Review of Literature
3. REVIEW OF LITERATURE

3.1 Pharmacognosy, Phytochemistry and Pharmacology of Zingiber officinale

Zingiber officinale Roscoe commonly known as ginger is one of the commonly used spices in India and around the world. Zingiber officinale Roscoe is a perennial herb with a subterranean, digitately branched rhizome belonging to the family Zingiberaceae. Zingiber officinale is commonly known as ginger. Ginger is a medicinal plant extensively used in Ayurvedic medicine as home remedy for various diseases. In India the plant is known by different local names in different languages like ada in Bengali, sunth, adu in Gujarati, adrak, sunth in Hindi, sunti in Kannada, inji in Malayalam, allamu in Telugu. Throughout the world ginger is called by various names few of them are as follows chiang, inchi, khuong, shengiang, tangawizi, zinjibil. Ginger is used as a food additive (Spice) in Asian countries and many other parts of the world (Blumenthal, 1998).

Ginger is described as Z. officinale and its taxonomic position is as follows.

- Kingdom: Plantae
- Division: Angiosperma
- Class: Monocotyledoneae
- Order: Scitaminae
- Family: Zingiberaceae
- Genus: Zingiber
- Species: officinale Roscoe
Geographical Distribution

The plant is probably native to South East Asia and is cultivated in the tropical regions in both the eastern and western hemispheres. It is commercially grown in Africa, China, India and Jamaica. India is the largest producer of ginger in the world.

Morphology of the plant

It is a perennial herb with a subterranean, digitately branched rhizome producing stems upto 1.5 cm in height with linear lanceolate sheathing leaves that are alternate, smooth and pale green. Flower stems are shorter than leaf stems and bearing a few flowers, each surrounded by a thin bracket and situated in axis of large, greenish yellow obtuse bracts. Each flower shows a superior tubular calyx, split part way down one side, corolla is orange and yellow colored it is composed of a tube divided above into 3 linear oblong, blunt lobes. Fruit is a capsule with small arillate seeds (Keys, 1976; Youngken, 1950).

Plant material of interest: Dried Rhizome

General Appearance

Ginger occurs in horizontal, laterally flattened, irregular branching pieces, 3-16 cm long, 3-4 cm wide and upto 2 cm thick. It sometimes splits longitudinally. Externally it is pale yellowish buff or light brown colored with longitudinal striations. Internally rhizomes are yellowish brown, showing a yellow endodermis separating the narrow cortex from the wide stele. The cortex contains numerous scattered fibrovascular bundles, abundant scattered oleoresin cells with yellow contents and numerous larger grayish points, vascular bundles, scattered on the whole surface are generally seen (Blumenthal, 1998).

Organoleptic Properties

Ginger possesses characteristic aromatic odour, pungent and aromatic taste, externally it has yellowish buff or light brown in colour and internally it is yellow to brown in colour.

Microscopic Characteristics

Histologically the rhizomes are differentiated mainly into cork, cortex and stele. Cork occurs only in a single zone and are much irregularly arranged. The rhizomes possess isodiametric cortex with thin walled parenchyma cells that contain abundant starch granules. Starch grains are ovoid, elongated and irregularly rounded in shape. Some of the starch grains possess hilum. Stele has parenchymatous ground tissue with
numerous yellow oleoresin secretion cells and vascular bundles. The trachea is often nonlignified and has reticulate thickenings on their secondary walls. Fibers are long, somewhat linear, some of them possess septa (Blumenthal, 1998).

**Powdered Plant Material**

Dried powdered ginger is yellowish white to yellowish brown in colour. The dried powder of ginger contains parenchymatous cells containing starch granules, septate fibers and non lignified vessels with pungent cells. Oleoresin present in oil cells and resin cells are scattered in parenchyma. Starch granules are flat oval, oblong in shape and possess a hilum (Blumenthal, 1998).

**Chemical composition of *Zingiber officinale***

Ginger contains various chemicals which can be grouped into major and minor composition. The major composition includes oleoresin (5.3 to 8.6%), volatile oil (1.5-2.2%), lipids (6-8%), proteins (10%) and starch (40-60%). Oleoresin contains nonvolatile pungent principals gingerols mainly 6-gingerol, non pungent substances like fats and waxes and volatile oil. Volatile oil contains sesquiterpene hydrocarbons like α-zigiberene, β-sesquiphellandrene and ar-curcumene as major constituents. Minor constituents of ginger includes following monoterpene and sesquiterpene hydrocarbons and their oxygenated derivatives in volatile oil. Pungent principals like shogaols, paradols, gingerdials, gingerdiacetates, gingerdiones, 6-gingersulfonic acid, gingerenones and a number of diarylheptanoids, diterpenes and gingerglycolipids A, B and C are present in ginger (Blumenthal, 1998).

**Figure-2. Structures of some important chemicals from *Zingiber officinale***

![Chemical Structures](image-url)
Medicinal Uses of Zingiber officinale

Uses supported by clinical data

Ginger possess usefulness in prophylaxis of nausea and vomiting associated with motion sickness, postoperative nausea, pernicious vomiting in pregnancy and seasickness (Mowrey et al., 1982; Grontved et al., 1988; Holtmann et al., 1989; Yamahara et al., 1989; Bone et al., 1990; Fischer et al., 1991; Yamahara et al., 1991; Srivastava and Mustafa, 1992; Reynolds, 1993; Schmid et al., 1994; Blumenthal, 1998).

Uses described in pharmacopeias and in traditional systems of medicine

Ginger is used in the treatment of dyspepsia flatulence, colic, vomiting, diarrhea, spasms, and other stomach complaints. Powdered ginger is further employed in the treatment of colds and flu, to stimulate the appetite as a narcotic antagonist and as an anti-inflammatory agent in the treatment of migraine headache and rheumatic and muscular disorders (Srivastava and Mustafa, 1992; Blumenthal, 1998).

Uses described in folk medicine, not supported by experimental or clinical data

Ginger is used in treating cataracts, toothache, insomnia, baldness, and haemorrhoids and to increase longevity (Blumenthal, 1998).

Pharmacology of Zingiber officinale

Ginger is one of the widely used drugs in traditional system of medicine, systematic screening of ginger extracts has reported various pharmacological activities. Some of the reported pharmacological activities of ginger are discussed below.

Antiemetic activity

Various ethnobotanical, experimental and clinical studies indicate that ginger possess significant anti-emetic activity.

Clinical studies have demonstrated that oral administration of powdered ginger root was more effective than dimenhydrinate in preventing the gastrointestinal symptoms of motion sickness (Mowrey et al., 1982). It was suggested that ginger may act centrally on vomiting centre, but it was found to possess a direct effect on the gastrointestinal tract through its aromatic, carminative, and absorbent properties, by increasing gastric motility and adsorption of toxins and acids (Mowrey et al., 1982).

In a double blind randomized clinical study, the effect of powdered ginger root was tested as a prophylactic treatment for seasickness. The results of study demonstrated that orally administered ginger to possess greater activity as compared to placebo in...
decreasing the incidence of vomiting and cold sweating 4 hours after ingestion of ginger extracts or placebo (Grontved et al., 1988). The other clinical investigation compared the effects of seven over the counter and prescription antiemetic drugs on prevention of seasickness in 1489 subjects. The study concluded that ginger was as effective as other antiemetic drugs tested (Schmid et al., 1994).

At least eight clinical studies have assessed the effects of ginger root on the symptoms of motion sickness. Four of these investigations showed that orally administered ginger root was effective as prophylactic therapy of nausea and vomiting. The other three studies showed that ginger was no more effective than a placebo in treating motion sickness (Wood et al., 1988; Holtmann et al., 1989). The conflicting results appear to be a function of the focus of these studies. Clinical studies that focused on the gastrointestinal reactions involved in motion sickness recorded better response than those studies that concentrated primarily on responses involving the central nervous system.

