

Abstract

Hepatology. 2009 May 6. [Epub ahead of print]

Aggravation by prostaglandin E(2) of interleukin-6-dependent insulin resistance in hepatocytes.

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BACKGROUND: Hepatic insulin resistance is a major contributor to fasting hyperglycemia in patients with metabolic syndrome and type 2 diabetes. Circumstantial evidence suggests that cyclooxygenase products in addition to cytokines might contribute to insulin resistance. However, direct evidence for a role of prostaglandins in the development of hepatic insulin resistance is lacking.

OBJECTIVE: Therefore, the impact of prostaglandin E(2) (PGE(2)) alone and in combination with interleukin-6 (IL-6) on insulin signaling was studied in primary hepatocyte cultures.

METHODS: Rat hepatocytes were incubated with IL-6 and/or PGE(2) and subsequently with insulin. Glycogen synthesis was monitored by radiochemical analysis; the activation state of proteins of the insulin receptor signal chain was analyzed by western blot with phosphospecific antibodies.

RESULTS: In hepatocytes, insulin-stimulated glycogen synthesis and insulin-dependent phosphorylation of Akt-kinase were attenuated synergistically by prior incubation with IL-6 and/or PGE(2) while insulin receptor autophosphorylation was barely affected. IL-6 but not PGE(2) induced suppressors of cytokine signaling (SOCS3). PGE(2) but not IL-6 activated extracellular signal-regulated kinase 1/2 (ERK1/2) persistently. Inhibition of ERK1/2 activation by PD98059 abolished the PGE(2)-dependent but not the IL-6-dependent attenuation of insulin signaling. In HepG2 cells expressing a recombinant EP3-receptor, PGE(2) pre-incubation activated ERK1/2, caused a serine phosphorylation of insulin receptor substrate 1 (IRS1), and reduced the insulin-dependent Akt-phosphorylation.

CONCLUSION: PGE(2) might contribute to hepatic insulin resistance via an EP3-receptor-dependent ERK1/2 activation resulting in a serine phosphorylation of insulin receptor substrate, thereby preventing an insulin-dependent activation of Akt and glycogen synthesis. Since different molecular mechanisms appear to be employed, PGE(2) may synergize with IL-6, which interrupted the insulin receptor signal chain, principally by an induction of SOCS, namely SOCS3.

PMID: 19575453