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Disordered Metabolism in Diabetes: Have We Underemphasized the Fat Component?

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Abstract Despite intensive investigation, a clear understanding of the metabolic disturbances in *diabetes mellitus* and their temporal relationship to each other during disease development has still not emerged. With emphasis on non-insulin-dependent diabetes (NIDDM), three possibilities are explored here: (1) that the insulin resistance characteristic of obesity/NIDDM syndromes is the result rather than the cause of hyperinsulinemia, as is widely held, (2) that the linkage between hyperactivity of the pancreatic β-cell and peripheral insulin resistance is vested in excessive delivery of lipid substrate from liver to the muscle bed, and (3) that conceivably hyperamylinemia works in concert with hyperinsulinemia in promoting overproduction of very-low-density lipoproteins by the liver, and thus in the etiology of muscle insulin resistance.

Key words: diabetes, hyperinsulinemia, insulin resistance, lipogenesis, fat metabolism, amylin, hepatic triglyceride synthesis, muscle fat accumulation

INTRODUCTION

Diabetes mellitus manifests primarily in two forms, insulin-dependent (IDDM) and non-insulin-dependent (NIDDM), collectively afflicting some 10–15 million people in the United States alone. IDDM results from autoimmune destruction of the pancreatic β cell and has a peak age of onset at 7–14 years. Afflicted individuals are absolutely dependent on exogenous insulin for survival. Far more common is NIDDM, which occurs later in life and is generally associated with obesity. In this case, at least in the early stages of the disease, the main problem is not one of insulin insufficiency but of failure of the hormone to act efficiently in promoting glucose uptake into muscle cells. In genetically predisposed individuals, this state of insulin resistance and glucose intolerance gives way to frank diabetes when the increased demand for insulin can no longer be met because of β-cell failure. A subgroup of NIDDM, referred to as maturity-onset diabetes of the young (MODY), exhibit hypoinsulinemia because of an inherited defect in the glucokinase gene [Vionnet et al., 1992].

It has long been known that, regardless of type, uncontrolled diabetes represents a serious disruption of fuel homeostasis with far reaching pathological consequences. But what has yet to emerge, despite seven decades of intensive investigation (since the discovery of insulin), is a clear picture of the underlying pathophysiological events at work. A major problem has been that delineation of the precise biochemical mechanisms through which insulin elicits its wide array of responses in target tissues has proved a formidable task. A second obstacle relates to the fact that there still is a lack of consensus on what exactly is meant by the term *insulin resistance* and its relationship to the status of β-cell function as individuals progress from the normal state to one of impaired glucose tolerance (IGT) and finally to full-blown diabetes. A third consideration has to do with the question of whether the traditional "glucocentric" view of diabetes might have carried the wrong emphasis. In recent years, there has been growing recognition of the fact that diabetes is also characterized by profound derangements in lipid metabolism. The possibility that these might exacerbate, perhaps even underly, many of the abnormalities in glucose dynamics is now receiv-

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ing increasing attention. In the sections that follow, this notion is briefly explored with reference to three clinical entities: (1) IDDM, (2) NIDDM, and (3) pre-NIDDM (the special case of MODY is not considered here). Because the relevant literature is voluminous, citations are, of necessity, highly selective. It should also be kept in mind that the views expressed here are of a speculative nature and in large measure at odds with conventional wisdom. The intent is to stimulate new thinking and research in a highly controversial and murky area of fuel homeostasis.

FATTY ACID–GLUCOSE INTERACTIONS IN IDDM

Complete loss of circulating insulin leads to life-threating diabetic ketoacidosis (DKA). The dramatic acceleration of hepatic ketone body production in this condition is triggered by two events. First, there is loss of the powerful negative control normally exerted by insulin on hormone-sensitive lipase of adipose tissue, causing plasma free-fatty acid (FFA) levels to rise markedly. Second, glucagon action on the liver, in the absence of restraint by insulin, sets in motion a series of cAMP-mediated events that causes a switch in the metabolic set of the organ from fatty acid synthesis to fatty acid oxidation; a pivotal event is depletion of the tissue malonyl-CoA content with attendant de-repression of carnitine palmitoyltransferase I, the rate-controlling enzyme in the pathway of long-chain fatty acid oxidation [McGarry and Foster, 1980]. Similar metabolic adaptations occur in simple starvation. However, the distinguishing feature between the physiological ketosis of starvation and the pathological ketosis of uncontrolled IDDM is the difference in plasma FFA concentration. In the former case, this seldom exceeds 1 mM because of the modulating effect of basal insulin levels on adipose tissue lipolysis; as a result, peripheral utilization of the ketone bodies is only marginally less than their rate of production by the liver. By contrast, with complete insulin deficiency FFA levels may climb to the region of 3 mM, forcing an inappropriately high rate of ketone production such that severe ketoacidosis develops. The point to be emphasized is that this protective effect of residual insulin in starvation is exerted primarily on the process of fatty acid mobilization from fat deposits.

