Liver ER stress and Intrauterine growth retardation in rats

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BACKGROUND

Endoplasmic reticulum (ER) is the site of protein synthesis and folding. Perturbation of ER homeostasis activates a set of ER-to-nucleus signaling reactions known as the unfolded protein response (UPR). Metabolic stress causes UPR activation which contributes to the development of insulin resistance and metabolic syndrome. As UPR can be activated by nutrient and oxygen starvation, we postulated that intrauterine growth restriction may trigger UPR signaling and thereby contribute to the metabolic risk of IUGR subjects.

AIMS

1) to evaluate liver UPR and 2) to determine the functional consequences of UPR in IUGR rat pups.

METHODS

Sprague-Dawley pregnant rats underwent surgery for uterine artery ligation at day 19 of gestation. Approximately 8 h after delivery, pups were weighed and killed. Tissue was immediately harvested and stored at <80 C. The expression of genes that regulate liver UPR and their metabolic targets were investigated in 14 SHAM and 14 IUGR pups.
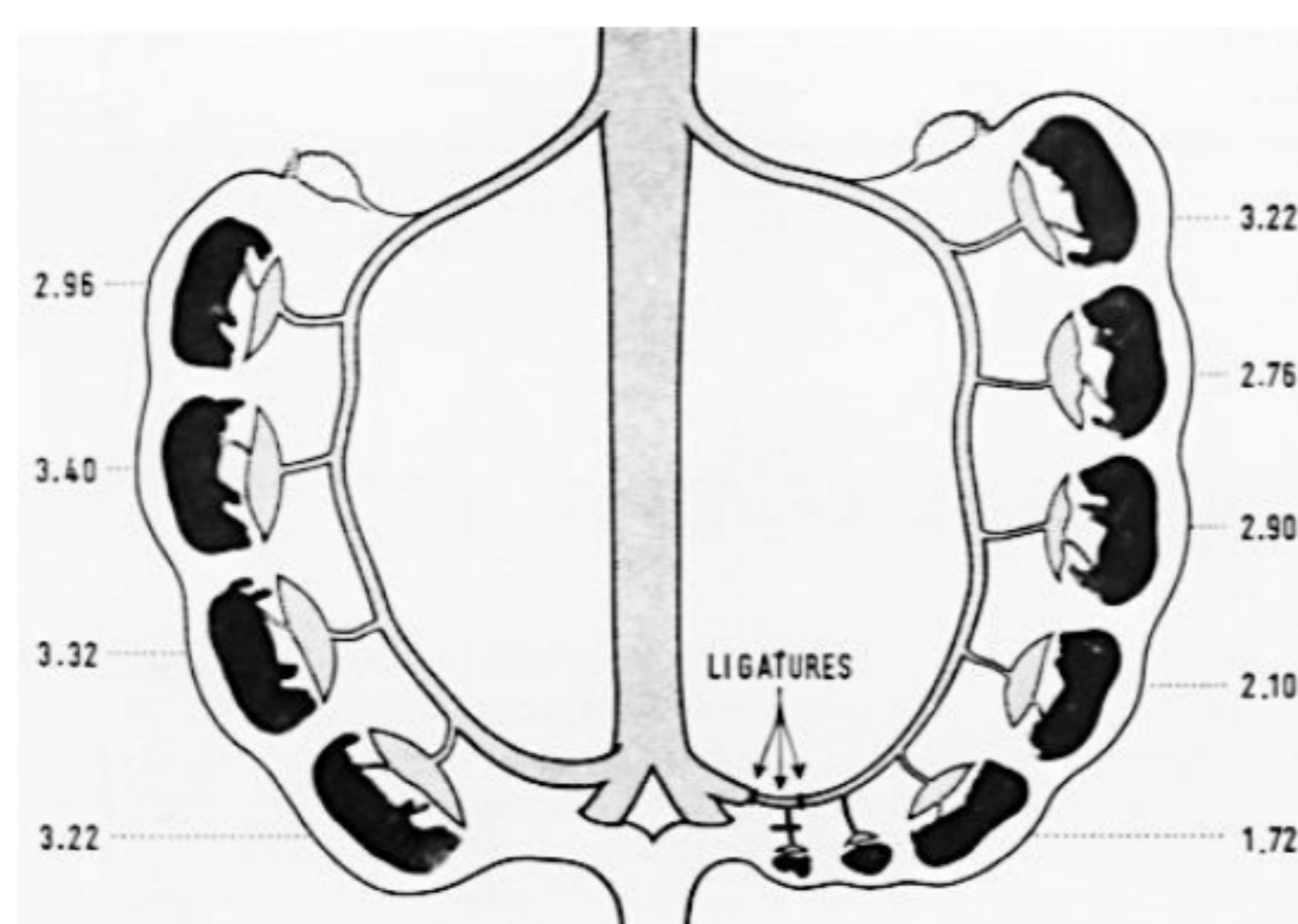

Figure 1. Animal Model.

