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## Insulin Secretion in Sheep with Autotransplants of the Pancreas

THE adrenal gland[1,2], the ovary[3,4] and the thyroid gland[5] have been transplanted to the exteriorized carotid artery–jugular vein loop in the neck of the merino sheep, where it is readily accessible for physiological studies. Recently, successful transplantation of a portion of the pancreas to a similar neck loop in the merino sheep has been achieved[6]. The blood supply to the pancreas in sheep is such that the tail of the pancreas is supplied by a single branch of the splenic artery, and the venous drainage is by way of the splenic vein. By sacrificing the spleen, this part of the pancreas can be resected with its blood supply intact and transplanted to a vascular anastomosis with the vessels in the neck. To reduce the secretion of the exocrine pancreas, the pancreatic duct was ligated 2 or 3 months before the pancreatic transplantation.

Histological examination of biopsy specimens and occurrence of insulin secretion from the gland prove that transplants in the neck contain viable islet tissue. We have prepared four animals bearing viable pancreatic transplants and studied factors controlling insulin secretion at monthly intervals for periods up to nine months after pancreatic transplantation.

Details of maintenance of the animals and the procedure for catheterization and collection of the venous effluent have been described[2]. Close-arterial infusions were given using a Harvard constant infusion pump connected through a three-way tap to a needle inserted in the left carotid artery between the caudal cuff below and the pancreatic transplant above. When test solutions were not being infused, the needle was kept clear by the slow infusion of normal saline.

After the insertion of catheters, the animal was allowed to stand quietly for at least 3 h before infusing test solutions. During this period, simultaneous samples of pancreatic venous blood and peripheral (right jugular) blood were taken hourly so that baseline conditions could be determined. Blood sugar was measured by the Technicon auto-analyser ferricyanide method and plasma insulin by a modification of the radio-immunoassay method of Yalow and Berson[7]. Insulin secretion from the transplant (μU/min) was calculated from the difference between pancreatic venous and peripheral venous concentrations, and the plasma flow through the gland (ml./min). We found no significant difference between the peripheral venus (right jugular) and loop arterial blood concentrations of insulin or glucose.

Fig. 1 shows an example of the response of the pancreatic transplant to test solutions. When a 10 per cent glucose solution was administered by close infusion into the pancreatic artery at a rate of 0·33 ml./min, a brisk response in insulin secretion occurred within 4 min of the start of the infusion and a peak response occurred after 12 min. The subsequent infusion of glucose 90–100 min later evoked an even greater insulin response in some animals. Brisk responses have also been observed following the close arterial infusion of short-chain fatty acids such as butyrate, glucagon and acetylcholine solutions. The response of the transplant to tolbutamide solutions has been variable and generally less than the response to glucose (Fig. 1). One animal, however, responded vigorously to tolbutamide infused at a rate of 5 mg/min, the peak response being 20 min after the start of the infusion.

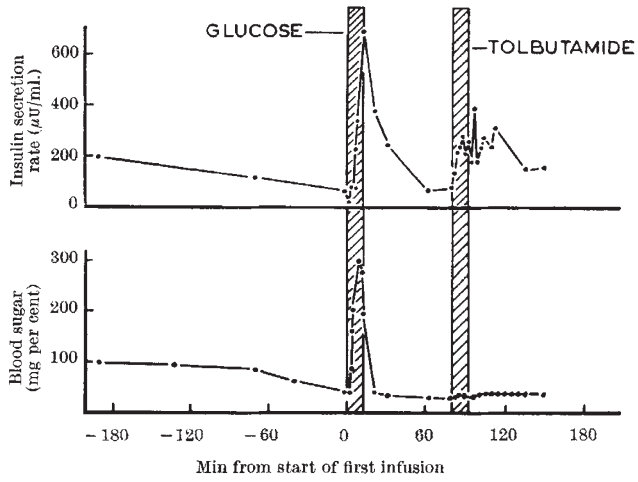


Fig. 1. Insulin secretion rate (μU/ml.) and corresponding blood sugar levels (mg per cent) in the venous effluent during the infusion of glucose and tolbutamide through a pancreatic transplant. Catheters were inserted approximately 3 h before the start of the infusion. Glucose was infused at a rate of 33 mg/min for 12 min and tolbutamide (Rastinon, Hoechst) at 5 mg/min for 12 min. Venous effluent was collected continuously throughout each infusion and for 2 min after the infusion, preventing entry of the test substances into the general circulation. Sampling was continued intermittently as shown.

These experiments show that insulin secretion from the pancreas continues for at least 9 months after denervation and transplantation to a vascular anastomosis in the neck of the sheep. Apart from the significance of the experiments to future transplantation of the pancreas in humans, our data indicate that the preparation offers a unique opportunity to study factors directly influencing insulin secretion, with the minimal disturbance to the animal.

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