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Early disturbances in insulin secretion in the development of type 2 diabetes mellitus

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Abstract

After a short description of normal glucose homeostasis, recent findings in relation to insulin release in three groups with a high risk of future development of type 2 diabetes are described. Hyperglycemic clamps in subjects with impaired glucose tolerance (IGT) clearly indicate that pancreatic beta cell function is decreased, in addition to the decreased insulin sensitivity. In women with former gestational diabetes mellitus (GDM), insulin release is also lower than in controls. In Caucasian first-degree relatives (FDRs) with normal glucose tolerance, various studies have shown that beta cell function is lower than in controls, while on the average insulin sensitivity is normal. This implies that beta cell function is disturbed earlier in subjects at risk of developing diabetes than is often appreciated. In the near future, the genetic studies currently underway will presumably unravel the pathogenesis of disturbances both in insulin secretion and in insulin action, in type 2 diabetes mellitus.

Keywords: Insulin secretion; Insulin resistance; Diabetes mellitus

1. Normal glucose homeostasis

Normally, plasma glucose levels are kept within fairly narrow limits even after a meal, or after prolonged fasting and which may vary somewhat between species (generally between 4 and 7 mmol/l in humans). For example, during the well-known oral glucose tolerance test (OGTT) 75 g of glucose is given by mouth. Although this is equivalent to 417 mmol of glucose, plasma glucose should normally not rise above 7.8 mmol/l, which points to a powerful regulation of plasma glucose level.

Glucose homeostasis entails an intricate interplay of various mechanisms, which can be divided into glucose elevating and glucose lowering mechanisms, for which the liver plays a central role (Gerich, 1993). The liver normally contains a large amount of carbohydrate in the form of glycogen, and is capable of converting glucose into glycogen and of converting glycogen back into glucose. Moreover, the liver is equipped with the machinery of gluconeogenesis. During a meal, insulin is released from the pancreas B cell. Already before glucose is absorbed, various signals lead to insulin release. These include vagal nerve activation during swallowing, and release of Glucagon-Like Peptide I (GLP-I) and Gastric Inhibitory Polypeptide (or Glucose-dependent Insulinotropic Polypeptide, GIP) upon contact of the duodenum with food (Creutzfeldt and Nauck, 1992; Nauck, 1999). An identical amount of glucose given by mouth elicits about twice as much insulin release as when given intravenously, which underlines the physiological importance of these mechanisms.

Insulin will rapidly diminish hepatic gluconeogenesis and glycogen breakdown, already at low plasma insulin levels. After an overnight fast, plasma insulin levels are sufficient to keep hepatic glucose production at about one third of its maximum capacity (DeFronzo, 1988). At the higher plasma insulin levels seen after a meal, insulin will also stimulate muscle and adipocyte glucose uptake, by activating glucose transporter-4 (GLUT-4; Kahn, 1992).

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2. Diabetes mellitus: derangement of glucose homeostasis

Diabetes mellitus is a state of (almost) permanent hyperglycemia; either a fasting level of 7.0 mmol/l or a non-fasting level of >11.1 mmol/l are sufficient for the diagnosis (American Diabetes Association, 1997). Various types of diabetes mellitus exist. In this review 'diabetes mellitus' will be used for type 2 diabetes mellitus (formerly non-insulin dependent diabetes mellitus). This is the most prevalent type of diabetes, mainly seen in subjects with an onset of diabetes over 40 years of age; many of these individuals are obese, and many have a family history of diabetes mellitus.

In type 2 diabetes, hepatic glucose production is around 15% higher than in non-diabetic subjects in the fasting state (DeFronzo, 1988; Staehr et al., 2001). In diabetic subjects, hepatic glucose production is less reduced after a meal than in non-diabetic controls, which (also) points to insulin resistance, and which is responsible for the post-prandial rise in plasma glucose level (Groop et al., 1989; Gerich, 1993). This has also been observed in studies with OGTT's in subjects with Impaired Glucose Tolerance (IGT; Mitrakou et al., 1992). In type 2 diabetes patients, peripheral glucose uptake is less stimulated by insulin after a meal than in healthy controls.

