# New Pharmacologic Agents for Diabetes

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**Current Diabetes Reports** 2001, **1**:119–126
Current Science Inc. ISSN 1534–4827
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New agents are being developed to address the underlying endocrinopathies and metabolic disturbances of type 2 diabetes. Stimulants of the nuclear peroxisome proliferator-activated receptor γ (PPARγ) are being identified to selectively improve insulin actions, and dual agonists of PPARγ and PPARα are being evaluated for enhanced control of hyperglycemia and dyslipidemia. Novel activators of insulin receptor phosphorylation and inhibitors of receptor dephosphorylation are offering encouraging leads for new agents. Analogues of glucagon-like peptide-1 that increase glucose-induced insulin secretion may additionally increase β-cell neogenesis from progenitor duct cells. The amylin analogue pramlintide, which suppresses glucagon secretion and reduces weight, is advancing in clinical trial. Direct stimulants of glucose utilization and partial inhibitors of gluconeogenesis are providing useful new drug templates. Thus, new pharmacologic approaches are emerging to treat the multiple lesions of type 2 diabetes.

## Introduction

Established and recently introduced oral agents for the treatment of type 2 diabetes offer substantial efficacy through a range of actions (Table 1). However they seldom reinstate and sustain normal glycemic control [1], leaving an urgent need for improved therapies. This article evaluates strategies for the future drug treatment of type 2 diabetes with agents other than insulins. It examines proposed sites of intervention and potential new pharmacologic approaches to improve glycemic control.

## Current Treatment Strategies

It is now abundantly clear that improved glycemic control translates into benefits against the chronic vascular complications of type 2 diabetes. Hence, current treatment strategies are designed to achieve the best possible glycemic control, consonant with the circumstances of the individual patient [2]. Approaches to the treatment process have been shaped by an appreciation that type 2 diabetes typically emerges through the composite effects of insulin resistance and β-cell dysfunction, often aggravated by the impositions of dyslipidemia [3]. Thus, early and intensive intervention against each of these underlying pathogenic features is advisably taken into account in the selection of drug therapy, often requiring combinations of two and possibly three differently acting agents. The choice and timing of therapies can also provide a balanced control of basal and postprandial components of the hyperglycemia. The latter component is presently receiving added attention following reports that it is strongly predictive of fatal vascular events [4].

Hyperglycemia is one of a constellation of risk factors for the macrovascular complications of type 2 diabetes, collectively encompassed within the insulin resistance (or metabolic) syndrome. All of these risk factors, which include body weight, lipids, blood pressure, and clotting status should be considered in the treatment process. In this context the concept of "treating to target" has emerged as a valuable, if somewhat arbitrary guide to the ideal, or least damaging, values to strive for [2].

## Future Treatment Strategies

Future treatment strategies for type 2 diabetes are expected to integrate existing and new agents against insulin resistance, β-cell failure, and dyslipidemia to improve the prospect of attaining and consolidating treatment targets (Fig. 1) [5,6•]. The treatment algorithm might therefore reflect more closely the natural history of type 2 diabetes, which presents different therapeutic challenges at different stages throughout its progression. Because insulin resistance has been implicated in the early metabolic disturbances of type 2 diabetes as well as many accompanying vascular risk factors, it may be appropriate to underpin the treatment process from the outset with agents that will improve or mimic the metabolic actions of insulin. As the various intracellular defects of insulin action become better characterized, additional agents to counter insulin resistance by new cellular mechanisms can be anticipated.

