OXIDATIVE STRESS IN ACUTE ISCHEMIC STROKE

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Abstract

Interruption of focal cerebral blood flow causes ischemic injuries to local brain tissue. The mechanism of ischemic injury, so-call ischemic cascade, is a primary damage. The primary injury leads to tissue necrosis then apoptosis. Secondary injury begins when ischemic tissue is reperfused. This secondary damage adds up the injuries to not only ischemic tissue but also surrounding normal tissue. Oxidative stress plays the major role in reperfusion injury. Neuroprotective therapies that intervened with mechanism of oxidative stress may show beneficial results in treatment of acute ischemic stroke.. *(J Thai Stroke Soc 2014; 13: 85-89.)*

Introduction

Stroke is the leading cause of adult disability particularly in elderly and remains the third most common cause of death worldwide.[1-3] However, only three interventions for acute ischemic stroke treatment have been approved for improving stroke outcomes including intravenous recombinant tissue plasminogen activator (rtPA), admission to stroke unit and 48-hours aspirin therapy.[4,5] Physicians have remained powerless regarding protection and recovery of neurons from ischemic insults. This encouraged the interest in the development of neuroprotective therapies. The concept of neuroprotection mainly came from the studies of the pathology and pathophysiology of ischemic brain injury.[6] It has been well documented that abrupt deprivation of oxygen and glucose to neuronal tissues as well as reperfusion elicit a series of pathological cascades, leading to spread of neuronal death. Neuroprotective agents intended to block these cascades.[7]

Mechanism of Ischemic cascade

Ischemic brain injury results from the cessation of cerebral blood flow. Interruption of cerebral blood flow results in multiple neurologic injuries, the so-call ischemic cascade.[8] Lack of oxygen and blood supply leads to adenosine triphosphate (ATP) producing failure.[9] Neurons and glials switch to anaerobic process, result in lactic acidosis.[10] Na^+-K^+ ATPase pumps fail, causing cells to become depolarized, allowing ions, especially calcium (Ca^{++}), influx the cells. Intracellular calcium levels become rising, then stimulate the release of the excitatory amino acid

neurotransmitter glutamate.[11] Glutamate allows more calcium influx by trigger opening of Ca^{++}-permeable N-methyl-D-aspartate (NMDA) receptors and alfaamino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors. The generation of dangerous chemicals including free radicals, reactive oxygen species, endonucleases, ATPases, and phospholipases, the so-call excitotoxicity, begins after excess calcium influx.[7] Cell membrane and mitochondria break down causing necrotic cells and apoptosis. Glutamate and other toxic chemicals are released into the environment by these necrotic cells.[12] These toxins damage surrounding cells. Further damage, the so-called reperfusion injury, begins when the brain is reperfused.[13] Inflammatory cells accumulate to swallow up damaged tissue and release many cytokines.[14] Harmful chemicals destroy the blood-brain barrier (BBB). Damaged BBB leads to leakage of large molecules especially albumins causing cerebral edema.[15] Cerebral edema causes compression of and further damage to brain tissue.[16] Ischemic cascade is shown in figure 1.

