Methylglyoxal-derived AGEs-Induced mitochondrial dysfunction/ER stress

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Advanced glycation end products (AGEs) are formed via nonenzymatic reactions between reducing sugars and proteins. Recent studies have shown that methylglyoxal, a potent precursor for AGEs, causes a variety of biological dysfunctions, including diabetes, inflammation, renal failure, and cancer. However, little is known about the function of methylglyoxal-derived AGEs (AGE4) in kidney cells. Therefore, we verified the expression of endoplasmic reticulum (ER) stress-related genes and apoptosis markers to determine the effects of AGE4 on human proximal epithelial cells (HK-2). Moreover, our results showed that AGE4 induced the expression of apoptosis markers, such as Bax, p53, and kidney injury molecule-1, but downregulated Bcl-2 and cyclin D1 levels. AGE4 also promoted the expression of NF-κB, serving as a transcription factor, and the phosphorylation of c-Jun NH2-terminal kinase (JNK), which induced cell apoptosis and ER stress mediated by the JNK inhibitor. Furthermore, AGE4 induced mitochondrial dysfunction by inducing the permeabilization of the mitochondrial membrane and ATP synthesis.

Keywords: methylglyoxal-derived AGEs ; kidney injury ; endoplasmic reticulum stress ; mitochondrial dysfunction ; JNK signal pathway

1. Introduction

Unlike type 1 diabetes, which is induced by an inherited disorder of insulin production in pancreatic islet β-cells [1], type 2 diabetes is caused by a variety of factors, including a lack of exercise, alcohol intake, genetic factors, and diet [2]. Diabetic nephropathy occurring in proximal renal epithelial cells is one of the main complications of diabetes [3]. Expression of receptors for advanced glycation end products (RAGE) is upregulated by abundant advanced glycation end products (AGEs) during diabetes-associated complications. The AGE–RAGE axis is involved in the onset of diseases such as Alzheimer's disease, cancer, and osteoporosis [4][5][6]. According to recent studies, AGEs affect the glomerular filtration rate, resulting in chronic renal failure [7]. Alikhani et al. (2005) reported that N-ε-(carboxymethyl) lysine (CML)–collagen induced the apoptosis of fibroblasts, as well as increased caspase-3, -8, and -9 activity in an in vivo test [8]. Glyceraldehyde-derived AGEs induce apoptosis in human dermal fibroblasts by increasing reactive oxygen species (ROS) and activating the NLRP3 inflammasome [9]. Methylglyoxal (MGO), a major electrophilic dicarbonyl compound, is generated as a nonenzymatic breakdown product of a triosephosphate intermediate in the glycolytic process and has been linked to dicarbonyl stress, which leads to the development of AGEs and related cellular dysfunction [10][11]. We previously showed that the treatment of NRK-52E kidney cells with MGO-derived AGEs (AGE4) leads to an increase in the protein levels of matrix metalloproteinase-2 (MMP-2) and MMP-9 via AGE4–RAGE interactions [12]. Endoplasmic reticulum (ER) stress is an important mechanism that induces diabetes [13]. Moreover, mitochondrial functions include calcium homeostasis in cells, respiration, and biogenesis regulation through c-Jun NH2-terminal kinase (JNK) pathways [14][15][16], which are also closely related to cell apoptosis response pathways [17]. Although ER stress affects mitochondria directly or indirectly [18], the exact effects of AGE4 on the signaling pathways associated with ER stress and cell apoptosis are unknown. Therefore, we used in vitro and in vivo models to investigate the involvement of the AGE4–RAGE axis and specific signaling pathways that induce ER stress and mitochondrial dysfunction, which contribute to apoptosis.

2. Current Inishgts

Takeuchi et al. employed various sugar sources, including glucose, α-hydroxyaldehydes, and dicarbonyl compounds, to glycate proteins and classified AGEs into glucose-derived AGEs (AGE1); glyceraldehyde-derived AGEs (AGE2), glycolaldehyde-derived AGEs (AGE3), methylglyoxal-derived AGEs (AGE4), glyoxal-derived AGEs (AGE5), and 3-deoxyglucosone-derived AGEs (AGE6) [19][20]. Methylglyoxal, a reactive dicarbonyl produced during glucose metabolism, accumulates in diabetic patients [20], and its derived AGE4 is known to cause several diseases, including diabetes and cancer [11].

