Diabetologia. 2013 Dec 5. [Epub ahead of print]

Magnitude and mechanisms of glucose counterregulation following islet transplantation in patients with type 1 diabetes suffering from severe hypoglycaemic episodes.

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Abstract

AIMS/HYPOTHESIS:

Pancreatic islet transplantation stabilises glycaemic control in type 1 diabetes mellitus patients with neuroglycopoenia, despite them not achieving insulin independence because of limited graft function. However, the extent and underlying metabolic pathways of restored glucosecounterregulation are unknown. We therefore compared systemic glucose turnover, including lactate gluconeogenesis (GN) and muscle glucoseuptake, in individuals with type 1 diabetes who were transplant recipients with partial graft function (T1DM/ITx$^+$), matched non-transplanted individuals with type 1 diabetes (T1DM/ITx$^-$) and matched healthy non-diabetic individuals.

METHODS:

Participants (n= 12 in each group) underwent a euglycaemic and a hypoglycaemic (2.5 - 2.8 mmol/l) hyperinsulinaemic clamp (0.8 mU kg^{-1} min^{-1}) in a randomised crossover fashion. Systemic and skeletal muscle glucose and lactate kinetics were assessed using a combination of isotopic and forearm balance techniques.

RESULTS:

Whole-body glucose counterregulation, the difference in glucose infusion rates required to maintain the glycaemic goal between the hypoglycaemic and euglycaemic clamps, was improved in T1DM/ITx$^+$ (7.8± 1.3 µmol kg^{-1} min^{-1}) compared with T1DM/ITx$^-$ (0.3± 0.9 µmol kg^{-1} min^{-1}), but was ~45% lower than in controls (14.1± 2. 1 µmol kg^{-1} min^{-1}). Increased endogenous glucose production (EGP) and decreased systemicglucose disposal accounted for 49% and 39% of glucose counterregulation in T1DM/ITx$^+$, respectively, compared with 60% and 36% in controls. Lactate GN increased in T1DM/ITx$^+$ (2.7± 0.4 µmol kg^{-1} min^{-1}) and controls (1.7± 0.5 µmol kg^{-1} min^{-1}), such that it accounted for 70% and 20% of the increased EGP, respectively. Skeletal muscle accounted for similar proportions of the decrease in systemic glucose disposal in controls (49%) and T1DM/ITx$^+$ (41%).

CONCLUSIONS/INTERPRETATION:

Partial islet graft function improves hypoglycaemia counterregulation by increasing EGP, largely via lactate GN and decreasing systemic glucose disposal. This may explain the reduction in severe hypoglycaemic events in T1DM/ITx$^+$ individuals. Trial registration: ClinicalTrials.gov NCT01668485.