Chapter 1

Current Therapeutic Approaches for the Management of Diabetes Mellitus
1.1 Introduction

Diabetes mellitus or metabolic syndrome is characterized by increased blood sugar level. Despite various advances in molecular pharmacology and drug development diabetes mellitus affects around 6% of adults in western society, which is expected to be 300 million\textsuperscript{1,2} by 2010.

Type 2 diabetes (T2D) is identified by insulin resistance/obesity, associated\textsuperscript{3,4} with microvascular complications (blindness, neuropathy and nephropathy)\textsuperscript{5,6} and macrovascular complications like atherosclerosis, limb amputation.\textsuperscript{7,8} T2D is the most common form of diabetes prevalent in 90-95% of diabetics.\textsuperscript{1} Type 1 diabetes (T1D) accounts for 5-10% of all diabetes, is caused by insufficient insulin secretion due to autoimmune destruction of pancreatic $\beta$-cells.\textsuperscript{9,10} T1D is prevalent in children while T2D is a disease of adults. However this classification seems to be insufficient as prevalence of T2D is increasing in younger age group.\textsuperscript{11,12} In this situation presence of C-peptide and absence of markers of autoimmunity such as antibodies to glutamic acid decarboxylase may help to diagnose\textsuperscript{13} T2D.

In view of rapidly increasing diabetes WHO and American Diabetes Association have reduced the figure of the blood glucose level from 140 mg/dl to 126 mg/dl for the risk of diabetes.\textsuperscript{14,15} Glycosylated haemoglobin (HbA\textsubscript{1c}) which is a marker of average plasma glucose concentration is still valid for the diagnosis of T2D.\textsuperscript{17}

Current therapeutic approaches for the management of T2D have been developed on the basis of understanding of molecular pathways of cell and targets available. Diet, physical exercise and antidiabetic drugs are main treatment for the type 2 diabetes.

1.2 Insulin or Insulin Secretagogues

1.2.1 Insulin

Insulin is a peptide hormone secreted from $\beta$-cells of pancreas, which mediates glucose transport from blood to the cells. For past few years insulin is being used for the treatment\textsuperscript{17} of T2D. It regulates the blood glucose primarily by stimulating translocation of glucose transporter GL\textsubscript{UT4} from intracellular sites to the membrane. It also controls the blood sugar level by inhibiting gluconeogenesis, glycogenolysis\textsuperscript{18} and metabolism of free fatty acid.\textsuperscript{19} Insulin acts through signal transduction mechanism by interacting with insulin receptor present on cell membrane of all cell types mostly liver and fats. Insulin receptor is tetrameric glycoprotein consisting of 2$\alpha$ and 2$\beta$ subunits, linked by disulfide bond and spread across the membrane. The $\alpha$- and $\beta$-subunits function as allosteric enzymes in which $\alpha$-subunit inhibits
the tyrosine kinase activity of β subunit. Binding of insulin to the binding site present in α-subunit induces aggregation and internalization of receptors along with the bound insulin molecule leading to the stimulation of kinase activity in β-subunit followed by transphosphorylation and a conformational change of receptor that further increases kinase activity of β-subunit which ultimately leads to the stimulation of insulin metabolizing enzymes. Insulin action is also mediated by certain second messengers like phosphatidyl inositol glycan (PIG) and diacylglycerol (DAG) formed by specific phospholipase C.

Very recently, a new chemical substance, hepatic insulin sensitizing substance (HISS) has been discovered which is yet to be identified chemically. HISS is secreted from liver in response to the injection of insulin and brings about 50-60% of glucose disposal in a dose dependent manner of insulin for a wide range (5-100 mL/Kg).

Insulin is administered by subcutaneous injection, which is not always convenient mode of drug administration. Moreover, exogenous insulin does not replicate the normal pattern of the nutrient related and basal insulin secretion. The difference in the action of injected and endogenously secreted insulin is due to difference in their pharmacokinetic paths. These shortcomings have been minimized by developing rapid acting insulin analogs, insulin lyspro and insulin aspartate. Long acting insulin analogs, insulin glargine and insulin detemir are available for the treatment of type 2 diabetes. Another insulin analog insulin glusine is currently in advance clinical trials.

