New agents for Type 2 diabetes

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Current agents for the treatment of Type 2 diabetes mellitus improve the metabolic profile but do not reinstate normality. They also reduce chronic diabetic complications, but they do not eliminate them. Thus, new agents with novel actions are required to complement and extend the capabilities of existing treatments. Insulin resistance and beta-cell failure, which are crucial components in the pathogenesis of Type 2 diabetes, remain the underlying targets for new drugs. Recently introduced agents include a short-acting non-sulphonylurea insulin-releaser, repaglinide, which synchronizes insulin secretion with meal digestion in order to reduce post-prandial hyperglycaemia. The thiazolidinedione drugs, troglitazone, rosiglitazone and pioglitazone represent a new class of agonists for the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPAR\(\gamma\)). PPAR\(\gamma\) increases the transcription of certain insulin-sensitive genes, thereby improving insulin sensitivity. The intestinal lipase inhibitor orlistat and the satiety-inducer sibutramine are new weight-reducing agents that may benefit glycaemic control in obese Type 2 diabetes patients. Several further new insulin-releasing agents, and agents to retard carbohydrate digestion and modify lipid metabolism stand poised to enter the market. The extent to which they will benefit glycaemic control remains to be seen. However, the prospect of permanently arresting or reversing the progressive deterioration of Type 2 diabetes continues to evade therapeutic capture.

Key words: anti-diabetic drugs; insulin resistance; sulphonylureas; metformin; acarbose; thiazolidinediones.

Type 2 diabetes mellitus is a most difficult disease to define. The phenotype differs widely at presentation, from a slim patient with mild symptoms and complications at diagnosis, to the obese patient without symptoms or the obese patient with acute and intense symptoms including significant weight loss. It is unclear whether these presentations represent different genotypes, although it would seem difficult to persevere with the view that Type 2 diabetes is a homogeneous entity.

Between genotype and phenotype, translating the former into the latter, we have the pathogenesis of the condition, and it is fortunately that a modest degree of homogeneity of findings and views exists in this area. Few would disagree with the generality of statement that the pathogenesis of Type 2 diabetes receives a contribution from deficient insulin secretion and impaired insulin action.
THE PATHOGENESIS OF TYPE 2 DIABETES

The pathogenesis of the condition is considered here only as a means of identifying a logical approach to drug treatment. What follows is in no way a comprehensive review of the pathophysiology of Type 2 diabetes.

Insulin secretion in Type 2 diabetes

Insulin secretion is the end result of a complex cascade of actions within the beta-cell. Nutrient metabolism by the beta-cell increases ATP concentrations, which results in closure of the ATP-sensitive potassium channels. The decrease in potassium ion efflux leads to depolarization of the cell membrane, allowing the voltage-dependent influx of calcium ions. This in turn leads to the extrusion of insulin. There is no evidence to suggest that this series of steps required for insulin secretion differs qualitatively between normal subjects and Type 2 diabetes patients. Quantitatively, however, there is a major difference in the relation of stimulus to resultant secretion.

The interpretation of basal insulin levels and insulin secretion in response to stimuli such as oral or intravenous glucose in Type 2 diabetes patients is problematical. Some findings of elevated insulin levels in patients with Type 2 diabetes are not consistent with studies using highly specific insulin assays.1,2 Much of the apparent insulin measured by the non-specific antibodies used in radio-immunooassays can be accounted for by pro-insulin or split pro-insulin products, as shown when specific immunoradiometric assays are employed. Indeed, this reveals a particular beta-cell defect in pro-insulin processing, which can be identified in Type 2 diabetic patients and subjects at high risk of diabetes.

If intravenous glucose is used as a stimulus to insulin secretion, the situation is somewhat more clear. The normal response to intravenous glucose is biphasic.3 In Type 2 diabetes, first-phase insulin secretion is lost, but the second phase may be normal or even exaggerated. An inadequate first-phase insulin release inevitably results in hyperglycaemia and thus a greater stimulus to second-phase secretion. At a later stage of the disease, the second-phase response also becomes impaired.

Impaired insulin secretion could arise from either beta-cell dysfunction or reduced beta-cell mass. In animals, more than 85% of the islet tissue must be destroyed to give insulinopaenic diabetes, and it is likely therefore that both lesions co-exist. Of interest is the increasing recognition that hyperglycaemia per se may impair insulin secretion. Animal studies show islet damage following prolonged exposure to hyperglycaemia, which can be prevented by treatment4, and several studies show an improved insulin response after the correction of hyperglycaemia.