Incessant deterioration of β-cell function and loss of β-cell mass are crucial determinants of antidiabetic therapy, because a severe decline in insulin concentrations eventually precludes the effective use of current oral agents. It is still uncertain whether β-cell function or mass can be preserved by early and aggressive intervention with current agents. Intermittent (*eg*, prandial) rather than continual stimulation of β-cell function, early use of insulin therapy or agents to relieve insulin resistance, and unique β-cell

**Table 1. Oral agents for the treatment of type 2 diabetes**

| Agents | Examples of agents | Mode of action | Time of action |
|---|---|---|---|
| Alpha-glucosidase inhibitors | Acarbose, miglitol, voglibose | Slow rate of carbohydrate digestion | Mainly postprandial |
| Sulfonylureas | Glimepiride, glyburide,* glipizide, gliclazide, tolbutamide | Stimulate insulin secretion | Basal and postprandial |
| Meglitinides | Repaglinide, nateglinide | Stimulate insulin secretion: prandial (short-acting) | Mainly postprandial |
| Biguanide | Metformin | Improve insulin action | Basal and postprandial |
| Thiazolidinediones | Rosiglitazone, pioglitazone | Improve insulin action (PPARγ agonists) | Basal and postprandial |

*Glyburide is also known as glibenclamide. Fixed-dose combination tablets of glyburide with metformin are available.

