Review

Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), Antioxidants, and Cerebral Vascular Tone

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Abstract: The brain's unique characteristics make it exceptionally susceptible to oxidative stress, which arises from an imbalance between reactive oxygen species (ROS) production, reactive nitrogen species (RNS) production, and antioxidant defense mechanisms. This review explores the factors contributing to the brain vascular tone vulnerability in the presence of oxidative damage, which can be of clinical interest in critically ill patients or presenting acute brain injuries. The brain's high metabolic rate and inefficient electron transport chain in mitochondria lead to significant ROS generation. Moreover, non-replicating neuronal cells and low repair capacity increase susceptibility to oxidative insult. ROS can influence cerebral vascular tone and permeability, with a potential impact on cerebral autoregulation. Different ROS species, including superoxide and hydrogen peroxide, exhibit vasodilatory or vasoconstrictive effects on cerebral blood vessels. Reactive nitrogen species (RNS), particularly NO and peroxynitrite, also exert vasoactive effects. This review further investigates the neuroprotective effects of antioxidants, including superoxide dismutase (SOD), vitamin C, vitamin E, and the glutathione redox system. Various studies suggest that these antioxidants could be used as adjunct therapies to protect the cerebral vascular tone during high oxidative stress conditions. Nevertheless, more extensive research is required to comprehensively grasp the relationship between oxidative stress and cerebrovascular tone, as well as to explore the potential benefits of antioxidants as adjunctive therapies in critical illnesses and acute brain injuries.

Keywords: oxidants; reactive oxygen species; reactive nitrogen species; antioxidants; cerebral vascular tone

1. Introduction

Brain tissue is exceptionally susceptible to the harmful effects of oxidative stress due to its unique characteristics. Despite accounting for only 2% of the body weight, the brain consumes approximately 20% of the total basal oxygen [1,2]. This heightened oxygen consumption is essential for ATP production, which is necessary to maintain the brain's high metabolic rate. Unfortunately, the electron transport chain in the mitochondria, responsible for ATP synthesis, leads to the leakage of reactive oxygen species (ROS) [3]. Consequently, the brain cells ceaselessly generate a significant

amount of ROS. Additionally, the brain comprises non-replicating neuronal cells, possesses a high cell surface-to-cytoplasm ratio, and has a relatively low repair capacity. These structural and functional features further contribute to its vulnerability to oxidative damage [4]. A summary of the main factors contributing to the brain tissue's high susceptibility to oxidative insults are described in Table 1.

Table 1. Factors contributing to the heightened vulnerability of brain tissue to oxidative insults.

Factors of high susceptibility and vulnerability of the brain tissue
Intense production or ROS
High energy requirements
Neurodegeneration
Non – replicating neuronal cells
High ratio of membrane surface to cytoplasm
Weak antioxidant capacity
High lipid content
Low repair capacity

The regulation of vascular tone in cerebral vessels is controlled by both muscular and endothelial mechanisms [5]. The former is regulated by myogenic mechanisms, which originate from vascular smooth muscle. The latter is regulated by endothelial factors, such as nitric oxide and endothelin, which can decrease or increase the vascular tone, respectively. In addition, local hormones, metabolic by-products, ROS and RNS, as well as drugs, can influence and contribute to cerebral vascular tone. Notably, ROS can arise from all the layers of the vascular wall and adjacent tissues through several mechanisms, and, among these, the NADPH-oxidase enzyme may be the primary source of ROS production from the vascular cells [6].

This widespread existence of ROS within and surrounding cerebral blood vessels aligns with their ability to influence the vascular tone and vascular permeability [7–10], and their effects may be greater in the cerebral vasculature than in any others [11,12]. Even cerebral autoregulation (CAR), a complex physiological mechanism that adjust cerebrovascular tone to maintain cerebral blood flow within desired ranges in response to changes in cerebral perfusion pressure, may be altered by ROS [13]. All these vascular effects may come from the direct activity of ROS on ion channels [14,15], through their interrelation with reactive nitrogen species (RNS), particularly nitric oxide (NO), or other vasoactive mechanisms still unknown.

The balance of redox reactions, given by ROS and RNS, may be of clinical interest especially in critically ill settings when high oxygen levels could be provided (thus increasing reactive species production), or in acute brain injuries when these species are more frequently produced [16,17]. In this review, we describe the primary ROS and RNS and their documented impact on cerebral vascular tone. Furthermore, since oxidative stress relies on oxidant species production and antioxidant defense mechanisms, we will also explore the main antioxidants and their effects on cerebral vascular tone.

2. Reactive Oxygen Species

The term Reactive Oxygen Species (ROS) refers to oxygen-containing chemical species that are unstable and highly reactive, capable of causing damage to various biological molecules. These species arise from the uptake of electrons from molecular oxygen, i.e. O_2. Multiple sources contribute to their formation, first-of-all, the electron transport chain within the mitochondria, where, during cellular respiration, electrons are transferred through a series of protein complexes. When there's a

leak or premature transfer of an electron to molecular oxygen, superoxide anion (O_2^-) is formed. Other ways in which ROS are formed encompass, among others, metabolizing enzymes, NAD(P)H oxidases (NOS), ionizing radiation, the Fenton reaction [which can be simplified as $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + HO^\bullet$], cell uptake of microbes or xenobiotics.

Given their strong ability to react chemically with their environment, ROS are well known to lead to several pathological consequences [18]. Surprisingly, depending on the specific context, ROS can exhibit both protective and deleterious effects on the organism, the same molecule exerting opposing interferences on biological processes [19]. The impact of these effects relies on the interplay between the production of ROS and their clearance rates, wherein antioxidants and scavengers assume a critical role [20]. When this balance is disrupted, these reactive molecules can unopposedly interact with and damage vital cellular components such as DNA, proteins, and lipids. This molecular damage can compromise the normal function of cells, leading to tissue injury. This harmful state, characterized by the overwhelming presence of oxidative species and the resultant cellular and tissue damage, is termed "oxidative stress" [21].