1.2.2 Sulfonyl Urea Receptors (SUR)
Sulfonylurea receptor represents one of the most important classes of KATP channels, found in β-cells of pancreas. Sulfonylurea insulin secretagouges act through these receptors, which exert their actions in response to the cytosolic concentration of ATP as shown in Figure 1. The increase in ATP concentration on glucose metabolism in normal conditions closes the KATP channels leading to membrane depolarization of the β-cells of pancreas. The depolarized membrane opens voltage dependent calcium ion channels resulting Ca\(^{2+}\) entry into the cell. The increase in intracellular calcium ion concentration triggers insulin exocytosis. Advances in molecular biology and electrophysiology indicate that KATP channel consists of two subunits, a regulatory subunit (SUR1, SUR2) and pore forming K\(^{+}\) inward rectifier (Kir 6.1, Kir 6.2). Assembling of a pore forming subunit Kir 6.2 and regulatory SUR1 in 4:4 stoichiometric ratio form heteroctameric functional sulfonylurea receptor Figure 2. The sulfonylurea receptor subunit comprises of seventeen transmembrane proteins while
Figure 1. KATP channels respond to changes in ATP/ADP to regulate $K^+$ current driven by a concentration gradient.

inward $K^+$ rectifier has only three membrane spanning proteins with N and C terminal lying inside the cytosol.$^{28,29}$

Figure 2. Composition and stoichiometry of KATP channels are assembled from a sulfonylurea receptor, SUR and either $K_{IR6.1}$ or $K_{IR6.2}$ in an octameric stoichiometry. Some of the results, which support an octameric model, are outlined.
1.2.3 Sulfonylureas as Insulin Secretagogues

Sulfonylurea insulin secretagogues being the first line of oral antidiabetic therapy have been studied extensively. Carbutamide, the first sulfonylurea was initially discovered serendipitously, later other members of this series followed the pursuit. These compounds have been classified as first generation and second-generation sulfonylureas. The important first generation sulfonylureas are shown in Table 1.

![Chemical structure](image)

Table 1

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name of the drug</th>
<th>R₁</th>
<th>R₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbutamide</td>
<td>NH₂</td>
<td>C₄H₉</td>
</tr>
<tr>
<td>2</td>
<td>Tolbutamide</td>
<td>CH₃</td>
<td>C₄H₉</td>
</tr>
<tr>
<td>3</td>
<td>Chlorpropamide</td>
<td>Cl</td>
<td>C₃H₇</td>
</tr>
<tr>
<td>4</td>
<td>Tolazamide</td>
<td>CH₃</td>
<td>Piperidin-1-yl</td>
</tr>
<tr>
<td>5</td>
<td>Acetohexamide</td>
<td>H₃CCO</td>
<td>Cyclohexyl</td>
</tr>
</tbody>
</table>

These compounds act by blocking K<sub>ATP</sub> channel of β-cells causing membrane depolarization and calcium ion influx into the cell causing insulin secretion as described above. Refractory failures, hypoglycemia and weight gain<sup>31,32</sup> are major side effects of these agents. To avoid hypoglycemic episodes, sulfonylureas are given alongwith potassium ion channel opener dizoxide, a cardiovascular drug.

![Chemical structures](image)

The clinically available second generation sulfonylureas are glyburide (glibenclamide or micronase), glipizide (glucotrol), gliclazide (diamicron) and glimepiride (amaryl). The second generation sulfonylureas are safe as compared to first generation probably because of...
their better pharmacokinetic profile. Like first generation of sulfonylureas these agents also bring about insulin secretion by blocking ATP sensitive K⁺ channels\textsuperscript{33,34} of β- cells in pancreas. Recently, it has been observed that the binding sites of second-generation sulfonylureas on KATP channels\textsuperscript{35,36} are different from that of first generation sulfonylureas.

1.2.4 Non-sulfonylureas as Insulin Secretagogues

These compounds have rapid onset but short duration of action, which make them suitable agents for treatment of hyperglycemia as well as hyperinsulinemia. Initially meglitinide the first member of this series an analog of glibenclamide was studied for its antidiabetic and insulinotropic activity more than two decades ago.\textsuperscript{37} Structural manipulations of this compound led to the development of other members.\textsuperscript{38} Repaglinide (prandin), nateglinide mitiglinide and an interesting morpholinoguanidine derivative BTS 67 582 are new insulinotropic agents. Mitiglinide is under regulatory review\textsuperscript{27} and likely to be released into the market soon.

