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Oxidative stress in subarachnoid haemorrhage: significance in acute brain injury and vasospasm

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Summary

Aneurismal subarachnoid haemorrhage (SAH) is a devastating disease that is associated with significant morbidity and mortality. The mortality is approximately 50%, with 30% of survivors having significant morbidity. There is substantial evidence to suggest that oxidative stress is significant in the development of acute brain injury and cerebral vasospasm following SAH. There are several sources for the excessive generation of free radicals following SAH, including disrupted mitochondrial respiration and extracellular hemoglobin. There is also the upregulation of free radical producing enzymes such as inducible nitric oxide synthase (iNOS), xanthine oxidase, NADPH oxidase (NOX), as well as enzymes involved in the metabolism of arachidonic acid. Additionally, intrinsic antioxidant systems such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) are inhibited. Experiments have linked free radicals to the apoptosis of neurons and endothelial cells, BBB breakdown and the altered contractile response of cerebral vessels following SAH. Antioxidant therapy has provided neuroprotection and antispasmotic effects in experimental SAH and some therapies have demonstrated improved outcomes in clinical trials. These studies have laid a foundation for the use of antioxidants in the treatment of aneurismal SAH.

Keywords

Subarachnoid haemorrhage; oxidative stress; acute brain injury; cerebral vasospasm

Introduction

Spontaneous rupture of a cerebral aneurysm gives rise to subarachnoid haemorrhage (SAH), a disease that carries significant morbidity and mortality, and affects a significant percentage of the population worldwide. Autopsy studies show that roughly 5% of the population harbors intracranial aneurisms and 10/100,000 people suffer from aneurismal SAH [72]. SAH carries an initial mortality of 15–20% and a 40% mortality at one month with roughly one-third of survivors harboring significant morbidity in the form of cognitive and/or motor deficits [95, 96]. Research has concentrated primarily on vasospasm and its sequelae, in an attempt to combat the high morbidity and mortality associated with SAH [43]. More recently, treatment modalities have also focused on acute brain injury following SAH, as this has also been linked to significant morbidity and mortality [11]. The mechanisms of acute brain injury are still

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poorly understood and the study of vasospasm has still not yielded a therapy that effectively eliminates the problem. Many studies have provided evidence that oxidative stress plays a significant role in the processes of acute brain injury as well as cerebral vasospasm, and these will be reviewed in this paper. Normal mammalian cellular respiration results in the production of free radicals, and the brain, as a result of its high metabolic demands, is especially susceptible to free radical injury when cellular respiration becomes disrupted. An imbalance that favors the production of reactive oxygen species (ROS) versus their neutralization by intrinsic antioxidant systems has been demonstrated in the brain following SAH in both experimental models and humans [23,46,64,66], and the most common free radicals involved in oxidative stress are superoxide anion, hydroxyl radical, nitric oxide, and peroxynitrite [98]. This mini-review will discuss the production of excessive free radicals in SAH and their connections to acute brain injury as well as cerebral vasospasm.

Sources of free radicals in subarachniod haemorrhage

Mitochondrial oxidative stress

The foremost considered sources of free radicals following SAH are the leakage of superoxide anions from mitochondria due to an ischemic disruption of the electron transfer chain, and the cascade of free radicals produced from the auto-oxidation of hemoglobin [1,64,68]. Electron transfer during normal mitochondrial respiration is accompanied by the leakage of electrons from the transport chain and their subsequent reaction with O_2 to produce superoxide. This free radical is normally cleared by superoxide dismutase, but following periods of ischemia, such as those that follow SAH [9,28,40], the mitochondria becomes a source of excessive free radical production that cannot be cleared by antioxidant enzymes before they have the potential of causing significant lipid, protein, and DNA damage [19]. The mechanisms for ROS production by mitochondria are under intensive investigation, but in general, the production of reactive oxygen species is maximal when the components of the transport chain are maximally reduced [78,80]. Excessive mitochondrial Ca^{2+} accumulation following ischemia interrupts the electron transport chain and collapses the mitochondria membrane potential by formation of the membrane permeability transition, which represents the opening of nonspecific pores allowing solutes of less than 1500 daltons to equilibrate across the membrane. Opening the high-conductance pore induces a maximal rate of substrate oxidation and O_2 consumption in an attempt by the mitochondria to establish an electrochemical gradient, leaving more free electrons to interact with oxygen and create superoxide [78,80,122]. Specific investigations into mitochondrial activity following SAH have found disrupted mitochondrial respiration that favors the production of ROS [7,63,65]. Marzatico and Baena *et al.* have each recorded increased levels of state 4 mitochondrial respiration and decreased respiratory control ratios following SAH [7,65], a state that is associated with the increased production of ROS. Future approaches to inhibiting the excessive generation of mitochondrial ROS in SAH include the uncoupling of the electron transport chain and the inhibition of membrane permeability transition.