The main mechanisms of the formation of ROS, further described later, are illustrated in Figure 1.
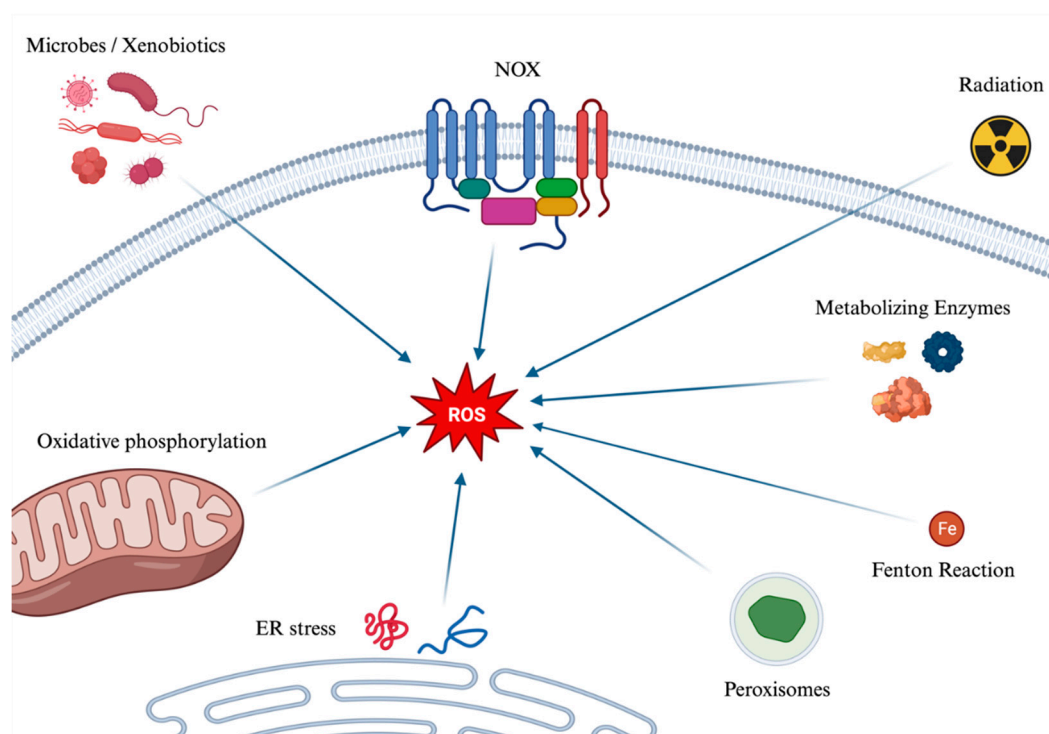

Figure 1. The main pathways of the formation of ROS. ROS are formed through various pathways, contributing to their accumulation, which can have beneficial and detrimental effects on cellular processes. 1) Microbes and Xenobiotics: microbes can produce ROS as part of their metabolism or defense mechanism, xenobiotics can be metabolized to produce ROS; 2) NOX: it is an enzyme that produces superoxide by transferring electrons from NADPH to molecular oxygen; 3) Radiation: ionizing radiation, such as X-rays or gamma rays, can cause the ionization of water molecules, leading to the formation of hydroxyl radicals; 4) Metabolizing Enzymes: some enzymes involved can produce ROS as by-products of their reactions; 5) Fenton Reaction: a chemical reaction in which iron (Fe2+) reacts with hydrogen peroxide to produce hydroxyl radicals; 6) Peroxisomes: organelles that contain enzymes involved in a variety of metabolic processes, including the breakdown of fatty acids and the detoxification of harmful substances, during which they can produce ROS; they also have catalase, an enzyme that breaks down hydrogen peroxide into water and oxygen; if the production of ROS exceeds the capacity of catalase to break it down, ROS can accumulate; 7) Endoplasmic Reticulum (ER) Stress and Unfolded Protein Response: the ER is an organelle in the cell that is responsible for the synthesis, folding, and modification of proteins; when the ER becomes overwhelmed with misfolded proteins, it triggers a response known as ER stress, caused by various factors, including

nutrient deprivation, hypoxia, and changes in calcium levels; the accumulation of misfolded proteins in the ER can cause oxidative stress; moreover, in response to ER stress, the cell activates the Unfolded Protein Response, a signaling pathway that aims to restore ER homeostasis by halting protein synthesis, increasing the production of chaperone proteins that assist in protein folding, and enhancing the degradation of misfolded proteins; thus, the demand for energy increases, leading to an increase in mitochondrial activity; 8) Oxidative Phosphorylation in the mitochondria: electrons are transferred through the electron transport chain to produce ATP; some electrons may leak and react with oxygen to form superoxide. *ROS: Reactive Oxygen Species; NOX: NADPH Oxidase; ER: Endoplasmic Reticulum.*

2.1. The main Reactive Oxygen Species

As previously mentioned, ROS originate from O_2, a diradical, meaning it has two unpaired electrons in its molecular orbital. Despite being relatively stable under standard conditions, its diradical nature makes O_2 more reactive than if it were a closed-shell molecule, and prone to participate in various chemical reactions, especially those involving electron transfer.

When O_2 acquires an electron, primarily from the mitochondrial electron transport chain as earlier described, it gives rise to *superoxide anion* (O_2^-). This species carries both a negative electric charge and an unpaired electron, making it both an anion and a radical and it can be seen as the precursor to ROS and, as we will see later, it also plays a role in the formation of RNS. It is a free radical, i.e., a molecule that contains one free unpaired electron in its outer orbital. However, despite its name, O_2^- does not seem to act as a potent oxidizing agent. Instead, its detrimental effects stem from its secondary interactions, particularly when it reacts with nitric oxide (NO). Due to its low permeability, the actions of superoxide are primarily related to the compartment in which it is produced; however, it can also influence the surrounding cellular environment by crossing the cell's ion channels exerting its effects at a distance from the production point, even with a half-life, at normal pH, of about 5 seconds [22].

Hydrogen Peroxide (H_2O_2) is generated from O_2^- through a reaction called dismutation (i.e., a reaction in which the same species is both reduced and oxidized), in which 2 superoxide molecules are transformed in H_2O_2 and O_2, catalyzed by the enzyme superoxide dismutase (SOD). H_2O_2 is not a free radical, and therefore it does not directly oxidize other molecules. However, it can move quickly through the cell membranes and, transforming into a potent compound (hydroxyl radical, described further in the text), it can exert the effect of ROS at different sites instead of its production site. Indeed, due to a non-enzymatic reaction that requires iron in its reduced state (Fe^{2+}), known as the Fenton reaction, the most reactive compound known, *hydroxyl radical* (OH^-), can be generated from H_2O_2. The OH^- can also be formed through the reaction between O_2^- and nitric oxide (NO), and the Haber-Weiss reaction [which can be simplified as $O_2^- + H_2O_2 \rightarrow OH^\cdot + OH^- + O_2$] [13,23]. Due to its tendency to react quickly with the first available molecule, this radical has a short half-life [20]. To prevent the continuation of the reaction chain, catalases can decompose H_2O_2 into water and O_2, thereby preventing the formation of $OH^\cdot$. Because of this cooperative capability, both SOD and catalase are classified as antioxidants.