Insulin action in Type 2 diabetes

The first step in any action of insulin is its binding to a specific receptor.5 There follows instigation and amplification of the signal via second-messenger pathways that control the various membranal, cytoplasmic and genomic actions of insulin. Crucial for signal transmission is the activation of insulin receptor tyrosine kinase activity and the autophosphorylation of tyrosine residues in the receptor. Several intracellular proteins have been implicated as insulin receptor substrates, the phosphorylation of which directs the insulin signal into different intracellular pathways.
Decreased insulin action (insulin resistance) in diabetic patients was noted long ago by Himsworth. More recent techniques for studying this problem—forearm perfusion, quadruple infusions of glucose, insulin, adrenaline and propanalol, and the euglycaemic hyperinsulinaemic clamp technique—produce similar results. It is clear that in established Type 2 diabetes, there is insulin resistance, which is manifest as inadequately restrained hepatic glucose production, impaired peripheral glucose uptake and even increased lipolysis.

Glucose-mediated glucose uptake into cells is an interesting concept that has been relatively underexplored. By definition, glucose-mediated (insulin-independent) glucose uptake cannot be insulin resistant, yet it may be impaired in Type 2 diabetes.

The conclusion that insulin resistance is a feature of obesity, Type 2 diabetes and impaired glucose tolerance, as well as a host of other physiological and pathophysiological conditions, is overwhelming. The precise lesions that interrupt the intracellular signalling cascades in the majority of Type 2 diabetic patients are as yet unclear.

Causes of insulin resistance

It is important at this stage to consider, however briefly, causes of insulin resistance, since they might point to logical targets for therapy. Currently available evidence indicates that most presentations of insulin resistance in Type 2 diabetes are multifactorial in origin. Inherited susceptibility is conferred through the genetically determined levels of expression of signalling components within the pathways of insulin action within insulin-sensitive cells. This susceptibility to decreased insulin sensitivity is aggravated by environmental factors including diet (e.g. high fat) and a sedentary lifestyle. Insulin resistance results when the collective impositions of genetic susceptibility and environmental factors produce severe reductions in one or more signalling pathways, seriously compromising the biological actions of insulin.

Metabolites

The concept that certain circulating metabolites cause insulin resistance has been recognized for many years since the pioneering work of Randle et al. They observed that the addition of fatty acids or ketone bodies to the perfusion media of rat hearts significantly reduced glucose oxidation by the heart. This led to the suggestion of a cycle in which a fall in the blood glucose concentration, as occurs in starvation, leads to fatty acid mobilization from adipose tissue. The increase in fatty acid mobilization will lead to increased fatty acid oxidation and decreased glucose oxidation. Thus, in this competitive environment of fatty acids and glucose, it would seem a logical approach to attempt to enhance glucose uptake and oxidation by the manipulation of fatty acids, either decreasing their supply to the liver or reducing their intra-mitochondrial metabolism.

Hormones

The hormonal antagonism of insulin action induces insulin resistance. The prime counter-regulatory hormones—catecholamines, glucagon, cortisol and growth hormone—are clearly capable of insulin antagonism to the extent that diabetes occurs or diabetic control is severely compromised. Other hormones, for example, thyroxine, prolactin, ACTH and vasopressin, may have actions opposing insulin when
secreted in excess or when conditions allow. The manipulation of one or more hormones for therapeutic advantage is, however, fraught with difficulty and danger, and has been little explored.

TARGETING TREATMENT IN TYPE 2 DIABETES

An ideal approach to the treatment of patients with Type 2 diabetes would be to target the underlying defects in the pathophysiology of the condition. Later in this chapter, we discuss potential oral hypoglycaemic agents that are being developed with this aim in mind.

Drug development in the second half of the 20th century has, however, tended not to follow this entirely logical approach but might be best described as serendipitous. Currently available treatments for Type 2 diabetes are not exempt from this. Thus, sulphonylureas, with their insulin stimulatory and extra-pancreatic effects, were introduced at a time when the pathophysiology of Type 2 diabetes was less clear and, indeed, the disease was regarded as a somewhat milder form of Type 1 diabetes. Metformin, with a glucose-lowering effect achieved at the same time as lowering the circulating insulin level, was used long before there was the substantial weight of evidence pointing to insulin resistance as part of the pathophysiology.

An alternative approach, more suitable for the pragmatist, is to identify the biochemical picture, which is the end result of the pathogenesis, and targets therapy at any abnormalities. Of course, the biochemical abnormalities of diabetes are legion and extend far beyond glucose metabolism, but it is to that area of abnormality that we will restrict ourselves.

It is readily apparent that when glucose profiles are performed, two major abnormalities are detected (Figure 1). First, the fasting plasma glucose level is abnormally high in Type 2 diabetes, and this is well recognized as part of the diagnostic criteria of diabetes and as a target for treatment. Indeed, in the UK Prospective Diabetes Study (UKPDS), the fasting plasma glucose was the prime abnormality around which changes in treatment were made. Second, and somewhat under-emphasized, however, is the abnormality of an increased glucose excursion after meals. In terms of glucose control, these abnormalities represent targets for the development of effective treatments.

