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COMMENTARY

Insulin Resistance and Antidiabetic Drugs

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ABSTRACT. Insulin resistance describes an impaired biological response to insulin, which underpins the development of type 2 (non-insulin-dependent) diabetes mellitus (T2DM). Initially, insulin resistance causes a compensatory hyperinsulinaemia, which gives way to pancreatic β-cell failure. Insulin resistance and hyperinsulinaemia conspire together in the development of a diverse collection of risk factors for coronary heart disease, namely obesity, T2DM, dyslipidaemia, hypertension, atherosclerosis, and a pro-coagulant state. This collection of factors is commonly found in T2DM patients, and is recognised as the Insulin Resistance Syndrome or Syndrome X. By targeting insulin resistance as a treatment strategy for T2DM, it should be possible to broaden the potential benefits, so that improved glycaemic control is complemented with improvements to other components of Syndrome X. At present, metformin and thiazolidinediones are the only therapies for T2DM that directly address aspects of insulin resistance. Increasing awareness of the clinical implications of insulin resistance, and increasing knowledge of the cellular basis of insulin resistance, provide the rationale and a means for developing an anti-insulin resistance approach to the treatment of T2DM. BIOCHEM PHARMACOL **58**;10: 1511–1520, 1999. © 1999 Elsevier Science Inc.

KEY WORDS. insulin; insulin resistance; Syndrome X; diabetes mellitus; antidiabetic drugs

Insulin resistance has emerged as a far-reaching endocrine phenomenon. The term insulin resistance signifies an impaired biological response to insulin, and insulin resistance is known to underlie the deterioration of glucose homeostasis that leads to the typical forms of T2DM†, particularly with obesity. The development of insulin resistance is met initially with a compensatory increase in insulin secretion. The coexistence of insulin resistance and hyperinsulinaemia appears to contribute directly or indirectly to many other disorders, such as dyslipidaemia, hypertension, atherosclerosis, and a pro-coagulant state. All of these disorders are risk factors for coronary heart disease.

The frequent occurrence in the same individual of several or all of the disorders linked with insulin resistance has now assumed the status of a syndrome in its own right. It is variously referred to as the Insulin Resistance Syndrome, Metabolic Syndrome, Syndrome X, or Reaven's Syndrome.

The combined forces of insulin resistance and hyperinsulinaemia are also implicated in the pathogenesis of polycystic ovary syndrome and the metabolic effects of glucocorticoid therapy, as well as contributing to the metabolic adaptations of pregnancy. However, this commentary will restrict its focus to Syndrome X. A perspective of insulin resistance will be traced from its clinical manifestations back to its molecular origins. This will provide the basis for suggesting that insulin resistance deserves a much higher profile as a therapeutic approach to the treatment of T2DM.

INSULIN SENSITIVITY AND INSULIN RESISTANCE

The acute metabolic actions of insulin and their crucial importance for survival are well recognised [1]. Insulin directs the selection of metabolic fuels for energy production (Table 1), and in so doing it is the only hormone committed to the prevention of hyperglycaemia [2]. Several metabolic processes are exquisitely sensitive to insulin; hence, modest alterations of insulin sensitivity can incur widespread metabolic disturbances.

Insulin resistance describes an impaired biological response to insulin [3], but there is sufficient variability in "normal" sensitivity to insulin that there is no specific boundary at which sensitivity ends and resistance begins. The need for a flexible interpretation of insulin resistance is emphasised by evidence that insulin resistance affects different tissues and different actions of insulin to different extents. For example, insulin-stimulated glucose transport in muscle can be impaired while the liver is normally

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† *Abbreviations*: β-cell, pancreatic islet beta-cell; FFA, free (non-esterified) fatty acids; GLUT, glucose transporter; HDL-C, high-density-lipoprotein cholestrol; IGT, impaired glucose tolerance; IL-6, interleukin-6; IRS, insulin receptor substrates; LDL-C, low-density-lipoprotein cholesterol; MAP, mitogen-activated protein; PAI-1, plasminogen activator inhibitor-1; PI-3K, phosphatidylinositol-3 kinase; PKB, phosphokinase B (also known as Akt); PPARγ, peroxisome proliferator-activated receptor gamma; SH2, src homology 2; TKA, tyrosine kinase activity; TNFα, tumour necrosis factor alpha; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; and VLDL-TG, very-low-density-lipoprotein triglyceride.

TABLE 1. Key actions of insulin in nutrient fuel selection

Action*	Tissue	Mediator*	Sensitivity (mol/L)†	Time of onset (min)
↑ Glucose uptake	Muscle, fat	↑ Glucose transporters‡	$\sim 5 \times 10^{-11}$	<1
↑ Glycogenesis	Liver, muscle, fat§	↑ Glycogen synthase‖	$\sim 2 \times 10^{-10}$	<5
		↓ Glycogen phosphorylase¶	$\sim 2 \times 10^{-10}$	<5
↑ Glycolysis	Liver, muscle, fat	↑ Glucokinase (liver)**		>10
		↑ Pyruvate kinase‖		<5
		↑ Pyruvate dehydrogenase‖	$\sim 2 \times 10^{-10}$	<5
↓ Gluconeogenesis	Liver	↓ Phosphoenolpyruvate carboxykinase††		>10
↑ Lipogenesis	Liver, fat	↑ Acetyl CoA carboxylase‡‡	$\sim 2 \times 10^{-10}$	<5
↓ Lipolysis	Fat	↓ Triacylglycerol lipase¶	$\sim 10^{-11}$	~1
↑ Protein synthesis	Liver, muscle	↑ RNA synthesis	$\sim 10^{-9}$	>10