Hemoglobin free radical generation

The liberation of oxyhemoglobin (oxyHb) into the CSF following SAH is a major producer of superoxide anion ($O_2^{\bullet}$) and hydrogen peroxide (H_2O_2) as it undergoes auto-oxidation to methemeglobin [3]. The iron or ferrous ion liberated from oxyHb then catalyzes the generation of the more damaging hydroxyl radical ($OH^{\bullet}$) from $O_2^{\bullet -}$ and H_2O_2 (metHb) [30,33,75]. Methemoglobin and oxyhemoglobin react with hydrogen peroxide to generate ferrylhemoglobins (Fe^{4+}), which is also a strong oxidizing agent [26]. Ferryl haeme protein can initiate a cycle of lipid oxidation which can react with further lipids in an auto-catalytic cycle [90]. Many studies demonstrate the oxidizing capacity of hemoglobin on lipid membranes, proteins, and DNA [26,91,94]. Subarachnoid hemolysate also increases

cytochorome c mediated DNA fragmentation and apoptosis in mouse brains [69,71]. This damage correlates inversely with superoxide dismutase expression, implicating free radicals in the mechanism [69–71]. Studies have also linked hemoglobin generated free radicals to vasospasm and have found iron chelators to successfully inhibit vasospasm [1,2,37,38,114]. Iron chelation has not been studied in the acute brain injury of SAH, but it is worth investigating because hemoglobin free radial production has been linked to neuronal cytotoxity [10,107, 116] and damage to vascular endothelium [26]. Iron chelators have also shown neuroprotection in other CNS injuries [92].

Enzymatic sources of free radicals

In addition to the mitochondria and hemoglobin, a number of other enzymatic pathways to free radical production have been investigated. The accumulation of intracellular Ca^{2+} in neurons through voltage-sensitive and glutamate-sensitive channels due to the extracellular hemoglobin and the substantial ischemic insult of SAH [9,28,40] has been found to produce free radicals through the activation of several pro-oxidant pathways: phospholipases, xanthine oxidase, and nitric oxide synthase.

Esterified arachidonic acid (AA) is released through the breakdown of membrane phospholipids by phospholipase A2 activity. AA is metabolized by cyclooxygenase, lipoxygenase, and cytochrome P450. Each of these pathways produces $O_2^{\bullet -}$ as a byproduct [17,122]. This mechanism of free radical production is considered a significant source of free radicals in models of traumatic brain injury and ischemia [17,25,79,89,122], and may also be a significant source of free radicals in subarachnoid haemorrhage. Neuronal cell culture studies suggest that the cellular damage mediated by AA metabolism is through free radicals, as antioxidants were able to prevent AA induced damage [45,110]. Increased phospholipase A2 activity follows SAH [107,113], and numerous studies demonstrate increased expression of cyclooxygenase [86,87,111] and lipoxygenase [6,97,102,119] following SAH. Inhibiting these pathways has been effective at reducing cerebral vasospasm, but it is unclear if reducing the oxidative stress or decreasing the eicasanoids produced by these pathways was responsible for the therapeutic effect [8,97,105]. Several studies show that cytochrome P450 is a substantial source of arachidonic acid derived metabolites and ROS in several disease processes [13], but its significance in SAH remains to be determined. Miyata *et al.* has shown that the inhibition of this enzyme following SAH reduced cerebral vasospasm in rats [76].

Xanthine dehydrogenase (XDH) is an enzyme present in cerebral endothelium and is required for the metabolism of purines to uric acid. XDH does not produce free radicals but is converted to xanthine oxidase (XO) during ischemia, hypoxia, and excitotoxity by Ca^{2+} activated proteases [83]. XO in turn catalyzes the oxidation of hypoxanthine to xanthine, resulting in uric acid, superoxide and hydrogen peroxide. XO inhibition has resulted in a reduction in oxidative damage in several ishemic brain injury models [83,118], and studies have suggested an increase in the activity of this enzyme following SAH [50,62,117]. The study of XO inhibition in SAH is limited, and there is some speculation that this pathway may not be significant owing to the many other pathways for free radical production. Kim showed that XO inhibition had no effect on free radical mediated vasospasm in dogs following experimental SAH [50].

