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Research Progress of Regulating Endoplasmic Reticulum Stress by Traditional Chinese Medicine in the Treatment of Vascular Dementia

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Abstract: ***Vascular dementia (VaD) is a cognitive dysfunction syndrome directly related to cerebral hypoperfusion caused by cerebral vascular injury. The pathogenesis of this disease is complex, and the western medicine is not effective in the treatment of this disease. Traditional Chinese medicine believes that the disease is located in the brain, due to the stasis of the brain collaterals and resulting in the emptying of the marrow sea. Traditional Chinese medicine (TCM) has the advantages of individualization and integration in the treatment of this disease, and its mechanism has been studied from the perspectives of oxidative stress, central cholinergic system, neuroinflammation, neuronal apoptosis and synaptic plasticity. At present, it is a new research direction to treat vascular dementia by regulating endoplasmic reticulum stress with traditional Chinese medicine. Therefore, this paper systematically elaborated the mechanism of ER stress in vascular dementia, and the mechanism of TCM regulation of ER stress in the treatment of VaD, in order to provide new ideas and new methods for TCM clinical diagnosis and treatment of VaD and basic research.***

Keywords: Vascular dementia, Endoplasmic reticulum stress, Review.

1. Introduction

Vascular dementia (VaD) [1] is a neurodegenerative disease, which is a cognitive dysfunction syndrome directly related to cerebral hypoperfusion caused by cerebral vascular damage. VaD is the most common type of dementia in the elderly after Alzheimer's disease, and its incidence has also been increasing worldwide in recent years. The pathogenesis of VaD is very complex. At present, researchers mainly discuss the pathogenesis of vascular dementia from the perspectives of oxidative stress, central cholinergic system, neuroinflammation, neuronal apoptosis and synaptic plasticity [2]. Studies have shown that Endoplasmic Reticulum Stress (ERS) also plays a key role in the formation of VaD [3]. Therefore, the control of endoplasmic reticulum stress to prevent vascular dementia is a new research direction. Studies have shown that TCM can delay VaD progression by intervening in ERS. Therefore, this article elaborated the mechanism of regulating endoplasmic reticulum stress by traditional Chinese medicine in the treatment of VaD, in order to provide new ideas and new methods for the clinical diagnosis, treatment and basic research of VaD.

2. Overview of Endoplasmic Reticulum Stress

Endoplasmic reticulum (ER) is an organelle present in all eukaryotic cells except mature red blood cells, and is mainly responsible for functions such as protein secretion and folding, calcium storage and release, and lipid synthesis and distribution [4]. ER plays an important role in maintaining cell homeostasis. Endoplasmic reticulum stress (ERS) is induced when cells are subjected to endogenous or exogenous stimuli and the function of the ER is impaired and the unfolded or misfolded proteins accumulate in the ER cavity [5]. To alleviate ERS, three interconnected transmembrane signal transducers (Inositol-requiring enzyme1(IRE1), protein kinase R-like ER kinase, (PERK), and activated transcription factor 6(ATF6)) are activated to mediate the unfolded protein response (UPR) and subsequent cellular stress response pathways [6]. When the degree of ERS is low or the duration is short, the purpose of UPR is to restore endoplasmic reticulum homeostasis, but when the degree of ERS is high or the duration is long, the main purpose of the terminal stage of UPR is to promote apoptosis. UPR regulates transcription and translation of proteins in cells to mitigate damage and reduce the likelihood of protein misfolding. If this mechanism fails to achieve its purpose, inflammation and apoptosis pathways may be activated, leading to increased inflammation in the nervous system and affecting cell survival [4].

3. ERS and VaD

3.1 IRE1 and VaD

IRE1 is a transmembrane sensing protein located in the endoplasmic reticulum with dual activity of protein kinase and endoribonuclease (RNase). After activation of IRE1, it catalyzes the unconventional splicing of mRNA encoding X-box binding protein-1 (XBP1), eliminating 26 nucleotide introns [7]. This process can lead to the expression of the active transcription factor XBP1s, which in turn controls the expression of chaperones and other mediators of protein quality control mechanisms [8]. Overexpression of XBP1s has been shown to regulate the expression of multiple proteins associated with various neurodegenerative diseases, including VaD. In mouse models, significant expression of UPR transcription factor XBP1, in addition to reducing cellular aging, restores synaptic and cognitive function [9]. In addition to the classical IRE1/XBP1 pathway, existing studies have found that IRE1 can play a role through several other pathways, such as activating the NLRP3 inflammasome through signaling molecules ASK1, JNK, p38MAPK, NOX, TXNIP, etc. [10]. The NLRP3 inflammasome is modulated to interfere with the inflammatory response during VaD formation. In addition, IRE1 can also induce apoptosis and

autophagy, which have an important effect on VaD.