Repaglinide, like second-generation sulfonylurea (glibenclamide) initiates insulin secretion by closing KATP channel. A high affinity repaglinide binding site compared to glibenclamide has been identified in β-TC3 insulinoma cells. Repaglinide unlike glibenclamide neither cause insulin secretion from β-TC3 in absence of blood glucose nor enhances exocytosis in voltage clamped β-cell,\textsuperscript{39} which make it a safer drug for treatment of Type 2 diabetes.\textsuperscript{40} Nateglinide and mitiglinide both bind to sulfonylurea receptor like glibenclamide. But mitiglinide has been found to be more selective in COS-1 cell for (Kir 6.2/SUR1) than nateglinide which also interact with extra pancreatic KATP channel.\textsuperscript{41} Nateglinide interacts with the KATP channel faster than repaglinide but slower than glibenclamide thus nateglinide restore insulin secretion fast as compared to repaglinide.\textsuperscript{42,43}

However the effect of nateglinide last faster than that of repaglinide or glibenclamide.\textsuperscript{44} The BTS 67 582 does not act through sulfonylurea receptor but mainly through KATP channels.\textsuperscript{45,46} These compounds are useful in the treatment of refractory hyperglycemia of 1st and 2nd generation sulfonylurea. Non-sulfonylurea compounds are superior drugs with respect to first and second generation sulfonylureas because they do not cause hypoglycemia and weight gain. Repaglinide is more active compared to nateglinide.\textsuperscript{47} These drugs are taken before meal which induce a rapid postprandial insulin response. Pharmacological activity of repaglinide, mitiglinide and glibenclamide has recently been compared very elegantly.\textsuperscript{48}
1.3 Enhancing Glucose Mediated Insulin Secretion

1.3.1 GLP-1 (Glucagon like peptides)

Glucagon like peptides, GLP-1 (7-36 amino acids) and GLP-2 (33 amino acid) belong to the super family of glucagon hormone secreted from enteroendocrine L-cells located in distal intestine in response to enteral nutrient ingestion especially carbohydrate and fats.\(^49\)

**Structural Organization of Mammalian Preproglucagon**

![Structural Organization of Mammalian Preproglucagon](image)

**Figure 3.** Structure of proglucagon and molecular forms GLP-1 and GLP-2. The molecular forms GLP-2-immunoreactive peptide peptides include the major proglucagon fragment(MGF), bioactive GLP-2\(^1-33\) and bioinactive GLP-2\(^3-33\).
In the precursor proglucagon, both GLP-1 and GLP-2 are found next to the glucagons as shown in Figure 3. Glucagons like peptides are liberated from proglucagon by enzymes hormone convertases.\textsuperscript{50,51}

GLP-1 and GLP-2 induce insulin secretion to transport glucose across plasma membrane in response to food intake (Figure 4). The other major physiological functions of GLPs are inhibition of glucagons secretion, gastric emptying, and satiety.\textsuperscript{52} The insulinotropic function of GLP-1 and GLP-2 are mediated by glucagon like peptide-1 receptor and glucagon like peptide-2 receptor. The structures of these receptors are quite similar with each other and possess significant homology with other endocrine hormone glucagon, and glucose dependent insulinotropic polypeptide (GIP) receptors. These are G-protein linked receptors localized mainly in $\beta$-cells. GLP-1 and GLP-2 activate second messenger cAMP to provoke their insulinotropic activity (Figure 4).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.png}
\caption{The biological activities of glucagons GLP-2 secreted from intestinal endocrine cells.}
\end{figure}

It is also predicted that GLP-2 mediates its biological activity via activating $\text{Ca}^{2+}$ inositol triphosphate pathways.\textsuperscript{51} The GLP therapy is preferred over sulfonylurea because they effect insulinotropic properties only in presence of glucose and do not cause hypoglycemia, which is generally associated with sulfonylurea. But basic limitation of this therapy is the low bioavailability of these peptides due to short half-life as they are degraded by enzyme dipeptidylpeptidase IV (DPP IV). These limitations have been minimized either by synthesizing inhibitors for dipeptidylpeptidase enzyme\textsuperscript{53} or by developing analogs of GLPs which are resistant to DPP-IV. The Ile-thiazolidide and NVP-DPP728 orally active inhibitors
A natural peptide agonist, exendin-4 has been isolated from lizard venom with increased half-life in plasma and a prolonged antidiabetic effect.

