Etoposide-induced mitochondria-dependent apoptosis through c-jun N-terminal kinases, extracellular signal-regulated kinases, and glycogen synthesis kinase 3α/β pathway in pancreatic β-cells

kuan-I Lee[1], Shan-Shu Hsieh[1], Chin-Chuan Su[2], Dong-Zong Hung[3], Kuo-Liang Chen[4], To-Jung Tseng[5], Tien-Hui Lu[6], Shing-Hwa Liu[7], Ya-Wen Chen[6], Chun-Fa Huang[8]

[1]Department of Emergency, Buddhist Tzu Chi General Hospital, Taichung Branch, Taichung 427, Taiwan
[2]Department of Otorhinolaryngology, Head and Neck Surgery, Changhua Christian Hospital, Changhua 500, Taiwan
[3]Division of Toxicology, Trauma & Emergency Center, China Medical University Hospital, Taichung 404, Taiwan
[4]Department of Urology, China Medical University Hospital, Taichung, Taiwan
[5]Department of Anatomy, China Medical University, Taichung 404, Taiwan
[6]Department of Physiology and Graduate Institute of Basic Medical Science, China Medical University, Taichung, Taiwan
[7]Institute of Toxicology, National Taiwan University, Taipei, Taiwan
[8]School of Chinese Medicine, China Medical University, Taichung, Taiwan

Abstract:

Etoposide, a semisynthetic derivative of podophyllotoxin, is an important chemotherapeutic agent and widely used to treat human cancers. Etoposide also can produce the severe side effects and cause cell damages and the physiological dysfunctions. However, the toxicological effects of etoposide-induced pancreatic β-cell death remain unclear. Here, we investigate the cytotoxic effect and its possible mechanisms of etoposide on pancreatic β-cells. Treatment of pancreatic β-cell-derived RIN-m5F cells with etoposide (1-100 M) for 24 h significantly reduced cell viability and underwent apoptosis, accompanied with mitochondrial dysfunctions

(decreased mitochondrial membrane potential, increased cytosolic cytochrome c release and Bax/Bcl-2 ratio), increased sub-G1 hypodiploid cell population, caspase-3 activity, and caspase-3/-6/-7/-9 protein expression. Moreover, etoposide triggered the protein phosphorylation of glycogen synthesis kinase (GSK)-3α/β at 8 h treatment and maintained to 24 h, which could be reversed by lithium chloride (LiCl, a specific inhibitor of GSK-3α/β). In addition, etoposide (20 μM) markedly increased the phosphorylation of JNK and ERK1/2, but not p38. Pharmacological inhibitors SP600125 and PD98059 effectively attenuated etoposide-induced caspase-3 activity and JNK and ERK1/2 activation, but LiCl could not reverse the phosphorylation of JNK and ERK1/2 induced by etoposide. In conclusion, these results suggest that etoposide exerts its cytotoxicity on pancreatic β-cells by inducing the mitochondria-dependent apoptosis through JNK/ERK activation-regulated GSK-3α/β signaling pathway.