Diabetes and insulin resistance associated disorders: Disease and the therapy

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An overwhelming increase in metabolic syndrome, i.e., obesity, insulin resistance and dyslipidemia has led to type 2 or insulin-resistant diabetes mellitus assuming epidemic proportions. Currently, there are five distinct classes of oral hypoglycemic agents available. These are – sulphonylureas, meglitinides, biguanides, thiazolidinediones and alpha-glucosidase inhibitors. United Kingdom Prospective Diabetes Study has shown that, normalization of hyperglycemia can prevent majority of diabetes complications. Unfortunately, the current treatment regime does not adequately normalize the blood glucose level in type 2 diabetes patients. With the growing awareness of the phenomenon of insulin resistance, current research efforts are focused on insulin sensitizers, insulin secretagogues and inhibitors of hepatic glucose output. This review provides an overview of the available treatment options and the trends in diabetes research.

DIABETES is a major health problem; approximately 5% of the world's population suffers from diabetes. Independent forecasters have suggested that the global prevalence of the disease will increase from 150 m in 2000 to 220 m in 2010 and to 300 m by 2025. Diabetes is a disease where the body either produces little insulin/ceases to produce insulin, or becomes progressively resistant to its action. The disease has been classified as type 1 and type 2. Type 1 is prevalent in 10% of diabetes patients, and is an autoimmune disease of the pancreas, which causes decreased insulin secretion. On the other hand, Type 2 is prevalent in 90% of the patients, where insulin resistance and abnormal carbohydrate metabolism are considered to be the causative factors. Analysts predict that a major increase in the incidence of the disease will be driven by type 2 diabetes. According to a recent estimate, by year 2025, the global cost of treating diabetes and its complications could reach US$ 1 trillion annually.

Type 2 diabetes mellitus (DM) is a heterogeneous disease with both genetic and environmental causative factors. The pathophysiology of type 2 DM can be summarized as follows[1]. Initially (probably on a genetic basis) the pancreatic beta cells are not able to respond with appropriate insulin secretion to glucose challenge. At the same time, an increased demand for insulin due to environmentally (e.g., obesity) induced insulin resistance has also set in. At this juncture, a compensatory increase of the insulin secretion is still sufficient to maintain a normal glucose level. By gradual decrease of insulin secretion and increase of insulin resistance, a reduced suppression of hepatic glucose output and impaired glucose tolerance appear. With further increase in insulin resistance, an absolute increase in hepatic glucose output occurs which leads to fasting hyperglycemia. At the same time, pancreas fail to compensate for the increased demand of insulin any further and hyperglycemia sets in. If untreated, hyperglycemia and insulin resistance in type 2 DM increase the risk of several macro and microvascular complications such as, hypertension, coronary vascular disease, cardiomyopathy, stroke and retinopathy, nephropathy, neuropathy[2,3]. The majority of type 2 DM patients suffer from visceral obesity and they often have high circulating levels of lipids including cholesterol, triglycerides, low levels of high density cholesterol, which also contribute to the development of vascular complications. Independent of coronary artery complications, complex changes in the mechanical and electrical properties of the heart may contribute to diabetic cardiopathy. The devastating consequences of these complications include lower-limb amputation, end stage renal failure, loss of vision and myocardial infarction.

From the discussion above, it is clear that the contributory abnormalities in type 2 DM are – insulin deficiency, insulin resistance and increased hepatic glucose output. With this in mind, therapies used to treat patients with this disease are aimed at correcting one or more of these physiological abnormalities. Current recommendations of the American Diabetes Association (ADA) include a trial of diet and exercise as first line therapy for the treatment of type 2 diabetes. If the desired level of glycemic control cannot be achieved with diet and exercise within a three-month period, pharmacological intervention is recommended[4]. Generally, initiation of therapy in most cases starts with insulin. Although the diabetes control and complications study (DCCT)[5] and the United Kingdom Prospective Diabetes Study (UKPDS)[6] demonstrated that good metabolic control through intensive drug therapy and strict lifestyle management could reduce the risk of developing diabetes complications, relatively few dia-

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betes patients have adopted this strict regimen. Current therapeutic approaches were largely discovered in the absence of defined molecular targets or understandings. Advent of molecular biology techniques, knockout experiments, genomics, etc. have increased our understanding of the pathophysiology of diseases. This resulted in several knowledge-based new therapeutic approaches for the treatment of diabetes and insulin resistance associated disorders. Currently, six different classes of hypoglycemic agents are being used – insulin, sulfonylureas, meglitinides, biguanides, alpha-glucosidase inhibitors and thiazolidinediones (Table 1).