*(↑) increase; (↓) decrease.
†Approximate concentration of insulin at which action can be detected. Normal circulating insulin concentrations in venous plasma are basally < 10 μU/mL ≈ 0.4 ng/mL ≈ 7×10^{-11} mol/L = 70 pM. Postprandial insulin concentrations rarely exceed 150 μU/mL ≈ 6 ng/mL ≈ 10^{-9} mol/L = 1 nM.
‡Predominantly isoform GLUT4.
§Glycogenesis is not a major fate of glucose in fat.
‖ Activated by dephosphorylation.
¶Suppressed by dephosphorylation.
**Induced.
††De-induced.
‡‡Activated by phosphorylation.

responsive to insulin-stimulated lipogenesis. Thus, it is difficult to choose a single representative method to measure whole body insulin resistance.

Individuals are often shielded from the metabolic consequences of insulin resistance by a compensatory increase in insulin concentrations. However, there is no absolute definition of hyperinsulinaemia, since an insulin concentration that is "raised" for a given individual is usually still well within the wide range of normality. While hyperinsulinaemia may compensate for resistance to some actions of insulin, it can result in overexpression of actions that retain normal or nominally impaired sensitivity to insulin. Also, high concentrations of insulin might act via receptors for insulin-like growth factor-1. Thus, accentuation of some actions of insulin with simultaneous resistance to other actions gives rise to a diversity of clinical presentations and sequelae of insulin resistance [4, 5].

INSULIN RESISTANCE IN TYPE 2 DIABETES

Whole body insulin-stimulated glucose utilization, measured by the euglycaemic-hyperinsulinaemic clamp technique, is reduced in obesity and T2DM [6]. In T2DM, this measure of insulin sensitivity is often less than half that of the average healthy individual with normal glucose tolerance (Fig. 1). The major site of impaired insulin-stimulated glucose utilization is skeletal muscle, which shows reductions in glucose uptake, glycogenesis, and glucose oxidation [6–8]. Insulin-stimulated glucose uptake is impaired and suppression of lipolysis is decreased in adipocytes from T2DM patients [9, 10], although responsiveness to insulin may vary considerably between different adipose depots. Elevated circulating FFA will disrupt the glucose–fatty acid (Randle) cycle, aggravating insulin resistance in muscle and liver. Insulin-induced suppression of hepatic glycogenolysis and gluconeogenesis is impaired in T2DM, but usually this is not sufficiently marked to make a significant impact on hyperglycaemia until the hyperglycaemia is severe [11].

A typical scenario for the development of T2DM shows insulin resistance as an early feature of the disease process (Fig. 1A). Initially, this is compensated for by increased insulin concentrations (Fig. 1B), such that glucose homeostasis remains normal or only mildly disturbed (Fig. 1C). Interestingly, about 25% of adults with normal glucose tolerance show a degree of insulin resistance similar to that of patients with T2DM, indicating how effective compensatory hyperinsulinaemia can be. The ability of insulin-resistant individuals to ward off T2DM will depend largely upon the adaptive capacity of the pancreatic β-cells to maintain increasing insulin concentrations [12]. Those who cannot sustain sufficient hyperinsulinaemia suffer a deterioration in glucose homeostasis (IGT). An increasing mismatch between escalating insulin resistance and inadequate compensatory hyperinsulinaemia causes a progression of IGT into frank T2DM. By the time T2DM has developed, insulin resistance appears to be almost fully established (Fig. 1A). However, hyperglycaemia continues to worsen due to increasingly compromised β-cell function. As hyperglycaemia becomes severe, β-cell failure is usually clearly evident, with a delayed and diminished insulin response to a glucose challenge [12].

Although this scenario can take place without the occurrence of obesity, obesity is frequently a confounding factor. Obesity promotes both insulin resistance and hyperinsulinaemia [13], and a majority of patients with T2DM in western societies have a history of obesity or overweight [12].

THE INSULIN RESISTANCE SYNDROME

The concept of a syndrome linked to insulin resistance and hyperinsulinaemia emerged from a realisation that obesity

