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Effectively Improve Ischemic Stroke's Strategy: Attenuate Oxidative Stress

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Abstract

Stroke, as the second mortality ranks after heart disease all over the world, belongs to a cardiovascular and neurological illness and result in a huge burden on medical resources and seriously threatens people's lives and health. And Ischemic Stroke is the most common type of stroke, accounting for more than four-fifths of stroke. Therefore, how to effectively treat Ischemic Stroke is urgent. Currently, there are many treatments for Ischemic Stroke, such as drug therapy, physical therapy, stem cell transplantation and so on. Interestingly, oxidative stress is found to be a vital factor in Ischemic Stroke, and attenuating oxidative stress can effectively improve the Ischemic Stroke disease. Therefore, the purpose of this review is to appraise the recent progress and draw more researchers attention to improving Ischemic Stroke in terms of attenuating oxidative stress.

Keywords: Ischemic Stroke; Oxidative Stress; Traditional Medicine; Biochemical Drug; Physiotherapy

Abbreviations: IS: Ischemic Stroke; ROS/RNS: Reactive Oxygen and Nitrogen Species; SOD: Superoxide Dismutase; MDA: Malondialdehyde; LDH: Lactate Dehydrogenase; GSH-Px: Glutathione Peroxidase; Gpx: Glutathione Peroxidase; MDA: Malondialdehyde; Activator 1: Act1; NO: Nitric Oxide; MCP: Melon Polysaccharide; IR: Ischemic Stroke/Reperfusion; EA: Ellagic Acid; ZO-1: Zonula Occludens-1; MMP-9: Matrix Metalloprotein 9; AQP-4: Aquaporin 4.

Introduction

Ischemic Stroke (IS), also known as cerebral infarction, is one of the most disabling and fatal diseases in cerebrovascular diseases. Due to its high incidence, high disability rate, high mortality rate, and high recurrence rate, IS brings great harm and a heavy economic burden to patients' families and society [1,2] and has an explosive growth trend, posing a great threat to public health [3].

The basic cause of neurological impairment caused by IS is a brain injury of nerve cell death or apoptosis, acute phase for brain energy metabolism disorder caused by glucose and oxygen supply and oxygen free radical formation, nerve cells Ca2+ overload, the formation of excitatory amino acids and noninfectious inflammatory reaction, resulting in a large number of nerve cell necrosis and apoptosis, causes corresponding neurological defects, including hemiplegia, motor, sensory, language dysfunction, etc. [4,5]. What's more,

cerebral embolism induced by nerve damage or vascular blockage caused by hypoxia is the leading cause of IS, and oxidative stress, inflammatory, and blood-brain barrier failure play a huge role in this process [6].

A large number of studies have shown that oxidative stress caused by ROS/RNS can cause nerve cell damage [7] and further lead to a cellular inflammatory, implying that oxidative stress may be the primary cause of IS and targeting oxidative stress is critical for IS treatment [8]. Meanwhile, antioxidant research mainly focuses on traditional medicine, biochemical medicines, physical therapy and so on. Therefore, we will review the use of these antioxidants in attenuating oxidative stress in IS.

Oxidative stress

Oxidative stress occurs when the body's oxidation and antioxidation systems are out of balance, resulting in cellular overproduction of reactive oxygen and nitrogen species (ROS/RNS) that aren't removed by antioxidant processes, and it's associated with aging and disease development. ROS includes superoxide (O_2), hydrogen peroxide (H_2O_2), and hydroxide radicals (OH-), while RNS includes nitric oxide (NO), nitrogen dioxide (NO_2), and peritonitis, to name a few (ONOO-). Different oxidases for the synthesis of oxygen free radicals, such as Nicotine adenine dinucleotide phosphate (NADP), oxidase (NOX), and xanthine oxidase (XO), are recognized as biomarkers for the treatment of cerebral ischemia by anti-oxidative [9]. Copper-zinc SOD (SOD1) in the cytoplasm, manganese SOD (SOD2) in the mitochondria, and superoxide dismutase (SOD) in the nucleus are all required for the conversion of O2 to H2O2. Catalase (CAT) and glutathione enzyme (GSH) are engaged in hydrogen peroxide hydrolysis, with glutathione enzymes such as Glutathione reductase (GR), glutathione peroxidase (GSH-Px), peroxidase (POD), besides, its biomarkers also include malondialdehyde (MDA) and lactate dehydrogenase (LDH).

Traditional Medicine

Traditional medicine, which literally means "classical formula," is a type of medicine that has been passed down from ancient times to the present day in China. According to the report, Coix seeds decreases oxidative stress by activating the TGF/ALK1 signaling pathway, reducing MDA, and increasing superoxide dismutase SOD and GSH when compared to the ischemic stroke/reperfusion (IR) group, GSH and SOD have been shown to protect the brain from ischemia [10]. When compared to the IR group, the Metformin group reduced oxidative stress damage by changing lncRNA-H19 and boosting Rock 2 expression, which reduced MDA, NO, and activated GSH-Px [11].

