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VELDHOVEN

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Contribution of gut factors to canine isolated islet function?

Techniques for isolating islets of Langerhans from the large mammalian pancreas have improved to the point where islet transplantation as a therapeutical approach to human diabetes has become more realistic. The quality of metabolic control is however largely unknown. We studied canine isolated-islet function both in vivo after autotransplantation, a well as in vitro by perifusion.

Five normal dogs underwent total pancreatectomy. Islets were isolated from the excised pancreas by collagenase digestion, dispersion and purification with filtration and density gradients. Isolated islets were autotransplanted into the spleen of the dog by retrograde venous infusion. Graft function was assessed up to 3 mo by determining the glucose and insulin response to an intravenous glucose injection (IVGTT), i.v. arginine injection during 35 mM glucose clamp (AT), and a meal. In addition (n=4) the in vitro insulin response of overnight cultured canine islets was studied by perifusion with cholecystokinin (CCK-33) and glucose-dependent insulinotropic polypeptide (GIP).

The islet dose at transplantation ranged from 3500-13000 islets/kg b.w.. One animal became overtly hyperglycemic (fasting glucose 18 mM) within 7 days after receiving 3500 islets/kg b.w.. The other grafts (>6000 islets/kg b.w.) were successful (fasting glucose < 7 mM) but demonstrated, compared to preoperative values, a 50% reduced glucose clearance and insulin response at IVGTT, and a 90% reduced insulin secreting capacity at AT. Postprandially hyperglycemia (~10 mM) and in contrast to i.v. glucose and arginine, a normal insulin response was observed. The in vitro insulin response at 7.5 mM glucose to equimolar (0.1-1-10 nM) concentrations of either CCK, GIP or both, demonstrated a sustained dose-response to GIP (up to 5x basal values) and a significant albeit small and transient effect of CCK as off 1 nM. No synergistic effect was observed.

In dogs "one-to-one" transplantation was successful in 4/5 recipients of isolated islets. The difference in the effect of islet transplantation on the insulin response to intravenous glucose or - arginine and a meal, may be related to the postprandial, hyperglycemia enhanced, activation of the entero-insular axis, especially GIP.