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Review Article

The Role of Hemoglobin and Iron in Acute Brain Injury Following Aneurysmal Subarachnoid Hemorrhage

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Abstract

SAH is a severe disease with a high mortality rate, especially within the first few days following hemorrhage. The treatment of SAH remains one of the major challenges, and a specific therapy is still not available. In addition to abrupt increase in intracranial pressure and simultaneous fall in cerebral blood flow leading to cerebral ischemia, extensive accumulation of subarachnoid hemoglobin and iron may play an important role in early brain injury following SAH. Acute therapy with an iron chelator could be a useful adjunct in the treatment of SAH.

ABBREVIATIONS

SAH: Aneurysmal Subarachnoid Hemorrhage; HO: Heme-Oxygenase; ICH: Intracerebral Hemorrhage; DFO: Deferoxamine; TUNEL: Terminal Deoxynucleotidyl Transferase-Mediated dUTP Nick End-Labeling

INTRODUCTION

Since first clinical presentation of ruptured intracranial aneurysm in a young woman by Blackall in 1813 [1], subarachnoid hemorrhage (SAH) still continues to represent a significant cause of morbidity and mortality throughout the world. SAH is usually caused by spontaneous rupture of an aneurysm of cerebral artery affecting approximately 30.000 people annually [2]. Despite improvement of functional outcomes due to early aneurysm occlusion together with aggressive management of complications such as hydrocephalus and delayed cerebral ischemia, population-based mortality rate is still as high as 45% with significant morbidity among survivors [3].

Early brain injury has been shown to be the principal cause of mortality from SAH. Approximately 30% of patients with aneurysmal SAH die within the first few days [4] and postmortem examinations in such cases showed extensive brain damage [5]. It has been suggested that a sudden rise in intracranial pressure and fall in cerebral blood flow leading to global cerebral ischemia may play an important role. However, the exact underlying injury mechanisms during this early period following SAH have not been fully identified [6]. Therefore, no effective treatment is available, and therapeutic options are greatly limited to maintenance of vital parameters and reduction of intracranial pressure through insertion of ventricle drainage in the case of posthemorrhagic hydrocephalus.

Since publication of a review article about "early brain injury" following SAH by Cahill [6], there has been an increasing interest in the mechanisms of secondary brain injury during acute phase [7]. Among various mechanisms for the secondary brain injury, subarachnoid blood clot and degradation products of red blood cell may additionally trigger cellular and molecular responses resulting in secondary brain injury. In this review, we discuss the hemoglobin and iron-mediated mechanisms of secondary brain injury as a result of subarachnoid blood accumulation and potential therapeutic targets.

SUBARACHNOID BLOOD

It is well known that the amount of blood released during SAH correlates with neurological deficits and poor clinical outcome [8]. With rupture of a cerebral aneurysm, a large amount of hemoglobin is released into the subarachnoid space. Using three-dimensional computed tomography, a mean hemorrhage volume of 44 ml was found in patients with aneurysmal rupture on admission [9], i. e. subarachnoid hemoglobin concentration might reach approximately 6-7 g. In an endovascular perforation rat model of SAH, the amount of subarachnoid hemoglobin was estimated as 9.9±3.0 mg [10]. Blood released into the subarachnoid space clots almost immediately and clot lysis starts early with oxyhemoglobin and xanthochromia present in cerebrospinal fluid within a short time [11]. Moreover, Turner [12] showed that subarachnoid hemoglobin could distribute rapidly over the entire brain and penetrate easily into the deeper layers of the cortex within a few hours.

PATHOPHYSIOLOGY OF NEURO-GLIAL CELL INJURY

Matz [13] showed apoptotic cell death following subarachnoid exposure of hemolysate over the parietal cortex. Moreover, *in vitro* studies have revealed that exposure of neocortical cell cultures to human hemoglobin resulted in widespread neuronal cell death in dependence on concentration [14,15,16]. demonstrated that local injection of lysed red blood cells into the basal ganglia of rats caused marked brain edema formation within 24 h. Furthermore, depression of cortical activity as well as occurrence of cortical spreading depolarization upon placement of blood or blood products in the subarachnoid space was observed possibly leading to cerebral infarction [17,18].