The antioxidant effect of monomeric Chinese medicine components has recently been the subject of a growing number of studies. Polyphenols [12] reduce mitochondrial oxidative stress by suppressing oxidative enzymes, superoxide generation, and oxidatively modified low-density lipoprotein (OxLDL) synthesis while also enhancing antioxidant enzymes. Quercetin [13], for example, decreases damage by upregulating antioxidant enzymes, poly (ADP-ribose) polymerase (PARP), and caspase-3 activity expression, as well as lowering MDA levels. Furthermore, acid, base and salt monomers lessen oxidative stress. Through the IL-6/ STAT3 pathway, oleic acid [14] lowers MDA and ROS levels while increasing SOD and CAT expression. Through the Nrf2 pathway, chlorogenic acid [15] boosted SOD activity and GSH levels while lowering ROS and LDH generation and MDA build up. Rhodizone [16] decreased ROS generation by lowering total SOD and SOD2 activity. To reduce brain injury in MCAO rats, ephedrine [17] increases GPx and CAT activity, lowers MDA and NO levels, and promotes phosphorylation of PI3K and AKT proteins by stimulating the Erk/CREB/eNOS pathway [18].

Glycosides, compounds formed by linking the end group carbon atom of a sugar or sugar derivative to another class of non-sugar substances. Among, Forsythiaside A [19] causes a significant augment in the expression levels of Nrf2, NAD(P)H, and glutathione transferase, decreasing the expression of malondialdehyde and enhances the expression of superoxide dismutase and glutathione. Pinoresinol diglucoside [20] reduces NO, ROS, and MDA levels and significantly increases SOD, GSH, and GSH-Px by modulating NF-κB pathway and Nrf2/HO-1 pathway. In addition, other analogues such as bitter melon polysaccharide (MCP) [21], it had direct scavenging effects on NO, O2(-) and ONOO- and inhibits lipid peroxidation by inhibiting the activation of JNK3/C-jun/Fas-L and JNK3/cytochrome C/caspase-3 signal cascades to attenuate oxidative stress.

And we also made many of works to clarify the mechanism of alleviation of IR damage, ellagic acid (EA) treats IR, TTC (2,3,5-triphenyltetrazolium chloride staining) shows that it can reduce the infarct area, infarct areas were stained white (Figure 1 A). It is obvious that EA degrades the expression of MMP-9, AQP-4 and upgrades ZO-1 by western blot essay (Figure 1 B). In addition, the level of oxidative stress markers MDA and SOD also is changed and samples were respectively taken from serum and brain (Figure 1C and D), which indicate that EA alleviates the brain damage by anti-oxidative response, it can restore the dysfunction of brain blood barrier (BBB). These results shows that anti-oxidative can reduce IR damage and oxidative stress play crucial roles in ischemic stroke.

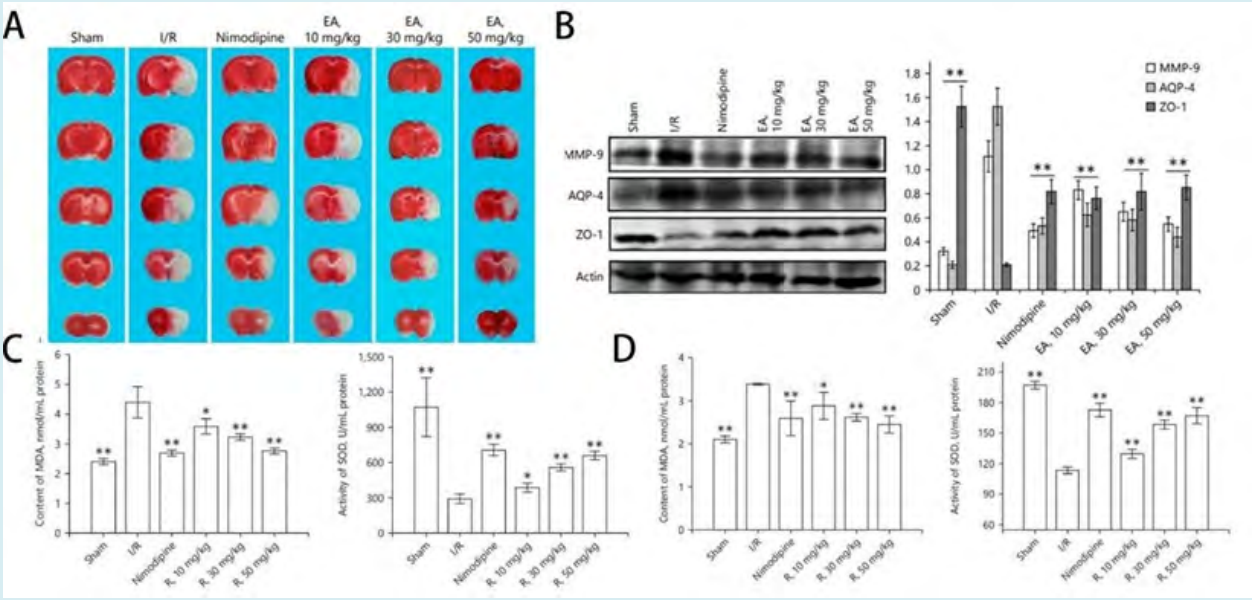

Figure 1: Effects of EA on cerebral ischemia model in rats [22].

