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Review

Mechanisms of Mitochondrial Oxidative Stress in Brain Injury: From Pathophysiology to Therapeutics

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Abstract: Mitochondrial oxidative stress has been implicated in various forms of brain injury, both traumatic and non-traumatic. Due to its oxidative demand, the brain is intimately dependent on its mitochondrial functioning. However, there remains appreciable heterogeneity in the development of these injuries regarding ROS and their effect on the sequelae. These include traumatic insults such as TBIs and intracranial hemorrhaging secondary to this. In a different vein, such injuries may be attributed to other etiologies such as infection, neoplasm, or spontaneous hemorrhage (strokes, aneurysms). Clinically, the manner of treatment may also be adjusted in relation to each injury and its unique progression in the context of ROS. In the current review, then, the authors highlight the role of mitochondrial ROS in various forms of brain injury, emphasizing both the collective and unique elements of each form. Lastly, these narratives are met with the current therapeutic landscape and the role of emerging therapies in treating reactive oxygen species in brain injuries.

Keywords: mitochondrial oxidative stress; reactive oxygen species; brain injury; traumatic brain injury

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1. Introduction

Mitochondrial oxidative stress has been implicated in an array of pathologies and afflictions, namely injuries of the central nervous system (CNS). As a central organ, the brain is acutely dependent on the metabolic role of oxygen to function [1]. With this, it is also sensitive to the malignant consequences of oxidative damage in the setting of injury and pathology. These events typically occur following the acute demonstration of injury, manifesting clinically later than the initial event, often hours to days after. The core reactive oxidative species (ROS) are the superoxide anion ($O_2^{\cdot -}$), hydroxide radical ($OH^{\cdot}$), and hydrogen peroxide (H_2O_2). These are intricately related to other elemental species such as reactive nitrogen species (RNS), including peroxynitrite ($ONOO^-$), nitric oxide ($NO^{\cdot}$), among others, in their ability to react with each other forming highly noxious compounds [2–5]. These events include lipid peroxidation of polyunsaturated fatty acids within lipid membranes, and unintended interactions with nucleic acids and proteins [5]. The body has developed defense and repair mechanisms to alleviate the pathologic overburdening of such elements. These endogenous mechanisms broadly include antioxidizing enzymes and small molecules, and secondly, repair mechanisms to mitigate damage. The antioxidant enzymes include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) with low-molecular weight compounds being glutathione (GSH). Damage control mechanisms include DNA repair, ubiquitin-proteasome, and lipase systems. Nonetheless, disease can manifest in the likelihood that these systems are unable to counteract abnormal production of ROS. Excitotoxicity is an initial major proponent of this cascade, catalyzing a slew of events—N-methyl-D-aspartate (NMDA) binding, depolarization and exacerbated ion flux (particularly Ca^{2+}) promoting mitochondrial ROS release and acidosis, along with immunopathology such as neutrophil ROS release [5]. Overall, this progression

is tightly intertwined from the gross initial injury up until the sequence of degeneration at the molecular level.

Broadly, injuries of the brain can be separated into non-acquired and acquired brain injuries (ABI). ABIs differ from non-ABIs primarily in the timeline of onset, with some distinguishable characteristics regarding the mechanism of injury (MOI) or nature of illness (NOI). ABIs are those injuries generally occurring following the postpartum period, with other criterion designating this distinction after the 6-month mark following birth—the primary matter of these discrepancies being that injuries not immediately after birth fall within the category of ABIs [6]. Non-ABIs, then, are those that share an infliction in the gestational period of development, or immediately after birth, for the most part during the immediate event of delivery itself [7,8]. Mechanistically, non-ABIs can involve traumatic, physical forms of damage or derive from molecular impairments such as hypoxia or vascular disturbances. Likewise, ABIs originate in either manner also with traumatic circumstances comprising the majority of these injuries (Figure 1).

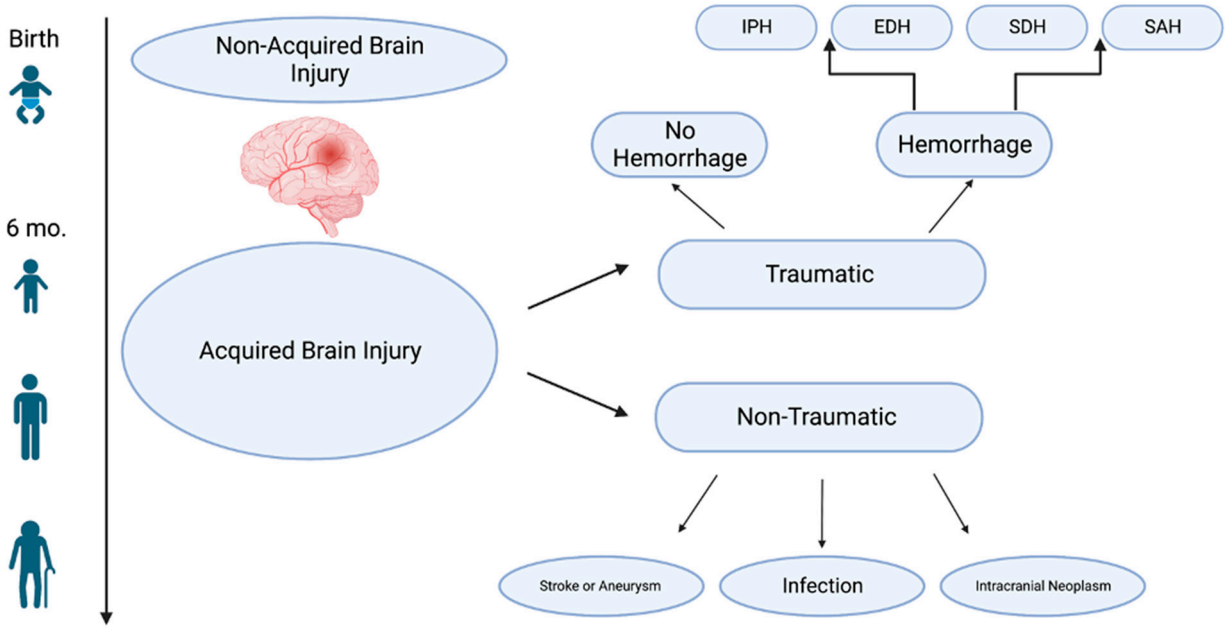

Figure 1. Overview of brain injury classification and pertinent timeline. IPH (intraparenchymal hemorrhage); EDH (epidural hemorrhage); SDH (subdural hemorrhage); SAH (subarachnoid hemorrhage).