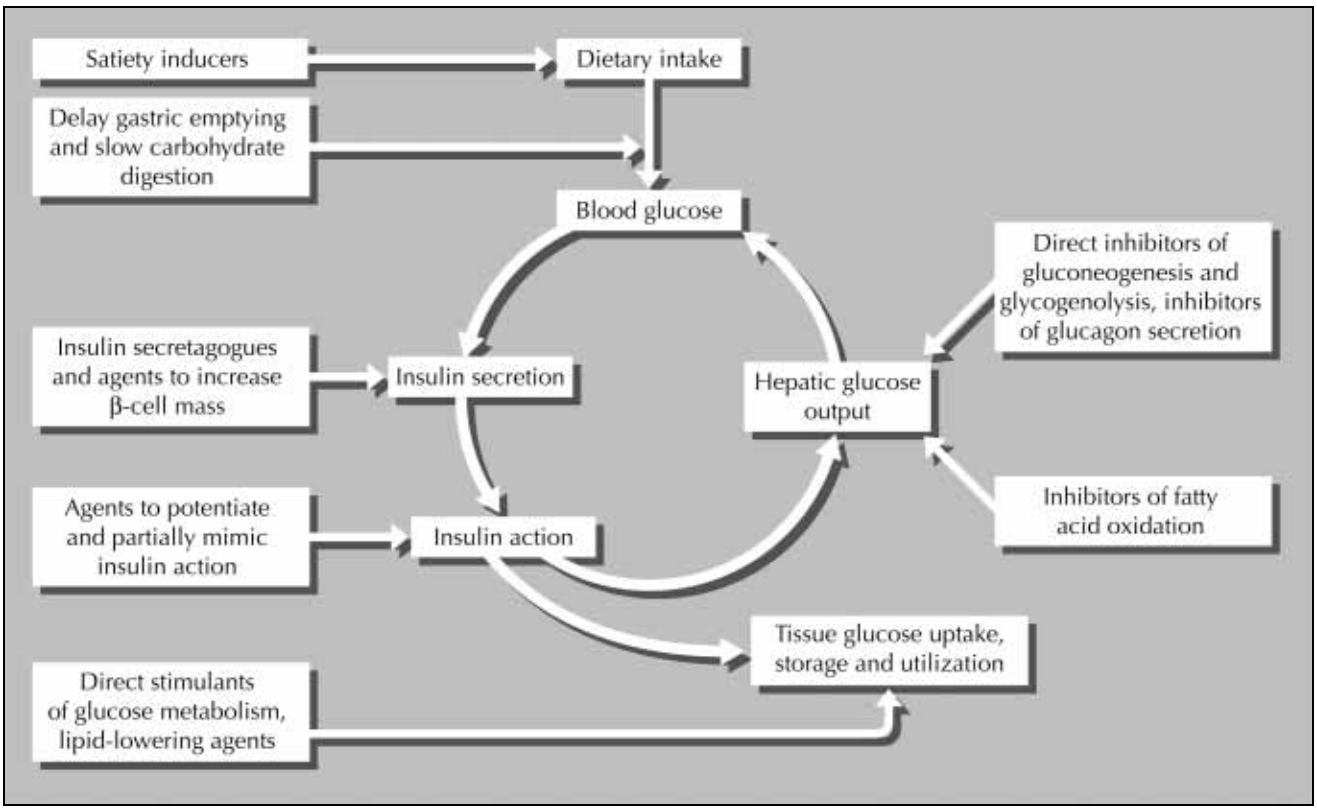


**Figure 1.** Potential intervention sites for new agents to treat type 2 diabetes.

effects of thiazolidinediones have all been mooted in this respect. An important future focus of antidiabetic therapy must be to prevent the apoptosis and promote replacement neogenesis of β cells. From a functional perspective it will be advantageous for new insulin secretagogues to act in a glucose-dependent manner to strongly counter postprandial hyperglycemia and obviate hypoglycemia. β-cell function would also be improved if such agents stimulated insulin biosynthesis commensurate with their stimulation of secretion. For the interim, substantial benefits can be gained by mixing oral agents with insulin, and taking advantage of the expanding range of insulin preparations, delivery routes, and devices.

In the future, dyslipidemia might be considered for primary intervention in type 2 diabetes. The lipotoxic effects of chronically raised fatty acid and triglyceride concentrations involve detrimental influences on insulin action and β-cell function, and independently increase vascular risk. Glucotoxicity also exacerbates insulin resistance and β-cell failure while promoting glycation and its clinical sequelae. Thus, agents that reduce blood glucose concentrations by any safe means could, in principle, serve a useful therapeutic purpose. Because the hyperglycemia of type 2 diabetes derives in part from excess hepatic glucose output, agents that suppress gluconeogenesis and glycogenolysis are suitable candidates, but they must not cause

**Table 2. Examples of PPARγ agonists and dual PPARγ and α agonists under investigation as potential new oral antidiabetic agents**

| PPARγ agonists | Manufacturer |
|---|---|
| Thiazolidinediones | |
| BM-13.1246 and BM-15.2054 | Boehringer Mannheim |
| CS-011/CI-1037* | Sankyo |
| MCC-555 | Mitsubishi Chemical |
| NC-2100 | Nipon Chemipharm |
| NIP-221* and NIP-223 | Nissan Chemical |
| T-174 | Tanabe |
| TZD-300512* | Takeda and Lilly |
| Nonthiazolidinediones | |
| BM-17.0744 | Boehringer Mannheim |
| GI-262570* | GlaxoSmithKline |
| GW-1929 | GlaxoSmithKline |
| L-764406 | Merck |
| Dual PPARγ and α agonists | |
| Thiazolidinediones | |
| DRF-2189 | Dr. Reddy's Research Foundation |
| KRP-297 | Kyorin Pharmaceutical |
| Nonthiazolidinediones | |
| JTT-501 | Japan Tobacco and Pharmacia |
| BMS-298585 | Bristol-Myers Squibb |
| AZ-242 | AstraZeneca |
| NN-622 | NovoNordisk |

*Peroxisome proliferator-activated receptor γ (PPARγ) agonists reported to significantly lower plasma triglycerides may be acting in part via weak PPARα agonism. Dual PPARγ and α agonists are selected for plasma triglyceride-lowering activity as well as improved insulin sensitivity and glucose-lowering.

extensive or irreversible inhibition of hepatic glucose output if hypoglycemia is to be avoided. Impaired glucose uptake and utilization by tissues that are acutely insulin-dependent could be addressed, at least in part, by agents that directly stimulate these functions.

Weight loss in overweight type 2 diabetic patients can effectively reduce hyperglycemia [2]. There is an opportunity for greater use of safe antiobesity agents as initial intervention. In anticipation that rigorous control of hypertension and other modifiable cardiovascular risk factors will be routine in type 2 patients, new antidiabetic agents should be compatible with existing standard treatments and prophylactic measures against these risks.

