Advanced Glycation End-Products Induce Mitochondrial Fission and Disrupt Autophagic Flux in C6 Astroglioma Cell Line

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INTRODUCTION: Diabetes mellitus is a common metabolic disease characterized by a state of persistent hyperglycemia. It is known that chronic hyperglycemic conditions elicit an accumulation of methylglyoxal (MG), which has been involved in the formation of advanced glycation end-products (AGEs). **OBJECTIVES:** This study aimed to investigate the effects of hyperglycemia-linked metabolite, AGEs, on mitochondrial dynamics and autophagy of C6 astroglioma cell line. **MATERIAL AND METHODS:** C6 cells were exposed to BSA (controls) or MG-BSA (AGEs, 0.1 or 1 mg/mL) for 24 h or 48 h. Mitochondrial number and morphology were analyzed by transmission electron microscopy (TEM). Flow cytometry was used to analyze the content of proteins related to mitochondrial fission (Drp1 and phosporlylated-Drp1 [P-Drp1]) and autophagy (ATG5, ATG7, ATG16, LC3B and Beclin). **RESULTS AND DISCUSSION:** TEM revealed that cells exposed to MG-BSA presented an increased count of mitochondria of reduced size and punctuated morphology. These results suggest mitochondrial fission, which was confirmed with an increase of Drp1 and P-Drp1 content when cells were exposed to MG-BSA 0.1 mg/mL. MG-BSA exposure during 24 h caused an induction of autophagy in C6 cells, due to an increment of ATG5, LC3B and Beclin protein content. However, after 48 h of exposure there was only an increase of ATG7 protein and a decrease of ATG5 and Beclin content, indicating a decrease in autophagic flux. **CONCLUSIONS:** AGEs induces mitochondrial fission and primarily activates autophagy to avoid cell death. Moreover, due to the failure of the autophagic flux with the persistent exposure to AGEs, dysfunctional mitochondria eliminated from the network persist in the cell, and a state of chronic oxidative stress will be perpetuated, leading to cell death. Therefore, the altered mitochondrial dynamic that AGEs induces could increase the predisposition to develop neurodegenerative/neurological disorders in individuals affected by DM.

Keywords: AGEs; autophagy; mitochondrial fission.

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