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Antioxidant strategies in the treatment of stroke☆

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Abstract

Excessive production of free radicals is known to lead to cell injury in a variety of diseases, such as cerebral ischemia. In this review, we describe some of the numerous studies that have examined this oxidative stress and the efficiency of antioxidant strategies in focal cerebral ischemia. Besides using genetically modified mice, these strategies can be divided into three groups: (1) inhibition of free radical production, (2) scavenging of free radicals, and (3) increase of free radical degradation by using agents mimicking the enzymatic activity of endogenous antioxidants. Finally, the clinical trials that have tested or are currently testing the efficiency of antioxidants in patients suffering from stroke are reviewed. The results presented here lead us to consider that antioxidants are very promising drugs for the treatment of ischemic stroke.

Keywords: Focal cerebral ischemia; Free radicals; Oxidative stress

Contents

Abbreviations: BBB, blood–brain barrier; CAT, catalase; COX 2, cyclooxygenase 2; CSF, cerebrospinal fluid; DHA, dehydroascorbic acid; Edaravone, 3-methyl-1-phenyl-2-pyrazolin-5-5-one or MCI-186; GOS, Glasgow Outcome Scale; G6PD, glucose-6-phosphate deshydrogenase; GPX, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; ICV, intracerebroventricular injection; IG, intragastric injection; IP, intraperitoneal injection; IV, intravenous injection; LOOH, lipid peroxide; MCA, middle cerebral artery; MCAo, middle cerebral artery occlusion; MDA, malondialdehyde; NAC, *N*-acetylcysteine; NO, nitric oxide; NOS, NO synthase; P, permanent; PBN, α-phenyl-*N*-*tert*-butyl nitrone; PCO, photochemical occlusion; PEG, polyethylene glycol; PMN, polymorphonuclear leukocyte; PO, per os; post-O, postocclusion; post-R, postreperfusion; pre-O, preocclusion; pre-R, prereperfusion; RANTTAS, Randomized Trial of Tirilazad in Acute Stroke; r-TPA, recombinant tissue plasminogen activator; ROS, reactive oxygen species; SC, subcutaneous injection; SOD, superoxide dismutase; STAZN, stilbazulenyl nitrone; STIPAS, Study of Tirilazad mesylate in Patients with Acute ischemic Stroke; TBARS, thiobarbituric acid-reactive substances; TESS, Tirilazad Efficacy Stroke Study; XDH, xanthine deshydrogenase; XO, xanthine oxidase.

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

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Introduction

Stroke is the third most common cause of death in most industrialized countries after cardiovascular disease and cancer, and its incidence is expected to rise with the projected increase in the number of the aging population. Although preventive treatments, intended for reducing the risk factors (for example, hypertension, hypercholesterolemia, and diabetes) have been demonstrated beneficial, there are, to date, no efficient curative treatments, except the thrombolytic recombinant tissue plasminogen activator (r-TPA), that has been proven effective when given within 3 h after the onset of neurological symptoms.

Experimental models of cerebral ischemia have been developed to improve our understanding of the deleterious mechanisms involved in brain ischemic damage, and to study the potential efficiency of therapeutic strategies. Rodents (mice or rats) are the species used in most of the studies dealing with in vivo cerebral ischemia. Models can be divided into two groups mimicking either global or focal cerebral ischemia (see, for review, [1]). Models of global cerebral ischemia reproduce notably cerebral ischemia subsequent to cardiac arrest. Models of focal ischemia have been developed in the past 3 decades, as the most common cause of stroke in human is the occlusion of the sylvian artery, also called middle cerebral artery (MCA). Furthermore, spontaneous reperfusion, or more recently r-TPA-induced reperfusion, may occur after the ischemic period. Accordingly, to be as close as possible to the human pathology, models of focal cerebral ischemia now consist in permanent or transient (reperfusion) occlusion of the MCA.

Compared to other organs, the brain appears to be particularly vulnerable to oxidative stress as [2]: (1) the cells of human brain utilize 20% of the oxygen consumed by the body, but constitute only 2% of total body weight, indicating that the brain generates many more free radicals than the other tissues, (2) various regions of the brain contain high concentrations of iron, which can catalyze the generation of free radicals, (3) the brain is rich in lipids with unsaturated fatty acids, targets for lipid peroxidation, and (4) the brain possesses low to moderate protective antioxidant systems compared to kidney or liver.

The hypothesis that an oxidative stress, consecutive to a free radical production, essentially during the postischemic reperfusion stage, is involved in the ischemic damage emerged for the first time in the mid 1980s [3]. Since this period, the role of oxidative stress in postischemic lesion has been extensively studied.

This review regroups most of these studies that have been carried out in rodents using different models of focal cerebral ischemia (either permanent or transient), which are, as noted above, most relevant to human stroke.

Mechanisms of free radical production after cerebral ischemia

In normal brain tissue, the production of reactive oxygen species (ROS), such as superoxide anion radical, hydrogen peroxide, hydroxyl radical, and peroxinitrite anion, is balanced by endogenous enzymatic (superoxide dismutase or SOD, glutathione peroxidase or GPX, catalase) and nonenzymatic (for example, glutathione, uric acid, vitamins C and E) antioxidative defenses. Thus, SOD represents the first line of defense against oxidative stress, by catalyzing the dismutation reaction of superoxide anion to hydrogen peroxide, whereas GPX and catalase protect the cells from the toxic effects of hydrogen peroxide by catalyzing its decomposition into water without free radical production. However, after cerebral ischemia and particularly reperfusion, this free radical production is dramatically increased and overwhelms endogenous antioxidant systems, leading to a disruption of the equilibrium. This massive free radical production may be generated by various pathways [4] (Fig. 1), including those described in the following sections.

Xanthine oxidase

Several experimental studies suggest that xanthine oxidase (XO) might not be a major source of free radicals [5,6]. This enzyme catalyzes the oxidation of hypoxanthine to xanthine and also xanthine to uric acid, generating superoxide anions. Moreover, xanthine deshydrogenase (XDH), another form of this enzyme, catalyzes a similar