3. Insulin resistance

It has become clear that most, but not all (Arner et al., 1991), patients with type 2 diabetes have insulin resistance. Many subjects have fasting hyperinsulinemia in the face of elevated fasting plasma glucose, and in spite of the (further) elevation of plasma insulin levels after a meal, hyperglycemia is marked. Similarly, the elevation of hepatic glucose output in the face of hyperinsulinemia and the diminished peripheral (muscle and adipose tissue) glucose clearance (that is glucose uptake divided by plasma glucose level) are signs of insulin resistance (DeFronzo, 1988; Reaven, 1995). Plasma insulin levels at 120 min post-OGTT are often used as a surrogate for insulin resistance. However, use of multiple linear regression analysis of beta cell function and insulin sensitivity has indicated, that both fasting and 120 min plasma insulin levels relate mainly to insulin sensitivity in NGT subjects only. In IGT subjects, both fasting and 120 min plasma insulin levels relate mainly to second phase insulin secretion (Van Haeften et al., 2000).

So far, various mechanisms for the occurrence of insulin resistance have been delineated. First, hyperglycemia itself is known to induce insulin insensitivity. This partially reversible phenomenon is known as glucose toxicity (Rosetti et al., 1990; Yki-Jarvinen, 1992). For example, while muscle biopsies taken from type 2 diabetes subjects show decreased insulin-induced glucose uptake after 30 min, a further incubation for only 2 h at a euglycemic glucose concentration, results in normal insulin-induced glucose uptake (Zierath et al., 1994). Indeed, improvement in metabolic control in diabetic subjects leads to marked improvement of insulin sensitivity as measured with intravenous Glucose Tolerance Tests (ivGTT; Beck-Nielsen et al., 1979) or clamp techniques (Freidenberg et al., 1988; Bak et al., 1992), irrespective of which measure was taken to improve metabolic control (use of diet, or of insulin injections Andrews et al., 1984).

Second, insulin resistance can be largely explained by disturbances in insulin signal transduction (Garvey and Birnbaum, 1993). Insulin receptor tyrosine kinase (the first step in insulin signaling) has a 50% lower activity in diabetes, possibly due to phosphorylation of serine and threonine residues of the intracellular part of the insulin receptor. Disturbances further down stream include decreased phosphorylation of Insulin Receptor Substrate-1 (IRS1) and PI-3 kinase, and disturbances in protein kinase C-isoforms, Akt-kinase and in GLUT-4 activity (translocation and trafficking; Zierath et al., 2000).

Several substances have been found to be able to inhibit insulin action (Leong and Wilding, 1999). Free fatty acids, which are often elevated in type 2 diabetes (Kruszynska et al., 1997), and tumor-necrosis-factor-alpha (TNF-alpha), which is secreted by 'full' adipocytes (Hotamisligil et al., 1995), are known to inhibit insulin action, possibly by inhibition of insulin receptor function (phosphorylation of serine and threonine residues; Matthaei et al., 2000), or by post-receptor events leading to inhibition of GLUT-4 activity. It is of importance to note that these disturbances also occur in obesity without diabetes. Possibly, elevated glucose levels can worsen insulin resistance also by interference with insulin receptor tyrosine kinase (Muller et al., 1991), and presumably by interference with the second messenger Akt (Kurowski et al., 1999). The protein resistin, recently discovered in mice, but so far of uncertain importance in man, which is also produced by adipocytes can also diminish insulin action (Steppan et al., 2001). Again, the importance of these findings resides in the potentially reversible nature of insulin insensitivity, for example after weight reduction in overweight diabetic subjects, which should diminish plasma free fatty acid (and possibly TNF-alpha and resistin) levels.

Finally, it has been proposed that insulin resistance is genetically transmitted. Indeed, insulin action has been shown to vary between families (Martin et al., 1992). So far, few mutations in susceptibility genes have been found (Matthaei et al., 2000). Since obesity itself is under marked genetic control (Bouchard, 1996; Stunkard et al., 1986), and since it leads to insulin resistance, this might explain that many type 2 diabetic subjects are

obese and insulin resistant, and that this occurs in families. Indeed, at least one polymorphism (of the beta-2 adrenoceptor gene) is highly prevalent in obese subjects (Large et al., 1997). Presumably, genome-wide scan will lead to several genetic causes of obesity and diabetes both separately and combined together (Leong and Wilding, 1999; Matthaei et al., 2000; Parker et al., 2001).

4. Disturbances in insulin secretion

Intravenous glucose tolerance tests (ivGTT) and, lately, hyperglycemic glucose clamps have sufficiently shown two disturbances in insulin secretion to be present in type 2 diabetes. In hyperglycemic glucose clamps, plasma glucose level is acutely elevated with an intravenous glucose infusion, and kept at a predetermined level with a variable glucose infusion; plasma glucose levels are being measured frequently at short intervals (5 min). Normally, augmentation of the glucose level immediately induces a sharp increase in insulin secretion which is short lasting (a few minutes), known as the first phase, which is then followed by a more slowly evolving second phase, which lasts as long as the elevation in glucose level. An ivGTT consists of a single intravenous glucose injection; plasma insulin levels after the injection are used to assess (mainly first phase) insulin secretion. After the initial rise in plasma glucose levels, plasma glucose levels rapidly decrease which makes this method cumbersome for the interpretation of second phase secretion.

In type 2 diabetic subjects, the first phase is very low, often absent, and actually a small decrease in insulin levels has been noted in some patients (Ward et al., 1984; Van Haeften et al., 1991). 'Second' phase secretion has been shown to be lower than secretion occurring in non-diabetic controls at identical plasma glucose. It is of note, that insulin resistance itself has been shown to lead to 'upregulation' of the B-cell secretion (Tayek et al., 1997; Kahn et al., 2001), which underlines the importance of matching study subjects for obesity and age.

This 'upregulation' has been studied by (graphic) representation of measures of insulin secretion versus insulin resistance, which will typically show a hyperbolic relationship. Various authors have used the multiplication of a measure for first phase secretion times the insulin resistance of a particular subject as an index for the adaptation of the B-cell for the prevailing insulin sensitivity. This has been referred to as disposition index (Bergman et al., 1981; Ahren and Pacini, 1997). Since first phase is generally very low in type 2 diabetes subjects, their disposition index is typically also low, even if arginine is used for the assessment of fist phase secretion. Its assessment has recently been advocated in subjects at risk for future development of diabetes.

There is still debate whether insulin resistance is present before the onset of a disturbance of glucose homeostasis. Therefore, various research groups have recently turned to studies in subjects who have a predisposition to develop diabetes in the future.

5. Insulin secretion in subjects at risk of type 2 diabetes mellitus

In general, various studies have been undertaken in subjects with a predisposition to type 2 diabetes, the most important of whom are (1) IGT, (2) former gestational diabetes mellitus (GDM), (3) normoglycemic first-degree relatives (FDRs) of type 2 diabetes patients. Subjects born with a low birth weight are also at risk for future development of type 2 diabetes mellitus, but this will not be discussed here.

5.1. Impaired glucose tolerance

Subjects with IGT are characterized by a fasting plasma glucose level in the non-diabetic range (below 7.0 mol/l), and by plasma glucose levels between 7.8 and 11.1 mmol/l 2 h after an OGTT. Various studies have shown that many of these subjects are overweight, and that they are moderately insulin-resistant (Reaven et al., 1989; Berrish et al., 1995). Early studies have already demonstrated increased plasma insulin levels after an OGTT in IGT subjects (Reaven et al., 1989). However, by definition, the IGT subjects had higher plasma glucose levels than the controls, and were more obese, which hampers the interpretation of the increased insulin levels. Walker et al. (1997) noted lower plasma insulin levels at 2 h after the OGTT in IGT subjects with a family history than in IGT subjects without a family history of diabetes, suggesting that families may have a genetic tendency to have lower beta cell function. Others have noted delayed insulin responses after an OGTT, with lower plasma insulin increases during the first 30 min in IGT as compared with controls, with subsequent hyperinsulinemia later on (Mitrakou et al., 1992; Chen et al., 1995). This has also been observed in African-Americans with IGT (Osei et al., 1997). This points to impairment of beta cell function as an additional cause of the defect in insulin induced reduction of hepatic glucose production which is observed in IGT. There is considerable debate about the relative importance of insulin secretion and insulin sensitivity for the elevated hepatic glucose production seen in type 2 diabetes and IGT (DeFronzo, 1988; Mitrakou et al., 1992; Pratley and Weyer, 2001). In recent studies of Bavenholm et al. (2001), in which insulin secretion (after an OGTT) and insulin sensitivity (with hyperinsulinemic clamp) were assessed in 57 subjects, it was estimated that both contribute significantly to hepatic glucose output, with

preponderance of hepatic insulin sensitivity. In studies in 283 non-diabetic subjects in whom insulin sensitivity and beta cell function were assessed with hyperglycemic clamps, we found that both are important for fasting and 2 h post OGTT plasma glucose levels, with tissue insulin sensitivity having the largest impact (Van Haeften et al., 2000). One of the intrinsic problems is that insulin sensitivity has a marked impact on beta cell function (Tayek et al., 1997; Kahn et al., 2001); it may, therefore, remain cumbersome to dissect the impact of each of them.

Various studies have addressed the acute insulin release seen after ivGTT, which have shown decreased (Davies et al., 1994; Ahren and Pacini, 1997) normal (Berrish et al., 1995), increased (Walker et al., 1997) or disturbed first phase release (Lillioja et al., 1988; Byrne et al., 1996). Again, matching for obesity (and age) is important for the interpretation of these results (Kahn et al., 2001). Indeed, in studies in which obesity and insulin resistance was taken into account acute insulin release was reported to be inappropriately low in insulin-resistant FDRs of diabetes patients (Nyholm et al., 2000). In studies in which 28 h hyperglycemic glucose infusions were used, disturbances in insulin secretion were noted in IGT (O'Meara et al., 1993).

The notion that insulin release should be studied at identical plasma glucose levels has led to use of hyperglycemic clamps, which has shown that both first and second phase secretion are lower in IGT than in controls (Van Haeften et al., 2000). It may well be that this decrease in insulin secretion is most evident during prolonged hyperglycemia (see Fig. 1). Most of these IGT subjects had normal fasting glucose levels (i.e. below 6.1 mmol/l, according to the American Diabetes Association, 1997). These subjects with 'isolated IGT' also have lower beta cell function than controls (when age and obesity are taken into account; Van Haeften et al., 2001). Similarly, in studies with ivGTT's in Pima Indians, Weyer et al. (1999) found lower (first phase) insulin secretion both in subjects with 'isolated' Impaired Fasting Glucose (plasma glucose between 6.1 and 7.0 mmol/l, American Diabetes Association, 1997), and in subjects with 'isolated' IGT, as compared with controls. The disposition index (multiplication of first phase secretion measures with insulin sensitivity) has been used in order to assess the adaptation of the B-cell to the prevailing insulin resistance. Ahren and Pacini (1997), Larsson and Ahren (2000) have shown a markedly decreased disposition index in postmenopausal IGT women as compared with controls.

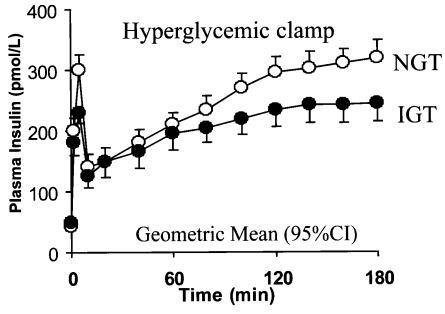

Fig. 1. Geometric mean (±95% CI) plasma insulin levels during 3 h hyperglycemic glucose clamps in 98 subjects with IGT (closed circles), and 185 controls with Normal Glucose Tolerance (open circles). Figure is slightly adapted from data from Van Haeften et al. (2000) with permission of the Editor.

5.2. Former gestational diabetes mellitus

During normal pregnancy, insulin resistance occurs as a consequence of placental hormone release, and presumably as a consequence of this in susceptible women, this can lead to GDM in about 3% of pregnant women. They are at high risk of developing type 2 diabetes mellitus later in life. In a number of studies with OGTT, or ivGTT, in women who had had gestational diabetes (former GDM), a decreased insulin release has been noted, as reviewed recently (Gerich, 1998). Actually, in most studies insulin sensitivity had returned to normal after delivery. Grill and Efendic (1987) have performed hyperglycemic clamps in gestational diabetes, and found insulin release, which was lower than in their 'high responder' group, but comparable to the 'low responder' group.

5.3. Normoglycemic first-degree relatives of type 2 diabetes patients

Clearly, FDRs of subjects with type 2 diabetes mellitus are at risk for diabetes mellitus; this has been estimated to be between 20 and 40% (Bennet, 1990; Pierce et al., 1995). Studies of insulin release in families has shown heritability (Elbein et al., 1999). A large number of studies have addressed insulin levels following OGTT's, as reviewed by Gerich (1988). Most of these studies find normal plasma insulin levels, although sometimes increased, or slightly lower plasma insulin levels have been reported. The largest series of OGTT's (in 584 FDRs) has been reported by Haffner et al. (1988), who found increased plasma insulin levels in Mexican Americans. It is of note that in several studies, the FDR's did have slightly higher plasma glucose levels, which may make interpretation more difficult (since higher plasma glucose levels should elevate insulin secretion). In a large series of studies in 154 Caucasian relatives, Volk et al. (1999) observed a lower 30 min insulin release after an OGTT, similar to the lower insulin release at 30 min during an OGTT seen in IGT (see above).

In studies involving ivGTT in FDR's, almost all studies show a decrease in insulin responses; the largest two series of studies (containing over 100 FDR's)

concluded to decreased (Boberg et al., 1976) and normal (Warram et al., 1990) insulin release, respectively. In the latter studies, the FDR's were more obese, which in itself should augment insulin release (Tayek et al., 1997; Kahn et al., 2001). Perseghin et al. (1997) studied insulin release in relation to insulin resistance in studies with ivGTT's. They found that the most insulin-resistant non-diabetic offspring of white type 2 diabetic subjects had a lower than normal (first phase) insulin secretion considering their insulin resistance, that is they found an inappropriately low disposition index in the most insulin-resistant (non-diabetic) FDRs.

Interestingly, Elbein et al. (2000) compared disposition indexes in lean and obese relatives of type 2 diabetes patients, and showed that the DI decreased with obesity only in the relatives but not in controls. This again points to an interaction of obesity and/or insulin resistance in B-cell fucntion in relatives of type 2 diabetes.