The main ROS described, and their formation mechanisms, are schematically depicted in Figure 2.
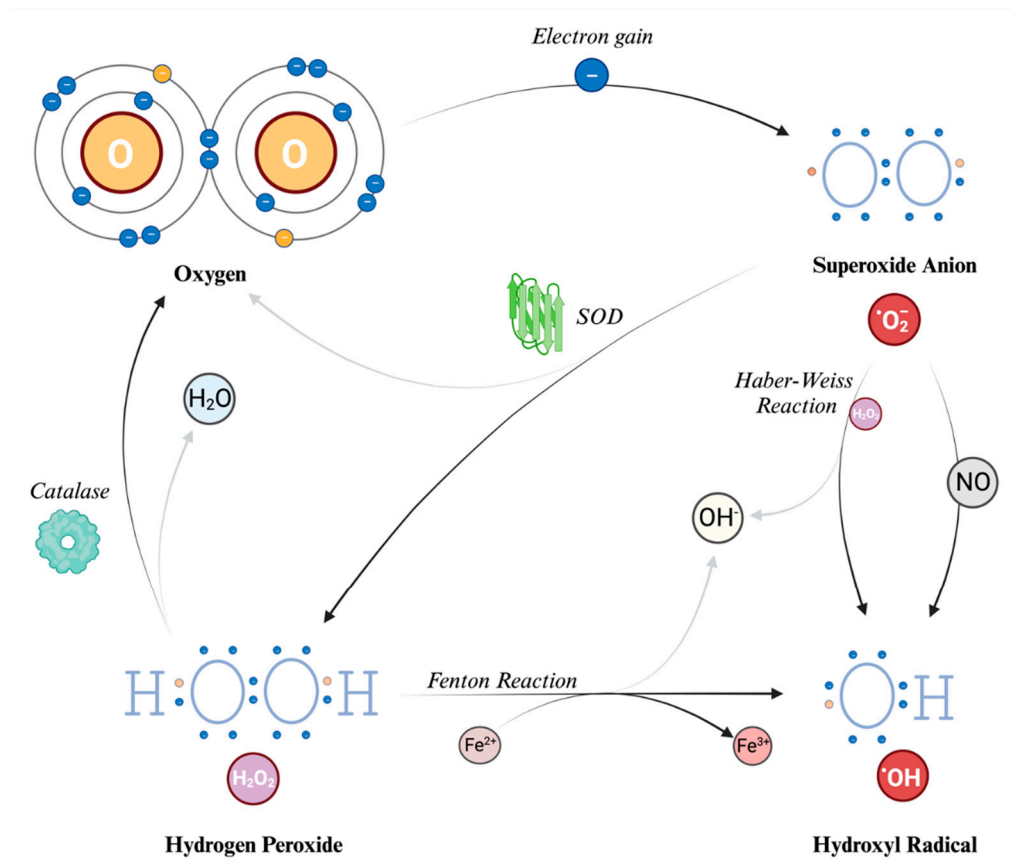
Figure 2. Reactive Oxygen Species (ROS): their structure and formation. The process begins with molecular oxygen (O_2), which has two unpaired electrons in the outer orbital. Thus, it can acquire an electron to form the superoxide anion (O_2^-), which is a radical (i.e., with an unpaired electron). Superoxide dismutase (SOD) converts superoxide into hydrogen peroxide (H_2O_2) and oxygen. Catalase can further break down H_2O_2 into water and oxygen. In the presence of transition metals, the Haber-Weiss reaction generates hydroxyl radicals ($OH^{\cdot}$) and hydroxyl ions (OH^-) from superoxide and H_2O_2. The Fenton reaction also produces hydroxyl radicals and hydroxyl ions by reducing H_2O_2 in the presence of iron ions. *O: Oxygen atom; H: Hydrogen atom; H_2O: water molecule; $O_2^{\cdot}$: superoxide anion; H_2O_2: Hydrogen Peroxide; $OH^{\cdot}$: Hydroxyl Radical; OH-: Hydroxyl Ion; NO: Nitric Oxide; Fe^{2+}: iron in reduced state; Fe^{3+}: iron in oxidized state; SOD: superoxide dismutase.*

2.2. The effects of ROS on cerebral vascular tone

In the brain, whose metabolism relies almost exclusively on the presence of oxygen, ROS appear to have a decisive influence on cerebral flow [13,24]. Indeed, the brain has a unique neurovascular coupling structure, facilitating functional and anatomical interactions among neurons, astrocytes, pericytes, microglia, and blood vessels, known as the neurovascular unit [25]. This unit allows selective adaptation of blood flow in different brain regions, influenced by ROS and nitric oxide (NO), which act on smooth muscle cells and pericytes [13,26]. For example, in animal models, ROS have been shown to have a role in microvascular reperfusion disturbances [27].

ROS can affect cerebral vascular smooth muscle tone in several biochemical pathways [28], potentially in a more pronounced way in the presence of cerebrovascular diseases [29]. The overall vasoactive effect varies based on 1) the specific type of molecule involved and 2) its concentration. For example, O_2^- can act as a direct endothelium-dependent vasodilator and a smooth-muscle vasoconstrictor through the inactivation of NO [30,31]. Indeed, O_2^-, as well as H_2O_2, can affect the vascular tone, causing vasodilation, by activating calcium-dependent potassium channels (K_{ca}), which are the most common K^+ channel expressed on cerebral arteriolar musculature, and which are sensitive to the redox state of the environment [13]. By contrast, O_2^- leads to vasoconstriction through

a powerful inhibition of endothelial NO-mediated dilation. The equilibrium between these two opposite results depends on the net concentration of the reactive species. Indeed, findings from numerous in vitro and in vivo animal studies confirm that both O_2^- and H_2O_2 exhibit a biphasic impact on cerebral blood vessels, contingent upon their concentration. At low concentrations, O_2^- leads to vasodilation, while at high concentrations, it causes vasoconstriction. Similarly, H_2O_2, when present in very high concentrations, initially induces vasoconstriction, and later leads to vasodilation [30].

In addition to the aforementioned mechanisms, the modulation of cerebral arteriolar tone through chloride channels has also been suggested [32]. Moreover, O_2^- can react with arachidonic acid and other unsaturated fatty acids, to form isoprostanes. They are known as strong vasoconstrictors that can cause a reduction of cerebral blood flow. Thus O_2^- can indirectly further affect vascular tone and may be of pathological interest in traumatic brain injuries [13,30]. Finally, H_2O_2 would also act in some cases as a membrane depolarizer, exerting, with a hyperpolarization, a vasodilatory effect [13,30,31].

Finally, at different oxygenation levels, both the production of ROS and antioxidants exhibit distinct kinetics [33]. Therefore, it is conceivable to assume that the vasoactive activity of ROS, as well as RNS and antioxidants, may depend not only on the type of ROS and their concentration but also on a third feature, i.e., the kinetics of their production and degradation. Indeed, compensatory mechanisms might come into play when a stimulus becomes a new steady state. This can occur especially in pathological conditions, such as in acute brain injury or in critically ill patients, where elevated ROS levels may increment acutely, and persist for an extended period.

The vascular impacts of ROS on cerebrovascular tone are diverse and involve complex mechanisms. These also include interactions with NO and RNS, which will be further discussed later.

2.3. NADPH Oxidases

The nicotinamide adenine dinucleotide (phosphate) oxidases (NADH/NADPH oxidases, or Nox) are prominently involved in the enzymatic generation of ROS [34]. These membrane-bound enzymes produce superoxide radicals by utilizing NADH or NADPH as electron donors. In mammals, there exist seven isoforms of Nox. Among them, Nox1, Nox2, Nox4, and Nox5 are expressed in various tissues such as endothelium, vascular smooth muscle cells, fibroblasts, and perivascular adipocytes [35]. Under normal physiological conditions, vascular Nox exhibits a relatively low baseline activity. However, in response to various stimuli like cytokines, the enzyme activity can be augmented both in the short term and over an extended period. This response to stimuli disrupts vascular homeostasis, leading to pathological changes and associated health issues, such as increased blood pressure [36].

The involvement of NADH and NADPH reinforces the notion that the redox state is critical in influencing the tone of cerebral circulation. Indeed, interestingly, studies have shown that NADPH oxidase activity exhibits a significantly higher magnitude in cerebral arteries than in systemic arteries [12]. As electron acceptors, both NADH and NADPH facilitate the activity of Nox enzymes, leading to the production of O_2^- [24,37], which is in the end responsible for the impact on the vascular tone. Thus, ROS production derived from NADPH oxidase may contribute to vascular pathology while also to the maintenance of normal physiological vascular tone.

