Non-Insulin Dependent Diabetes Mellitus: Present Therapies and New Drug Targets‡

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Abstract: Type 2 Diabetes Mellitus (DM) or Non-Insulin Dependent Diabetes Mellitus (NIDDM) accounts for 90-95% of all diabetes cases and has become a major health concern over the years. This disease has assumed frightening proportions due to unhealthy food habits and sedentary life style. About a decade ago, due to the absence of defined molecular targets or an understanding of disease pathophysiology, treatment of this disease was mostly focused on insulin secretion or administration of external insulin. During the past decade however, advent of genomics and proteomics has helped in understanding the molecular alteration characteristics of NIDDM. Untreated type 2 diabetes leads to several complications such as hyperlipidemia, hypertension and atherosclerosis – collectively known as Syndrome X. Though United Kingdom Prospective Diabetes Study (UKPDS) showed that normalization of hyperglycemia could prevent majority of diabetes complications, the available treatment regime does not adequately normalize the blood glucose level in type 2 diabetic patients. Currently, four distinct classes of oral hypoglycemic agents are available, some of which can act as lipid lowering agents as well. The efficacy and side effect profiles of these drugs are still to be optimized, so there is an unmet need for better candidates. Several new targets as well as better drugs for old targets are under investigation across the world. Availability of such drugs, based on the validated targets, may lead to a new therapeutic paradigm for the prevention of diabetes as well as complications arising out of it. The current review will deal with existing oral therapies for type 2 diabetes as well as the emerging therapeutic targets.

INTRODUCTION

Type 2 diabetes mellitus (DM) or non-insulin dependent diabetes mellitus (NIDDM) accounts for 90-95% of all diabetes cases worldwide. Due to globalization of western dietary habits [1,2], it becomes a major concern both in developed as well as developing countries. According to a recent estimate, the annual cost of treating diabetes and related complications could reach as high as US$ 1 trillion globally. NIDDM patients suffer from defects in insulin action and insulin's effect on glucose uptake in skeletal muscles and adipose tissues, glucose production in liver and kidney; and lipolysis in adipose tissue is impaired [1,3,4].

Insulin resistance is a characteristic of most type 2 DM and is universally true for overweight type 2 diabetes patients [5-7]. Body tries to compensate this with an increased insulin secretion from pancreatic β-cell, which leads to hyperinsulinemia [5-7]. At this stage, impaired glucose tolerance (IGT) is detected. Eventually the β-cell compensatory response declines and relative or absolute insulin insufficiency develops in type 2 diabetes prone patients. At this juncture, insulin secretion cannot keep pace with the underlying insulin resistance and hyperglycemia develops eventually leading to frank type 2 diabetes. If untreated, DM carries an increased risk of macrovascular diseases such as hypertension, cardiomyopathy, myocardial infarction and stroke; and microvascular diseases such as retinopathy, nephropathy and neuropathy [8,9] and are considered to be the major causes for mortality and morbidity among patients with type 2 DM [2,8-12]. Another cluster of problems associated with majority of these NIDDM patients is the visceral obesity, increased plasma lipids mainly triglycerides, small dense low-density lipoproteins (LDLs) and low levels of high-density lipoproteins (HDLs), which collectively contribute to vascular complications. Consequently, untreated type 2 diabetes also leads to several lethal complications such as hyperlipidemia, hypertension and atherosclerosis – collectively known as Syndrome X.

It is evident that the contributory abnormalities in type 2 DM are insulin insufficiency, insulin resistance and increased hepatic glucose production. Therapies used to treat these patients are aimed at correcting one or more of these pathophysiological disorders. Restriction of diet and exercise have been recommended as the first line of therapy for the treatment of type 2 diabetes by the American Diabetes Association (ADA). Pharmacological intervention has been recommended [13] in case the desired level of glycemic control cannot be achieved through diet and exercise within the stipulated three-month period. In most of the cases the therapy starts with insulin. Although the Diabetes Control and Complications Study (DCCT) [14] and the United Kingdom Prospective Diabetes Study (UKPDS) [15] have demonstrated that good metabolic control through intensive drug therapy and strict lifestyle management could reduce the risk of microvascular complications, the drugs available in the market are far away from fulfilling the expectations leaving scope for new targets.

About a decade ago, due to the absence of defined molecular targets or an understanding of disease pathophysiology, treatment of this disease was mainly based

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‡ DRL Publication No. 329.

1389-5575/05 $50.00+.00

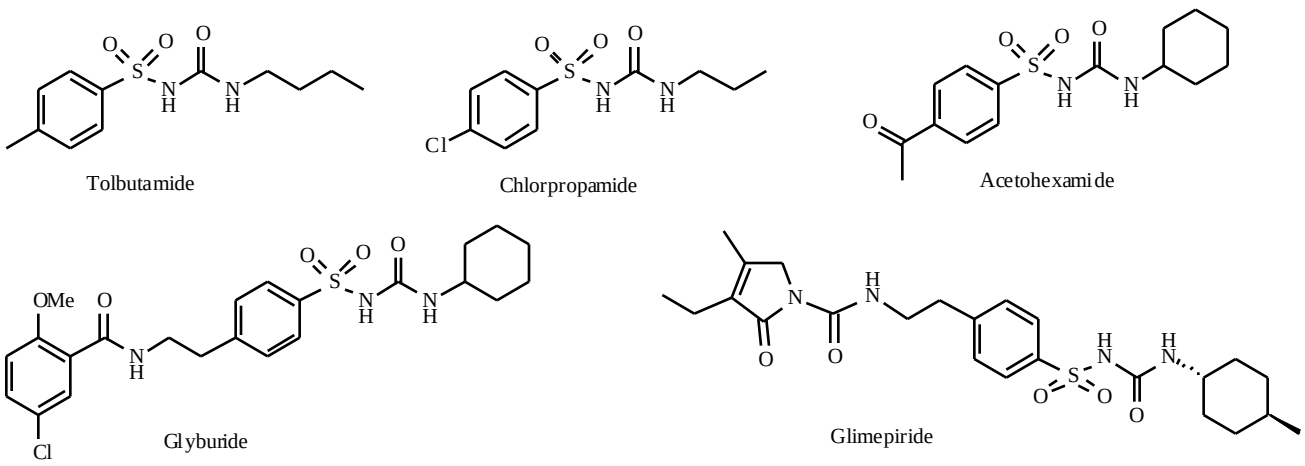


Fig. (1). Structures of sulfonylureas.

on insulin secretion or administration of external insulin. During the past decade advent of genomics and proteomics have helped understanding the molecular alteration, which are characteristics of NIDDM. This has resulted in several target-based new therapeutic approaches for the treatment of diabetes and other insulin resistance associated abnormalities. Currently, four distinct classes of oral hypoglycemic agents are available, some of which can act as lipid lowering agents as well. These are – sulfonylureas and meglitinides as insulin secretagogues, acarbose as absorption inhibitors, metformin as inhibitor of hepatic glucose production and metformin and thiazolidinediones for insulin resistance. With the increasing awareness of the etiology of type 2 diabetes, current research efforts are focused on different targets involved in insulin resistance, insulin secretion and hepatic glucose production. The purpose of this review is to provide a timely though selective summary of the existing therapies and some forefronts stressing the development of an antidiabetic "drug of future".

A. EXISTING THERAPY

1. Insulin Secretagogues

1.1. Sulfonylureas

Sulfonylureas (SUs) have been in the mainstay of oral treatment for type 2 diabetes over 40 years. While the beneficial effects of these drugs on glycemic levels are well documented, the prevention of progressive nature of the disease and its micro- and macrovascular complications was modest and not always very effective. Although many patients initially achieve up to 40% glycemic controls subsequently secondary failure is also observed [16]. In addition, the longer-term effects of SUs on morbidity and mortality remain unclear [17].

Carbutamide (1-butyl-3-sulfonylurea) was the first drug in diabetes care, which was later withdrawn due to adverse effect on bone marrow. Among two generations, first generation SUs include tolbutamide, acetohexamide, tolazamide, chlorpropamide (Fig. **1**) where the side chain is a simple aliphatic open chain in contrast to second generation alicyclic SUs (glyburide, glipizide, glimepiride). With the release of a study report by University Group Diabetes Program (UGDP) [18] implicating tolbutamide for increased mortality secondary to cardiovascular events, the first generation SUs quickly fell out of favor. Recent report [19] contributed to the renewed popularity of SU drugs supporting the benefits of SUs as well as the availability of second generation of SUs with favorable side effect profile. SU receptor has recently been cloned and characterized in pancreas [20].

Overt hypoglycemia is the most worrisome side effect of SUs. It is of particular concern with agents that are metabolized to an active moiety 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 are associated with weight gain and thus, may not be optimal first choice for obese patients [19].

1.2. Meglitinides

Repaglinide is the first drug of the meglitinide class, a member of carbamoylmethyl benzoic acid family (glinides). This is structurally different from SUs but shows

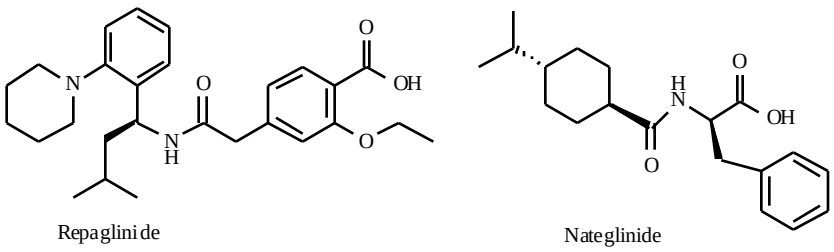
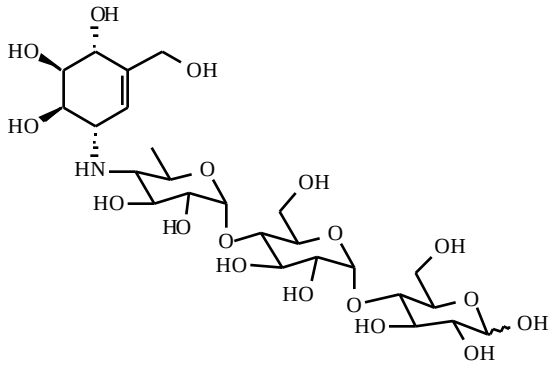
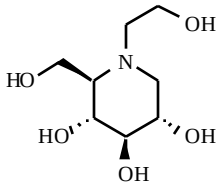


Fig. (2). Chemical structures of benzoic acid derivatives.