ABIs, as discussed, can be separated into traumatic events and non-traumatic events. The former includes blunt injuries, penetrations, and collisions that may commence traumatic brain injuries (TBIs) [5]. This can be exacerbated in the setting of intracranial hemorrhaging following TBI such as subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), or intraparenchymal (IPH). Spontaneous, non-traumatic events include strokes, aneurysms, infections, and intracranial neoplasms. In this review, the authors seek to cohesively organize the present knowledge of the role of mitochondria and their oxidative species in injuries of the brain. This will be described in the context of acquired brain injuries, both traumatic and non-traumatic, and be precluded by the general pathophysiology of each injury before digressing towards oxidative stress. Lastly the review will divulge on the current realm of therapeutics, ongoing developments, and their future trajectories.

2. Traumatic Brain Injury

Traumatic brain injuries (TBI) can be attributed to various means such as penetrating, blunt, or explosive-related mechanisms. These injuries comprise the first stage of TBI-related pathophysiology—primary injury [9]. Primary injury involves the consequences immediately following afflicting forces, often causing gross, structural changes towards

the brain. These can involve either focal or diffuse damage, of which focal damage is mostly attributable to the immediate and direct impact and force [2]. Diffuse damage, while still comprising the primary injury stage, is the result of contact damage generated by acceleration–deacceleration shearing forces; the impact of the initial force can be translated to distal regions of the point of contact through various media such as cerebrospinal fluid [10]. Secondary injuries of the brain most often involve delayed processes hours to years following primary injury, clinically manifesting along this same timeline. The processes underlying secondary injury involve molecular and biochemical sequelae that are the key contributors to lifelong repercussion and morbidities associated with TBIs.

As discussed, mechanical force is the principal agent for primary injury. These may present as bruising of gross brain matter, hematomas which can be categorized by region of affliction. Epidural hematomas occur within the space between the dura and calvarium. Subdural hematomas occur between the layers of the dura mater and arachnoid mater and subarachnoid hematomas between the arachnoid and pia mater. Hemorrhaging may exist in more severe forms of TBI, likewise classified by their region of occupation; intracerebral hemorrhage is confined to the parenchyma, deep to the meninges of the brain [11]. The potential occurrences of hematoma and hemorrhage will be discussed in further sections. Regardless, the primary injury often results in gross structural damage accompanied by underlying neuronal and glial cell damage, and consequential necrosis. This is comprised of many events at the cellular level encapsulated in the stages of secondary injury.

Many of the events in secondary injury of TBIs can be visualized as a positive feedback loop, with others occurring in a more linear sequence. It is important to highlight this concurrent chronology, as one event often exacerbates another. Non-oxidative insults are closely linked to ROS related insults—these include release of apoptotic elements from mitochondria during progression, such as caspases and calpains. Furthermore, neuroinflammation occurs simultaneously in the setting of injury causing release of pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6 [5]. Inflammation increases vascular permeability, lowering the integrity of the blood–brain barrier (BBB), a contributor to excitotoxicity, following which vasogenic edema ensues [12].

Though ROS production is not limited to the mitochondria alone, the metabolic significance of the mitochondria makes it particularly profound in ROS exacerbation following injuries. Indeed, the role of the mitochondria in TBI is particularly unique based on its volume within neuronal cells as necessitated by the metabolic requirements of the CNS [1]. The aforementioned consequences upon release of apoptotic factors, ROS, and RNS occur within the secondary injury initiated upon insult. The common reactive oxygen species responsible for injury following TBI include $O_2^{\cdot -}$, $OH^{\cdot}$, H_2O_2. Their presence induces tissue damage in the form of events such as lipid peroxidation, and DNA and protein damage. The ROS are joined by the lethal effects of RNS, effectively responsible for similar consequences such as macromolecule damage—these include lipid peroxidation and protein nitration [13]. In particular, protein nitration is facilitated by both $ONOO^-$ and nitric oxide (NO_2), of which the former is directly produced when coupled to $O_2^{\cdot -}$.

Regarding the further role of oxidative species, excitotoxicity is driven by a weakening in the integrity of the BBB as previously mentioned. This results in an abnormal presence of neurotransmitters, such as aspartate and glutamate, and ion flux. Glutamate, a key excitatory neurotransmitter of the CNS, plays a key role binding to three classes of ligand-gated ion channels [receptors]—NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), and kainic acid receptors [14]. NMDA binding results in depolarization of the mitochondria, typically due to Na^+, K^+, and to a lesser degree Ca^{2+}, to a pathological extent in brain injury. Exacerbated Ca^{2+} mitochondrial influx results in overgeneration of ROS and other metabolic impairments in oxidative phosphorylation of the electron transport chain (ETC). Mitochondrial damage lends itself to mitochondrial permeability transition pore (mPTP) opening, which further exacerbates ROS leakage into extracellular spaces, systemizing the toxicity of mitochondrial ROS (damaging neighboring mitochondria and harming the cell as a whole) [15]. In summary, it is the primary, traumatic insult which

initiates inflammation in the setting of necrosis and apoptosis. Inflammation is followed by increased vascular permeability—in the setting of brain injuries, this is particularly detrimental to the function of the BBB. Decreased restraint in chemical flow through the BBB induces an imbalance in ions creating excitotoxicity. It is this excitotoxicity that creates aberrant depolarization of the mitochondria and release of ROS which exacerbates other physiological processes creating a positive feedback loop [3].