There are just a small number of clamp studies: In early studies, Gulli et al. (1992) examined a small group of offspring of two Mexican American parents with type 2 diabetes mellitus, both with hyperinsulinemic clamps which indicated substantial insulin resistance, and with hyperglycemic glucose clamps, which showed elevated insulin secretion. Eriksson et al. (1989) showed increased insulin secretion in offspring of Caucasian type 2 diabetes subjects. However, their subjects were not well-matched for age and obesity. In later studies in FDR's of Caucasian type 2 subjects (Pimenta et al., 1995; Van Haeften et al., 1998) subjects were carefully matched for gender, age, and obesity (and in the latter studies also for aerobic capacity, VO_2Max, which is correlated with insulin sensitivity). These studies indicated that first and second phase secretion was lower in the FDR's (see Fig. 2). In addition, Pimenta et al. (1995) also performed euglycemic hyperinsulinemic clamps in the same subjects, and showed normal insulin sensitivity. The latter studies, therefore, showed for the first time that defects in beta cell function are present in a large group of relatives without the presence of insulin resistance, which points to beta-cell dysfunction as a primary pathogenetic phenomenon for the development of type 2 diabetes in Caucasians. The above-mentioned studies of Gulli et al. (1992) on the other hand clearly show that in Mexican Americans with two parents with type 2 diabetes, insulin resistance is a primary pathogenetic mechanism. These opposing findings point to differences in pathogenesis between different ethnic groups.

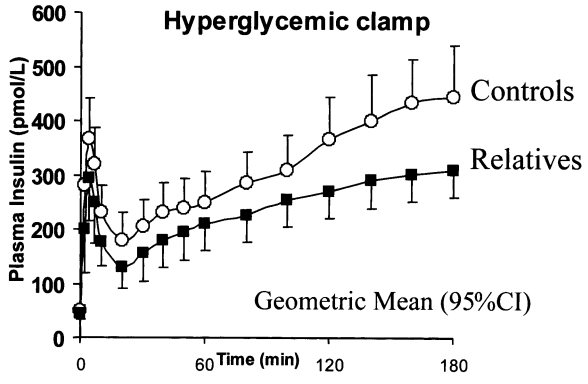

Fig. 2. Geometric mean (±95% CI) plasma insulin levels during 3 h hyperglycemic glucose clamps in 21 FDRs of type 2 diabetes patients, (closed symbols), and matched 21 controls without a family history of diabetes (open circles). All subjects had Normal Glucose Tolerance. Data from Van Haeften et al. (1998) with permission of the Editor.

It is well known, both from in vitro studies and from in vivo studies, that insulin release occurs in a pulsatile manner, showing waves of about 10–13 min in various organisms including man. In early studies, it has been shown that this pulsatile release is lost in type 2 diabetes mellitus subjects. O'Rahilly et al. (1988) have shown that this pulsatility of insulin release is diminished in non-diabetic FDRs. Recently, Nyholm et al. (2000) also observed more irregular and non-stationary insulin release in studies with ivGTT's in relatives.

Insulin release also shows circadian changes, with early morning rises in insulin release peaking in the afternoon, and declining in the night (Boden et al., 1999). These authors reported that the circadian (24-h) cycle of insulin release is disrupted in six African-American relatives, who had a normal glucose tolerance. These relatives were also insulin resistant, which may point to a combined defect (in beta cell function and insulin action) in the pathogenesis in African-Americans.

5.4. Future directions

Currently, a number of genetic studies is underway, especially in the field of sib-pair analysis of sibs with type 2 diabetes mellitus (Van Tilburg et al., 2001). As a result of such studies, recently polymorphisms in the Calpain-10 gene were found to be related to type 2 diabetes in Mexican Americans (Horikawa et al., 2000), and presumably a number of genes will follow in these and other ethnic groups. This should be followed by research to uncover how polymorphisms of these genes act to disturb glucose homeostasis. It will be clear that focus should not only be on insulin action, but also on insulin secretion, and/or the interrelationship between the two, and how this can be translated into more specific therapy or prevention. Other approaches are the more classic candidate gene approach, in which polymorphisms of candidate genes are uncovered in subjects with type 2 diabetes. Again, studies will focus on how these polymorphisms interact with glucose homeostasis. For example, Hart et al. (2000) recently found that a very common intron-variant of the sulfonylurea receptor, which is essential to the normal functioning of the

pancreatic beta cell and insulin release, leads to a lower insulin secretion. It could well be that the causes of type 2 diabetes may turn out to be very diverse, especially between different ethnic groups.

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