Ile-thiazolidide  
NVP-DPP728

1.3.2 α2-Adrenoceptor Antagonist and Imidazoline Receptor

α2-Adrenoceptor agonists are basically cardiovascular drugs, which act on KATP channels present on smooth muscles in cardiomyocytes. These agonists can be used as insulinotropic agents by blocking channels of pancreatic β-cells. Imidazoline derivatives bind to a putative imidazoline binding sites in KATP channel resulting insulin secretion. These agents stimulate direct Ca$^{2+}$ entry into cell to secrete insulin in a dose dependent manner. Moxonidine and midazlizole well known antihypertensive drug have been studied for α2-adrenoceptor antagonistic activity. Thus these compounds could be useful for the treatment of hypertension.

Moxonidine  
Midazlizole

1.4 Inhibitors of Hepatic Glucose Production

1.4.1 Glucagon Antagonist

Liver being a metabolic organ maintains normal blood glucose level by regulating production of endogenous glucose through gluconeogenesis and glycogenolysis in diabetics. Hepatic glucose production occurs due to insufficient insulin secretion or development of insulin resistance in the liver. Glucagon a 29 amino acid peptide hormone secreted from α-cells of pancreas catalyzes both gluconeogenesis as well as glycogenolysis. Thus glucagon antagonists are highly desirable to suppress formation of glucose by the liver. Several
enzymes that regulate rate-controlling steps in gluconeogenesis and glycogenolysis are obvious targets to inhibit hepatic glucose output Figure 5.

**Key to numbered enzyme**
1. Glucose-6-phosphatase
2. Glucokinase
3. Phosphofructokinase-1
4. Fructose-1,6-bisphosphatase
5. Pyruvate kinase
6. Pyruvate dehydrogenase
7. Pyruvate carboxylase
8. PEPCK
9. Glycogen synthase
10. Glycogen phosphorylase

**Figure 5. Important pathways and regulatory enzymes**
Glucagon is a seven transmembrane G-protein coupled receptor, which mediates its effect via stimulation of cAMP. Numerous glucagon antagonists have been reported from natural and synthetic sources.\textsuperscript{58,59} Styrylquinoxazoline CP-99711 (1) has been reported for glucagon antagonistic activity in rats.\textsuperscript{60}

Pyrrolo[1,2-a]quinoxaline\textsuperscript{61} (2), quinoline hydrazone\textsuperscript{62} (3) showed high affinity for glucagon receptor. The representative examples of each of these classes are shown below.

Mercaptobenzimidazole\textsuperscript{63} NNC-92-1687 (4) the first non-peptide competitive human glucagon receptor antagonist has been reported by Novo-Nordisk. Other human glucagon receptor antagonists include alkylidine hydrazide (5), \(\beta\)-alanine urea,\textsuperscript{64} triaryl imidazoles\textsuperscript{65} (6) and triarylpyrroles (7).\textsuperscript{66}
Recently, an entirely new class of compounds, substituted biaryls has been identified through high-throughput screening as glucagons receptor antagonist. These compounds act by inhibiting cAMP stimulated by glucagons. Out of many derivatives the compounds (8) and (9) were selected for clinical trial but due to undesirable side effects and low bioavailability (40%), further development have been discontinued. Glucagon receptor antagonists have been extensively reviewed.\textsuperscript{67}

![Chemical structures of compounds 8 and 9](image)

The other enzymes that regulate hepatic glucose production are glycogen phosphorylase, fructose-1, 6-bisphosphatase and glucose-6-phosphatase as described in Figure 5.