The results clearly indicated that a significant decrease in cyclin D1 protein level was caused by AGE4. This decrease may result in an accumulation of cells in the sub-G1 and G1 phases. Cyclin D1 has been shown to be necessary for progression through the G1 process of the cell cycle in order to cause cell migration [21]. In addition, the activation of NF-κB by AGE4 treatment can be regulated through the JNK signaling pathway, according to the findings. RAGE–AGE4 axis-induced apoptosis is correlated with the induction of ER stress markers, such as CHOP, ATF4, and GRP78, via JNK pathway. In the previous study, AGE4 treatment induced RAGE-dependent cell inflammation in rat kidney epithelial cells (NRK-52E) through the ERK, JNK, and NF-κB pathways [12]. JNK and NF-κB are the main oncogenic signaling pathways linked to ER stress, which leads to nonalcoholic steatohepatitis and hepatocellular carcinoma [22].

The major source of ROS generation is the mitochondrial respiratory complexes, and the JNK pathway is involved in mitochondrial apoptosis [23][24]. AGEs play an important role in developing various diseases such as myocardial dysfunction and atherosclerosis [25][26], induce ROS through interaction with receptors, and regulate the JNK signal pathway [27][28]. In this study, AGE4 treatment of HK-2 human kidney cells induced ROS production through interacting with RAGE and activating the JNK signaling pathway, both of which play important roles in cellular apoptosis. Recent studies have shown that chronic inflammation induced by intracellular ROS is related to cell signaling in mitochondria and the development of metabolic diseases such as diabetes [29][30][31]. Cellular apoptosis is caused by oxidative stress-induced signal cascades related to cellular apoptosis involving Bcl-2 family proteins [32][33]. When Bcl-2 family proteins interact with the outer mitochondrial membrane, apoptosis proteins are activated [34][35]. On the other hand, due to physiological or pathological conditions, ER stress triggers inflammation, apoptosis, and cell death [36][37][38]. ER stress activates GRP78 and ATF4 through the phosphorylation of eIF2α and promotes the CHOP gene belonging to the C/EBP family, leading to cellular apoptosis [39].

3. Conclusions

In summary, the following points are suggested: (1) RAGE–AGE4 can cause ER stress that leads to apoptosis in kidney cells. (2) The functions of the ER and mitochondria are interconnected, and the cellular mechanism of disorders is induced by the JNK signal pathway through AGE4–RAGE axis. Understanding the mechanism by which AGE4 induces ER stress and mitochondrial dysfunction during diabetic nephropathy will serve as a basis for a new therapeutic approach. Since AGE4, a type of AGE, causes cellular renal apoptosis, future research addressing the active component in AGE4 that causes diabetic nephropathy will aid in the delivery of treatments for diabetic complications.

References

1. AlRashidi, F.T.; Gillespie, K.M. Biomarkers in islet cell transplantation for type 1 diabetes. Curr. Diab. Rep. 2018, 18, 94–104.
2. Zheng, Y.; Ley, S.H.; Hu, F.B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat. Rev. Endocrinol. 2018, 14, 88–98.
3. Marketou, N.P.; Chrousos, G.P.; Gantenbein, C.K. Diabetic nephropathy in type 1 diabetes: A review of early natural history, pathogenesis, and diagnosis. Diabetes Metab. Res. 2017, 33, e2841.
4. Chou, P.S.; Wu, M.N.; Yang, C.C.; Shen, C.T.; Yang, Y.H. Effect of advanced glycation end products on the progression of Alzheimer's disease. J. Alzheimers Dis. 2019, 72, 191–197.
5. Zhang, C.; Wei, W.; Chi, M.; Wan, Y.; Li, X.; Qi, M.; Zhou, Y. FOXO1 mediates advanced glycation end products induced mouse osteocyte-like MLO-Y4 cell apoptosis and dysfunctions. J. Diabetes Res. 2019, 6757428, 1–11.
6. Lee, K.J.; Yoo, J.W.; Kim, Y.K.; Kim, Y.K.; Choi, J.H.; Ha, T.Y.; Gil, M. Advanced glycation end products promote triple negative breast cancer cells via ERK and NF-kB pathway. Biochem. Bioph. Res. Co. 2018, 495, 2195–2201.
7. Rabbani, N.; Thornalley, P.J. Advanced glycation end products in the pathogenesis of chronic kidney disease. Kidney Int. 2018, 93, 803–813.
8. Alikhan, Z.; Alikhani, M.; Boyd, C.M.; Nagao, K.; Trackman, P.C.; Graves, D.T. Advanced glycation end products enhance expression of pro-apoptotic genes and stimulate fibroblast apoptosis through cytoplasmic and mitochondrial pathways. J. Biol. Chem. 2005, 280, 12087–12095.
9. Dai, J.; Chen, H.; Chai, Y. Advanced glycation end products (AGEs) induce apoptosis of fibroblasts by activation of NLRP3 inflammasome via reactive oxygen species (ROS) signaling pathway. Med. Sci. Monito. 2019, 25, 7499–7508.
10. Sibbersen, C.; Johannsen, M. Dicarbonyl derived post-translational modifications: Chemistry bridging biology and aging-related disease. Essays. Biochem. 2020, 64, 97–110.