Sulfonylureas

Sulfonylureas (SU) have remained the mainstay of antidiabetic therapy for almost three decades. Following the release of University Group Diabetes Program (UGDP)[7] study report, which implicated tolbutamide in increased mortality secondary to cardiovascular events, the use of first generation SUs (acetohexamide, chlorpropamide, tolbutamide and tolazamide) quickly fell out of favour. Recent data, supporting the benefits of SUs as well as the availability of second generation SUs with more favourable side effect profile (glyburide, glipizide and glimiperide) have contributed to their renewed popularity. The mode of action of SUs could be chiefly explained by inhibition of K_{ATP} channels initiating insulin secretion. Thus, these drugs could be used only in patients with type 2 DM having functional beta cells for endogenous insulin production. Other contributory mechanisms for these compounds have also been suggested, such as, involvement of protein kinase C, increase in cAMP level and calcium ionophore-like activity.

Table 1. Current therapeutic agents for diabetes

Drug class	Molecular target	Site(s) of action
Insulin	Insulin receptor	Liver, fat, muscle
Sulphonylureas:	SU receptor K^+/ATP channel	Pancreatic beta cell
First Generation: Tolbutaminde, chlorpropamide		
Second Generation: Glyburide, glipizide, gliclazide, glimepiride		
Biguanides: Metformin	Unknown	Liver, muscle
Alpha-glucosidase inhibitors: Acarbose	Alpha glucosidase	Intestine
Thiazolidinediones: Rosiglitazone Pioglitazone	PPAR gamma	Fat, liver, muscle

Overt hypoglycemia is the most worrisome side effect of SUs. It is of particular concern with agents that are metabolized to an active metabolite with significant renal excretion (e.g. chloropropamide and glyburide). These agents should be avoided in case of elderly patients with impaired renal function. Glipizide and glimepiride are associated with lower incidence of hypoglycemia. All SUs have been associated with weight gain and thus, may not be optimal first choice for obese patients.

Meglitinides

Repaglinide is an insulin secretagogue, the first of the meglitinide class. It is a member of the carbamoyl methyl benzoic acid family (glinides), which is structurally different from the traditional SUs, but shows chemical resemblance to the nonsulfonylurea moiety of the glibenclamide molecule. Nateglinide, the newest member of the class has recently become available.

The meglitinides stimulate the release of insulin from the pancreatic beta cells. However, this action is mediated through a different binding site on the 'sulfonylurea receptor' of the beta cells and the drugs have somewhat different characteristics when compared with sulfonylureas[8]. In contrast to glibenclamide, meglitinides do not stimulate calcium dependent exocytosis. Glibenclamide, not meglitinide, can stimulate insulin secretion *in vitro* even in the complete absence of glucose, whereas in presence of 5 or 10 mmol/l of glucose, meglitinides are 5 times more potent than glibenclamide in insulin secretion. Unlike commonly used SUs, the meglitinides have a very quick onset of action and a short half-life. Some potential advantages of this class of agents include a greater decrease in post-prandial glucose and a decreased risk of hypoglycemia. Because of the quick onset of action (15 to 30 min), patients should be instructed to administer a dose immediately before a meal. If a meal is omitted throughout the day, patients should be instructed to skip the corresponding dose to prevent hypoglycemia. Likewise, if an extra meal is added throughout the day, the patient should add a dose to cover that meal. Thus, unique dosing regimen may allow greater flexibility for patients who have difficulty in maintaining a regular meal schedule.

Besides the two above-mentioned drugs, Servier has a molecule (Mitiglinide) in Phase III clinical trial in this class.