Acarbose



Miglitol

Fig. (3). Chemical structures of Acarbose and Miglitol.

resemblance with glyburide. Recent addition to this class of compounds is nateglinide (Fig. **2**). Meglitinides stimulate the secretion of insulin from pancreatic β-cells. However, the action is mediated through a different binding site compared to the SUs receptor of the β-cells and the drugs have different characteristics than that of SUs [21]. Among potential advantages, these agents can reduce the postprandial glucose level to a higher degree and have a decreased risk of hypoglycemia.

Because of their quick onset of action doses are prescribed just before meals. Whenever the meal is omitted throughout the day, the doctors advise the patients to skip the drug too. Similarly, for an extra meal, extra dose of the drug is required. Repaglinide having a better pharmacokinetics profile (rapid absorption, short duration of action) offers a good long-term glycemic control combined with a low risk of severe hypoglycemia [19].

2. Absorption Inhibitors

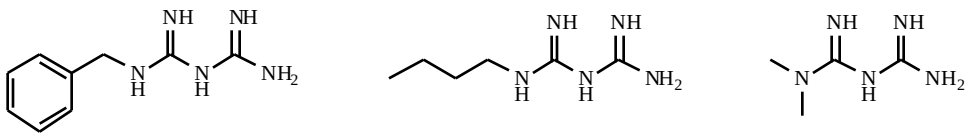
α–Glucosidase inhibitors (AGIs) reduce intestinal absorption of dextrin and disaccharides by inhibiting the action of brush border enzyme α–glucosidase in the small intestine, which degrade more complex carbohydrates into sugars. The AGI is a class of drug that does not target specific pathophysiological defects in type 2 DM. Acarbose (Fig. **3**) is a competitive inhibitor of α-glucosidase enzyme. The other agent available in the market is miglitol. These agents delay the degradation of carbohydrates as well as retard the absorption of meal-derived glucose into circulation. Therefore, the largest impact of these drugs is on postprandial hyperglycemia [22]. The advantage of the AGIs is that they are not associated with hypoglycemia and weight gain.

The most alarming side effects associated with these drugs are at gastrointestinal level including abdominal discomfort, bloating, flatulence and diarrhea but are reversible when discontinued. Acarbose therapy is linked to elevation in serum transaminase levels and use of this agent is contraindicated in patients with liver cirrhosis. Similarly, concentrations of AGIs have been shown to increase the degree of renal dysfunction proportionally and their use in patients with serum creatinine level >2.0 mg/dl is not recommended. However, the long-term implications of the use of this class of drugs on chronic complications have not been examined [19].

3. Biguanides

Metformin, phenformin and buformin (Fig. **4**) were introduced in the market shortly after SUs. Buformin was introduced in a limited manner but the other two were widely used till 1977 when phenformin was withdrawn in many countries due to reported cases of lactic acidosis. Metformin is currently the only drug in this antidiabetic class available in US, where it has attained the top-selling oral hypolipidemic agent position. It works by reducing hepatic glucose output (HGO) through inhibition of gluconeogenesis [23,24] and to a lesser extent, enhancing insulin sensitivity in hepatic and peripheral tissues. Other effects include decreased appetite and food absorption and reduction in LDL-cholesterol levels [19]. Recent report [25] indicates that effects of metformin may be mediated at least in part *via* Adenosine Monophosphate-activated Protein Kinase (AMPK) activation. Interestingly, metformin has been found to lower the body weight unlike other antidiabetic drugs [26].

In general, metformin does not show any hypoglycemia. It is a stable compound, does not bind to plasma proteins and is excreted unchanged through urine. The disadvantage of this drug is that due to its low bioavailability clinical dose is very high. During metformin treatment 20% of patients suffer from diarrhea, abdominal discomfort, nausea, metallic taste and anorexia [27]. The biguanides, phenformin



Phenformin Buformin Metformin

Fig. (4). Chemical structures of biguanides.

and metformin, are associated with an increased incidence of lethal lactic acidosis [28]. Several attempts have failed to get a better biguanide than metformin for side effects.

4. Insulin Sensitizers

Insulin resistance is the underlying factor that occurs in a vast majority of Type 2 diabetes and is a result of a decrease in sensitivity and/or insulin responsiveness in target organs [29]. Insulin resistance leads to impairment in glucose uptake and storage, lipid metabolism and endothelium dysfunction [30-32]. This post-receptor defect, present in liver, fat and skeletal muscle is central to the pathobiology of syndrome X and type 2 diabetes. In most of the cases insulin resistance develops before hyperglycemia. Several years of research in pharmaceutical companies worldwide recently led to the discovery of novel drugs targeted for sensitization of peripheral tissues to insulin.

4.1. Thiazolidinediones

They constitute a new class of oral antidiabetic agents that selectively enhance insulin resistance and partially mimic certain actions of insulin on carbohydrate and lipid metabolism in type 2 DM. Thiazolidinediones (TZDs) increase insulin sensitivity in fat and muscle tissues and to a lesser extent inhibit hepatic glucose production. As a class, it is also shown to change the lipid profile to a certain extent in type 2 diabetes patients. TZD is an agonist for Peroxisome Proliferator Activated Receptor-γ (PPAR-γ) [33]. PPAR-γ is an orphan receptor of nuclear superfamily that mediates adipocyte differentiation and modulates insulin sensitivity through regulation of gene expression [33]. Grippingly, triglycerides-lowering fibrates are revealed as PPAR-α agonists, another isoform of the same PPAR family.

Historically, the thiazolidine-2,4-dione ring was derived from an earlier series of α-halo and α-thiocarboxylic acid antihyperlipidemic agents [34-36] by Sohda and coworkers. Exhaustive search for novel, potent and selective antidiabetic agents based on thiazolidine-2,4-dione yielded the first member of this class, ciglitazone [37], by Takeda and was reported to be a novel oral hypoglycemic agent that potentiates the peripheral actions of insulin. Clinical trials for ciglitazone and its successor englitazone [38] were discontinued due to adverse effects on the liver [39]. Introduction of trolax moiety in place of substituted cyclohexylmethyl moiety yielded troglitazone (Sankyo). Troglitazone was first approved in Japan and USA. It is interesting to note that troglitazone possesses an accessory anti-oxidant property related to its structural similarity with vitamin E. However, despite its proven antidiabetic efficacy, Glaxo Wellcome and Sankyo voluntarily suspended [40-43] its use in UK and afterwards in the USA due to the risk of hepatotoxicity in some patients [44]. Troglitazone when incubated in human hepatoma cell line, HepG2 cells as well as human primary hepatocytes yielded one major metabolite, which was identified as an epoxide from trolax moiety. This metabolite showed weak cytotoxicity in HepG2 cells at low concentrations [45]. Since epoxides are generally recognized as chemically reactive species, this metabolite might also play a role in idiosyncrasy of troglitazone hepatotoxicity *via* individual differences either in the formation or degradation of this metabolite [45]. Subsequently, rosiglitazone and pioglitazone [38,46] (Fig. **5**), developed by SmithKlineBeecham and Takeda/Pfizer, are the two TZDs now in the world market. Both the drugs show triglycerides lowering, the effect being much prominent with pioglitazone. There is seldom any effect on HDL-cholesterol levels. However, some studies report an increase in total and LDL-cholesterol levels [47]. Finally, the importance of

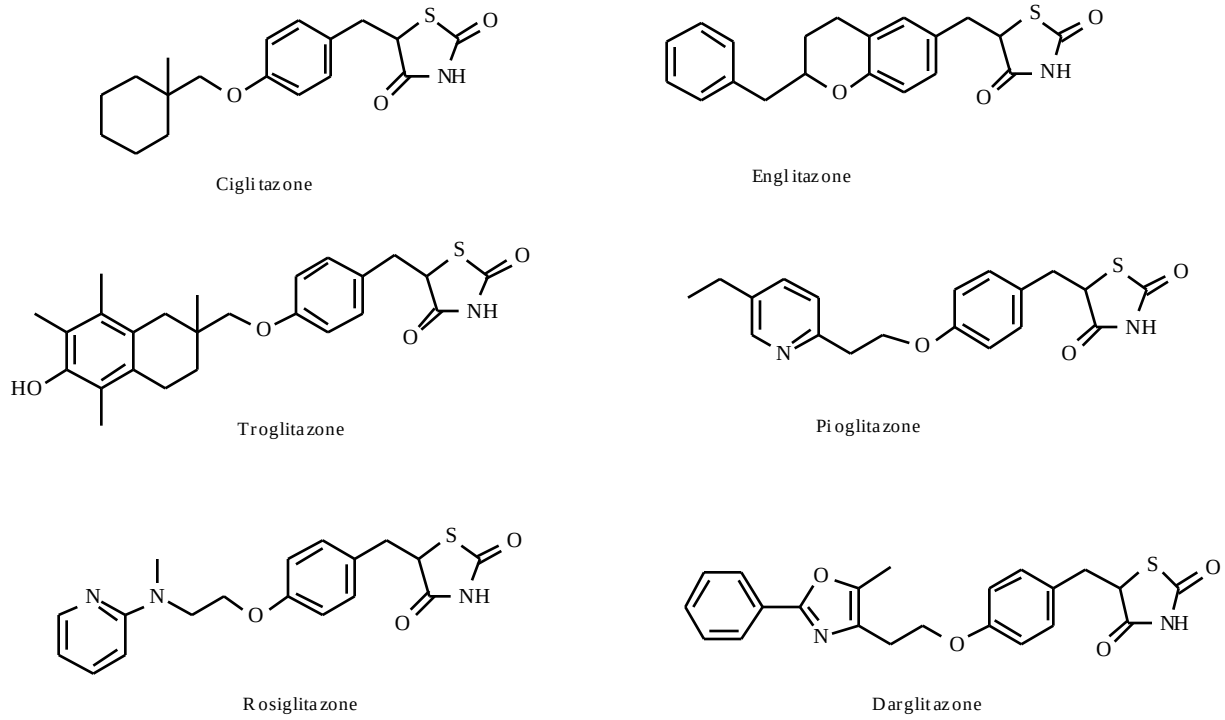


Fig. (5). Chemical structures of thiazolidinediones.