ESTABLISHED AGENTS

The progressive nature of Type 2 diabetes and the pursuit of good glycaemic control typically require a succession of pharmacological interventions. When dietary modification fails to control glycaemia, the remorseless progression begins from a single oral hypoglycaemic agent, via the addition of a second or more agents, to insulin given either alone or in combination with an oral agent (Figure 2). Given the heterogeneity of Type 2 diabetes and the consequent multifactorial pathophysiology, there is clearly a place for the use of different agents directed at the different manifestations of the disease. The main agents currently available and their actions are summarized in Table 1.

Unfortunately, none of the currently available agents is ideal (Table 2). The blood glucose-lowering effect of these agents is constrained by the natural history of the condition. An extensive loss of beta-cell mass, function or both can severely limit the
Figure 1. Blood glucose concentration throughout the day in 23 normal (non-diabetic) volunteers, 12 Type 2 diabetic patients on diet alone, 12 Type 2 diabetic patients taking a sulphonylurea, and 212 Type 2 diabetic patients taking metformin with or without a sulphonylurea (Su).
Figure 2. A typical algorithm for the treatment of Type 2 diabetes mellitus.

### Table 1. Actions of agents used in the treatment of Type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Slow rate of carbohydrate digestion</td>
</tr>
<tr>
<td>Sulphonylureas and repaglinide</td>
<td>Stimulate insulin secretion</td>
</tr>
<tr>
<td>Metformin</td>
<td>Reduce insulin resistance</td>
</tr>
<tr>
<td>Insulin</td>
<td>Increase peripheral glucose utilization</td>
</tr>
<tr>
<td></td>
<td>Decrease hepatic glucose output</td>
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### Table 2. Some limitations of current treatments for Type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Blood glucose-lowering efficacy</th>
<th>Side-effects and exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Mainly post-prandial, relatively modest effect</td>
<td>Poor tolerability due to gastrointestinal reactions</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>Generally good</td>
<td>Hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Mainly post-prandial</td>
<td>Possible hypoglycaemia</td>
</tr>
<tr>
<td>Metformin</td>
<td>Generally good, potential advantages against syndrome X</td>
<td>Poor renal and hepatic function, and any predisposition to hypoxic disease excluded: risk of lactic acidosis</td>
</tr>
<tr>
<td>Insulin</td>
<td>Good</td>
<td>Hypoglycaemia, weight gain, injections required</td>
</tr>
</tbody>
</table>
effectiveness of oral agents. Most tellingly, they do not reinstate an entirely normal metabolic state, and their use does not lead to the elimination of microvascular complications, even when used ‘intensively’.9–11 For example, in the UKPDS, more than 50% of patients intensively treated with either an oral agent or insulin showed poor control (a fasting plasma glucose level of over 7.8 mmol/l) within 6 years of diagnosis.12 Moreover, despite intensive drug treatment, 50% of patients had either died or experienced a serious clinical event such as a myocardial infarction, stroke, heart failure, amputation, blindness or proliferative retinopathy within 14 years.9 While hyperglycaemia was initially reduced by the introduction of intensive therapeutic regimens, no treatment prevented the relentless gradual deterioration in glycaemic control, believed to reflect the continued decline of the beta-cell. There is thus an urgent requirement for new agents that will alter the natural history of the disease.

RECENTLY INTRODUCED AGENTS

Drugs recently introduced for the treatment of diabetes are glimepiride, repaglinide and troglitazone (Table 3). In addition, two new anti-obesity agents (orlistat and sibutramine) have been introduced, which may be relevant to the treatment of Type 2 diabetes. Further agents, namely rosiglitazone, pioglitazone and miglitol are due to be introduced in the USA in 1999.

<table>
<thead>
<tr>
<th>Year introduced</th>
<th>Agent</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>1996</td>
<td>Glimepiride</td>
<td>Medium-to-long-acting sulphonylurea, stimulates insulin secretion</td>
</tr>
<tr>
<td>1997</td>
<td>Troglitazone</td>
<td>Long-acting PPARγ agonist, enhances insulin sensitivity</td>
</tr>
<tr>
<td>1998</td>
<td>Repaglinide</td>
<td>Rapid, short-acting insulin-releaser to control post-prandial hyperglycaemia</td>
</tr>
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</table>

* Additional new agents that have a place in the treatment of Type 2 diabetes are the anti-obesity agents orlistat and sibutramine, and the rapid, short-acting insulin analogue Lys-Pro insulin.

† Available in the USA and Japan.

