Cerebral Metabolic Dysfunction after SAH

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Cerebral metabolic dysfunction has been shown to extensively mediate the pathophysiology of brain injury after subarachnoid hemorrhage (SAH).

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1. Introduction

Subarachnoid hemorrhage (SAH) is an acute cerebrovascular disease. Despite accounting for only 5% of all stroke cases[1][2], some features render SAH as one of the most devastating diseases. Not only does SAH tend to affect individuals of a younger age compared to other types of stroke, but it also causes high mortality and significant morbidity[3][4]. Approximately 12% of patients die prior to receiving medical management, and 50% within 30 days of SAH. Half of the survivors suffer from a permanent disability[5]. Etiologically, approximately 85% of cases are caused by the rupture of a cerebral aneurysm[6]. Followed by the sudden rupture, blood accumulates within the subarachnoid space, resulting in a series of pathophysiological changes, impacting both brain vasculature and parenchyma, causing secondary brain injury[7]. Mechanisms mediating secondary brain injury after SAH are multifactorial. Initially, delayed vasospasm was considered to be a primary factor resulting in the deterioration of neurological outcomes in SAH patients. However, successful relief of vasospasm has failed to improve functional outcomes in clinical trials[8]. Later, the concept called early brain injury (EBI), which is defined as pathophysiological changes within the first 72 h after the onset of bleeding, has been emphasized and gained increasing attention by the SAH research community [5]. Importantly, dysregulation of energy metabolism in brain tissue is one of the driving forces contributing to pathological changes in various acute brain injuries, such as traumatic brain injury[9]. Similarly, cerebral energy dysfunction occurs rapidly and could extend to a prolonged period of time after SAH[10]. Hence, measuring and monitoring the alterations in post-SAH energy metabolism inside the brain would be essential for not only improving patient management in clinical practice but for understanding the mechanisms underlying the post-SAH cerebral energy dysregulation, as well as its correlation with outcomes[11].

Cerebral microdialysis (CMD) is an approach using a concentric probe with a semipermeable membrane to collect brain interstitial fluid (ISF) that has been extensively used in both clinical and experimental studies for analyzing the status of cerebral energy metabolism[10]. Solutes, such as energy metabolites, neurotransmitters, or amino acids in ISF diffuse down the concentration gradient moving across the semipermeable membrane and are eventually collected as dialysate or analyte, followed by the concentration measurement by using analytical chemistry techniques, such as high-performance liquid chromatography with mass spectrometry. Indeed, using CMD allows researchers to see a more comprehensive picture of bioenergetic metabolism during and after SAH and help clinicians guide patient treatment and monitor brain metabolic changes preceding the clinical deterioration[12]. Simultaneously, other monitoring data, such as intracranial pressure (ICP), cerebral perfusion pressure, and brain tissue oxygen tension, are collected together with CMD data and may thus provide a direct way to measure the process of energy failure at the cellular level[13]. Interestingly, several studies have also demonstrated that monitoring patients with brain injury by CMD might be beneficial for reducing the mortality rate[14][15].

2. Cerebral Metabolic Dysfunction after SAH

As mentioned above, the current concept dividing the post-SAH pathophysiological process into two phases: the phase of EBI occurred within the first 72 h after the onset of ictus, followed by a delayed phase typically occurs 3–14 days after SAH where the cerebral vasospasm and subsequent delayed cerebral ischemia (DCI) ensue and affect up to half of the SAH patients[16]. Both phases involve prominent derangements in the brain's bioenergetic profile[17]that can be measured intracellularly and extracellularly.

