NEW PROBES TO STUDY INSULIN RESISTANCE IN MEN;
FUTILE CYCLE AND GLUCOSE TURNOVER

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ABSTRACT

Insulin resistance has been measured in man by nonsteady state tracer methodology. Increase in overall glucose utilization and suppression of glucose production was measured when hyperglycemia was achieved either by infusing glucagon or glucose. With the first method, insulin resistance was assessed in obese man and in lean hypertriglyceridemic patients. With the second method, insulin resistance was assessed in lean mild type II diabetics. These methodologies can only assess deficiencies in overall glucose utilization and glucose production, but cannot delineate the defect in glucose uptake by the liver. However, if a given metabolic event is essentially characteristic of only one organ, metabolic abnormalities specific to that organ can be detected in vivo provided there is a probe specific to that metabolic pathway. Therefore, in lean mild type II diabetics the liver glucose futile cycle was assessed by a double tracer method. Previously it was shown that liver glucose futile cycling is increased in diabetic dogs. In healthy control subjects in basal state and during glucose infusion, the futile cycle could not be detected, but it represented a major part of glucose metabolism in liver of type II diabetics. It appears, therefore, that most of the glucose taken up by the liver during the glucose challenge in diabetics reenters the blood stream without being oxidized or polymerized. On the basis of these studies, it was concluded that excessive hyperglycemia in the diabetics during glucose infusion is due to a decrease in irreversible glucose uptake (impaired phosphorylation and futile cycling) and to a decrease in...
suppression of glucose production. The relative contribution of the liver and periphery to hyperglycemia seems to be almost equivalent. The mechanism behind the increased glucose cycle activity is not clear. It may be due to a relative decrease of glycogen synthase or increase in glucose-6-phosphatase or both. These observations in mild lean type II diabetics may have implications also in some other types of diabetes, since we have observed that futile cycling is even more marked in obese type II diabetics and that it could account in part for the diabetogenic effect of growth hormone in acromegalis.

With respect to metabolic abnormalities in diabetes, we wish to discuss some new probes to study insulin resistance particularly as they relate to developments of tracer methodology and their impact in the understanding of the etiopathology of diabetes. An important factor in the etiopathology of diabetes is decreased insulin sensitivity, which has been more extensively studied in Type II than in Type I diabetics.

Insulin resistance has been measured using a variety of different steady state experimental techniques based on glucose clamp and insulin suppression test. It is also possible to outline whether the abnormality of insulin sensitivity resides primarily at the receptor and/or postreceptor level. In order to study insulin release and insulin sensitivity in type 2 diabetics, Cerasi and Luft designed a glucose infusion test (GIT) which led to development of a mathematical model. This made it possible to make quantitative measurements in a large population of diabetics. They suggested that impaired insulin release is a primary defect, whereas others felt that it is insulin resistance. The evidence that islet β-cell function is indeed abnormal in NIDDM became very convincing and it is also apparent that not only in NIDDM but also in impaired glucose tolerance there is abnormal insulin secretion and decreased sensitivity to insulin. More recently a new mathematical approach based on minimal modelling has been proposed. This latter approach allows for estimation of the insulin sensitivity index from the dynamic responses of plasma glucose and insulin to a glucose injection. By the use of computer modelling it was possible to sever the feedback loop between plasma insulin and glucose. The modelling approaches require only simple experimental design and therefore can be used for wide epidemiological studies to define more precisely the abnormalities of insulin secretion and sensitivity.

The use of radioactive glucose tracers made it possible to assess insulin resistance with respect to glucose production and glucose uptake since this methodology was validated both in and out of steady state.