RESULTS

IUGR animals had significantly lower birth weight than controls (p<0.001). No significant differences were observed in blood glucose and insulin levels at birth. IUGR animals showed significantly higher NEFA blood levels (p<0.001). A significant increased expression of XBP1s mRNA (p<0.01), Erdj4 mRNA (p<0.05) and Bip mRNA (p<0.05) was observed in liver of IUGR pups. In IUGR pups the gene expression of Pck1 and G6pc (gluconeogenesis genes) and Acc2, Dgat2 and Scd1 (lipogenesis genes) was significantly upregulated (p<0.05).

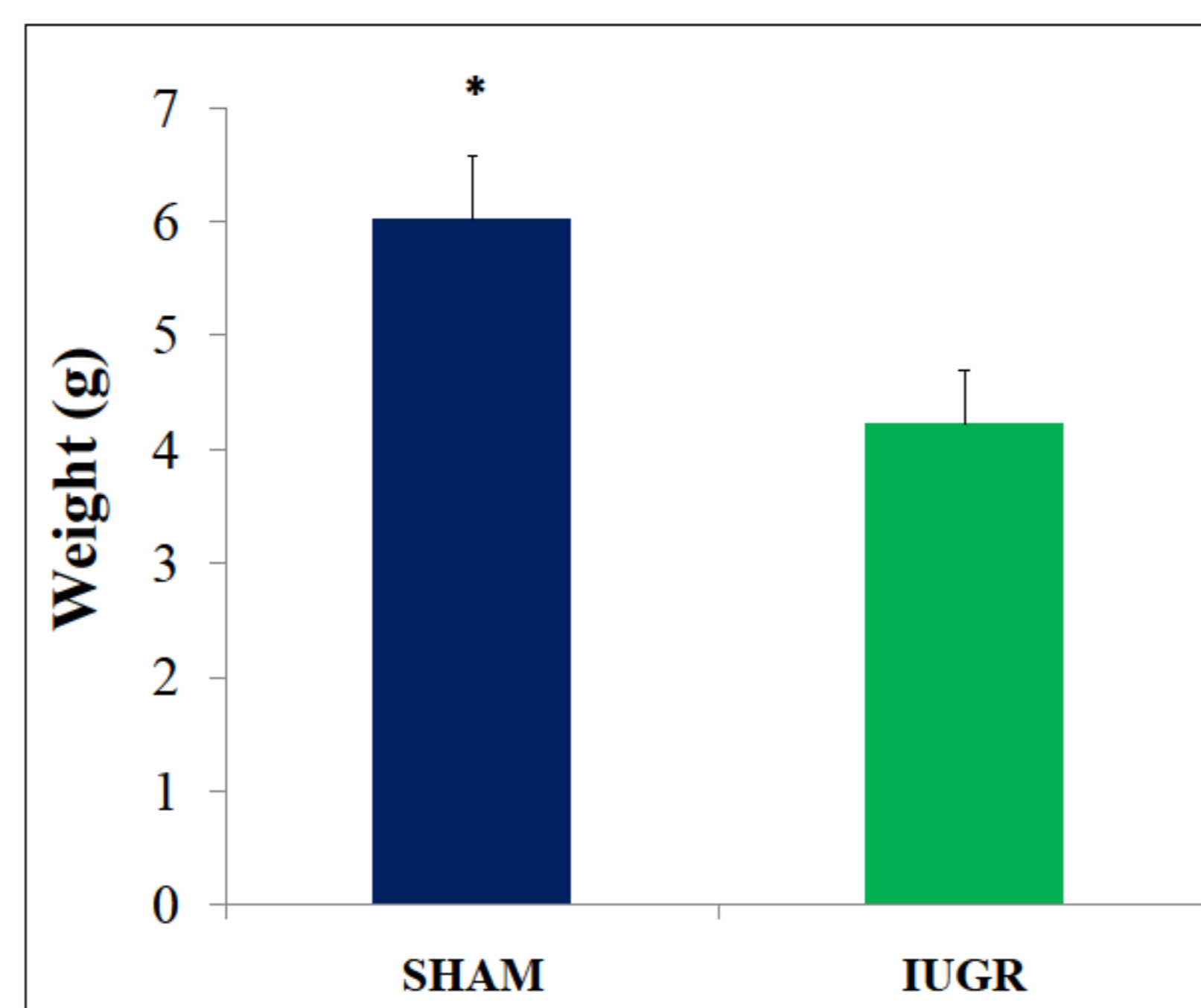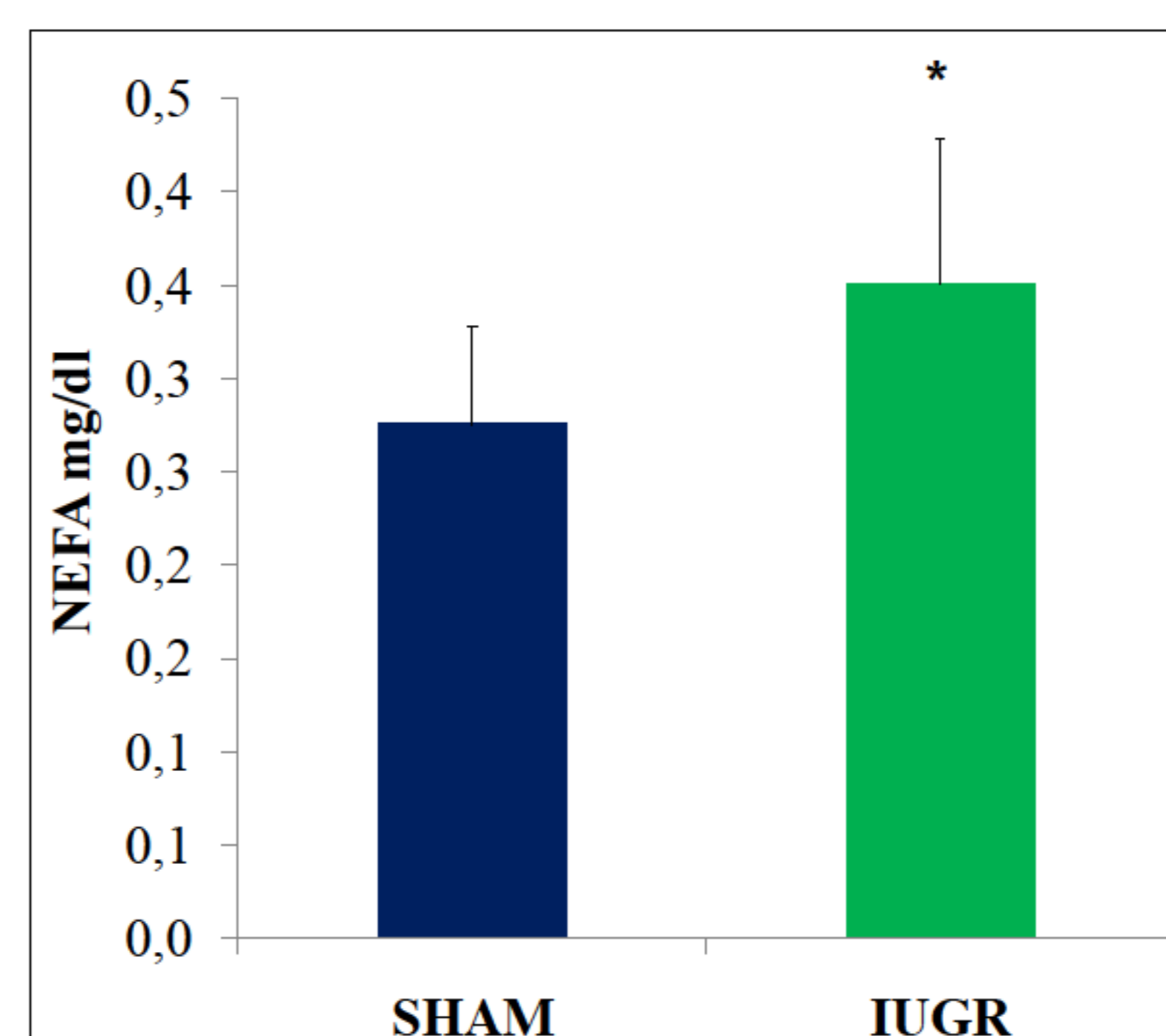**Figure 2.** Birth weights of IUGR (n=14) and SHAM (n=14) animals. (mean weight SD, *p<0.001)

