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Central and peripheral insulin resistance in a large animal model of obesity

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Actions of insulin in the periphery and within the brain are critical for normal tissue glucose metabolism and the overall regulation of energy balance, yet insulin resistance is a common feature of obesity. Here we examine how both peripheral and central insulin sensitivity are simultaneously altered in an obese large animal model of similar size to humans. This model has been used previously to demonstrate that apparent central leptin resistance in obesity may be attributable to decreased efficiency of blood-brain leptin transfer rather than decreased intra-hypothalamic sensitivity[1,2].

Young adult sheep surgically prepared with intracerebroventricular (icv) cannulae were fed complete diet for 40 weeks either *ad libitum* to gain maximum body weight and become obese (OB) or at a control level to achieve normal adult body weight and adiposity (C; n 9 per group). At 16, 28 and 40 weeks, dual X-ray absorptiometry (DEXA) scans were carried out to measure total body fat; jugular blood and ventricular cerebrospinal fluid (CSF) were collected after overnight fast for insulin radioimmunoassay to assess endogenous blood-brain insulin transfer, and intravenous insulin tolerance (IT) and glucose tolerance (GT) tests were performed to assess peripheral insulin sensitivity; and one week later the acute voluntary food intake (VFI) response to icv-administered insulin was measured to assess intra-hypothalamic insulin sensitivity.

From initial 51 (SE 0.6) kg body weight and 22 (SE 1.4) % body fat, OB sheep increased to 89 (SE 4.4) kg and 46 (SE 2.6) %, respectively, while C sheep increased only to 63 (SE 1.0) kg and 29 (SE 2.0) % at 40 weeks. Fasting plasma insulin was initially similar between the groups (9 (SE 3.3) IU/ml) but was higher in OB than C sheep from 16 weeks (17 (SE 3.0) *v.* 9 (SE 1.0) IU/ml) to 40 weeks (22 (SE 4.6) *v.* 9 (SE 1.9) IU/ml) ($P<0.001$). CSF and plasma insulin concentrations were linearly correlated across both groups throughout the experiment (slope 0.13, $r = 0.60$, $P<0.001$). Fasting plasma glucose concentration was not different between the groups at 16, 28 or 40 weeks (range 560–620 mg/L), but the glucose 'area under the curve' during peripheral IT and GT tests was higher in OB than C sheep at each time point (all $P<0.001$) and correlated positively with DEXA total body fat mass values across both groups (IT, $r = 0.47$, $P<0.001$; GT, $r = 0.48$; $P<0.001$). Appetite inhibition, measured by the decrease in VFI during 3 h following icv insulin compared with control icv saline injection, in C sheep was 35 (SE 8.4), 47 (SE 4.8) and 43 (SE 8.6) %, and in OB sheep was 39 (SE 7.9), 22 (SE 11.5) and 33 (SE 10.6) % at 16, 28 and 40 weeks, respectively. Overall there was a significant negative correlation between appetite inhibition by icv insulin and DEXA total body fat mass ($r = -0.29$, $P<0.05$).

Therefore, in obese animals, there was no evidence for decreased proportional blood-brain CSF entry for insulin, unlike leptin[1,2], but both peripheral and intra-hypothalamic sensitivity to insulin were decreased with increasing adiposity.

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1. Adam CL, Findlay PA, Forno JS & Petrie AW (2008) *Proc Nut Soc* **67**, Issue OCE8, E384.
2. Adam CL & Findlay PA (2010) *Int J Obes (Lond)* **34**, 980–988.