Glimepiride

The sulphonylurea glimepiride (Figure 3) is a preparation designed to be taken once daily, having its maximum plasma glucose-lowering effect within about 4 hours.13,14 Glimepiride shows similar efficacy to glibenclamide, gliclazide and glipizide, reducing the HbA1c level by 1–2% (absolute) compared with placebo. However, glimepiride provokes a less marked stimulation of insulin secretion proportional to its effect upon plasma glucose, leading to the suggestion of a more potent extra-pancreatic effect. Thus, glimepiride enhanced insulin-stimulated glucose transport, glycogenesis and lipogenesis in isolated adipocytes associated with an increased translocation of GLUT-4 glucose transporters into the plasma membrane.14 Nevertheless, the main site of action of glimepiride is the pancreatic beta-cell, where the drug initiates insulin secretion by binding to the sulphonylurea receptor (SUR). This causes closure of the
ATP-sensitive potassium channel, depolarization and voltage-dependent calcium ion influx, with the activation of calcium-dependent regulatory proteins that direct exocytosis.

Glimepiride binds predominantly to a different part of the SUR from glibenclamide, that may reduce any effect on the potassium channels in vascular tissue. Tolerability is good, and the drug has been reported to cause fewer hypoglycaemic episodes than glibenclamide, especially during the initiation of therapy.

**Repaglinide**

Repaglinide is a member of the meglitinide family of benzoic acid derivatives, developed from the non-sulphonylurea moiety of glibenclamide (see Figure 3 above). It
is designed to be taken immediately before a meal so that insulin secretion coincides with the time of nutrient absorption, and its insulin secretory effect is of rapid onset and short duration. The drug binds to the SUR on pancreatic beta-cells, probably at the same site as, and also at a different site from, glibenclamide, to give a potent insulin-releasing effect. The prompt, yet brief time course of action results from its pharmacokinetic properties. Absorption is quick (peak concentration being achieved in less than 1 hour, with a bio-availability of more than 80%) and is followed by fast elimination (plasma half-life being less than 1 hour), mainly through hepatic metabolism and biliary excretion.

Preliminary reports of clinical trials in Type 2 diabetes indicate that repaglinide (0.5–4 mg with each main meal) reduces fasting plasma glucose concentration, reduces the HbA1c level and, in addition, reduces post-prandial glucose excursions. This latter effect, which is not seen with other sulphonylureas to a comparable extent, has led to the claim of a new class of drug, the post-prandial glucose regulator. Overall, however, the daily glucose-lowering effect of repaglinide is similar to that of glibenclamide. Like the sulphonylureas, repaglinide exerts an additive glucose-lowering effect with metformin. The drug is well tolerated, and its short duration of action points to less hypoglycaemia and particular value in those patients with irregular meal patterns.

The full potential of a rapidly acting, short-duration insulin-releaser has yet to be fully realized. The obvious comparison is with the four times daily, basal-bolus regimen for insulin in Type 1 diabetes. Against this lies a wealth of clinical experience that highlights the difficulty of persuading patients to take drugs three times daily.

**Troglitazone**

The thiazolidinedione drug troglitazone (Figure 4) is the first of a new class of oral agents that selectively enhance or partially mimic certain actions of insulin by
activating the peroxisome proliferator-activated receptor-gamma (PPAR\textsubscript{\textgamma}).\textsuperscript{20,21} PPAR\textsubscript{\textgamma} is a nuclear receptor expressed mainly in adipose tissue but to a small extent in skeletal muscle, liver and other tissues. It acts in a complex with the retinoid X receptor to increase the transcription of several insulin-sensitive genes. These include lipoprotein lipase, the fatty acid transporter protein, adipocyte fatty acid-binding protein, acyl CoA synthetase, malic enzyme and the glucose transporter isoform GLUT-4. Accordingly, thiazolidinediones increase the uptake of glucose and fatty acids by adipocytes, promoting lipogenesis and adipogenesis (Figure 5). They also increase glucose uptake, glycogenesis and glucose utilization by muscle tissue, and may reduce glucose production by the liver.\textsuperscript{22}

Troglitazone exerts a slowly generated blood glucose-lowering effect in Type 2 diabetes. A single daily dose titrated up to 600 mg achieves a maximum reduction in blood glucose by 2–3 months.\textsuperscript{23} As a monotherapy, this is typically modest, decreasing the HbA\textsubscript{1c} level by less than 1% (absolute).\textsuperscript{24} Thus, monotherapy with this agent is not widely recommended as a first choice. Efficacy appears to be greater in patients who still secrete significant amounts of insulin, for example those with a fasting plasma C-peptide level of more than 1.5 ng/ml. Indeed, when troglitazone is given in combination with a sulphonylurea, insulin or metformin, it has an additive effect with the other therapy, thus achieving greater efficacy.\textsuperscript{22,25}

A study of Type 2 patients on insulin (average 73 units per day) found that the addition of 200 and 600 mg per day troglitazone for 6 months reduced the HbA\textsubscript{1c} level from more than 9% to less than 8% in 30% and 57% of patients respectively (Figure 6). At the same time, the insulin dose was decreased (by 11% in the 200 mg group and 29% in the 600 mg group) in 15% and 42% of patients respectively.\textsuperscript{22} Although troglitazone is prone to causing weight gain, similar in extent to the sulphonylureas and insulin, it reduces serum concentrations of triglyceride, non-esterified fatty acids (NEFAs), and insulin.