2.4. Additional viewpoints

ROS have more effects than expected, and they could work as signal molecule. In this way it is thought ROS play a role in the degradation of HIF-1α, as there is evidence of a negative correlation between these two [26]. HIF-1α, known as the hypoxia-inducible factor, is a cytosolic transcription factor that moves to the nucleus during hypoxia. It binds to HIF-β and activates the expression of genes containing hypoxia-responsive elements (HRE), which results in the production of hypoxia-related proteins such as erythropoietin (EPO). The production of ROS is implicated in the proposed "normobaric oxygen paradox" [38], where intermittent hyperoxic stimulation could paradoxically mimic a hypoxic-like condition, leading to the activation of HIF-1α [39]. Moreover, ROS production via NADPH oxidase, especially Nox2, may intervene in the evoked HIF-1α synthesis and stability

[40]. These mechanisms may be especially relevant in brain cells, as they tend to increase ROS production under injured conditions. However, the existence of this phenomenon and its potential effects on the brain tissue have not been thoroughly investigated.

2.5. Regional Differences

It has been observed that the mechanisms that intervene in oxidative equilibrium may have differences between cerebral and systemic circulation [12]. Additionally, there may be differences in susceptibility to oxidative stress among cerebral microvessels in various brain regions [41]. This could account, for example, for the increased vulnerability of the hippocampus and cortex to oxidative stress and endothelial dysfunction compared to the cerebellum. These regional differences may also be influenced by the local availability of NO, which has been demonstrated in experimental animal models [42]. Therefore, it appears conceivable that even small changes in ROS and RNS concentrations can lead to clinical changes via their effect on the brain vasculature, especially during brain injuries and cerebrovascular diseases. Nevertheless, further human research is required to gain data and a deeper comprehension of these aspects, moving beyond theoretical discourses.

3. Reactive Nitrogen Species

Reactive Nitrogen Species (RNS) are a group of highly reactive nitrogen-containing molecules that are generated as by-products of nitrogen metabolism. These molecules are crucial in various physiological and pathological processes, including vascular control [43].

3.1. The formation of the main Reactive Nitrogen Species

Nitric Oxide (NO) is the most well-known and significant member of the RNS family. Also formerly known as endothelium-derived relaxing factor (EDRF), it is constantly generated in the body through the enzymatic action of Nitric Oxide Synthases (NOS) on L-Arginine and Oxygen. There are three distinct isoforms of NOS present in the body: iNOS (inducible), eNOS (endothelial), and nNOS (neuronal) [44,45]. NOS generates in loco NO, which readily exerts its biological activity. Although its half-life is limited to a few seconds, NO can react with hemoglobin, forming S-nitroso hemoglobin, or be converted to nitrite. S-nitroso hemoglobin (SNO-Hb) is a derivative of hemoglobin that has been modified by the addition of a nitric oxide (NO) group to a cysteine thiol group, in a reaction called S-nitrosylation.

Nitrite (NO_2^-) is a chemical compound that consists of one nitrogen atom and two oxygen atoms. It is an anion that can form salts such as sodium nitrite ($NaNO_2$) or potassium nitrite (KNO_2). SNO-Hb and NO_2^- salts act as NO reservoirs, which can be transported through systemic circulation and released under certain conditions to promote vasodilation and increase blood flow to tissues distant from the site of origin [46,47].

Other molecules can be categorized into RNS, produced as metabolites in NO decomposition or by reaction between other compounds such as CO_2 and ROS. For example, peroxynitrite ($ONOO^-$) is formed from the reaction between NO and superoxide ions, thus reducing NO concentrations [48]. Although evidence addresses NOS as responsible for nitroxyl (HNO) production, it is still unclear how this compound is synthesized in vivo [49,50]. Indeed, HNO can also be generated after the reduction of NO by mitochondrial cytochrome C, xanthine oxidase, ubiquinol, hemoglobin, and manganese superoxide dismutase (SOD) [50].

Nitrate (NO_3^-) is a chemical compound that consists of one nitrogen atom and three oxygen atoms. Similarly to NO_2^-, it carries a negative charge, and thus, it is found in salts chemical form. A significant amount of nitrate comes from leafy green vegetables. Salivary glands actively take up nitrate from circulation, resulting in saliva concentration 10-fold higher concentration than in plasma [51]. A certain quantity of NO_3^- is converted to NO_2^- by reductase enzymes in the salivary glands [51]. Finally, some nitrites are absorbed when ingested and become part of the "nitrate-nitrite-nitric oxide pathway" [52]. Kapil et al. have demonstrated how nitrate supplementation can lower blood pressure and that depleting oral microbiomes can jeopardize endogenous nitrate production, leading to

hypertension [53]. There are other endogenous ways to synthesize nitrate and nitrite [52]. Over the years, many trials have established the conversion of NO to nitrite occurring naturally in vivo. This reaction has been linked to hypoxia, deoxyhemoglobin, and lower pH [54–58]. Furthermore, a significant increase in plasma nitrite was displayed during the administration of 80ppm iNO in a murine model [59]. With all these observations, nitrates and nitrites can be considered as of NO reservoir [60]. Indeed, while NO has a half-life limited to 2 ms, that of nitrite is much longer and can quickly spread all over the organism [52].

The formation of the main RNS described is schematically depicted in Figure 3.
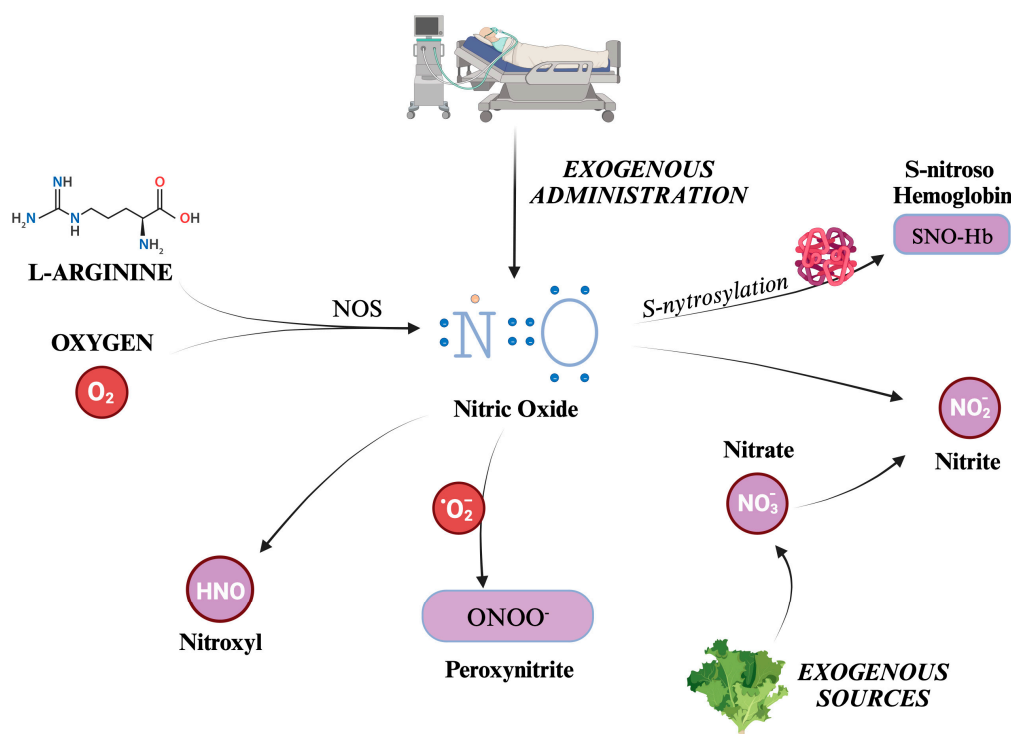

