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The Importance of the Liver in Insulin Replacement Therapy in Insulin-Deficient Diabetes

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In this issue, Wang et al. (1) present data comparing subcutaneously (SC) administered hepatic targeted pro-insulin-transferrin fusion protein compared with regular recombinant insulin. Their data demonstrate both primary hepatic insulin effects in insulin-deficient mice: inhibition of hepatic glucose production during fasting and stimulation of glycogen deposition during feeding. This study focuses needed attention on the role of the liver in insulin replacement therapy.

Physiologically, 100% of endogenous insulin flows from the pancreas to the liver (Fig. 1*A*) via the pancreatic and portal veins. The pancreas releases insulin in quantal bursts every 4–5 min (2), with the liver retaining a major fraction of the pancreatic insulin (3). Insulin is always in portal blood, and during fasting insulin inhibits hepatic glucose release by inhibiting either glycogenolysis or gluconeogenesis. During a meal, insulin stimulates glucose storage by the liver as glycogen. The insulin released from the liver acts on adipose and muscle tissue to stimulate glucose uptake. These actions of insulin at the three main insulin-sensitive tissues maintain blood glucose levels within a narrow range of approximately 80−120 mg/dL.

Type 1 diabetic patients receive lifesaving insulin SC with meals and a once- or twice-per-day basal injection in an effort to mimic the normal peripheral blood insulin pattern. However, SC insulin replacement fails to "normalize" glucose metabolism in type 1 diabetic patients (Fig. 1*B*). Their usual daily clinical course is to administer enough SC insulin to control postmeal hyperglycemia, but not enough to induce postmeal hypoglycemia. Long term, the disease becomes more complicated with microvascular disease, renal failure, cardiovascular complications, and blindness. Attempts to improve therapy have included multiple variations in insulin structure and formulations, and these advances have produced incremental improvements in treatment and extended life expectancy, but intensive insulin therapy is plagued by sometimes dangerous hypoglycemic reactions and ever-progressive vascular-related complications.

Wang et al. propose that type 1 diabetic patients would have a more stable blood glucose profile if a larger fraction of injected insulin was distributed to the liver (Fig. 1*C*). In an autoradiograph study in intact rats, Canfield et al. (4) showed that injected tritiated polyalanyl insulin did distribute to fat and muscle tissue but did not distribute to the liver when injected at therapeutic doses. The data suggest that SC insulin, in therapeutic doses, is retained by peripheral tissues and does not reach the liver. Dose-response studies in dogs demonstrated that a peripheral infusion of insulin (at a supertherapeutic dose of 6 mU insulin/kg body weight/min) was required to provide portal insulin levels sufficient to convert insulin-deficient dogs from hepatic glucose output to uptake when glucose was supplied via the portal vein to the liver (5), pharmacologically confirming the aforementioned autoradiographic study reported by Canfield et al. Hepatic glucose uptake only occurred with portal administration of glucose and did not occur with peripheral glucose administration. Observations such as these led to hypotheses of the existence of a portal signal (6,7).

Hepatic targeted insulin has been demonstrated to significantly reduce the postmeal hyperglycemic area under the curve (AUC) by using oral glucose tolerance tests (OGTTs) in dogs (5). Postmeal blood glucose AUCs in dogs are elevated after pancreatectomy due to insulin deficiency, but blood glucose AUCs are not normalized after pancreatectomy when treated with replacement SC insulin. However, SC insulin formulations that include hepatocyte-specific insulin restored postmeal AUCs to those of intact dogs.

An OGTT study in human type 1 diabetic patients (8) demonstrated a 38% reduction in the OGTT AUC with a SC insulin formulation in which a portion of insulin is