2.1. Cerebral Metabolic Dysfunction in Early Phase after SAH

The definition of EBI includes the evaluation of initial clinical symptoms, neuroimaging findings, and cerebral electrophysiological and/or metabolic changes using multimodal neuromonitoring, including CMD. During the initial vessel rupture, blood enters the subarachnoid space, increasing ICP, leading to a reduction in cerebral perfusion pressure and cerebral blood flow (CBF)[18]. This clinical pattern has been successfully replicated in rodent studies, implying that the EBI's pathophysiology between the two species share similar mechanisms[18][19]. The sudden changes in CBF and cerebral perfusion deficit result in multiple metabolic disturbances[18]. In fact, some studies have demonstrated the similarities between SAH and transient global cerebral ischemia[20]. Normal functions of neurons heavily rely on the oxidative phosphorylation within the mitochondria via the electron transport chain for ATP generation. Acute cerebral ischemia depletes oxygen supply and reduces mitochondrial respiration, forcing the shift from oxidative phosphorylation to enhanced anaerobic glycolysis in neurons and other brain-resident cells, followed by an accumulation of lactate developing a local or diffuse acidosis[21]. Additionally, dramatic reductions in intracellular adenosine triphosphate (ATP) derived from the energy failure after SAH leads to ion channel dysfunction and disruption of the normal cell membrane potential. All these processes could enhance the production of reactive oxygen species (ROS) and brain tissue damage[22]. Moreover, cerebral hypoperfusion has been correlated with an increase in extracellular glutamate[23][24]. Excess extracellular glutamate that cannot be recycled causes the prolonged activation of both NMDA and AMPA receptors. The following supraphysiological influx of calcium into neurons and glial cells can eventually lead to apoptosis[25]. Astrocytic apoptosis, accompanied by the loss of astrocytic foot processes, plays a key role in BBB permeability after SAH[26]. CMD data obtained during the acute phase of SAH has shown a sharp reduction in glucose, while there was an elevation in glutamate, lactate, and lactate to the pyruvate ratio (LPR), which is a marker indicating the cerebral ischemia-related energy crisis[27].

In addition, non-ischemic mechanisms also mediate cerebral energy dysfunction in the EBI phase after SAH since clinical data, based on microdialysis analysis, showed that more pronounced CMD abnormalities, including the increased LPR, were observed in SAH patients with hyperemic or normal CBF. Extravascular hemolysis of red blood cells in subarachnoid space causes free hemoglobin to enter the cerebral interstitial system[22]. Consequently, the hemoglobin scavenges nitric oxide, reducing its availability to endothelium and smooth muscle cells[22] and disrupting the ionic homeostasis of smooth muscle cells, resulting in vasoconstriction of the cerebrovasculature and further energy insufficiency[28]. Hence, multiple factors contribute to the cerebral energy dysregulation involved in EBI after SAH. However, further investigations targeting the interaction and association between these factors are still needed.

2.2. Cerebral Metabolic Dysfunction in Late Phase after SAH

DCI has the highest incidence 3–14 days after ictus[29]. Previously, cerebral vasospasm has been considered a culprit in DCI. However, many clinical trials have failed to improve post-SAH outcomes by using anti-vasospasm agents[30]. Recent evidence has shown a weak correlation between the vasospasm and the location of DCI [31]. The current concept deems DCI a multifactorial process, including microvasculature dysfunction, microthrombi formation, inflammation, and cortical spreading depolarizations (SDs)[31][32]. Previous data demonstrated that persistent constriction of brain arterioles could last up to 72 h post-SAH[33]. Further evidence showed that the development of significant microthrombi in these constricted brain arterioles compared to arterioles without constriction[33], suggesting the cerebrovascular dysfunction starting at the early phase after SAH may sustain to an extended period of time and also strengthening the correlation between EBI components and the development of DCI[34]. Additionally, the inflammatory reaction induced by the interaction of hemoglobin released from lysed red blood cells and surrounding brain tissue can elicit the infiltration of peripheral immune cells and subsequent production of pro-inflammatory cytokines into the adjacent brain parenchyma[35].

During the late phase of subarachnoid hemorrhage, metabolic profiling using microdialysis has shown a similar pattern as the early phase after SAH[27]. Interestingly, in addition to the reduction in glucose and elevation of lactate, glutamate, and glycerol, an aggravation of energy crisis is reflected by a further increase in LPR, which can be detected during this delayed phase after SAH and may be partially due to the decreased level of pyruvate, suggesting the occurrence of delayed cerebral ischemia. Moreover, LPR deterioration can be detected as early as 16 h before DCI, rendering the possibility for early prevention of severe complications in the delayed phase of SAH[27].

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