In a double-blind, randomized, crossover trial, oral administration of powdered ginger is reported to be effective in treating pernicious vomiting in pregnancy (Fischer et al., 1991). Both the degree of nausea and the number of vomiting attacks were significantly reduced (Fischer et al., 1991). Furthermore, in a prospective, randomized, double-blind study, there were statistically significant decrease in cases of postoperative nausea and vomiting in patients receiving ginger compared to a placebo (Bone et al., 1990). The effect of ginger on postoperative nausea and vomiting was reported to be good and comparable to that of metoclopramide (Bone et al., 1990; Fischer et al., 1991). In contrast, another double blind randomized study concluded that orally administered ginger was ineffective in reducing the incidence of post operative nausea and vomiting (Arfeen et al., 1995).

In another study the emetic action of the peripherally acting agent copper sulfate was inhibited in dogs given an intragastric dose of ginger extract, but emesis in pigeons treated with centrally acting emetics such as apomorphine and digitalis could not be inhibited by a ginger extract. These results suggest that antiemetic activity produced by ginger is peripheral action and does not involve the central nervous system. The antiemetic action of ginger has been attributed to the combined action of zingerones and shogaols (Ghazanfar, 1994).
Anti-inflammatory Activity

Various experimental and clinical studies indicate that ginger possess significant anti-inflammatory activity.

In-vivo studies have shown that oral administration of ginger extracts decreased rat paw oedema (Masclo et al., 1989; Sharma et al., 1994). The drug is reported to be a potent inhibitor of thromboxane synthase, and produces increased prostacyclin levels without a concomitant rise in prostaglandins E₂ or F₂α (Srivastava, 1984). The potency of the extracts was comparable to that of acetyl salicylic acid. In vivo studies have demonstrated that a hot-water extract of ginger inhibited the activities of cyclooxygenase and lipoxygenase in the arachidonic acid cascade, thus its anti-inflammatory effects may be due to decrease in the formation of prostaglandins and leukotrienes (Mustafa et al., 1993). 6-shogaol is reported to inhibit carrageeenn-induced paw oedema in rats by inhibiting cyclooxygenase activity (Sukewa et al., 1986). Two labdane-type diterpene dialdehydes isolated from ginger extracts have been shown to be inhibitors of human 5-lipoxygenase in vitro (Kawakishi et al., 1994).

In one of the clinical studies conducted in China reported that patients with rheumatic pain and chronic lower back pain, injected with a 5-10% ginger extract into the painful points or reaction nodules, experienced full or partial relief of pain, decreased joint swelling, and improvement or recovery in joint function. Oral administration of powdered ginger to patients with rheumatism and musculoskeletal disorders has been reported to provide varying degrees of relief from pain and swelling (Grontved et al., 1988).

Cholagogic Activity

Intracanalicular administration of an acetone extract of ginger root to rats is reported to increase bile secretion while the aqueous extract was found inactive. The active constituent of the essential oil were identified as 6 and 10-gingerol (Yamahara et al., 1985). Oral administration of an acetone extract of ginger, 6-shogaol or gingerols is reported to enhance gastro-intestinal motility in mice and activity was comparable to or slightly weaker than that of metaclopromide and domperidone (Yamahara et al., 1991).

Cardiotonic Activity

Ginger extract is reported to possess cardiotonic activity when studied on the guinea pig isolated left atria. Further, when methanolic extract was subjected to isolation of potential compounds for the cardiotonic activity 6, 8 and 10 gingerols were found to
be active principles. Gingerols enhanced contractility in isolated guinea pig atrial muscles. 8-gingerol was found to possess greater cardiotonic activity as compared to 6 and 10 gingerol (Kobayashi et al., 1988). Gingerols are also reported to possess positive inotropic and positive chronotropic effects (Shoji et al., 1982; Kobayashi et al., 1988).

**Antihyperlipidemic Activity**

Various experimental studies have reported ginger to possess antihyperlipidemic activity and hypolipidemic activity. Ginger is reported to act as a hypolipidemic agent in cholesterol-fed rabbits (Sharma et al., 1996; Bhandari et al., 1998). Rats when fed with ginger is reported to significantly elevate the activity of hepatic cholesterol-7-hydroxylase, the rate-limiting enzyme in bile acids biosynthesis, thereby stimulating cholesterol conversion to bile acids, resulting in elimination of cholesterol from the body (Srinivasan and Sambaiah, 1991). In addition, a pure constituent from ginger [E-8 beta, 17 epoxylabd-12-ene-15, 16-dial (ZT)], was shown to inhibit cholesterol biosynthesis in homogenated rat liver (Tanabe et al., 1993). Consumption of ginger extract is reported to reduce macrophage-mediated oxidation of LDL, reduced uptake of oxidized LDL by macrophages, reduced oxidative state of LDL and reduced LDL aggregation. All these effects of ginger extract lead to a reduced cellular cholesterol accumulation and foam cell formation and attenuate atherosclerosis development. 6-gingerol and other gingerols are reported to reduce macrophage-mediated oxidation of LDL and hence gingerols were considered partly to be responsible for the antiatherosclerotic activity demonstrated by ginger extract (Fuhrman et al., 2000).

**Antilulcer Activity**

Ginger is shown to protect gastric ulcers, some components from ginger like beta-sesquiphellandrene, beta-bisabolene, gingesulfonic acid, curcumene and 6-shogaol, demonstrated antilulcer effects, protecting gastric mucosa against alcohol, non-steroidal anti-inflammatory drugs and hydrochloric acid (Yamahara et al., 1985; Al-Yaha et al., 1989).

**Antihyperglycemic Activity**

Ethanolic extract of ginger when treated to rabbits loaded with glucose is reported to possess blood glucose lowering activity. The effect of ginger extract was compared to that of tolbutamide (Mascolo et al., 1989). Another study with ethanolic extract of ginger is reported to produce antihyperglycemic activity in rats (Ahmed and Sharma, 1997).
Anti-Platelet Activity

Ginger extracts have shown to inhibit platelet cyclooxygenase production, thromboxane generation and platelet aggregation in a dose-dependent fashion in vitro (Srivastava, 1984; Backon, 1986; Srivastava, 1986). Gingerols are also shown to inhibit thromboxane-mediated platelet aggregation (Guh et al., 1995). Studies on human volunteers also reported anti-platelet activity of ginger (Verma et al., 1993; Bordia et al., 1997).

Antimicrobial Activity

Ginger is reported to possess antibacterial, antiviral and antifungal activities, in few in vitro studies and several sesquiterpenes from ginger have displayed antirhinoviral effects (Denyer et al., 1994). Ginger has shown antibacterial effects against both gram positive and gram negative bacteria such as Clostridium, Listeria, Enterococcus and Staphylococcus species, but some of this effect is destroyed by heating (Janes et al., 1990). In vitro studies for antifungal activity have demonstrated the usefulness of few of the chemical constituents of ginger like diaryleptanoids, ginerenones A, B and C and isogingerenone B, have displayed antifungal activity in vitro (Endo et al., 1990).

Antineoplastic Activity

Ginger is shown to have antineoplastic activity, it is shown to inhibit Epstein-Barr virus activation in vitro (Murakami et al., 1998; Vimala et al., 1999). 6-gingerol and 6-paradol are reported to possess inhibitory effects on the viability and DNA synthesis of human promyelocytic leukemia cells (Lee et al., 1998; Surh et al., 1998). Essential oil of ginger is reported to suppress formation of DNA adducts by aflatoxin B1 in a microsomal enzyme-mediated reaction (Hasim et al., 1994). Ginger extract has also shown to protect experimentally induced skin tumors in mice (Katiyar et al., 1996; Surh et al., 1999).

