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Oxidative stress during the chronic phase after stroke☆

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Abstract

Stroke is a complex disease originating and developing on the background of genetic predisposition and interaction between different risk factors that chronically damage blood vessels. The search for an effective treatment of stroke patients is the main priority of basic and clinical sciences. The chronic phase of stroke provides possibilities for therapy directed toward stimulation of recovery processes as well as prophylaxis, which reduces the probability of subsequent cerebrovascular events. Oxidative stress is a potential contributor to the pathophysiological consequences of stroke. The aim of the present review is to summarize the current knowledge of the role of oxidative stress during the chronic phase after stroke and its contribution to the initiation of subsequent stroke. The relationship among inflammation, hemostatic abnormalities, and platelet activation in chronic stroke patients is discussed in the context of ongoing free radical processes and oxidative damage. Free radical-mediated effects of increased plasma level of homocysteine and its possible contribution to the processes leading to recurrent stroke are discussed as well. The status of the antioxidant defense system and the degree of oxidative damage in the circulation of stroke survivors are examined. The results are interpreted in view of the effects of the vascular risk factors for stroke that include additional activation of inflammatory and free radical mechanisms. Also, the possibilities for combined therapy including antioxidants in the acute and convalescent stages of stroke are considered. Future investigations are expected to elucidate the role of free radical processes in the chronic phase after stroke and to evaluate the prophylactic and therapeutic potential of anti-radical agents.

Keywords: Stroke; Chronic phase; Oxidative stress; Free radicals; Lipoperoxidation products; Antioxidants; Homocysteine; Inflammation

Contents

Abbreviations: AA, arachidonic acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; BBB, blood brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; CRP, C-reactive protein; DNA, deoxyribonucleic acid; EAA, excitatory amino acids; GSH, reduced glutathione; GSH-Px, glutathione peroxidase; HDL, high-density lipoproteins; INF, interferon; IL, interleukin; ICAM, intracellular adhesion molecules; LDL, low-density lipoproteins; MDA, malondialdehyde; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; NMDA, *N*-methyl-D-aspartate; NOS, nitric oxide synthase; NO•, nitric oxide; PKC, protein kinase C; PMN, polymorphonuclear leukocytes; ROOH, lipid hydroperoxides; RBC, red blood cells; ROS, reactive oxygen species; sICAM, soluble isoforms of intracellular adhesion molecules; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reactive substances; TNF, tumor necrosis factor; WBC, white blood cells.

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Introduction

Stroke is a leading cause of death and long-term disability in industrialized countries. The main priority of basic and clinical sciences is the search for effective treatment of stroke patients. The numerous investigations published so far show that stroke is a disease susceptible to treatment in the hyperacute phase but its effectiveness is rather limited [1]. They provide optimism for development of new therapies aiming to improve the functional outcome of patients and their recovery. On the other hand, the opportunities for therapy during the subacute and chronic stages of stroke should not be ignored. Survivors of stroke are at a high risk of subsequent vascular complications and new vascular accidents. It is a problem of significant social and economic consequences since nowadays there are over 50 million stroke survivors alive in the world. That is why the efforts in stroke patients should be directed to both the stimulation of neurological recovery mechanisms and a reduction in the probability of appearance of subsequent cerebrovascular events.

In recent years, the identification of a number of molecules contributing to the neuronal death, particularly apoptosis, has thrown light on the pathogenesis of brain damage after ischemic and hemorrhagic stroke. Oxidative stress is believed to be one of the mechanisms taking part in the neuronal damage of stroke.

Oxidative stress is a state of imbalance between free radical production, in particular, reactive oxygen species (ROS), and the ability of the organism to defend against them, leading to progressive oxidative damage. The study of oxidative stress in stroke is difficult to conduct because of the complexity of ongoing processes, each of which may cause radical overproduction and oxidative damage, as well as because of the complicated interaction between these processes due to the presence of direct and reverse relations, some of which may exacerbate or reduce the degree of damage. It is assumed that oxidative stress contributes to the initiation and development of stroke via different interrelated mechanisms: excitotoxicity resulting in cellular enzyme activation and ROS generation; inflammation leading to leukocyte priming and activation and accompanied by an excessive radical production; activation and oxidative damage of endothelium resulting in reduced bioavailability of nitric oxide ($NO^{\bullet}$); free radical-mediated hyperhomocysteinemia; lipid peroxidation of plasma and cellular components including those in the arterial vessel wall and macrophages, processes each one of which may exacerbate oxidative damage through mechanisms of positive feedback.

There is ample evidence from experimental models for enhanced free radical generation in the brain during cerebral ischemia/reperfusion. Direct clinical studies verifying the relation between stroke and oxidative stress are yet missing mainly because of morphological difficulties arising when measuring free radicals in cerebral tissue. ROS are short-living compounds. Nevertheless, they initiate complex chain reactions that produce a range of molecular structures, many of which are yet unknown. The elevation in lipid peroxidation products in the circulation and the weakened cellular antioxidant defense system are considered an indirect proof of oxidative stress arising in stroke. New and reliable markers for oxidative stress are still being sought by scientists in their research work [2].

Studies monitoring the changes in the oxidative stress indicators during the chronic phase after stroke are scarce. The interpretation of results obtained in chronic stroke patients is getting more complicated by the fact that stroke is an etiologically and pathologically heterogeneous disease and the risk factors for a given type of stroke may not be risk factors for another stroke subtype. Risk factors bring about a chronic change in the walls of blood vessels that include additional activation of inflammatory and free radical mechanisms. Approximately one-fifth of stroke patients have diabetes mellitus, a considerable amount of them have high blood pressure, and some of them have or have had a recent infection or inflammation. Furthermore, in the presence of more than one risk factor, their combined influence on the free radical processes should also be taken into consideration, as it may be an additive or synergistic