## Addressing Insulin Resistance

Several agents are in development to improve or mimic insulin action. Particular research interest is presently focused on stimulants of the nuclear peroxisome proliferator-activated receptor γ (PPARγ). However, clinical studies with most of these compounds are in their early stages and a new product is not imminently poised to enter the market.

### PPARγ agonists

Stimulating PPARγ is now an established route to improve insulin sensitivity in type 2 diabetes, as illustrated by the thiazolidinediones in present clinical use, namely rosiglitazone and pioglitazone [7•]. PPARγ is expressed mainly in adipose tissue where it promotes adipogenesis, lipogenesis, and glucose uptake. Stimulation of PPARγ causes transcription of certain insulin-sensitive genes such as lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid–binding protein (aP2), fatty acyl-CoA synthase, malic enzyme, glucokinase, phospho*enol*pyruvate carboxykinase, and glucose transporter isoform-4 (Glut-4) [8,9]. The blood glucose-lowering effect of PPARγ agonists is at least partly due to increased adipocyte lipogenesis. This decreases circulating concentrations of nonesterified fatty acids, which resets the glucose-fatty acid (Randle) cycle to favor glucose utilization by muscle [10]. PPARγ agonists also improve insulin action by reducing adipocyte production of the cytokine tumor necrosis factor α (TNFα) and the hormone resistin, as well as activating phosphatidylinositol 3-kinase (PI3K) and possibly reducing leptin levels [10–12]. However, PPARγ agonists remain effective in animal models that are almost devoid of adipose tissue, emphasizing the importance of effects on other tissues [13]. PPARγ is expressed in skeletal muscle and liver, and direct actions of PPARγ agonists in these tissues could contribute to the blood glucose-lowering effect [14,15]. However, the actions of PPARγ in these tissues have yet to be resolved [16•]. Hypomagnesemia is believed to aggravate insulin resistance in some type 2 diabetic individuals, and PPARγ agonists have been reported to address this problem [17]. Also, some actions of thiazolidinedione PPARγ agonists occur too rapidly to be explained by a genomic action, suggesting that some effects are independent of the PPARγ receptor [10].

Many new PPARγ agonists are reported to be under investigation as potential antidiabetic agents (Table 2). Some of these are thiazolidinediones [14,17–23], but there are several nonthiazolidinedione PPARγ agonists [24–27]. The thiazolidinediones have previously shown a close positive correlation between their binding affinity for PPARγ and their blood glucose-lowering efficacy in animal models of type 2 diabetes [28]. However, several new thiazolidinediones with weak PPARγ agonism, such as MCC-555 and NC-2100, have shown potent glucose-lowering activity in glucose intolerant and type 2 diabetic animal models [19,20]. This indicates that variations in the nonthiazolidinedione moiety make an important contribution to the glucose-lowering efficacy. This could partly reflect the structure of the ligand-binding domain of PPARγ, which is sufficiently large to allow the different PPARγ agonists to produce slightly different conformational changes to the receptor. This in turn will alter the recruitment of coactivators that will modify the selection of genes that are transcribed [29,30]. Thus, the actions of PPARγ agonists can be modified by structural changes to the nonthiazolidinedione part of the molecule for customized selection of the required therapeutic profile.

Although PPARγ is expressed by pancreatic β cells, most studies have shown little or no direct effect of thiazolidinediones on total insulin secretion [7•,10]. However, thiazolidinediones may improve the pattern of insulin secretion and the morphology of the pancreatic islets in diabetic states, and defer or prevent β-cell hyperplasia while restoring granulation in animal models [31,32]. Interestingly, the peroxisome proliferator response element has been identified in the promoter of the *GLUT2* gene, which is expressed in β cells [33]. The prospect that PPARγ agonists might limit detrimental changes to β cells in patients with impaired glucose tolerance raises the possibility of a preventative application for these agents.