Antioxidant Activity

In human aortic endothelial cells, zingerone demonstrated significant anti-oxidant effects on low-density lipoproteins (Pearson et al., 1997; Zhou and Xu, 1992). In human erythrocyte membranes, ginger extracts inhibited lipid peroxidation (Sujatha and Srinivas, 1995). In human chondrocytes, volatile oil of ginger effectively prevented the production of hydrogen peroxide usually induced by fulvic acid (Guo et al., 1997). Rats fed on high fat diet, when supplemented with ginger significant anti-oxidant effect,
raising tissue concentrations of superoxide dismutase and catalase and reducing glutathione were observed (Jeyakumar et al., 1999).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

The mutagenicity of ginger extracts is a controversial subject a hot water extract of ginger was reported to be mutagenic in B2911 cells and salmonella typhimurium strain TA 100, but not in strain TA 98 (Yamomoto et al., 1982). 6-gingerol and shogaols have been determined to be mutagenic in a salmonella/microsome assay (Nagabhushan et al., 1987) and increased mutagenesis was observed in a Hs 30 strain of E. coli, treated with 6-gingerol (Nakamura and Yamamoto, 1982). However, the mutagenicity of 6-gingerol and shogaols was suppressed in the presence of various concentrations of zingerone, an anti-mutagenic constituent of ginger (Nagabhushan et al., 1987).

**Safety Aspects**

Excessive doses of ginger may interfere with existing cardiac, anti-diabetic or anticoagulant therapy. Doses of ginger that greatly exceed the amounts used in foods should not be taken during pregnancy or lactation.

**Posology**

The dose of ginger for motion sickness in adults and children more than 6 years is 0.5 gm, 2-4 times daily. In conditions of dyspepsia the dose is 2-4 gm daily, as powdered plant material or its extracts.

**5-HT AND ZINGIBER OFFICINALE**

*Zingiber officinale* is an herbal drug which is proven to possess beneficial activity in various disease conditions. Antiemetic activity, antiplatelet activity, cardiotonic activity and anxiolytic activity of ginger appears to be due to its 5-HT antagonistic activity. Various extracts and compounds from ginger have been reported to possess significant 5-HT antagonistic activity. The pungent principals of ginger, gingerols and shogaols are reported to possess significant 5-HT antagonistic activity (Yamahara et al., 1989). A diterpenoid galanolactone isolated from ginger is reported to possess significant 5-HT₃ antagonistic activity and is reported to play a significant role in antiemetic activity of ginger (Huang et al., 1991). The mechanism of antiemetic effect of ginger was reported due to 5-HT antagonism and it was shown to mediate 5-HT₃ receptors. 5-HT receptors play a vital role in cardiovascular functions, like cardiotonic activity and antiplatelet aggregation. Extracts of ginger is reported to possess significant
cardiotonic activity. Gingerols, 5-HT antagonists of ginger are reported as the active constituents for the cardiotonic activity. 8-gingerol is reported to possess greater cardiotonic activity as compared to 6 and 10 gingerols (Kobayashi et al., 1988). Gingerols are also reported to possess positive inotropic and positive chronotropic effects (Shoji et al., 1982; Kobayashi et al., 1988). Ginger extracts have shown to inhibit platelet aggregation in a dose-dependent fashion in vitro and is reported to possibly mediated through 5-HT receptors (Srivastava, 1984; Backon, 1986; Srivastava, 1986). Gingerols being 5-HT antagonist are also shown to inhibit thromboxane-mediated platelet aggregation (Guh et al., 1995). Studies on human volunteers also have shown that ginger has anti-platelet activity (Verma et al., 1993; Bordia et al., 1997). The anxiolytic actions of ginger are reported to mediate through 5-HT receptors (Hasenohrl et al., 1996). Taken together many of the important pharmacological activities reported for ginger appears to involve 5-HT receptors.
3.2 Dietary supplements used in diabetes and obesity

3.2.1 Dietary supplements used in diabetes

Diabetes is a predominant public health concern, affecting millions of persons worldwide. The disease causes substantial morbidity, mortality, and long-term complications and remains an important risk factor for cardiovascular disease. With increasing rates of childhood and adult obesity, diabetes is likely to become even more prevalent over the coming decade. Despite good agents available for treatment of diabetes, increasing use of complementary and alternative medicine systems of healing such as herbs or other dietary supplements are in great use these days. This review gives an outline on agents used as dietary supplements for use in diabetes.

*Coccinia indica*

*Coccinia indica* (ivy gourd) is a creeping plant that grows wildly in many parts of the Indian subcontinent, and is used to treat “sugar urine” (madhumeha) in Ayurveda. The mechanism of action of *Coccinia indica* is not well understood, but the herb appears to have insulin-mimetic properties (Kuppurajan et al., 1986; Kamble et al., 1996; Kamble et al., 1998). The one randomized clinical trial of this herb reported significant changes in glycemic control following 6 weeks use of powder from locally obtained crushed dried leaves in poorly controlled or otherwise untreated patients with type 2 diabetes (Azad et al., 1979). Another three-arm controlled clinical trial compared 12 weeks use of dried herb pellets made from fresh leaves with no treatment and oral hypoglycemic agents (chlorthalidone) in patients with type 2 diabetes (Kamble et al., 1996). The magnitude of change seen with the herb was similar to that with a conventional drug. Two other open-label prospective trials offer supporting evidence of a hypoglycemic effect (Kuppurajan et al., 1986; Kamble et al., 1998). No adverse events were reported in these trials. The preliminary evidence suggests that the potential role for *Coccinia indica* in diabetes warrants further study.

*Ginseng species*

Several different plant species are often referred to as ginseng. These include Chinese or Korean ginseng (*Panax ginseng*), Siberian ginseng (*Eleutherococcus senticosus*), American ginseng (*P. quiquefolius*), and Japanese ginseng (*P. japonicus*). *Panax* species (from the root panacea) are often touted for their “cure-all” adaptogenic properties, immune-stimulant effects, and their ability to increase stamina, concentration, longevity, and overall wellbeing (Ernst, 1997). Preparations use the herb’s root; some
sources report greater efficacy with roots that are greater than 3 years old. Principal components are believed to be the triterpenoid saponin glycosides (ginsenosides or panaxosides). Hypoglycemic effects have been shown in streptozotocin rat models (Shapiro et al., 2002). Reported mechanisms of action include decreased rate of carbohydrate absorption into the portal hepatic circulation, increased glucose transport and uptake mediated by nitric oxide, increased glycogen storage, and modulation of insulin secretion (Shane, 2001). Most clinical trials using American ginseng, have examined the herb's short-term effects on patients with type 2 diabetes after a standard oral glucose tolerance test (Vuksan et al., 2000a; Vuksan et al., 2000b). Two longer-term trials administered American ginseng for 8 weeks, both reported decreases in fasting blood glucose and HbA1c (Sotaniemi et al., 1995; Vuksan et al., 2001a). Only one case of insomnia was reported in these trials. Three other short-term metabolic trials in healthy volunteers also found decrease in postprandial glucose (Vuksan et al., 2000a; Vuksan et al., 2001b; Vuksan et al., 2000c). The available evidence for American ginseng in diabetes suggests a possible hypoglycemic effect.

**Allium species: sativum and cepa**

*Allium sativum* (garlic), a member of the lily family, is most commonly used worldwide for flavorful cooking. Much of the clinical literature on garlic has focused on its potential antioxidant activity and microcirculatory effects (e.g., allicin and ajoene for use in hypertension and hyperlipidemia). Few studies have examined its effects on insulin and glucose handling, although some attention has been given to allyl propyl disulfide, a volatile oil, and S-allyl-cysteine sulfoxide, a sulfur containing amino acid (Shane, 2001). Experiments in animal models with alloxan-induced diabetes have shown moderate reductions in blood glucose; no effect is seen in pancreatectomized animals.

*Allium cepum* (onion) also contains allyl propyl disulphide and has similar purported hypoglycemic properties. Reported mechanisms of allium species include increased secretion or slowed degradation of insulin, increased glutathione peroxidase activity, and improved liver glycogen storage (Bailey et al., 1989; Shane, 2001). The highest quality randomized clinical trial of *Allium sativum* in humans was actually designed to examine thrombocyte aggregation in nondiabetic individuals. However, the investigators found significant decrease in fasting serum glucose (Keisewetter et al., 1991). The only available trial of garlic in patients with type 2 diabetes did not find consistent glucose or insulin responses after 1 month of supplementation (Sitprija et al., 1987). The only
clinical trial available for *Allium cepa* is a small randomized clinical trial of allylpropyl disulphide extract capsules from onion in non-diabetic volunteers, investigators showed an acute decrease in fasting blood glucose and increase in insulin, supporting an insulin-mediated effect (Augusti, 1975).