The severe hyperglycemia that accompanies DKA stems from overproduction of glucose by the liver coupled with diminished peripheral glucose uptake (PGU). In this context also we see a detrimental effect of fatty acids. Thus, whereas in starvation the controlled availability of FFA to body tissues serves to conserve glucose for use by the central nervous system, the excessive fatty acid oxidation in DKA contributes to the development of hyperglycemia. Operative factors include elevation of the mitochondrial acetyl-CoA/CoA ratio, which in liver drives gluconeogenesis through stimulation of pyruvate carboxylase, and in muscle interferes with glucose utilization through mechanisms elaborated by Randle and co-workers 30 years ago and summarized in Figure 1 [see Randle et al., 1988, for review]. Many of the individual components of the glucose-fatty acid cycle have been verified in in vitro experiments with animal tissues [Randle et al., 1988]. That the overall formulation has relevance in vivo is evident from studies demonstrating that fat loading interfered with glucose disposal in healthy individuals [Schalch and Kipnis, 1965; Gomez et al., 1972; Balasse and Neef, 1974; Saloranta et al., 1993]. Conversely, the use of antilipolytic agents to reduce plasma FFA levels promoted an increase in whole-body glucose oxidation [Paul et al., 1966; Gomez et al., 1972; Balasse and Neef, 1973; see below]. Also, in diabetic rats, suppression of fatty acid oxidation with inhibitors of CPT I proved to be both hypoketonemic and hypoglycemic [McGarry and Foster, 1973; Tutwiler et al., 1985; see below].

FATTY ACID–GLUCOSE INTERACTIONS IN NIDDM

Fully established NIDDM is characterized by fasting and postprandial hyperglycemia, due to the combined effects of excessive hepatic glucose production (HGP) and peripheral insulin resistance, together with impaired responsiveness of the pancreatic β cell to high glucose concentrations. As noted by DeFronzo et al. [1992], the enhanced basal HGP in NIDDM results primarily from increased gluconeogenesis, while the peripheral insulin resistance stems largely from inefficient uptake and storage of glucose as glycogen in skeletal muscle. Here again it is evident that excessive lipid oxidation is instrumental in

bringing about the derangements in glucose homeostasis [Felber, 1992]. In this context, Reaven et al. [1988a] conducted an around-the-clock study in nonobese normal, mildly diabetic, and severely diabetic subjects. In addition to the expected elevation of plasma glucose levels in the diabetic patients, it was shown that both plasma FFA and lactate concentrations were also increased at most time points, and in rough proportion to the degree of hyperglycemia. It also emerged that the patients with mild NIDDM displayed higher-than-normal FFA and lactate levels despite marked hyperinsulinemia. Moreover, in absolute terms, insulin levels in the severely diabetic group were only modestly reduced during the day and were no different from normal between midnight and 8:00 a.m.—yet it was during this period in particular that their FFA levels were abnormally high. The same laboratory [Chen et al., 1987] established that during a hyperglycemic clamp (250 mg/dl) nonobese subjects with NIDDM exhibited higher than normal FFA levels under conditions of basal insulin (~ 10 μU/ml) and that these failed to suppress appropriately when the insulin concentration was raised to 60 μU/ml. These derangements were exaggerated in obese NIDDM patients. In all subjects, HGP and insulin-mediated glucose disposal correlated positively and inversely, respectively, with the fasting plasma FFA concentration [Golay et al., 1987; Chen et al., 1987].