\textbf{Figure 5.} Diagramatic representation of cellular mechanism of action of thiazolidinediones on an adipocyte. TZD = thiazolidinedione; PPAR\textsubscript{\textgamma} = peroxisome proliferator-activated receptor-gamma; RXR = retinoid X receptor; GLUT-4 = glucose transporter isoform 4; FATP = fatty acid transporter protein; aP2 = adipocyte fatty acid binding protein; LPL = lipoprotein lipase.
small increase in high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol may also occur, but the LDL-to-HDL ratio is generally unaltered. The increase in LDL cholesterol may be associated with an increase in particle size, which carries a lower cardiovascular risk. Preliminary reports have suggested that troglitazone may increase the concentration of lipoprotein (a), an independent risk factor for coronary heart disease. Conversely, the alpha-tocopherol moiety (vitamin E) of troglitazone could offer cardioprotective anti-oxidant properties.22

Pre-clinical studies with several thiazolidinediones have observed haemodilution, cardiomegaly and anaemia, which have not surfaced as a problem in the clinical use of troglitazone.26 In contrast, markedly raised liver enzymes and fatal episodes of hepatic failure have emerged as the serious adverse event with troglitazone use. Raised serum alanine aminotransferase (ALT/SGPT) to more than 3 times the upper limit of normal occurs in about 2% of patients, and greater than 1.5 times the upper limit of normal in about 5% of patients taking troglitazone. This is most likely to occur within the first 6 months of therapy, and generally appears to be reversible if the problem is identified and the drug withdrawn.27 Unfortunately, jaundice and severe hepatic failure can develop and, at the time of writing, 18 fatalities have been reported from 1.1 million patients starting troglitazone therapy during the first year of its use in the USA. From the case reports available, there is usually extensive hepatocellular damage without significant cholestasis. There is no apparent association with the drug’s hepatic metabolites or with hepatitis A, B or C.22

The hepatotoxicity represents an idiosyncratic response, and it is therefore not possible to identify patients at risk in advance. Clearly, immediate discontinuation of the drug is needed by those in whom a rise in liver enzymes is observed, and strict monitoring is mandatory. In the USA, the drug is contra-indicated in patients with a base-line ALT level of more than 1.5 times the upper limit of normal, ALT being monitored monthly for 8 months, bimonthly up to 1 year and periodically thereafter. Patients with an ALT level of 1.5–2.0 times the upper limit of normal should be monitored weekly and the drug stopped if there is any deterioration. It should be borne in mind that some of the patients suited to this drug are likely to have some degree of fatty liver and minor liver enzyme abnormalities.

Recent reports suggest that thiazolidinediones stimulate PPARγ in the colonic epithelium, thus increasing the frequency of colonic tumours in genetically susceptible mice. Conversely, the stimulation of PPARγ reduced the growth of human colon cancer cells in vitro and after transplantation into nude mice, leaving this issue unresolved.28
Weight-reducing agents

Successful weight-management programmes for obese Type 2 diabetic patients are notoriously difficult to achieve and are frequently abandoned in frustration. Nevertheless, there is convincing evidence that even modest weight reduction will increase insulin sensitivity, improve glycaemic control, improve lipid profiles and generally enhance prognosis. Two new anti-obesity agents may assist weight reduction in diabetic patients when used in conjunction with a prudent energy-restricted diet. They can also be used in combination with conventional anti-diabetic drugs.

Orlistat

Orlistat (Figure 7) is a gastrointestinal lipase inhibitor that binds to the active site of lipases, reducing triglyceride hydrolysis. This slows the digestion of dietary fat, causing a reduction by up to about 30% in the amount of fat absorbed. In a 1-year clinical trial, dietary restriction plus orlistat increased weight loss beyond that achieved by energy restriction alone by about 4 kg in obese non-diabetic subjects, but by only about 2 kg in diabetic patients. However, the overall weight loss (over 6 kg) with diet and orlistat afforded a useful improvement in glycaemic control (a decrease in HbA1c level of more than 0.8% absolute). Moreover, in patients with an HbA1c level of more than 8%, orlistat decreased HbA1c by 0.5% absolute. Orlistat also produced a small reduction in LDL cholesterol and triglyceride, as well as reducing waist circumference by 2.8 cm.