3.2 PERK and VaD

PERK is a transmembrane protein kinase located in the endoplasmic reticulum that plays a dual role in promoting apoptosis and survival depending on the level of stress imposed on the cells [11]. We found that under endoplasmic reticulum stress, free PERK self-phosphorylates, further inducing downstream eukaryotic initiation factor 2α (eIF2α) phosphorylation, p-eIF2α can promote the translation of transcription factor ATF4, ATF4 by initiating a series of gene transcription to relieve endoplasmic reticulum stress on multiple levels. If the degree of ER stress is too severe, ATF4 will initiate CHOP transcription to initiate the pro-apoptotic process and promote apoptosis [12]. Cerebral ischemia/reperfusion (IR) after ischemic stroke can lead to harmful microglial activation [13], which in turn can promote neuroinflammation and promote the occurrence of VaD [14]. Studies have shown that inhibition of PERK/eIF2α pathway activation can alleviate endoplasmic reticulum stress induced by glucose deprivation/reperfusion (OGD/R), inhibit PC12 cell apoptosis, and protect brain neuronocytes from ischemia/reperfusion injury [15]. Head acupoint acupuncture can alleviate the hippocampal inflammatory response of VaD rats by down-regulating the protein expression of p-PERK and p-eIF2α, and improve the degree of lesions in VaD rats [16].

3.3 ATF6 and VaD

ATF-6 is the third ER receptor protein that initiates UPR in cells and is also an important apoptotic regulator in ER stress pathways. As the proximal sensor of ER, ATF-6 has multiple BiP binding sites and two Golgi localization signals (GLS); In addition, the lumen domain of ATF-6 is occupied by glucose-regulatory protein 78 (GRP78) [17]. Under normal circumstances, ATF-6 (p90ATF-6) is located on the surface of the endoplasmic reticulum cavity and is inactive. When ER stress occurs, ATF-6 dissociates from GRP78/BiP and is transported to the Golgi apparatus. p90ATF6 in the Golgi is hydrolyzed by site-1 protease (S1P) and site-2 protease (S2P) to release the transcriptional activity of p50ATF6 [18]. Subsequently, p50ATF6 is transferred to the nucleus to activate transcription and expression of proteins associated with ER stress and apoptosis [19]. Apoptosis plays an important role in the pathogenesis of vascular dementia. Apoptosis can lead to the death of nerve cells, aggravate the neurological function deficit of patients, and greatly increase the risk of cognitive function decline. Some researchers have found that acupuncture at the points of the governor vein can inhibit ERS and improve cognitive impairment in VaD rats, and the specific mechanism is probably related to inhibiting the expression of GRP78, ATF6 and CHOP proteins and alleviating ischemic injury in the hippocampus [20].

4. TCM Regulates ERS and Improves VD

The clinical use of traditional Chinese medicine to treat VaD is mainly based on the treatment of tonifying deficiency, promoting blood circulation and eliminating phlegm, and pays attention to the synergistic treatment of deficiency, stasis and phlegm. Chen Xueyan [21] et al., after searching a large number of relevant literatures, found that in the traditional Chinese medicine treatment of vascular dementia, medicines for tonifying kidney, promoting blood circulation and removing blood stasis appeared most frequently, followed by drugs for resolving phlegm, supplementing qi and opening body. At present, the treatment of the disease is mainly to tonifying the kidney, promoting blood circulation and removing blood stasis, and then according to the different symptoms of the patient and the differentiation of phlegm, qi, opening and other methods.

4.1 Single Chinese Medicine and Medicine Pair

When Li Jingjing et al. [22] explored the rule of traditional Chinese medicine treatment for vascular dementia through data mining, they found that calamus is one of the core Chinese medicines for the treatment of this disease. β-asarone is the main component of volatile oil extracted from Gladiolus calamus, which has antioxidant, anti-inflammatory and anticancer effects [23,24]. Studies have shown that it can inhibit NLRP3 inflammasome mediated hemolytic cell death to alleviate myocardial ischemia/reperfusion (I/R) injury [25], and reduce endoplasmic reticulum stress response by regulating NLRP3 inflammasome. Geng Daoming et al. [26] found in their experiments that β-asarone could reduce the expression of PERK protein in rat hippocampus, which suggested that β-asarone could reduce endoplasmic reticulum stress and induced apoptosis by regulating various pathways, thus delaying the progression of vascular dementia.