Some further potentially advantageous effects of thiazolidinedione PPARγ agonists include vascular protection through decreased platelet aggregation, increased fibrinolysis, and possibly an indirect decrease in plasminogen activator inhibitor-1 [7•]. Independent effects on glomerular structure, which reduce nephropathic symptoms, have also been reported [32,34]. Additionally, thiazolidinediones have been ascribed with putative effects on inflammation, atherogenesis, and tumor proliferation [35]. It is pertinent to note that the idiosyncratic liver toxicity that occurred during use of the first clinically available thiazolidinedione, troglitazone, has not been observed with later thiazolidinediones in clinical use, but preclinical tests may not discriminate the potential for hepatotoxicity in humans [36]. PPARγ agonists are prone to cause fluid retention [7•,10], and newer agents should be chosen to minimize this effect. Weight gain is another unwanted effect of PPARγ stimulation [7•,10], but weaker agonists, which also increase the expression of uncoupling proteins (and combination with a PPARα or a retinoid X receptor [RXR] agonist), could be helpful in this respect [20].

Thiazolidinedione PPARγ agonists have consistently reduced circulating nonesterified fatty acids, but effects on other lipid parameters are variable. Limited evidence from the clinical use of thiazolidinediones suggests that the diversity of lipid changes probably reflects the structure of the nonthiazolidinedione part of the molecule and the pretreatment lipid profile of the patient [7•,8–10]. In hyperlipidemic patients, circulating total triglycerides can decline, and cell culture studies indicate increased lipid oxidation, implying reduced fat deposition in muscle [16•]. Low-density lipoprotein (LDL) cholesterol and high-density lipoprotein cholesterol may increase during initial treatment with a thiazolidinedione, although the ratio of these fractions is little changed. Preliminary reports indicate that LDL cholesterol may return to pretreatment levels during chronic use.

### Dual PPARγ and PPARα agonists

Peroxisome proliferator-activated receptor α is expressed in muscle, liver, and various other tissues where it promotes the oxidation of fatty acids through increased transcription of enzymes such as acyl-CoA synthase, acyl-CoA oxidase, and thiolase [9]. Stimulation of PPARα (*eg*, by fibrates) is an established mechanism to lower circulating lipid concentrations. Several established PPARγ agonists are known to bind PPARα with low affinity, and enhanced stimulation of PPARα is associated with a greater lipid-lowering effect. Hence, dual agonists of PPARγ and PPARα are now seen as an opportunity to achieve both glucose- and lipid-lowering effects (Table 2). Several thiazolidinedione and nonthiazolidinedione compounds are receiving particular attention in this respect [37–39]. It will be important for such agents to selectively balance the two agonistic effects for optimal therapeutic efficacy at the same circulating concentration.

### Dual PPARγ and RXR agonists

Peroxisome proliferator-activated receptor γ exists as a heterodimer with the RXR, and coactivation of PPARγ and RXR has been reported to cause an additive or synergistic improvement of insulin action in skeletal muscle compared with stimulation of PPARγ alone [16•]. Stimulating RXR alone may be ineffective or produce variable effects such as reduced food intake, reduced body weight gain, increased expression of uncoupling proteins, and increased expression of the p85a subunit of PI3K [40–42]. Each of these effects could facilitate insulin action, but they may depend on structural components of the RXR agonist that do not actually bind to the RXR ligand-binding site of the RXR receptor. Thus, binding of an RXR agonist to the RXR may be accompanied by interactions of the agonist with other regions of the receptor, and this will alter the profile of genes transcribed. Thus, there is a potential for selective RXR agonists and dual PPARγ-RXR agonists.

### Mineral enhancers of insulin action

Several mineral supplements, notably magnesium and chromium, will improve insulin action in patients who are deficient in these minerals. The roles of these minerals in insulin signaling and energy metabolism have been reviewed previously [5].

