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Walnut-Derived Peptide Activates PINK1 via the NRF2/KEAP1/HO-1 Pathway, Promotes Mitophagy, and Alleviates Learning and Memory Impairments in a Mice Model

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ABSTRACT: Mitophagy has a pivotal protective function in the pathogenesis of neurological disorders. However, the mechanism of its modulation remains elusive, especially in PINK1-mediated mitophagy. Here, we investigated the neuroprotective effects of a walnut-derived peptide, YVLLPSPK, against scopolamine-induced cognitive deficits in mice and explored the underlying PINK1-mediated mitophagy mechanisms in H_2O_2-treated HT-22 cells. Using the Morris water maze, we showed that YVLLPSPK relieved the cognitive deficiency by alleviating oxidative stress. Mitochondrial morphology was observed in mice hippocampal tissues using transmission electron microscopy (TEM). Both Western blot and immunofluorescence analysis illustrated YVLLPSPK promoted the expression of mitophagy-related proteins and activated the NRF2/KEAP1/HO-1 pathway. Subsequently, an NRF2 inhibitor (ML385) was used to verify the contribution of the YVLLPSPK-regulated NRF2/KEAP1/HO-1 pathway in PINK1-mediated mitophagy in H_2O_2-treated HT-22 cells. These data suggested that YVLLPSPK improved learning and memory in scopolamine-induced cognitive-impaired mice through a mechanism associated with PINK1-mediated mitophagy via the NRF2/KEAP1/HO-1 pathway.

KEYWORDS: *walnut-derived peptide, cognitive deficiency, PINK1, mitophagy, oxidative stress, NRF2/KEAP1/HO-1 pathway*

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INTRODUCTION

Mitophagy is a complex process involving the crosstalk between mitochondria and the autophagy machinery.[1] Selective classification and removal of damaged or unwanted mitochondria comprise a critical mechanism for maintaining mitochondrial quality.[2] Hence, defective mitophagy has been shown to lead to the accumulation of damaged mitochondria, mitochondrial fragmentation, and oxidative stress.[3,4] In particular, the lack of mitophagy in the brain has been reported to be highly reminiscent of the cognitive defects in patients with Alzheimer's disease (AD).[5] PTEN-induced putative protein kinase 1 (PINK1) is a mitochondrial serine/threonine kinase on the outer mitochondrial membrane, thought to be involved in protection against reactive oxygen species (ROS),[6] which is known to regulate mitochondrial network homeostasis and quality control by removing damaged mitochondria. Emerging evidence has demonstrated that mitophagy is highly regulated by the PINK1/Parkin system[1,7] with loss of PINK1 leading to defective mitophagy.[3]

Nuclear factor erythroid 2-related factor 2 (NRF2) and its interaction with Kelch-like ECH-associated protein 1 (KEAP1) are known to function as key regulators of ROS.[8,9] Consequently, NRF2 has been widely considered as a potential therapeutic target for associated diseases. Briefly, NRF2 has been shown to be an emerging regulator of the cellular expression of a number of genes encoding antioxidant enzymes, detoxifying factors, antiapoptotic proteins, and drug transporters, which can regulate the gene expression of diverse cytoprotective proteins, such as antioxidant enzymes, including heme oxygenase 1 (HO-1).[10,11] Recent studies have supported the involvement of NRF2 in cognitive deficits.[12] Moreover, emerging evidence has revealed that NRF2 could modulate mitochondrial function and metabolism.[13] However, the specific mechanisms by which NRF2 attenuates oxidative stress and mitochondrial dysfunction through PINK1-mediated mitophagy have not been fully elucidated.

An increasing number of food-derived peptides have been demonstrated to ameliorate oxidative stress and rescue learning and memory deficiency. Chai et al. reported that protein hydrolysate from *Benthosema pterotum* increased the latency time and arrival frequency and took a significantly shorter time to reach the platform than the model group in D-galactose-induced neurodegenerative/aging ICR mice. In addition, the FYY and DW peptides in protein hydrolysate from *Benthosema pterotum* were reported to significantly reduce H_2O_2-induced ROS and apoptotic cell death in human neuroblastoma SH-SY5Y cells by activating the intracellular antioxidant defense system.[14] Wang et al. exhibited that

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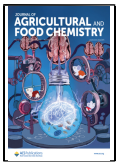

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