combination therapy with one or more of these agents should be highlighted as a possible option to improve the control of blood glucose levels. In fact, complementary mechanisms of action of different classes of oral agents demonstrate synergistic effects when used in combination.

It is worthy to note that since these agents do not increase the secretion of insulin, hypoglycemia can be ruled out when TZDs are prescribed as monotherapy. TZDs, although effective, suffer from severe safety aspects. These drugs are relatively unsafe for the patients with renal dysfunction. There are also a few reports of liver dysfunction after rosiglitazone treatment [19]. TZDs are known for weight gain [48], which is definitely a matter of concern as most of the NIDDM patients are obese. This effect seems to be mechanism based mediated through PPAR-γ. Mild to moderate edema was reported for 5-7% patients who were on rosi- or pioglitazone treatment [49]. Haemodilution, observed with TZD treatment, is of concern for the patients with congestive heart failure [50].

B. FUTURE TARGETS

Present pharmacotherapy of type 2 diabetes as described above although effective is far from optimum. In light of shortcomings of current therapies, intensive efforts in the pharmaceutical industry are directed towards the discovery of novel, orally active agents that improve insulin sensitivity and are antihyperglycemic with added effect on hypertriglyceridemia. Several new compounds, which have a mode of action similar to those discussed earlier, are being developed. In addition, compounds with novel modes of action are also in development. As the discussion follows it is now evident that the existing drugs fall short of fulfilling the needs of the patients as they do not adequately control blood glucose levels and their use is also restricted due to several contraindications and undesirable side effects. Therefore, the development of new antidiabetic agents with no or minimum side effects is an unmet need.

Table 1. Targeted Agents for Diabetes in Future

Drug class	Site(s) of action
1. Insulin Receptor Mimetics	Insulin receptors
2. Insulin Sensitizers	
2.1 PPAR Agonists	Liver, fat, muscle
2.2 Adipocyte derived Proteins as Targets	Adipose tissue
2.3 RXR Agonists	Liver, fat, muscle
2.4 PTPase Inhibitors	Liver, fat, muscle
2.5 11β-HSD-1	Liver, Adipose tissue, muscles
3. Insulin Secretagogues	
3.1 GLP-1	GLP-1 receptor
3.2 DPP IV	GLP-1
4. β_3-Adrenoceptor Agonists	Fat tissues
5. HGO Inhibitors	Liver, muscle, kidney
6. AMPK Activators	Liver, muscle, kidney

In this section we will confine our discussions on some promising targets as have been tabulated in Table **1**. These targets represent a challenge for drug therapy in that the biological finesse involved in organisms temporal, regional and quantitative control over gene transcription is far more intricate than the contemporary therapy.

1. Insulin Receptor Mimetics

Insulin mimetic was thought to supplant the need for daily insulin injections with a more palatable option. In 1999, 14 years after the cloning of insulin receptor, Merck Research Laboratories identified a small molecule fungal metabolite from *Pseudomassaria* sp., L-783281 (Fig. **6**) from cell based screening assay. This compound was shown to be a selective insulin receptor activator that mimicked insulin effects including phosphorylation of insulin receptor substrate-1 (IRS-1), activation of PI3K and Akt, increased glucose uptake in skeletal muscle and adipocytes. Oral administration to db/db and ob/ob mice resulted in significant decrease in blood glucose levels [51]. Other compounds, which are apparently insulin sensitizer rather than mimetics, will be described in subsequent sections. Proof of concept for small molecule insulin mimetics holds significant promise as an alternative treatment for diabetic patients.

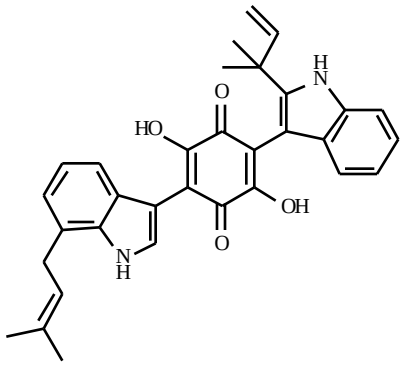


Fig. (6). Chemical structure of L-783281.

2. Insulin Sensitizers

Different new targets as well as new molecules for old targets are being exploited by the pharmaceutical companies in this area. There are many front-runners in this area. The modification of existing therapy i.e., PPAR agonists, is still persuaded in a big way worldwide. We will start our discussion with this type.

2.1. PPAR Agonists

Nuclear hormone receptors have received an immense amount of scientific attention in last few years, reflecting primarily clinical advances in drugs targeting PPAR. There are three characterized isoforms of PPARs in humans; PPAR-γ, α, and β/δ [52]. On ligand binding, PPAR forms a heterodimer with RXR and then binds to specific Peroxisome Proliferator response elements (PPRE) on a number of key target genes involved in carbohydrate and lipid metabolism.

*2.1.1. PPAR-*γ

PPAR-γ is mainly found in adipose tissues [53]. At low concentration, it is also expressed in skeletal muscles and endothelium. Prominent among modulators of the PPAR-γ is a class of drugs known as glitazones. The most pronounced effect of PPAR-γ modulation by TZDs is the

promotion of adipocyte differentiation resulting in change in body composition towards peripheral rather than the central obesity. This is the only component of the insulin-signaling cascade that has been shown to be up regulated in response to TZDs, and as such offers a direct effect of these compounds on insulin sensitivity. Prostaglandin J2 [54] and polyunsaturated fatty acids [55] have been discovered as endogenous ligands for PPAR-γ. Two isoforms of PPAR-γ, namely PPAR-γ1 and PPAR-γ2, have been identified. PPAR-γ2 is found predominantly in adipose tissues [56]. Two PPAR-γ compounds of this class are in the advanced stages of clinical trials – balaglitazone from Dr. Reddy's/Novo Nordisk and FK-614 from Fujisawa [57]. In last year's ADA meeting [58,59] Balaglitazone was also claimed in preclinical study as a partial PPAR-γ agonist with a better cardio vascular safety profile and glycemic control compared to full PPAR-γ agonist rosiglitazone.

2.1.2. PPAR-α

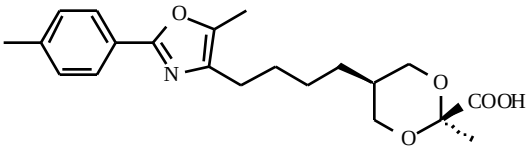
PPAR-α is expressed in liver, monocytes and macrophages, where it regulates genes involved in lipid metabolism and is responsible for the triglyceride lowering and HDL-modulating effect of fibrates [60]. PPAR receptors were cloned with the realization that they were responsible for peroxisome proliferation observed in rodent liver after treatment with fibrates. Several groups implicated fatty acids as natural ligands for PPAR-α. A search for natural PPAR-α ligands in human serum identified palmitic acid, oleic acid, linoleic acid and arachidonic acid as endogenous activators of rat PPAR-α [61]. Recently Nippon Shinyaku has reported [62,63] a compound (NS-220, Fig. **7**) as potent and selective PPAR-α agonist (3000-fold selective over PPAR-γ and PPAR-δ) as a promising drug candidate for overall management of metabolic syndrome in type 2 diabetes. In KK-A^y mice at 1 mg/kg oral dose it lowered triglycerides, blood glucose and VLDL by 71%, 21% and 50% respectively, while raising HDL by 34% [63]. Eli Lilly has a triazolone based highly potent and selective PPAR-α agonist (LY-518674, Fig. **7**) [64], which is in phase I clinical trial. Dr Reddy`s Laboratories is developing DRF-10945, an oral PPAR-α agonist, for the potential treatment of dyslipidemia and metabolic disorders. In February 2004, phase I trials have been initiated in Canada [IDdb report]. Fu and coworkers [65] have shown that oleylethanolamide (OEA), a naturally occurring lipid, binds with high affinity to PPAR-α receptor and that it also regulates satiety and body weight. Roche has recently reported [66] on K-111, a potent PPARα agonist. In non-human primates, K-111 showed significant reduction in body weight and triglyceride along with insulin sensitization. These two reports indicate the potential of PPARα agonists for body weight reduction along with its lipid lowering activity. Skeletal myopathy and rhabdomyolysis have been reported with all the currently marketed fibrates [67]. Although it is not clear whether these effects are mediated through PPAR-α, but it will be important to carefully monitor these side effects of more potent and selective PPAR-α agonists now in clinical trials.

