

DOCTORAL THESIS

Investigation on the correlation between methylglyoxal and diabetic complications: neurodegeneration and Osteoporosis

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Abstract

Diabetes Mellitus is a chronic disease characterized by uncontrollable chronic high blood glucose (hyperglycemia) and complications, leading to serious damage to different tissues. In clinical studies, diabetic patients are found to have a higher risk of developing neurodegeneration and osteoporosis, and hyperglycemia-induced formation of advanced glycation endproducts (AGEs) may contribute towards the pathogenesis of diabetes-induced neurodegeneration and osteoporosis. Therefore the aim of this project is to investigate the role of hyperglycemia-induced methylglyoxal (MG) on neurodegeneration, neuroinflammation and osteoporosis.

Firstly, the role of MG on neurodegeneration of neuronal astrocytes, a kind of major glia in the brain, was studied. Astrocyte plays roles in the structural and functional support of the brain neurons and maintains normal brain physiology. In the present study, MG disturbed insulin signaling and led to apoptosis in rat primary astrocytes. Furthermore, the protective effects of ginsenosides were studied. From the results, impairment of insulin signaling was found in astrocyte culture under MG treatment. Moreover, cleavage of caspase and Poly ADP ribose polymerase (PARP) was observed together with insulin signaling disruption, showing the neurotoxic effects of MG towards astrocytes. The effects of ginsenosides in MG-treated astrocytes were also investigated. The ginsenosides Rd and R-Rh2 were shown to ameliorate the cell viability of MG-treated astrocytes and improve insulin signaling and inhibit apoptosis, indicating that Rd, R-Rh2, and related compounds may have therapeutic potential in treating diabetes-induced neurodegeneration.

Secondly, the role of MG on neuroinflammation was studied. The effects of MG in astrocytic cultures and hippocampi of experimental animals were compared. The astrocyte DITNC1 and C57BL/6 mice were treated with MG solution and hippocampi were harvested. MG induced astrogliosis in DITNC1 astrocytic cultures and C57BL/6 mice. Also, activation of the proinflammatory JNK signaling pathway was observed. Furthermore, increased gene expression of pro-inflammatory cytokines and astrocytic markers were observed. In addition, inhibition of JNK activities resulted in down-regulation of TNF- α in MG-treated astrocytes. Our results suggest that MG may contribute to the progression of diabetes-related neurodegeneration through JNK pathway activation in astrocytes and the subsequent neuroinflammatory responses in the central nervous system.

Thirdly, the role of MG on osteoporosis and osteoclasts were studied. The osteoclasts are bone cells having catabolic action in the bone remodeling cycle. The effects of MG on osteoporosis in both animal and cell models were investigated. SD rats were treated with either MG or streptozotocin and the macrophage RAW264.7 was treated with MG. MG was shown to induce osteoclastogenesis by increased gene expression of osteoclast bone biomarkers CTSK, OSCAR and TRACP5. The results of MG-treated rats were similar to type 1 diabetic model. Furthermore, in MG-treated macrophages activation of the JNK was observed, and inhibition of JNK activities resulted in down-regulation of osteoclast biomarkers. Our results, suggested that MG may contribute to the progression of diabetes-related osteoporosis and the imbalanced bone remodeling through the JNK pathway in osteoclasts.

To conclude, MG causes different diabetic complications in multiple organs. It may be a

potential therapeutic target to reduce and delay the development of neurodegeneration, neuroinflammation, and osteoporosis in diabetes.

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