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Diabetes 2019: PSTi8 modulates glucose and lipid homeostasis by regulating the AMPK pathway in dexamethasone induced insulin resistance - Anand P Gupta - Central Drug Research Institute, India

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Dexamethasone (DEX, a glucocorticoid) is used as an anti-inflammatory agent for the treatment of disorders such as allergic and auto-immune disease etc. But its clinical applications are restricted due to various metabolic side effects, including progression of fatty liver, insulin resistance, diabetes, etc. Therefore in the present study, we aimed to investigate whether PSTi8, a pancreastatin inhibitor has a potential to treat dexamethasone-induced fatty liver disease associated insulin resistance. We found that PSTi8 suppresses hepatic glucose release, lipid deposition and stimulates the ATP/AMP ratio in HepG2 cells. It improves lipid homeostasis and enhances insulin sensitivity and glucose tolerance in DEX induced diabetic mice. The above cellular effects are the result of activated AMPK signaling pathway in liver which increases Srebp1c and ACC phosphorylation. The increased ACC phosphorylation suppresses protein kinase C (PKC) activity and enhances insulin sensitivity. The improvement in insulin sensitivity, furthermore suppress hepatic gluconeogenesis and increases hepatic glycogen. In addition, increased expression of UCP3 in liver elicits fatty acid oxidation and energy expenditure. Thus the activation of AMPK signaling improves lipid homeostasis, enhances insulin sensitivity through inhibition of PKC activity. Hence, PSTi8 may be a potential therapeutic agent to treat glucocorticoid-induced fatty liver associated diabetes.