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High-fat–cholesterol-fed pigs are insulin resistant and have decreased expression of insulin receptor substrate-1 (IRS-1) and PPARα in muscle and fat

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Increased intake of lipid has been linked to the development of the metabolic syndrome (type-2 diabetes, CVD) in human subjects[(1)]. An investigation has been conducted into whether an increased intake of fat and cholesterol increases insulin resistance and is accompanied by changes in tissue expression of IRS-1, PPARγ co-activator 1α (PGC-1α) and PPARα using the pig as a model of diet-induced metabolic syndrome.

Commercial pigs (25% Meshian, 12.5% Duroc, 62.5% Large White Landrace; 3 months old; 15 kg) were divided into control (*n* 8) and lipid-fed (*n* 4) groups and gradually adapted to the experimental diets over 3 weeks. The control group was fed *ad libitum* a commercial ration containing (/kg) 178 g protein and 48 g fat and 13 MJ metabolisable energy, and the lipid group were offered the same ration mixed with 15 g lard and 2 g cholesterol/kg. After 10 weeks on the diets ear veins in both ears were cannulated and an insulin tolerance test performed. After 12 weeks on the diets the pigs were killed and tissue samples taken for measurement of mRNA concentrations by quantitative real-time PCR.

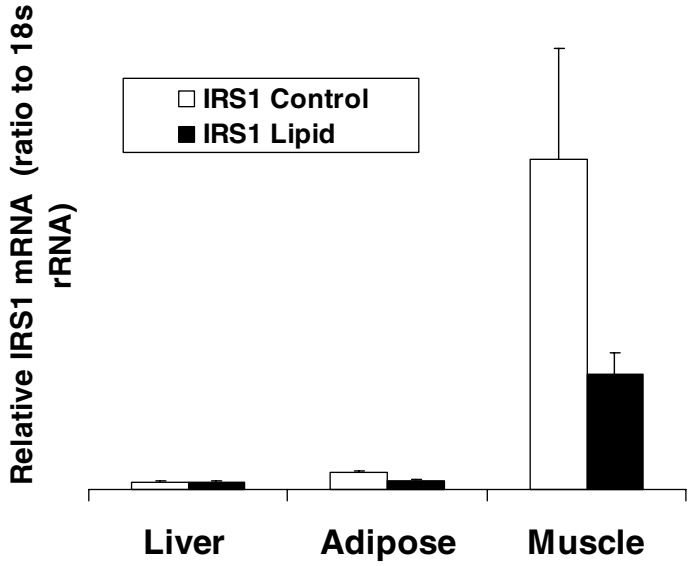

Figure. Tissue IRS1 mRNA in control and lipid fed pigs.

There was no effect of the lipid diet on growth rate over the 12 weeks (average growth rate 0.99 kg/d). Plasma cholesterol was doubled by the lipid diet (mM; control, 2.91 (SEM 0.29); lipid, 5.48 (SEM 0.29)) with the LDL–VLDL-cholesterol fraction more than doubled. Lipid-fed pigs were more insulin resistant, with the rate of decrease in blood glucose after an intravenous insulin challenge (0.05 IU/kg body weight) being one-third that observed in the control animals (mM/min; control, 0.15; lipid, 0.04). Expression of IRS-1 (Figure) but not the insulin receptor was decreased ($P<0.05$) in muscle and visceral fat of lipid-fed pigs and there was no change in the liver. PPARα mRNA was decreased in muscle and visceral fat ($P<0.05$) in lipid-fed pigs but there was no change in liver. The lipid diet decreased PGC-1α mRNA only in liver while adiponectin and adiponectin receptor 2 mRNA was decreased in visceral fat ($P<0.05$). Adiponectin receptor R2 mRNA was increased with lipid feeding in muscle and liver.

The data suggest that insulin resistance caused by increased lipid intake is associated with decreased adiponectin mRNA expression in adipose tissue despite a compensatory increase in adiponectin receptor 2 expression in muscle and liver. Reduced expression of PPARα in muscle and PGC-1α in liver may indicate reduced oxidative capacity in these tissues.

1. Krebs M & Roden M (2005) *Diabetes Obes Metab* **7**, 621–632.