Biochemical Drug

Biochemical drugs are mainly classified into nucleic acids, proteins, enzymes, lipids, etc., due to their convenience drug delivery, operability, and strong editability, they occupy a pivotal position in basic scientific research. With the advent of the post-genomic era, the structure and function of DNA, amino acids, peptides, and proteins have been comprehensively cognized. This chapter address non-coding RNAs [23], a class of genetic, epigenetic, and translational regulatory factors, which is composed of microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circRNAs (circRNAs). Due to the development of deep sequencing technology, Non-coding RNAs transcriptions were identified, and their role in disease mechanism is increasingly clear. The following Table 1 summarizes non-coding RNAs regulating IR by influencing oxidative stress (experimental group versus the IR group).

NcRNAs		Biomarkers	Pathway(s)	Reference(s)
LncRNA		↓MDA	via sponging miR-186-5p negative regulation to CTRP3 by inhibiting the NF-κB and activating the Nrf2 pathway	Chen, et al. [24]
	OIP5-AS1	↑SOD、GSH-Px		
	LncRNA NKILA	↓MAD、NO	Inhibit NF-κB	Gao, et al. [25]
		↑SOD、GSH-Px		
Micro-RNA	LncRNA SNHG15	↓MAD、NO	bound to miR-421 to facilitate XIAP expression	Kang, et al. [26]
		↑SOD、GSH-Px		
	miR-31	↓MAD	Inhibit PKD1 and JAK/STAT3	Li, et al. [27]
	miR-98-5p	↑NAD(P)H、HO-1	inhibit SRC-mediated MAPK	Yu, et al. [28]
	miR-137	↓ROS	suppress the IRAK1	Tian, et al. [29]
			/TRAF6/TAK1/NF-κB	
	miR-203a-3p	↓ROS、MDA	enhance the	Li, et al. [30]
	miR-153-3p		phosphorylation of	
		↓MDA、ROS	ERK/JNK/MAPK	

	miR-193b-3p	↑SOD	the seven in absentia homolog 1/Jun N-terminal kinase	Yang, et al. [31]
	miR-217	↓MDA、ROS	miR-217/MEF2D/HDAC5,	Shi, et al. [32]
			miR-217/MEF2D/ND6	
	miR-340-5p	↑SOD	Downregulate Act1/NF-κB	Li, et al. [33]
	miR-410	↑SOD、GSH-Px	inhibit of the TIMP2-dependent MAPK pathway	Liu, et al. [34]
	miR-424	↓MDA、LDH		Liu, et al. [35]
		↑SOD2		

Table 1: Emerging ncRNAs on oxidative stress regulating ischemic stroke.

Physiotherapy

Acupuncture originated from Taoism and Confucianism has the highest recognition and dissemination. A large number of randomized controlled experiments have confirmed the clinical efficacy of acupuncture and moxibustion, and some technologies can systematically evaluate the effect of acupuncture and moxibustion on brain treatment [36]. At the same time, Acupuncture also shows the effect of anti-oxidative stress for IS. Jittiwat found that Laser Acupuncture [37] can reduce the activities of MDA and SOD, and improve the expression of CAT and GSH-Px to alleviate the injury of IS. There are also teams exploring new physical methods, such as Extremely Low-Frequency Electromagnetic field (ELF-EMF), to improve antioxidant capacity through activation of LDH and SOD [38].

Conclusion

Currently, when many free radicals are produced, the main strategy of antioxidant stress process is to make various measures to promote free radical degradation and inhibit the production of free radicals. Physiotherapy, a non-invasive measure, mainly can reduce free radicals via inhibiting oxidation generation. However, a repeated experiment cannot be realized because of the complex internal environment. Moreover, the specific molecular mechanism of physiotherapy is difficult to explain and still unclear. Many clinical trials show that traditional Chinese medicine can alleviate IS injury and improve the patient's condition, which mainly through promoting the generation of antioxidant enzymes and free radical degradation. But it's difficult to guarantee the dosage of administration and utilization rate. Nucleic acid drugs have clear targets and strong editability, which are the main means of target mining. However, when nucleic acid drugs enter the physical complex microenvironment, their degradation rate is significant. At present, nanomaterials that targeted modification have been frequently reported as drug delivery carriers, which has a small size, convenient delivery ways and sustained release function. And it may be a "rising star" for the antioxidant protection of IS. As above, the main regulating chemical stress pathways include activating the classic ERK pathway or inhibiting the NF-κB Pathway. Excessive oxidative stress can produce ROS/RNS, which not only leads to the death of nerve cells but also causes inflammation. In conclusion, oxidative stress plays a vital role in the treatment of IS. It is desirable for us to further explore antioxidant drugs and clarify their mechanisms, which will bring an expectation to patients with cerebral ischemia.

Conflicts of Interest: Authors declare no conflict of interest.

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