ACTA DIABETOLOGICA

An International Journal Devoted to the Study of Clinical and Experimental Diabetes and Metabolism

VOLUME XXXV

1998

4

Continuation of Acta Diabetologica Latina

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Meditsinskij Referativnyj Zhurnal (Sect. 1)

35 (4) 169–248
December 1998
Printed on acid-free paper

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NON-INVASIVE OPTICAL GLUCOSE SENSING VIA CHEMICAL AMPLIFICATION

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Introduction: Numerous reports of non-invasive measurement of glucose using a variety of optical methods are in the literature. None of these reports have as yet lead to a viable product since the optical measurement of glucose *in vivo* is extremely difficult and interference from water and other components are often larger than the desired glucose signal.

We have developed a novel method for glucose sensing using optical amplification and excited state photoelectron transfer. The technology is based on reversible binding of glucose to a fluorescent substrate that shows photoelectron transfer and fluorescence quenching in the absence of glucose while showing increased fluorescence when glucose is bound to the substrate.

We will describe the theoretical background of this optical technology, the chemistry of the reversible binding and data from both in vitro investigations and a preliminary investigation in rodents. The in-vitro data show reversible glucose binding up to 1000 mg/dl. In addition, the excited state lifetimes of the substrate change upon addition of glucose. Since the system is non-enzymatic, the potential for a long-term implanted sensor is good.

The optical properties of the current system are not yet suitable for human use; we will discuss the improvements that are required to implement this type of glucose sensing in man.

EFFICACY OF THE NOVEL IODIXANOL- UWS DENSITY GRADIENT FOR HUMAN ISLET PURIFICATION

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Consistent human islet isolation and purification success is hampered by the large variability of donor and procurement related factors. Substantial progress in purification has nevertheless been made over the past few years by simple changes in (pre-) purification solutions, suggesting that considerable scope still exists for further improvement in the density gradient purification of human islets. We recently developed a ~100% efficient (~ complete islet recovery and purity) density gradient of iodixanol (OptiPrep) in University of Wisconsin solution (UWS) in the difficult pig model. This success prompted us to test this gradient during 5 consecutive human islet isolations. Pancreases distantly procured from multiorgan cadaveric donors (27–57 y) and cold preserved with UWS for ~12 h were digested with 1.4 mg/ml Liberase-HI in HBSS by the automated method. The digest was collected with cold RPMI, and a small sample of the digest was taken for these pilot experiments — the remainder was used in non-related experiments. Next, the tissue was incubated 60 min in UWS on ice. After taking an aliquot for assessment, half of the prep was loaded in an 1.086-1.075-UWS gradient in 50 ml conical tubes, the other half was saved on ice for optional testing of other density layers. The 1.086 bottom was prepared by mixing 30 ml digest (in UWS) with 10 ml Working OptiPrep (WOP; an 1:1 mixture of OptiPrep and double-strength UWS). The 1.075 (or 1.070) barrier layer was prepared by mixing 5 ml WOP with 22.6 ml (or 28.3) UWS. After 5 min 500 g centrifugation at 4°C tissue was collected from the top (UWS-1.075 interface) and second layer. The 1.086-1.075-UWS gradient was successful (≥ 80% purity and recovery) during all first 4 experiments. In the last experiment, purity was 35%, but again ≥ 80% purity and recovery were obtained by using an 1.070 barrier with the other half of this digest prep. On average the digest loaded in the gradients contained 15287 ± 3712 IEQs and the volume-average islet diameter was 238 ± 22 μm. After purification at the top 12766 ± 3129 IEQs were recovered (83 ± 2 % recovery), islet diameter was 204 ± 13 μm (NS) and purity was 89 ± 3%. Viability of the islets was corroborated histologically 1 to 3 wk after transplantation under the kidney capsule in 3 nude mice. Thus, the consistent high efficacy of this simple OptiPrep-UWS gradient under mild hyperosmotic conditions (~360 mOsm) in this pilot, and other favourable characteristics such as a low endotoxin content, suggest that the gradient may become a new powerful tool for human islet purification.

AUTOLOGOUS INTRAPORTAL AND SPLENIC HUMAN ISLET TRANSPLANTATION TO PREVENT DIABETES AFTER PANCREAS RESECTION FOR CHRONIC PANCREATITIS

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Pancreas resection for chronic pancreatitis can render patients insulin dependent. Over a 5 year period 22 patients (14 F: 8 M) have undergone pancreas resection (20 total {2 completion total}, 2 subtotal) combined with islet autotransplantation in an effort to provide pain relief and prevent diabetes. After resection islets were immediately isolated using collagenase distension combined with a semi-automated pancreas digestion. Where possible (70%) islets were also purified on a continuous density gradient.

In 17 patients islets were embolized directly into the liver via the portal vein (PV), 3 received combined splenic and PV autografts and 2 splenic alone (total median volume 10ml). The median number of islets transplanted was 1820 IEQ/kg (range 320-9240). Portal pressure was transiently raised during the transplant procedure (median 8 cm of water). Post-operative islet autograft function was demonstrated in all patients by elevated serum C-peptide levels.

In our experience there was no operative mortality related to the islet transplant procedure. One patient died of a CVA post-operatively (known carotid stenosis). Significant complications included duodenal ischaemia (n=3), partial portal or splenic vein thrombosis (n=2) and a peri-portal abscess (n=1). Eight patients have developed transient insulin independence (range 2 days to 3 years) and 2 patients are currently insulin independent (Both > 1year). Furthermore patients having total pancreatectomy (TP) have significantly lower HBA1c's compared to patients having TP without an islet autotransplant. Only 2 patients have failed to gain relief of their pre-operative abdominal pain.

In conclusion pancreas resection, particularly TP provides good pain relief for chronic panceatitis. We regard a purified autologous islet transplant a safe addition, with no risk of operative mortality related to the transplant itself, but patients are likely to remain insulin dependent. Despite the need for insulin autotransplant recipients have significantly better glucose control compared to those patients having a TP alone.