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ORAL PRESENTATION Open Access

Chronic treatment with valproate protects INS1 cell from palmitate-induced ER stress and apoptosis by inhibiting GSK3β

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Objective

Reduction of β-cell mass is increasingly recognized as one of the main contributing factors to the pathogenesis of type 2 diabetes. Chronic free fatty acid (FFA) exposure has been shown to induce endoplasmic reticulum (ER) stress that may contribute to promoting pancreatic β-cell apoptosis. In the present study, we first investigated whether anticonvulsant sodium valproate (VPA), at clinically relevant doses, protects pancreatic β-cell from palmitate-induced apoptosis and the mechanism underlying anti-apoptosis.

Methods and results

INS1 cells exposed to 0.25~1.0 mM palmitate for 24~48 h under serum-free conditions showed marked apoptosis in time- and concentration-dependent as assessed by CCK-8 assay, Hoechst 33342/PI, flow cytometric cell apoptosis assay and electron microscopy. Palmitate triggered ER stress and apoptosis in INS1 cells as evidenced by increased mRNA levels of C/EBP homologous transcription factor (CHOP), activating transcription factor 4 (ATF4) and X box-binding protein 1 (XBP-1) in a time-dependent fashion. Western blot analysis also showed significant increase of CHOP and caspase-3 in protein level. We also found that palmitate activated GSK3β by inhibiting phosphorylation at serine 9. While chronic, not acute, 1~2 mM VPA and 2 mM LiCl remarkable reduced palmitate-induced cytotoxicity. Furthermore, INS1 cells treated with 10~20 μM TDZD-8, a specific GSK3β inhibitor, also elicited cytoprotective responses against 0.25~0.5 mM palmitate for 6~48 h and decreased mRNA level of CHOP, but not ATF4 or XBP-1. The protein levels of CHOP, caspase-3 and GSK3β activity were remarkable reduced by co-treatment of INS1 cells with 0.25mM palmitate and 1 mM VPA, compared with 0.25mM palmitate only. Finally, down-regulation of CHOP expression in INS1 cells by small interfering RNA (SiRNA) did not show apparent cytoprotective responses against 0.25mM palmitate.

Conclusion

ER stress and GSK3β involved in palmitate-induced β-cell apoptosis, however, GSK3β other than ER stress is likely playing a more prominent role. Valproate protected pancreatic β-cell from palmitate-induced apoptosis and ER stress by inhibiting GSK3β.

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