The implication from these studies is that once NIDDM is in place the fat cell exhibits resistance to the action of insulin with the result that plasma FFA levels are chronically elevated. This might be expected to impact negatively on glucose utilization in muscle, possibly causing increased cycling of lactate from muscle to liver (although reliable kinetics for lactate turnover in NIDDM are still not available). The net result would be expansion of the blood glucose pool size according to the operation of the Cori–Randle cycles (Fig. 1). Consistent with this interpretation, acute administration of nicotinic acid (an antilipolytic agent) or Etomoxir (an inhibitor of CPT I) to nonketotic streptozotocin diabetic rats (used by some as a model for NIDDM) rapidly lowered the blood sugar level [Reaven et al., 1988b]. In a more recent study, Etomoxir was administered to diabetic rats for a period of 3 weeks. The result was a striking reduction of glycemia and HGP, coupled with improved peripheral insulin sensitivity [Collier et al., 1993]. Similarly, acute treatment with the nicotinic acid derivative, Acipimox, lowered plasma FFA levels in patients with NIDDM and improved both the suppression of HGP and stimulation of

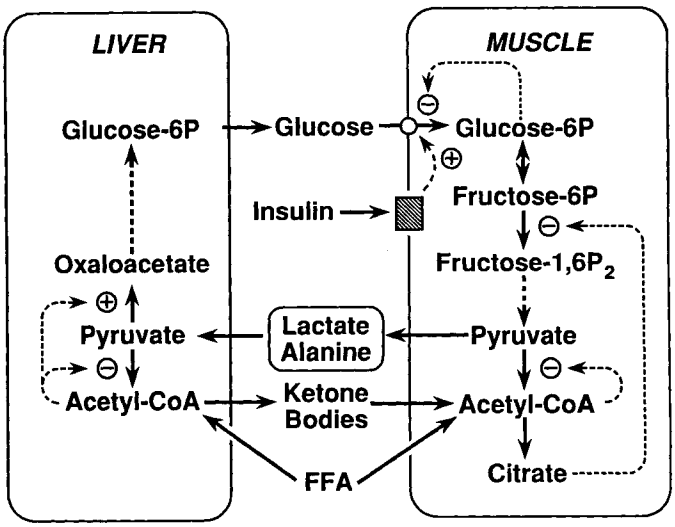

Fig. 1. The Cori–Randle cycles. Excessive oxidation of FFA in liver, in addition to causing ketoacidosis, stimulates gluconeogenesis by providing the acetyl-CoA necessary to activate pyruvate carboxylase (as well as the ATP and NADH needed for conversion of pyruvate into glucose at high rates). In muscle (as in liver) the oxidation of FFA and ketone bodies will cause elevation of the intramitochondrial acetyl: CoA and NADH: NAD^+ ratios with subsequent inactivation of pyruvate dehydrogenase. The concomitant increase in citrate concentration is thought to inhibit phosphofructokinase, causing accumulation of glucose-6-phosphate, which in turn suppresses hexokinase and thus glucose utilization.

PGU induced by insulin infusion under euglycemic conditions [Saloranta et al., 1991]. Etomoxir was also found to be hypoglycemic in obese patients with NIDDM [Ratheiser et al., 1991].

WHAT CAUSES INSULIN RESISTANCE IN PRE-NIDDM?

