Antioxidant effects of diallyl trisulfide on high glucose-induced apoptosis are mediated by the PI3K/Akt-dependent activation of Nrf2 in cardiomyocytes

Wei-Wen Kuo[1], Chih-Yang Huang[2]

[1]Departments of Biological Science & Technology College of Life Sciences, China Medical University, Taichung, Taiwan, ROC.
[2]Graduate Institute of Basic Medical Science, China Medical University,
[3]Department of Health and Nutrition Biotechnology, Asia University, Taichung, Taiwan, ROC

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Background: Hyperglycemia-induced reactive oxygen species (ROS) generation contributes to development of diabetic cardiomyopathy. Nuclear factor E2-related factor 2 (Nrf2), a redox-sensing transcription factor, induces the antioxidant enzyme expressions. Diallyl trisulfide (DATS) is the most powerful antioxidant among the sulfur-containing compounds in garlic oil.

Objective: We investigated whether DATS inhibits hyperglycemia-induced ROS production via Nrf2-mediated activation of antioxidant enzymes in cardiac cells exposed to high glucose (HG).

Methods and results: Treatment of H9c2 cells with HG resulted in an increase in intracellular ROS level and caspase-3 activity, which were markedly reduced by the administration of DATS (10μM). DATS treatment significantly increased Nrf2 protein stability and nuclear translocation, upregulated downstream gene HO-1, and suppressed its repressor Keap1. However, apoptosis was not inhibited by DATS in cells transfected with Nrf2-specific siRNA. Inhibition of PI3K/Akt signaling by LY294002 (PI3K inhibitor) or PI3K-specific siRNA not only decreased the level of DATS-induced Nrf2-mediated HO-1 expression, but also diminished the protective effects of DATS. Similar results were also observed in high glucose-exposed neonatal primary cardiomyocytes and streptozotocin-treated diabetic rats fed DATS at dose 40 mg/kg BW.

Conclusion: Our findings indicate that DATS protects against hyperglycemia-induced ROS-

mediated apoptosis by upregulating the PI3K/Akt/Nrf2 pathway, which further activates Nrf2-regulated antioxidant enzymes in cardiomyocytes exposed to HG.

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Corresponding Author: Wei-Wen Kuo, PhD, Dept. of Biological Science & Technology, School of Life Science, China Medical University,,No. 91, Hsueh-Shih Road, Taichung, 40402, Taiwan, E-mail: wwkuo@mail.cmu.edu.tw, Phone number: 886-4-2205-3366 ext. 2510

Main presenting author: Wei-Wen Kuo, PhD, Dept. of Biological Science & Technology, School of Life Science, China Medical University,,No. 91, Hsueh-Shih Road, Taichung, 40402, Taiwan, E-mail: wwkuo@mail.cmu.edu.tw, Phone number: 886-4-2205-3366 ext. 2510

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Co-authors:
Chih-Yang Huang, PhD, E-mail: cyhuang@mail.cmu.edu.tw