Figure 3. Overview of the main reactive nitrogen species (RNS) and their formation pathways. The figure illustrates the generation of nitric oxide (NO), a small, gaseous molecule that acts as a signaling molecule in the body. It is produced by the enzyme nitric oxide synthase (NOS) from the amino acid L-arginine and molecular oxygen. Through S-nitrosylation, a NO group is added to the thiol group of a cysteine residue, for example, Hb. Otherwise, NO can be transformed into salts or esters of nitrous acid, containing the anion nitrite (NO_2^-) which can be converted back to NO under certain conditions. Nitrates are taken into the body from external sources, such as food or supplements. They can be converted into nitrites (and thus potentially into NO). This process is known as the nitrate-nitrite-NO pathway and is an alternative source of NO, especially when the enzymatic production of NO is impaired. Peroxynitrite is a highly reactive nitrogen species formed by NO with O2−. Finally, Nitroxyl (HNO) is a reactive nitrogen species isoelectronic with NO, formed by the reduction of NO or the decomposition of certain NO donors. *O_2: molecular Oxygen; NO: Nitric Oxide; NOS: Nitric Oxide Synthase; N: Nitrogen atom; Hb: Hemoglobin; NO_2^-: Nitrite; NO_3^-: Nitrate; $ONOO^-$: Peroxynitrite; HNO: Nitroxyl.*

3.2. The effects on cerebral vascular tone

3.2.1. Nitric Oxide

Since its recognition as the endothelium-derived relaxing factor [61,62], several studies have described NO as a strong vasodilator agent [44]. After synthesizing in the endothelium, NO increases cyclic guanosine monophosphate (cGMP) in smooth muscles, by stimulating soluble guanylyl cyclase. cGMP finally inhibits proteins responsible for contraction, causing vasorelaxation [44,63]. In adjunct to this mechanism, NO induces the reduction of intracellular calcium, mediated by ATPases

that actively transport calcium inside the sarcoplasmic/endoplasmic reticulum [44,63]. Other pathways toward vasodilation include the reduction in 20-hydroxyeicosatetraenoic acid [64] and prostaglandins [65]. NO may be key in regulating cerebral blood flow (CBF) [66]. Indeed, in hyperoxia [67–69], hypoxia [67,68], and hypercapnia [70], it was found to be an essential mediator of CBF in animal models. Moreover, NO also has a leading role in coupling CBF and neuronal activity [71].

Several studies explored the role of NO in critical neurologic illnesses. Indeed, early stages of severe brain injuries recognize a depletion of NO, probably contributing to secondary brain damage [72]. By contrast, when present NO reduces injuries and has neuroprotective properties in ischemia/reperfusion animal models, both in stroke and cardiac arrest [72]. For this reason, a prospective trial has been performed, proving the feasibility of iNO administration in cardiac arrest, and showing promising results in terms of survival [73].

In subarachnoid hemorrhage, NOS inactivation is associated with alterations in microvascular density and hemostasis, leading to rebleeding, intracranial hypertension, and larger hemorrhage volume [74]. Conversely, NO reduction is also correlated with a lower grade of neuroinflammation and better neurobehavioral function in rats [75]. Studies in humans showed a correlation between elevated asymmetric dimethylarginine (which is an inhibitor of iNOS, and thus of the vasodilator molecule NO) with vasospasm and worse outcome [76]; another small human study found elevated levels of NO metabolites, especially in subjects with poorer outcomes [77]. Although results may be controversial, the literature suggests deleterious effects of NO depletion, supported by increased microthrombi formation and reduced cortical activity [72]. A pilot human trial established the safety of iNO administration and showed promising results in treating delayed cerebral ischemia [78].

Pathways in traumatic brain injury (TBI) appear more complex. Mechanical insults may induce up-regulation of iNOS and over-production of NO and $ONOO^-$. The RNS stimulate the production of glutamate, which triggers nNOS. Nevertheless, NO plays an uncertain role in this disease, and its implications are still unknown [79]. Studies in newborn animal models are also contradictory. Some reports showed protective properties of NO by vasodilation, reducing ROS concentrations and scavenging radicals; others linked it to deleterious effects and greater brain injuries. These discrepancies might depend on the timing of production and concentrations of NO [80].

The brain controls blood flow by interacting with vessel diameter. Autoregulation ensures constant blood supply; changes in systemic blood pressure -if they occur within certain limits- induce vasodilation or vasoconstriction. Additionally, the brain increases blood flow in areas where neurons are more active through a mechanism named neurovascular coupling. Although other pathways and elements participate, NO plays a significant role in both of them. NOS inhibition (and thus lowering NO production) increases the lower limit of mean arterial blood pressure where autoregulation acts, reducing its efficiency [52–54]. Through neurovascular coupling, blood flow is directed to more active areas, where glutamate (the main excitatory neurotransmitter) induces calcium entry in neurons and activation of neuronal nNOS finally resulting in NO production and vasodilation [65].

Interestingly, CO_2 may act as a regulator of NO. Indeed, the process of adjusting cerebral vascular tone in response to changes in arterial carbon dioxide partial pressure ($PaCO_2$) is known as chemoregulation, which could be the main trigger of endothelial NO-release [81]. In humans, hypocapnia leads to vasoconstriction and reduced CBF, while hypercapnia and changes in perivascular pH result in vasodilation and increased CBF [81]. Cerebral endothelial cells and astrocytes have been shown to release NO under normocapnic conditions, while NO production increases during hypercapnia and decreases during hypocapnia, regardless of pH levels [82]. It has been proposed that these NO variations in response to $PaCO_2$ are specific to NOS regulation and that administering exogenous NO may influence the CO_2-dependent chemoregulation mechanism [82].

Finally, as an NO reservoir, the vasodilating effects of nitrites have long been investigated. Although some results failed to find any vasoactive activity [83], most studies confirmed that nitrite has vasorelaxant effects through the activation of guanylate cyclase [46,84–87]. >

In summary, NO stands as a potent vasodilator, playing diverse roles in the regulation of blood flow and brain protection. Its mechanism is intricate and involves numerous interactions. When it

comes to brain injuries, a deficiency in NO could contribute to secondary brain damage, while NO possesses neuroprotective qualities in animal models of ischemia/reperfusion, including stroke. Interestingly, NO inhalation has been suggested as a neuroprotective intervention during cardiopulmonary resuscitation [88]. Consequently, extensive research is needed to gain a deeper understanding of its mechanisms and potential therapeutic effects.