*Ocimum sanctum*

*Ocimum sanctum* (holy basil) is another commonly used herb in Ayurveda (related species include *Ocimum album* and *Ocimum basilicum*). Studies in animal models suggest hypoglycemic effects (Chattopadhyay, 1993), although the mechanism of action remains unknown. Postulated effects include enhanced β-cell function and insulin secretion. The one available controlled clinical trial of *Ocimum sanctum* showed positive effects on both fasting and postprandial glucose in patients with type 2 diabetes using a local preparation of fresh leaf powder mixed in water for 4 weeks (Agrawal et al., 1996).

*Bauhinia forficata* and *Myrcia uniflora*

Indigenous to rainforests and tropical areas of South America, *Bauhinia forficata* has been used in traditional treatment of diabetes in that area. In Brazilian herbal medicine, Bauhinia species have been referred to as “vegetable insulin.” Another commonly used South American herb is *Myrcia uniflora*. As part of a national effort to identify potential plant species useful in glucose control, two small crossover studies by one investigator administered each of these herbs as tea infusions to separate groups of patients three times daily for 8 weeks. No significant differences in glucose or HbA1c were detected between study herb infusion and a placebo tea using *Imperata brasiliensis*. No adverse effects were reported (Russo et al., 1990).

*Ficus carica*

*Ficus carica* (fig leaf) is a popular plant used for patients with diabetes in Spain and other areas in Southwestern Europe. Its active component is unknown. Several studies in animal models with diabetes have shown both short and long term hypoglycemic effects, although human trials are lacking. Potential hypolipidemic effects in diabetic rats have also been shown (Campillo et al., 1991; Torres et al., 1993; Perez et al., 1996). The one available clinical trial is a small crossover study of fig leaf tea for 4 weeks in patients with type 1 diabetes, investigators showed a decrease in postprandial glucose and insulin requirements, but no change in fasting glucose when compared with the control commercial tea (Serralaara et al., 1998). No effect were seen in C-peptide levels, thereby results supports a non insulin mediated effect.
Opuntia streptacantha

*Opuntia streptacantha* (nopal) or the prickly pear cactus can be found in arid regions throughout the Western hemisphere, including the southwestern U.S., and is commonly used for glucose control by those of Mexican descent. It has a high soluble fiber and pectin content, which may affect intestinal glucose uptake, partially accounting for its hypoglycemic actions (Shapiro et al., 2002). Animal models have reported decreases in postprandial glucose and HbA1c with synergistic effects with insulin. Studies in pancreatectomized animals report that hypoglycemic activity is not dependent on the presence of insulin (Frati et al., 1991). Two controlled short-term metabolic trials (Frati et al., 1988; Frati et al., 1990) reported improvements in patients with type 2 diabetes with decreased fasting glucose and decreased insulin levels, suggesting enhanced insulin sensitivity.

Silibum marianum

*Silibum marianum* (milk thistle), a member of the aster family, has been primarily studied for its purported effects on alcoholic and viral hepatitis, rather than for glycemic control. However, silymarin is rich in flavonoids, potent antioxidants, and some have postulated a potential benefit for those who have insulin resistance secondary to hepatic damage (Shane, 2001). Mechanisms are based on the herb's antioxidant activity and effects on hepatocyte stabilization with decreased glutathione oxidation, as well as on restoration of normal malondialdehyde concentrations. The one available clinical trial examined cirrhotic patients with type 2 diabetes using a commercially available preparation ("Legalon" 600 mg/day; IBI Lorenzini, Milan, Italy) for 12 months, with significant improvements in glycemic control when compared with no treatment (Velussi et al., 1997).

Gymnema sylvestre

*Gymnema sylvestre* is another commonly used herb in Ayurveda. The plant is a woody climber that grows in tropical forests of central and southern India. According to common folklore, chewing the leaves causes a loss of sweet taste, hence the popular Hindi name of the plant "gurmar," meaning "destroyer of sugar." Early animal studies reported blood glucose-lowering effects in animals with residual pancreatic function, but no effects were reported in total pancreatectomized animals. Studies of an ethanol leaf extract, GS4, in diabetic rat and rabbit models have reported regeneration of islets of Langerhans, decrease in blood glucose, and increase in serum insulin.
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(Shanmugasundaram et al., 1990). Mechanism of action is unknown; postulated theories include an increase in glucose uptake and utilization, increase in insulin release through cell permeability, increase in β cell number, and stimulation of β cell function (Persaud et al., 1999; Shane, 2001). Two nonrandomized controlled clinical trials are available, patients with type 1 diabetes and type 2 diabetes showed improved glycemic control with chronic adjunctive use of GS4 extract compared with those who received conventional treatment alone (Baskaran et al., 1990; Shanmugasundaram et al., 1990).

**Momordica charantia**

*Momordica charantia* is a vegetable indigenous to tropical areas, including India, Asia, South America and Africa. It is also known as balsam pear, karela (karolla), and bitter melon. Reported preparations of the herb range from injectable extracts to fruit juice to fried melon bits (Leatherdale et al., 1981; Welhinda et al., 1986; Srivastava et al., 1993; Shane et al., 2001). Active components are thought to be charantin, vicine, and polypeptide-p (an unidentified insulin-like protein similar to bovine insulin). Theoretical mechanisms include increased insulin secretion, tissue glucose uptake, liver muscle glycogen synthesis, glucose oxidation, and decreased hepatic gluconeogenesis. Studies in alloxan-induced diabetic rabbits have suggested hypoglycemic effects (Akhtar et al., 1981). Two controlled short-term metabolic trials in patients with type 2 diabetes have reported acute effects on blood glucose with *Momordica charantia* fruit juice, as well as subcutaneous vegetable insulin extract (Baldwa et al., 1977; Welhinda et al., 1986). Two other small, uncontrolled open-label trials also reported positive effects on glycemic control after longer-term use (7–11 weeks) (Leatherdale et al., 1981; Srivastava et al., 1993).

**Aloe vera**

*Aloe vera* is the most well-known species of aloe, a desert plant resembling the cactus in the Liliaceae family. It is popularly used to treat burns and promote wound healing. The dried sap of the *Aloe vera* is a traditional remedy for diabetes in the Arabian peninsula (Pandey et al., 1995), although aloe gel is preferred over the sap as the latter contains the laxative anthraquinone (Yongcharyudha et al., 1996). Aloe gel, obtained from the inner portion of the leaves, contains glucomannan, a hydrosoluble fiber which may in part account for its hypoglycemic effects (Shane, 2001). Reports in animal models have been inconsistent (Ghannam et al., 1986; Ajabnoor, 1990; Koo, 1994; Yongcharyudha et al., 1996). Two nonrandomized clinical trials reported improved
fasting blood glucose with 6-weeks of juice made from aloe gel (Bunyapraphatsara et al., 1996; Yongchaiyudha et al, 1996). Case reports of five type 2 diabetic individuals reported decreases in fasting blood glucose as well as HbA1c (Ghannam et al., 1986).

