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Research Report

Posttraumatic administration of luteolin protects mice from traumatic brain injury: Implication of autophagy and inflammation

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ABSTRACT

Secondary brain insult induced by traumatic brain injury (TBI), including excitotoxicity, oxidative stress, inflammatory response, and neuronal degeneration, is sensitive to therapeutic interventions; therefore, searching for neuroprotective agents represents a promising therapeutic strategy for TBI treatment. Luteolin, a member of the flavonoid family, has recently been proven to modulate autophagy. However, whether it activates autophagy after TBI thereby alleviating the secondary insult is not yet understood. Here, we aimed to evaluate the neuroprotection of luteolin against TBI and the potential role of autophagy where it is involved. For this purpose, mice were randomly divided into four groups and then subjected to TBI. The treatment mice received luteolin at a dose of 30 mg/kg 30 min post-TBI based on our previous study. We employed western blot, immunofluorescence and quantitative real-time PCR to determine autophagy process and inflammatory response among different groups. Autophagy was found to be enhanced after luteolin treatment according to the expressions of autophagic markers. Furthermore, luteolin decreased nuclear accumulation of p65 induced by TBI, indicating attenuation of inflammation. In line with these observations, luteolin decreased mRNA and protein expressions of pro-inflammatory factors IL-1b and TNF-a. At last, luteolin reduced neuronal degeneration, and alleviated brain edema and blood–brain barrier (BBB) disruption. In conclusion, these results implied that luteolin protected mice brain from traumatic brain injury by inhibiting inflammatory response, and luteolin-induced autophagy might play a pivotal role in its neuroprotection.

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1. Introduction

Traumatic brain injury (TBI) is a worldwide health problem affecting millions of people. It leads to a substantial number of deaths and cases of permanent disability every year (Brooks et al., 2013). Primary brain insult occurring at the moment of impact, which is not sensible to therapy, initiates subsequent physiological and pathological reactions, providing a chance for clinical interventions. These reactions include release of excitatory neurotransmitters, production of oxyradical and activation of inflammatory response, contributing to delayed neuronal cell death which last for days or months (Kumar and Loane, 2012). Despite recent development in understanding the pathological process after TBI, a formidable problem facing us is, effective pharmacological therapy remains limited (McConeghy et al., 2012); therefore, searching for neuroprotective agents still represents a promising therapeutic strategy for the treatment of TBI.

Autophagy is an evolutionarily conserved, dynamic cellular process. During autophagy, cytosolic materials including dysfunctional proteins, organelles and pathogens are sequestered into membrane vesicles called autophagosomes, and then delivered to the lysosome for degradation (Ryter et al., 2013). It is critical for cellular homeostasis against a wide variety of stresses, including nutrient deprivation, oxidative stress, infection, and hypoxia. Specifically, autophagy exerts important physiological functions in protein turnover and organelle quality control, by maintaining appropriate organelle numbers, and disposing of dysfunctional or damaged organelles (Murrow and Debnath, 2013).

The role of autophagy in diseases is an emerging area of investigation, with recent studies indicating that autophagy may exert multifunctional roles in specific diseases. Alter expression of autophagy proteins has been found in cancers (Miracco et al., 2007), aging (Rubinsztein et al., 2011), infectious diseases (Rubinsztein et al., 2012), as well as neurodegenerative diseases (Ghavami et al., 2014; Tan et al., 2014). Autophagic activities were observed after TBI from different laboratories; however, the roles of autophagy in TBI do not yet reach an agreement, some considered that autophagy aggravates brain injury after TBI (Luo et al., 2011), while others insist that activation of autophagy could protect animal from brain injury in models of TBI (Erlich et al., 2007; Zhang et al., 2008).

Flavonoids have a wide spectrum of pharmacological properties including antioxidant, anti-inflammation, and cancer preventive effects (Dajas et al., 2013; Romagnolo and Selmin, 2012). Luteolin, which is a common studied flavonoid existing in many kinds of vegetables and fruits, exhibit these properties in different diseases. In our previous study, we have proven that it conferred neuroprotection against TBI by activation of Nrf2-ARE pathway (Xu et al., 2014). More recently, researches demonstrated that luteolin could activate autophagy in breast cancer cells and lung carcinoma cells (Huang et al., 2010; Park et al., 2013). However, whether luteolin can induce autophagy in TBI has not yet been studied. Here we investigated the influence of luteolin on

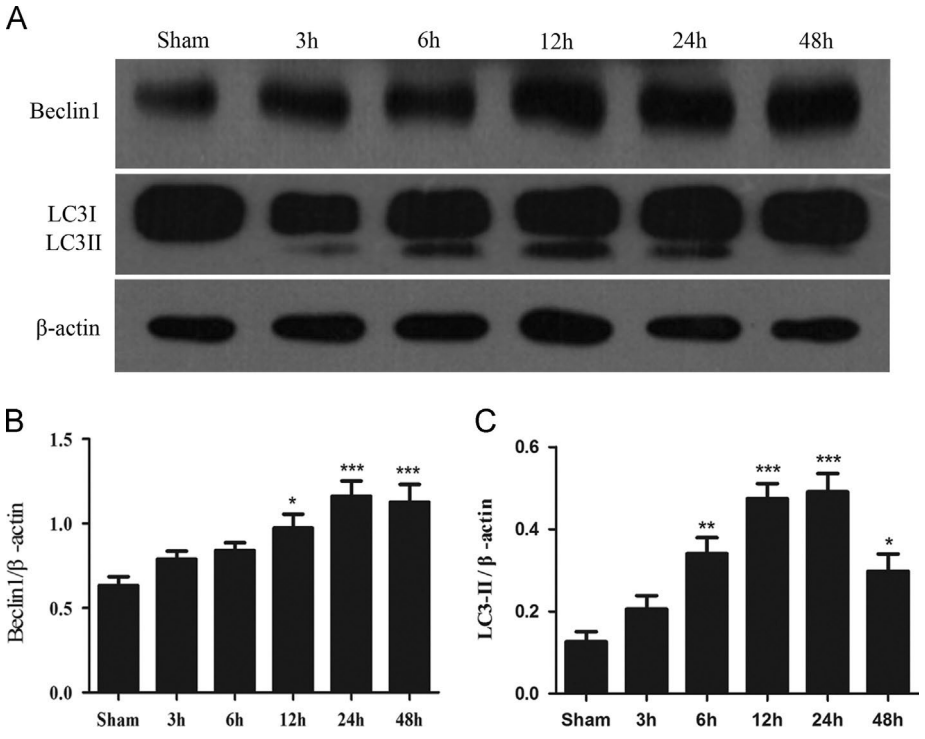

Fig. 1 – Autophagy was up-regulated after TBI in pericontusional cortex. The pericontusional cortex was collected at different time points after TBI; expressions of beclin1 and LC3 were detected to evaluate autophagy using Western blot. Data was normalized to β-actin. (A) A typical Western blot result, (B) quantification of the expression of beclin1, increased level of beclin1 was observed after TBI and (C) quantification of the expression of LC3II, significant up-regulation of LC3II was found from 6 h to 48 h after TBI. Data represent mean ± SEM ($n=6$). *$P<0.05$, **$P<0.01$, ***$P<0.001$ versus the sham group.