Nitric oxide ($NO^{\bullet}$) is a free radical generated from L-arginine, NADPH and oxygen by nitric oxide synthase (NOS) which has three isoforms: endothelial NOS (eNOS), neuronal NOS (nNos) and inducible NOS (iNOS) [12,106]. Neuronal and inducible nitric oxide synthases are upregulated following SAH [99,125], and levels of $NO^{\bullet}$ metabolites are significantly elevated in the days following SAH [47,82,106]. It is debated whether the production of NO leads to either toxicity or neuroprotection. Some investigators believe $NO^{\bullet}$ might reduce toxicity by modifying the NMDA receptor response [57,58], in addition to having beneficial actions on

cerebral blood flow immediately following SAH [57,121]. Sehba and Bederson hypothesized a three phase change in cerebral $NO^{\bullet}$ levels after SAH, each with different effects on the ischemic brain that helps to explain the conflicting actions attributed to $NO^{\bullet}$. In their model, the oxidative damage caused by $NO^{\bullet}$ occurs 6 h after injury when $NO^{\bullet}$ can no longer augment blood flow. The major producer of $NO^{\bullet}$ at this time is iNOS [98]. With regards to free radical damage, it is known that once synthesized, $NO^{\bullet}$ can interact with Superoxide ($O_2^{\bullet}$) to form peroxynitrite ($ONOO^{-}$), which can also decompose to form hydroxyl radical ($OH^{\bullet -}$) [25]. $NO^{\bullet}$ and peroxynitrite are neurotoxic free radicals [15,20] which exert significant DNA and mitochondrial damage leading to cell death. [55]. Yatsushige investigated the role of iNOS inhibition in acute brain injury following SAH and found that there was no significant reduction in edema or BBB integrity [125]. In constrast, Yang *et al*. looked at increasing $NO^{\bullet}$ following SAH by the administration of its precursor L-arginine. This group found significant reductions in brain edema [124], suggesting that $NO^{\bullet}$ is neuroprotective rather than cytotoxic in acute brain injury after SAH.

NADPH oxidase is a membrane-bound enzyme expressed in neurons [100,108,109,126] which may produce superoxide anions directed toward the neuronal cell's interior [54]. NADPH oxidase has been found to directly contribute to oxidative stress and neuronal apoptosis in *in vitro* studies [108], and increased expression of neuronal NOX been associated with oxidative stress in rat models of SAH [84,85]. Increased NOX expression in cerebral vasculature has been associated with free radical mediated vasospasm following SAH, and NOX inhibition in these studies was found to prevent arterial contraction and improve cerebral blood flow [49, 74,88,103,104,127]. Neuronal NOX activity in acute brain injury after SAH has been conducted more recently. Ostrowski *et al*. found that the neuroprotection provided by hyperbaric oxygen in SAH involves the reduction of neuronal NOX and associated free radical mediated cell damage. These reductions in NOX activity were associated with significant reductions in mortality, neurological deficits, and neuronal cell death [84,85]. Significant reductions in acute brain injury and neurological deficits were also observed in NOX knockout mice following intracerebral haemorrhage [109], but the direct inhibition of NOX in SAH has not been studied.

Disrupted antioxidant protection

In the brain there are several enzymatic protective systems that are in place against free radical production, and during normal cellular respiration, superoxide dis-mutases, glutathione peroxidases, and catalases are the significant enzymatic scavengers in brain tissue [56]. However, following SAH these enzymatic systems become downregulated or modulated in a way that reduces their antioxidant capabilities [21,23,56,64]. Decreases in the activity of Zn and Cu–SOD have been demonstrated following SAH in rats [21,64], and investigation of human SAH has shown significant increases in the ratio of SOD/GSH-Px activity. Under normal physiological conditions, hydrogen peroxide (H_2O_2) is produced from $O_2^{\bullet -}$ by SOD which is scavenged by GSH-Px, preventing the formation of the potent $OH^{\bullet -}$ free radical [17,23,34]. However, an increase in SOD activity relative to GSH-Px activity creates a state of excess $OH^{\bullet -}$ production. An increase in the SOD/GSH-Px activity ration following SAH correlates with the incidence of vasospasm [23] and has the potential of being a significant source of free radical mediated damage.

