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Controversies and evolving new mechanisms in subarachnoid hemorrhage

Sheng Chen [a,b,1], Hua Feng [c,1], Prativa Sherchan [b], Damon Klebe [b], Gang Zhao [d], Xiaochuan Sun [e], Jianmin Zhang [a], Jiping Tang [b], John H. Zhang [b,f,*]

[a] Department of Neurosurgery, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China
[b] Department of Physiology & Pharmacology, Loma Linda University, Loma Linda, CA, USA
[c] Department of Neurosurgery, Southwest Hospital, Third Military Medical University, Chongqing, China
[d] Department of Neurology, Xijing Hospital, Fourth Military Medical University, Xi'an, Shanxi, China
[e] Department of Neurosurgery, First Affiliated Hospital, Chongqing Medical University, Chongqing, China
[f] Department of Neurosurgery, Loma Linda University, Loma Linda, CA, USA

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ABSTRACT

Despite decades of study, subarachnoid hemorrhage (SAH) continues to be a serious and significant health problem in the United States and worldwide. The mechanisms contributing to brain injury after SAH remain unclear. Traditionally, most *in vivo* research has heavily emphasized the basic mechanisms of SAH over the pathophysiological or morphological changes of delayed cerebral vasospasm after SAH. Unfortunately, the results of clinical trials based on this premise have mostly been disappointing, implicating some other pathophysiological factors, independent of vasospasm, as contributors to poor clinical outcomes. Delayed cerebral vasospasm is no longer the only culprit. In this review, we summarize recent data from both experimental and clinical studies of SAH and discuss the vast array of physiological dysfunctions following SAH that ultimately lead to cell death. Based on the progress in neurobiological understanding of SAH, the terms "early brain injury" and "delayed brain injury" are used according to the temporal progression of SAH-induced brain injury. Additionally, a new concept of the vasculo-neuronal-glia triad model for SAH study is highlighted and presents the challenges and opportunities of this model for future SAH applications.

Contents

Abbreviations: SAH, subarachnoid hemorrhage; DIND, delayed ischemic neurological deficit; DCI, delayed cerebral ischemia; TCD, transcranial Doppler; EBI, early brain injury; DBI, delayed brain injury; ICP, intracranial pressure; CPP, cerebral perfusion pressure; CBF, cerebral blood flow; CSD, cortical spreading depolarization; BBB, blood–brain barrier; NMDA, N-methyl D-aspartate; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CSWS, cerebral salt-wasting syndrome; SIADH, syndrome of inappropriate secretion of anti-diuretic hormone; VGCC, voltage-gated calcium channel; VAP-1, vascular adhesion protein-1; MAPKs, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; STAT3, signal transducer and activator of transcription; Kv, voltage-gated K+ channel; NO, nitric oxide; NOS, nitric oxide synthase; MEK, mitogen activated protein kinase kinase; SOD, superoxide dismutase; IL-1α, interleukin-1α; TNF-α, tumor necrosis factor-α; MCP-1, chemotactic protein-1; CCL5, chemokine (C-C motif) ligand 5; CXCL1, chemokine (C-X-C motif) ligand 1; CAMs, cell adhesion molecules; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; CHOP, C/EBP homologous protein; EGF, epidermal growth factor.

* Corresponding author at: Department of Neurosurgery, Loma Linda University School of Medicine, Loma Linda, CA 92354, USA. Tel.: +1 909 558 4723; fax: +1 909 558 0119.
E-mail addresses: johnzhang3910@yahoo.com, jhzhang@llu.edu (J.H. Zhang).
[1] Both authors contribute equally to this work.