Biguanides

Although biguanides have been in use for many years outside of US, their reintroduction in US has been relatively recent. Metformin is currently the only agent in this antidiabetic class available in US, but it has already attained the top-selling oral hypoglycemic agent (OHA)

position. Metformin works by reducing hepatic glucose production through inhibition of gluconeogenesis and to a lesser extent, enhancing insulin sensitivity in hepatic and peripheral tissues[9].

Other effects include a reduction in plasma triglyceride levels and low-density lipoprotein (LDL) cholesterol levels. Metformin is unusual among the oral antidiabetic drugs in that its therapy has been associated with a lack of weight gain and even weight loss in some obese patients. On the whole, metformin has a favourable side effect profile, most of which is transient and commonly reported only during initiation of therapy. A rare, but more worrisome potential adverse effect is that of lactic acidosis. Phenformin, another drug in this series was withdrawn from US in 1970 due to this severe side effect. On the other hand these effects are almost unknown in case of metformin, if there is no other underlying diseases, particularly renal insufficiency. Other situations, in which metformin therapy should be avoided, include cardiogenic or septic shock, congestive heart failure, severe liver disease, and pulmonary insufficiency with hypoxemia or severe tissue hypoperfusion. Sparta has a pyrozinoyl guanidine compound in Phase II trial.

Thiazolidinediones

Reduction of insulin resistance is necessary to improve the blood glucose level in type 2 diabetic patients with obesity and insulin resistance. A thiazolidinedione-based compound, ciglitazone, was derived from fibrate lipid-lowering agents by Takeda and was reported to be a novel oral hypoglycemic agent that potentiated the peripheral actions of insulin. Subsequently, many attempts to synthesize new analogues have been made and the molecular target of thiazolididiones has been determined by researchers from Glaxo. Thiazolidinedione is an agonist for peroxisome proliferator activated receptor γ (PPARγ)[10]. This is an orphan member of nuclear hormone superfamily that mediates adipocyte differentiation and modulates insulin sensitivity through regulation of gene expression[10]. Interestingly, triglyceride-lowering fibrates have been revealed to be PPARα agonists, another isoform of PPAR family.

Among the thiazolidinedione compounds, troglitazone of Sankyo was first to be approved in Japan and USA. But, following reports of severe liver toxicity in patients taking this drug, the product was withdrawn from the market. Rosiglitazone, developed by SmithKline Beecham and pioglitazone, developed by Takeda/Pfizer are the two thiazolidinedione analogues now in the market. Thiazolidinediones increase insulin sensitivity in fat and muscle tissues and to a lesser extent inhibit hepatic glucose production. As a class, thiazolidinediones have also been shown to alter the lipid profiles in patients with type 2 diabetes. Both the compounds show decrease in triglyceride, although the effect is much significant with Pioglitazone. The effects on HDL-cholesterol levels have been mostly neutral, while some studies report an increase in total and LDL-cholesterol levels[11].

Because these agents do not increase insulin secretion, hypoglycemia does not pose a risk when thiazolidinediones are taken as monotherapy. Significant weight gain has been reported with all thiazolidinediones, which is a matter of concern as most of the type 2 patients are already obese. The thiazolidinediones are relatively safe in patients with impaired renal function, but caution should be used in patients with hepatic dysfunction. There are a few reports of deterioration of liver function in such patients after rosiglitazone treatment. The manufacturers recommend these agents not to be prescribed for patients with serum transaminase levels that exceed 2.5 times the upper limit of normal. Mild to moderate edema has been reported in 5 to 7% of patients treated with rosiglitazone and pioglitazone. The increase in plasma volume is of concern in patients with congestive heart failure – particularly those with New York Heart Association class III or IV functional status.

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors act by inhibiting the enzyme alpha-glucosidase found in the brush border cells that line the small intestine, which cleaves more complex carbohydrates into sugars. Because these drugs inhibit the breakdown and subsequent absorption of carbohydrates from the gut following meals, the largest impact of these drugs is on postprandial hyperglycemia[12]. Acarbose and miglitol are the two agents available in the market in this class.

The most bothersome side effects observed with these agents are gastrointestinal; including abdominal discomfort, bloating, flatulence and diarrhea but are reversible with discontinuation. Therapy with acarbose has been linked to elevations in serum transminase levels and use of this agent is contra indicated in patients with liver cirrhosis. Likewise, concentrations of the alpha-glucosidase inhibitors have been shown to increase proportionally to the degree of renal dysfunction and their use in patients with serum creatinine level more than 2.0 mg per dl is not recommended. Other contra indications include patients with inflammatory bowel disease or a history of bowel obstruction.