An increased elimination of fat in the faeces is inevitably associated with some unpleasant gastrointestinal events, including frequent defaecation, loose oily stools, diarrhoea and sometimes even faecal incontinence. These make the drug unacceptable to some patients. Minimizing the side-effects requires the patient to maintain a reduced fat intake. Although vitamin deficiencies during therapy have not been reported, it must be borne in mind that orlistat can potentially impair the absorption...
of fat-soluble vitamins. It can also alter the absorption of other medication, with a concomitant need for dose adjustment.

**Sibutramine**

Sibutramine (see Figure 7) is a serotonin and noradrenaline re-uptake inhibitor that acts centrally to enhance the post-ingestive satiety response. In rodents, sibutramine also increases energy expenditure through thermogenesis, via an enhanced sympathetic stimulation of brown adipose tissue.

One-year clinical trials in obese, non-diabetic subjects have shown that sibutramine (15 mg per day) increases weight loss by 4–5 kg beyond that obtained with an energy-restricted diet. There is a corresponding reduction in waist circumference and reduction in LDL cholesterol and triglyceride.

Preliminary observations in obese Type 2 diabetic patients indicate an improvement in glucose tolerance with a decrease in the HbA1c level of about 0.5% (absolute) with sibutramine. It should be recognized that sibutramine can cause a small increase in heart rate and blood pressure, but it is not addictive and has no known effect upon the heart valves or pulmonary vascular function.

**DESIGNING NEW AGENTS**

The specific cellular lesions responsible for insulin resistance and beta-cell failure in most 'common' forms of Type 2 diabetes remain to be clarified. Multiple aetiologies with consequent multiple pathogeneses are to be anticipated. Insulin resistance appears to emerge through the collective influence of several distinct disturbances in the cellular signalling pathways for insulin action. Beta-cell failure involves defective glucose sensing and impaired signal coupling to insulin biosynthesis and secretion in individual cells, as well as alterations in the turnover of the beta-cell population. Thus, a single, universally effective therapeutic agent is deemed unlikely. This in turn indicates that future approaches may utilize a number of therapeutic agents early in the disease rather than follow the sequence alluded to earlier of a single agent progressing to combination therapy late in the disease. Future developments will therefore be aimed at the different lesions of Type 2 diabetes or, where they remain unidentified, at the phenotypic expression of the underlying defect.

By the time of diagnosis of Type 2 diabetes, insulin resistance is usually well established, the first-phase insulin response to glucose has been lost, pro-insulin–insulin processing is defective, and other features of impending beta-cell failure are evident. Many of the cellular aberrations are sufficiently advanced that they can only be arrested or partially reversed but not normalized. Thus, the desirable properties of a new agent to restore normal metabolic control and mitigate diabetic complications (Table 4) must be tempered with the realization that some cellular faults in overt Type 2 diabetes are probably irreparable.

<table>
<thead>
<tr>
<th>Table 4. Desirable properties of new agents to treat Type 2 diabetes.</th>
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<tbody>
<tr>
<td>Blood glucose-lowering efficacy</td>
</tr>
<tr>
<td>Benefit other components of syndrome X</td>
</tr>
<tr>
<td>Treat fundamental defects of the disease</td>
</tr>
<tr>
<td>Complementary to existing agents</td>
</tr>
<tr>
<td>Safe, well tolerated and conducive to compliance</td>
</tr>
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</table>
From a practical point of view, agents are required that are capable of improving peripheral glucose disposal and reducing (but not completely inhibiting) hepatic glucose output. These goals can be achieved in a number of different ways, for example enhancing the insulin sensitivity of these major metabolic processes by increasing insulin secretion sufficiently to overcome the insulin resistance present, or by independent insulin-like effects.

The somewhat simple solution of raising the insulin level by enhancing its secretion has a superficial attraction that is lessened on closer consideration. First, the available insulin-releasing agents do not correct the glucose sensor defect and fail to increase insulin biosynthesis commensurate with secretion. Second, they fail to ameliorate the relentless decline in beta-cell function or mass that appears to be part of the natural history of Type 2 diabetes.27 Third, there is the problem of increasing insulin concentration and the impact of this upon tissues that do not display insulin resistance.37 Also, an attack upon insulin resistance alone is not likely to be overwhelmingly successful. Lipolysis is exquisitely sensitive to inhibition by insulin, and increasing sensitivity is likely to lead to difficulty in fat mobilization and consequently obesity. Thus, enhancing insulin sensitivity is likely to be counteracted by an increase in obesity. Another example of the treatment dilemma is that insulin increases hepatic triglyceride-rich very low-density lipoprotein synthesis, an excess of which is also a risk factor for macrovascular disease. Accordingly, any new treatments will be required to balance these issues.

