INCREASED LIVER EXPRESSION OF INFLAMMATORY MEDIATORS IS ASSOCIATED WITH HEPATIC INSULIN RESISTANCE IN LEAN, NON-DIABETIC CHC PATIENTS

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Background and aims. Chronic hepatitis C (CHC) has been associated with type 2 diabetes and insulin resistance. A crucial role of inflammatory cytokines in the pathogenesis of the HCV-associated insulin resistance state has been suggested. This study was undertaken to explore the relationship between liver expression of inflammatory mediators and hepatic insulin resistance in a group of lean, non-diabetic CHC patients.
Methods. We performed a euglycaemic hyperinsulinaemic clamp ($1\,mU\,min^{-1}\,kg^{-1}$) coupled with tracer infusion ([6,6-^{2}H2]glucose) in 10 lean, non-diabetic patients with biopsy-proven CHC, and in seven matched healthy controls. We also measured the gene expression of tumor necrosis factor-α (TNF-α), interleukin-18 (IL-18) and suppressor of cytokine signaling 3 (SOCS3) in liver biopsies by quantitative PCR and tested their association with the metabolic parameters.
Results. Compared to controls, in CHC patients basal endogenous glucose production (EGP) was 20% higher ($p = 0.011$) and its suppression during the clamp (hepatic insulin sensitivity) was markedly reduced ($p = 0.007$), resulting in a 3.5-fold higher EGP. Patients had an increased hepatic expression of TNF-α (median, 5.7-fold increase; range 2–10-fold), IL-18 (median, 5.7-fold increase; range 3–11-fold) and SOCS3 (median, 0.84-fold increase; range 0.5–1.2-fold). Notably, in CHC a decreased insulin-stimulated suppression of EGP was associated with increased hepatic IL-18 ($r = 0.63$, $p < 0.05$) and SOCS3 expression ($r = 0.68$, $p < 0.05$), whereas the hepatic expression of TNF-α showed only a positive trend ($p = 0.09$).
Conclusions. Hepatitis C infection *per se* is associated with hepatic insulin resistance. Increased hepatic expression of SOCS3 and IL-18 are associated with defective glucose regulation in the liver.

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UDCA UP-REGULATES HUMAN PLACENTAL BCRP EXPRESSION: PRELIMINARY RESULTS

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In intrahepatic cholestasis of pregnancy (ICP) an accumulation of bile acids (BA) in the fetal compartment occurs. It is known that a BA efflux is induced by UDCA administration but the molecular basis of this transplacental transport is only partially defined.
Aim. Aim of the present study was to determine if placental BCRP, able to transport BA, is regulated by UDCA in ICP.
Methods. 14 pregnant women with ICP (six untreated, 37.5 ± 1.33 years; eight treated with UDCA—25 mg/(kg day), 32.14 ± 2.16 years) and seven age-matched healthy controls (34.2 ± 1.2 years) have agreed to participate to the study (none had gallstone disease, abnormal liver tests, liver steatosis on ultrasonography). Placentas were obtained at delivery and processed for membrane extraction. Protein expression was evaluated by standard immunoblotting techniques using actin as an internal control. Chemiluminescence was quantified with a luminograph measuring emitted photons. Statistical differences between groups were evaluated by one-way ANOVA with Dunn's Multiple Comparison test.
Results. BCRP was expressed only on the apical membrane of the syncytiotrophoblast. A significant difference was observed between the three groups (ANOVA, $p = 0.01$). BCRP expression was similar in controls and in the untreated ICP group. The administration of UDCA induced a significant increase in placental BCRP expression compared to controls ($254.5 \pm 58.46\%$ vs. $100 \pm 8.002\%$ of control, $p < 0.05$).
Conclusion. In this preliminary study we are able to confirm that BCRP is expressed only on the apical membrane of the syncytiotrophoblast. ICP treatment with high dose UDCA significantly up-regulates placental BCRP expression favouring BA transport towards the foetal compartment.

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