Future targets

From the discussion above, it is clear that current pharmacological treatment using sulfonylureas, metformin and thiazolidinediones do not adequately control blood glucose levels and their use is hampered by several contraindications and undesirable side effects. Therefore,

Table 2. Drugs under development for diabetes

Drug class	Molecular target	Site(s) of action
PPAR ligands:		
PPARγ ligands		
Balaglitazone, nataglitazone, etc.	PPARγ	Fat, liver, muscle
PPARα and γ ligands		
Ragaglitazar, tesaglitazar, reglitazar KRP-297, BMS-298585	PPARα and γ	Fat, liver, muscle, vascular tissues
PTPase inhibitors:		
PTP-112	PTPase 1B	Fat, liver, muscle, etc.
β_3 *Adrenorecptor agonists:* SR-58611, TAK-677	β_3 Adrenorecptor	Fat
HGO inhibitors: GP-3034, CP-368296, etc.	F1, 6 Bpase, GP, PEPCK, etc	Liver
Insulin secretogogues: Insulinotropin, betatropin, P32/98, NN-2211, LAF-237, etc.	GLP-1, DPP-IV	Pancreas

development of oral agents with unique mechanism of action is highly desirable.

Insulin sensitizers

Different new targets as well as new molecules for the old targets have been exploited by the pharmaceutical companies in this area.

PPAR agonists

There are three PPARγ compounds which are in phase II clinical trial: Balaglitazone (Dr Reddy's Laboratories Ltd./Novo Nordisk); Natoglitazone (Mitsubishi) and FK-614 (Fujisawa)[13]. As mentioned earlier, PPARα isoform, which is predominantly present in liver, plays a key role in modulating the expression of different genes that oxidize lipids, reducing plasma triglyceride and increasing HDL-cholesterol. Majority of the type 2 DM patients suffer from dyslipidemia and if left untreated, increases the risk of cardiovascular disease. Any compound which targets the PPARα isoform in addition to PPARγ will have beneficial effects on both lipid and glucose metabolism and thereby will be a potential drug candidate for diabetic dyslipidemia. Ragaglitazar (Dr Reddy's Laboratories Ltd./Novo Nordisk), a non-TZD dual PPAR activator is in phase III clinical trial. The compound has shown excellent insulin sensitizing; triglyceride and free fatty acid lowering and HDL-Cholesterol elevating property in type 2 DM patients in phase II (ref. 14). Tesaglitazar (Astra Zeneca); KRP-297 (Kyorin/Merck); BMS-298585 (Bristol Myers Squibb), Regaglitazar (Japan Tobaco/ Pharmacia) are some other dual activators in phase II trial. Besides these, there are several dual activators at different stages of development[13].

Protein tyrosine phosphatase inhibitors

PTPase regulates many biological responses by dephosphorylating tyrosine residues. In 1966, PTP-1B was identified as the enzyme responsible for the inhibition of insulin-stimulated receptor autophosphorylation and its accompanying downstream effects. An inhibitor of this enzyme is expected to increase insulin signaling and thereby its action[15]. Wyeth-Ayerst is developing PTP-112, a PTPase 1B inhibitor and is now in phase II clinical trial.

β_3 Adrenoreceptor agonists

Weight loss can improve insulin sensitivity, but non-pharmacological methods of achieving this are often unsuccessful due to patient non-compliance. β_3 Adrenoreceptor, a member of G-Protein coupled adrenoreceptor family is present in brain and white adipose tissues. β_3 Adrenoreceptor agonists show marked selectivity for stimulation of lipolysis and hence oxygen and energy consumption in skeletal muscle and adipose tissues. Initial compounds, which showed excellent activity in rodents failed in human trials, due to the difference in the β_3 receptor isoforms in different species. Recent cloning of human β_3 receptor has enabled companies to develop compounds selective for human β_3 receptor[16].

SR-58611 (Sanofi-Synthelabo) and TAK-677 (Takeda) are some of the compounds in this series undergoing phase II clinical trial.