Studies in First-Degree Relatives of *Patients* With NIDDM

From the above discussion, it is evident that in both IDDM and NIDDM abnormally high levels of circulating FFA and their attendant excessive oxidation in body tissues play major roles in the maintenance of hyperglycemia (and, although not emphasized here, hypertriglyceridemia). However, in the case of NIDDM, this leaves unanswered a question of even more fundamental importance. It is now clear from longitudinal and cross-sectional studies in a large number of ethnic groups that individuals destined to develop NIDDM pass through an earlier stage of simple insulin resistance, at which time both their fasting plasma glucose concentration and glucose tolerance may be in the normal range [see, e.g., Saad et al., 1989; Lillioja et al., 1991; Martin et al., 1992; DeFronzo et al., 1992; Zimmet et al., 1992; Felber et al., 1993; Groop and Eriksson, 1992].[1] Yet, such people invariably display two other characteristics, namely, fasting hyperinsulinemia and an exaggerated postprandial insulin response (particularly of second phase insulin secretion).[2] How can this be explained? It is unlikely that the answer will come from further studies of patients who have already developed diabetes, where fuel homeostasis is so seriously deranged. A more promising approach is to examine the situation in offspring of individuals with NIDDM where the risk of developing the disease is much greater than that in the overall population but in whom metabolic equilibrium is still reasonably intact. A case in point is the recent report by Vaag et al. [1992]. Here the test subjects were 25-year-old first-degree relatives of patients with NIDDM who were tightly matched to a control group with no family history of diabetes. Of all the parameters measured in the basal state, the only abnormal feature of the relatives was a twice-normal level of plasma insulin and C peptide. However, during a hyperinsulinemic-euglycemic clamp procedure, the relatives proved to be insulin resistant, primarily in terms of nonoxidative glucose disposal. Similar observations were made by Gulli et al. [1992] in Mexican-American offspring of two diabetic parents. Furthermore, at least in the study by Vaag et al. [1992], no abnormality in FFA (or triglyceride) dynamics, either basally or during the insulin/glucose infusion, was discernible. On the basis of muscle biopsy analyses before and after the clamp, Vaag and colleagues concluded that the insulin resistance of the relatives reflected a diminished capacity of their muscles to convert glucose into glycogen, and that this in turn was caused by a defect in muscle glycogen synthase. It was suggested that the latter abnormality might represent the primary genetic defect leading to NIDDM. Importantly, there was no difference in the blood glucose profile between relatives and controls during an oral glucose tolerance test, but an exuberant insulin response in the former group was clearly evident.[3] In keeping with the prevailing view, the postglucose load hyperinsulinemia was viewed by Vaag et al. [1992] as a compensatory response to the demonstrated insulin resistance in this group of subjects, many of whom will presumably succumb to NIDDM in later years.

On its face, the notion that offspring of patients with NIDDM inherit a defective muscle glycogen synthase gene and that this accounts for their early insulin resistance is attractive. If true, it could explain the generally accepted sequence of events whereby in the early stages of NIDDM insulin resistance is seen as the primary defect, which then gives rise sequentially to glucose intolerance and hyperinsulinemia. Extending this scenario to the eruption of frank

[1]The insulin resistance referred to in this article is the form that is generally accepted as stemming from a post-insulin receptor defect(s). Inherited mutations in the insulin molecule or in its receptor probably account for a very small fraction of the total cases.

[2]It has been suggested that the commonly described hyperinsulinemia associated with NIDDM is an artifact due to cross-contamination of proinsulin and its split products in most radioimmunoassays employed for the measurement of insulin [Temple et al., 1989]. While this might be true in established NIDDM, it is clear from measurements using specific antibodies that individuals exhibiting simple glucose intolerance are hyperproinsulinemic and hyperinsulinemic both in the basal state and after glucose loading [Yoshioka et al., 1988].

[3]Qualitatively similar findings were reported by Gulli et al. [1992]. However, in this case it appears that some of the subjects studied had already developed impaired glucose tolerance.

NIDDM, two subsequent derangements, presumably also genetically programmed (since many individuals do not progress beyond the point of mild glucose intolerance), must be invoked: (1) loss of insulin sensitivity at the level of the fat cell, with concomitant elevation of plasma FFA levels and exacerbation of the insulin resistance; and (2) β-cell failure. According to this formulation, the abnormality of lipid metabolism would be seen as a late event in the overall etiology of NIDDM.

On the other hand, if an inherited defect in muscle glycogen synthase were a widespread cause of insulin resistance in pre-NIDDM, it is difficult to understand why insulin sensitivity is so readily improved after short-term caloric restriction and weight loss in obese type 2 diabetics [Golay et al., 1985; Kelley et al., 1993; Wing et al., 1994]. This leads to consideration of an alternative explanation.

Which Comes First—Insulin Resistance or Hyperinsulinemia?