Figure 3. Plasma concentrations of NEFA (mg/dl) in 14 IUGR and 14 SHAM (mean weight   SD, *p<0.001)
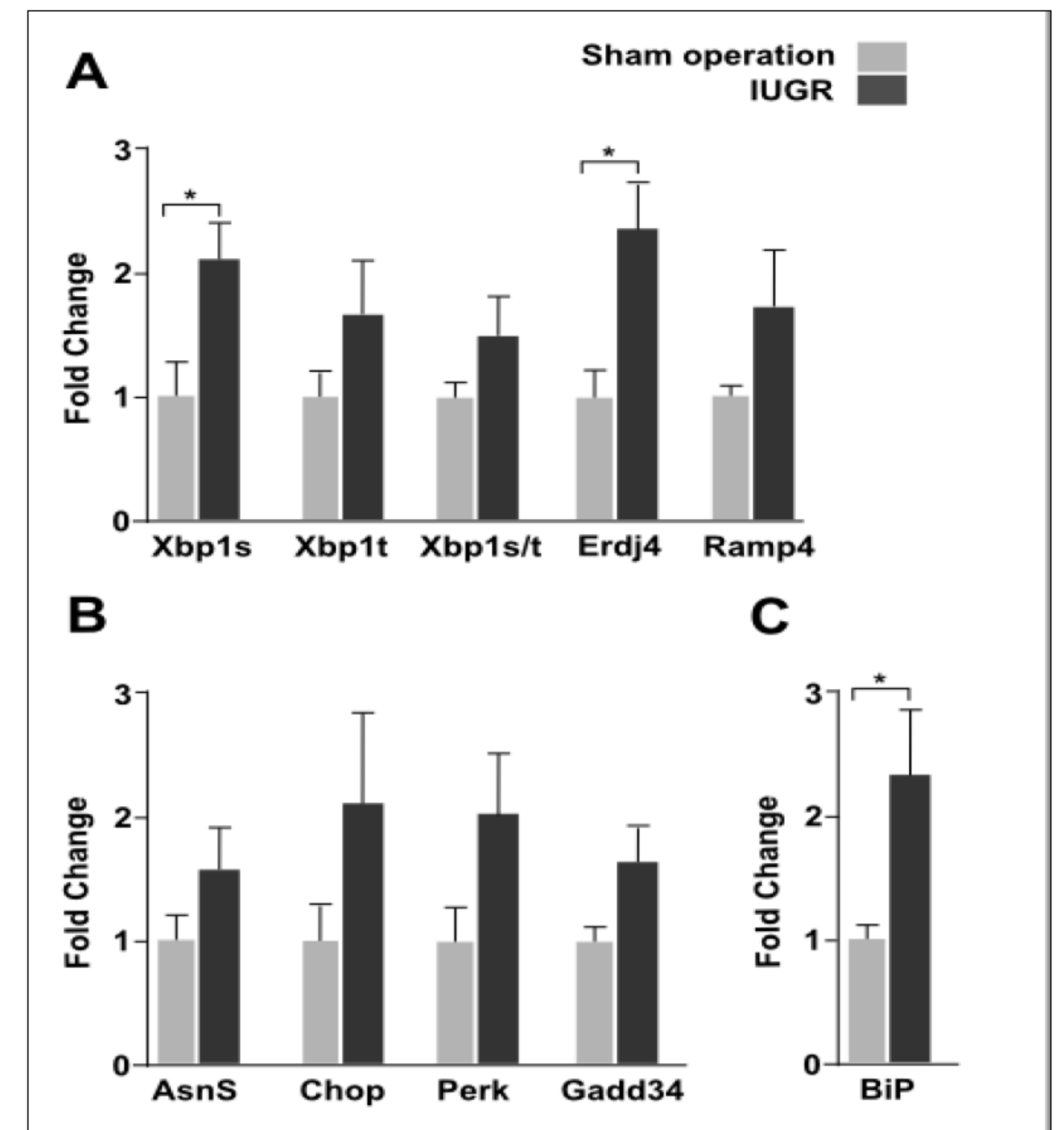

