IL-1 receptor type 1-knock-out mice fed a high-fat diet for 16 weeks become obese but remain insulin sensitive

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Obesity is the key aetiology factor that predisposes individuals to insulin resistance. Obesity leads to a sub-acute pro-inflammatory state with infiltration of macrophages into adipose tissue. It is proposed that adipose tissue macrophages release pro-inflammatory mediators impeding adipocyte insulin signalling, ultimately resulting in insulin resistance. Previous work has demonstrated that IL-1 receptor type 1-knock-out (IL-1R¹⁻/⁻) mice are protected against obesity-induced insulin resistance following a high-fat diet (HFD). The present time-course study aimed to investigate when obesity-induced insulin resistance develops in C57Bl/6 wild type (WT) mice and compare this HFD-induced phenotype in IL-1R¹⁻/⁻ mice.

L-1RI⁻/⁻ and C57Bl/6 WT mice were fed an HFD (45% energy as fat) for 16 weeks. Glucose tolerance tests (GTT) were completed at 0 (n 8), 4 (n 6), 6 (n 6, C57Bl/6 WT group; n 5, IL-1RI⁻/⁻ group), 12 (n 6) and 16 (n 8, C57Bl/6 WT group; n 4, IL-1RI⁻/⁻ group) weeks. Fasting plasma glucose, insulin, TAG and NEFA concentrations were determined at 0, 6 and 12 weeks. Throughout the study body weight and food intake were recorded. Repeated measures ANOVA identified significant differences in the GTT between C57B1/6 WT and IL-1RI⁻/⁻ mice over time. One-way ANOVA determined significant differences in fasting metabolic markers within and between groups during the time-course study.

At weeks 6, 8, 10, and 12 the C57BL/6 WT mice gained significantly more weight than the IL-1R¹⁻/⁻ mice; however, by week 14 there was no significant difference between body weights. Interestingly, at weeks 12 and 16 the IL-1R¹⁻/⁻ mice had significantly lower epididymal adipose tissue and visceral adipose tissue mass. Furthermore, the IL-1R¹⁻/⁻ mice had higher energy intake at weeks 8, 12 and 16 compared with the C57BL/6 WT mice. In the C57BL/6 WT mice there was a clear time-dependent deterioration in insulin sensitivity from week 6 onwards compared with week 0. Initially, at week 0 the IL-1R¹⁻/⁻ mice had a higher glucose peak, although clearing the glucose effectively by 120 min as compared with the C57BL/6 WT mice. At week 4 and 6 the IL-1R¹⁻/⁻ mice cleared glucose more effectively than the C57BL/6 WT mice; however, at week 12 the IL-1R¹⁻/⁻ mice seemed to have reached a point of insulin resistance similar to the C57BL/6 WT mice. Interestingly, at week 16 the IL-1R¹⁻/⁻ mice seemed to become more insulin sensitive compared with the C57BL/6 WT mice since they cleared glucose more effectively. The IL-1R¹⁻/⁻ mice had significantly lower fasting insulin levels by week 6 compared with C57BL/6 WT mice. Fasting NEFA concentrations were significantly higher in the C57BL/6 WT compared to the IL-1R¹⁻/⁻ mice at week 6 and TAG levels were significantly higher at weeks 6 and 16 in the C57BL/6 WT mice compared with the IL-1R¹⁻/⁻ mice. Fasting plasma leptin levels increased over time in the C57BL/6 WT mice while the IL-1R¹⁻/⁻ mice showed lower levels of leptin and adiponectin throughout the study.

The present study shows that IL-1RI⁻/⁻ mice are partly protected from obesity-induced insulin resistance by progressing more slowly to an insulin-resistant state. Further work is continuing to establish the specific molecular mechanisms involved in this protection.

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