Recently, a small molecule inhibitor of liver glycogen phosphorylase (CP-91149) has been reported that transiently lowers plasma glucose in ob/ob mice, a mouse model of diabetes, after single oral dose.\textsuperscript{68} Fructose-1,6-bisphosphatase controls a rate limiting step in gluconeogenesis while glucose-6-phosphatase catalyzes final step common to both gluconeogenesis and glycogenolysis for release of glucose from liver, non essential fatty acids, phosphoenol pyruvate. In recent past, glucose-6-phosphatase\textsuperscript{69,70} has been found to be a significant antidiabetic target and an entirely new class of compounds, biaryls are (10,11,12) reported to display for its inhibitory properties.\textsuperscript{71}

![Chemical structures of compounds 10, 11, and 12](image)
1.4.2 Biguanides

Guanidine derivatives constitute a well known class of antimalarials. The antidiabetic properties of guanidine derivatives discovered as a side effect of proguanil, an antimalarial drug. Since then metformin, phenformin and buformin were synthesized as potent antidiabetic drug. The molecular targets of these agents have not yet been identified. Their primary mode of action seems to be inhibition of hepatic gluconeogenesis. Currently, only metformin is in clinical use while other biguanides have been withdrawn due to their side effects of lactic acidosis and weight gain etc.

\[
\begin{align*}
\text{Propguanil} & \quad \text{Metformin} \\
\text{Phenformin} & \quad \text{Buformin}
\end{align*}
\]

Metformin monotherapy is considered to be the first line treatment for patients prone to weight gain and/ or are dyslipidemic and who have failed to achieve adequate glycemic control on dietary management. Metformin is also used in combination with other antihyperglycemic agents and insulin. Metformin at higher doses of 0.5g to 1.50g has an absolute oral bioavailability of 50-60%. The bioavailability of the drug declines at higher oral doses.

1.4.3 Carnitine Palmitoyltransferase Inhibitors

Gluconeogenesis is the process of production of endogenous glucose, which may lead to hyperglycemia as well as hyperinsulinemia. The free fatty acids (FFA) present in plasma undergo β-oxidation in mitochondria, which drives gluconeogenesis at higher rates. Translocation of FFA and its acylated CoA ester across membrane occur through enzyme carnitine palmitoyltransferase. The carnitine palmitoyltransferase I (CPT I) is present on outer
mitochondrial membrane and carnitine palmitoyltransferase II (CPT II) in the inner membrane. CPT I carries CoA ester of FFA across the membrane and then CPT II reconverts long chain acylcarnitine into long chain-CoA ester. These are then β-oxidized to acetyl CoA which activates a key gluconeogenetic enzyme pyruvate carboxylase.\textsuperscript{77} RO-25-0187 and oxfenicine have been reported to inhibit CPT I at manonyl CoA site in rat.

\begin{align*}
\text{RO-25-0187} & \quad \text{Oxfenicine} \\
\text{Etomoxir} &
\end{align*}

Several glycidic esters have been reported for CPT I inhibitor. Etomoxir, a representative example of glycidic acid ester\textsuperscript{78,79} is shown above. Carnitine palmitoyltransferase inhibitors have been more extensively reviewed recently.\textsuperscript{80}

1.5 Targetting Insulin Signalling Pathways

1.5.1 Protein Tyrosine Phosphatase Inhibitors

Protein tyrosine phosphatase forms a large family of enzymes that serve as key regulatory enzyme in signal transduction of various cell signals.\textsuperscript{81} PTP1B is an intracellular enzyme responsible for down regulation of insulin, which was examined in an experiment carried out by deleting PTP in mice. Animals were found healthy, lean and obesity resistant with low level of plasma glucose and insulin. This observation was further supported by gene knock out experiment, which resulted in enhanced insulin signalling through the insulin receptor and insulin receptor substrate (IRS-1). Figure 6 shows proposed substrate for PTP1B in the phosphorylation cascade that is initiated by the insulin receptor. In this cascade, the insulin receptor itself and IRS1 have been implicated as substrate.\textsuperscript{82,83} In the Figure another phosphatase, PTEN/NMAC (phosphatase and tensin homolog) is part of this pathway as phospholipid phosphatase that indirectly stimulates phospho-inositol 3-kinase (PI3K).\textsuperscript{84} PTEN has been recently validated as significant antidiabetic drug target.\textsuperscript{85}
Figure 6. Insulin signalling through the insulin receptor and negative regulation by PTP1B. Binding of insulin (Ins) to the α-chain of the insulin receptor results in dimerization and receptor β-chain kinase activation. This results in autophosphorylation and phosphorylation of insulin receptor substrate-1(IRS-1), -2,-3,-4. The pathway branches into Ras-MAPK cascade and a phospho-inositol-3-kinase (PI3K) catalyzed pathway that results in the transcriptional and post transcriptional activation of GLUTs (glucose transporters). Inhibition of PTP1B and two other phosphatases PTEN and SHP2 stimulate this pathway. However, inhibition of PI3K by PTEN and SHP2 is indirect. Abbreviations: Grb-2, growth factor receptor bound protein-2. GS3β, glycogen synthase kinase. BPTEN, phosphatase and tensin homolog deleted on chromosome ten; SHC, Src-homology-2-containing transforming protein; SHP, Src homology 2-containing tyrosine phosphatase; SOS, son of sevenless protein homolog1.

