Stroke: Unifying Mechanism Involving Antioxidant Therapy, Reactive Oxygen Species, and Oxidative Stress

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Abstract

Reactive oxygen species (ROS) and oxidative stress (OS) play roles in stroke, as also in Alzheimer’s (AD), Parkinson’s (PD) disease and Schizophrenia (SCZ). Various sources, including oxidases, serve as generators of ROS-OS, such as mitochondria, NADPH, cytochromes P450, monoamines, ET metal complexes, G72 gene, and microglia. Many novel examples of antioxidants (AOs) exert a positive influence on the harmful effects, namely through a unifying mechanism based on ET-ROS-OS-AO. Drugs for treatment of stroke are discussed in relation to the unifying theme including phenolic and phenolic ethers.

Keywords: Stroke; Ischemia; Radicals; Oxidative Stress; Reactive Oxygen Species; Antioxidants

Abbreviations: ET: Electron Transfer; ROS: Reactive Oxygen Species; OS: Oxidative Stress; AO: Antioxidant.

Introduction

Symptoms

Stroke is a leading cause of death and disability [1] and ischemic stroke is the second leading cause of death worldwide [2]. A stroke is a brain injury that takes place due to disruption of blood supply for various reasons [3]. This event is classified into these categories, hemorrhage (bleeding in diverse parts of the brain, and thrombotic (clot formation in the artery due to atherosclerosis, the most common type), embolic (a blood clot or other debris traveling to the brain causing harm). Symptoms, which can occur in different areas of the brain, are as follows: dizziness or confusion, numbness, visual disturbance or loss, difficulty walking, slurred speech, seizures, stupor, coma, and irregular breathing [4]. Stroke may be preceded by transient, ischemic attacks. Risk factors include smoking, diabetes, high blood pressure, heart disease, and genetics.

Unifying Mechanism

Figure 1: Redox cycling with superoxide and ROS Formulation.

Stroke fits into the unifying mechanism which has been widely applied, previously in an article involving electron transfer (ET), reactive oxygen species (ROS) and oxidative stress (OS) [5]. This unifying mechanism argues that the preponderance of bioactive substances, usually as the metabolites, incorporate ET functionalities. We believe these ET-metabolites play an important role in
physiological responses. The main group includes quinones (or phenolic precursors), metal complexes (or complexes), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or iminium species). Resultant redox cycling is illustrated in Figure 1. In vivo redox cycling with oxygen can occur, giving rise to OS through generation of ROS, such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl, and superoxide) (Figure 1). Cellular and mitochondrial enzymes can also perform catalytically in the reduction of O2.

In some cases, ET results in involvement with normal electrical effects (e.g. neurochemistry). Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range. Hence, ET in vivo can occur resulting in production of ROS, which can be beneficial in cell signaling at low concentrations but produce toxic results at high levels. Electron donors consist of phenols, N-heterocycles or disulfides in proteins, which produce relatively stable radical cations. ET, ROS and OS have been increasingly implicated in the mode of action of drugs and toxins, e.g. anticancer drugs [6], carcinogens [7], cardiovascular toxins [8], toxins [9], ototoxins [10] and various other categories [11].

In addition to the above, there is a plethora of experimental evidence supporting the theoretical framework. This evidence includes generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, effect of exogenous AOs, and DNA oxidation and cleavage products, as well as electrochemical data [5]. This comprehensive, unifying mechanism is consistent with the frequent observation that many ET substances display a variety of activities (e.g. multiple-drug properties), as well as toxic effects. It is important to recognize that mode of action in the biodomain is often involved with many physiological actions and is multifaceted. In addition to ET-ROS-OS in relation to mechanism, much attention in the literature is paid to AO action entailing physiological effects.

**ROS-OS**

ROS can be beneficial, but at high levels toxic effects often predominate. There are various sources for these species [5]. NAPDH oxidase is an important producer of the ROS in various organs. The G72 gene increased radical generation in cells. The gene acts as an activator of oxidase. ROS generated by NO synthase have been implicated in an array of harmful behaviors. Mitochondria provide another source of ROS-OS which appears to contribute to aging. Leakage of electrons occurs in the ET chain which react with oxygen to produce superoxide, a precursor of another ROS. Other examples of ROS producers are cytochrome P450, metal complexes, monoamine oxidase and microglia.

There is literature for specific sources of ROS-OS in stroke, which is rare in brain illness. A study found systemic oxidative damage to lipids and proteins at baseline in stroke [12]. Malondialdehyde, an OS marker, concentrations correlated with stroke severity and was associated with hemorrhage complications. ROS generated by NO synthase have been implicated in an array of harmful behaviors. Mitochondria provide another source of ROS-OS which appears to contribute to aging. Leakage of electrons occurs in the ET chain which react with oxygen to produce superoxide, a precursor of another ROS. Other examples of ROS producers are cytochrome P450, metal complexes, monoamine oxidase and microglia.

