The role of nuclear hormone receptors in hepatic insulin resistance

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The oxysterol-activated liver X receptor (LXR) and the bile acid-activated farnesoid X receptor (FXR) are nuclear hormone receptors. These receptors induce or inhibit transcription of target genes upon activation. LXR controls cholesterol metabolism and lipogenesis, whereas FXR regulates bile acid synthesis and lipoprotein metabolism. Although both receptors might influence transcription of genes involved in carbohydrate metabolism, their role in glucose metabolism and hence insulin sensitivity is largely unknown. To investigate their roles in insulin sensitivity, we applied hyperinsulinemic euglycemic clamps to conscious mice. Hepatic glucose production (HGP) and metabolic clearance rate (MCR) of glucose under clamped conditions were determined with [U-^{13}C]-glucose added to infused solutions. Lean and *ob/ob* mice were treated with LXR agonist GW3965, resulting in increased hepatic triglyceride content in lean (61.7±7.2 vs. 12.1±2.0 nmol/mg, P<0.05) and obese mice (221±13 vs. 176±19 nmol/mg, P<0.05). In lean mice, LXR activation did not affect glucose infusion rate (GIR) needed to maintain euglycemia, indicating unaffected whole-body insulin sensitivity. Hyperinsulinemia almost completely inhibited HGP (86 vs. 94% inhibition, treated vs. control). MCR was not affected by the agonist. In *ob/ob* mice, LXR activation improved insulin sensitivity: GIR increased 49% (P<0.05). LXR activation marginally enhanced insulin effectiveness in suppression of HGP (61 vs. 48% inhibition) and resulted in improved MCR (18.2±1.0 vs. 14.3±1.4 ml/kg/min, P=0.05).
Upon chow diet, FXR knockout mice showed reduced insulin sensitivity compared to wild-type littermates: GIR was 19% reduced (P<0.05). Knockout mice had unaffected HGP, but reduced MCR (64.9±4.4 vs. 79.3±5.6 ml/kg/min, P<0.05). Upon a high fat-diet, knockout mice had lower fasting blood glucose (10.2±0.7 vs. 8.3±0.3 mM, P<0.05), but FXR deficiency did not affect GIR, MCR, and HGP.
In conclusion, LXR and FXR play roles in glucose clearance, probably by facilitating insulin sensitive peripheral glucose uptake, but their role in hepatic glucose metabolism needs further study.

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