PTP1B has been established as antidiabetic and antiobesity,86 target that led to design and synthesize inhibitors of the following structures (13, 14, 15) for the enzyme.
Several PTP1B inhibitors are in clinical development.\textsuperscript{87} Since catalytic sites of all the known (112 PTPs) contain common sequence which create selectivity problem in the development of PTP inhibitors.\textsuperscript{88} Recently, diaryloxamic acid\textsuperscript{89} (16) has been identified as selective and potent PTP1B inhibitor for using a linked-fragment strategy at 100 µM concentration.

1.6 Inhibition of Glucose Uptake

These agents slow down the absorption of dietary glucose and consequently controls the blood glucose level. There are basically two strategies to achieve it.

1.6.1 Inhibition of α-Glucosidase Enzyme

α-Glucosidase is an enzyme responsible for the absorption of meal and carbohydrate. Acarbose,\textsuperscript{90} miglitol\textsuperscript{91} and vogalibose\textsuperscript{92} are the important members of this class of compounds. Acarbose is a competitive inhibitor of α-glucosidase enzyme, which retards the process of carbohydrate absorption and delays meal derived glucose in diabetic as well as in normal subjects. These drugs are taken before the meal. The striking side effects of these agents are gastrointestinal, abdominal discomfort, and diarrhea.\textsuperscript{93}
1.7 Enhancers of Insulin Action

Compounds which decrease insulin resistance, called insulin sensitizer or enhancer of insulin action. Thiazolidinediones (TZDs) are chemical compounds that selectively reduce insulin resistance. Ciglitazone, the first member of this class of compounds was discovered serendipitously. Troglitazone, pioglitazone, rosiglitazone are the other important agents of this series. TZDs act by binding to peroxisome proliferator activated receptor-γ (PPARγ) which regulate the transcription of a number of insulin responsive genes intimately involved in the control of glucose and lipid metabolism. 

Liver toxicity the main side effect of TZDs is probably because of elevation of liver enzyme concentration by approximately 2%. In case of troglitazone liver toxicity is so severe that it has been withdrawn from the market and relegated to second line therapy. Rosiglitazone and pioglitazone are comparatively a safe members among all the TZDs. Current status of therapeutic importance of peroxisome proliferator activated receptor in diabetes has been reviewed extensively.

1.8 Antiobesity Agents

Obesity is a multigenic disease associated with several metabolic abnormalities such as insulin resistance, cardiovascular morbidity and cancer etc. This has established obesity as
therapeutic targets for the management of type 2 diabetes. Basically, following three synthetic approaches are currently being practised.

1. Agents reducing energy intake or appetite suppressants
2. Agents affecting energy expenditure.
3. Agents affecting dietary absorption of fats.

1.8.1 Agents Reducing Energy Intake or Appetite Suppressants

Agents, which reduce energy, is called appetite suppressants. These compounds affect secretion of various biogenic amines. Based on the nature of the amines (neurotransmitters) secreted, these agents have been classified into following two categories.