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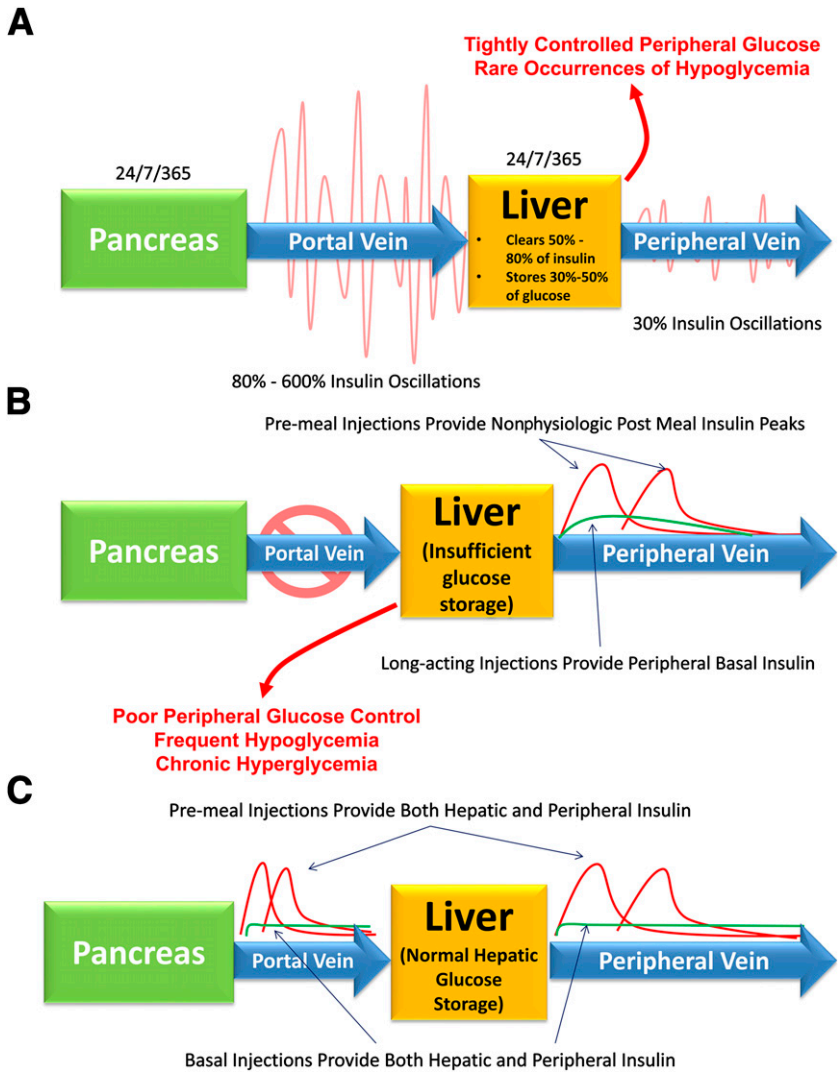

Figure 1—*A*: Normal metabolism: in response to insulin, the liver continuously micromanages glucose. *B*: Current insulin therapies: insufficient hepatic delivery. *C*: Preferred form of insulin therapies: hepatic and peripheral insulin in a single dose.

hepatospecific compared with equal SC doses of regular human recombinant insulin. In this study, peripheral blood insulin levels were identical for both the hepatospecific insulin formulation and the nontargeted SC regular insulin. Glucagon or other glucoregulatory blood hormone levels were similar in both the control regular insulin and hepatospecific treatment groups. The data suggest that when administered at therapeutic doses, SC human recombinant insulin does not reach the liver in sufficient amounts to activate hepatic glucose storage during a meal as measured by the postmeal blood glucose AUC. A failure of the liver to store ingested carbohydrate as glycogen has two major implications for patients with diabetes. First, the peripheral tissues have to dispose of much more glucose following a meal, thus requiring more injected insulin to control hyperglycemia. Second, the liver does not have the normal store of glycogen to supply peripheral glucose and may enhance the incidence and severity of postmeal hypoglycemia. Basu et al. (9) have suggested that failure of hepatic glucose/glycogen storage is a significant aspect of type 2 diabetes.

Wang et al. (1) describe a proinsulin-transferrin fusion protein that is targeted to hepatocytes where hepatocytes convert proinsulin to active insulin. This construct does not have significant insulin action on peripheral adipose and muscle tissues. The intended use of this construct is for improved long-acting insulin as basal insulin with hepatic action. The construct's dual action of inhibiting hepatic glucose production during fasting along with stimulation of glycogen storage during feeding both contributed to normalizing glucose metabolism in insulin-deficient mice. The authors have also shown activation of relevant insulin-activated hepatocyte markers. The marker activation confirms the construct's action at the liver,

including conversion of proinsulin to insulin. Their several blood glucose data sets suggest that hepatic insulin action conveys greater stability of blood glucose control over nonhepatic insulin dose forms in insulin-deficient mice.

This work is important because it focuses on the liver as a major, insulin-sensitive glucoregulatory organ. Pharmaceutical development work on insulin products is often based on hypoglycemic actions of insulin by either the stimulation of muscle and adipose tissue uptake of blood glucose or the inhibition of fasting glucose production by the liver. Euglycemic clamp methods have become the gold standard for evaluating efficacy of insulin products. The clamp method originally developed by DeFronzo et al. (10) involves peripheral infusion of glucose along with the test insulin or other material that enhances insulin action and variation of the glucose infusion rate to maintain a constant blood glucose level. The peripheral infusion of glucose bypasses the liver's glucose uptake mechanism (7) and only permits evaluation of the peripheral utilization of glucose at fat and muscle tissues. Wang et al. (1) have demonstrated improved peripheral glucose control with a dose form of insulin that has major action at the liver and very little efficacy at peripheral tissues. Although stimulating glycogen storage during feeding was not the primary goal, the authors did demonstrate the glycogen storage effect of hepatospecific proinsulin-transferrin fusion protein. This work should encourage developers of insulin-based therapies to expand criteria for efficacy to include hepatic stimulation meal-time hepatic glycogen storage in addition to the evaluation of the inhibition of fasting hepatic glucose production.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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