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1. Introduction: it is time to reawaken interest in the mechanisms of subarachnoid hemorrhage pathophysiology

Subarachnoid hemorrhage (SAH) is a devastating cerebrovascular disease with complex mechanisms that threaten brain perfusion and function. The definition of a SAH has recently been updated to mean *bleeding into the subarachnoid space*, i.e., the area between the arachnoid membrane and the pia mater of the brain or spinal cord (Sacco et al., 2013). Despite recent improvements our knowledge of SAH pathophysiology and the management of ruptured aneurysms, which can include surgical clipping or endovascular treatment, SAH remains a serious and significant health problem in the United States and throughout the world (Sehba et al., 2012). Although it accounts for only 5% of all strokes, its burden to society is significant, given the young age at which it occurs, its high rates of mortality and disability, and poor clinical outcomes (Venti, 2012). Approximately one in six patients die during the sudden onset of bleeding. The mean age at which SAH occurs is 50 years old, and the onset of SAH in this younger population renders members of an otherwise productive age group unable to return to work. Additionally, it necessitates long-term care. Those who survive initially may succumb to early rebleeding or a delayed ischemic neurological deficit (DIND) that occurs with or without cerebral vasospasm.

Hippocrates demonstrated the presentation of spontaneous SAH followed by subsequent delayed neurological deficient nearly 2400 years ago. Delayed cerebral vasospasm, a syndrome first reported in 1951 (Ecker and Riemenschneider, 1951) was regarded as the single most crucial and treatable cause of mortality and morbidity after SAH in subsequent decades. The Fisher Grade was applied in predicting the onset of vasospasms (Fisher et al., 1980). Arterial vasospasm after SAH can be visualized and evaluated by digital subtraction angiography or magnetic resonance angiography in clinical research and by India ink angiography, synchrotron radiation angiography or H&E staining in basic research (Bederson et al., 1998; Cai et al., 2012; Suzuki et al., 2010a).

Historically, considerable efforts have been made to investigate vasospasm as the primary mechanism underlying SAH injury that leads to tissue ischemia, and ultimately to infarctions and poor neurological outcome. However, in recent years, that theory is being questioned increasingly. First, the peak incidence of angiographic vasospasm during the second week post-SAH is approximately 70% (Dorsch and King, 1994), but the incidence of clinically delayed cerebral ischemia (DCI) is only around 30% (Dorsch, 2011). Secondly, the relationship between vessel constriction and cerebral infarction is somewhat poor (Minhas et al., 2003). It is unlikely that all cases of cerebral infarction are due to a SAH-induced vasospasm, because in some instances infarction can occur immediately after a SAH, and a vasospasm in the territorial artery is not always detected by angiography (Naidech et al., 2006). Furthermore, the presence of angiographic or transcranial Doppler (TCD) vasospasm had only 67% positive predictive value, but 72% negative predictive value for the occurrence of cerebral infarction, respectively (Rabinstein et al., 2005). Cerebral infarction can develop even in an unaffected vascular distribution without vasoconstriction after SAH (Brown et al., 2013; Naidech et al., 2006). Cerebral infarction contributed to poor outcome by both vasospasm-dependent and -independent effects in the majority of 194 patients with moderate to severe vasospasm (Naidech et al., 2006). Therefore, poor outcome seems to be directly dependent on infarction, but independent of vasospasm (Vergouwen et al., 2011). Thirdly, a wide range of cerebral perfusion disturbances has been observed among patients who developed delayed neurological deficits after SAH (Minhas et al., 2003). Cerebral blood flow (CBF) measured via CT perfusion in areas supplied by vessels with vasospasm ranged from 26.4 to 41.5 ml/100 g/min (Dankbaar et al., 2009; Sviri et al., 2006; Wintermark et al., 2006), which is higher than the assumed threshold for ischemic injury (25 ml/100 g/min) (Murphy et al., 2006). This raises a critical question for future studies: Are the effects of vasospasm on CBF sufficient to cause cerebral ischemia and brain infarct?

The treatment of SAH has not improved despite nearly four decades experimental studies targeting vasospasms. Additionally, the calcium channel antagonist nimodipine, which is the only proven drug treatment to improve outcomes after SAH, seems to provide beneficial effects without angiographic evidence of cerebral vasodilation (Petruk et al., 1988). Finally, treating vasospasm does not always lead to improvement in functional outcomes (Macdonald et al., 2008; Polin et al., 2000). Disappointing results were observed in the two randomized, double-blind, placebo-controlled, phase III trials using endothelin A receptor antagonist, clazosentan (CONSCIOUS-2 and CONSCIOUS-3) (Macdonald et al., 2011, 2012).