1.8.1.1 Noradrenergic Agents

These agents induce release of noradrenaline from nerves endings in hypothalamus. Noradrenaline release activates postsynaptic $\alpha_1$- and $\beta_1$-adrenoceptor that suppress appetite. Phentermine,$^{105,106}$ phenylpropanolamine,$^{107}$ diethylpropion and mazindol$^{108}$ are the drug of this class for the treatment of obesity. Mazindol is the only drug approved for clinical use. These drugs cause addiction.$^{105}$

1.8.1.2 Serotonergic Agents

This group of appetite suppressants act by inhibiting reuptake of serotonin (5-hydroxytryptamine). Dexfenfluramine, serteraline and fluoxetine are drugs of this class. But they are no longer in clinical use for the treatment of obesity due to untolerable side effects. They have been reviewed extensively.$^{109-111}$
1.8.2 Agents Affecting Energy Expenditure

1.8.2.1 Serotonin-noradrenaline Reuptake Inhibitors

These agents are also called thermogenic agents because they affect energy expenditure. Sibutramine\textsuperscript{104} (4), duloxetine\textsuperscript{112} (5) and venlafaxine\textsuperscript{113} (6) are the drugs available for clinical use. This group of compounds acts by preventing reuptake of serotonin. Sibutramine clinically the most important member of this series also inhibit reuptake of noradrenaline, which minimizes its side effect. Sibutramine metabolized into two metabolites $M_1$ and $M_2$. These metabolites potentiate the effect of sibutramine.

<table>
<thead>
<tr>
<th>Sibutramine</th>
<th>Duloxetine</th>
<th>Venlafaxine</th>
</tr>
</thead>
</table>

1.8.3 Agents Affecting Absorption of Fats

Although number of natural products\textsuperscript{114} have been identified for their pancreatic lipase inhibitory properties but currently only one compound orlistat is available for the management of obesity. Orlistat is a potent and highly specific inhibitor of intestinal lipases. Lipases are the enzymes which breakdown fat, triacylglycerol (TAGs) into free fatty acids and 2 mole of monoacylglycerols. Subsequently these free fatty acids and monoacylglycerols

\[\text{Orlistat}\]

are absorbed. Orlistat is not reported for any serious side effect except steatorrhea.\textsuperscript{104} These agents have been critically reviewed.\textsuperscript{111}
1.9 β₃-Adrenoceptor Agonists

β₃ adrenoceptor is a member of G-protein coupled adrenoceptor family. The agonists of this receptor are very effective for thermogenic antiobesity, lipolysis and insulin sensitizing activity in rodents. Their main sites of action are white and brown adipose tissue and muscle. The β₃-adrenoceptor mRNA levels are lower in human than in rodent adipose tissue and adult human have little brown adipose tissue. β₃-Adrenoceptor agonists fall into three main chemical classes: arylethanolamines (BRL 37344, BRL 35135), aryloxypropanolamines (CGP 12177), and trimetoquinols (CL 316243). The above compounds are in advanced clinical trials. Oral bioavailability and tissue selectivity are striking problems of these compounds.

![Chemical Structures]

BRL 37344, R=H
BRL 35135 R= Me

CL 316243

1.10 Miscellaneous

1.10.1 Tumor Necrosis Factor Alpha (TNF-α)

TNF-α is a proinflammatory cytokines responsible for pathogenesis of a spectrum of diseases. The overproduction of these cytokines (TNF-α) leads insulin resistance that has been established by null mutation in obese. This notion was further supported by significant increase in peripheral insulin stimulated glucose uptake on neutralization of TNF-α in obese fa/fa.
1.10.1.1 Antibodies
These are protein based anti TNF-α drugs available in the form of injectables.\textsuperscript{121} Etanercept, infliximab and adalimumab are drugs recently approved\textsuperscript{122} by US FDA. Patients receiving this therapy have high risk of tuberculosis. Congestive heart failure is the potential risk in patients taking etanercept, infliximab. PEG-sTNFR1 and CDP-870 are in clinical development but further work on PEG-sTNFR1 discontinued due to intolerable side effects.\textsuperscript{123-125}

1.10.1.2 Small Molecules
Thalidomide the first anti-inflammatory agent has been studied for the treatment of diabetes.\textsuperscript{126} Thalidomide acts by altering the synthesis of cytokines. Thalidomide analogs, which have been synthesized after failure of the thalidomide due to serious side effects of teratogenicity and neurotoxicity were found 200-400 folds more active than thalidomide. These are compounds are in advanced clinical trials.\textsuperscript{127}

\textbf{Thalidomide}
\[ \begin{array}{c}
\text{O} \\
\text{O} \\
\text{N} \\
\text{CH} \\
\text{NH} \\
\end{array} \]

\begin{align*}
CC 1069, & R=H, R'=NH_2 \\
CC 1104, & R=H, R'=OCH_3 \\
CC 1115, & R=NH_2, R'=OCH_3
\end{align*}

1.10.1.3 Inhibitors of Phosphodiesterase Type 4 (PDE4)
Intracellular adenosine-3',5'-cyclic monophosphate (cAMP) that inhibit TNF-α formation through activation of protein kinase A (PKA). Activation of PKA prevents transcription factors responsible for the synthesis of TNF-α.