NEW POTENTIAL ANTI-DIABETIC AGENTS

Many new agents have been identified that could potentially reduce glucotoxicity and at least partly address the fundamental problems of beta-cell failure and insulin resistance. While some are essentially modifications of existing drugs, others represent novel mechanistic approaches, but, to date, none would appear to offer an ideal or complete solution to the progressive nature of the disease process.40–42

Improving beta-cell function

Two short-acting insulin-releasers are well advanced in development: A4166 (nateglinide) and KAD-1229 (see Figure 3). Like repaglinide, their pharmacokinetic properties enable their rapid absorption and elimination. They act directly upon the SUR of the beta-cell membrane, causing closure of the ATP-sensitive potassium channels (Figure 8).43,44

Another short-acting insulin-releaser is the morpholinoguanidine BTS 67 582, that may act directly or indirectly on the SUR (Figure 8).45

Agents that stimulate insulin secretion by actions at the beta-cell membrane that are distal to glucose metabolism and ATP production do not appear to rectify the defect of glucose sensing and do not enhance insulin biosynthesis. Succinate esters, which stimulate energy production by beta-cells, have been shown to increase both the biosynthesis and secretion of insulin, but they have widespread effects upon metabolism throughout the body, which are likely to limit their application.46

Glucagon-like peptide 1 (GLP-1) 7–36 amide is an intestinal hormone that acts on the beta-cell via a cyclic AMP-dependent mechanism to enhance glucose-induced insulin secretion and biosynthesis (Figure 8). While GLP-1 provides an opportunity to amplify the effects of glucose on the beta-cell, it requires parenteral delivery, and its
short biological half-life has limited its therapeutic potential during clinical trials. Novel routes of GLP-1 delivery, such as sublingually or intranasally, agents that restrict GLP-1 degradation (e.g. dipeptidyl-peptidase IV inhibitors), and non-peptide GLP-1 receptor agonists are being explored as possible options. Whether GLP-1 exerts extra-pancreatic insulin-like effects in man is still unclear, and it remains uncertain whether there would be any clinically significant effect upon satiety and gastric emptying.

Other putative approaches to the ailing beta-cell include the use of α₂-adrenoceptor antagonists to relieve the tonic sympathetic suppression of insulin secretion, and inhibitors of type III phosphodiesterases to enhance cyclic AMP. Achieving a selective effect on the beta-cell has to date thwarted their application.

**Figure 8.** Schematic representation of a pancreatic beta-cell showing the main pathways controlling pro-insulin biosynthesis and insulin secretion. The sites of action of insulin-releasing agents are identified. PKA = protein kinase A; CAMP = cyclic adenosine monophosphate; ATP = adenosine triphosphate; IP₃ = inositol trisphosphate; PLC = phospholipase C; PKC = protein kinase C; GLP-1 = glucagon-like peptide-1; PDE = phosphodiesterase; SUR = sulphonylurea receptor; Kir = potassium inward rectifier; GLUT-2 = glucose transporter isoform 2; CCK = cholecystokinin; GIP = gastric inhibitory polypeptide.
Improving insulin action

The discovery that thiazolidinediones stimulate PPARγ, which in turn activates insulin-sensitive genes, has led to a succession of PPARγ agonists designed to improve insulin sensitivity. Both rosiglitazone and pioglitazone are advanced in development (see Figure 4), and related PPARγ agonists such as the isoxazolidinedione JTT-501 are under consideration. From the published information available, these agents appear to have qualitatively similar effects upon glucose metabolism to those of troglitazone, although there are considerable differences in potency. They have all been shown to reduce hyperglycaemia, hyperinsulinaemia and triglyceride concentrations in obese diabetic and glucose-intolerant animal models. However, it is not clear whether all the effects are consequent to the activation of PPARγ or whether some effects depend upon the non-thiazolidinedione moiety of the molecule.

The range of PPARγ agonists under development offers a selection of agents with differing pharmacokinetic features to provide choice in this approach to the treatment of insulin resistance. Preliminary data suggest that PPARγ agonists generally provide additive blood glucose-lowering efficacy in combination with other classes of oral agents, and reduce the insulin requirement. The impact upon body weight and the adverse event profiles await the test of widespread clinical usage.

Vanadium and trivalent chromium salts have been shown to improve glycaemic control in animal models and in clinical trials. Vanadium salts are phosphatase inhibitors that may enhance the action of insulin by slowing the dephosphorylation and inactivation of insulin receptors after insulin binding. Interestingly, vanadium salts have been shown to reduce hepatic glucose output and increase glucose disposal in Type 2 diabetes for several weeks after their administration has been discontinued. A question mark over toxicity has stimulated research into peroxo-vanadium salts with a higher potency that can be used in a lower dosage. Trivalent chromium has long been associated with improved glucose tolerance, but its mode of action is unclear. Nevertheless, its efficacy has been clearly demonstrated in several studies of patients with Type 2 diabetes.