Figure 4. Expression of target genes from the three branches of the UPR: A IRE 1 a, B. PERK and C. ATF6. Values are expressed as fold change (mean   SD), *p<0.01
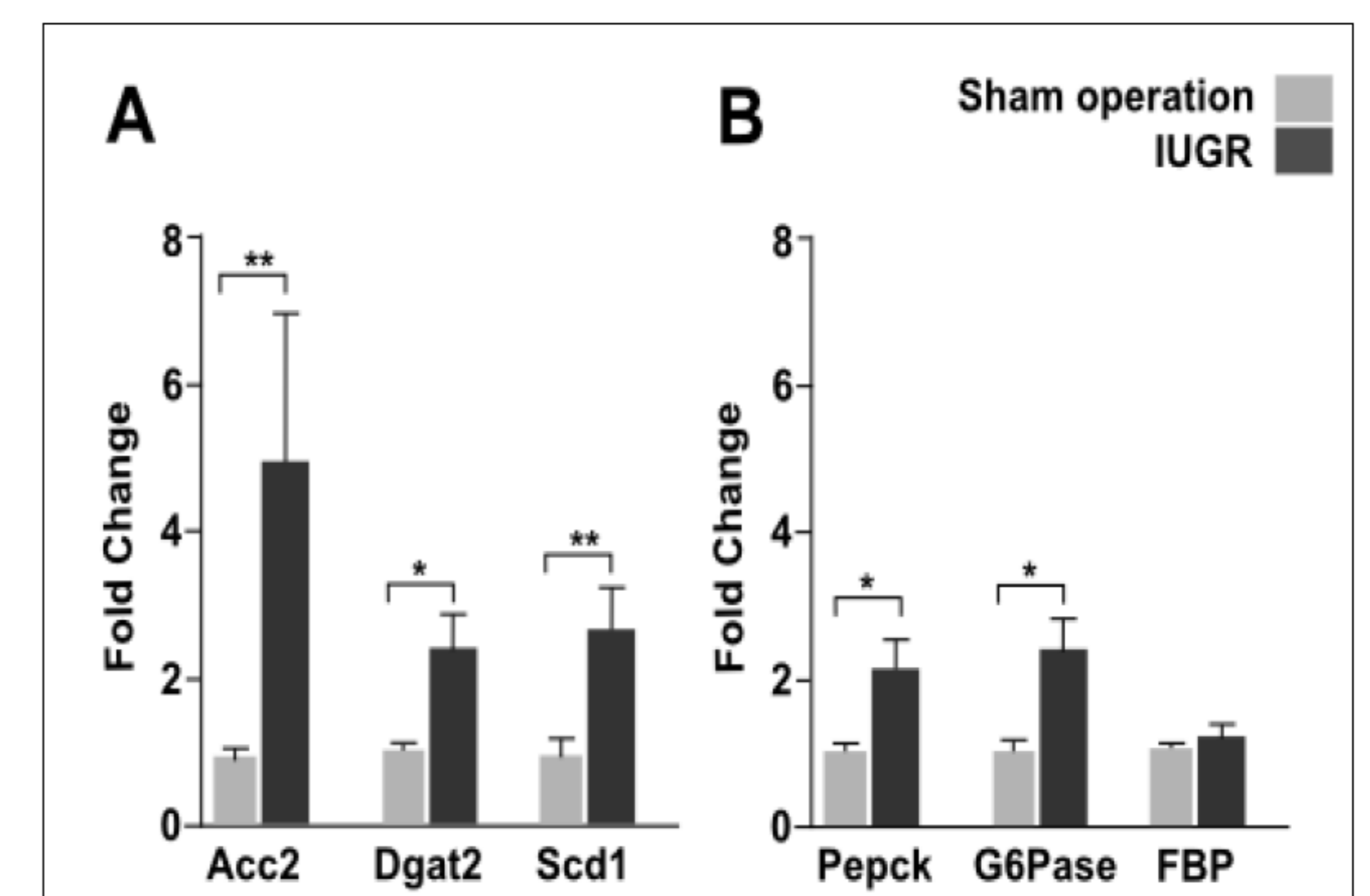

Figure 5. Expression of main lipogenesis (A) and gluconeogenis (B) genes in liver . Values are expressed as fold change (mean   SD), *p< 0.01, **p< 0.005

CONCLUSIONS

In IUGR newborn pups, UPR activation associates with the increased levels of mRNAs encoding lipogenic and gluconeogenic enzymes. Our findings suggest that hepatic ER stress/UPR signaling may play a role in the metabolic risk associated to intrauterine growth retardation

Poster presented at: