

T1-19

Regulation of mitophagy in ischemic neurons

ZHENG Yan-rong, ZHANG Xiang-nan, CHEN Zhong
(*Institute of Pharmacology & Toxicology, College of Pharmaceutical Sciences, Department of Pharmacology, Key Laboratory of Medical Neurobiology of the Ministry of Health of China, Zhejiang University, Hangzhou 310058, China*)

Abstract: Cerebral ischemia remains the top causes of mortality and disability worldwide. The pathological mechanisms underlying ischemic brain injury are not fully illustrated. Cerebral ischemia induces massive mitochondrial damage, which are cleared by mitochondrial autophagy (mitophagy). Our previous studies indicated mitophagy is critical for neuronal survival after ischemic injury, thus raise the conception of rescuing ischemic brain injury by regulating neuronal mitophagy. We further explored the molecular mechanisms underlying ischemia-induced mitophagy, in particular with the regulations of Nix. Our ongoing study focuses on the spatial features of neuronal mitophagy after ischemic insult. Distinct from other cell types, neurons are highly-polarized cells with elaborate dendrites and axons, in which extensive mitochondria are distributed. Despite the facts that neuronal mitophagy is promptly activated by ischemia, the intracellular locations of mitophagy in neuron, however are largely unknown. The primary cultured mice cortical neurons were treated with oxygen-glucose deprivation (OGD), which mimics ischemia. We confirmed mitochondrial loss both in neuronal cell bodies and axons. However, we found that axonal mitochondria elimination was not compromised in autophagy deficient neurons, suggesting the absence of direct mitophagy in axons. We unexpectedly found that axonal mitochondria underwent a prompt retrograde transportation upon reperfusion while the anterograde mitochondrial mobility was irreversible lost after OGD. We labelled the axonal mitochondria and found they were degraded by autophagic machin-

ery in neuronal soma. Inhibition of axonal mitochondria retrograde transportation by expression Syntaphilin, an anchoring protein, blocked neuronal mitophagy. Conversely, chimeric expression of a fusion protein targets mitochondria to dynein complex reinforced mitochondrial retrograde transport and enhanced mitophagy. These evidences indicated a somatic autophagy of axonal mitochondria in ischemic neurons. This pattern may facilitate neuronal mitophagy in the scenario of acute ischemia. Taken together, we found that axonal mitochondria are not cleared locally in axons but are retrograde transported to neuronal soma for mitophagy in ischemic neurons. The present study identified a novel pattern for neurons to eliminate damaged mitochondria and provided the missing link between mitochondrial mobility and mitophagy in ischemic neurons.

Key words: cerebral ischemia; autophagy; mitochondria; oxygen-glucose deprivation

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Corresponding author: CHEN Zhong, E-mail: chenzhong@zju.edu.cn; ZHANG Xiang-nan, E-mail: xiangnan_zhang@zju.edu.cn

T1-20

天麻素对缺血性脑卒中血管新生的影响

许鑫², 楚世峰¹, 陈乃宏¹

(1. 中国医学科学院药物研究所 & 神经科学中心, 北京 100050; 2. 华南师范大学, 广东 广州 510631)

摘要:天麻素是中药天麻一个主要活性成分之一。近年来有很多研究已经证明,天麻素对缺血性脑卒中有显著的保护和改善作用,保护途径涉及很多细胞因子。关于天麻素通过某一信号通路或因子保护缺血性脑卒中的报道很多,但大多研究尚未取得突破性进展。为了研究天麻素对缺血性脑卒中的影响及其影响途径,总结国内外研究文献,提出天麻素对缺血性脑卒中的保护作用可能与M2型巨噬细胞分泌的VEGFA活化血管内皮细胞而促进血管新生有关。

关键词:天麻素;缺血性脑卒中;血管新生