Dietary supplements mentioned above are a small list of agents which are proven to possess beneficial effects in diabetes. Many of the agents mentioned above are widely used in traditional system of medicine and other practices for diabetes treatment. Recently standardized extracts of such drugs are widely used in western countries. World over systematic studies of such herbs and dietary supplements are ongoing. Dietary supplements and herbs which show less toxicity and greater therapeutic efficacy in future may be used alone or in combination with existing allopathic drugs in diabetes treatment.
3.2.2 Dietary supplements used in weight reduction or obesity

Excess body weight is one of the most important risk factors for all cause morbidity and mortality. The likelihood of developing conditions such as type 2 diabetes, heart disease, cancer, and osteoarthritis of weight-bearing joints increases with body weight (Field et al., 2001; Kenchaiah et al., 2002; Key et al., 2002). One factor responsible for overweight and obesity is a continuous decrease in energy expenditure from physical activity during recent decades (Prentice and Jebb, 1995). Compliance with conventional weight management programs is poor, which indicates a need for safe, effective, and acceptable therapeutic options. It is therefore not surprising to see the use of dietary supplements in reducing body weight. This review will address the effectiveness of dietary supplements in reducing body weight and hence their use in obesity.

**Chitosan**

Chitosan is a cationic polysaccharide, which is produced from chitin, a substance derived from the exoskeleton of crustaceans. It is promoted as a remedy to reduce fat absorption (Kanauchi et al., 1995), and data from preclinical studies exist to support this notion (Nagyvary, 1979; Nauss et al., 1983; Vahouny et al., 1983). However, data from meta-analysis of 5 double-blind RCTs, which included patients who were described as either obese, overweight, or having 10–25% excess body weight, showed that the effectiveness of chitosan for body-weight reduction is not established beyond a reasonable doubt (Ernst and Pittler, 1998).

**Chromium picolinate**

Chromium, an essential trace mineral and cofactor to insulin, enhances insulin activity and has been the subject of studies assessing its effects in carbohydrate, protein, and lipid metabolism (Offenbacher and Pr-Sunyer, 1988; Mertz, 1993; Anderson 1998). Reported effects include an increase in lean body mass, a decrease in percentage body fat, and an increase in the basal metabolic rate (Anderson, 1989; Anderson, 1998; Crawford et al., 1999). Chromium picolinate is an organic compound of trivalent chromium and picolinic acid, a naturally occurring derivative of tryptophan. The results of meta-analysis of 10 double-blind RCTs suggest a relatively small reduction of 1.1–1.2 kg (ie, 0.08–0.2 kg/wk) compared with placebo during an intervention period of 6–14 wk in patients with an average BMI of 28–33 (Pittler et al., 2003). The studies concluded the
observed effect with chromium picolinate is, although statistically significant, not clinically meaningful.

**Garcinia cambogia**

Hydroxycitric acid is obtained from extracts of *G. cambogia* and has been shown to inhibit citrate cleavage enzyme, suppress de novo fatty acid synthesis and food intake, and decrease body weight gain (Heymsfield et al., 1998). Two double-blind RCTs report effects in favor of treatment with *G. cambogia* compared with placebo, they were supported by a trial testing the effects of hydroxycitric acid (Thom, 1996). However, a double-blind RCT, which tested the effects of 3g *G. cambogia* extract/d, which contained 50% hydroxycitric acid, in patients with an average BMI of 32, suggest the absence of a significantly greater weight loss in the treatment group than in the placebo group (Heymsfield et al., 1998).

**Glucomannan**

Glucomannan is a component of konjac root, derived from *Amorphophallus konjac* C. Koch. Its chemical structure is similar to that of galactomannan from guar gum and comprises a polysaccharide chain of glucose and mannose (Walsh et al., 1983). A one double-blind RCT including patients with body weight greater than 20% over their ideal showed a significantly greater weight loss in the treatment group than in the placebo group (Doi, 1995).

**Ephedra sinica**

*E. sinica*, or ma-huang, is an evergreen shrub native to central Asia (Doi, 1995). Ephedrine, the primary active constituent of the botanical *E. sinica*, has been studied alone and in combination with caffeine. A systematic review of 5 double-blind trials, including 2 trials show that the combination of ephedrine and caffeine is effective for reducing body weight and appears to outweigh the risks (Greenway, 2001). Another clinical study of *E. sinica* and ephedrine with 8 week of follow-up concluded that *E. sinica* and ephedrine promote a modest short-term weight loss. The intake of supplements containing *E. sinica*, however, is associated with a 2.2 to 3.6 fold increase in odds of psychiatric, autonomic, or gastrointestinal symptoms and heart palpitations (Haller and Benowitz, 2000; Fontanarosa et al., 2003).

**Hydroxy-methylbutyrate**

β-Hydroxy-β-methylbutyrate is a metabolite of leucine that has shown anticatabolic actions through inhibiting protein breakdown (Nissen et al., 1996). β-
Hydroxy-β-methylbutyrate is available as a dietary supplement and is primarily used by bodybuilders as a supportive measure to induce changes in body composition. Two double blind RCTs reported significant intergroup differences with respect to fat mass (Nissen et al., 1996; Vukovich et al., 1997), while at least a trend toward an increase in lean body mass was reported from all trials.

**Pyruvate**

Pyruvate is generated in the body via glycolysis, and supplementation with pyruvate seems to enhance exercise performance and improve measures of body composition (Stanko et al., 1994; Stanko and Arch, 1996). Two double-blind RCTs, which included patients with BMIs greater than 25, assessed the effects of pyruvate supplementation (Kalman et al., 1998; Kalman et al., 1999). The results show a significant body-weight reduction of 1.2 kg from baseline (Kalman et al., 1999), while both studies reported significant reductions in fat mass and percentage body fat from baseline (Kalman et al., 1998; Kalman et al., 1999).

**Yerba maté**

Yerba maté (*Ilex paraguariensis*) is an evergreen tree that is native to South America. In a combination preparation also containing guarana (*Paullinia cupana*) and damiana (*Turnera diffusa*), it was tested in patients with a BMI of 26–30 (Andersen and Fogh, 2001). *I. paraguariensis* and in particular *P. cupana* contain relatively large amounts of caffeine and have been shown by ultrasound scanning to prolong gastric emptying time. The results of that study indicated that the combination preparation might potentially be effective in lowering body weight (Andersen and Fogh, 2001).

The list of dietary supplements mentioned above are few among many presently used as over the counter agents at various countries of the world. Since world over population with obesity are growing, search for drugs useful in obesity is ongoing. In the present day there are only two drugs to treat obesity. The existing agents useful in obesity have some adverse effects which make uncompatible to many subjects and hence increased use of dietary supplements in obesity are seen these days. There appears a need to study the dietary supplements under controlled conditions and those agents showing greater efficacy and lesser safety concern than existing drugs have to be found to complement the existing drugs in conditions of obesity.
3.3 Diabetes and Obesity

3.3.1 Diabetes

Diabetes mellitus is a group of diseases characterized by increase in fasting and post-prandial blood glucose resulting from defects in insulin production, insulin action, or both. It is now clear that aggressive control of hyperglycemia in patients with type 2 diabetes can attenuate the development of chronic complications such as retinopathy and nephropathy (Geirch, 2003).

**Diagnostic criteria for considering patients to be diabetic individuals are mentioned below.**

Various international organizations define diabetes based on fasting blood sugar levels and few other parameters. World Health Organization (1999) defines a person to be diabetic if the person exhibit impaired glucose regulation with fasting venous plasma $\geq 6.1$ mmol/L (110mg/dl) to 6.9 mmol/L (125mg/dl) and $2h < 11.1$ mmol/L (200 mg/dl). Together with the above factor, other factors considered are hypertension $\geq 140/90$ mmHg, hypertriglyceridaemia $\geq 1.7$ mmol/L (150 mg/dl) or low HDL-cholesterol $< 1.0$ (40 mg/dl), waist to hip ratio $> 0.90$ for men, $0.85$ for women and / or body mass index $\geq 30$ kg/m$^2$ and microalbuminuria-urinary albumin excretion rate $\geq 20$ mg/min or albumin /creatinine ratio $> 30$ mg/g. The US National Cholesterol Education Program (2001) has embraced a broadly similar definition. However European group for the study of insulin resistance (1999) classify subjects as diabetics based on the factors that the subjects fasting plasma insulin levels in the highest 25% for the population, together with two of the following: fasting plasma glucose $\geq 6.1$ mmol/L (110 mg/dl), hypertension (blood pressure $\geq 140/90$ mmHg (or treated), dyslipidaemia: plasma triglycerides $> 2.0$ mmol/L (180 mg/dl) or HDL-cholesterol $< 1.0$ mmol/L (40 mg/dl) and central obesity: waist circumference $\geq 94$ cm in men and $\geq 80$ cm in women.
3.3.1.1 Insulin signalling and the regulation of glucose and lipid metabolism