3.2.2. Peroxynitrite

Peroxynitrite ($ONOO^-$) has shown vasoactive properties, producing vasorelaxation of arterioles in vitro [89] and in vivo [20], although its potency seems very low, up to 50-fold less than that of NO [90]. The effect doesn't appear to involve the endothelium [91], and the vasoactive mechanism is still unclear. Some authors proposed that the effect is linked to the opening of ATP-sensitive potassium channels [20,92], by directly activating the channels or reducing ATP concentration by interfering with cellular metabolism [20,92,93]. Other mechanisms proposed to explain this vasodilating activity include elevation of cGMP levels, membrane hyperpolarization via K^+ channel activation, activation of myosin phosphatase activity, and interference with cytosolic calcium movement and cellular membrane Ca^{2+} entry [89].

However, in contrast with all the above results, Daneva et al. induced an increase in $ONOO^-$ by upregulating iNOS in mice, reporting an increase in pulmonary arterial pressure by impeding calcium entry in smooth muscle cells of pulmonary arteries [94]. Similarly, Ottolini et al. investigated the same pathway in diet-obese mice, finding a link between obese hypertension and high $ONOO^-$ levels [95]. Finally, in vitro and animal studies [96,97] have observed that peroxynitrite may induce vasoconstriction in cerebral arteries. This effect is likely due to inhibiting the cerebral K^+-dependent calcium channel. Interestingly, the addition of glutathione inhibited this cerebral vasoconstrictive effect.

Therefore, the net effects of peroxynitrite appear conflicting, and are not completely understood, probably being dose and time-dependent [98].

3.2.3. Nitroxyl

HNO has been proven to act as an endothelium-derived vasorelaxant [99–102] not susceptible to tolerance [100]. Moreover, HNO has multiple effects, including inhibiting platelet aggregation, limiting vascular smooth muscle proliferation, and interacting with metallo and thiol-containing proteins.

HNO promotes vasodilation by activating several molecular pathways [50,101–103]. These pathways include the stimulation of soluble guanylyl cyclase (sGC), leading to an increase in cGMP. From animal studies, it has been suggested that the sGC-cGMP pathway may be necessary and sufficient for HNO-induced vasodilation in vivo [104]. Others proposed that HNO may activate ATP-sensitive potassium (K_{ATP}) channels and voltage-dependent potassium (K_v) channels, resulting in the outflow of potassium ions. This causes the cell membrane to become hyperpolarized and leads to a reduction in intracellular calcium levels. Finally, from an elegant animal study, Eberhardt et al. suggested a vasodilation HNO mediated vasodilation via the transient receptor potential channel A1 (TRPA1) and calcitonin gene-related peptide (CGRP) [105]. This HNO-TRPA1-CGRP signaling pathway could be a crucial component in the neuroendocrine regulation of vascular tone, mediated by HNO.

4. Antioxidants

Antioxidants are substances that protect from the deleterious effects of free radicals. Their action, which can be enzymatic and non-enzymatic, can be further divided into two groups: 1) preventing the generation of ROS and blocking the generated ROS, and 2) repairing the damages the free radicals have caused. The main antioxidants are graphically depicted in Figure 4.
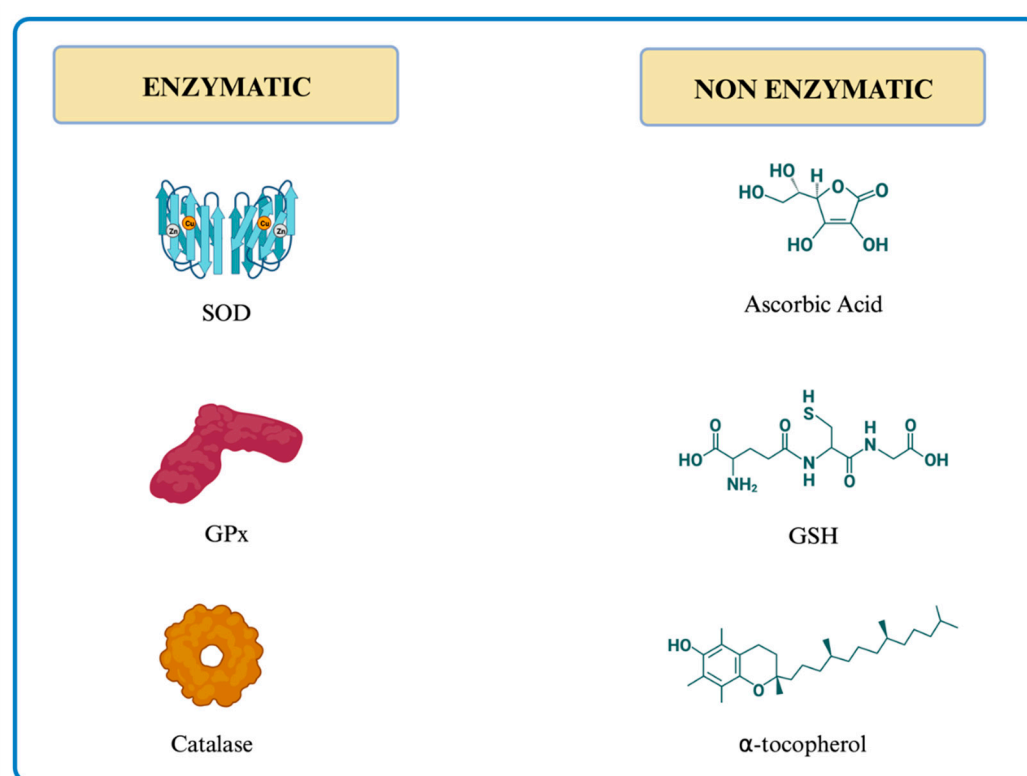
Figure 4. Classification of the main antioxidants into enzymatic and non-enzymatic. Enzymatic antioxidants include enzymes that help to catalyze the breakdown of reactive oxygen species (ROS). Glutathione Peroxidase (GPx) catalyzes the reduction of hydrogen peroxide to water using glutathione as a reducing agent. Catalase catalyzes the decomposition of hydrogen peroxide into water and oxygen, it is found in the peroxisomes of nearly all aerobic. Superoxide Dismutase (SOD) intervenes in the dismutation of superoxide into oxygen and hydrogen peroxide. Non-enzymatic antioxidants directly neutralize free radicals and prevent oxidative damage. Vitamin C (Ascorbic Acid) is a water-soluble vitamin that acts as a potent antioxidant by directly scavenging free radicals and regenerating other antioxidants, such as vitamin E. Vitamin E (Tocopherols and Tocotrienols) is a group of fat-soluble vitamins that act as antioxidants by scavenging lipid peroxyl radicals and preventing the propagation of lipid peroxidation. Thus, it is important for maintaining the integrity of cell membranes and protecting against oxidative damage. Finally, glutathione (GSH) is a tripeptide composed of cysteine, glycine, and glutamate, that acts both independently and in conjunction with GPx. *SOD: Superoxide Dismutase; GPx: Glutathione Peroxidase; GSH: Glutathione.*

Reducing the level of antioxidants leads to an increase in oxidative stress, thus indirectly influencing the cerebrovascular tone. Indeed, a more oxidative cellular environment can contribute to an increase in vascular tone by reducing the activity of NO [106,107]. For this reason, antioxidant mechanisms are widely expressed in vascular cells and brain tissue.