Insulin-like growth factor-1 (IGF-1) has a low affinity for the insulin receptor and can weakly activate the post-receptor steps of the insulin signalling pathway via its interaction with the IGF-1 receptor. While this might not benefit ‘common’ presentations of Type 2 diabetes, it might assist patients with severe congenital insulin resistance caused by defects of the insulin receptor or in the early signalling steps.

Slowing carbohydrate absorption

Diets rich in natural vegetable fibre play an important part in the diabetic diet. They delay carbohydrate digestion by impeding the accessibility of digestive enzymes and reducing sugar diffusion to the surface of the intestinal mucosa. Fibre supplements such as guar gum have been reported to exaggerate these effects, although poor palatability and malabsorption reduce the tolerability of this approach.

Several new agents have been developed that compete with disaccharides and oligosaccharides for alpha-glucosidase enzymes in the brush border of intestinal epithelial cells. By inhibiting the action of the alpha-glucosidases, they slow the rate of carbohydrate digestion. The subsequent delay in glucose absorption smooths the entry of glucose into the circulation and reduces post-prandial glycaemia. New agents in this class, namely miglitol and voglibose, are in the image of acarbose (Figure 9). Their efficacy as monotherapy is generally held to be modest, but they may be used in
combination with any of the other classes of anti-diabetic agent. Drug titration is critical to minimize the side-effect of excessive flatulence.

The amylin analogue pramlintide has been shown to slow the rate of gastric emptying and thereby reduce post-prandial hyperglycaemia.\textsuperscript{63} It may also induce satiety. As it is a peptide, it needs to be delivered by subcutaneous injection, and its coincident use with insulin is under investigation.

### Modifying lipid metabolism

Adipose tissue is normally exquisitely sensitive to the anti-lipolytic effect of insulin. Insulin resistance allows an inappropriate release of NEFAs. These are used as an energy source by muscle and liver, sparing glucose consumption by muscle (the Randle cycle) and promoting hepatic gluconeogenesis. Hence disturbance of lipid metabolism has important consequences for hyperglycaemia.

Attempts to target NEFA reduction as a means of reducing hyperglycaemia have proved attractive but so far elusive. Anti-lipolytic agents such as acipimox (Figure 10) have shown some promise, but more potent and longer-acting derivatives are required before it can be ascertained with certainty that this approach will be successful.\textsuperscript{64} One confounding factor in this approach is the much-neglected hierarchy of insulin action.\textsuperscript{37} In attempting to link the suppression of lipolysis with the enhancement of glucose uptake into muscle, it must be borne in mind that the effects of insulin upon lipolysis and the effects of insulin upon glucose oxidation by muscle occur at vastly different timescales.
circulating insulin concentrations. Thus, it may not be entirely logical to involve insulin to attempt to link the two processes when devising therapies.

Lipid-lowering fibrates also reduce plasma NEFA levels sufficiently to confer a small improvement in glycaemic control, but this is rarely of significant clinical value.\(^65\) Agents that reduce the synthesis of fatty acids and triglycerides, for example benfluorex and long-chain dicarboxylic acids, may be helpful (Figure 10), and they may in addition have independent glucose-lowering activity.\(^66,67\)

Compounds that inhibit fatty acid oxidation have been examined extensively as potential anti-diabetic agents. The main approach has been to inhibit carnitine palmitoyl transferase-1, the rate-limiting enzyme for the transfer of long-chain fatty acids into the mitochondrion.\(^68\) While this effectively reduces hyperglycaemia, it is not readily reversed and will therefore temporarily prevent gluconeogenesis. Without the safety net of gluconeogenesis, the patient is vulnerable to hypoglycaemia.
The stimulation of $\beta_3$-adrenoceptors in adipose tissue increases lipolysis and reduces adipose mass. In obese-diabetic animal models, this is accompanied by an improvement in glycaemic control. Achieving complete selectivity for the $\beta_3$-receptor subtype has proved elusive, and the efficacy of putative agents similar to CL 316 243 has so far proved modest.\(^\text{69}\)

Other approaches

Other approaches to the control of hyperglycaemia that have been considered include glucagon receptor agonists, agents that directly stimulate glucose metabolism or inhibit gluconeogenic enzymes, and agents that inhibit glucose-6-phosphate activity.\(^\text{70-73}\) It is too early to say whether any of these lines are likely to be fruitful.

CONCLUSION

We may conclude on a note of optimism that several new agents have recently become available or are soon to become available, thus extending the range of therapy for Type 2 diabetes. While these will undoubtedly offer an enhanced opportunity to improve glycaemic control and hence diminish the number of complications, a cloud continues to cast its shadow over this field. None of the agents currently available, and probably none of those that we can foresee, appears to offer the potential for a sustained arrest or reversal of the pathogenic process of Type 2 diabetes once the condition is established.

REFERENCES


New agents for Type 2 diabetes