Salts of vanadium, molybdenum, selenium, and tungsten can improve or mimic some metabolic actions of insulin in isolated cells and tissues. They also improve glycemic control in insulin-deficient and hyperinsulinemic animal models of diabetes, suggesting a possible therapeutic use [43–47]. Vanadium salts appear to prolong insulin receptor signaling by inhibiting phosphatases that dephosphorylate and deactivate the tyrosine kinase activity of the β subunit. They also improve muscle glucose uptake and suppress hepatic glucose output by other uncharacterized mechanisms that bypass the known pathways of insulin action—hence, attracting the label of insulin mimetic agents [44]. Concerns about toxicity and bioavailability of vanadium salts may be allayed by highly potent peroxovanadium salts and other organic vanadium complexes [6•,43,44]. Molybdenum and tungsten salts act predominantly to decrease hepatic glucose output, but the mecha-

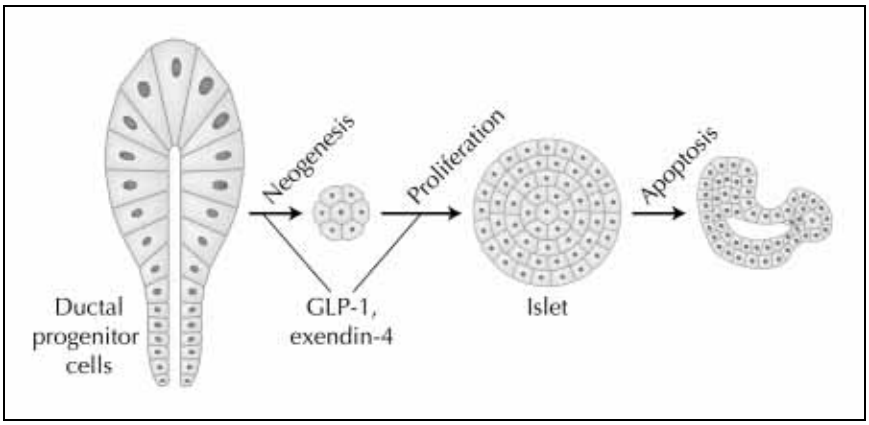


**Figure 2.** Actions of glucagon-like peptide-1 (GLP-1) analogues to promote neogenesis and proliferation of pancreatic β cells.

nism of action of these salts and selenium salts remains to be established [45–47].

**Other insulin action enhancers**

One approach to overcome the multiple postreceptor signaling defects of insulin resistance [48] has been to interrupt the intracellular negative feedback effects of downstream signals such as PI3K and protein kinase B, which normally cause a temporary suppression of subsequent insulin signaling [49]. For example, like vanadium salts, various compounds such as benzonaphthofurans and thiophenes inhibit protein tyrosine phosphatase 1B, improving insulin action in insulin-resistant obese-diabetic animals [50]. The tyrosine kinase activity of the insulin receptor and insulin receptor substrates is inhibited by serine-threonine phosphorylation. Certain isoforms of protein kinase C (PKC) have been implicated in this process, providing a potential intervention target [51].

Direct stimulation of insulin receptor tyrosine kinase activity has recently been reported using metabolite (LY783281) from a Pseudomassaria fungus [52] and a synthetic molecule (TLK16998) [53•]. Both compounds appear to promote phosphorylation of the intracellular segment of the β subunit of the insulin receptor. Other agents that enhance or partially mimic insulin-signaling intermediates by undefined mechanisms could also provide leads for the development of new antidiabetic agents, as considered elsewhere [5,6•,54–56].

## Addressing β-cell Dysfunction

Although current insulin-releasing agents make an important contribution to the treatment of type 2 diabetes, they do not actually reinstate normality of the glucose-sensing process or the pathways of insulin production by individual β cells. Also, they do not restore the diminishing β-cell mass. Several agents in development promise to address these issues.