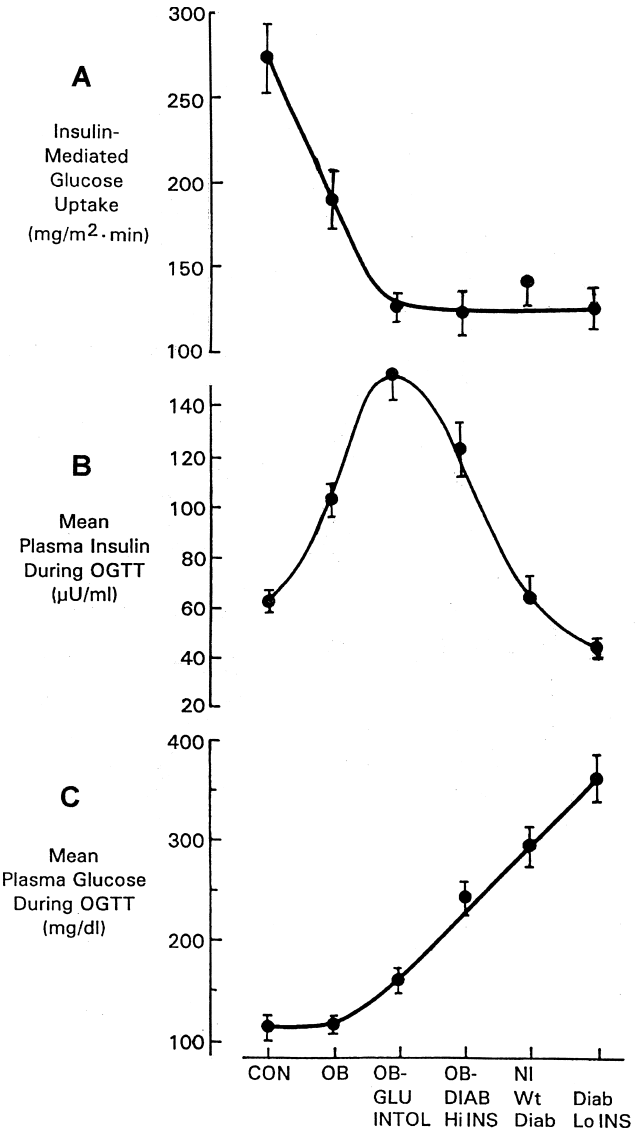

FIG. 1. Insulin resistance: an early feature in the development of T2DM. The data illustrate a typical scenario for the progression from normal (control) glucose homeostasis through obesity to T2DM. Panel A shows the decline in insulin-mediated glucose uptake (determined by a euglycaemic-hyperinsulinaemic clamp), which is a measure of insulin resistance. Panel B shows that this is compensated for initially by increased insulin secretion (during a 100 g oral glucose tolerance test), before eventually giving way to low insulin concentrations. Panel C shows the progressive deterioration of glucose tolerance (during a 100 g oral glucose tolerance test, OGTT). Abbreviations: CON, non-obese non-diabetic normal control; OB, obese normal glucose tolerance; OB-GLU INTOL, obese with glucose intolerance (IGT); OB-DIAB Hi INS, obese with T2DM and hyperinsulinaemia; NI Wt Diab, nonobese T2DM with lower insulin concentrations; and Diab Lo INS, severely hyperglycaemic T2DM with absolute hypoinsulinaemia. Based on Ref. 6, and reproduced with permission from *Diabetes* 37: 667–687, 1988. Copyright (1988) American Diabetes Association.

and T2DM are associated with a high prevalence of multiple metabolic abnormalities and other disturbances that are risk factors for coronary heart disease (Table 2). These include dyslipidaemia (increased triglyceride and small dense LDL-C, and decreased HDL-C), hypertension, atherosclerosis, and a pro-coagulant state [14]. Accordingly, obesity and T2DM are associated with a substantial increase in cardiovascular morbidity and mortality.

TABLE 2. Components of the Insulin Resistance Syndrome (Syndrome X)

Insulin resistance
Hyperinsulinaemia
Obesity*
Glucose intolerance or T2DM
Dyslipidaemia†
Hypertension
Atherosclerosis
Pro-coagulant state
Hyperuricaemia

*Android (truncal) obesity.
†Increased VLDL-TG, increased small dense LDL-C, decreased HDL-C.

Presentation of the syndrome is inevitably varied due to differences between individuals in the expression of its components. Moreover, events that give initial momentum to the syndrome will change as the syndrome evolves. Thus, more severe states of T2DM may no longer exhibit hyperinsulinaemia, while dyslipidaemia, hypertension, and atherosclerotic vascular disease may be advanced [5]. Alternatively, insulin resistance may be well compensated for by hyperinsulinaemia, limiting the disturbance of glucose homeostasis to IGT, while other features of the syndrome may range from subclinical to advanced.

Establishing that insulin resistance is the unifying culprit for the syndrome has posed many conundrums, especially where the boundaries between physiology and pathology are blurred [5, 14]. Several features of the syndrome are difficult to separate from the normal ageing process or the consequences of diabetes itself. Many of the events are prompted by insulin resistance and inseparable from raised insulin concentrations, and it is the coexistence of the two conditions that may provide a significant pathogenic insult to the vascular system. However, it should be remembered that most components of Syndrome X also can occur quite independently, without the presence of insulin resistance or hyperinsulinaemia.

Proposed associations between the different components of Syndrome X have been assembled into a hierarchical and aetiologically dependent scheme in Fig. 2. The evidence to support this proposal has been presented and argued in detail elsewhere [4, 5, 15], and the following paragraphs are limited to a synopsis of the putative mechanisms that link the syndrome to insulin resistance and hyperinsulinaemia.

Obesity

Obesity is a cause of insulin resistance. Android obesity, which is characterised by a gross excess of adipose tissue within and around the abdomen, is the main type of obesity associated with T2DM and increased vascular risk [15].

