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Progression of obesity-induced insulin resistance in response to a high-fat diet is delayed in IL-1 receptor type I-knock-out mice

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Obesity is the key aetiological factor that predisposes individuals to insulin resistance. Adipose tissue-derived pro-inflammatory stressors induce insulin resistance by inhibiting insulin signalling[1–3]. Recent studies have shown that obese adipose tissue is characterised by increased infiltration of macrophages[4]. Previously, it has been shown that mice lacking the IL-1 type 1 receptor (IL-1RI$^{-/-}$) are protected from developing type 2 diabetes mellitus (T2DM), although they become obese after 16-week on a high-fat diet (HFD) (S Toomey, J Browne, M Claessens, E Oliver, CE Loscher, KHG Mills and HM Roche, unpublished results).

The present study was an investigation of how obesity-induced insulin resistance develops in C57Bl/6 mice and how and at what stage this development is abolished in IL-1RI$^{-/-}$ mice.

IL-1RI$^{-/-}$ and C57Bl/6 wild-type (WT) mice were fed a HFD (45% energy from fat, mainly consisting of palm oil) for 6 weeks. The insulin-resistant state of subgroups of mice was determined by glucose tolerance tests (GTT) before (n 8 in both groups) and after 4 (n 6 in both groups) and 6 (n 6 in WT and n 5 in IL-1RI$^{-/-}$ mice) weeks on the HFD. Furthermore, plasma samples were collected before and after 6 weeks on the HFD for measurement of fasting glucose, insulin, TAG and NEFA concentrations and epididymal adipose tissue was collected for mRNA expression analysis. Body weight and food intake were recorded throughout the study. Repeated measures ANOVA was used to analyse the postprandial effect of the intraperitoneally-injected glucose load on plasma glucose (at 0, 30, 60, 90 and 120 min). Fasting metabolic marker data were analysed by one-way ANOVA to determine differences within and between groups.

Over this 6-week feeding study IL-1RI$^{-/-}$ mice gained significantly less weight than their counterparts ($P<0.05$). In the WT mice fasting insulin, TAG and NEFA concentrations increased significantly at week 6 compared with week 0 ($P<0.05$). Interestingly, within the IL-1RI$^{-/-}$ group there was no significant increase in either fasting glucose or insulin in response to the HFD, although fasting TAG and NEFA concentrations were significantly higher after 6 weeks on the HFD compared with week 0. There was no significant difference between groups in the change in fasting glucose, insulin, TAG and NEFA concentrations over time. Interestingly, IL-1RI$^{-/-}$ mice cleared glucose more efficiently after 6 weeks on the HFD than C57Bl/6 mice (at 15, 60 and 120 min: $P \leq 0.05$). Epididymal adipose tissue mRNA expression for IRS-1 and GLUT4 was significantly higher at baseline and after 6 weeks on the HFD in IL-1RI$^{-/-}$ mice as compared with mRNA expression in C57Bl/6 mice at week 0.

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. Although fasting markers for insulin sensitivity were not different between groups, postprandial GTT results showed reduced insulin sensitivity in WT mice compared with IL-1RI$^{-/-}$ mice, which is in agreement with epididymal adipose tissue gene-expression analysis.

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