**GLP-1, exendin-4, and DPP-IV inhibitors**

The intestinal hormone glucagon-like peptide-1 (GLP-1) is released during meal digestion and potentiates nutrient-induced insulin secretion and proinsulin biosynthesis [57•]. It acts on the β cell via specific receptors coupled to the adenylate cyclase-cAMP protein kinase A (PKA) pathway and other intracellular mediators. Release of endogenous GLP-1 is reduced in diabetic states [58], and the ability of GLP-1 to enhance predominantly glucose-stimulated insulin secretion facilitates the control of postprandial hyperglycemia without increased risk of hypoglycemia. GLP-1 increases both the acute and chronic phases of glucose-stimulated insulin secretion, and partly restores the normal pulsatile pattern of insulin secretion [57•,59]. This is complemented by increased β-cell granulation, resulting from increased stimulation of proinsulin biosynthesis through PKA-dependent and independent mechanisms [60]. (It is noteworthy that meglitinide insulin secretagogues are also used to target postprandial hyperglycemia, but they act on the β cell in a similar manner to sulfonylureas, which "induce" rather than "potentiate" insulin secretion [5]).

The main biologically active form of GLP-1 (the truncated 7-36 amide) and various analogues are being assessed as potential antidiabetic drugs. Receptors for GLP-1 are widely distributed, and GLP-1 exerts a satiety-inducing effect, reduces glucagon secretion, and slows gastric emptying [57•]. Animal studies have suggested that GLP-1 has further extra-pancreatic effects that improve insulin action, but this has not been a consistent finding in human type 2 diabetes [61]. A recent study in type 1 patients indicated that GLP-1 improves insulin-mediated peripheral glucose disposal but may reduce insulin-induced suppression of hepatic glucose output [62].

A particularly attractive and novel feature of GLP-1 and its analogues is increased β-cell neogenesis, growth, and differentiation [63•,64,65]. GLP-1 increases expression of the transcription factor PDX-1 (IDX-1) that is involved in the early differentiation of β cells from ductal progenitor cells, and the proliferation of established β cells (Fig. 2). PDX-1 is also involved in glucose-mediated gene transcription; thus, GLP-1 offers a possible means to recruit progenitor cells into β cells and to expand the β-cell mass while improving glucose-mediated proinsulin biosynthesis and glucose-stimulated insulin secretion.

Glucagon-like peptide-1 is a short-acting peptide. In clinical trials it has been delivered by either intravenous infusion or repeated subcutaneous injection. The short biological half-life (about 1 minute) is largely due to inactivation by the circulating enzyme dipeptidylpeptidase-IV (DPP-IV), which cleaves the N-terminal dipeptide. Orally effective inhibitors of this enzyme are now under consideration to enhance the activity of endogenous and exogenously administered GLP-1 [66], as well as analogues that are resistant to DPP-IV [67]. A long-acting analogue of GLP-1 is exendin-4, a 39 amino acid peptide from the venom of the Gila monster (*Heloderma suspectum*), having 52% sequence homology with GLP-1. Exendin-4 activates GLP-1 receptors and produces similar biological effects, making it an interesting prototype drug. To circumvent the problem of repeated parenteral delivery, depot implants of GLP-1 analogues are being considered, and buccal and oral delivery of GLP-1 analogues have recently been reported [67].

**Other insulin releasers**

Stimulation of insulin release using phosphodiesterase inhibitors, α-2 adrenoceptor antagonists, or succinate esters has been difficult to exploit therapeutically, because the actions of these agents are not specific to the β cell [5,6•]. Recognition that imidazoline compounds can stimulate insulin secretion by closure of Kir 6.2 channels and activation of intracellular calcium mobilization has prompted exploration of the therapeutic potential of these types of compounds. A recently described imidazoline, BL11282, enhanced glucose-induced insulin secretion without affecting Kir 6.2 channels, possibly by activating PKA and PKC [68].