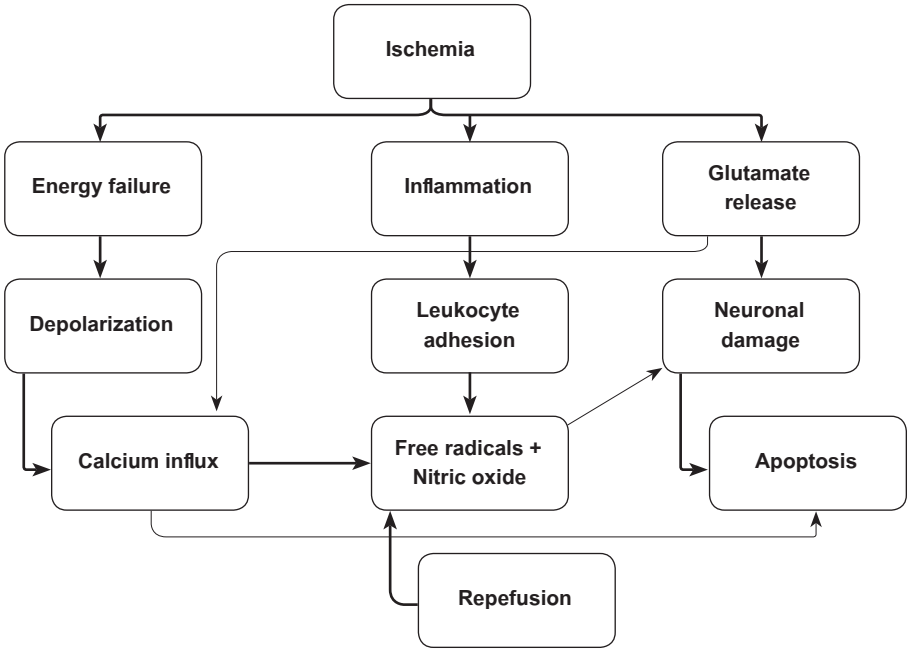

Figure 1 Ischemic cascade

Oxidative stress: a role in pathophysiology of ischemic cascade

Ischemic stroke results from the abrupt interruption of focal cerebral blood flow. Interruption of cerebral blood flow results in primary neurologic injury. Oxidative stress is postulated to occur after the subsequent reperfusion of the ischemic territory. This secondary injury following ischemic cascade is thought to be initiated by a numerous of metabolic and biochemical changes that occur within minutes to hours following the initial injury.[17] Following the initial insult, many mechanisms of secondary neurologic injury have been proposed to occur, most of which involve the increased activity of excitatory amino acids particularly glutamate.[12] The increased activity of glutamate results from the activation of voltage-dependent sodium and calcium channels, leading to an intracellular influx of sodium and calcium ions.[18] The influx of these ions compromises the function of the sodium-potassium exchange pump, resulting in the massive release of glutamate.[12] Glutamate activates the *N*-methyl-D-aspartate (NMDA) and alfaamino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMDA) receptors, impairing calcium and sodium homeostasis.[11,12,18]

Elevated intracellular calcium concentrations detain phosphorylation processes in the mitochondria, inhibiting the production of adenosine triphosphate (ATP) and also compromising the function of the ionic pump of the cell.[18] As well, the increase in intracellular calcium affects cell membranes by activation of phospholipase,

resulting in hydrolysis of membrane phospholipids and release of free fatty acids.[19] The resulting effects of lipase stimulation are vasodilation and oxygen free radical production with lipid peroxidation, resulting in oxidative stress.[20]

Oxidative stress is defined as a disturbance in the pro-oxidant-antioxidant balance in favor of the pro-oxidant, leading to potential damage.[21,22] The brain consumes a large quantity of oxygen, making it susceptible to oxidative stress.[23] Oxidative stress can be mapped out primarily to formation of superoxide and nitric oxide.[24] The highly reactive products of superoxide and nitric oxide include the peroxynitrite and hydroxyl radical. Both molecules have important roles in health, serving as regulators of blood flow and neurotransmission.[19,22] Disturbance in the production and metabolism of either molecule can have pathologic consequences. Lipid peroxidation as a result of formation of these free radicals was one of the first mechanisms explored to explain this secondary injury insult and may be a result of intracellular dysfunction caused by oxidative stress.[20,24]

Translation to neuroprotective agents

The final purpose for understanding the mechanism of oxidative stress in ischemic cascade is to build up neuroprotective therapies. Several methods have been evaluated for examples inhibition of lipid peroxidation by tirilazad, a non-glucocorticoid steroid, inhibition of xanthine oxidase by allopurinol, superoxide dismutases and their mimetics, catalase and glutathione peroxidase, nitric oxide synthase inhibition and mitochondrial permeability transition inhibitors.[11] Unfortunately, all methods have promised results in laboratory but failed when got tested in human. Recently, a spin trap was considered to be one of the most likely compounds to be successfully converted into the human stroke model.[25]

The overabundance of failed clinical trials with neuroprotective drugs for acute ischemic stroke have raised justifiable concerns about how best to proceed for the future development of such interventions. To help in the identification of potential treatments, the Stroke Therapy Academic Industry Roundtable (STAIR) proposed Recommendations for Standards Regarding Preclinical Neuroprotective and Restorative Drug Development in 1999.[26]

NXY-059, a Nitrone-based compound, is a free radical scavenger that reduces the size of the infarct and preserves brain functioning in animal models of acute ischemic stroke and is a neuroprotectant that meets the STAIR criteria.[25,27] SAINT (Stroke-Acute Ischemic-NXY Treatment) is a multicenter, randomized, double-blind, placebo-controlled trial undertaken to assess the safety and efficacy of NXY-059 in acute ischemic stroke. SAINT-I enrolled 1699 patients presenting within 6 hours of stroke onset to randomly receive NXY-059 (n = 858) or placebo (n = 847). The Study significantly improved the primary outcome (reduced disability at 90 days), but it did not significantly improve other outcome measures, including neurologic functioning as measured by the NIHSS score.[27] Given the disappointments of the past, the sponsors and investigators quite rightly insisted on a second phase III, SAINT-II trial. The sample size for the SAINT-II trial was increased from 1700 to 3200 in order to achieve 80% power for confirmation of the improvement in modified Rankin scale reported in SAINT-I.[28] Unfortunately, the results of SAINT-II trial were completely negative.[28,29] Finally, the sponsors decided to quit further development of NXY-059 in acute ischemic stroke.[30]

Although the results were negative, these SAINT studies gave substantial impact to neuroprotective research. After failure of SAINT-II trial, the new roadmap for neuroprotection was proposed. The roadmap recommended that neuroprotection research should be pursued but with a very different and more rigorous approach.[31]

Conclusions

Oxidative stress is a major contributor to ischemic brain injury. Neuroprotective therapies that intervened with mechanism of oxidative stress showed beneficial results. However, absolute profit in human still requires to be approved in clinical trial. The further trials on neuroprotective therapy should invent with the most rigorous experiments.

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