2.1.3. PPAR-δ

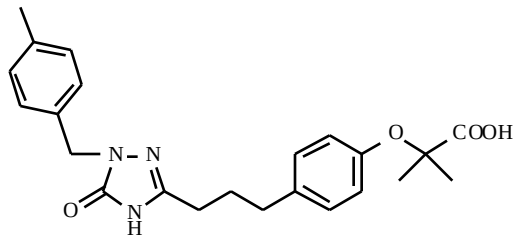
PPAR-δ (also known as PPAR-β) is expressed in a range of tissues. The natural ligand of this nuclear receptor remains unclear, although long chain fatty acids have been proposed as candidates [68,69]. Recent reports have indicated the beneficial effect of PPAR-δ modulation in various disease conditions associated with metabolic syndrome. Oliver and coworkers have suggested [70] that PPAR-δ agonists increase reverse cholesterol transport. In another recent report Lee and coworkers [71] indicated that PPAR-δ ligands could attenuate inflammation and slow down the progression of atherosclerosis. These two reports demonstrated the potential of PPAR-δ agonists for amelioration of cardiovascular disorders. Wang and coworkers [72] have indicated that PPAR-δ serves as a widespread regulator of fat burning and thus could be a target for the treatment of obesity and associated disorders. PPAR-δ has also been reported to be associated with undesired biological effects. One report has suggested that activation of PPAR-δ is causally associated with colon polyp formation, and that increased expression was required to modulate target genes that regulate proliferation of colon tumor cells [73-75]. However, recent report [76] has shown that PPAR-δ attenuates colon carcinogenesis, which is in sharp contrast to the previous report. More detailed studies hopefully will clear this confusion in future. GlaxoSmithKline has a PPAR-δ agonist (GW-501516), which is very potent (K_i and EC_{50} value of 1 nM) and selective (1000 fold over PPAR-γ or PPAR-α), in phase II clinical trials. At the highest dose, GW-501516 caused 80% increase in HDL cholesterol levels, 50% decrease in VLDL, 29% decrease in LDL and a 56% decrease in triglycerides in obese rhesus monkeys [77]. At a dose of 3 mg/kg over 4 weeks, ApoA-1 level was increased by 43%, ApoA-II by 21% and there was a decrease in fasting insulin by 48% [70].

2.1.4. Dual PPAR-α/γ

In spite of the impact the TZDs have made on the clinical management of type 2 diabetes, they were unable to take care of lipid profiles. In addition to the characteristic combination of insulin resistance and insulin deficiency, the type 2 diabetic often displays cardiovascular risk factors including dyslipidemia, hypertension and obesity. The recent publication of the UKPDS [78] has revealed that in



NS-220



LY-518674

Fig. (7). Structures of NS-2202 and LY-518674.

type 2 diabetes, intensive glucose lowering therapy is ineffective at reducing cardiovascular complications, despite decreasing microvascular complications such as retinopathy. The profile of a dual PPAR-α,γ agonist appears well suited as a treatment for type 2 diabetes [79] because of the insulin-sensitizing/glucose-controlling potential of PPAR-γ agonists, the molecular target of TZDs [80-83], in combination with the positive lipid- and cholesterol modulating activities of PPAR-α agonists, the molecular target of the fibrates [84]. To fulfill this dual action a new class of compounds, α-alkoxyphenylpropanoic acid derivatives, were made and tested. This subtle change in 'pharmacophore' rendered the compounds with additional pronounced activities of PPAR-α. It is pertinent to note that troglitazone and pioglitazone have later been found to provide PPAR-α agonist property although at very high concentrations.

The first of its kind is ragaglitazar from Dr. Reddy's Laboratories/Novo Nordisk, which is an α-alkoxyphenylpropanoic acid derivative (Fig. **8**). Although this compound showed an excellent profile in sensitizing insulin, lowering blood glucose and free fatty acid, elevating HDL-cholesterol in phase II clinical trials [85], due to some incidence of bladder tumor in rodents, the trials have been discontinued. Another PPAR-α,γ dual activator belonging to TZD class, KRP-297 (Kyorin/Merck), has been dropped because of similar problem [IDdb report]. In both the cases it is not clear yet, whether the observed tumorigenicity is mechanistically related to PPAR activator and also the human relevance of such findings. Tesaglitazar(AstraZeneca) another propanoic acid derivative dual activator is still in phase III clinical trials [IDdb report]. A dual PPAR-α,γ agonist from Eli Lilly (LY-510929, Fig. **8**), has demonstrated comparable to superior efficacy compared to rosiglitazone in a 12 wk phase II study [86]. Another balanced PPAR-α/γ dual activator muraglitazar, a benzylglycine derivative, has been reported by BristolMayersSquibb (Fig. **8**). Merck & Co has in-licensed this molecule and it is being co-developed by BristolMayersSquibb and Merck & Co. This compound has entered phase III clinical trials for type 2 diabetes by August 2003 [IDdb report]. In a 26 days phase II study 24-h mean glucose and fasting glucose reduction were greater in subjects treated with ≥ 5 mg of muraglitazar than those treated with 45 mg pioglitazone. Muraglitazar was safe and well tolerated up to 20 mg dose level [87]. The hypothesis that a dual activator with significant PPAR-α component can also induce body weight reduction has been supported

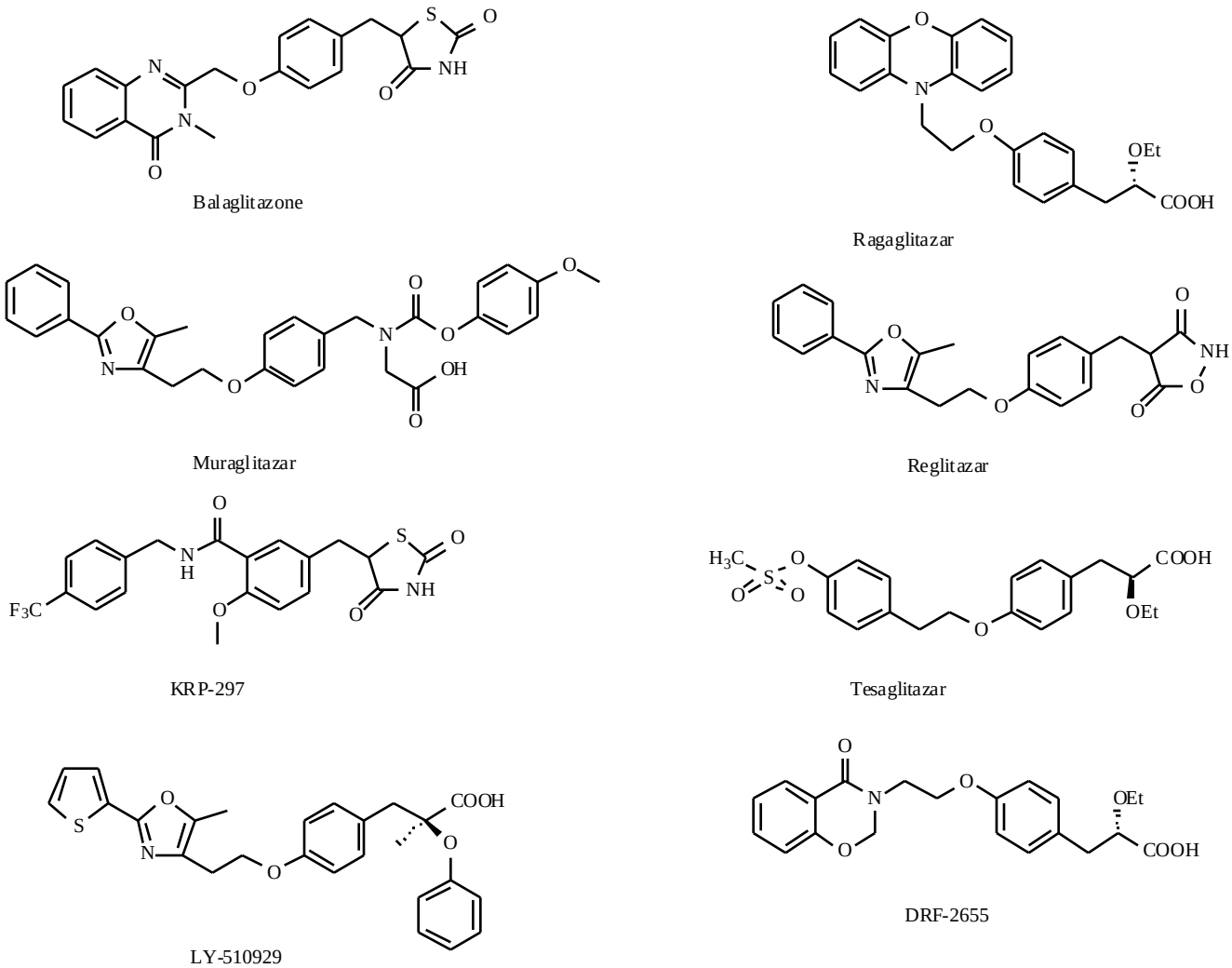
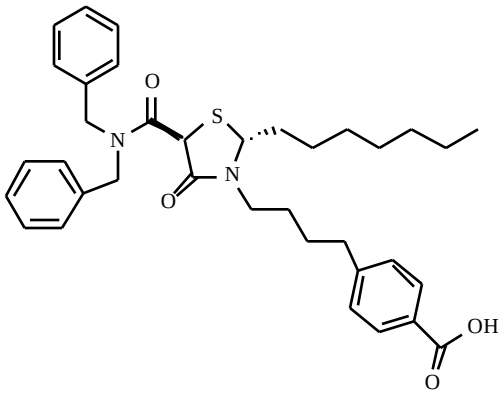
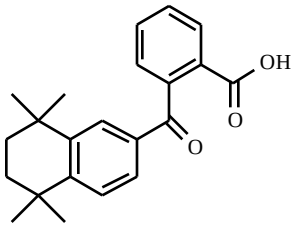


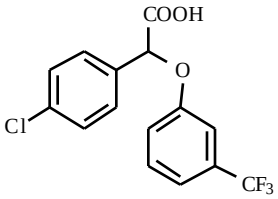
Fig. (8). Chemical structures of some PPAR-α & -γ ligands.