This adipose depot shows a high rate of turnover, possibly

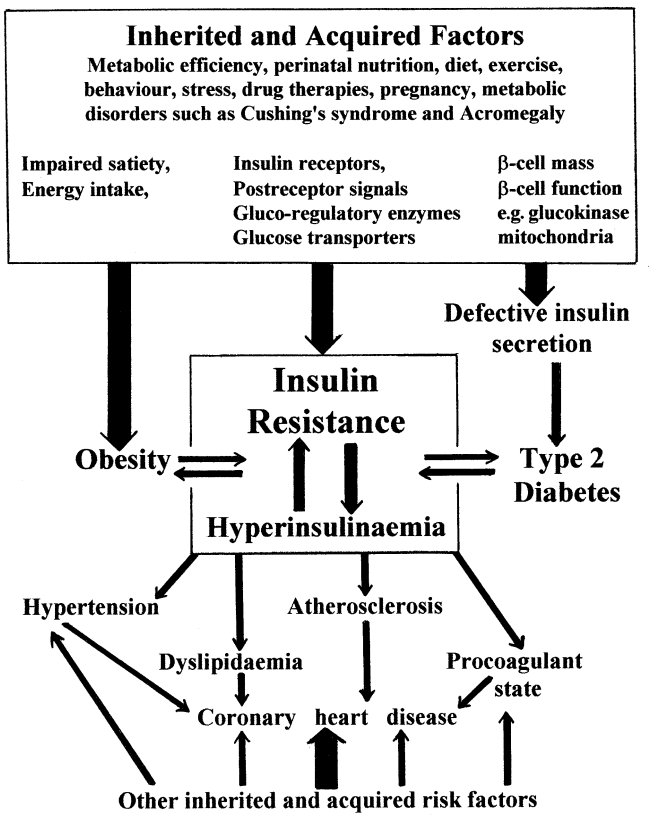

FIG. 2. Scheme to indicate potential links between different components of the Insulin Resistance Syndrome (Syndrome X). Inherited and acquired disturbances affecting energy balance, insulin sensitivity, and pancreatic β-cell function give rise to obesity, insulin resistance, defective insulin secretion, and T2DM. Insulin resistance and/or hyperinsulinaemia contribute to other key features of the syndrome, which are risk factors for coronary heart disease.

due to increased catecholamine-mediated β-adrenoceptor activity, with high activities of hormone-sensitive lipase as well as lipoprotein lipase. Adipose tissue turnover increases plasma FFA and may promote insulin resistance further by the release of certain cytokines (e.g. TNFα and IL-6). Increased nutrient intake and decreased nutrient utilization due to low levels of physical activity will foster the vicious spiral of hyperinsulinaemia and insulin resistance.

Hyperinsulinaemia and Insulin Resistance

It is presumed that subtle increases in glycaemia stimulate extra insulin secretion, e.g. in obesity. Hyperinsulinaemia, in turn, down-regulates insulin receptors by increasing receptor internalization and degradation. Insulin probably also exerts other negative effects on insulin signalling at the post-receptor level [16]. The cellular lesions responsible for insulin resistance are considered in more detail later.

Dyslipidaemia

The dyslipidaemia of obesity and T2DM usually features increased VLDL-TG. The production of VLDL-TG is increased by insulin, and this effect appears to persist when other actions of insulin are reduced by insulin resistance [14]. Small dense LDL-C, which is the more atherogenic subclass of LDL-C, often is increased in association with insulin resistance and hyperinsulinaemia, together with a reduction in HDL-C [14]. Mechanisms to explain the association remain putative.

Hypertension

Raised blood pressure is commonly accompanied by reduced sensitivity to insulin and higher insulin concentrations. Also, hypertension is highly prevalent in obesity and T2DM [5]. Since hyperinsulinaemia has been implicated as a cause of increased renal sodium reabsorption, increased Na^+-H^+ exchange in arterial smooth muscle, and increased sympathetic vascular tone, this offers a mechanism to account for the link with hypertension.

Atherosclerosis

The dyslipidaemia and hypertension of Syndrome X are established risk factors for atherosclerosis [5]. It has also been suggested that hyperinsulinaemia might enhance atherogenesis via other mechanisms such as increased incorporation of cholesterol and fatty acids within the vascular wall and increased proliferation of vascular smooth muscle. However, it is questionable whether the extent of hyperinsulinaemia is sufficient to operate these mechanisms during the normal pathogenesis of atherosclerosis.

Pro-coagulant State

T2DM is an athero-thrombotic disease, and unstable plaques and clots in the coronary arteries are a major cause of the high incidence of myocardial infarctions. Among the pro-coagulant features of T2DM is an increased concentration of plasminogen activator inhibitor-1 (PAI-1), reducing the early lysis of clots [17]. This has been attributed tentatively to insulin resistance and hyperinsulinaemia [14].

Hyperuricaemia

Several features of Syndrome X appear to show more than a casual association with raised serum uric acid concentrations. Since insulin resistance has been reported to reduce urinary clearance of uric acid, hyperuricaemia might also shelter beneath the umbrella of Syndrome X [14].

Justifying a Syndrome

Thus, we have established that insulin resistance and compensatory hyperinsulinaemia are associated with a collection of risk factors for coronary heart disease, notably obesity, IGT or T2DM, dyslipidaemia, hypertension, atherosclerosis, and a pro-coagulant state. There is evidence to

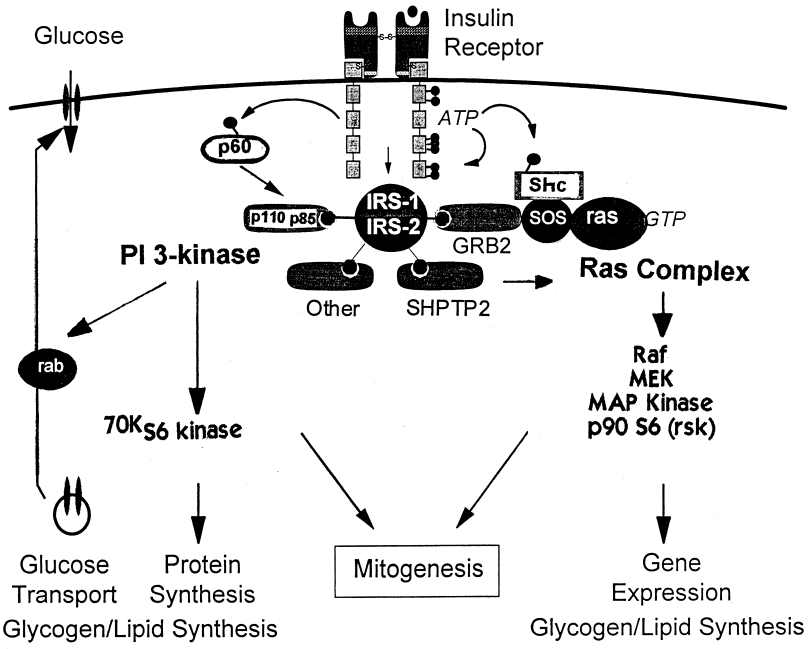

FIG. 3. Intracellular signalling pathways of insulin action. Reproduced, with permission, from Ref. 16. Copyright (1997) John Wiley & Sons Limited.