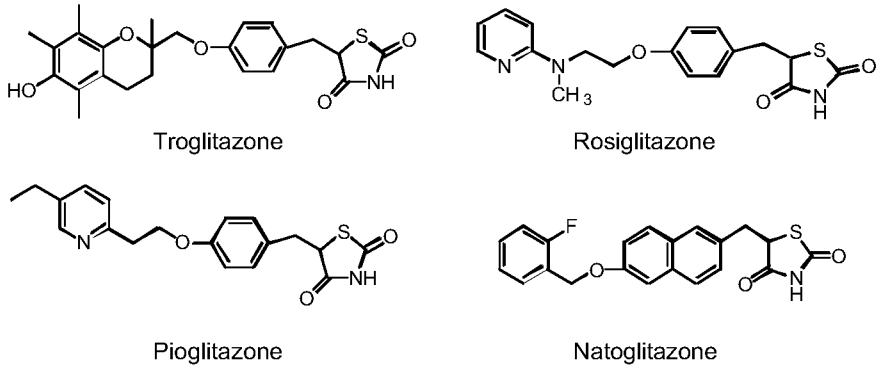

Figure 1. PPARγligands.

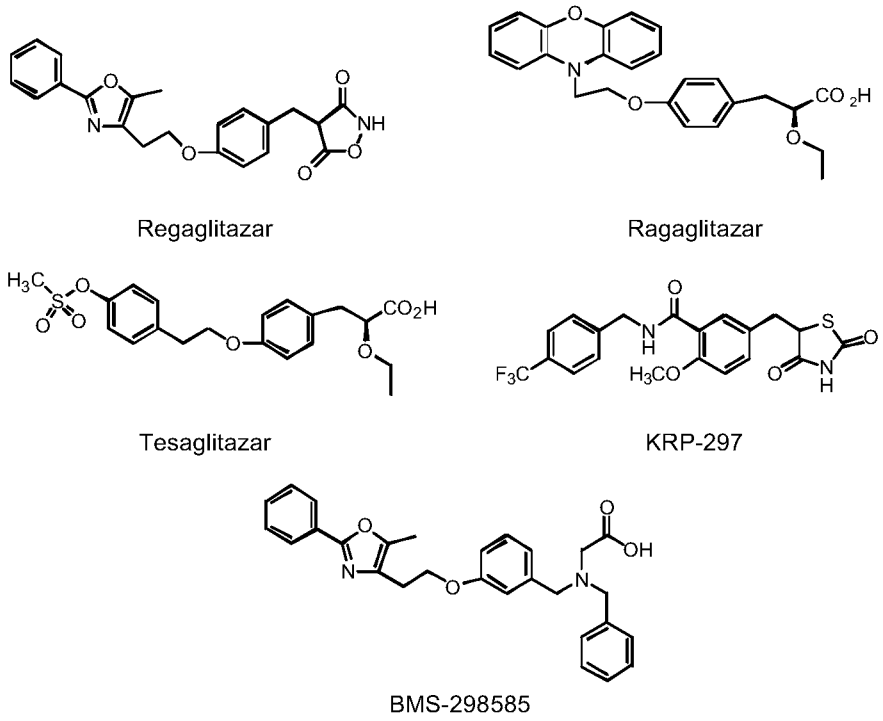

Figure 2. PPARαand γligands.

Inhibitors of hepatic glucose output

A major contributing factor to fasting hyperglycemia is an inappropriately high production of glucose in liver. Hepatic glucose output (HGO) is a consequence of two distinct and highly regulated processes: gluconeogenesis and glycogenolysis. In the gluconeogenesis pathway, pyruvate is first converted to phosphoenolpyruvate by PEPCK, followed by entry into the fructose 1,6-*bis*-phosphate/fructose 6-phosphate cycle controlled by fructose 1,6-*bis*phosphatase (F1, 6 Bpase) and phosphofructokinase (PFK-1). Conversion of fructose-6-phosphate to glucose-6-phosphate is followed by hydrolysis to glucose mediated by G6Pase. Glycogen breakdown in the liver is regulated by glycogen phosphorylase (GP), catalysing the release of gl-1-P which is subsequently converted to gl-6-P and metabolized by glucose6phosphatase (G6Pase) to glucose. It is difficult to quantify the relative contribution of gluconeogenesis versus glycogenolysis in HGO; approaches that impact either or both of the pathways have been pursued[17].

