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journal or publication title	Diabetologia
volume	50
number	Supplement 1
page range	S44-S44
year	2007-09
URL	http://hdl.handle.net/2241/91512

doi: 10.1007/s00125-007-0809-7

EPA prevents palmitate-induceḍ β-cell lipotoxicity by suppression of SREBP-1c

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Background and Aimes; Molecular mechanisms of pancreatic islet β-cell failure, a crucial pathological contributor to the development for diabetes mellitus have been extensively explored. Impairment of glucose-stimulated insulin secretion (GSIS) is an early feature of type2 diabetes, and influx of fatty acids into β-cells, β-cell lipotoxicity, has been thought to be involved in its pathogenesis. Sterol regulatory element-binding protein (SREBP)-1c is a transcription factor that controls hepatic lipogenesis and inhibited by polyunsatulated fatty acids such as eicosapentaenoate (EPA). In pancreatic β-cells, activation of SREBP-1c has been shown to be involved in impaired insulin secretion and glucose intolerance. In the current studies, the contribution of SREBP-1c to palmitate (PA) induced lipotoxicity and protective effect of EPA from lipotoxicty was investigated.

Materials and Methods; Pancreatic islets isolated from C57BL/6 mice or SREBP-1-null mice were incubated without or with palmitate (PA) or PA-EPA. After incubation of islets, GSIS or potassium-(KSIS) stimulated insulin secretions and cellular insulin contents were measured. Expression profiles of mRNA and proteins were determined by real-time PCR and immunoblot analyses, respectively. Insulin secretion of pancreatic islet isolated from PA-rich diet fed mice and KK-A^y mice treated with or without EPA were also measured.

Results: Incubation of isolated islets from C57BL/6 mice with PA caused inhibition of both GSIS and KSIS in dose-dependent manner, but addition of EPA restored both inhibitions. Concomitantly, PA activated, and EPA inhibited both mRNA and nuclear protein of SREBP-1c, accompanied by reciprocal changes of SREBP-1c-target genes such as IRS-2 and granuphilin. Suppression of IRS-2/Akt pathway could be a part of the downstream mechanism for the SREBP-1c-mediated insulin secretion defect because adenoviral constitutive activation of Akt (dominant positive form) compensated it. Uncoupling protein-2 also plays a crucial role in the PA inhibition of insulin secretion as confirmed by knockdown experiments, but that regulation is independent of SREBP-1c. The PA-EPA regulation of insulin secretion was similarly observed in islets from C57BL/6 mice pretreated with dietary manipulations. Furthermore, administration of EPA to diabetic KK-A^y mice ameliorated impairment of insulin secretion in their islets.

Conclusions: EPA prevents PA-mediated insulin secretion defect through SREBP-1c inhibition, implicating a therapeutic potential for diabetes related to lipotoxicity.