Time course of diet-induced hepatic and skeletal muscle insulin resistance - examining the mechanisms

C.R. Bruce, Department of Physiology, Monash University, VIC 3800, Australia.

Insulin resistance is a key metabolic defect associated with obesity and type 2 diabetes. Our understanding of the mechanisms that play a causal role in the development of insulin resistance have been greatly enhanced by studies in rodents fed a high-fat diet (HFD). Indeed, rodent models provide the capacity to tightly manipulate dietary constituents and also allow access to tissues that cannot be readily studied in humans. Although it is well known that diet-induced obesity causes insulin-resistance, the precise mechanisms underpinning the initiation of insulin resistance are unclear. To determine factors that may cause insulin resistance, detailed time course studies have been performed in mice fed a HFD.

Male C57Bl/6 mice were fed a chow or HFD from 3 days to 16 weeks and glucose tolerance and tissue-specific insulin action were determined. Tissue lipid profiles were analysed by mass spectrometry and inflammatory markers were measured in adipose tissue, liver and skeletal muscle. Glucose intolerance developed within 3 days of HFD and did not deteriorate further out to 12 weeks. Whole-body insulin resistance, measured by hyperinsulinaemic euglycaemic clamp, was detected after 1 week of HFD, which was due to hepatic insulin resistance. Adipose tissue was insulin resistant after 1 week, while skeletal muscle displayed insulin resistance at 3 weeks, coinciding with a defect in glucose disposal. Interestingly, no further deterioration in insulin sensitivity was observed in any tissue after this initial defect. Diacylglycerol content was increased in liver and muscle when insulin resistance first developed, while the onset of insulin resistance in adipose was associated with increases in ceramide and sphingomyelin. Adipose tissue inflammation was only detected at 16 weeks of HFD and did not correlate with the induction of insulin resistance. HFD-induced whole-body insulin resistance is initiated by impaired hepatic insulin action and exacerbated by skeletal muscle insulin resistance and is associated with the accumulation of specific bioactive lipid species.