Proceedings of the Nutrition Society (2010), **69 (OCE5)**, E342 doi:10.1017/S002966511000203X

Irish Section Meeting, 16–18 June 2010, Nutrition – Getting the Balance Right in 2010

Vaccination against (Pro^3)GIP prevents aspects of metabolic dysfunction associated with high fat feeding in mice

I. A. Montgomery[1], P. R. Flatt[1] and N. Irwin[1]
[1]*Diabetes Research Group, School of Biomedical Sciences, University of Ulster, Coleraine BT52 1SA, UK*

Obesity and related type-2 diabetes are major health care problems and a significant cause of preventable death. Recent research has shown that a knockout of gastric inhibitory polypeptide (GIP) receptor signalling can prevent or reverse many of the adverse consequences associated with a high-fat diet. The present study was designed to assess the ability of vaccination against (Pro^3)GIP to counter the aspects of metabolic dysfunction associated with high fat feeding in mice. Normal male mice in the Swiss National Institutes of Health were injected subcutaneously once every 14 d for 98 d with complexed (Pro^3)GIP peptide. This ought to have dual therapeutic utility as antibodies generated neutralise endogenous circulating GIP, while the complexed (Pro^3)GIP-conjugate itself could function as a GIP-receptor antagonist. The mice were transferred to a high-fat diet (45% fat) on day 21 when circulating GIP antibodies should be present. Vaccination against (Pro^3)GIP resulted in significantly ($P<0.05$ to $P<0.01$) depressed circulating blood glucose concentrations compared to high fat control mice from day 84 onwards. Indeed, by the end of the study period, circulating glucose levels were not significantly different from lean controls. Furthermore, following an intraperitoneal glucose challenge, vaccinated mice had a significantly (1.8-fold; $P<0.01$) decreased overall glycaemic excursion compared to high fat controls as assessed by 0–60 min area under the curve (AUC) measures (632 *v.* 1118.7 mmol/l.min, respectively). In addition, circulating and glucose-stimulated plasma insulin levels were significantly ($P<0.01$ to $P<0.001$) depressed compared to high fat control mice. In keeping with this, the pancreatic insulin content was significantly reduced in vaccinated mice compared to high fat controls (1.5-fold; $P<0.001$) and there was a tendency for improved insulin sensitivity in these mice. Furthermore, liver TAG and circulating LDL-cholesterol levels were also significantly reduced ($P<0.001$ and $P<0.05$, respectively) in (Pro^3)GIP-vaccinated mice. Finally, the glucose lowering effect of native GIP was annulled in (Pro^3)GIP-vaccinated mice compared to high fat controls (0–60 min AUC were 681.3 *v.* 383.5 mmol/l.min, respectively). This is consistent with the induction of biologically effective GIP-specific neutralising antibodies. Moreover, ELISA technologies confirmed that (Pro^3)GIP vaccination was associated with the induction of GIP-specific antibodies, with GIP antibody levels gradually increasing over the treatment period. All observed changes were independent of any effects on food intake or body weight. These results suggest that vaccination against (Pro^3)GIP represents an effective means of countering many of the adverse effects associated with high fat feeding.