

Agonist of growth hormone-releasing hormone enhances retinal ganglion cell protection induced by macrophages after optic nerve injury

Ling-Ping Cen (1) , Tsz Kin Ng (1,2,3) , Jia-Jian Liang (1) , Ciyan Xu (1) , Xi Zhuang (1) , Yu-Fen Liu (1,2) , Shao-Lang Chen (1) , Yanxuan Xu (1) , Qichen Yang (3) , Xiang-Ling Yuan (1,2) , Yong Jie Qin (4) , Sun On Chan (5) , Haoyu Chen (1) , Mingzhi Zhang (1) , Andrew V Schally (6,7,8,9,10) , Chi Pui Pang (11,3)

1 Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong, Shantou University Medical College, 515041 Shantou, China.

2 Shantou University Medical College, 515041 Shantou, China.

3 Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong.

4 Department of Ophthalmology, Guangdong Eye Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, 510080 Guangzhou, China.

5 School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong.

6 Department of Pathology, Miller School of Medicine, University of Miami, Miami, FL 33136; andrew.schally@va.gov cppang@cuhk.edu.hk.

7 Division of Medical Oncology, Department of Medicine, Miller School of Medicine, University of Miami, Miami, FL 33136.

8 Division of Endocrinology, Department of Medicine, Miller School of Medicine, University of Miami, Miami, FL 33136.

9 Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Miami, FL 33136.

10 Cancer Institute, Veterans Affairs Medical Center, Miami, FL 33125.

11 Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong, Shantou University Medical College, 515041 Shantou, China; andrew.schally@va.gov cppang@cuhk.edu.hk.

Optic neuropathies are leading causes of irreversible visual impairment and blindness, currently affecting more than 100 million people worldwide. Glaucoma is a group of optic neuropathies attributed to progressive degeneration of retinal ganglion cells (RGCs). We have previously demonstrated an increase in survival of RGCs by the activation of macrophages, whereas the inhibition of macrophages was involved in the alleviation on endotoxin-induced inflammation by antagonist of growth hormone-releasing hormone (GHRH). Herein, we hypothesized that GHRH receptor (GHRH-R) signaling could be involved in the survival of RGCs mediated by inflammation. We found the expression of GHRH-R in RGCs of adult rat retina. After optic nerve crush, subcutaneous application of GHRH agonist MR-409 or antagonist MIA-602 promoted the survival of RGCs. Both the GHRH agonist and antagonist increased the phosphorylation of Akt in the retina, but only agonist MR-409 promoted microglia activation in the retina. The antagonist MIA-602 reduced significantly the expression of inflammation-related genes *Il1b*, *Il6*, and *Tnf*. Moreover, agonist MR-409 further enhanced the promotion of RGC survival by lens injury or zymosan-induced macrophage activation, whereas antagonist MIA-602 attenuated the enhancement in RGC survival. Our findings reveal the protective effect of agonistic analogs of GHRH on RGCs in rats after optic nerve injury and its additive effect to macrophage activation, indicating a therapeutic potential of GHRH agonists for the protection of RGCs against optic neuropathies especially in glaucoma.