4.1. Superoxide dismutase

Superoxide dismutase (SOD) is an enzymatic defense system catalyzing O_2^- into H_2O_2. It exists in 3 different forms: copper-zinc SOD (SOD1 or Cu-Zn SODI), manganese SOD (SOD2 or MnSOD), and extracellular SOD (SOD3 or ecSOD). They are one of the most important protective mechanisms against oxidative stress in the body, and decreased SOD levels may be associated with a worse outcome in acute ischemic stroke (AIS) patients, faster vascular damage, and blood-brain barrier breakdown [108]. It has been proposed as a marker of cardiovascular alterations in hypertensive and diabetic patients, as fluctuations in serum levels are linked to alterations in vascular structure and function [109].

SOD1 is predominantly found in the cytoplasm and nucleus of cells, where it helps neutralize superoxide radicals generated during normal metabolic processes. The copper and zinc ions are essential for its enzymatic activity. SOD2 is usually located in the mitochondria, thus representing a critical defense mechanism against oxidative damage to mitochondrial components. Finally, SOD3 is primarily found in the extracellular matrix and fluids, acting as a defense outside the cells, protecting from oxidative stress caused by superoxide radicals released from inflammatory cells. Moreover, it is active in the arterial wall, strategically between endothelium and smooth muscle, thus controlling reactivity to oxygen levels and vascular tone [110], by regulating nitric oxide. Indeed, from animal studies, SOD regulates in vivo both the basal tone and the vascular response to different pressure of oxygen [110]. In TBI patients, SOD levels may be reduced already during the first day and may persist low for 7 days [111]. Indeed, exogenous SOD has been proposed as a therapeutic adjunct in several conditions [112], and may reduce vasospasm after SAH [113]. The reduction of cerebral vasospasm in experimental SAH animal models obtained by administering SOD [114] underscores the significant involvement of superoxide anions and redox equilibrium in vascular regulation, particularly during pathological conditions.

4.2. Glutathione Redox System

Glutathione peroxidase (GPx) is an enzyme that reduces hydrogen peroxide to water via a tripeptide, called glutathione (GSH). GSH is the most common thiol, i.e., a molecule that contains a sulfhydryl group (SH), and which is present in the cytosol and its organelles. Composed of glutamine, cysteine, and glycine, glutathione works as an electron donor, passing from its reduced state (GSH), the active form, to an oxidate state (GGS). The enzyme glutathione reductase converts GSSG back into GSH, using NADPH as an electron donor. GPx has a central role in reducing hydrogen peroxide to water, keeping it away from the production of hydroxyl radicals. Moreover, GSH can directly and independently neutralize free radicals, acting as a non-enzymatic antioxidant. Indeed, it can donate electrons to free radicals, an activity called "*scavenging*", oxidizing to form glutathione disulfide (GSSG).

This mechanism is one of the most important antioxidants in the body. Indeed, GSH is the most abundant intracellular antioxidant, as its concentration within the cytoplasm where it is produced is in mmol, where the ratio GSH:GSSG is normally maintained around 100:1 (but it can fall lower than 10:1 during oxidative stress). It can move into the extracellular fluids, but plasma levels are 1.000 less concentrated than intracellular levels. An exception is in the lining fluid in the lungs, where the concentration is 140 times more than the plasma.

Other molecules can also intervene in this system. For example, as already described, NADPH serves to maintain GSH reduced. The pentose phosphate pathway generates NADPH, and glucose-6-phosphate dehydrogenase (G6PD) is one of the enzymes in the pathway. Deficiency of this enzyme, which affects millions of people worldwide, can result in GSH deficiency, predisposing to oxidative injury. Thiamine is a cofactor in the way of the pentose phosphate. Indeed, evidence has been found that thiamine administration may alleviate oxidative stress, even in cases where it is not attributable to thiamine deficiency [115,116]. Finally, selenium is necessary for the glutathione peroxidase activity. Indeed, this enzyme contains selenium in the active site [117]. In sepsis and septic shock, selenium is abnormally low and, when infused, has been shown to reduce mortality [118]. This has also been reported by a recent meta-analysis, even if with a low quality of evidence [119].

Glutathione deficiency is a common finding in neurological disorders [120], and it may be related to several cardiovascular diseases [121]. Even in the brain vasculature, GSH may have protective effects. Despite apparently being the most convenient and safe method of GSH administration, oral GSH is not frequently utilized in clinical trials due to its limited effectiveness [122].

An alternative approach to increase GSH production involves employing N-acetylcysteine (NAC). NAC is smaller than GSH, can move into the cells, and acts as a cysteine precursor, a crucial factor in limiting GSH synthesis [118]. NAC administration presents various neuroprotective effects, such as a reduction in the size of cerebral stroke [123] and better outcomes in neurological deficits

and disability [124]. Moreover, NAC can potentially reduce ischemia-reperfusion injury [125,126], and may enhance the vasodilator effects of other compounds, such as acetylcholine [127]. As shown with other antioxidants, NAC treatment may effectively reduce cerebral vasospasm in SAH animal models [128], potentially carrying significant clinical implications that will require clinical trials to determine efficacy, despite promising pre-clinical data.

4.3. Vitamin C

Vitamin C, also known as ascorbic acid (AA), is a crucial water-soluble antioxidant that plays multiple roles in the body, including acting as a cofactor for various enzymes and inhibiting the generation of ROS. Additionally, it directly scavenges ROS and RNS while repairing other oxidized scavengers. One fascinating aspect of ascorbic acid is its neuroprotective activity, and AA has been proposed as a therapeutical adjunct in several neurological conditions [129].

Indeed, the brain exhibits one of the highest ascorbic acid concentrations in the body, thanks to an active uptake from the bloodstream. The brain concentration of AA varies from 200–400 μM in the extracellular space to 10 mM intracellular, i.e., almost 100 times the concentration in the plasma [130,131].

The effect of AA on vessels started to be investigated more than forty years ago [132]. It has demonstrated that it has the potential to enhance impaired endothelium-dependent vasodilation in peripheral arteries in various conditions characterized by endothelial dysfunction [133]. However, the impact of vitamin C on peripheral and cerebral circulations may differ [134].

Although blood hyperoxia does not appear to be convincingly associated with cerebral vasospasm following a subarachnoid hemorrhage [135], animal studies have shown that intracisternal injected Oxy-Hb (oxyhemoglobin) may result in a concentration-dependent contraction of cerebral artery strips. However, the presence of ascorbic acid significantly modifies the biological activity of Oxy-Hb, suppressing its vasoconstrictor activity and minimizing its ability to reduce vasodilator actions [136].

The cerebrovascular effects of AA were recently evaluated in an elegant study by Mattos et al. [137], investigating the effects of isocapnic hyperoxia (IH) on cerebral blood flow (CBF) and metabolism. Ten male participants underwent a 10-minute IH trial with intravenous saline and AA infusion (3g). AA infusion inhibited ROS production and preserved NO bioavailability, as indicated by reduced ROS biomarkers and unchanged nitrite levels. The infusion also prevented regional and total CBF decline and restored the cerebral metabolic rate of oxygen (CMRO$_2$) during IH. This study further confirms that ROS play a role in CBF regulation and metabolism, and antioxidants such as AA can have indirect vasoactive effects.