\textbf{Pentoxifylline}
\[ \begin{array}{c}
\text{H}_3\text{C} \\
\text{O} \\
\text{N} \\
\text{CH}_3 \\
\text{N} \\
\text{O} \\
\text{CH}_3 \\
\end{array} \]

\textbf{Theophylline}
\[ \begin{array}{c}
\text{H}_3\text{C} \\
\text{O} \\
\text{N} \\
\text{CH}_3 \\
\text{N} \\
\text{O} \\
\text{H}_3\text{C} \\
\text{O} \\
\end{array} \]

\textbf{Rolipram}
\[ \begin{array}{c}
\text{H}_3\text{C} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{H} \\
\end{array} \]

\textbf{RO-20-1724}
But cAMP is broken down by enzyme phosphodiesterase enzyme type 4. These findings led to the synthesis of pentoxifylline, theophylline and rolipram as inhibitors of PDE4. Rolipram and other PDE4 inhibitors cross blood brain barrier & cause nausea, which limits the clinical use of rolipram. However, CDP-840 and SB207499, the second-generation orally active PDE4 inhibitors devoid of this side effect of nausea have been in advanced clinical trials. The inhibitors of PDE4 have been reviewed recently.

1.10.1.4 Preparation of P38 MAP Kinase Inhibitors

P38 Mitogen-activated kinase plays a central role in the synthesis of TNF-α. This protein belongs to a group of serine/threonine kinases that include c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK). The compounds \( \text{RWJ67657} \) and \( \text{VX-702} \) potent inhibitors of \( \text{P38 MAP kinase} \) are in advanced clinical stage. Another compound pyrazole derivative \( \text{BIRB 796} \) a potent selective inhibitor of \( \text{P38α} \) is in human clinical trial for treatment of autoimmune diseases.

1.10.2 Glucokinase Activators

The pathogenesis of type 2 diabetes is not only obesity/or insulin resistance but also mutations in the genes of regulatory enzymes of glucose. This was established with the discovery of a mutated gene \( \text{encoding glucokinase (GK)} \) in maturity onset diabetes of the young type 2 (MODY2). GK is an enzyme responsible for the phosphorylation of glucose in pancreatic β-cell and hepatocyte leading to glycogen synthesis and decrease in hepatic glucose production. In MODY2 patients there is a net reduction in the formation of glycogen and increase in the production of the glucose in liver. Based on this data, it was proposed to synthesize compounds that can up regulate GK activity [GKA].
Screening of 120,000 synthetic organic compounds of diverse chemical structures led to the discovery of a compound RO-28-1675. It has been found to activate recombinant human glucokinase potentially in a dose dependent manner. Grimsby et al. [unpublished data] have also described that RO-28-1675 caused insulin secretion by a distinct mechanism than sulfonylureas. However, no side effects of RO-28-1675 are reported so far.

1.11 Summary
Recent reports on progress of diabetes have highlighted the importance of antihyperglycemic agents for the management of diabetes mellitus and associated microvascular/macrovascular complications. Majority of the earlier therapeutic agents for the management of diabetes had been developed without defined molecular targets or on the basis of understanding of disease pathogenesis. Advances in molecular pharmacology and medicinal chemistry have given a new insight of molecular pathways of diabetes and its complications. These targets have been identified on the basis of predicted roles in modulating one or more aspects of pathogenesis of diabetes. Important strategies for management of diabetes are: 1) augmenting glucose mediated insulin secretion and insulin sensitivity, 2) inhibiting hepatic glucose production and its absorption by the cells, 3) targeting specific molecular targets in insulin signaling pathways, 4) control of obesity and altered lipid metabolism to improve insulin sensitivity. Most of the targets and compounds have been described in this article with their merits and demerits.

1.12 References
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