A question to which no satisfactory answer has emerged from any of the studies cited above is the following: If in the early stages of NIDDM there is a point at which both the fasting blood glucose concentration and glucose tolerance are apparently normal, what is the signal for insulin hypersecretion[4] in the basal and glucose-stimulated states? It is this nagging biological conundrum that has invited questioning of the conventional view that insulin resistance leads to hyperinsulinemia, allowing speculation that, in fact, hyperinsulinema might precede the insulin resistance [Cusin et al., 1990; Jeanrenaud et al., 1992; DeFronzo et al., 1992; McGarry, 1992; Blair et al., 1993]. Admittedly, it may never be possible to separate these two entities in time, at least not until pre-NIDDM subjects can be studied before they are 25 years of age. Nevertheless, a large body of literature would be consistent with a primary role for hyperinsulinemia. Representative examples are as follows:

1. Alloxan treatment of insulin resistant ob/ob mice improved their insulin sensitivity [Mahler and Szabo, 1971]. The same effect was seen in sucrose-fed rats when β-cell function was attenuated by diazoxide treatment [Gutman et al., 1985].
2. Glucose-stimulated insulin release from the perfused pancreas of the obese Zucker rat was found to be twice that of lean controls at only 2 weeks of age [Blonz et al., 1985].
3. Hyperinsulinemia imposed on normal rats decreased the glucose utilization index of several muscles [Cusin et al., 1990].
4. Mexican-Americans in the highest quartile of plasma insulin levels had almost 7 times the risk of developing NIDDM as did subjects in the remaining three quartiles combined [Haffner et al., 1990].
5. Segregation analysis revealed a major gene effect for hyperinsulinemia in familial NIDDM pedigrees [Schumacher et al., 1992a].
6. Hyperinsulinemia in youth was found to be a predictor of NIDDM in Nauruans [Zimmet et al., 1992], Pima Indians [Pettitt et al., 1993], and normal offspring of type 2 diabetics at the Joslin Diabetes Center [Warram et al., 1990].
7. Transgenic mice overexpressing the human insulin gene became insulin resistant [Marban, 1992].
8. Patients with insulinoma displayed a degree of insulin resistance proportional to the extent of their hyperinsulinemia [Pontiroli et al., 1992]; they also exhibited visceral fat deposition proportional to the product of their plasma insulin level and disease duration [Inadera et al., 1993].
9. Basal and glucose-stimulated hyperinsulinemia preceded changes in glucose tolerance and body weight gain in gold thioglucose-treated mice [Blair et al., 1993].

If Hyperinsulinemia Is the Earlier Event, What Is Its Cause, and How Might It Lead to Insulin Resistance?

In addressing these questions, Jeanrenaud et al. [1992] proposed a model whereby obesity/NIDDM syndromes might have their origins in disorders of the central nervous system. One of the results envisioned is dysregulation of the autonomic nervous system, which in turn leads to hypersecretion of insulin by the pancreatic β cell. Such a construct seems quite plausible and deserves further exploration. Regardless of mechanism, oversecretion of insulin by the β cell could be expected to promote lipogenesis in

[4]For the purposes of this discussion it is assumed that the hyperinsulinemia in pre-NIDDM reflects excessive insulin secretion from the pancreatic β cell, as opposed to delayed insulin clearance from the blood. It cannot be excluded, however, that the latter phenomenon might contribute to hyperinsulinemia in some circumstances.

liver and adipose tissue, thus favoring the development of obesity. In addition, increased flux of very-low-density lipoproteins (VLDLs) from liver to muscle, initially to a degree that might be undetectable by conventional measurements of their turnover rate or plasma concentration, could, over the course of years, result in accumulation of triglyceride in the muscle cell [McGarry, 1992]. An expected accompaniment would be elevation of the intracellular fatty acyl-CoA content, enhancement of β-oxidation and impairment of glucose utilization via the Randle mechanism (Fig. 1). Presumably, there is concomitant interference with insulin stimulation of glycogen synthase activity, possibly via an inhibitory effect of fatty acyl-CoA on the enzyme [Wititsuwannakul and Kim, 1977]. An additional, possibly more relevant, factor might be inhibition of the function of the "glycogen cycle" in muscle as a consequence of decreased glucose utilization resulting from increased lipid oxidation [see Felber et al., 1993, for review]. In any event, the net effect could be that diminution of glucose incorporation into glycogen becomes the major observable defect during clamp studies. Note that if the early stages of insulin resistance were to proceed in this way, the process would be independent of elevated circulating FFA concentrations. Rather, the root cause would be at the level of increased endogenous hepatic triglyceride production, driven in part by the hyperinsulinemia and probably exacerbated by overeating.