Considering all this, the use of ascorbic acid in protecting the cerebral vascular tone during high oxidative stress conditions, like those seen in critically ill patients or acute brain injuries, requires further study as there are few adverse reactions [129].

4.4. Vitamin E

Vitamin E is not a single molecule, but rather a group of fat-soluble substances with similar vitamin activity, which includes 4 tocopherols (alpha, beta, gamma, delta) and 4 tocotrienols (alpha, beta, gamma, delta). The biologically most active isoform among them is alpha-tocopherol [139]. These compounds protect the integrity of cellular membranes by shielding them from free radicals that can generate and by directly neutralizing superoxide and hydroxyl radicals. Vitamin E may have potential neuroprotective effects, particularly in neurodegenerative diseases, stemming from its activity in reducing neuroinflammation [140].

Besides its role as an antioxidant, vitamin E plays a significant role in various cellular processes, such as in the vascular vessels. For example, in patients with coronary spastic angina, administering alpha-tocopherol acetate at 300 mg/day restored flow-dependent vasodilation [141]. This improvement was accompanied by a reduction in levels of plasma lipid peroxidation substances and a decrease in anginal attacks.

Endothelial cells, when replete with vitamin E, are better equipped to prevent blood-cell components from adhering to their interior surface in blood vessels. Moreover, vitamin E enhances the expression of two enzymes that suppress arachidonic acid metabolism, leading to increased release of prostacyclin from the endothelium, promoting blood vessel dilation and inhibiting platelet aggregation [6]. Its administration can improve arteriolar compliance [142] and endothelium-dependent relaxation [143]. Furthermore, a meta-analysis indicates that vitamin E might provide protection in preventing ischemic stroke [144], but another recent one failed to show a benefit [145], concluding that further well-designed randomized controlled trials are required to reach a conclusive result.

4.5. Other antioxidants

Other antioxidants can be promising adjunct therapies in critically ill patients or those with brain injuries. For instance, catalase, which degrades hydrogen peroxide, when administered intracisternal in meningitis models demonstrated a reduction in the elevation of rCBF (regional cerebral blood flow), ICP (intracranial pressure), and brain water content, primarily caused by superoxide or its derivatives [146]. Indeed, hydrogen peroxide induces relaxation in cerebral arteries, regardless of the presence of intact endothelial cells. However, these relaxations were suppressed by catalase, while SOD (superoxide dismutase) had no impact, suggesting that the relaxations result from the direct effect of hydrogen peroxide [147]. Likewise, other than improving endothelial function [148], flavonoids may elicit favorable impacts on the vascular system, resulting in ameliorating cerebrovascular blood flow [149], potentially preventing vasospasm in SAH [150], and with therapeutic effects on ischemic stroke-induced models [151].

Vitamin D has demonstrated the potential to improve neurological outcomes in brain-injured patients with significant vitamin D deficiency [152]. Interestingly, its levels have shown a correlation with intracranial aneurysm rupture in patients with SAH [153]. Furthermore, it has been suggested that the vasoprotective effects induced by vitamin D may be attributed to a reduction in oxidative stress [154]. Nevertheless, its ability to effectively prevent oxidative stress remains still inconclusive, and its role as an antioxidant cannot currently be definitively established [155].

Finally, circulating uric acid may act as a significant water-soluble antioxidant, particularly against peroxynitrites ($ONOO^-$) in hydrophilic settings. However, within the cells, uric acid may turn into a potent pro-oxidant, triggering oxidative stress cells and mitochondria and promoting the production of inflammatory cytokines [33], in a paradoxical dualism [156]. This exemplifies the difficulties in evaluating these data and underscores the need for high quality clinical studies.

5. Future perspectives

The regulation of vascular tone in cerebral vessels is a complex process that involves multiple factors and mechanisms [157], which include pressure-induced regulation, shear stress, local metabolism, and the control of the vascular diameter by neuronal activity. As described, the presence of ROS, RNS, and antioxidants can result in vasodilatory and vasoconstrictive effects in cerebral blood vessels, with a complex interplay activity [158]. In situations of intense hyperoxia, where there's a significant rise in O_2^-, the existing NO can be neutralized by O_2^-. The rate of this reaction matches the combined rates of other known superoxide degradation reactions [159]. The chemistry of NO suggests that its half-life is likely controlled by ROS, which increases in proportion to the partial pressure of oxygen in the brain, leading to an increase in arterial tone. Interestingly, during hyperbaric oxygenation in animal models, the vasodilating effect of superoxide dismutase when animals were pre-treated with a NO-synthase inhibitor, was not seen [160], suggesting that one cause of vasoconstriction in the brain during hyperoxia might be the neutralization of NO by O_2^-, impacting its natural ability to relax blood vessels.

Critically ill patients and those with acute brain injuries are particularly vulnerable to oxidative stress due to elevated oxygen levels [161] and increased ROS and RNS production [162]. In these patients, the balance of redox reactions becomes essential, making antioxidants potential therapeutic agents to counteract oxidative damage. Antioxidants have been considered as a potential adjunctive

treatment for various critical illnesses and have notably been suggested as a potential therapeutic option for patients with sepsis [163]. Nevertheless, they have been studied and shown to be ineffective in a clinical study of sepsis [164]. In the context of patient-tailored therapy, it is plausible that also antioxidant therapy should be targeted toward those who truly require it, and it is conceivable that antioxidant levels should be evaluated in the intensive care unit, as most ICU patients experienced swift and severe deficiencies in antioxidants [165]. Future research should focus on how to assess antioxidant levels and identifying its most valuable indicators within this patient population.

Antioxidants can neutralize ROS and RNS, prevent their generation, and repair the damage caused by free radicals. For this reason, they have been proposed and tested to reduce the effects of reactive species on cerebral blood flow [137]. Indeed, even the mildest reduction in the regional cerebral blood may lead to cognitive dysfunction [166]. Therefore, utilizing antioxidants may potentially serve as a relatively safe supplementary therapy for specific critically ill patients or those with brain injuries. This may mitigate cognitive impairments in the former group and reduce secondary brain damage in the latter pending clinical trials. For example, ascorbic acid has demonstrated its ability to preserve NO bioavailability, prevent CBF decline, and protect the cerebral metabolic rate of oxygen during conditions of high oxidative stress [137]. N-acetylcysteine (NAC) administration has shown neuroprotective effects in reducing the size of cerebral stroke and improving neurological deficits [167].

While antioxidants hold promise for potential benefits, there is currently limited human evidence available. To our knowledge, as of now, there are no FDA-approved antioxidant therapies for TBI. Thus, further research is required to elucidate their precise mechanisms of action, optimal dosages, combinations of antioxidants, and potential interactions with other treatment modalities.

6. Conclusions

Understanding the complex interplay between ROS, RNS, antioxidants, and cerebral vascular tone is crucial for developing effective therapeutic strategies for neurological disorders. Antioxidants show promise as potential adjunct therapies to mitigate the harmful effects of oxidative stress and preserve cerebral blood flow in critically ill patients and acute brain injury cases. As research in this area continues to evolve, new opportunities may be unlocked to improve the prognosis and quality of life for patients with neurological conditions through targeted antioxidant interventions.

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