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Research Article

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Evidence for Restoration of Hepatic Glucose Processing in Type I Diabetes Mellitus

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A B S T R A C T   The role of muscle in the processing of dietary carbohydrate in nine type I diabetic patients was assessed using combined forearm-indirect calorimetry-glucose meal (100 g) studies performed before and after 72 h of artificial β-cell directed insulin therapy. On conventional insulin therapy, initially elevated arterial glucose concentrations rose markedly, free insulin increased slightly, and the respiratory quotient (R.Q.) did not change during the study. The forearm glucose extraction rate increased significantly over basal at 60 min. After 72 h of artificial β-cell therapy and while still on the instrument, arterial glucose increased moderately, and free insulin levels increased markedly. The R.Q. increased significantly at 60 and 120 min. The forearm glucose extraction rate increased significantly over basal at 30 and 60 min. Importantly, forearm glucose extraction rates did not differ during the two studies at each of the measured time points. These observations demonstrate that conventional insulin therapy is effective in facilitating glucose entry into muscle. In addition, they suggest that the marked improvement in glucose processing exhibited by type I diabetic patients after 72 h of artificial β-cell therapy is primarily attributable to the liver. Finally, the data strongly imply that the primary clinical objective of insulin therapy in type I diabetes mellitus should be reactivation of the hepatic component of the glucose disposal system.

INTRODUCTION

Liver and muscle are the primary components of the dietary carbohydrate processing system in man. In turn, the metabolic performance of these tissues in this process is a function of pancreatic β-cell secretory activity. When normal subjects ingest a 100-g glucose meal, ~50 g are retained within the splanchnic bed

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to be oxidized and/or converted to glycogen and fat (1–4). The remainder passes into the systemic circulation where it is primarily removed by muscle and brain and to a much lesser extent by adipose tissue, and kidney (3, 5). These observations underscore the primary role of the liver, and the secondary role of muscle, in the processing (oxidation and storage) of dietary carbohydrate. Furthermore, they suggest that the integrity of this process is dependent upon the release of adequate amounts of insulin (4–10 U/meal) by pancreatic β-cells at the appropriate times (between and during meals) and with appropriate time constants. In contrast to normal individuals, the processing of dietary carbohydrate is markedly distorted in poorly regulated type I diabetic subjects in whom only 25–35% of the glucose load is retained by the splanchnic bed, while ~70% passes into the systemic circulation (1).

This laboratory has recently reported that dietary carbohydrate processing in type I diabetic individuals is restored to normal after 72 h of artificial β-cell therapy (6). A progressive rise in carbohydrate oxidation rates in response to the ingestion of a mixed meal demonstrated that restoration of this process was an "inducible" phenomenon and suggested that the primary defect in the glucose processing system was at the level of the splanchnic bed, probably the liver. Improvement in glucose processing was evidenced with respect to both oxidation and storage.

The experimental design used in the preceding investigation precluded quantitation of the amount of dietary carbohydrate retained by liver and muscle. It is possible, however, to quantitate splanchnic performance in this regard by hepatic vein catheterization, liver biopsy, and/or isotopic studies. The role of the second member of the glucose processing system, namely muscle, can be assessed, as in this inquiry, utilizing the forearm procedure.

Peripheral glucose utilization has been examined in diabetic patients off insulin therapy for 24 h (7).

However, forearm glucose extraction rates in such patients following the ingestion of 100 g of glucose before and after 72 h of artificial β-cell directed insulin therapy have not been reported. If forearm glucose extraction rates in type I diabetic subjects do not change significantly with artificial β-cell therapy, the marked improvement in glucose storage observed must be attributed to the liver. In order to explore these issues, forearm glucose extraction rates following the ingestion of 100 g of glucose in nine type I insulin-dependent diabetic subjects have been measured before and after 72 h of artificial β-cell therapy.

METHODS

The nine type I diabetic participants (see Table I) reported to the Clinical Research Area at the Joslin Diabetes Center at 7:30 a.m. after an overnight fast. After they had read and signed the informed consent form, they assumed a recumbent position. The appropriate catheters were then inserted, and blood flow was measured by capacitance plethysmography (8). After basal blood samples for glucose and free insulin (6) had been collected and 30 min after they had taken their usual insulin injections, the subjects ingested, over a 1-min period, 100 g of glucose dissolved in water. Subsequent blood samples were collected at 60 and 120 min since both arterial glucose and free insulin concentrations, based on previous experience (6), would be relatively stable at these times, thereby permitting comparisons of forearm glucose extraction rates. In five subjects, additional samples were collected at 30 min. Respiratory gas exchange was monitored at 0, 30, 60, and 120 min as previously described (6). The participants were subsequently maintained on their usual insulin regimens until admitted to the Clinical Research Center at the Brigham and Women's Hospital, where they were placed on artificial β-cell (Life Science Division, Miles Laboratory, Elkhart, IN) directed insulin therapy as previously described (6). The above protocol was then repeated after 72 h of artificial β-cell therapy.

Statistical analyses were performed using the t test for paired groups (0 vs. other time points both before and after

artificial β-cell therapy). The forearm glucose extraction rate is the product of the arterial-deep venous glucose difference multiplied by forearm blood flow and is expressed as μmol/100 ml forearm per minute. All values shown are the mean±SEM.