GW-0072



LG-100641



MBX-102

Fig. (9). Structures of GW0072, LG-100641 and MBX-102.

by a recent publication on DRF-2655 (Fig. **6**) [88]. It has been shown that this potent PPAR-α agonist along with its PPAR-γ character have excellent euglycemic and hypolipidemic activities in insulin resistant, hyperlipidemic genetic db/db mice models, zucker fa/fa rats and fat fed hyperlipidemic rat and hamster models.

Due to several reports of rodent carcinogenicity findings with PPAR agonists, US FDA has recently ruled that for all new PPAR agonists, clinical studies of six months or longer must be delayed until two year rodent carcinogenicity studies are completed and reviewed [89]. This will delay the development of such molecules considerably.

2.1.5. SPPARM

Insulin sensitizer TZDs have several shortcomings, so there is a desperate need for improved PPARγ ligands that could retain metabolic efficacy with some reduction in deleterious effects. Selective PPAR-γ Modulator (SPPARM) [90] is a relatively new concept to address this need. This model greatly expands the signaling repertoire of a specific nuclear receptor since it would allow single receptor to respond to a given endogenous ligand in a way that would be gene context-specific [33]. In this kind of modulators, PPAR-γ activity is a key factor. Structural studies have revealed that full agonist ligands activate the PPARs through direct interactions with the C-terminal region of the ligand-binding domain, which includes the activation function 2 (AF2) helix. GW0072 was identified as a high-affinity PPAR-γ ligand that was a weak partial agonist of PPAR-γ transactivation [91]. In cell culture GW0072 (Fig. **9**) was found to be a potent antagonist of adipocyte differentiation. PAT5A, a TZD analogue has been reported by Dr. Reddy's Lab [92] as a partial agonist of PPAR-γ. In animal studies this molecule showed similar efficacy to rosiglitazone with significantly less adipogenicity. The molecule showed differential coactivator recruitment and binding in PPAR-γ pocket compared to rosiglitazone. Metabolex is developing MBX-102 (structure shown in Fig. **9**), an insulin sensitizer with partial PPAR-γ agonist/antagonist activity, for the potential treatment of type 2 diabetes. Phase II studies were initiated in March 2004. In preclinical animal studies, MBX-102 has been shown to enhance insulin sensitivity and lower triglycerides and cholesterol. In a 10-d phase I study of MBX-102 at doses up to 1000 mg/kg/day, showed good dose-proportional pharmacokinetics and was well tolerated [IDdb report]. Recently Tularik has reported T-131, a selective modulator of PPARγ, which shows better antidiabetic efficacy than rosiglitazone in animal models without eliciting the haemodynamic or cardiovascular side effects of full agonists [93]. This molecule is also now in phase II trial. Reports from these clinical trials will validate the concept of SPPARM for an efficacious PPAR agonist without side effects.

2.1.6. PPAR PAN Agonists

Another new concept which accounts for all the three PPAR characters in one molecule is also being explored by researchers. These PAN agonists are thought to have variable PPAR-α, PPAR-δ and PPAR-γ agonist properties. Due to unique isoform specific activities as well as overlapping effects of different PPARs as described before, with an insulin resistance, hyperglycemia, dyslipidemia and atherosclerosis these molecules could serve as an ideal drug for overall management of metabolic syndrome. It has been hypothesized that by manipulating the ratio of PPAR-α, γ and δ in these molecules, the side effect profile can also be regulated. Plexxikon is investigating orally active PPAR PAN agonists active against the PPAR-α, γ and δ isoforms, for the potential treatment of type 2 diabetes, impaired glucose tolerance, dyslipidemia, hypertension and metabolic syndrome X. By September 2003, studies in obese ZDF rats were completed. There was a reduction in triglyceride and

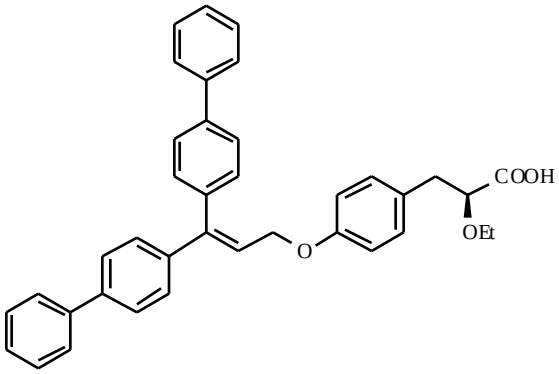


Fig. (10). Structure of a reported PAN agonist.

fasting glucose levels, and an increase in HDL-cholesterol and adiponectin [IDdb report]. There was no weight gain or toxicity observed in the rats after 21 days. GW-677954 is another molecule from GlaxoSmithKline in phase II clinical trials. Another recently reported compound (Fig. **10**) was found [94] to lower blood glucose and plasma insulin levels by 47% and 71% respectively at 1 mg/kg dose in db/db mice after 7 days treatment. The PPAR-α,γ and δ EC_{50}s are 1.1, 0.3 and 0.5 μM, respectively, which are quite impressive.

2.2. Adipocyte Derived Proteins as Targets

There is a well-established bonhomie between obesity and type 2 diabetes. Randle hypothesized [95] that an excess release of NEFA from enlarged fat depots competes with substrate in glucose metabolism and results in hyperglycemia. In addition, adipocytes secrete several factors that play different roles in determining insulin sensitivity such as TNF-α, adiponectin, leptin, resistin, etc. Some of these factors have been recognized as therapeutic targets.

TNF-α is a pro-inflammatory cytokine produced predominantly by macrophages and also synthesized by adipose tissues [96]. Early observations indicated that TNF-α levels are elevated in animal models of obesity and insulin resistance [96] and the neutralization of TNF-α in these animal models increases insulin sensitivity. However, in humans with or without diabetes, single dose of TNF-α neutralizing antibody [97] and a TNF receptor recombinant fusion protein [98] showed no improvement in insulin sensitivity.

Adipose tissues were earlier thought to be only the storage depots of triglycerides. Recent reports indicate that they can also act as endocrine organ as numerous hormones and adipokines are secreted in response to a variety of stimuli. Adiponectin is a circulating protein secreted from adipose tissues [99] with insulin sensitizing, anti-inflammatory and potentially anti-atherogenic actions. Plasma levels of adiponectin, a TNF binding protein, are reduced in obese human [100]. The identification of an adiponectin receptor has recently been reported [101] which should facilitate the understanding of the signaling pathways. Adiponectin administration in rodents decreases adiposity, increases insulin sensitivity and muscle free fatty acid (FFA) oxidation [102] and diminishes hepatic glucose production [103]. A recent study has demonstrated that adiponectin administration diminishes hepatic lipid accumulation in ob/ob mice [104].

2.3. RXR/RAR Agonists

Retinoid X receptors (RXRs) exist in three subtypes - α, β and γ forms [105]. While RXRs act as retinoid receptors, their key role is in heterodimer formation with various nuclear receptors including RARs, vitamin D_3 receptors, thyroid hormone receptors and PPARs. Originally RXR compounds were developed for cancer and dermal treatments. Recent literature and clinical data have shown their use against diabetes. Selective RXR compounds have been reported to modulate hyperglycemia and hyperinsulinemia in animal models [106]. Tetrahydronaphthalene compounds **1** and **2** (Fig. **11**) from Novo Nordisk are highly selective RXR agonists [107,108]. 'RAR modulators' **3** and **4** [109,110], have been disclosed as potent PPAR-γ—RXR-α heterodimer transactivators by Takeda. Ligand Pharmaceuticals has developed a number of RXR agonists, the lead compound being LG101506 (**5**, Fig. **11**) [111] for potential treatment of type 2 DM. This compound was shown to bind selectively to RXRs with IC_{50} being 8 nM, 15 nM and 29 nM respectively, for RXRα, β and γ. The compound was found to be efficacious in diabetic animal models showing a 55% reduction of plasma glucose level in male db/db mice at 30 mg/kg/d dose after 7 days treatment.