Free radical mediated acute brain injury

At a cellular level, free radicals lead to neuronal damage by promoting, lipid peroxidation, protein breakdown, and DNA damage that in turn leads to cellular apoptosis, endothelial injury, and blood brain barrier (BBB) permeability [17,56,69,71]. Lipid peroxidation of cell membranes can lead to the formation of many lipid peroxides altering membrane fluidity and permeability [17,56,69,71]. Protein oxidation affects the functions of enzymes and cell

receptors. Free radicals can also initiate apoptotic cascades or send the cells into necrosis through mitochondrial mediated mechanisms [18,81]. Oxidative stress has been shown to induce apoptosis by increasing p53, inducing cytochrome c release and activating caspase-9 and caspase-3 [18]. Other studies have shown oxidative stress to activate p38 mitogen-activated protein (MAP) kinase and signal-regulated kinase (ERK) mediated apoptosis [81]. Reductions in oxidative stress have been shown to inhibit apoptosis. SOD overexpression in transgenic rats has shown significant reductions in apoptosis following experimental SAH [16,69], and this reduction may be mediated by the activation of the Akt/glycogen synthase kinase-3β survival pathway [16]. Other studies show the efficacy of the systemic administration of antioxidants in SAH. Imperatore *et al*. and Germano *et al*. showed that nicaraven, a hydroxyl radical scavenger, improved neurobehavior following SAH. Turner *et al*. showed that the administration of tirilazad-like antioxidants U101033E and U74389G prevented the induction of heat shock proteins in the brain following SAH [24,39,112]. Endothelial cells are also susceptible to oxidative stress [26,36,61,107], and oxidative stress has been shown to disrupt the BBB in various CNS injuries [29,36,101] while free radical induced BBB breakdown is likely to be important in SAH. Antioxidant therapy has been shown to protect the BBB in several animal models [24,32,39,128].

Oxidative stress and vasospasm

Vasospasm is a frequent complication of subarchnoid haemorrhage and is critical to the prognosis of patients following SAH [59]. There are still many unanswered questions about the pathogenesis of cerebral vasospasm following SAH, and effective therapies are still being sought. Evidence suggests that oxidative stress is one of the factors contributing to post-hemorrhagic vasospasm [21,48,60]. Elevated superoxide anion levels in the cerebrospinal fluid after SAH have been reported to correlate to cerebral vasospasm [77]. Free radical scavengers such as iron chelators, ebselen, tirilazad, nicaracen, and inhibitors of free radical generating enzymes have been shown to reduce cerebral vasospasm in animal models of SAH [8,22,35, 38,41,42,67,73,114,115,120,127,129]. Oxidative stress stimulates the proliferation and hypertrophy of smooth muscle cells [27], and induces endothelial apoptosis. These alterations are associated with changes in the contractile response of the cerebral vasculature. Maeda *et al*. showed that isolated strips of the bovine middle cerebral artery exposed to oxidative stress inhibited bradykinin-induced endothelium-dependent relaxation [61]. These contractile changes were prevented by free radical scavengers, as well as by the inhibition of either p38 MAP kinase or tyrosine kinase. It is also likely that the lipid peroxidation of phospholipids is connected to the production of diacylglycerol and the subsequent activation of protein kinase C (PKC), a key element to the mechanism of smooth muscle contraction [4]. Investigation continues to further elucidate how oxidative stress alters cerebral vascular contractile responses.

Clinical implications and future directions

Given the numerous sources of free radical production and evidence of significant oxidative stress in SAH, there is substantial support for the use of free radical scavengers for the treatment of brain injury and cerebral vasospasm in this disease. Many free radical scavenging compounds have been tested in clinical trials for the treatment of SAH with variable results. Ebselen is an organic antioxidant which poses glutathione peroxidase-like activity, has been successful at reducing vasospasm in animal models [35,120], and has modest effects in clinical trials. Although ebeselen adminstration within 96 h of SAH failed to show differences in Glasgow Outcome Scale (GOS) versus the control, subgroup analysis showed that patients with delayed ischemic neurological deficits (DINDS) had better outcomes with treatment [93]. Tirilazad mesylate is another free radical scavenger with pre-clinical success, but this drug failed to demonstrate efficacy in clinical trials. Four randomized controlled trials, two