**Direct modulators of metabolism**

A selection of substances that directly stimulate glucose uptake and metabolism or suppress gluconeogenesis, and might be considered as potential leads for the development of new antidiabetic agents, is reviewed elsewhere [5]. Among these substances aminoimidazole carbox-amide ribonucleotide (AICAR), a ribofuranoside activator of AMP-activated protein kinase, is interesting because it inhibits (by inhibiting fructose-1, 6-bisphosphatase) hepatic gluconeogenesis and increases the expression of Glut-4 and hexokinase in muscle [69]. Inhibitors of glucose-6 phosphatase (G-6-Pase) translocase and G-6-Pase catalytic protein are under investigation as novel routes for the suppression of excess hepatic glucose output in type 2 diabetes [70,71]. Glycogen phosphorylase inhibitors provide another potentially useful means to suppress hepatic glucose output [72].

Reactive oxygen species are believed to contribute to the development of insulin resistance, but a beneficial effect of antioxidants in the treatment of type 2 diabetes has not been demonstrated. Recently, the antioxidant lipoic acid was shown to prevent insulin resistance caused by oxidative stress in cultured muscle cells [73]. Lipoic acid has been reported to improve insulin sensitivity in type 2 diabetic patients, although this could be due to other actions: for example, lipoic acid is a co-factor for mitochondrial dehydrogenases and could therefore facilitate glucose oxidation. Lipoic acid has also been reported to enhance postreceptor insulin signaling [73]. Interestingly, lipoic acid is being considered as a treatment for diabetic neuropathy.

Manipulations of lipid metabolism provide opportunities to improve the circulating lipid profile and reduce hyperglycemia [5]. Agents that suppress fatty acid oxidation have received considerable interest in this respect. By reducing the supply of energy for gluconeogenesis and by facilitating peripheral glucose utilization, inhibitors of fatty acid oxidation can effectively lower blood glucose concentrations. However, it has been difficult to titrate the dosages of drugs acting in this manner to avoid episodes of hypoglycemia [5]. The concept of suppressing fatty acid oxidation has also been called into question by evidence that this causes intracellular accumulation of lipids, which then aggravates insulin resistance [74].

## Antiobesity agents

The antiobesity agent sibutramine, which induces satiety via serotonin norepinephrine reuptake inhibition (SNRI), may improve glycemic control by mechanisms other than weight loss in obese type 2 diabetic patients. The primary amine metabolite of sibutramine increases basal and insulin-stimulated glucose uptake by cultured muscle cells via a mechanism that is independent of PI3K and unrelated to SNRI activity [75].

Developing a potent and highly specific $\beta_3$-adrenoceptor agonist as an antiobesity agent has been hampered by differences in receptor structure between rodents and humans. $\beta_3$ agonists promote lipolysis and increase energy expenditure by thermogenesis through increased expression of uncoupling proteins (UCPs), principally UCP-1, in brown and white adipose tissue. The $\beta_3$ agonist AJ-9677 has recently been shown to decrease expression of TNFα and increase expression of Glut-4 in adipose tissue associated with reduced hyperglycemia and improved insulin action in obese-diabetic animals [76].

The amylin analogue pramlintide produces a range of beneficial actions to improve glycemic control in type 1 and type 2 diabetic patients [77]. These include reduced appetite and weight reduction, suppression of glucagon secretion, and slowing of gastric emptying. Trials have delivered the peptide by injection immediately before meals, but it should be possible to devise preparations for administration by other routes.

## Conclusions

The multiple endocrine and metabolic disturbances that constitute type 2 diabetes provide many potential opportunities for intervention by new oral antidiabetic agents.

Although it would be advantageous to address insulin resistance and β-cell dysfunction as the primary endocrinopathies, any safe interventions that will improve glycemic control deserve consideration in the quest for future generations of antidiabetic drugs.

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