2.4. Protein Tyrosine Phosphatase Inhibitors

The interaction of insulin with its receptor leads to phosphorylation of certain tyrosine moieties (Tyr 1146, 1150 and 1151) within the receptor protein, thus activating the receptor kinase. Protein tyrosine phosphatases (PTPases) dephosphorylate the activated IR, attenuating the tyrosine kinase activity. Thus, PTP1B specific inhibitors are expected to enhance insulin sensitivity and act as effective therapeutics for the treatment of type 2 diabetes, insulin

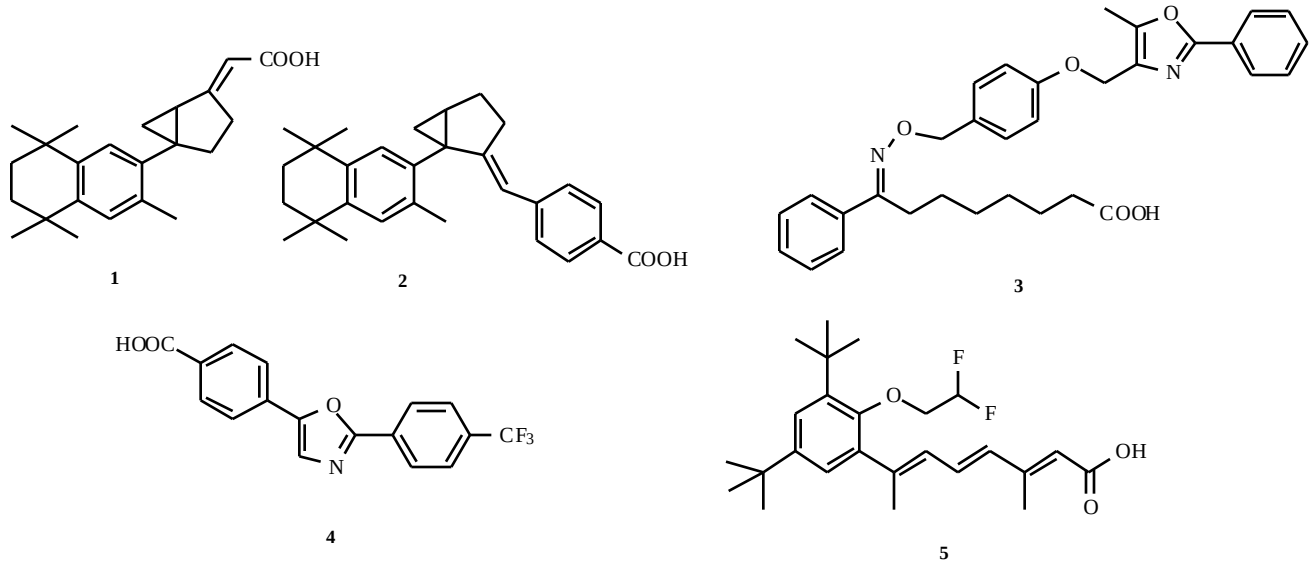


Fig. (11). Chemical structures of some RXR agonists.

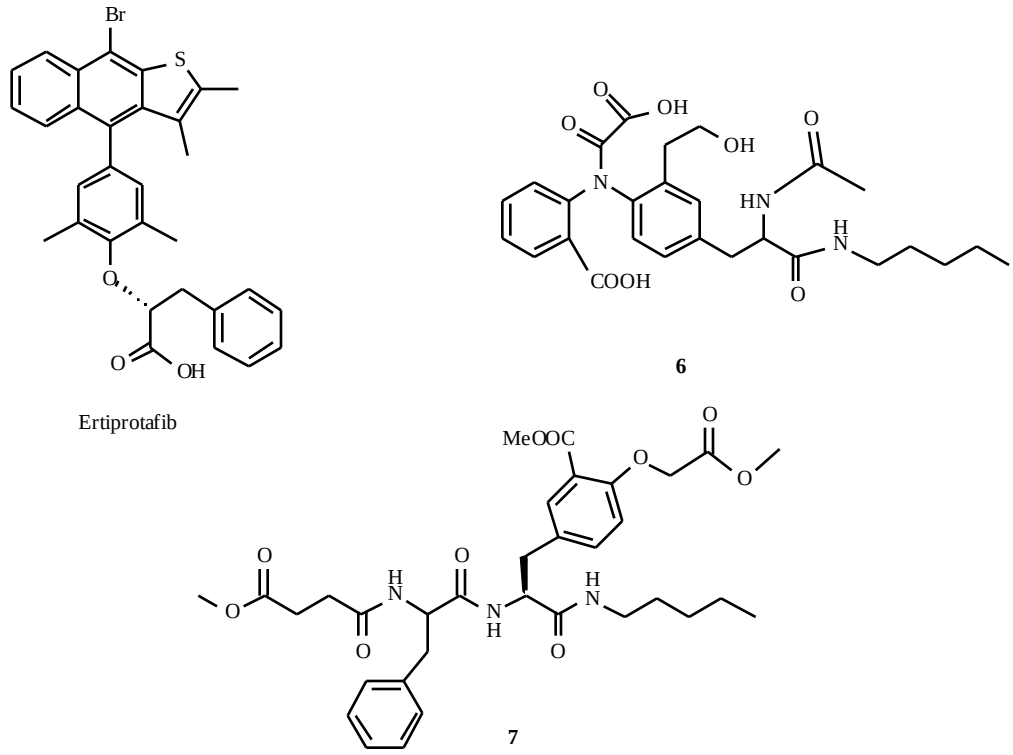


Fig. (12). Chemical structures of some PTP1B inhibitors.

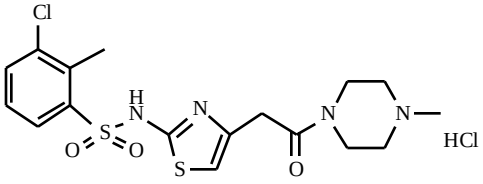
resistance and obesity. Although there are a number of molecules in discovery and early preclinical stages, there is no single compound in development. Ertiprotafib (Fig. **12**) was being developed by Wyeth (formerly Wyeth-Ayerst); however, development was discontinued after phase II in June 2002 [IDdb report]. One benzoic acid derivative (**6**) from Abbott and a series of peptidomimetics, of which **7** (Fig. **12**) is a lead from Biovitrum, are being investigated for treatment of diabetes.

The issue of specificity in developing protein phosphatase inhibitors has been raised as residues in protein kinases, which interact with ATP, are conserved. A principal challenge that lies beyond the discovery and characterization of novel PTPases will be the ability to select the appropriate target enzyme for modulation.

2.5. 11β-Hydroxysteroid Dehydrogenase Type 1

The major "glucostatic" organ liver provides glucose from glycogenolysis and gluconeogenesis to maintain circulating concentration of ~110 mg/dL. Insulin normally attenuates hepatic glucose output by inhibiting key gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase) and glycogen phosphorylase. On the contrary, glucocorticoids increase hepatic glucose production through induction of PEPCK and G6Pase, and excessive concentration of glucocorticoids can cause glucose intolerance and insulin resistance, probably through dysregulated hepatic gluconeogenesis and impaired insulin action in skeletal muscle and adipose tissue. The enzymes 11β-hydroxysteroid dehydrogenase (11β-HSD) types 1 and 2 interconvert glucocorticoids between inactive and active forms, thereby regulating the agonist concentration and activation of corticosteroid receptors [112]. Chronic exposure to high circulating glucocorticoid levels (Cushing's syndrome) causes visceral obesity and the associated metabolic abnormalities of insulin resistance, type 2 diabetes, dyslipidemia, and hypertension. A working hypothesis is that local production of active glucocorticoid from the inactive form can impair glucose metabolism and that selective inhibition of 11β-HSD-1 could ameliorate excessive hepatic glucose output and improve peripheral glucose uptake by preventing the conversion of cortisone to cortisol, the active glucocorticoid.

Novel antidiabetic arylsulfonamidothiazoles were presented by Barf and co-workers [113], which exert action through selective inhibition of the 11β-HSD1 enzymes, thereby attenuating hepatic gluconeogenesis. The amide derivative **8** was shown (Fig. **13**) to potently inhibit human 11β-HSD1 (IC_{50}=52 nM).



8. BVT-2733

Fig. (13). Chemical structure of BVT-2733.

Biovitrum and Amgen are co-developing BVT-3498 (AMG-311) together, the lead in a series of 11β-HSD1 inhibitor for the potential treatment of type 2 diabetes with BVT-2733 (**8**) as back up. Bayer Corporation disclosed some of their early discoveries [114] in 2002 but no development is reported. Merck & Co also reported [115]

preparation of 1,2,4-triazole derivatives as 11β-HSD1 inhibitors useful for the treatment of diabetes, obesity and dyslipidemia. Very recently AstraZeneca reported [116] some ketone derivatives as 11β-HSD1 inhibitors for the treatment of diabetes, obesity, hypertension and dyslipidemia.

3. Insulin Secretagogues

3.1. Glucagon-Like Peptide-1 (GLP-1)

Glucagon-like peptide-1 (GLP-1) is an incretin peptide hormone released upon absorption of nutrients from the endocrine (L) cells of the distal intestinal mucosa followed by glucose-dependent increase in secretion of insulin. This 30-amino acid peptide is known to improve insulin synthesis and secretion, stimulate β-cell growth, promote satiety, delay gastric motility, increase glucose disposal in fat, muscle and liver, improve insulin receptor binding and decrease glucagon and gluconeogenesis, all of which collectively contribute to overall normalization of glucose level [117]. All of these effects taken together put GLP-1 to be an obvious drug candidate for the treatment of type 2 diabetes. Apart from food intake lowering the glucagonostatic effect is particularly interesting as type 2 diabetic patients are characterized by increased plasma glucagon levels, which again leads to an increased hepatic glucose output [118,119]. The stimulatory effect of the cleavage fragment (7-36 amide) of proglucagon produced by small intestinal L-cells on insulin release is the result of multiple effects on the stimulus-secretion coupling chain. Near normalization of diurnal plasma glucose concentrations were obtained during continuous intravenous infusion of GLP-1 in type 2 diabetic patients [120]. However, it was proved that simple subcutaneous injections of GLP-1 are ineffective [121]. GLP-1 is metabolized extremely rapidly (half-life is ~ 5 min) by the ubiquitous enzyme Dipeptidyl peptidase IV (DPP-IV), which cleaves a dipeptide from GLP-1 and thereby inactivates it. In fact, the metabolite of GLP-1 may act as a GLP-1 receptor inhibitor [122]. As this peptide must be administered parenterally, this may limit its use. Again very short half-life restricts its use as drug. Slow-release formulations and sublingually absorbed form of GLP-1 are being considered as effective agent for the treatment of type 2 diabetes.