conducted across Europe, Australia, and New Zealand, and two in North America, failed to consistently show improvements in mortality, GOS, or symptomatic vasospasm [31,44,52, 53]. Nicaraven, or AVS ((+/−)-*N*, *N*′-propylenedinicotinamide), a synthetic compound capable of scavenging hydroxyl radicals, has prevented vasospasm shown neuroprotective properties in experimental SAH [24,39,123]. Nicaraven treatment also demonstrated a significant reduction in symptomatic vasospasm and cumulative mortality in a randomized controlled trial [5]. In summary, the results of clinical trials with antioxidants have been mixed, but the potential for therapeutic efficacy still exists and is worth investigating. The failure of antioxidants in clinical trials may be attributed to the fact that oxidative stress is only one parameter of the injury. It is also possible that inappropriate dosing, or the severity and heterogeneity of the brain injury made it difficult to obtain statistically significant results. However, it is more likely that antioxidant therapy will be most effective as one component in a treatment regime that addresses the many pathways to brain injury and vasospasm following SAH.

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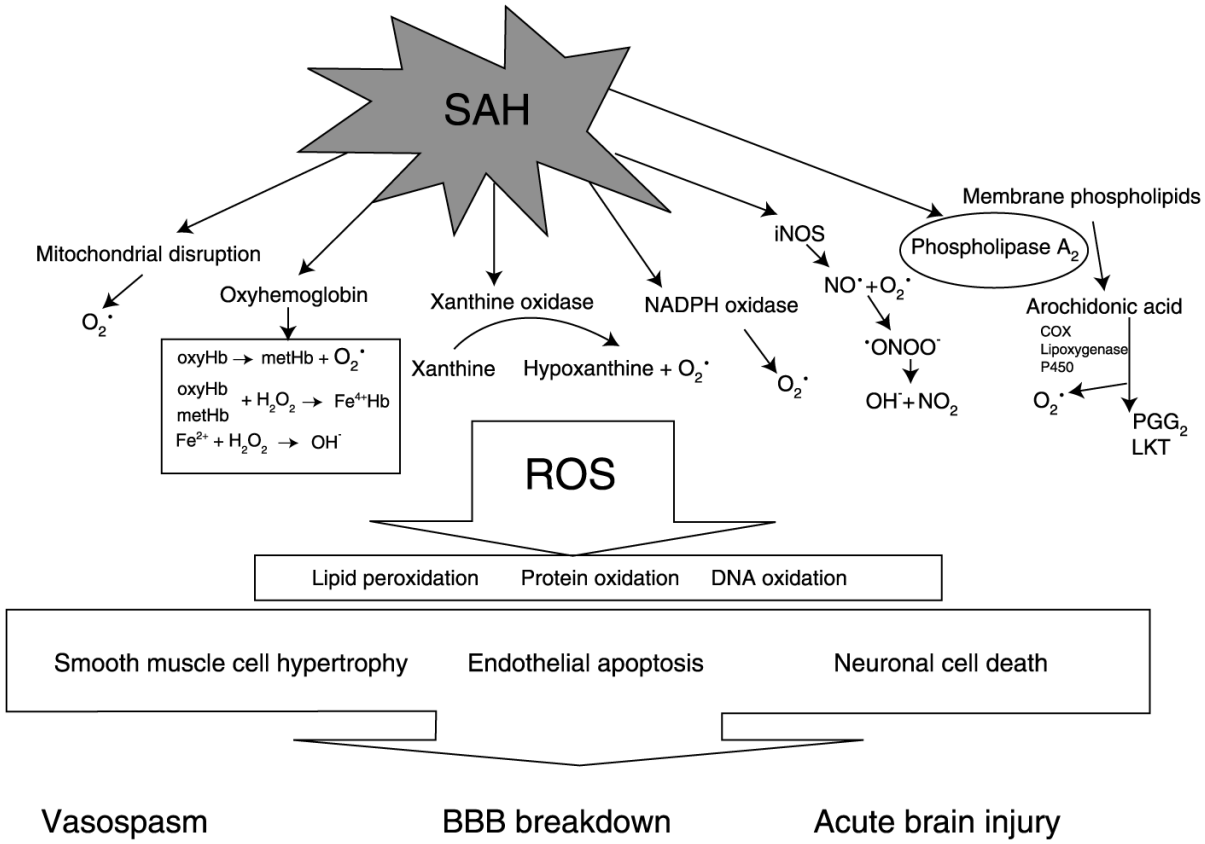

Fig. 1.
Schematic representation of major intracellular pathway in the generation of reactive oxygen species radicals in subarachnoid haemorrhage. *ROS* Reactive oxygen species; *SAH* subarachonoid haemorrhage