11. Bellier, J.; Nokin, M.J.; Larde, E.; Karoyan, P.; Peulen, O.; Castronovo, V.; Bellahce'ne, A. Methylglyoxal, a potent inducer of AGEs, connects between diabetes and cancer. Diabetes Res. Clin. Pract. 2019, 148, 200–211.
12. Jeong, S.R.; Park, H.Y.; Kim, Y.S.; Lee, K.W. Methylglyoxal-derived advanced glycation end products induce matrix metalloproteinases through activation of ERK/JNK/NF-κB pathway in kidney proximal epithelial cells. Food Sci. Biotechnol. 2020, 29, 675–682.
13. Hasnain, S.Z.; Prins, J.B.; McGuckin, M. Oxidative and endoplasmic reticulum stress in b-cell dysfunction in diabetes. J. Mol. Endocrinol. 2016, 56, 33–54.
14. Yang, C.; Song, G.; Lim, W. Methiothepin mesylate causes apoptosis of human prostate cancer cells by mediating oxidative stress and mitochondrial dysfunction. Free Radic. Biol. Med. 2020, 150, 12–22.
15. Murata, H.; Khine, C.C.; Nishikawa, A.; Yamamoto, K.I.; Kinoshita, R.; Sakaguchi, M. c-Jun N-terminal kinase (JNK)-mediated phosphorylation of SARM1 regulates NAD cleavage activity to inhibit mitochondrial respiration. J. Biol. Chem. 2018, 293, 18933–18943.
16. Jin, Q.; Li, R.; Hu, N.; Xin, T.; Zhu, P.; Hu, S.; Ma, S.; Zhu, H.; Ren, J.; Zhou, H. DUSP1 alleviates cardiac ischemia/reperfusion injury by suppressing the Mff-required mitochondrial fission and Bnip3-related mitophagy via the JNK pathways. Redox Biol. 2018, 14, 576–587.
17. Jian, K.L.; Zhang, C.; Shang, Z.C.; Yang, L.; Kong, L.Y. Eucalrobusone C suppresses cell proliferation and induces ROS-dependent mitochondrial apoptosis via the p38 MAPK pathway in hepatocellular carcinoma cells. Phytomedicin 2017, 25, 71–82.
18. Morón, E.B.; Jiménez, Z.A.; Marañón, A.M.D.; Iannantuoni, F.; López, I.E.; Domènech, S.L.; Salom, C.; Jover, A.; Mora, V.; Roldan, I.; et al. Relationship between oxidative stress, er stress, and inflammation in type 2 diabetes: The battle continues. J. Clin. Med. 2019, 8, 1385.
19. Takeuchi, M.; Makita, Z.; Bucala, R.; Suzuki, T.; Koike, T.; Kameda, Y. Immunological evidence that non-carboxymethyllysine advanced glycation end-products are produced from short chain sugars and dicarbonyl compounds in vivo. Mol. Med. 2000, 6, 114–125.
20. Takeuchi, M.; Yanase, Y.; Matsuura, N.; Yamagishi, S.I.; Kameda, Y.; Bucala, R.; Makita, Z. Immunological detection of a novel advanced glycation end-product. Mol. Med. 2001, 7, 783–791.
21. Neumeister, P.; Pixley, F.J.; Xiong, Y.; Xie, H.; Wu, K.; Ashton, A.; Cammer, M.; Chan, A.; Symons, M.; Stanley, E.R.; et al. Cyclin D1 governs adhesion and motility of macrophages. Mol. Biol. Cell 2003, 14, 2005–2015.
22. Xu, W.; Zhang, X.; Wu, J.; Fu, L.; Liu, K.; Liu, D.; Chen, G.; Lai, P.; Wong, N.; Yu, J. O-GlcNAc transferase promotes fatty liver-associated liver cancer through inducing palmitic acid and activating endoplasmic reticulum stress. J. Hepatol. 2017, 67, 310–320.
23. Su, S.C.; Hung, Y.J.; Huang, C.L.; Shieh, Y.S.; Chien, C.Y.; Chiang, C.F.; Liu, J.S.; Lu, C.H.; Hsieh, C.H.; Lin, C.M.; et al. Cilostazol inhibits hyperglucose-induced vascular smooth muscle cell dysfunction by modulating the RAGE/ERK/NF-κB signaling pathways. J. Biomed. Sci. 2019, 26, 68–81.
24. Ding, Y.; Xie, Q.; Liu, W.; Pan, Z.; Fan, X.; Chen, X.; Li, M.; Zhao, W.; Li, D.; Zheng, Q. Neochamaejasmin a induces mitochondrial-mediated apoptosis in human hepatoma cells via ROS-dependent activation of the ERK1/2/JNK Signaling Pathway. Oxid Med. Cell Longev. 2020, 3237150, 1–12.
25. Christensen, R.K.; Johannsen, M. Methylglyoxal metabolism and aging-related disease: Moving from correlation toward causation. Trends Endocrinol. Metab. 2020, 31, 81–92.
26. Yua, Y.; Wang, L.; Delguste, F.; Durand, A.; Guilbaud, A.; Rousselin, C.; Schmidt, A.M.; Tessier, F.; Boulanger, E.; Neviere, R. Advanced glycation end products receptor RAGE controls myocardial dysfunction and oxidative stress in high-fat fed mice by sustaining mitochondrial dynamics and autophagy-lysosome pathway. Free Radic. Biol. Med. 2017, 112, 397–410.
27. Son, W.R.; Nam, M.H.; Hong, C.O.; Kim, Y.S.; Lee, K.W. Plantamajoside from Plantago asiatica modulates human umbilical vein endothelial cell dysfunction by glyceraldehyde-induced AGEs via MAPK/ NF-κB. BMC Compl. Altern. Med. 2017, 17, 66–78.
28. Chen, J.; Jing, J.; Yu, S.; Song, M.; Tan, H.; Cui, B.; Huang, L. Advanced glycation endproducts induce apoptosis of endothelial progenitor cells by activating receptor RAGE and NADPH oxidase/JNK signaling axis. Am. J. Transl. Res. 2016, 8, 2169–2178, PMCID:PMC4891429.
29. Wang, S.; Ren, X.; Hu, X.; Zhou, L.; Zhang, C.; Zhang, M. Cadmium-induced apoptosis through reactive oxygen species-mediated mitochondrial oxidative stress and the JNK signaling pathway in TM3 cells, a model of mouse Leydig cells. Toxicol. Appl. Pharmacol. 2019, 368, 37–48.