Metabasis/Sankyo has GP-3034, a F1, 6 Bpase inhibitor in phase II clinical trial. Aventis and Novo Nordisk have reported compounds which inhibit GP and these compounds showed interesting activity in animal models. Hoffmann-LaRoche has reported PEPCK inhibitor, which

showed inhibition of glucose production in liver cell lines.

Insulin secretogogues

Insulin secretion is reduced in type 2 diabetes. Several novel targets have recently been exploited to develop new drugs, which will increase insulin secretion and thereby glucose utilization. Glucagon like peptide-1 (GLP-1) is secreted by intestinal cells and enhances insulin secretion. Parenteral administration of GLP-1 derivatives normalizes blood glucose in type 2 diabetes, but because of its short half-life it has found little practical application. Dipeptidylpeptidase IV (DPP IV), an endopeptidase breaks down GLP-1 specifically, so if the activity of DPP IV can be inhibited, it will in turn increase circulating GLP-1 levels[18]. Several companies are working in this area.

LAF-237 (Novartis), P32/98 (Merck), DPP-728 (Novartis), NN 2211 (Novo Nordisk) are some of the compounds in this series which are in phase II clinical trial.

Conclusion

The limitations of currently available oral anti-diabetic agents either in terms of efficacy/safety coupled with the emergence of the disease into a global epidemic have encouraged a concerted effort the world over to discover drugs that can manage type 2 diabetes more efficiently. Also, the understanding that the disease is in fact a metabolic syndrome of interrelated symptoms has instigated the researchers to discover a unique solution that would effectively address these symptoms in one stroke. The discovery of the dual PPAR agonists is, perhaps, the first step in this direction. It is likely that in the foreseeable future, drugs having multiple actions would be discovered that could stem the progress of the epidemic of type 2 diabetes.

1. Gerich, J. E., *Horm. Metab. Res.*, 1996, **28**, 404–410.
2. Kannel, W. B. and McGee, D. L., *J. Am. Med. Assoc.*, 1979, **241**, 2035–2045.
3. Garcia, M. J., McNamara, P. M., Gordon, T. and Kannel, W. B., *Diabetes*, 1974, **23**, 105–112.
4. American Diabetes Assn., *Diab. Care*, 1995, **18**, 1510–1518.
5. Okubo, Y., Kishikawa, H. and Araki, E., *Diab. Res. Clin. Practice*, 1995, **28**, 103–117.
6. The United Kingdom Perspective Diabetes Study, *Lancet*, 1998, **352**, 837–857.
7. Feinglos, M. N. and Bethel, M. A., *Am. Heart J.*, 1999, **138**, 346–352.
8. Fuhlendorff, J., Rorsman, P., Kofod, H. and Brandt, C. L., *Diabetes*, 1998, **47**, 345–355.
9. DeFronzo, R. A., *Ann. Int. Med.*, 1999, **131**, 281–303.
10. Olefsky, J. M., *J. Clin. Invest.*, 2000, **106**, 467–472.
11. Luma, B. and Feinglos, M. N., *Am. Family Physician*, 2001, **63**, 1747–1756.
12. Rodger, N. W., Chiasson, J. L. and Foss, R. G., *Clin. Invest. Med.*, 1995, **18**, 318–324.
13. Perry, C. G. and Petrie, J. R., *Exp. Opin. Emerg. Drugs*, 2002, **7**, 165–174.
14. Saad, M. F., Osel, K. and Lewin, A. J., *Diabetes*, 2002, **51** (suppl. 2), A35–A36.
15. Zhang, Z. Y., *Curr. Opin. Chem. Biol.*, 2001, **5**, 416–429.
16. Laight, D. W., *Exp. Opin. Ther. Patents*, 2000, **10**, 1703–1709.
17. Moyer, M. Y. C., *ibid*, 2000, **10**, 787–801.
18. Holst, J. J. and Deacan, C. F., *Diabetes*, 1998, **47**, 1663–1682.

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