Involvement of oxidative stress-induced ERK/JNK activation in the Cu^{2+}/pyrrolidine dithiocarbamate complex-triggered mitochondria-regulated apoptosis in pancreatic β-cells

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Abstract:

Oxidative stress was demonstrated to promote the progression of diabetes mellitus (DM). It has been suggested that copper may play a specific role in the progression and pathogenesis of DM. Pyrrolidine dithiocarbamate (PDTC), a widely apply to the medicine and pesticide, was known to be capable of enhancing copper accumulation. In this study, we investigated the effect of submicromolar-concentration Cu^{2+}/PDTC complex on pancreatic β-cell damage and evaluated the role of oxidative stress in this effect. $CuCl_2$ (0.01~300 μM) did not affect the cell viability in β-cell line RIN-m5F cells. However, combination of $CuCl_2$ (0.5 μM) and PDTC (0.3 μM) markedly reduced RIN-m5F cell viability. Cu^{2+}/PDTC

complex could also increase in oxidative stress damage, and display several features of mitochondria-dependent apoptosis signals, which accompanied with the marked increase the intracellular Cu^{2+} levels. These apoptotic-related responses of Cu^{2+}/PDTC complex-induced could be effectively prevented by antioxidant *N*-acetylcysteine (NAC). Furthermore, Cu^{2+}/PDTC complex was capable of increasing the activation of ERK1/2 and JNK, and its upstream kinase MEK1/2 and MKK4, which could be reversed by NAC. Transfection with ERK2-siRNA and MAPK8-shRNA and specific inhibitors SP600125 and PD98059 could inhibit ERK1/2 and JNK activation and attenuate MMP loss and caspase-3 activity induced by the Cu^{2+}/PDTC complex. Taken together, these results are the first report to demonstrate that the Cu^{2+}/PDTC complex triggers a mitochondria-regulated apoptosis via an oxidative stress-induced ERK/JNK activation-related pathway in pancreatic β-cells.

Keywords: Copper; PDTC, Pancreatic β-cell; Oxidative stress; Apoptosis; ERK1/2; JNK