Amylin and Lilly are co-developing exenatide (AC-2993, synthetic exendin-4), a 39-amino acid, GLP-1 agonist derived from the saliva of the Gila monster lizard (*Heloderma suspectum*) as a potential injectable treatment for type 2 diabetes. In phase III trials, 155 subjects received exenatide 5 μg/kg bid for the first 4 weeks and 10 μg/kg bid for the remainder of the study. The mean HbA_{1c} level fell from 8.6 at baseline to 7.2 at week 20. Baseline fasting plasma glucose also decreased by 30.3 mg/dl at week 4, and was sustained throughout the study. Body weight decreased by 2.4 kg from the baseline 89.2 kg measurement. Mild-to-moderate nausea was the most frequent adverse event, and led to withdrawals of six patients from the study. In January 2004, 52-week data were presented at the J. P. Morgan Healthcare conference in San Francisco, CA. The data demonstrated an average reduction in HbA_{1c} of 1.2% (n = 52), with 46% of the patients achieving an HbA_{1c} measurement of 7% or less. A reduction in mean body weight of 8 lb at 52 weeks was observed [IDdb report]. FDA has already accepted the data.

ConjuChem Incorporation has a clinical candidate, CJC-1131, in phase II clinical trials. CJC-1131 is a peptidase-resistant GLP-1 analog, which selectively binds to serum albumin using DAC (drug affinity complex) technology. In June 2003, ConjuChem released interim results from ongoing trials showing control of glucose in diabetic patients with minimal adverse events. In June 2004, clinical data on this trial were presented at the 64th ADA scientific sessions in Orlando, FL. A total of 22 patients were treated at the same dose level for 14 days or for 20 days at 12 μg/kg. CJC-1131 was generally well tolerated and dose-dependently reduced glycemic levels. Interim data from more than 80 patients who had completed the titration stage showed that there was a significant reduction of HbA_{1c}, glucose normalization was achieved in 80% of patients and 27% of patients reached the target HbA_{1c} level of 7% or less. Some mild-to-moderate transient nausea and vomiting was observed. In July 2004, part of the main results from this trial was released. Glycemia was lower in treated patients by more than 30% compared to the no treatment cohort. DAC:GLP-1 resulted in weight loss of 2.5 kg, while the reduction of weight in the no treatment cohort was 1.5 kg. Average fasting glucose was lower in the treated patients compared to the no treatment control cohort by 29.7% [IDdb report].

Novo Nordisk, under license from Scios, is developing liraglutide (NN-2211), a stable analog of GLP-1, as a potential once-daily treatment of type 2 diabetes and diabetes-associated obesity. In June 2004, clinical data were presented at the 64th ADA scientific sessions in Orlando, FL. Liraglutide resulted in a significant reduction in fasting serum glucose (decrease of 1.37 mM) compared with metformin alone. In June 2003, at the 63rd ADA meeting in New Orleans, LA, a study report of treatment with liraglutide at 6 μg/kg qid for 1 week on 13 patients with type 2 diabetes showed a significant reduction in 24-h plasma glucose levels. No hypoglycemic events were reported. In October 2003, at IBC's Drug Discovery and Development for Metabolic Diseases conference in Copenhagan, Denmark, it was shown that following 12 weeks of treatment at 0.75 mg, qid, weight loss was modest (~1 kg) in conjunction with an approximate change in HbA_{1c} of 0.7 percentage points. This is expected to enter in phase III clinical trial soon where long-term efficacy will be evaluated [IDdb report].

3.2. Dipeptidyl Peptidase IV Inhibitors

Inhibition of DPP-IV, a ubiquitous yet highly proline specific serine protease that cleaves N-terminal dipeptides from polypeptides with L-proline or L-alanine at the penultimate position, is a novel therapeutic approach to the treatment of type 2 diabetes [123,124]. It is also known as lymphocyte cell surface protein CD26, which is a widely expressed glycoprotein that exhibits three principal biological activities: in humans it acts as an adenosine deaminase (ADA)-binding protein; it contributes to extra cellular matrix binding and it exhibits post proline or alanine peptidase activity. The active form of the incretin hormone GLP-1 (GLP-1[7-36] amide) falls rapidly following postprandial excursion to its inactive form (GLP-1[9-36]

amide) with a half-life of approximately one minute. DPP-IV is thought to be the primary enzyme responsible for this hydrolysis [125] *via* cleavage at the N-terminal region after L-proline or L-alanine, although, to a lesser extent, neutral endopeptidase (NEP 24.11) is also responsible [126]. Inhibition of DPP-IV, therefore, is expected to significantly reduce inactivation of GLP-1[7-36] and should lead to an increase in circulating levels of the active form of the hormone. Supporting evidence for this comes from DPP-IV deficient mice [127,128], which have elevated levels of GLP-1[7-36]. DPP-IV inhibitors act as indirect stimulators of insulin secretion by stabilization of GLP-1.

Serum DPP-IV activity is decreased during pregnancy [129], in patients with active Crohn's disease [130], active major depressive illness [131,132], eating disorders [133], active systemic lupus erythematosis [134] or rheumatoid arthritis [135]. Of other potential clinical relevance to diabetes therapeutics, DPP-IV activity is significantly reduced in hypertensive patients treated with angiotensin-converting enzyme (ACE) inhibitors [136].

Several small molecule inhibitors of DPP-IV have been reported in literature and some of them have entered into clinical trials [137-139]. Out of these, compounds **9** and **10** (Fig. **14**) from Novartis are the most potent inhibitors of DPP-IV (IC_{50} = 22 and 3.5 nM) respectively.

Limited information is presently available concerning the clinical efficacy of DPP-IV inhibitors in the treatment of patients with type 2 diabetes. Clinical proof of concept has already been established in phase II trials with DPP-728 (**9**) and LAF-237 (**10**) [137,140]. LAF-237 has entered phase III trials. In a placebo-controlled clinical study, LAF-237 reduced HbA_{1c} fasting and prandial glucose levels both in patients treated with 100 mg tid (n = 30) and 150 mg bid (n = 30) of the drug after 4 weeks of treatment, compared to no reduction of glucose levels in the 23 patients treated with placebo. The overall insulin exposure in the LAF-237 treated patients was not increased and good tolerability was observed [140]. Probiodrug AG is developing another compound, P32/98, in collaboration with Merck & Co (**11**, Fig. **14**). In type 2 patients, 60 mg/kg dose improved the insulin secretion by 70%; and in combination with acarbose or glibenclamide, improved excursions by 20.1 and 31.3% respectively [141]. LAF-237 has been reported to worsen the pre-existing hypertension and mild peripheral edema, suspected to be treatment related [142,143], underlining the need for careful monitoring of both cardiovascular function and fluid homeostasis.

DPP-IV is reported not only to degrade regulatory peptides with Pro or Ala in position 2 [144] but also to play an important role in the immune system. As a membrane associated molecule on the surface of T-cells DPP-IV has a function in the immune system by contributing to T-cell activation and proliferation [145].

GLP-1 is a substrate for the neutral endopeptidase 24.11 (NEP 24.11) [126], an enzyme found in kidney [146]. Dual inhibition of NEP and DPP-IV may allow the body to rescue more GLP-1 than the inhibition of DPP-IV alone. Indeed dual NEP and DPP-IV inhibition has been demonstrated to give more marked insulin release than DPP-IV inhibition alone in a pig glucose challenge model [147]. Compounds having dual inhibitory activity have been reported recently [148].

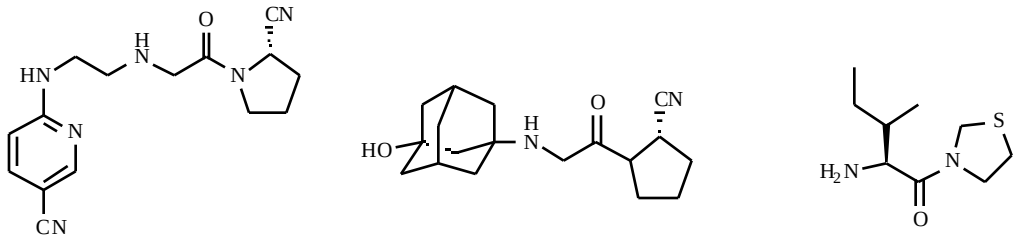
4. β_3-Adrenoceptor Agonists

β_3-Adrenoceptor, a member of G-protein coupled adrenoceptor family, is present in brown and white adipose tissues [149]. β_3-Adrenoceptor agonists regulate lipolysis and hence oxygen and energy consumption in skeletal muscle and adipose tissue [150]. The stimulation of this pathway by selective β_3-Adrenoceptor agonists has been reported to promote fat oxidation thereby improving insulin sensitivity in both rodents and humans [151-153]. But non-pharmacological methods of achieving this are often unsuccessful and attempts to stimulate metabolism in patients with obesity using sympathomimetic agents and thyroxine have led to unacceptable side effects [154]. In obesity, defective thermogenesis may contribute to insulin resistance. Drugs with β_3-Adrenoceptor agonist activities have been tested in patients with type 2 diabetes because of possible weight-lowering effects as well as for antihyperglycemic activity [155].

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 [44]. Among the compounds under active development SR-59611 (**12**) from Sanofi-Synthelabo is in phase III clinical trials. Apart from that Yamanauchi has a compound (YM-178) in phase II trials. KUL-7211 (**13**, Kissei), GW-427353B (**14**, GSK), N-5984 (**15**, Kyorin-Nisshin), L-796568 (**16**, Merck & Co.) and KUC-7483 (Kissei) are some of the compounds in phase I clinical trials (Fig. **15**).

