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Non-pharmaceutical therapies for stroke: Mechanisms and clinical implications

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ABSTRACT

Stroke is deemed a worldwide leading cause of neurological disability and death, however, there is currently no promising pharmacotherapy for acute ischemic stroke aside from intravenous or intra-arterial thrombolysis. Yet because of the narrow therapeutic time window involved, thrombolytic application is very restricted in clinical settings. Accumulating data suggest that non-pharmaceutical therapies for stroke might provide new opportunities for stroke treatment. Here we review recent research progress in the mechanisms and clinical implications of non-pharmaceutical therapies, mainly including neuroprotective approaches such as hypothermia, ischemic/hypoxic conditioning, acupuncture, medical gases and transcranial laser therapy. In addition, we briefly summarize mechanical endovascular recanalization devices and recovery devices for the treatment of the chronic phase of stroke and discuss the relative merits of these devices.

Contents

Abbreviations: ACP, antegrade cerebral perfusion; AMES, assisted movement with enhanced sensation; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; BAIPC, bilateral arm ischemic preconditioning; BBB, blood–brain barrier; BCI, Brain–Computer Interface; Bcl-2, B-cell lymphoma-2; BDNF, brain derived neurotrophic factor; CBF, cerebral blood flow; CREB, cyclic adenosine monophosphate response element binding protein; COOL AID, Cooling for Acute Ischemic Brain Damage; COX-2, cyclooxygenase-2; DADLE, ([D-Ala2, D-Leu5]-enkephalin); DOR, δ-opioid receptor; DWI, diffusion-weighted imaging; EA, electro-acupuncture; eNOS, endothelial nitric oxide synthase; ERK, extracellular regulated protein kinases; ENT1, equilibrative nucleoside transporter 1; FDA, Food and Drug Administration; FES, Functional Electrical Stimulation; GABA, gamma-aminobutyric acid; GluR2, glutamate receptor 2; GSK3β, glycogen synthase kinase-3β; HBO, hyperbaric oxygen therapy; HIF, hypoxia inducible factor; HPC, hypoxic preconditioning; HSP70, heat shock 70 kDa protein; IAS, intracranial arterial stenosis; ICTuS-L, Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke; IMS III, interventional management of Stroke III; IκB, inhibitor of NF-κB; IKK, inhibitor of NF-κB kinase; iNOS, inducible nitric oxide synthase; IPC, ischemic postconditioning; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MMP, matrix metalloproteinase; MR RESCUE, mechanical retrieval and recanalization of stroke clots using embolectomy; mRS, modified Rankin Scale; NADPH, nicotinamide adenine dinucleotide phosphate; NBO, normobaric hyperoxia therapy; NEST, NeuroThera Effectiveness and Safety Trial; nNOS, neuronal nitric oxide synthase; NF-κB, nuclear factor-κB; NIHSS, National Institutes of Health Stroke Scale; NMDA, N-methyl-D-aspartate; NO_x^-, nitrite plus nitrate; PI3-kinase, phosphatidylinositol 3-kinase; PGC-1α, αsubunit of peroxisome proliferators-activated receptor-γcoactivator-1; PKA, protein kinase A; PKC, protein kinase C; pO_2, partial oxygen; PPARγ, peroxisome proliferator-activated receptor γ; PTEN, phosphatase and tensin homologue; RIPostC, limb remote ischemic postconditioning; RNS, reactive nitrogen species; ROS, reactive oxygen species; ROSC, Return of Spontaneous Circulation; rTMS, repetitive Transcranial Magnetic Stimulation; rtPA, recombinant tissue plasminogen activator; SphK, Sphingosine kinase; SPOTRIAS, specialized program in acute stroke; STAIR, Stroke Therapy Academic Industry Roundtable; TCM, traditional Chinese medicine; tDCS, transcranial Direct Current Stimulation; TIA, transient ischemic attack; TLT, transcranial laser therapy; TNF-α, tumor necrosis factor α; VE, vessel endothelium; VNS, Vagus Nerve Stimulation; WHO, World Health Organization.

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1. Introduction

Stroke, deemed a worldwide leading cause of death and neurological disability in both immature and adult subjects, continues to wreak physical, psychological and financial havoc in developing and developed nations alike. Instances of acute ischemic stroke result in heterogeneous changes in CBF (cerebral blood flow) and brain metabolism in the affected region. The human brain and its meshwork of roughly 100 billion interwoven neurons receives close to 15% of the body's resting cardiac output while expending 20% of its oxygen, rendering the organ especially sensitive to such cases of hypoxic or ischemic insult (Clarke and Sokoloff, 1999; Fisher et al., 2009; Chao and Xia, 2010; Arai et al., 2011; Ding et al., 2012; Li et al., 2012; Albert-Weissenberger et al., 2013; He et al., 2013). As the brain is extremely sensitive to hypoxia or ischemia, protecting brain tissue from injury, simplified as "neuroprotection", has therefore been a long sought after strategy in quelling physiological damage following stroke onset. Decades of research efforts have investigated over 1000 pharmacological neuroprotectants, including excitatory amino acid antagonists, free radical scavengers, calcium channel blockers, and growth factors that are thought to target and correct different pathophysiological manifestations of ischemic brain injury. Unfortunately, almost all attempts at protecting the brain from ischemic injury have failed at making a successful transition into clinical use. The majority of these failures involved complex pharmaceutical targets and agents. Until now, intravenous rtPA (recombinant tissue plasminogen activator) is the only proven effective treatment in the acute setting. Most neuroprotectants alter only a single step in the broad cascade of biochemical events that lead to ischemic injury, and this over-specification may in part explain failure in the clinical setting (STAIR, 1999). Therefore, it is strongly suggested that stroke be approached with multiple, multifaceted neuroprotective methods capable of ameliorating a broader range of systems gone awry.

Non-pharmaceutical therapies are becoming more common and can be promptly initiated after stroke onset, marking them as ideal to combine with pharmaceutical or thrombolytic therapies which may further salvage affected brain tissue. Indeed, accumulating data suggest that "non-drug" approaches might provide new opportunities for stroke therapy, such as therapeutic hypothermia (Lakhan and Pamplona, 2012; Yenari and Han, 2012), ischemic/hypoxic conditioning (Liu et al., 2009b; Lim and Hausenloy, 2012), acupuncture (Guo et al., 2010; Xia et al., 2010, 2012), certain medical gases (Liu et al., 2011b; Sutherland et al., 2013) and other strategies.

In this review, we focus on the major clinical implications of non-pharmaceutical therapies for acute ischemic stroke and their underlying neuroprotective mechanisms. We also address the recent progress in mechanical endovascular recanalization and

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