**Acute administration of exogenous glucose-dependent insulinotropic polypeptide affects insulin secretion and sensitivity and cardiovascular function in type 2 diabetes**

**Aims**

The incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), has been overlooked as a therapeutic target because its insulinotropiceffect is markedly reduced in poorly controlled type 2 diabetes (T2D). Given the success of tirzepatide in the management of T2D, interest in GIP action has been renewed. This study evaluated the effects of intravenous GIP on glucose homeostasis and cardiovascular responses during hyperglycaemia in T2D.

**Methods**

Ten participants with T2D relatively well-controlled by diet and/or metformin monotherapy (4M/6F; age 68.2±3.4years, BMI 31.7±1.2kg/m2, HbA1c 6.9±0.6%), were evaluated on 2 days each in a double-blind, randomised, crossover fashion. On each day, a hyperglycaemic clamp was maintained at 15mmol/L between t=0-210min, while GIP(1-42) (4pmol/kg/min, a supraphysiological dose) or placebo was infused intravenously. Venous blood was sampled frequently for measurements of blood glucose and plasma insulin. Insulin sensitivity was calculated as the mean IV glucose infusion rate divided by mean plasma insulin between t=30-210 min. Blood pressure and heart rate were recorded at the ankle every 15min.

**Results**

All participants tolerated the protocol well and blood glucose was maintained at 15mmol/L on both days. GIP augmented plasma insulin levels by 183% (P=0.003) and increased the requirement for IV glucose by 26% (P=0.02), but reduced insulin sensitivity by 40% (P<0.001). GIP infusion was also associated with an increase in heart rate (P<0.001) and reductions in both systolic and diastolic blood pressures (P=0.01 each).

**Conclusion**

In well-controlled T2D, exogenous GIP at a supraphysiological dose stimulates insulin secretion during hyperglycaemia and increases whole-body glucose metabolism, albeit impairing insulin sensitivity. GIP also increases heart rate and reduces blood pressure. These observations indicate that GIP remains biologically active, rather than inert, in T2D, and potentially has important impacts on glucose metabolism and cardiovascular regulation.

**Figure 1.**