Type 2 diabetes and impaired glucose tolerance is one of the main causes of morbidity and mortality worldwide. In both conditions tissues such as muscle, fat and liver become less responsive or resistant to insulin. This state is also linked to obesity, hyperlipidemia and atherosclerosis. The pathophysiology of insulin resistance involves a complex network of signalling pathways, activated by the insulin receptor, which regulates intermediary metabolism and its organization in the cells (Saltiel and Kahn, 2001). Detailed study of insulin signalling provides good insight about understanding the defects in this system which is responsible for causing diabetes. Insulin signalling mainly involves, proximal insulin signalling pathways and insulin receptor substrates play a significant role. Modulation of insulin signalling gives great deal of information in understanding defects which leads to diabetes. Phosphatidyl inositol 3-kinase and the CAP/Cbl pathway including lipid rafts are essential for insulin action. Alteration in any of these enzyme actions or pathways leads to improper insulin action. Finally insulin being the anabolic hormone it plays vital role in storing energy and also maintains glycemic levels. Regulation of glycogen synthesis, gluconeogenesis, lipid synthesis and degradation by insulin are critical factors for maintaining normal glycemic levels. Various hormones and substances released from fat cells play a vital role in insulin action on fat cells. A link appears between altered functions of insulin on fat cells possibly modulated by substances released by fat cells. Finally, understanding all the above factors of insulin action allows one to understand possible causes for insulin resistance in diabetes.

Proximal insulin signalling pathways

The insulin receptor

The insulin receptor belongs to a subfamily of receptor tyrosine kinases that includes the insulin-like growth factor (IGF)-1 receptor and the insulin receptor related receptor (IRR) (Patti and Kahn, 1998). These receptors are tetrameric proteins consisting of two α and two β subunits that function as allosteric enzymes in which the α-subunit inhibits the tyrosine kinase activity of the β-subunit. Insulin binding to the α subunit leads to depression of the kinase activity in the β subunit followed by transphosphorylation of the β subunits and a conformational change that further increases kinase activity. Insulin, IGF-1 and the IRR receptors can form functional hybrids, thus an
inhibitory mutation in one receptor can inhibit the activity of the others (Butler and LeRoith, 2001).

**Insulin receptor substrates**

At least nine intracellular substrates of the insulin/IGF-1 receptor kinases have been identified. Four of these belong to the family of insulin-receptor substrates (IRS) proteins (White, 1998). Other substrates include Gab-1, p60<sup>dock</sup>, Cbl, APS and isoforms of Shc (Pessin and Saltiel, 2000). The phosphorylated tyrosines in these substrates act as docking sites for proteins that contain SH2 (Src-homology-2) domains. Many of these SH2 proteins are adaptor molecules, such as the p85 regulatory subunit of PI-3 kinase and Grb2, or crkII, which activate small G proteins by binding to nucleotide exchange factors. Others are themselves enzymes, which include phosphotyrosine phosphatase SHP2 and the cytoplasmic tyrosine kinase Fyn. Substrate binding to these SH2 proteins can regulate their activities, or in some cases their subcellular location. The different IRS proteins seem to serve different functions at the cellular level, probably owing to differences in tissue distribution, subcellular localization and intrinsic activity of the proteins (Saltiel and Kahn, 2001).

**Inhibition of insulin-receptor signalling**

In addition to tyrosine phosphorylation, both the insulin receptor and IRS proteins undergo serine phosphorylation, which may attenuate signalling by decreasing insulin stimulated tyrosine phosphorylation and promote interaction with 14-3-3 proteins (Carpora et al., 1997). These inhibitory phosphorylations provide negative feedback to insulin signalling and serve as a mechanism for cross talk from other pathways that produce insulin resistance. Several kinases have been implicated in this process, including PI-3 kinase, Akt, glycogen synthase kinase (GSK)-3 and mammalian target of rapamycin (mTOR). Recent studies show obesity-induced attenuation of insulin signalling might arise from sequential activation of protein kinase C (PKC) and inhibition of nuclear factor κB (IκB) kinase (Saltiel and Kahn, 2001).

Insulin action is also attenuated by protein tyrosine phosphatases (PTPases) which catalyze the rapid dephosphorylation of the receptor and its substrates. Knockout of PTP 1B leads to increased tyrosine phosphorylation of the insulin receptor and IRS proteins in muscle and improves insulin sensitivity. PTP 1B<sup>−/−</sup> mice are resistant to diet induced obesity, suggesting the brain as an important site of action. This combination
makes PTP 1B as a potential therapeutic target in diabetes and obesity (Saltiel and Kahn, 2001).

**PI-3 kinase and insulin action**

PI-3 kinase has a pivotal role in the metabolic and mitogenic actions of insulin and IGF-1 (Shepard et al., 1995). Inhibitors of class 1a PI-3 kinase, or transfections with dominant negative constructs of the enzyme, block most metabolic actions of insulin, including stimulation of glucose transport, glycogen and lipid synthesis. PI-3 kinase consists of a p110 catalytic subunit and a p85 regulatory subunit that possesses two SH2 domains that interact with tyrosine-phosphorylated pYMXM and pYXXM motifs in IRS proteins. At least 8 isoforms of the regulatory subunits have been identified. These are derived from 3 genes (p85α, p85β and P55PIK) and alternative slicing of p85α is predominant and thought to be the main response pathway for most stimuli (Fruman et al., 1996). Knockout mice with a disruption of all three isoforms derived from the p85α gene die shortly after birth. Whereas heterozygous knockout mice or mice lacking only full length p85α are viable and exhibit improved insulin sensitivity (Saltiel and Kahn, 2001).

The activation of PI-3 kinase may transmit multiple signals. PI-3 kinase catalyzes the phosphorylation of phosphoinositides on the 3-position to produce phosphatidylinositol-3 phosphates, especially phosphatidyl inositol trisphosphate, which bind to the pleckstrin homology (PH) domains of a variety of signalling molecules thereby altering their activity or subcellular localization. Moreover, PI-3 kinase also possesses serine kinase activity, and both the regulatory and catalytic subunits of the enzyme can interact with other signalling proteins (Kessler et al., 2001).

PI-3 phosphate regulates three main class of signalling molecules: the AGC family of serine/threonine protein kinases (Peterson and Schreiber, 1999), guanine nucleotide exchange proteins of Rho family of GTPases (Mackay and Hall, 1998) and the TEC family of tyrosine kinases (Ziegler et al., 1993). PI-3 kinase also activates the mTOR/FRAP pathway, and might be involved in the regulation of phosphatidic acid and diacylglycerol. The best characterized of the AGC kinases is phosphoinositide-dependent kinase 1 (PDK1), one of the serine kinases that phosphorylates and activates the serine/threonine kinase Akt/PKB. Akt possesses a PH domain that also interacts directly with PI-3 phosphate, promoting membrane targeting of the protein and catalytic activation. Akt has been suggested to be important in transmission of the insulin signal,
by phosphorylation of the enzyme GSK-3, the forkhead transcription factors and cAMP response element binding protein (Nakae et al., 1999). Deletion of Akt produces insulin resistance in mice. Other AGC kinases that are downstream of PI-3 kinase include serum and glucocorticoid-regulated kinases and the atypical PKCs, PKC-ζ and λ. Akt and or the atypical PKCs seem to be required for insulin-stimulated glucose transport (Saltiel and Kahn, 2001).