Natural oxidative control systems of the CNS include excitatory amino acid reuptake transporters, excitatory amino acid reuptake transporter 1 (EAAT1) and EAAT2 receptors concentrated in glial astrocytic cells [16]. Downregulation of these transporters and stunted activity have been demonstrated in astrocytes undergoing oxidative stress [17,18]. Direct regulators of antioxidant production include enzymes such as SOD, catalase, and thioredoxin, among others, in addition to low-molecular-weight antioxidants (e.g., GSH·, selenium, Coenzyme Q10) [19,20]. These antioxidants regulate oxidative species, explicitly dampening their volume through various chemical mechanisms. For example, GSH and catalase diminish ROS levels by facilitating the reduction of H_2O_2 into water [13]. This reaction is preceded by the conversion of $O_2^{\cdot -}$ to H_2O_2 via SOD. Furthermore, living systems appear to modulate antioxidant enzyme levels through neurotrophin growth factors, namely nerve growth factor (NGF). Specifically, NGF has been observed to increase SOD, GSH, and CAT following intraventricular infusion in rat models [21]. NGF and peptide mimics have also exhibited regenerative neuronal capacity, restoring injured cerebral tissue density, including within cholinergic neurons, post-TBI [22,23]. More recently, NGF has displayed utility within human patients, imparting marked improvement in clinical symptoms and upon radiographic assessment [23]. Damage control mechanisms include the ubiquitin–proteasome system for degrading defective, ROS-damaged proteins. These proteins are conjugated with ubiquitin and consequentially degraded by the 26S unit of the complex. Repair outlets are likewise comprised of general protective mechanisms such as base excision repair for substances such as 8-oxo-7, 8-dihydro-29-deoxyguanosine [24].

Current therapeutics in the realm of TBI involve several different classes of treatments—each targeting a specific form of pathology in the stage of secondary injury. Antagonists to two classes of receptors have exhibited potential utility. Non-competitive antagonists such as HU-211 and SNX-111 work by blocking NMDA and calcium channels, respectively, thereby mitigating sources of oxidative stress [25]. HU-211 has demonstrated effective control of hemodynamic parameters, such as cerebral perfusion and intracranial pressure, in those with head injuries in various clinical trials [26]. Cyclosporine A has also been explored with respect to its utility for mitigating oxidative damage following TBIs. It is a regulator of mPTP that acts by binding to sites on Cyclophilin-D (CypD), proteins comprising the mitochondrial matrix, regulating flux through the mPTP [27,28]. More established therapies have focused on targeting sequences within the inflammatory cascade, thereby protecting the integrity of the BBB. These have included non-steroidal inflammatory agents (NSAID) such as ibuprofen or indomethacin. NSAIDs possess capacity to reduce cyclooxygenase production, consequently decreasing thromboxane, prostaglandin, and their inflammatory effects [29]. Furthermore, a multitude of dietary substances have exhibited multiple antioxidant mechanisms to protect against ROS damage. Though the discussed list is not extensive, it is meant to emphasize the protective contribution of dietary sources—these include resveratrol, alpha-tocopherol (vitamin E derivative), and carotenoids. Resveratrol, prominently found within the skin of red grapes, has been associated with a decrease in NO while simultaneously increasing GSH. Alpha-tocopherol is found abundantly within vegetable oils and nuts. Its administration has been observed to decrease levels of malondialdehyde (MAO), a marker of lipid peroxidation secondary to oxidative stress, while increasing levels of SOD in a different experiment. Carotenoids, commonly found in plants, include specific subtypes. In particular, the presence of astaxanthin has been seen in association with reduced BBB permeability and inflammatory factors such as NF-kB. Similar results were likewise observed in experiments involving other carotenoids such as fucoxanthin, bexarotene, and crocin.

3. Traumatic Intracranial Hemorrhage

Intracranial hemorrhages are devastating conditions that refer to bleeding within the brain parenchyma or surrounding meningeal spaces [30]. Four broad types of hemorrhage are encompassed within this term: epidural hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, and intraparenchymal hemorrhage [31].

Sixty-nine million individuals suffer from a traumatic brain injury yearly, with subarachnoid hemorrhages serving as the most common cause [32]. These hemorrhages are most frequently caused by trauma that injures the cortical surface vessels, resulting in bleeding into the subarachnoid space [31]. Traumatic subarachnoid hemorrhage (tSAH) may lead to increased mortality and morbidity as a result of progressive neurologic degeneration [32]. As a substantial amount of blood flows into the subarachnoid space, a series of pathological injuries occurs [33]. Evidence suggests that oxidative stress is integral to the development of acute brain injury and cerebral vasospasm following tSAH [34]. Epidural hemorrhages could either be caused by arterial or venous bleeding into the epidural space, most commonly caused by bleeding of the middle meningeal artery [31]. Around 85% to 95% of cases occur following a skull fracture [31]. Subdural hemorrhage occurs due to blood entering the arachnoid space, and most commonly follows a head trauma which causes the blood vessels between the brain and skull to break or stretch, resulting in bleeding [31]. Intraparenchymal hemorrhages can be caused by trauma, neoplasm, aneurysm rupture, hypertension, coagulopathy, and vasculitis. Hemorrhages are due to the collection of blood in the brain parenchyma [31].

Notably, cellular progression following a TBI, irrespective of hemorrhage presence, presents many similarities. The main concern after a TBI, even in the context of intracranial bleeding, is a secondary injury resulting in inflammation, cell injury, and cell death [3]. Secondary injury can be caused by an overproduction of ROS [3]. The increase in free radicals is mediated by natural antioxidants in the body, such as SOD and GSH molecules [3]. Excessive free radicals interfere with mitochondrial respiration, leading to oxidative stress and changing the redox state of cells [3,34]. Additionally, free radical producing enzymes are upregulated, and intrinsic antioxidant systems are deregulated. The generated free radicals have been correlated with neuronal and endothelial cell apoptosis and blood–brain barrier breakdown [34].

