Effects of muscle-specific protein kinase C epsilon deletion, caloric dilution and gender on glucose homeostasis in fat-fed mice

Aims: Whole-body deletion of protein kinase C epsilon (**PKCe**) improves glucose tolerance in fat-fed mice. The mechanisms involved have not been fully elucidated, but are independent of changes in body weight. We examined the effects of muscle-specific **PKCe** deletion, and whether kinase deletion could synergise with reduced weight gain to improve glucose homeostasis.

Methods: Muscle-specific **PKCe** knockout (MEpsKO) mice were generated by crossing “floxed” **PKCe** mice with tamoxifen-inducible HSA-Cre mice. After tamoxifen treatment, mice were fed either a high fat diet (HFD, 45% energy from fat, 19 MJ/Kg) or a HFD diluted with cellulose (CD-HFD, 45% energy from fat, 14.9 MJ/Kg) for 6 weeks. Glucose tolerance was assessed either by ipGTT, or by oGTT with stable isotope-labelled glucose. oGTT blood samples were analysed by mass spectrometry to assess changes in endogenous and exogenous (labelled) glucose concentrations. Insulin was measured by ELISA.

Results: ipGTTs, which induced minimal insulin excursions, indicated improved glucose tolerance in HFD-fed male MEpsKO mice. oGTTs led to greater insulin responses in HFD-fed male mice, but no effect of genotype was then observed. CD-HFD-fed male mice were leaner and more glucose tolerant than HFD-fed mice, which was associated with effects on endogenous glucose production but not exogenous glucose disposal. HFD-fed WT female mice were more glucose tolerant than male mice, and the CD-HFD had minimal effect on this. Unexpectedly, HFD-fed MEpsKO female mice were glucose intolerant in oGTTs compared with WT mice, due to impaired exogenous glucose disposal, which was ameliorated by CD-HFD.

Conclusion: Beneficial effects of muscle-specific **PKCe deletion on glucose tolerance in fat-fed male mice are insulin-independent and masked by insulin responses in oGTTs. CD in the context of a HFD reduces endogenous glucose production in male mice. Muscle PKCe deletion is detrimental to exogenous glucose disposal in female fat-fed mice, which is improved by CD.**