MASTER'S THESIS

Investigation on the Effect of Hyperglycemia-induced Methylglyoxal in Neurodegenerative Disorder

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Date of Award:
2023

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Abstract

Diabetes mellitus (DM) is characterized by chronic hyperglycemia and diabetic complications. DM-induced induction of stress responses in the central nervous system (CNS) such as neuroinflammation and oxidative stress may result in numerous neurodegenerative disorders, which DM patients have an increased risk of developing Alzheimer's disease (AD), Parkinson disease (PD), and the related neuropsychiatric symptoms, anxiety, and depression. Methylglyoxal (MG), one of the most reactive advanced glycation end-product (AGE) precursors, is observed abnormally accumulated in the serum of DM patients. As MG is reported to promote brain cell impairment in the CNS and is highly associated with neurodegenerative diseases. Therefore, the effect of hyperglycemia-induced MG causing subsequent symptoms of neurodegenerative disorders and the underlying mechanism in cell model were investigated in this report.

5-week-old C57BL/6 mice were intraperitoneally injected with MG solution for 11 weeks. The Morris water maze (MWM), rotarod test, open-field test (OFT), light-dark box (LDB) test, force swim test (FST), and tail suspension test (TST) were used to examine the spatial learning ability and cognition, motor coordination and balance, and the anxiety- and depressive-like behavior of mice respectively. After MG treatment, MTT assay, real-time PCR analyses, and Western blot were performed to assess the harvested astrocytes and hippocampi. MG-treated astrocytes condition medium (ACM) was introduced to neuron cells to examine the astrocytes-neuron interaction.

Our *in vivo* results demonstrated for the first time that chronic MG accumulation may exhibit the behavioral pattern of AD, PD, anxiety, and depression in a more clinically comparable model. In the MWM, significantly increased escape latency of about 2-3 times in the MG-treated mice than the control was observed on days 2-5. Significant reduction of the percentage time spent in the target quadrant by about 15% of the MG-treated mice (44.1 2.72) than that of the control (58.3 ± 4.32) was also demonstrated. In the rotarod test, the MG-treated group (74.1 ± 5.33) has a significant reduction of around 20% of latency to fall off than the control (92.9 ± 5.80). In the OFT, the total traveled

distance of the MG-treated group (8.29 ± 1.01) was significantly reduced by about 40% than the control (13.4 ± 1.48). In the FST, significantly increased percentage of immobile time of about 10% was observed in the MG-treated group (77.6 ± 2.19) than the control (68.7 ± 2.42).

Afterwards, we have found in both *in vitro* and *in vivo* models that MG could induce astrogliosis, pro-inflammatory response, AD-related markers alteration, MMPs activation, apoptosis, and ERK activation. Further, the trend of normalization of the tested markers' mRNA expressions was observed after ERK inhibition implying that ERK may be a key regulator of inflammation and Aβ formation in MG-induced reactive astrocytes. Additionally, MG-ACM could promote neuroinflammation and Aβ formation in neuron cells though altering astrocytes' function.

Taken together, MG may participate in the dysfunction of brain cells resulting in possible diabetes-related neurodegeneration by promoting astrogliosis, Aβ production, and neuroinflammation through the ERK pathway. Our findings provide insight of targeting ERK as a therapeutic application for diabetes-induced neurodegenerative disorders and the importance of understanding the pathogenesis of DM-induced neurodegeneration.