Activity of this pathway is also determined by phosphotidylinositol-3-phosphates such as phosphatase and tensin homologue (Ogg and Ruvkun, 1998) and SH2 domain-containing inositol-5-phosphatase SHIP2. Over expression of these enzymes leads to decreased levels of phosphatidyl inositol triphosphates. This might terminate signal transduction and/or change the nature of the phosphoinositides, altering the binding specificity to PH or phox homology domains. Disruption of these genes or reducing expression of these messenger RNAs yields mice with increased insulin sensitivity.

The CAP/Cbl pathway and lipid rafts

In addition to PI-3 kinase activity, other signals seem to be required for insulin stimulated glucose uptake involve tyrosine phosphorylation of the Cbl protooncogene (Pessin and Saltiel, 2000). In most insulin responsive cells, Cbl is associated with the adapter protein CAP, which binds to proline rich sequences in Cbl through its carboxy terminal SH3 domain (Ribbon et al., 1998b). CAP is expressed in insulin sensitive tissues, which is markedly induced during adipocyte differentiation and its expression is increased by insulin-sensitizing PPARγ agonists (Ribbon et al., 1998a).

Glucose and lipid regulation

Regulation of glycogen synthesis

Insulin stimulates glycogen accumulation through a coordinated increase in glucose transport and glycogen synthase by promoting its dephosphorylation, through the inhibition of kinases such as PKA or GSK-3 (Cross et al., 1995) and activation of protein phosphatase 1 (PP1) (Brady et al., 1997). Upon its activation downstream of PI 3-kinase, Akt phosphorylates and inactivates GSK-3, decreasing the rate of phosphorylation of glycogen synthase, thus increasing its activity site (Cross et al., 1995). Insulin does not activate PP1 globally, but rather specifically targets discrete pools of the phosphatase, primarily increasing PP1 activity localized at the glycogen particle (Newgard et al., 2000). Four different proteins have been reported to target PP1 to the glycogen particle. Although the mechanism by which insulin activates glycogen-associated PP1 remains
unknown, inhibitors of PI-3 kinase block this effect, suggesting that phosophotidyl inositol triphosphate dependent protein kinases are involved. These scaffolding proteins have a critical permissive role in the hormonal activation of enzyme, perhaps that regulate the interaction of PP1 with glycogen synthase and phosphorylase (Newgard et al., 2000).

**Regulation of gluconeogenesis**

Insulin inhibits the production and release of glucose by the liver by blocking gluconeogenesis and glycogenolysis. This occurs through a direct effect of insulin on the liver, as well as by indirect effects of insulin on substrate availability (Bergman and Ader, 2000). Insulin directly controls the activities of a set of metabolic enzymes by phosphorylation or dephosphorylation and also regulates the expression of genes encoding hepatic enzymes of gluconeogenesis and glycolysis (Pilkis and Granner, 1992). It inhibits the transcription of the gene encoding phosphoenolpyruvate carboxylase, the rate limiting step in gluconeogenesis (Sutherland et al., 1996). The hormone also decreases transcription of the genes encoding fructose-1, 6-bisphosphatase and glucose-6-phosphatase and increases transcription of glycolytic enzymes such as glucokinase and pyruvate kinase, and lipogenic enzymes such as fatty acid synthase and acetyl-CoA carboxylase. Although the transcription factors that control the expression of these genes have remained elusive, new data suggest a potential role for the forkhead family of transcription factors through phosphorylation by Akt related protein kinases (Nakae et al., 1999), and the PPARγ co-activator PGC-1.

**Regulation of lipid synthesis and degradation**

Insulin promotes the synthesis of lipids, and inhibits their degradation. Studies suggest that many of these changes require an increase in the transcription factor steroid regulatory element binding protein (SREBP)-1c. Dominant negative forms of SREBP-1 can block expression of these gluconeogenic and lipogenic genes, whereas over expression can increase their transcription. Hepatic SREBP levels are increased in some rodent models of lipodystrophy, and this is coordinated with increases in fatty acid synthesis and gluconeogenesis, the exact phenotype observed in genetic models of obesity-induced diabetes. Thus, increased expression of SREBP-1c might contribute to the insulin resistance observed in liver of diabetic rodents, with increased rates for the changes in SREBP-1c expression in response to insulin or other metabolic changes are
not known, but probably lie downstream of the IRS/PI-3 kinase pathway (Saltiel and Kahn, 2001).

In adipocytes, glucose is stored primarily as lipids, owing to increased uptake of glucose and activation of lipid synthetic enzymes, including pyruvate dehydrogenase, fatty acid synthase and acetyl-CoA carboxylase. Insulin also profoundly inhibits lipolysis in adipocytes, primarily through inhibition of the enzyme hormone sensitive lipase (Anthonsen et al., 1998). This enzyme is acutely regulated by control of its phosphorylation state, which is activated by PKA-dependent phosphorylation, and inhibited as a result of a combination of kinase inhibition and phosphatase activation. Insulin inhibits the activity of the lipase primarily through reduction in cAMP levels, owing to the activation of cAMP-specific phosphodiesterase in fat cells.

**Regulation of insulin sensitivity by fat cell**

Adipose tissue has a special role in insulin resistance, circulating free fatty acids (FFAs) derived from adipocytes are elevated in many insulin-resistant states and have been suggested to contribute to the insulin resistance of diabetes and obesity by inhibiting glucose uptake, glycogen synthesis and glucose oxidation, and by increasing hepatic glucose output (Bergman and Ader 2000). The link between increased circulating FFAs and insulin resistance might involve accumulation of triglycerides and fatty acid-derived metabolites in muscle and liver. Transgenic mice with muscle or liver specific over expression of lipoprotein lipase exhibit increased tissue triglyceride content that correlate with decrease in insulin action and activation of IRS-associated PI-3 kinase (Hwang et al., 2001).

Adipokines are substances which are secreted from fat cells have shown to regulate lipid and glucose levels. Leptin, adiponectin and resistin are important paracrine hormones secreted from adipocytes. Expression of TNF-α is also found to be elevated in conditions of diabetes and obesity associated with insulin resistance. The above said hormones appear to play significant role in altering insulin sensitivity and hence glycemic levels in conditions of diabetes (Saltiel and Kahn, 2001).

**Possible causes of insulin resistance**

The insulin resistance of obesity and type 2 diabetes is characterized by defects at many levels, with decreases in receptor concentration and kinase activity, the concentration and phosphorylation of IRS-1 and 2, PI-3 kinase activity, glucose transporter translocation, and the activity of intracellular enzymes. Diabetes being a
polygenic disease involves polymorphisms in multiple genes encoding the proteins involved in insulin signalling, insulin secretion and intermediary metabolism. Knockout studies with targeted deletions of the components of insulin signalling elements like insulin receptor, IRS-2 or Akt, produces diabetes under *in vivo* conditions, however knockout studies of p85 subunit of PI-3 kinase, IRS-1 and GLUT 4 does not produce diabetes. Studies with combinatorial knockouts which mimic polygenic type 2 diabetes suggest involvement of defect in insulin signalling at multiple sites leads to diabetes. The heterozygous knockout studies with p85a regulatory subunits of PI-3 kinase showed improved insulin sensitivity, further superimposition of p85a heterozygosity on the insulin receptor/IRS-1 double heterozygous knockout protects against diabetes. Tissue specific knockout of GLUT 4 in skeletal muscle and adipose tissue have exhibited diabetes, however global knockout of GLUT 4 have not produced diabetes. Various knockout studies taken together suggest a unifying hypothesis for type 2 diabetes. It involves insulin resistance in classical target tissues, such as liver, muscle and fat, coupled with insulin resistance in β cell, brain and other tissues combine to produce the pathophysiology of type 2 diabetes (Saltiel and Kahn, 2001).
**3.3.1.2 Complications Associated With Diabetes.**

Diabetes being a metabolic disorder affect carbohydrate, lipid and protein metabolism. Poor control of glycemic levels as diabetes progresses leads to diabetes induced complications. Diabetes induced complications involve mainly diabetic retinopathy, diabetic cardiomyopathy, diabetic nephropathy and diabetic neuropathy.