5. Hepatic Glucose Output Inhibitors

Glucose homeostasis is the result of glucose utilization by the brain and the peripheral tissues (muscle and fat), the



9: DPP-728 **10:** LAF-237 **11:** P23/98

Fig. (14). Reported DPP-IV Inhibitors in Phase II clinical trials.

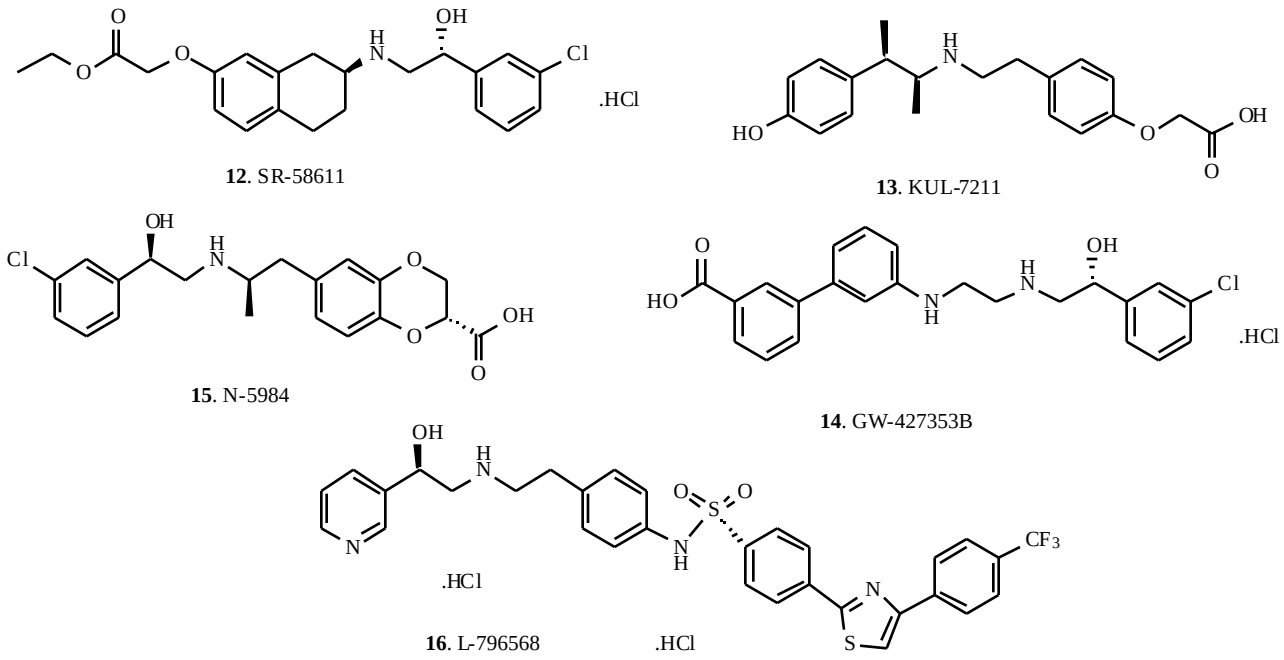


Fig. (15). Reported b3-Adrenoceptors in clinical trials.

intestinal absorption of carbohydrates after a meal and the uptake and release of glucose by the liver. The liver, therefore, plays a central role in maintaining the glucose homeostasis in blood. Under normal conditions, the liver's ability to produce and dispose of glucose is well balanced by the plasma concentrations of insulin and the counter-regulatory hormone glucagon [156-158]. In type 2 diabetes, fine-tuning between glucagon and insulin is disturbed resulting in an increased glucagon/insulin ratio [159]. A major contributing factor for fasting hyperglycemia is an inappropriately high production of glucose in liver. HGO is a consequence of two distinct and highly regulated processes: gluconeogenesis and glycogenolysis. Two main enzymes responsible are G-6-Pase and fructose-1,6-bisphosphatase (FBPase).

G-6-Pase catalyses the terminal step in both gluconeogenesis and glycogenolysis by converting Glucose-6-Phosphate (G-6-P) to glucose and inorganic phosphate [160,161] making it a key regulating step in blood glucose homeostasis [162]. On the other hand, glucose sensing ability of β-cells is represented by the activity of glucokinase (GK) [163,164], which controls the overall carbon flux through glycolysis. Novo Nordisk is investigating a series of 4,5,6,7-tetrahydrothienopyridines that act as G6Pase inhibitors [IDdb report]. Data presented in September 2000 at the 16th International Medicinal Chemistry Symposium indicates that there is an issue of species selectivity (rats vs human), which needs to be addressed.

In the gluconeogenesis pathway, FBPase enzyme catalyses the conversion of fructose-1,6-bisphosphate to fructose-6-phosphate [156]. The activity of FBPase in the liver is regulated by fructose-2,6-bisphosphatase and AMP. AICAR, an AMP mimetic, is a low affinity FBPase inhibitor, which has been shown to suppress hepatic gluconeogenesis in hepatocytes [165] and to lower hepatic glucose output *in vivo* in fasting mice [166]. Metabasis/Sankyo is developing CS-917 (MB-6322, a purine neucleotide analogue as FBPase inhibitor, which is in phase II clinical trials. Pfizer is investigating a series of indole carboxylic acid derivatives as FBPase inhibitors.

6. AMPK Activators

AMPK is a highly conserved sensor of cellular energy status found in all eukaryotic cells. It is activated by stimuli that increase the cellular AMP/ATP ratio. Essential to activation of AMPK is its phosphorylation at Thr-172 by an upstream kinase, Adenosine Monophosphate-activated Protein Kinase Kinase (AMPKK), whose identity in mammalian cells has remained elusive. AMP-related kinases are stimulated by metformin or AICAR, which activate AMPK. AMPK modulates many metabolic processes in response to fluctuations in cellular energy status. AMPK appears to be an important regulator of energy metabolism in skeletal muscle during exercise [167,168].

Treatment of diabetic animals with the AMPK activator AICAR reduces blood sugar levels [169,170]. AMPK is a heterotrimeric protein; each of its subunits exists in multiple isoforms, with differential tissue expression [171]. Target proteins for phosphorylation by AMPK include ACC, HMG-CoA reductase, and endothelial nitric oxide synthase. Recent data suggest that the effects of metformin [25], adiponectin [172], and other agents that regulate glucose and free fatty acid metabolism [173] may be mediated at least in part *via* AMPK activation. Chronic activation of AMPK mimics several effects of exercise in skeletal muscle, such as induction of mitochondrial oxidative enzymes, enhancement of glucose transport, and induction of GLUT4 expression [174]. Given that some of the targets of AMPK phosphorylation are involved in the control of lipid and lipoprotein metabolism, AMPK activation in diabetics might favorably modulate lipid metabolism as well as glucose metabolism. Very recently Les Laboratoires Servier has reported [175] some imidazopyridine derivatives as AMPK activators.

CONCLUDING REMARKS

Manifestation of non-insulin dependent diabetes mellitus could arise from uncontrolled hepatic glucose output or insulin resistance or impaired glucose tolerance in peripheral tissues or from a combination of any of them or all. Uncontrolled insulin resistant type 2 patients develop several macrovascular complications like hyperglycemia, hyperinsulinemia, dyslipidemia and hypertension and microvascular complications like neuropathy, retinopathy and atherosclerosis develop increasing the morbidity and mortality rate. Currently available oral anti-diabetic drugs not only fall short in terms of efficacy and safety but also address these defects only individually. This gap is slightly minimized by very recently initiated combination therapy.

Clinical trials of several molecules have helped understand the disease in the human context and validate the treatment hypotheses and strategies. The understanding that the disease is a metabolic syndrome of interrelated symptoms has instigated the researchers to discover a unique solution that would effectively address these issues in one go. The discovery of dual PPAR agonists with an unknown optimized ratio of PPAR-γ and α, with lesser side effects from PPAR-γ may be a step forward to this direction. PPAR PAN agonist or partial PPAR-γ agonist concepts might also lead to discovery of novel insulin sensitizers without side effects of TZDs. Other mechanisms, which target insulin secretion without excessive use of the pancreas and which effect insulin biosynthesis, may offer a better solution, including inhibition of DPP-IV or modulation of GLP-1. After the introduction of TZDs as insulin sensitizer, peptidase resistant GLP-1 peptides seem to be the major breakthrough for the treatment of type 2 diabetes. Given the beneficial role GLP-1 in other metabolic syndrome, this has the potential to become a major therapy for type 2 diabetes. As a therapy of type 2 diabetes, the choice of appropriate PTPase to target is problematic since none of the candidate PTPases has been validated. Inhibition of HGO has not been strictly validated in the clinic since metformin has multiple actions in addition to its effects in liver. The combined action in muscle and liver of glucose metabolism by AMPK activators may have broader impact but proof of concept is yet elusive. The hypothesis that active glucocorticoid cortisol can repair impaired glucose metabolism and that selective inhibition of 11β-HSD-1 could ameliorate excessive hepatic glucose output and improve peripheral glucose uptake by preventing the conversion of cortisone to cortisol, could take an important position in drug discovery research. The prevention or reversal of insulin resistance and glucose intolerance before the onset of overt type 2 diabetes will likely become the next target. It seems that in near future, the drugs with multiple actions will be the drugs of choice to combat the epidemic of type 2 diabetes and its associated disorders.

ACKNOWLEDGEMENTS

The authors extend their esteemed gratitude to Discovery Research management and Metabolic Disorders Group colleagues for their continuous support and encouragement for this review.

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