## The effects of acute and chronic central leptin infusion on metabolism in peripheral tissues

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**Introduction.** The adipocyte hormone leptin is known to regulate food intake and whole body energy expenditure. There is some evidence that adenosine monophosphate activated protein kinase (AMPK), a cellular energy sensor, may be involved. In rodents acute (6 h) peripheral administration of leptin activates skeletal muscle AMPK at its receptor (ObRb) and acute central administration activates skeletal muscle AMPK through sympathetic nervous system activation. Given that leptin is a long term hormonal regulator acute studies may not be physiologically relevant and investigation in species which are more closely related to humans are required. Sheep are not nocturnal and more closely resemble humans in terms of the hormonal regulation of metabolism and were therefore chosen for this study.

**Aim.** To examine the effects of acute (6 h) and chronic (7 days) central leptin administration on AMPK activation in skeletal muscle and adipose tissue of sheep.

**Methods.** Under general anaesthesia (induced by pentobarbitone and maintained with isofluorane and oxygen), Corriedale ewes underwent: 1) surgery for removal of the ovaries; and 2) A month later, surgery for the placement of an infusion cannula into the lateral ventricle (LV) of the brain. A month later ewes ($n$ = 4 per group) received either continuous infusion of leptin (50 μg/h; 60 μl/h) or artificial cerebrospinal fluid (aCSF) (50 μg/h; 60 μl/h) into the lateral ventricle for 7 days. A second control group received aCSF and was pair-fed to match the leptin treated group. Muscle and fat biopsies were obtained under local anaesthesia (1% lignocaine without adrenaline) before, and at 6 hours (acute) and 7 days (chronic) into the infusion period. Tritiated glucose was infused on day 1 and 7 for calculation of whole body rate of glucose appearance (Ra) and disappearance (Rd). On day 8 all animals were killed using an intravenous overdose of pentobarbitone (Lethabarb 25ml/animal) and tissues were collected. Plasma was analysed for insulin, free fatty acids and catecholamines. Tissues were analysed by western blot for protein abundance and phosphorylation of AMPK and its downstream target acetyl CoA carboxylase β (ACCβ).

**Results.** Chronic leptin infusion reduced ($p < 0.05$) food intake and was associated with a decrease ($p < 0.05$) in body weight. Plasma adrenaline concentration was increased ($p < 0.05$) following 6 hours and 7 days of leptin treatment suggesting increased sympathetic nerve activity. Chronic leptin infusion reduced ($p < 0.05$) glucose Ra and Rd compared with the control group. Despite central leptin infusion having these peripheral metabolic effects, no activation of skeletal muscle or adipose AMPK was observed at either 6 h or 7 days of leptin infusion.

**Conclusion.** Both acute and chronic administration of central leptin in sheep alters physiological function as indicated by reduced food intake, increased plasma adrenaline and reduced whole body glucose turnover. Despite this, no effect on skeletal muscle AMPK activity was observed suggesting that differences may exist between the rodent and ovine models in this regard. Given that sheep more closely resemble humans in terms of the hormonal regulation of metabolism, the present findings suggest that results of previous rodent studies may not be relevant to humans.