A number of studies, both in animals and humans, would be in keeping with the above scenario:

1. Chronic hyperinsulinemia and hepatic VLDL overproduction are known to be strongly associated [Steiner et al., 1984].
2. In normotriglyceridemic white men insulin-mediated glucose disposal was found to correlate negatively with both fasting plasma insulin and triglyceride levels [Garg et al., 1988].
3. In normoglycemic obese rhesus monkeys fasting plasma triglyceride concentrations increased in proportion to the insulin level. Both parameters related positively to the degree of insulin resistance [Hannah et al., 1991].
4. Rats fed diets rich in saturated fatty acids developed striking elevations in muscle triglyceride and fatty acyl-CoA levels [Storlien et al., 1991; Chen et al., 1992]. In the former study the muscle triglyceride content was positively related to the degree insulin resistance.
5. Normoglycemic members of NIDDM pedigrees had significantly higher basal plasma triglyceride and one-hour insulin levels during an oral glucose tolerance test when compared with their spouses [Schumacher et al., 1992b].
6. Muscle triglyceride levels in patients with NIDDM were found to be sixfold elevated above normal [Falholt et al., 1988].

Is There a Role for Amylin?

As noted by Rink et al. [1993], evidence is accumulating that the newly discovered oligopeptide, amylin, which is co-secreted with insulin from the pancreatic β cell, might be instrumental in the pathogenesis of NIDDM. Consistent with this view are the findings that (1) circulating levels of amylin, like those of insulin, are elevated in obese rats [Huang et al., 1992; Pieber et al., 1993] and humans [Sanke et al., 1991]; (2) amylin suppressed insulin-stimulated incorporation of glucose into glycogen and activated glycogen phosphorylase in rat skeletal muscle [Leighton and Foot, 1990; D. Young et al., 1990]; (3) when administered as a bolus to fasted rats, amylin caused a marked increase in blood lactate and glucose levels [A.A. Young et al., 1991]; and (4) when infused into rats during a euglycemic-insulin clamp study, amylin suppressed glycogen synthesis in skeletal muscle while increasing the contribution of glycolysis to whole body glucose disposal [Frontoni et al., 1991]. The implication from findings (2–4) is that amylin might play a role in Cori cycling of glucose carbon between muscle and liver. It must be emphasized that these reported effects of amylin were, for the most part, seen with pharmacological levels of the peptide. However, if they can be convincingly demonstrated in vivo at physiological concentrations of amylin, a number of intriguing possibilities are raised. First, it is conceivable that in the basal state amylin acts as a first line of defense against insulin-induced hypoglycemia, should the pancreatic β cell become hyperactive for any reason; i.e., the simultaneous secretion of amylin would promote the movement of lactate from muscle to liver in order to maintain euglycemia. Stated in another way, in this setting amylin would in effect bring about a physiologically beneficial state of insulin resistance. If, as has been suggested [Degano et

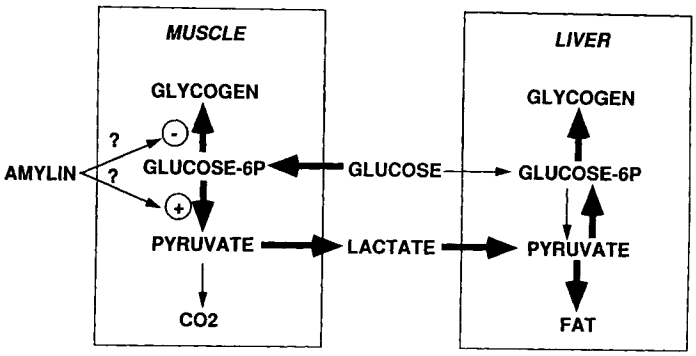

Fig. 2. Potential role of amylin in the disposition of a glucose load. The "indirect" pathway whereby dietary glucose is converted via lactate to liver glycogen and fat [McGarry et al., 1987] is highlighted. The possibility that amylin promotes the generation of lactate in muscle is indicated.[5]