suggest that insulin resistance and/or hyperinsulinaemia could participate in the aetiology and pathogenesis of these conditions (though not exclusively), and there is justification for assembling them within the definition of a syndrome—"a distinct group of symptoms or signs which, associated together, form a characteristic clinical picture or entity" [18].

CELLULAR BASIS OF INSULIN RESISTANCE

The binding of insulin to its receptor in the plasma membrane instigates an array of intracellular signalling pathways (Fig. 3) [2, 16, 19–22]. These give rise to the diverse biological actions of insulin on enzymes, transporters, and transcription factors. Current knowledge of these pathways and their control is far from complete, but enough of the key components are now in place to allow us to engage in some educated speculation about the sites of insulin resistance.

Insulin Action

Insulin binds to the α-subunit of the insulin receptor, causing a conformational change in the β-subunits. This exposes the ATP binding domain and activates TKA and autophosphorylation at tyrosine residues of the β-subunit. This, in turn, mediates phosphorylation of tyrosines on a range of protein substrates, notably insulin receptor substrates 1 & 2 (IRS 1 & 2), *shc*, and various uncharacterised proteins [20]. The phosphotyrosines of these proteins bind to SH2 domains on other signalling kinases, which open the multiple pathways of insulin action. Different IRS proteins appear to channel signal transduction preferentially into different pathways. However, there is sufficient overlap that elimination of one IRS protein severely impairs but does not completely obliterate any pathway. The PI-3K pathway, which signals through PKB (Akt), is particularly important for the acute metabolic effects of insulin. It stimulates the translocation of GLUT4 glucose transporters into the plasma membrane, and, therefore, is crucial for insulin-stimulated glucose transport. The PI-3K pathway also participates in the acute regulation of glycogenesis, lipogenesis, and protein synthesis [2, 21, 22]. Interaction of IRS proteins with GRB2 and *shc* routes signal transduction into the *ras*-MAP pathway, which appears to be the main conduit to the nucleus.

Inherited and Acquired Disturbances

At the cellular level, the aetiology and pathogenesis of insulin resistance are almost certainly multifactorial in the typical forms of T2DM. Genetically determined levels of expression of key signalling elements within the pathways of insulin action confer a low level of insulin sensitivity in resistance-prone individuals. This is aggravated by acquired factors from the internal and external environment. Collectively, the genetic and environmentally induced disabilities create signalling bottlenecks of sufficient severity to substantially impair one or more major transduction pathways. A single gene mutation to explain insulin resistance in the vast majority of T2DM patients has not been identified, although abnormal levels of expression of several genes may be suspected [19].

An inherited predisposition to low insulin sensitivity is supported by the high concordance of insulin resistance and T2DM in twins, and by reports of lower insulin sensitivity in first-degree relatives of patients with T2DM. The role of environmental factors is supported by the progressive na-

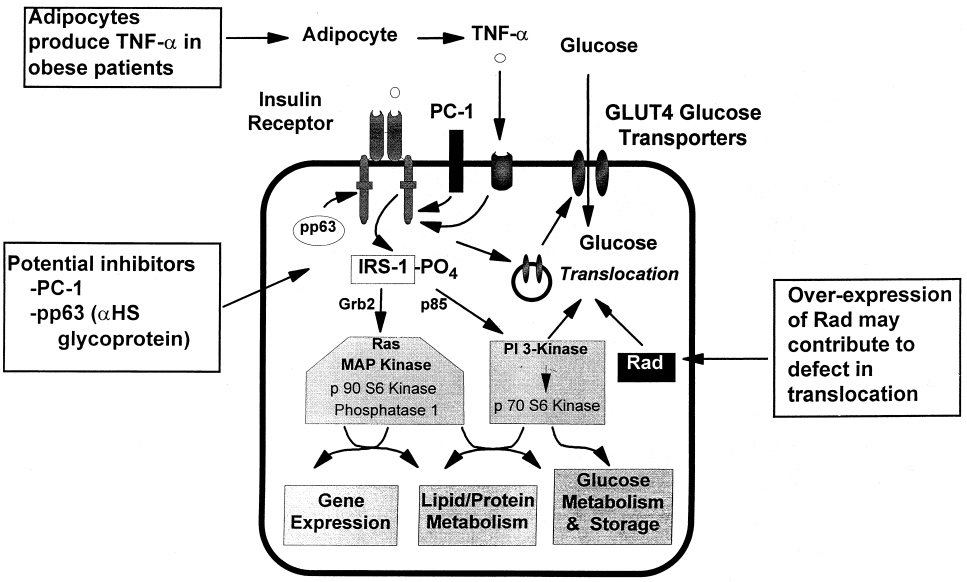

FIG. 4. Possible intracellular sites at which insulin resistance develops. Reproduced, with permission, from Ref. 16. Copyright (1997) John Wiley & Sons Limited.

ture of insulin resistance during the long prodromal accession to T2DM. Also, insulin resistance is reversed at least partially by alterations in the internal environment through dietary changes, weight loss, and drug therapies.

