CORRELATIONS AND DISCORDANCES BETWEEN HEPATIC INSULIN SIGNALING AND SENSITIVITY IN MICE WITH STEATOSIS

N. Lanthier, O. Molendi-Coste, M. Petit, V. Lebrun, Y. Horsmans, I.A. Leclercq

Laboratory of Gastroenterology, Université catholique de Louvain, Brussels, Belgium.

Background and aims:

Insulin resistance refers to dysregulation of insulin signaling. Here, we compare insulin signaling and *in vivo* insulin sensitivity in the liver and muscle of obese mice.

Methods:

The insulin signaling pathway upon insulin stimulus was analyzed by western blot and insulin sensitivity assessed *in vivo* by the gold standard hyperinsulinemic-euglycemic clamp in genetically obese (ob/ob) mice and in C57Bl6 mice fed a high fat diet (HFD) for 3 days or 16 weeks.

Results:

Hepatic lipid content was increased ~3 and ~2 times in mice fed the HFD for 3 days and 16 weeks, respectively owe to enhanced hepatic lipid uptake. Massive steatosis in ob/ob mice was related to *de novo* lipogenesis. After 3-day HFD, hepatic but not peripheral *in vivo* insulin sensitivity was decreased. This was concurrent to decreased insulin receptor expression and decreased insulin-dependent phosphorylation of insulin receptor and downstream Akt in the liver but not in muscles.

Mice fed the HFD for 16 weeks and ob/ob mice exhibited severe insulin resistance involving both the liver and peripheral compartments as assessed by clamp. In HFD-fed mice, severe defects of the insulin-stimulated signaling pathway were found in the muscle, but not in the liver. By contrast, insulin signaling was hampered both in the muscles and the liver of ob/ob mice.

Conclusions:

In the course of HFD feeding, hepatic insulin resistance, linked with alterations of the hepatic insulin signaling, is an early event. In more chronic models, insulin sensitivity is decreased both in the liver and peripheral organs. Contrasting with ob/ob mice, there was

no defect in hepatic insulin signaling in mice chronically fed the HFD. The mechanisms implicated in hepatic insulin resistance in this context remain to be clarified. Our observations imply that hepatic insulin sensitivity can not always be anticipated from the analysis of insulin signaling.