Mitochondria serve a critical role in maintaining homeostasis. However, they are also the main source of free radicals [35]. Under normal conditions, electrons leak from the transport chain and react with oxygen to create $O_2^{\cdot -}$ [35]. $O_2^{\cdot -}$ is then cleared by the enzyme SOD. This enzyme converts $O_2^{\cdot -}$ into molecular oxygen and H_2O_2 [35]. However, after a period of short ischemia, the electronegativity of the ETC is increased, resulting in a leakage of electrons, which form more ROS that cannot be cleared by antioxidant systems. ROS that is unable to be cleared has the potential to cause DNA, lipid, and protein damage [36]. If mitochondria experience minor damage, individual targets are chosen for degradation [36]. If ETC proteins are damaged, mitochondria have proteases which function to remove damaged proteins [36]. Mitochondria can also eliminate damaged proteins through the ubiquitin pathway [36]. If genotoxic damage occurs, mitochondria can target individual molecules for quality control [36]. When cells undergo metabolic stress and undergo major forms of damage, mitochondrial fission and fusion are critical for maintaining mitochondrial function [36]. Mitochondrial fission is the process by which mitochondria replicate and generate new mitochondria; however, it also serves as a quality-control mechanism for removing damaged mitochondria [36]. Mitochondrial fusion is the process by which damaged mitochondria are fused to help alleviate stress by compensating for missing components [36].

A significant number of studies have displayed evidence about the role of oxidative stress following TBIs in experimental models and human models [37,38]. Due to the brain's substantial metabolic demand, it is easily susceptible to damage by ROS when cellular respiration is disrupted [34]. An imbalance occurs where overproduction of ROS exceeds the body's antioxidant system's ability to neutralize ROS [34]. $O_2^{\cdot -}$, $NO^{\cdot}$, $OH^{\cdot}$,

and $ONOO^-$ are the most common free radicals involved [34]. A period of ischemia that follows TBI results in mitochondrial dysfunction, as electrons leak out from the ETC and react with oxygen to form $O_2^{\cdot -}$ [34]. These $O_2^{\cdot -}$ anions are unable to be cleared from the mitochondria by SOD, resulting in decreased ATP production and damage to proteins, lipids, and DNA [34]. Current research suggests that ischemia results in glutamate release into the blood, which reacts with NMDA receptors to cause Ca^{2+} accumulation in the mitochondria [39]. Excess calcium accumulation disrupts the mitochondrial ETC and causes the collapse of the mitochondrial membrane potential due to the opening of the mPTP, which allows solutes of less than 1500 Daltons to equilibrate through the membrane [40–42]. The mitochondria attempt to compensate and reestablish an electrochemical gradient by increasing oxygen consumption and substrate oxidation; however, this ultimately leads to more free electrons reacting with oxygen and producing superoxide [29]. This process also causes an increase in glucose consumption, depletion of energy stores, and a further increase in calcium influx, forming a positive feedback loop [43]. Edema and lactic acidosis follow due to impaired redox metabolism and glycolysis. Calcium overload causes loss of oxidative phosphorylation and decreased ATP production [44]. Excess calcium results in the release of cytochrome c, which activates caspase, and ultimately induces apoptosis activation [40]. Studies have been conducted that report mitochondrial respiration along with decreased respiratory control ratios following TBIs, leading to increased ROS production [38,45] (Figure 2).

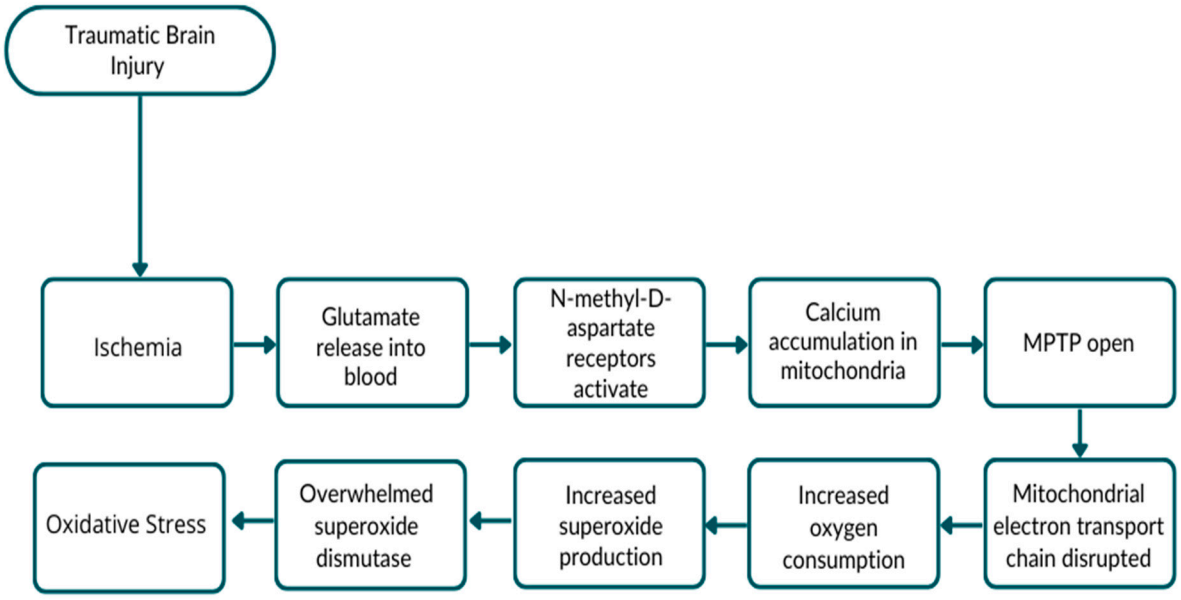

Figure 2. Mechanism of mitochondrial dysfunction leading to oxidative stress in traumatic brain injuries. MPTP (mitochondrial permeability transition pore).

Mitochondrial dysfunction occurs due to susceptibility to hypoxia and ischemic injury resulting in the release of ROS, further amplifying oxidative stress and stimulating the mitochondrial apoptotic pathway [46]. Identifying therapeutics that minimize oxidative stress and mitochondrial apoptosis is critical for improving the prognosis and management of TBIs [47]. MitoQ is an antioxidant that crosses the blood–brain barrier and can accumulate within mitochondria [43]. In a recent mouse model following TBI, MitoQ was shown to alleviate brain edema, inhibit cortical neuronal apoptosis, and improve neurologic deficits [25]. Mice demonstrated increased activity of SOD and GPx [21]. Additionally, Bax translocation and release of Cyt-c were reduced in mitochondria when MitoQ was administered, demonstrating anti-neuronal apoptosis properties [21]. Drp1, a mitochondrial fission protein, serves an important role in mitochondrial dysfunction [48]. Mdivi-1 serves as a selective inhibitor of Drp1 and can penetrate the blood–brain barrier [48]. Treatment with Mdivi-1 was shown to alleviate oxidative stress in rat models by improving neurologic

deficits, alleviating brain edema, and reducing apoptosis. Mdivi-1 also reduced expression of Drp1, inhibited excessive mitochondrial fission, and improved SOD ability. This study's data suggests that Mdivi-1 may offer neuroprotective benefits against cell death caused by tSAH [48]. Edaravone is an antioxidant drug that scavenges free radicals following an ischemic event [43]. This drug has been approved for use in acute ischemic brain injuries and for TBIs [49]. Its exact mechanism of action is unknown; however, it has been shown to decrease $NO^{\cdot}$ production, inflammation, matrix metalloproteinases activity, and cell death from apoptosis [43]. Edaravone penetrates the blood–brain barrier and suppresses free-radical-induced degeneration and death of neurons [43]. One study investigated the role of Edaravone in TBI rats and found that Edaravone improves apoptosis induction of nerve stem cells, enhancing their proliferation and vitality by activating the Nrf2/ARE signaling pathway [49]. In cells undergoing oxidative stress, Nrf2 is released and translocates to the nucleus, where it binds ARE [49]. ARE activates downstream antioxidative genes, improving antioxidative functions and decreasing cell injuries from oxidative stress. Cyclosporin A (CsA) is a small polypeptide immunosuppressant capable of specifically inhibiting the opening of mPTP [50]. Numerous studies have demonstrated the efficacy of CsA in improving mitochondrial functions following a TBI [51]. They found that CsA protects both the mitochondrial and axonal shafts, and improves cerebral perfusion pressure. Another study found that injection of CsA into rats 15 min after injury and continuous infusion reduces lesion volume and that continuous infusions extend the neuroprotective effects of CsA following a TBI [50].

Reactive nitrogen species (RNS) primarily include $NO^{\cdot}$, NO_2, and $ONOO^{-}$ [19]. Multiple enzymes such as nitric oxide synthase (iNOS), endothelial nitric oxide synthase (eNOS), cyclooxygenase (COX), xanthine oxidase (XO), and cytochrome P450 (CYP450) generate RNS [Schiavone]. RNS typically have longer half-lives than ROS and are primarily involved in causing oxidative tissue injury [52]. $ONOO^{-}$ and its derivatives can result in lipid peroxidation through the transfer of an electron from a hydrogen atom in polyunsaturated fatty acids or can also react with certain amino acids to cause protein carbonylation. Twenty-four hours after a TBI, the endothelial, neuronal, and inducible NOS isoforms are upregulated [52].

Antioxidants can also be used to reduce ROS and RNS species [53]. Two categories exist for antioxidants: hydrophilic and hydrophobic. After a TBI, SOD activity is diminished and may remain reduced for 7 days following a severe TBI. Therefore, antioxidant therapy focuses on reducing oxidative stress levels and has been found to reduce brain lesion volumes, cerebral edemas, and preventing further neurological deficits [4]. Ascorbic acid (Vitamin C) is a water-soluble antioxidant which serves as a reducing agent that interacts with diverse ROS and RNS species [54]. Studies have shown that reduced levels of ascorbic acid occur following a TBI, and that changes in ascorbic acid levels correspond to the severity of the TBI [55]. One study found that administering different doses of ascorbic acid for 2 weeks following a TBI resulted in increased activity levels of SOD and reduced mortality rate [56]. Reduced GSH plays an important role in detoxification reactions and acts as a scavenger of ROS [4]. N-acetyl-cysteine (NAC) is another scavenger of ROS and RNS that improves SOD and has been proven to be neuroprotective [57].

Neurotrophins are proteins which play a role in neural development, plasticity, and survival. Central nervous tissue destruction and cellular repair are initiated following a TBI [58]. Multiple studies have demonstrated that neurotrophins are important for mediating neuroinflammation, apoptosis, memory capacity, and blood–brain barrier permeability. New studies are currently being conducted to further elucidate the role of neurotrophins following TBI [59].

4. Ischemic Stroke

Stroke is one of the most common causes of death in the United States, claiming north of a million lives each year [60]. Globally, stroke represents the second leading cause of death, with especially high incidence reported in developing countries [61]. Precluding

syndromes for ischemic stroke (IS) include the following: middle cerebral artery infarction (involving the lateral cerebral cortex), anterior cerebral artery infarction (involving the medial cerebral cortex), posterior cerebral artery infarction (involving deep and superficial structures of the posterior brain), vertebrobasilar infarction (involving the cerebellum and brainstem), cerebellar infarction (involving the cerebellum), and lacunar infarction (involving occlusion of a small penetrating artery of the Circle of Willis) [60]. Despite its sweeping prevalence and sobering mortality rates, tissue plasminogen activator (tPa) remains the only effective and Food and Drug Administration-approved therapy for nearly the past three decades at the time of writing [62]. Yet, tPa boasts a short therapeutic window, thereby limiting its usage and, in addition to hemorrhagic transformation, underscoring the need for new targeted therapies [62,63]. One such target in surfacing research is the mitochondria. This focus largely stems from knowledge of (1) compensatory brain dysfunction and neuronal cell death in the ischemic stage and (2) enhancement of brain damage in the reperfusion stage (from overproduction of reactive oxygen species), both secondary to oxidative stress [64].

Mitochondrial dysfunction is an established member of IS pathophysiology. Indeed, the mitochondrial response, including calcium overload, disrupted mitochondrial quality control and dynamics, and excessive production of reactive oxygen species, is an integral contributor to post-IS neuronal loss [62,63,65]. These mechanistic changes are initiated by severe oxygen and glucose deprivation secondary to reduction of regional cerebral blood flow, which effectively depletes adenosine triphosphate reserves [62]. A wealth of recent research has implicated changing mitochondrial dynamics in ischemic neuronal death. For instance, mitochondrial fission is mediated by cytosolic protein Drp1 and, secondarily, outer mitochondrial membrane fusion protein Mfn1/2 [62]. Absence of the latter has interestingly been linked to mitochondrial fragmentation [58,65]. Moreover, expression of inner mitochondrial membrane fusion protein Opa1 evidence progressive downregulation in animal models of middle cerebral artery occlusion [62].

Accumulating evidence further implicates B-cell-lymphoma-family proteins in neuronal cell death regulation following an IS event [66]. Relatedly, pronounced upregulation of the pro-apoptotic BH3-only proteins has been reported in the context of cerebral ischemia, implicating the role of IS in triggering numerous apoptotic pathways that involve the mitochondria. In addition to the BH3-only pathway, various apoptotic pathways originated in the mitochondria. Continuing, polyphenols have emerged yet another therapeutic route in preclinical trials. In their review of the relevant literature, Panickar and Anderson discussed a role for polyphenols in reducing levels of apoptotic markers (namely caspase-3 and calpain activation) as well as reducing vasogenic brain edema events associated with ischemia, among other benefits [67]. More research is needed to exact their complete cellular and molecular interplay but these naturally occurring antioxidants remain intriguing at the time of writing. A comprehensive understanding of the influence of mitochondrial molecular mechanisms in ischemia-associated neuronal death and protection may facilitate grounds for developing novel therapeutics for ischemic stroke.

5. Hemorrhagic Stroke

Hemorrhagic stroke (HS) represents a rarer stroke subset (comprising approximately 20% of all strokes) that is paired with major sequalae in its surviving population [68,69]. HS is commonly subdivided as such: intracerebral hemorrhage (ICH), referring to hematoma development within the brain parenchyma [70], and subarachnoid hemorrhage (SAH), referring to bleeding between the arachnoid and pia mater [71]. ICH accounts for >10% of all strokes and purports a 1-year mortality rate > 50%, with variable outcomes based on hemorrhage location [72]. SAH etiology is primarily secondary to aneurysmal rupture (>80% of SAH cases) and affects upwards of 30,000 persons every year in the United States (global incidence of aneurysmal SAH: 7.9 per 100,000 persons each year) [71]. Lantigua et al. found that total in-hospital mortality for SAH patients was 18% (216/1200), with outcomes stratified by Hunt–Hess grade [73]. For example, in-hospital mortality for Hunt–Hess grade

1 or 2 SAH patients was 3%, compared to 71% among Hunt–Hess grade 5 patients [73]. Continuing, survivors demonstrate significant cognitive and emotional impairment. SAH associates with poorer memory and low executive function, in addition to lasting anxiety and depression, among other sequalae [74,75]. These data, in tandem with their predominantly nontraumatic etiology, elevate the demand for better control of secondary brain injury after an HS event.

The MISTIE III and STICH II clinical trials most significantly demonstrated that early hematoma clearance does not improve ICH prognoses, encouraging investigation of contributory cellular targets [76]. Similar to IS, recent HS research has largely zeroed in on mitochondrial dysfunction. Lu et al. reported upregulation of CytoC in ICH rat models, the release of which colocalizes with CNPase, implicating its expression in ICH-induced oligodendrocyte apoptosis [77]. Previous science has established that mitochondrial injury precluding CytoC release is owed to the erroneous opening of mPTP, thus disrupting the 80–140 mV mitochondrial membrane potential. Supporting these findings is the demonstration of the post-HS neuroprotective effects of selective reactive oxygen species scavengers Sirtuin3 and mitoquinone [78,79]. Other mitochondrial control and response mechanisms (namely mitophagy) remain areas of focused inquiry in HS research to date.

6. Aneurysm

Cerebral aneurysms are dilations of the brain's arterial architecture. The worldwide prevalence of cerebral aneurysms is >3%, with predominating appearance in the elderly female population [79]. Fortunately, most aneurysms are asymptomatic until rupture (occurring in approximately 10 per 100,000 individuals), but even unruptured aneurysms may manifest clinically, owing to mass effect symptoms [80,81]. Available data suggest that T-cell and macrophage populations mediate the histologic changes preempting the formation and development of cerebral aneurysms [82]. Current treatment options include microsurgical clipping and endovascular coiling, with the latter being favored following substantive results from the International Subarachnoid Aneurysm Trial (N = 2143) [83,84]. However, the 2021 Cochrane Review (conducted from inception to 25 May 2020) concluded that unruptured intracranial aneurysms remain a public health hazard for which there exists insufficient evidence to support interventional treatments. A smattering of recent research efforts have revealed a role for oxidative stress in the formation and rupture of cerebral aneurysms [85,86].

Zhao and colleagues discovered that microRNA (miR)-29a contributes significantly to the progression of intracranial aneurysm (IA), most directly through regulation of Mcl-1 apoptotic pathways [86]. They further realized profound dysregulation of miR-233, miR-433, and miR-489 in IAs compared to sham control arteries. Additional differential expression analysis revealed that GSK3B, a key regulator of mitochondrial biogenesis and axonal trafficking, among myriad other roles [66,87], is negatively implicated in IA rupture [58]. Further still, Shi et al. reported that activation of Nrf-2, another chief antioxidant, efficaciously suppressed the formation and progression of IAs in an elastase-induced rat model. Here, Nrf-2 agonist tBHQ maintained the contractile phenotype of vascular smooth muscle cells, under phenotype switching pressures secondary to induced oxidative stress [88]. These findings and more stress the value of continued research into the mitochondrial (and related oxidative stress) underpinnings of cerebral aneurysms, particularly in lieu of marked controversy surrounding their optimum management.