Sites of Insulin Resistance

Insulin resistance has been studied mainly in muscle, liver, and adipose tissue, where insulin exerts its main acute metabolic actions. The same general features appear to apply in all three tissues, although we have noted previously that different actions of insulin are affected to different extents in different insulin-resistant tissues.

The insulin receptor is structurally normal in T2DM, and the wealth of "spare" receptors ensures that a reduced population of insulin receptors in T2DM does not make a major contribution to insulin resistance in most patients. However, the variety of impaired actions of insulin in states of insulin resistance suggests that important rate-limiting constrictions are located early in the signal transduction process, before the different pathways are fully separated. Indeed, decreased phosphorylation and TKA of the insulin receptor β-subunit, decreased phosphorylation of IRS-1, and decreased activity of PI-3K have been observed in T2DM [16, 19].

Thus, disturbances at the level of insulin receptor signalling and receptor substrate activation undoubtedly provide a focus for the diversity of insulin resistance. How could these disturbances arise (Fig. 4)?

The unoccupied α-subunit of the insulin receptor normally exerts a negative effect on the TKA of the β-subunit, so the possibility that environmental agents or membrane components prevent conformational effects of insulin binding cannot be excluded. Site-directed mutagenesis of the β-subunit, which decreases the number of tyrosine residues phosphorylated, causes an approximately proportional decrease of insulin action [20]. This emphasises the detrimental consequences of subtle conformational adjustments to the β-subunit. Since different sites of β-subunit phosphorylation (of which there are at least 6) appear to affect the activation of different IRS proteins preferentially [20], it is theoretically possible for changes in the pattern of β-subunit phosphorylation to alter the balance of signal transduction into different post-receptor pathways.

Cross-talk between the insulin receptor, IGF1 receptor, and IRS proteins provides a further opportunity to alter the balance of IRS activation. Other receptors also appear to communicate directly or indirectly with IRS proteins or affect receptor phosphorylation (e.g. cytokines such as TNFα) [20]. Several putative inhibitors of receptor phosphorylation or IRS phosphorylation have been observed (e.g. PC1, pp63, and *rad*) [16]. Increased phosphatase-induced dephosphorylation of the insulin receptor or IRS proteins may be suspected in insulin resistance, since phosphatase inhibitors such as vanadium compounds can improve insulin action. Serine phosphorylation of the insulin receptor or IRS-1 inhibits signalling activity, and the action of TNFα has been reported recently to occur in this way [20].

Gene knockout studies in mice have established that the insulin receptor is essential for survival, whereas IRS-1 knockout causes insulin resistance and reduced growth, but not frank diabetes. Interestingly, IRS-2 knockout causes insulin resistance and reduced β-cell mass, resulting in severe (often fatal) diabetes. These observations concur with the possibility that reduced signalling through different IRS proteins could account for the heterogeneity of insulin resistance. The knockout experiments also remind

us that insulin resistance *plus* β-cell failure is consonant with T2DM.

In addition to disturbances of insulin signalling, insulin resistance may involve defects in the biological effectors of insulin action in some individuals. Gene polymorphisms associated with glycogen synthase and protein phosphatase 1 have been noted, and aberrations at the level of glucose transporter cycling, hexokinases, and other key mediators of insulin action remain under suspicion. Adverse effects of chronically raised glucose and lipid concentrations (glucotoxicity and lipotoxicity) in diabetes include the aggravation of insulin resistance [23, 24]. For example, hyperglycaemia has been reported to reduce GLUT4 production and divert glucose into the glucosamine-6-phosphate pathway [25]. The nutrient competition and insulin resistance potential of FFA have been considered previously. Other environmental factors such as raised concentrations of glucagon, glucocorticoids, catecholamines, and growth hormone regulate certain biological effectors of insulin in the opposite direction to insulin, and therefore extend their influence when insulin action is compromised. Thus, counter-regulatory hormones mostly antagonise the effects of insulin rather than causing insulin resistance *per se*, although the effects of glucocorticoids remain to be clarified in this respect.

Vascular Insulin Resistance

Although insulin resistance is portrayed as an underlying risk for coronary heart disease, its adverse effects on the cardiovascular system generally are ascribed to indirect influences via hyperinsulinaemia, dyslipidaemia, glucose intolerance, and athero-thrombotic effects. Vascular smooth muscle and endothelium possess an insulin signalling system, and insulin causes an acute vasodilatory effect, believed to occur via an insulin receptor–IRS–PI–3K–nitric oxide pathway [26]. Since the vasodilatory response appears to be reduced in insulin-resistant individuals, an insulin signalling lesion may occur in the vascular wall. Nevertheless, chronic hyperinsulinaemia, possibly acting via IGF-1, remains a controversial candidate for increased growth and division of vascular smooth muscle cells. The atherogenic potential of other components of Syndrome X has been described earlier. Interestingly, cardiac muscle does not appear to show a defect of insulin-stimulated glucose uptake when insulin resistance is evident in skeletal muscle [27].

TREATING INSULIN RESISTANCE

Given that insulin resistance is an early and pervading feature of typical forms of T2DM and other components of Syndrome X, it may be surprising that insulin resistance is not widely recognised as a clinical entity deserving its own therapeutic attention. Custom and practice have set a precedent for separately treating hyperglycaemia and each of the other components of Syndrome X as and when they become manifest with sufficient severity to be judged a clinical problem. In defence, we must concede that insulin resistance and Syndrome X have only come to the fore in the last decade. Also, there is no simple quantitative clinical test for insulin resistance, and there are few therapeutic options.