RESULTS

Conventional therapy. Basal forearm blood flow was 2.6±0.5 and did not change significantly at 30 (2.7±0.6), at 60 (2.6±0.4), and at 120 min (2.4±0.4 ml/100 ml forearm per min). Basal arterial glucose levels increased from 246±22 to 339±50 at 30, to 388±24 at 60, and to 406±30 mg/dl at 120 min. Basal free insulin levels increased from 13±2 to 21±3 at 60 and to 24±4 μU/ml at 120 min. Forearm glucose extraction rates (μmol/100 ml forearm per minute) were −0.36±0.90 at rest, 5.49±2.20 at 30 ($n = 5$), 2.48±1.20 at 60 ($P < 0.025$), and 1.97±1.70 at 120 min. The respiratory quotient was 0.778±0.01 at rest, 0.775±0.02 at 30, 0.776±0.01 at 60, and 0.780±0.01 at 120 min.

Artificial β-cell therapy. After 72 h on the artificial β-cell unit, basal forearm blood flow was 2.1±0.3, 2.3±0.4 at 30, 2.0±0.2 at 60, and 2.2±0.2 ml/100 ml forearm per min at 120 min. Basal arterial blood glucose was 65±6 rising to 110±11 ($n = 5$) at 30, to 167±15 at 60, and 153±15 mg/dl at 120 min. Basal arterial free insulin levels increased from 67±23 to 189±32 at 60 and to 227±53 μU/ml at 120 min. Glucose extraction rates (μmol/100 ml forearm per min) were 0.87±0.37 at rest, 2.42±0.32 ($P < 0.005$, $n = 5$) at 30, 3.45±0.86 ($P < 0.005$) at 60, and 1.55±1.04 at 120 min and did not differ significantly from those obtained while the participants were on conventional insulin therapy. Finally, the respiratory quotient, as expected (6), increased significantly from 0.810±0.01 in the basal state to 0.813±0.01 at 30, to 0.883±0.02 at 60, and to 0.924±0.01 at 120 min.

DISCUSSION

We have recently reported that restoration of glucose processing (oxidation, storage) in type I diabetic patients is a gradual process requiring 48–72 h of artificial β-cell directed insulin therapy (6). The present inquiry was directed at a comparison of forearm glucose extraction rates under similar experimental conditions in order to determine the contribution of such tissues to the marked improvement in glucose processing.

Forearm glucose extraction rates of the nine diabetic participants, following the ingestion of the glucose meal and while on conventional insulin therapy and again after 72 h on the artificial β-cell, did not differ significantly at any time point and were comparable to that of 25 normal subjects studied by Jackson et al.

TABLE I

Subjects	Sex	Age	Duration of diabetes mellitus	Height	Weight	Usual insulin dosage	
						a.m. CZI-NPH	p.m. CZI-NPH
				cm	kg	U/d	
1	M	19	12	177	78.5	8–34	8–8
2	F	22	12	170	69.5	18–52	7–10
3	F	22	18	166	63.7	8–20*	5–10*
4	F	27	22	165	68.2	6–12	0–10
5	M	22	7	184	79.8	6–24	5–5
6	F	27	5	165	63.0	4–14	2–10
7	F	26	18	170	73.5	6–14	4–6
8	M	27	13	161	58.1	0–44	0–0
9	F	32	30	166	58.0	4–14	4–8

* Lente insulin.

(9) using a similar protocol. In addition, we have performed similar studies ($n = 6$) in a slightly older (age: 36 ± 2 yr) group of normal male subjects (weight: $103\pm4\%$ of ideal body wt, Metropolitan Life Tables) and have found comparable forearm glucose extraction rates at 0 (0.40 ± 0.12), 30 (2.48 ± 0.34), 60 (2.47 ± 0.48), 120 (2.10 ± 0.62) and 180 (0.84 ± 0.4) min. The forearm glucose extraction rates manifested by the diabetic group on conventional insulin therapy occurred in the presence of markedly elevated concentrations of glucose with low (10–20 μU/ml) concentrations of free insulin. In contrast, in the same patients after 72 h on the artificial β-cell unit, similar forearm glucose extraction rates were observed with normal arterial glucose concentrations and markedly elevated concentrations of free insulin (200–300 μU/ml). Regardless of the underlying mechanism(s), since forearm glucose extraction rates were comparable in the diabetic subjects before and after 72 h of artificial β-cell therapy, the marked improvement in dietary glucose processing observed after artificial β-cell treatment must have primarily resulted from improved hepatic glucose sequestration. Thus, the postprandial hyperglycemia seen in these patients while on conventional insulin therapy is most likely due to excessive splanchnic release of dietary glucose, perhaps in part due to enhanced hepatic gluconeogenesis (10), and not to diminished muscle glucose uptake. In addition, with increased hepatic participation in the processing of dietary carbohydrate, as reflected by both normal respiratory quotient and blood glucose values following a mixed or glucose meal challenge as in this study, the amount of glucose to be extracted by muscle following the meal also decreases commensurately.

Finally, since hepatic dietary glucose processing is minimal in conventionally treated diabetic subjects, multiple small meals (to minimize the amount of glucose entering the systemic circulation at a given time) spread out over the day coupled to the administration of appropriate (4–10 U) amounts of insulin (to facilitate entry into muscle of the glucose that has escaped from the splanchnic bed) prior to each meal are desirable and indeed are the hallmarks of insulin regimens that have achieved some semblance of euglycemia in the fasting and postprandial state.

In summary, forearm glucose extraction rates, at rest and during a glucose meal, of nine type I diabetic subjects on conventional and artificial β-cell directed insulin therapy are comparable to that of normal subjects. These data indicate that the marked improvement in dietary glucose processing evidenced by artificial β-cell treated insulin-dependent diabetic sub-

jects is primarily, if not wholly attributable to enhanced hepatic glucose processing. Activation of the liver of the type I diabetic patient with respect to glucose handling, a previously ignored therapeutic goal, should become the primary objective of insulin therapy. Monitoring of the efficacy of such an approach can be accomplished by indirect calorimetry and venous blood sampling.

ACKNOWLEDGMENTS

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