7. Brain Tumor

The elevation of mitochondrial ROS has been linked to the progression and increased severity of individuals diagnosed with brain tumors and infections [89,90]. The literature has endorsed the definition of mitochondrial oxidative stress as an imbalance between pro-oxidants and antioxidants, such as RNS, reactive lipid species and the accumulation of free radicals, within the organelle [91,92]. Many of these ROS species have been shown to cause mitochondrial DNA damage, either through the prognosis of cancer or the treat-

ment administered for it [89,93]. In patients diagnosed with brain tumors, the ROS stress originating from the mitochondria can often interfere with the G2-phase of the mitosis replication stages in cancerous cells [92]. However, researchers such as Vishal et al. have confirmed that elevated ROS levels actually interfere in a positive way. They increase the growth of brain tumors by further activating signaling cascades that are important in cell growth [94]. Through these cascades, cancerous cells have been observed to use multiple mechanisms to survive the increased production and exposure to ROS. The rapid accumulation of mutations within cancer cells can often create tumor cell lines with p53 mutations that render them resistant to the apoptosis created by mitochondrial ROS [95]. Even when cancerous cells undergo apoptosis, the physiology has been found to be immunologically silent, with reduced secretion of cytokines and inflammatory mediators involved in Type 1 IFN production [95,96]. In addition, mitochondrial ROS species have been found to increase the expression of VEGF in cancer cell lines. Imaging has allowed researchers to examine increased amounts of abnormal microvessel development, thereby allowing cancerous cells to expand tumor growth while gaining an improved ability to distribute various nutrients and oxygen requirements [97] (Figure 3).

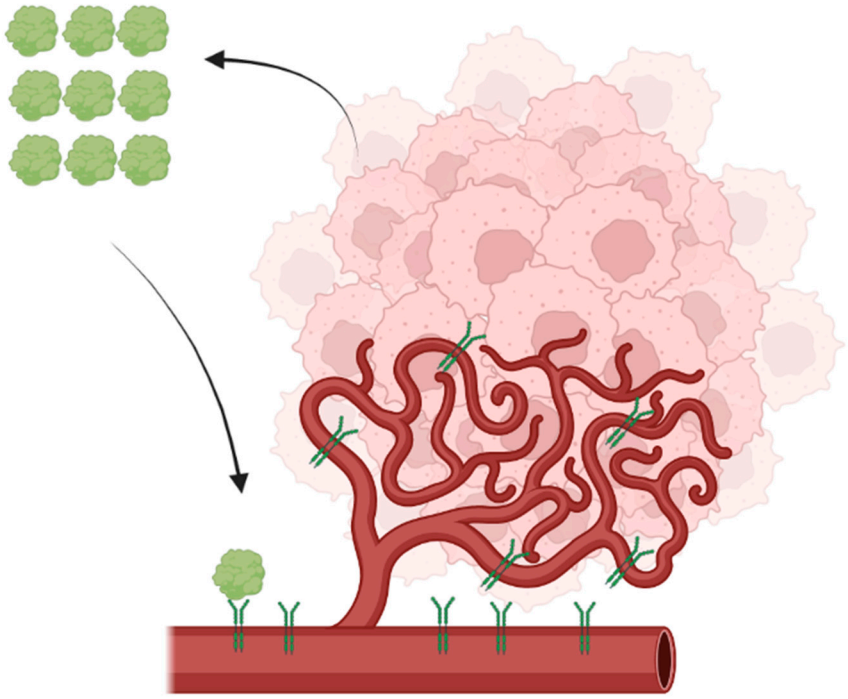

Figure 3. Increased production of mitochondrial reactive oxidative species causes the release of VEGF from tumor cells that binds to neural endothelial cells within the brain. This promotes the process of angiogenesis and further circulates nutrients to promote tumor growth. Therapies that decrease the secretion of ROS species have the potential to mitigate this pathway.

Changes in the morphology of the mitochondria due to ROS have been analyzed, as well. Sabatino and colleagues examined the structure of the mitochondria in slow growing cancerous cells and found larger and more pronounced mitochondrial structures in pituitary cancer cells, whereas faster-growing cancerous cells were found to have smaller and fewer mitochondria [98]. The difference of structure could relate to the increased lactate production and use of glycolysis, which are characteristic signs of the Warburg Effect that many adaptive cancerous cells utilize [98]. Furthermore, the proliferation of cyclin-dependent kinase-1, a molecule involved in the G1 checkpoint regulation stage, increases chemotherapy-resistant pathways in cancerous tissue. It allows the cell to undergo unchecked proliferation. Further oxidation of specific cysteine residues on the mitochondrial genome and proliferation of molecules such as cyclin D1, ERK and MAPK activation might also point towards similar resistant phenomena [92,94,99].

Many therapeutics have been designed to combat the resistant phenomenon exhibited by brain tumor cells based on studying and inhibiting molecules that foster mitochondrial oxidative stress in patients. For example, Ren et al. conducted a clinical study involving the etiology of chemotherapy induced cognitive impairment (CICI) with increased levels of tumor necrosis factor-alpha (TNF-a) as the potential contributor to mitochondrial oxidative stress within brain tumors [100]. After analyzing Doxorubicin, a specific chemotherapy drug that is known to activate ROS, in mice with induced brain tumors, the research team discovered an elevated increase in TNF-a and subsequent plasma protein damage within their brains [100]. Due to this chemotherapy drug's ability to cross the BBB via receptor-mediated endocytosis, its mechanism of action could be correlated with the harmful mitochondrial effects seen in mice. In a subsequent study, brain mitochondrial function was analyzed by the Seahorse-determined oxygen consumption rate (OCR) and found that those mice that did not get treated with Doxorubicin had less accumulation of harmful choline and phospholipase substances. Doxorubicin is one of the many drugs that the FDA has approved for the treatment of cancer that has been found to produce harmful ROS [78]. Many of the etiologies of these chemotherapy drugs necessitate further research due to their correlation between patient prognosis and recovery. Some molecules have exhibited harmful side effects despite their inability to cross the blood–brain barrier [100]. Studies have shown that post-cancer and chemotherapy patients are more likely to suffer through neurological symptoms such as anxiety and depression after the administration of specific chemotherapy drugs [78]. The increased production of mitochondrial ROS substances could be a potential answer to this recurring medical issue.