TABLE 3. Actions of antidiabetic drugs

Agents	Actions
Sulphonylureas and repaglinide	Increase insulin secretion
Metformin	Counter insulin resistance
Acarbose	Slow carbohydrate digestion
TZDs	Selectively increase insulin sensitivity
Insulin	Decrease hepatic glucose output and increase peripheral glucose utilization

Treating insulin resistance is not a simple matter of either giving more insulin to push the signalling pathways harder, or reducing insulin concentrations to reduce the consequences of hyperinsulinaemia. Either approach carries penalties. Giving more insulin can increase those actions of insulin that are impaired by the bottlenecks of signal transduction. However, creating the desired effect on a severely compromised pathway of insulin action (e.g. impaired glucose transport) can result in gross accentuation of other less desirable actions of insulin (e.g. lipogenesis, leading to hypertriglyceridaemia and obesity, or sodium retention, promoting hypertension). Indeed, excess insulin exacerbates insulin resistance at the receptor and post-receptor levels, as we have seen earlier. Thus, the detrimental effects of hyperinsulinaemia can be increased by insulin therapy, and there is the added serious risk that excess insulin will precipitate episodes of hypoglycaemia. Reducing insulin concentrations is a particular problem in T2DM. In the short term at least, this will further reduce vital metabolic actions of insulin and increase hyperglycaemia with its attendant clinical risks. Moreover, there is no guarantee that insulin resistance will subside to any clinically significant extent. Once established, insulin resistance usually can be reduced only by removing its current environmental components, and doing this is not necessarily compatible with maintaining glycaemic control.

Antidiabetic Drugs

For T2DM it is clearly a priority to provide effective control of the hyperglycaemia to reduce macro- and micro-vascular complications [28, 29]. The standard approach begins with dietary advice and exercise and healthy living advice, particularly designed to facilitate weight loss in the obese. These measures are ineffective in more than four-fifths of newly diagnosed T2DM patients, and the progressive nature of T2DM dictates that most patients require drug therapy. Oral agents, notably sulphonylureas, metformin, and acarbose, are instituted as monotherapy, and a new class—TZDs—has become available recently (Table 3). If adequate glycaemic control is not achieved with oral

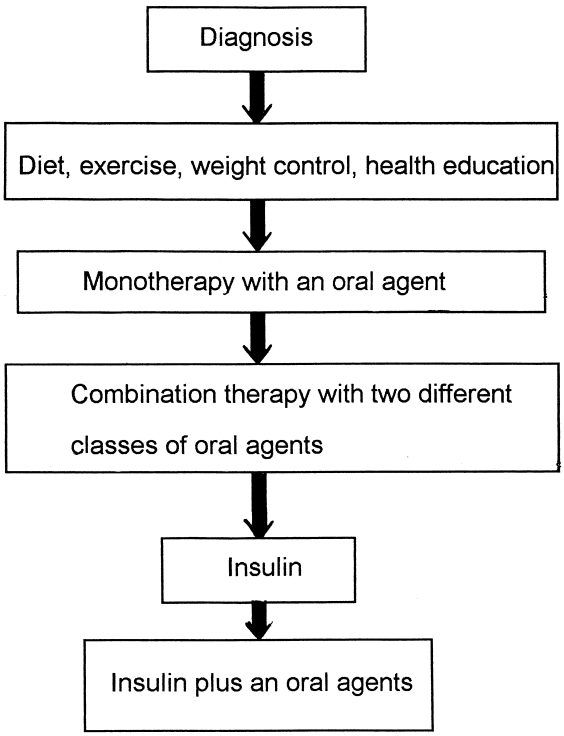

FIG. 5. Typical treatment paradigm for T2DM. When the patient exhibits inadequate glycaemic control, he/she is moved to the next treatment level. Patients with severe complications may be "jumped" immediately to insulin therapy.

monotherapy, then two different classes of oral drugs are used in combination (Fig. 5) [30]. Inadequate glycaemic control thereafter, which usually indicates severe β-cell failure and a marked reduction in β-cell mass, requires patients to be switched to insulin injections. Insulin therapy sometimes is supplemented with an oral agent to further improve glycaemic control and/or lower insulin dosage.

Acarbose competitively inhibits α-glucosidases in the brush border of the small intestine [31]. This slows carbohydrate digestion and lowers post-prandial hyperglycaemia. Although insulin resistance is not addressed directly, the blood glucose lowering effect will reduce glucotoxicity without increasing (and possibly decreasing) insulin concentrations, thereby reducing at least one facet of insulin resistance.

Sulphonylureas and a new short-acting insulin releaser (repaglinide) act directly on the islet β-cells to close ATP-sensitive K^+ channels, which stimulates insulin secretion [32, 33]. The efficacy of these agents depends on the presence of enough β-cells with sufficient functional reserve. Use of insulin-releasing agents is subject to reservations similar to those for insulin itself, particularly hyperinsulinaemia in the overweight. However, the endogenous insulin response to glucose is usually diminished in advanced states of T2DM. Thus, small drug-induced increases in insulin secretion, especially post-prandially, are clinically valuable to assist glycaemic control. Although one might expect that continuous pharmacological stimulation of β-cells could accelerate their demise, clinical experience rather suggests that once β-cell failure is set in train it proceeds steadily, irrespective of the treatment programme [12, 29].

Insulin therapy usually will provide effective glycaemic control when oral agents are inadequate [34]. However, insulin administration does not reinstate an entirely normal pattern of glycaemic control, and although glucotoxicity is decreased, the vicious spiral of insulin resistance and hyperinsulinaemia is not broken.