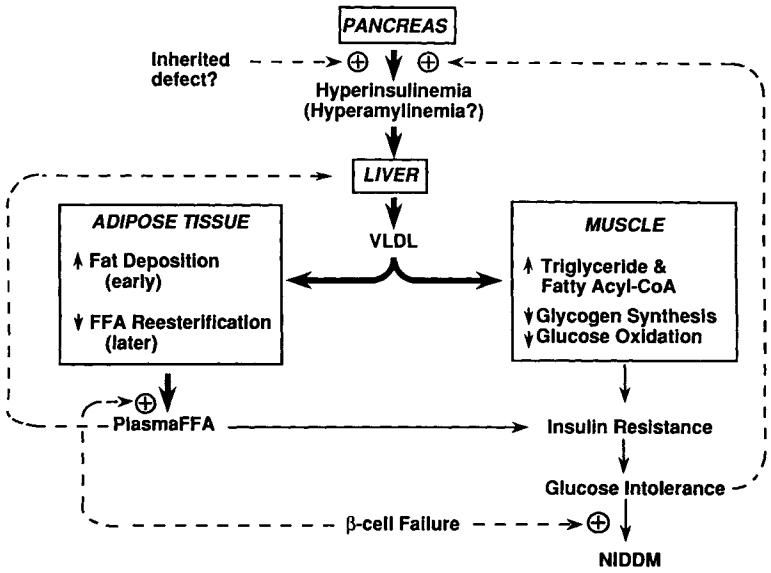

Fig. 3. Hypothetical steps in the etiology of NIDDM. See text for details.

al., 1993], elevated amylin levels also suppress insulin secretion from the β cell, this might provide additional protection from hypoglycemia. The secretion of well-established counter-regulatory hormones, such as glucagon and catecholamines, might then be seen as back-up mechanisms should the blood sugar level fall to dangerously low levels. Second, during refeeding after a fast the concomitant secretion of amylin together with insulin might facilitate the operation of the indirect pathway for hepatic glycogen repletion [McGarry et al., 1987], as illustrated in Figure 2.[5] Third, in contrast to these potentially physiological roles of amylin, prolonged hypersecretion of the hormone together with insulin could have the effect of further enhancing lipogenesis in liver. The operative mechanism here would be excessive flux from muscle to liver of lactate, which is far superior to glucose as a substrate for fatty acid synthesis [Boyd et al., 1981]. The net effect would be an extra stimulus to hepatic VLDL overproduction, and thus to the development of muscle insulin resistance as postulated above.

OVERVIEW

Based on the above considerations, a hypothetical sequence of events in the development of NIDDM is presented Figure 3. Its essential features are as follows. Hypersecretion of insulin and amylin by the pancreatic β cell (mecha-

[5]It is likely that the lactate derived from dietary glucose has multiple sources. Although one of these is depicted as muscle in Figure 2, this has not yet been established with certainty.

nism unknown) causes excessive VLDL production by the liver. Initially, the magnitude of the increase is probably very small, but with time leads to expansion of adipose tissue mass and to accumulation of triglycerides (and fatty acyl-CoA) in muscle. The latter leads to suppression of glucose oxidation (Randle mechanism) and impairs insulin activation of glycogen synthase (mechanism unknown). The resultant muscle insulin resistance produces glucose intolerance with further stimulation of β-cell hormone secretion, *setting up a vicious cycle*. At some point, the fat cell becomes refractory to insulin action such that plasma FFA levels rise, causing even greater rates of hepatic VLDL secretion, worsening of the muscle insulin resistance and, though not shown in the figure, accelerated hepatic glucose production. Finally, in genetically predisposed individuals β-cell failure occurs [Unger, 1991], with the result that impaired glucose tolerance progresses to frank NIDDM. The basis for β-cell failure is unknown. One factor might be the aggregation of amylin monomers into amyloid deposits within the pancreatic islet, a characteristic of NIDDM in humans [Cooper et al., 1987]. Another could be chronic exposure of the β cell to high levels of fatty acid substrate, a condition known to suppress glucose-stimulated insulin release in rat islets [Sako and Grill, 1990; Elks, 1993].

As stated at the outset, this is a speculative proposal that leaves a number of questions unanswered [McGarry, 1992]. Nevertheless, several of its components are amenable to experimental testing. Even if the model proves not to be correct in all aspects, it is hoped that it will prompt further discussion along three lines: (1) the temporal relationship between hyperinsulinemia and insulin resistance in the etiology of obesity/NIDDM syndromes; (2) whether the metabolic perturbations associated with diabetes would be more correctly viewed from a "lipocentric" as opposed to the traditional "glucocentric" standpoint; and (3) whether the newly recognized β-cell product, amylin, plays a physiological role in fuel homeostasis in the normal state while contributing to the pathogenesis of obesity and insulin resistance when secreted in excess.

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