Salvia miltiorrhiza is a classic drug for the treatment of vascular dementia. Its main active ingredients include tanshinone IIA, salvianolic acid B, Salvianic acid A and cryptotanshinone. Tao Yuan [27] found in his study on the treatment of spontaneous hypertension by gastrodia-Salvia miltiorrhizae, that this drug pair may down-regulate the expression of marker proteins GRP78, CHOP and Caspase-12 in PERK signaling pathway, inhibit ERS, and protect vascular endothelium. Other experiments have shown that tanshinone II.A can inhibit the phosphorylation of ER stress pathway proteins PERK and eIF2α, down-regulate the expression of ER stress-related proteins CRP78, ATF4 and CHOP in H9c2 cells induced by palmitic acid, and inhibit palmitic acid-induced apoptosis of H9c2 cells [28]. Wang Zhenli's experiments also demonstrated the positive role of cryptotanshinone (CPT) in apoptosis and regulation of endoplasmic reticulum stress in liver cancer cells [29]. All the above experiments showed that Salvia miltiorrhiza and its main active substances can relieve endoplasmic reticulum stress by regulating PERK/eIF2α pathway, and exert their role in inhibiting neuronal apoptosis and anti-vascular dementia.

Panax notoginseng saponin R1 (NGR1) is a saponin derived from Panax Notoginseng which is used to improve blood circulation and clotting. Studies have shown that NGR1 can up-regulate thioredoxin 1 (Trx-1) in PC12 cells and mice [30]. Trx-1 is an endogenous anti-apoptotic molecule, and its overexpression can reduce neuronal apoptosis by inhibiting the activation of the signaling pathway IRE1-JNK, alleviate cerebral ischemia-reperfusion injury, and improve cognitive function and nerve damage in VD rats [31].

GJ-4 is an extract of Chinese herb Gardenia, its main

metabolite is croceic acid, The mechanism study of Yuan Fangyu [32] showed that GJ-4 can greatly reduce the expression level of ERS-related GRP78 in the brain of VD rats, and alleviate ERS in the brain of rats by inhibiting the activation of PERK/eIF2α/ATF4/CHOP signaling pathway that regulates UPR, reduce neuronal apoptosis, and improve the learning and memory ability of VaD rats.

Dong Han [33] found in his experimental study that extracts of cartialgenous can down-regulate the expression of PERK and EIf2α in vascular dementia model rats and increase the expression of Bcl-2 in hippocampal cells of rats. As a negative regulator of apoptosis, overexpression of Bcl-2 can reduce apoptosis. In the regulation of UPR, the decrease of PERK and EIf2α can also relieve endoplasmic reticulum stress from multiple levels.

4.2 Traditional Chinese Medicine Compound

Among the common TCM syndrome types of VaD, the type of kidney deficiency and blood stasis is the most common, and there are many examples of clinical use of tonifying kidney and promoting blood circulation to treat vascular dementia [34-37]. Studies have shown [38] that Bushen Huoxue formula can inhibit the expression of GRP78 m RNA and protein through the PERK-ATF4-CHOP signaling pathway, and alleviate the apoptosis induced by ERS. Mai luo ning oral liquid [39] is a Chinese herbal compound preparation with the functions of clearing heat and nourishing Yin, promoting blood circulation and removing blood stasis. A clinical study [40] showed that compared with the control group treated with NBP softgel alone for vascular dementia, the observation group treated with NBP softgel combined with Mai luo ning oral liquid was more beneficial in improving cognitive function and improving daily living ability. In this study, the levels of GRP78, CHOP and Caspase-12 in the observation group were significantly lower than those in the control group ($P<0.05$), suggesting that Mai luo ning oral liquid combined with NBP can promote the apoptotic pathway with ER stress, resist oxidative stress, and thus improve cognition.

In addition, it has been found in animal experiments [41] that apoptosis mediated by ER stress plays an important role in cerebral ischemia-reperfusion injury. Hou Xiaochan found that Buyang Huanwu Decoction could inhibit the expression of GRP78 and reduce the expression of apoptosis-related proteins Bax/bcl-2 and Caspase-3, thereby alleviating brain I/R injury. In addition, the drug-containing serum of this formula can inhibit PERK pathway, down-regulate p-eIF2α expression, and reduce ERS-mediated apoptosis to alleviate OGD/R damage of PC12 cells.

5. Conclusion

Through the review of domestic and foreign literature, it is found that ER stress plays a key role in the pathogenesis of vascular dementia, and ER stress-related response pathways can treat VaD by restoring ER homeostasis, promoting cell survival, inhibiting cell apoptosis, etc. The effect of Chinese medicine on delaying VaD progression by intervening in ERS is accurate. However, there are few studies on the treatment of VaD by regulating endoplasmic reticulum stress with traditional Chinese medicine, and the research on its specific mechanism is still not very clear, and further research is still needed.

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