Metformin

Metformin is the only established antidiabetic drug that treats insulin resistance. Its glucose-lowering effect is mainly a consequence of reduced hepatic glucose output (gluconeogenesis and glycogenolysis) and increased insulin-stimulated glucose uptake and glycogenesis in skeletal muscle [35]. These effects involve both insulin-dependent and insulin-independent actions, although the latter are not a substitute for insulin. The different actions of metformin relate to its concentration in different tissues and give the drug a unique therapeutic portfolio. Metformin improves insulin action in tissues that are acutely sensitive to insulin by increasing insulin-stimulated insulin receptor phosphorylation and TKA [36]. The mechanism itself is not established, but may result from a membrane site of action of the drug. Metformin also appears to reinforce these actions through modest effects on glucose transport and glucose metabolism that are exerted independently of insulin. Another action of metformin is to reduce fatty acid oxidation in an apparently insulin-independent manner, which serves to redress the imbalance in the glucose–fatty acid cycle. A further important effect of metformin is increased glucose turnover, particularly in the splanchnic bed, which increases energy utilization and may account for the ability of the drug to stabilize or slightly reduce body weight.

Thus, metformin improves insulin sensitivity in liver and skeletal muscle without raising insulin concentrations. In fact, insulin concentrations tend to fall during chronic therapy [37]. Metformin also improves insulin action in adipose tissue, but obesity is offset by increased glucose turnover and lower insulin concentrations. Interestingly, metformin often improves the lipid profile in T2DM patients, and there are several reports of anti-thrombotic and anti-atherogenic effects. Accordingly, metformin offers a range of benefits that combat insulin resistance and various aspects of Syndrome X. Consistent with this, treatment regimens for T2DM that are initiated with metformin show a particularly favourable long-term reduction in morbidity and mortality from micro- and macrovascular complications [37]. Nevertheless, metformin must be used with care to exclude patients with renal insufficiency and guard against the potential risk of lactate accumulation.

TZDs

This new class of oral antidiabetic agents targets the nuclear PPARγ, which increases transcription of certain insulin-sensitive genes. Thus, TZDs provide a new approach to the treatment of insulin resistance [38]. Although their long-term clinical efficacy is still under investigation, their blood glucose-lowering activity appears to be increased in the presence of at least normal circulating levels of insulin. Hence, efficacy is greater in combination with insulin therapy or an oral insulin releaser. Consistent with the different cellular mechanisms of TZDs and metformin, preliminary clinical studies have suggested that the two classes of agents can be used in combination to achieve additive blood glucose-lowering activity.

PPARγ is expressed mainly in adipose tissue. It operates as a complex with the retinoid X receptor to enhance synthesis of lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein aP2, acyl CoA synthetase, malic enzyme, and the insulin-stimulated glucose transporter GLUT4. Thus, PPARγ mediates increased uptake of glucose and fatty acids, and lipogenesis in adipose tissue, and facilitates adipocyte differentiation. Whereas TZDs can thereby reduce circulating FFA and adjust the glucose–fatty acid cycle, it is anticipated that additional actions must occur to account for the clinical effects, particularly increased glucose utilization by skeletal muscle. PPARγ is expressed weakly in skeletal muscle, liver, and some other tissues, but the possibility of additional effects such as interactions with other nuclear receptors cannot be excluded. Clinical experience with TZDs is limited presently to one agent, troglitazone, and it is not yet clear whether this agent will be representative of the class. Potential benefits of TZDs against the range of components of Syndrome X await further study. However, if the PPARγ-mediated effects of TZDs are unimpeded, they are likely to increase adiposity, although insulin concentrations have been shown to fall. Safety issues surrounding liver toxicity and haemodilution remain to be fully appreciated, and effects of TZDs on PPARγ expression in the colon are uncertain. Thus, the potential for TZDs to counter insulin resistance is anticipated with cautious optimism.

Anti-obesity Agents

In obese T2DM patients, weight loss improves insulin sensitivity [5]. However, the effectiveness of this approach requires a sustained reduction in food intake and/or increased energy dissipation. The benefits of reduced energy intake are offset partially by increased metabolic efficiency, and may also be compromised by increased susceptibility to insulin-stimulated lipogenesis unless hyperinsulinaemia also is reduced. Although the use of anti-obesity agents does not have a universally accepted place in the treatment of overweight patients with T2DM, several anorexigenic agents have been shown to reduce insulin resistance and improve glycaemic control [38]. The new satiety-inducing serotonin–noradrenaline re-uptake inhibitor sibutramine may have potential in this respect [39], provided its propensity to increase heart rate and blood pressure in some individuals is duly respected. An intestinal lipase inhibitor (orlistat), which reduces fat digestion and absorption, is also now available to assist dietary management.

CONCLUSION

Insulin resistance, often in collusion with hyperinsulinaemia, has been identified as a link for the clustering together of obesity, IGT, and T2DM, and several other conditions that carry an increased risk of coronary heart disease, notably dyslipidaemia, hypertension, atherosclerosis, and a pro-coagulant state. The cluster constitutes Syndrome X.

Mechanisms through which this diverse collection of disorders are linked to insulin resistance and/or compensatory hyperinsulinaemia are now emerging. These highlight possible opportunities for treating insulin resistance in T2DM to reduce the morbidity and mortality of Syndrome X. Our growing knowledge of insulin resistance at the cellular level is indicating potential new therapeutic targets, and our experience to date suggests that early intervention against insulin resistance should become a primary strategy for the future treatment of T2DM.

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