**Therapy**

Curcumin (Figure 2) and derivatives of curcumin (Figures 3 & 4) were investigated in experimental stroke [23]. Phenolic ethers (see Figure 2) can undergo cleavage to phenols. Beneficial AO action was observed in all cases with the methoxy types being significantly better. Prior work deals with demethylation to AO phenolics [17]. Another article reports the neuroprotective effect of curcumin in a stroke model [24]. There was protection against ischemia via AO activity and neuronal apoptosis. Other studies of brain illnesses deal with phenolics and phenolic ethers [16,17].
5-Methoxyindole-2-carboxylic acid (MICA) (Figure 5) provides neuroprotection against stroke [25]. There was a decrease in OS in MICA treated rats based on decrease in H2O2 and lipid peroxidation. The mechanism likely involves AO protection, attenuation of OS, and maintenance of mitochondrial function. The mitochondrial aspect is related to another report [9]. Nobiletin (Figure 6) elicits protection against ischemic stroke [26]. There are accompanying AO and anti-inflammatory responses.

OS and inflammation are important factors in ischemic stroke. The neuroprotective effects were demonstrated in AO and anti-inflammatory pathways [28]. Ginsenoside Rd (Figure 10), an ingredient in ginseng, can improve stroke outcome [29]. Ginsenoside Rd also attenuates redox imbalance, along with enhancing AO activities. There are other examples of polyols acting as AOs, such as sugars like glucopyranose (Figure 11), which possess significant AO capacity [22].

The neuroprotective effects were studied of an AO mixture, Twendee X, composed of ingredients, such as cysteine (Figure 7), ascorbic acid (Figure 8), and coenzyme Q10 (Figure 9) [27]. Astaxanthin (Figures 1 & 2), a natural AO carotenoid, reduces cerebral injury in stroke [30]. Neuroprotection is provided via suppression of ROS and activation of AO defenses. Recovery was increased through promotion of AO defenses. There is inhibition of apoptosis and promotion of neural regeneration. Multiple mechanisms are involved. A related AO is amphotericin B [31].
Mitochondria damage appears to be involved in brain stroke [32]. Diphenyl diselenide (Figures 12 & 13) reduced mitochondrial damage in a stroke model. The neuroprotective action may be due to the maintenance of redox balance. The initial injury is attributed to an increase in ROS. There is a related article by Mancini, et al. (2014), in which the compound, diphenyl diselenide was determined to mimic endogenous antioxidant enzymes or be metabolized by thioredoxin reductase to form selenol intermediate, which can copy the function of the antioxidant selenoenzymes [33].

Risperidone (Figure 14), an antipsychotic drug, displays neuroprotective effects in ischemic stroke [34]. Significant protection was observed against neuronal death. The neuroprotective effect is attributed in part to maintenance of AOs. Losartan (Figure 15) and amlodipine (Figure 16) were studied for beneficial effects on stroke prone rats [35]. The two agents upregulated expression of superoxide dismutase (SOD) and decreased apoptosis. Amlodipine was more effective in decreasing apoptosis, which may be related to the AO properties of the agent in an OS environment.
Nitrones (Figure 17) are potent agents for stroke treatment based on AO, anti-inflammatory, and neuroprotective properties [36]. In vitro evaluation of brain blood barrier (BBB) penetration of select nitrones showed that all of them crossed. Nitrones are electrochemically analogous to iminium (Figure 18) as noted in the introduction. Manganese superoxide dismutase (MnSOD) is an important AO enzyme in the central nervous system [37]. MnSOD is an important therapeutic agent in ischemic stroke by alleviating OS and apoptosis Other preventative effects involve AO.

The following is a brief collection of summaries of other articles that speak to AO, ROS, OS in association with stroke. AO and antiapoptotic approaches have been examined in neuroprotection of stroke. In 2013, Rodrigo et al. noted that ROS has been implicated in stroke and suggests novel AO approaches for treatment of ischemic stroke involving OS and pathophysiology [39]. A 2018 report discusses reactive oxygen species – sensitive NO synthase inhibitor, an agent for stroke treatment, involving AO/NO donor [40]. In 2017, a report suggested that AO enzyme therapy would be useful for ischemic stroke [41]. Transglutaminase, a calcium dependent enzyme, was also involved as a therapeutic target for OS and excitotoxicity in stroke [42]. In another study, AO therapy was used on neuroprophils after stroke [43]. Earlier stroke research, in 2011, was performed involving AO therapy and thrombolysis, which suggested that co-administration of AO drugs could augment the value of thrombolytic therapy [44]. A study by Yi et al. demonstrated AO protection by mitochondrial HMG-CoA synthase contributed to healing in stroke prone rats [45]. In a 2010 study, AO therapy involving vascular targeting was carried out with stroke patients [46]. Later, in 2012, Brea et al. found OS markers are linked to vascular recurrence [47].

A 2013 report deals with the effects of OS on vascular reactivity of stroke prone rats [48]. A 2010 study reported on the effects of inflammatory processes on the brain of stroke rats, finding that they could significantly increase survival through the AO and anti-inflammatory effects of their treatment [49]. A receptor reduces ischemic stroke through reduction of OS inflammation [50]. Receptor agonist treatment ameliorates OS and neuroinflammation in ischemic stroke [51]. Traditional medicines have also been examined. In a 2016 study, Korean traditional medicine provided neuroprotection for stroke through AO/apoptotic pathways [52]. Additionally, green tea prevents OS in stroke models and may have a beneficial impact on cognitive function after stroke [53]. A 2016 study found that intervention with AOs may have protecting effects in severe heat stroke [54].

In 2011 another study examined the relationship between OS, autoimmunity, and heart risk in Africans with HIV/AIDS [55]. They found that these clustered factors along with OS may explain the high risk of stroke in HIV/AIDS patients.

References