8. Cranial Infection

For patients diagnosed with devastating brain infections such as meningitis and encephalitis, there are various cytotoxic effects mediated by mitochondrial ROS agents that have the potential to impact their prognosis [101]. One of the most common and debilitating brain infections is the encephalitis caused by Herpes Simplex Virus 1 [102]. This virus has recurrently been associated with mitochondrial damage, and therapies such as Minocycline have been used to combat this intracranial mitochondrial damage. Wnek et al. conducted an experimental study analyzing the mitochondrial genome of post mortem human brains from Oxford University that were infected with HSV. Their results involved an inverse relationship between mitochondrial function and the prognosis of brain infection. With increased severity of infection, mitochondrial functions of the CytC enzymes and succinate dehydrogenase enzymes decreased, resulting in an overall decrease in mitochondrial function [102]. This impairment of mitochondrial activity was further analyzed in the lab using cell lines infected with HSV-1, and most correlated with viral proteins decreasing the activities that involve DNA and proteins, such as transcription, translation, and mitochondrial electron transport [103]. Astrocytes that were later treated with Minocycline displayed increased transcript numbers of cytochrome oxidase, reflecting increased mitochondrial activity within the brain. However, it was difficult to analyze whether the initial mitochondrial damage was due to the viral proteins causing increased release of ROS agents and should be studied further to further produce novel therapeutics [102–104].

Another group of scientists analyzed the effect of mitochondrial ROS on astrocytes upon infection with the Zika virus. Many studies in the literature have aspired to analyze the Zika virus's prognosis in brain cells due to the devastating congenital malformations that can result in pregnant women [105]. iPSC-derived astrocytes were utilized and the amount of ROS species and DNA breakage within those cells increased when compared to healthy astrocyte cell lines [105]. Furthermore, another study analyzed the role of neuroinflammation as a potential key mediator in the mitochondrial ROS species produced during brain infections [106]. Long-term infection in patients can lead to sepsis symptoms that often result in brain damage. The increased mitochondrial oxidative damage and apoptosis led Gu et al. to examine the various caspase 3 and caspase 9 proteins that are involved in apoptotic cell death. The pathophysiology of virally infected cancerous glial

and hippocampal cells can be explained by the suppression of these caspase proteins and increase in the Bax/Bcl2 ratio discovered in these cell lines [106].

Furthermore, the human body's immune response to diseases such as pneumococcal meningitis often involves the overpowering and release of various cytokines mediated by NF-kB, a transcription factor involved in causing inflammatory responses. When cytokines are released, macrophages and neutrophils are recruited that often release harmful substances such as NADPH oxidase, NO, $O_2^{\cdot -}$, and H_2O_2 that can cause collateral damage to the tissues surrounding the brain, including mitochondrial damage. Barichello et al. support the idea of significant cell injury caused by the body's own production of ROS and destruction of mitochondrial DNA and enzymes vital to overcome the infection [107].

In addition to cytokines, new therapies and treatments should be targeted towards decreasing the production of $ONOO^-$, lipid peroxidation and Poly ADP-Ribose Polymerase (PARP) activation. Recently, thiol-containing compounds have been administered to help scavenge $ONOO^-$ and early clinical studies have shown improvements in treating traumatic brain injury. As production of $ONOO^-$ molecules is locally mediated, more research should be conducted upon the most likely location of the ROS molecules and how long their systemic or localized effects can cause harm [101]. This may help improve prognosis and limit the pathogenesis of brain infections in patients.

9. Conclusions

The mitochondria play a critical role in the metabolic framework of the central nervous system. In particular, the brain and its functioning are intimately tied to oxidative demand, thereby depending on the wellbeing of its mitochondria as its own. Indeed, mitochondrial damage in the context of various brain injuries has been implicated in the production of reactive oxygen species, being considerably responsible for the sequelae and long-term morbidities ensuing from such insults. Though different forms of brain injury share a common footing in the effects of mitochondrial ROS, such progression may be variably dictated by the form of injury. Furthermore, outlets for therapy may also vary across different injuries. As such, the current review highlights the role of mitochondrial ROS in different forms and types of brain injuries while describing the current landscape of therapeutics and their future utility.

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Abbreviations

CNS—central nervous system; ROS—reactive oxygen species; $O_2^{\cdot -}$—superoxide anion; $OH^{\cdot}$—hydroxide radical; H_2O_2—hydrogen peroxide; RNS—reactive nitrogen species; $ONOO^-$—peroxynitrite; $NO^{\cdot}$—nitric oxide; SOD—superoxide dismutase; GPx—glutathione peroxidase; CAT—catalase; GSH—glutathione NMDA—N-methyl-D-aspartate; ABI—acquired brain injury; MOI—mechanism of injury; NOI—nature of illness; TBI—traumatic brain injury; SAH—subarachnoid hemorrhage; SDH—subdural hemorrhage; IPH—intraparenchymal hemorrhage; BBB—blood–brain barrier; NO_2—nitrogen dioxide; AMPA—excitatory amino acid reuptake transporters; ETC—electron transport chain; mPTP—mitochondrial permeability pore; EAAT—excitatory amino acid reuptake transporter; NGF—nerve growth factor; CypD—Cyclophilin-D; NSAID—nonsteroidal inflammatory agent; MAO—malondialdehyde; tSAH—traumatic subarachnoid hemorrhage; MitoQ—mitoquinone; CsA—cyclosporin A; CytC—cytochrome C oxidase; iNOS—nitric oxide synthase; eNOS—endothelial nitric oxide synthase; COX—cyclooxygenase; XO—xanthine oxidase; CYP450—cytochrome P450; Vitamin C—ascorbic acid; NAC—N-acetyl-cysteine; IS—ischemic stroke; tPa; tissue plasminogen activator; HS—hemorrhagic stroke; ICH—intracerebral hemorrhage; miR—microRNA; IA—intracranial aneurysms; CICI—cognitive impairment; TNF-a—tumor necrosis factor-alpha; OCR—oxygen consumption rate; PARP—Poly ADP-Ribose Polymerase

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