major advantage that it can be monitored in real-time and graded in severity if it occurs and as it evolves, thus providing a mechanism to select patients for treatments and tailor the therapeutic intensity according to individual patient needs. Importantly, such clinical trials will be required to determine ultimately whether CSD and spreading ischemia play a causative role in DCI, or whether they are a reflection of other, more primary pathologic processes.

### Conclusion

Discovery of a novel patho-mechanism with a potential impact on the development of DCI, independent from angiographic arterial spasm, in itself constitutes a breakthrough in SAH research and provides an impetus for new research avenues that could explain current paradoxes in the pathophysiology of SAH. Cortical spreading depolarizations can be monitored continuously in real-time and may play a central role in the development of DCI after SAH, either as a direct mechanism or a common final pathway of antecedent events. The potential of spreading depolarizations and spreading ischemia as therapeutic targets, and of ECoG monitoring to guide therapy, need to be explored in depth in future clinical studies.
REFERENCES


Aneurysmal Subarachnoid Hemorrhage