30. Newsholme, P.; Cruzat, V.F.; Keane, K.N.; Carlessi, R.; de Bittencourt, P.I.H., Jr. Molecular mechanisms of ROS production and oxidative stress in diabetes. Biochem. J. 2016, 473, 4527–4550.
31. DeHart, D.N.; Fang, D.; Heslop, K.; Li, L.; Lemasters, J.J.; Maldonado, E.N. Opening of voltage dependent anion channels promotes reactive oxygen species generation, mitochondrial dysfunction, and cell death in cancer cells. Biochem. Pharmacol. 2018, 148, 155–162.
32. Spinelli, J.B.; Haigis, M.C. The multifaceted contributions of mitochondria to cellular metabolism. Nat. Cell Biol. 2018, 20, 745–754.
33. Mao, Y.X.; Cai, W.J.; Sun, X.Y.; Dai, P.P.; Li, X.M.; Wang, Q.; Huang, X.L.; He, B.; Wang, P.P.; Wu, G.; et al. RAGE-dependent mitochondria pathway: A novel target of silibinin against apoptosis of osteoblastic cells induced by advanced glycation end products. Cell Death Dis. 2018, 9, 674–688.
34. Ashkenazi, A.; Fairbrother, W.J.; Leverson, J.D.; Souers, A.J. From basic apoptosis discoveries to advanced selective BCL-2 family inhibitors. Nat. Rev. Drug Discov. 2017, 16, 273–284.
35. O'Neill, K.L.; Huang, K.; Zhang, J.; Chen, Y.; Luo, X. Inactivation of prosurvival Bcl-2 proteins activates Bax/Bak through the outer mitochondrial membrane. Genes Dev. 2016, 30, 973–988.
36. Vargas, M.P.A.L.; Chipuk, J.E. The deadly landscape of pro-apoptotic BCL-2 proteins in the outer mitochondrial membrane. FEBS J. 2016, 283, 2676–2689.
37. Meyerovich, K.; Ortis, F.; Allagnat, F.; Cardozo, A.K. Endoplasmic reticulum stress and the unfolded protein response in pancreatic islet inflammation. J. Mol. Struct. 2016, 57, 1–17.
38. Liu, Z.; Gu, H.; Gan, L.; Xu, Y.; Feng, F.; Saeed, M.; Sun, C. Reducing Smad3/ATF4 was essential for Sirt1 inhibiting ER stress-induced apoptosis in mice brown adipose tissue. Oncotarget 2017, 8, 9267–9279.
39. Abdullah, A.; Ravanan, P. Kaempferol mitigates endoplasmic reticulum stress induced cell death by targeting caspase 3/7. Sci. Rep. 2018, 8, 2189–2204.