Hemoglobin is degraded in brain parenchyma by heme-oxygenase (HO) into carbon monoxide, biliverdin and iron [19]. Following SAH-induction in rats, a significant increase in HO-1 expression was shown in the basal part of brain as a result of intraparenchymal hemoglobin overload after lysis of subarachnoid erythrocytes and subsequent penetration of hemoglobin into the adjacent brain tissue [20]. Whether HO-1 is beneficial or detrimental in cerebral injury is still unclear [19]. Although overexpression of HO-1 might protect neurons from oxidative injury [21], inhibition of HO has been associated with attenuation of perihematomal brain edema [22].

Iron is an essential element important for neuronal development, myelination and synthesis of neurotransmitters [23]. Under physiological conditions, iron is normally bound by transport proteins. The majority of iron is found in the major oxygen-carrying heme proteins and hemoglobin. The remainder non-heme iron is bound to circulating transferrin and intracellular storage proteins in glial cells, mostly to ferritin [23]. However, free iron can react with H_2O_2 and O_2^- to form hydroxyl radicals (OH•) in a sequence of Fenton or Haber-Weis reactions leading to cellular injury [23]. Nakamura found an increase in markers of DNA damage in perilesional area following intracerebral infusion of ferrous iron in rats, suggesting that iron-mediated oxidative stress contributes to DNA damage and brain injury after ICH [24]. The degree of brain lesion correlated directly with regional iron concentration [25]. In a recent experimental study of SAH, a significant increase in non-heme iron concentration was detected in the basal part of brain leading to increased expression of iron handling proteins, especially ferritin which is responsible for storing excess iron intracellularly to avoid free radical productions from free iron. However, the excessive accumulation of non-heme iron induced significant increase in DNA damaged neuronal cells. Additionally, cellular overload with ferritin was found to initiate both autophagic and apoptotic changes in neuro-glial cells [10]. Furthermore, many studies have reported an important role of iron in supporting the generation of reactive oxygen species which affect blood-brain-barrier permeability by activation of matrix metalloproteinases leading to degradation of vascular basement membrane collagen and modulation of tight junction protein complexes [22].

THERAPEUTIC OPTION USING IRON-CHELATOR

Deferoxamine is an iron chelator in clinical use for treatment of acute iron intoxication and chronic iron overload due to transfusion-dependent anemia that has a very high affinity for ferric iron inhibiting hydroxyl radical formation. Following s.c. administration (100 mg/kg SC) in rats, DFO accumulates rapidly in the brain reaching high concentration (between 100 - 200 μmol/L) within the first hour [25]. Treatment with DFO or phenanthroline effectively attenuated the production of reactive oxygen species and neuronal death induced by adding hemoglobin to mixed neuronal/astrocyte cell cultures [15]. Several studies have demonstrated that the treatment with DFO after experimental ICH reduced significantly hemoglobin-induced brain edema, neuronal death, neurological deficits and brain atrophy [25-30]. Recent study has demonstrated that treatment with DFO after SAH in rats reduced significantly oxidative cell injury as well TUNEL-labeled cell death [20]. Several mechanisms underlying neuroprotective functions of DFO have been proposed. These include chelation of the unbound labile iron responsible for catalyzing the production of reactive oxygen species, and the subsequent modulation of gene expression including the HIF-1α, preventing apoptosis induced by glutathione depletion and oxidative stress by activating signal transduction pathway leading to activation of transcription factor 1/cAMP response element-binding protein (ATF-1/CREB) and expression of genes known to compensate for oxidative stress, and blocking neurotoxic effects of hemoglobin through inhibition of glutamate-mediated excitotoxity [20]. These promising data have led to a clinical phase I trial with DFO in patients with ICH [31]. The study showed that infusions of DFO after ICH are feasible, well tolerated, and not associated with serious adverse events or mortality. A phase II trial to look at patient outcome has been initiated. Minocycline, which also chelates iron, prevented the neuronal death induced by ferrous sulfate in cortical cultures [32] and attenuated brain edema, brain atrophy, and neurological deficits in rat models of ICH [33]. Due to concomitant anti-inflammatory effect, minocycline may additionally represent an attractive therapeutic agent for SAH. Further studies are under way.

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