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Potential markers of oxidative stress in stroke☆

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Abstract

Free radical production is increased in ischemic and hemorrhagic stroke, leading to oxidative stress that contributes to brain damage. The measurement of oxidative stress in stroke would be extremely important for a better understanding of its pathophysiology and for identifying subgroups of patients that might receive targeted therapeutic intervention. Since direct measurement of free radicals and oxidized molecules in the brain is difficult in humans, several biological substances have been investigated as potential peripheral markers. Among lipid peroxidation products, malondialdehyde, despite its relevant methodological limitations, is correlated with the size of ischemic stroke and clinical outcome, while F_2-isoprostanes appear to be promising, but they have not been adequately evaluated. 8-Hydroxy-2-deoxyguanosine has been extensively investigated as markers of oxidative DNA damage but no study has been done in stroke patients. Also enzymatic and nonenzymatic antioxidants have been proposed as indirect markers. Among them ascorbic acid, α-tocopherol, uric acid, and superoxide dismutase are related to brain damage and clinical outcome. After a critical evaluation of the literature, we conclude that, while an ideal biomarker is not yet available, the balance between antioxidants and by-products of oxidative stress in the organism might be the best approach for the evaluation of oxidative stress in stroke patients.

Keywords: Free radical; Oxidative stress; Biomarker; Stroke; Antioxidant

Contents

Abbreviations: 4-HNE, 4-hydroxynonenal; 8-OH-dG, 8-hydroxydeoxyguanosine; CEOOH, cholesteryl ester hydroperoxides; COX, cyclooxygenase; CSF, cerebrospinal fluid; CT, computerized tomography; ELISA, enzyme-linked immunosorbent assay; eNOS, endothelial NOS; ESR, electron spin resonance; GC, gas chromatography; GC/MS, gas chromatography/mass spectrometry; GPx, glutathione peroxidase; GSH, glutathione; HPLC, high-performance liquid chromatography; HPLC-EC, high-performance liquid chromatography with electrochemical detection; HPLC MS/MS, liquid chromatography/mass spectroscopy; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; LOOH, lipid hydroperoxides; MDA, malondialdehyde; MRI, magnetic resonance imaging; MS, mass spectrometry; mSOD, mitochondrial superoxide dismutase; NMDA, *N*-methyl-D-aspartic acid; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; OH•, hydroxyl radical; ONOO−, peroxynitrite; ORAC, oxygen radical absorbance capacity assay; oxLDL, oxidized low-density lipoproteins; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARs, thiobarbituric acid-reactive substances; TNF-α, tumor necrosis factor-α; TRAP, total peroxyl radical–trapping potential.

☆ This article is part of a series of reviews on "Free Radicals and Stroke." The full list of papers may be found on the home page of the journal.

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Introduction

The past decade has witnessed tremendous achievements in the ability to diagnose stroke, but its treatment is still unsatisfactory [1]. Stroke remains the third most common cause of death, particularly in the elderly. The mortality rate of stroke in the acute phase is as high as 20% [2] and it remains higher for several years after the acute event in stroke patients than in the general population [3]. Stroke is also an important cause of morbidity and long-term disability: up to 40% of survivors are not expected to recover independence with self-care and 25% become unable to walk independently. Since life expectancy is continuing to grow, the absolute number of individuals with stroke will further increase in the next future.

Ischemic stroke accounts for about 75% of all cases while hemorrhagic stroke is responsible for almost 15% of all strokes. It has also been estimated that up to 30% of all ischemic strokes will eventually undergo hemorrhagic transformation [4].

Oxidative stress is defined as the condition occurring when the physiological balance between oxidants and antioxidants is disrupted in favor of the former with potential damage for the organism [5]. An increased production of free radicals and other chemical species has been demonstrated in both ischemic and hemorrhagic stroke, and oxidative stress is proposed as a fundamental mechanism of brain damage in these conditions [6]. Moreover, some compounds with significant antioxidant properties including ebselen [7], human serum albumin [8], dehydroascorbic acid [9], and uric acid [10] have been demonstrated to reduce stroke-related brain damage in animal models.

Since free radicals are extremely difficult to measure directly, the availability of reliable peripheral markers of oxidative stress occurring in the brain would allow: (1) confirmation of the role of oxidative stress in the pathogenesis of stroke; (2) measurement of the severity of the brain insult; (3) following the evolution of the brain lesion; and (4) quantification of the efficacy of therapeutic intervention.

The aim of this review is to present and critically evaluate the scientific literature concerning potential markers of oxidative stress in stroke patients.

Sources and selection criteria

In order to find all the relevant articles we searched PubMed by using the keywords: “oxidative stress,” “antioxidant,” “lipid peroxidation,” “protein oxidation,” “DNA oxidation,” and “stroke” in various combinations. We first included articles that related to human studies, and then evaluated the most relevant articles in animal models of stroke. We selected articles published in English between January 1965 and December 2004.

Oxidative stress in ischemic and hemorrhagic stroke

Although ischemic and hemorrhagic stroke have different risk factors and pathophysiological mechanisms, there is evidence of an increased generation of free radicals and other reactive species in both conditions, leading to oxidative stress [11].

Ischemic stroke is the consequence of the interruption or severe reduction of blood flow in cerebral arteries. According to the degree of hypoperfusion it is possible to identify an area with complete absence of flow, namely the core, where neuronal death occurs within a few minutes, and a surrounding area, called penumbra, which suffers from a moderate reduction of blood flow and contains functionally impaired but still viable brain tissue. The penumbra has a variable outcome. If blood flow is not restored within a relatively short time it undergoes the same destiny of the core region. On the other hand, reperfusion can save the brain tissue but might potentially have negative consequences: upon reoxygenation, oxidative stress is rapidly built up and numerous nonenzymatic oxidation reactions take place in the cytosol and/or in cellular organelles [6,12].

Independent of the mechanisms responsible for ischemic stroke, ischemia causes a cascade of events that can increase free radical production via several different pathways. The main change affecting neurons during ischemia is the exhaustion of the high-energy phosphate compound, ATP, due to the lack of the substrates for its production, i.e., oxygen and glucose. The energy failure causes membrane depolarization, due to reduced activity of ATP-dependent ion pumps, such as Na^+/K^+-ATPase. This impairment compromises in turn transmembranous ionic gradients, causing an influx of extracellular Ca^{2+} through voltage-sensitive Ca^{2+} channels and uncontrolled release of excitatory amino acids, such as glutamate in the extracellular space [13]. The excessive release of glutamate is also mediated by Ca^{2+}-induced stimulation of presynaptic terminals and the disturbance of the uptake and inactivation system of glutamate, which is ATP and voltage dependent. Glutamate