**Diabetic Retinopathy**

Diabetic retinopathy is one of the most common microvascular complications of diabetes, affecting 80% of patients over 20 years duration of diabetes. Despite remarkable advances in the diagnosis and treatment of diabetic retinopathy and its associated complications, diabetic retinopathy remains the leading cause of blindness among working age individuals.

*Clinical pathogenesis and classification of diabetic retinopathy*

Diabetic retinopathy is detected clinically by the presence of visible opthalmoscopic retinal microvascular lesions in an individual with diabetes mellitus. Retinopathy has been broadly classified as nonproliferative (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is further divided into NPDR with maculopathy, NPDR without maculopathy and pre-proliferative retinopathy. NPDR indicates progressive ischemia in the retina and an increased risk for the development of PDR and blindness. The prominent clinical features of NPDR include microaneurysms, dot or blot hemorrhages, venous abnormalities, and cotton wool spots. Preproliferative diabetic retinopathy is the stage before the onset of neovascularization and is characterized by a) extensive retinal hemorrhages, b) marked venous bleeding c) numerous cotton wool spots or retinal infarcts, d) intra-retinal vascular abnormalities (IRMA), and e) marked retinal ischaemia as evidenced by capillary drop outs in the fundus fluorescein angiogram. Proliferative diabetic retinopathy is characterized by retinal neovascularization, vitreous haemorrhage, vitreoretinal traction and localized retinal detachment.

**Biochemical defects in diabetic retinopathy**

Multiple biochemical pathways have been proposed to explain the pathogenesis of diabetic retinopathy all starting initially from hyperglycemia. These mainly include increased polyol pathway, increased advanced glycation end products (AGE) formation, activation of protein kinase C (PKC) and increased hexosamine pathway flux (Brownlee et al., 2001).


**Current treatments for diabetic retinopathy**

Laser photocoagulation is the primary means by which ophthalmologists control the progression of macular edema and neovascularization. The short and long term beneficial effects of photocoagulation have led to its wide clinical acceptance for the treatment of proliferative diabetic retinopathy. Unfortunately, there are many patients in whom laser therapy cannot be done due to an obstructing vitreous hemorrhage or severe fibrous proliferation. Since laser photocoagulation is still an invasive procedure destroying the retinal cells, future pharmacotherapeutic approaches should be developed to prevent retinal lesions in diabetic subjects.

Research during the past few decades has provided ample evidence that hyperglycemia is one of the main factors driving the onset and progression of diabetic retinopathy. Furthermore, hyperglycemia-induced events regulate a variety of cellular signals including the stimulation of growth factors that are implicated in retinopathy. It is possible that in the future, novel therapeutic measures may emerge for the treatment of diabetic retinopathy. In order to discover antipermeability and anti-angiogenic compounds, a more comprehensive understanding of the mechanisms governing the vascularization of the retina is required. Some of the experimental approaches currently under investigation, such as protein kinase C inhibitors, VEGF inhibitors, pigment epithelium-derived factor, and many other approaches in the treatment of various stages of diabetic retinopathy. Significant efforts have continued towards the evaluation of the mechanisms underlying diabetic retinopathy in order to achieve newer and better therapies for this potentially preventable cause of blindness (Balasubramanayam et al., 2002).

**Diabetic Cardiomyopathy**

Clinical studies have confirmed that the incidence of heart disease is much greater in diabetics, and is a leading cause of death in these patients (Kannel and McGee, 1979; Palumbo et al., 1981). Factors that have been implicated in the development of cardiovascular dysfunction during diabetes include atherosclerosis of coronary arteries (Young et al., 1994), microangiopathy and autonomic neuropathy (Ledet et al., 1979). However, it has also become apparent that these factors, although important, are not exclusive determinants of the cardiac problems associated with diabetes. Indeed, a significant number of patients with diabetes do not develop atherosclerosis continue to
suffer from cardiomegaly, left ventricular dysfunction, and clinically overt congestive heart failure (Hamby et al., 1974; Ahmed et al., 1975; Regan et al., 1977; D’Elia et al., 1979). This suggests that a specific cardiac muscle disease, i.e. diabetic cardiomyopathy, may also occur during diabetes (Fein and Sonnenblick, 1985; Galderisi et al., 1991) and could be a causal factor in producing the increase in mortality and morbidity of diabetes.

Metabolic changes in diabetic cardiomyopathy

In conditions of diabetes, as disease progresses altered metabolism of fatty acids and carbohydrates causes damaging effects on heart and leads to development of diabetic cardiomyopathy.

Fatty acids

Alterations in both fuel supply and utilization by the heart tissue are the causative factor for initiating the development of diabetic cardiomyopathy. As diabetes progresses excessive free fatty acids are consumed by cardiac tissue which can lead to an increased susceptibility to arrhythmias (Opie, 1970; Willebrands et al., 1973; Fields et al., 1986). Esterification to complex lipids and hence higher tissue levels of triglyceride, an increased requirement of oxygen for catabolism, reduction in both, basal and insulin stimulated glucose transport and metabolism (Randle et al., 1965). Modifications of the structure of sarcolemmal and other sub cellular membranes thereby alter membrane fluidity and molecular dynamics (Katz and Messineo, 1981). Inhibition of critical enzyme systems such as Ca\(^{2+}\)-ATPase of sarcoplasmic reticulum, and Na\(^+\), K\(^+\)-ATPase, Na\(^+\)/Ca\(^{2+}\) exchange and Ca\(^{2+}\) pump in myocardial sarcolemma (Adams et al., 1979; Kramer and Weglicki, 1985; Dhalla et al., 1991). Inhibition of the adenine nucleotide translocator in isolated mitochondria leading to a reduction in the myocardial levels of ATP (Vaartjes et al., 1972).

Carbohydrate metabolism

In conditions of diabetes, the major restriction to glucose utilization by the heart is the slow rate of glucose transport across the sarcolemmal membrane into the myocardium, probably as a result of cellular depletion of glucose transporters (Koboyashi and Olefsky, 1979). Diabetic state is associated with hypertriglycerideridemia and a considerable alteration in fatty acid profile of the membranes, which leads to decrease in glucose transporters and a reduction in insulin stimulated cardiac glucose utilization (Bjeger et al., 1984). Glucose oxidation in diabetic heart is markedly impaired, not only as a result of impaired glucose transport into the myocyte but also by
a reduced rate of phosphorylation of glucose within the cell. Another explanation for the reduced oxidation of glucose by the diabetic heart is that the activity of pyruvate dehydrogenase complex is also depressed may be as a result of an increased fatty acid oxidation that causes increased acetyl CoA/CoA ratio. The end result is an impaired pyruvate oxidation. This leads to inhibition of glucose oxidation by fatty acids (Wall and Lopaschuk, 1989).

**Subcellular remodeling in diabetic cardiomyopathy**

Various studies have shown that in conditions of diabetes subcellular remodeling of the myocardium along with the metabolic changes taking place in the heart. Animal studies have shown decreased activities of the Ca^{2+}-ATPase of cardiac myofibrils, actomyosin and myosin (Dillmann, 1980; Fein et al., 1981; Pierce and Dhalla, 1981). The depressed ATPase activities of contractile proteins can be seen to play an important role in the development of heart dysfunction due to diabetes. The protein contents of MLC and MLCK as well as MLC phosphorylation are decreased significantly in the diabetic heart and the change is reversible upon insulin treatment (Liu et al., 1997). In conditions of diabetes, the regulatory effects of the TnTm complex on actin and myosin are altered which lead to depressed myofibrillar ATPase activity. Remodeling of sarcoplastic reticulum and sarcolemmal membranes takes place in the heart during the development of chronic diabetes (Dhalla et al., 1985; Schaffer, 1991; Golfman et al., 1996). Remodeling of both sarcolemmal and sarcoplasmic reticular membranes is reported to result in Ca^{2+} handling abnormalities in cardiomyocytes and subsequent heart dysfunction during the development of diabetic cardiomyopathy.

**Diabetic Nephropathy**

Diabetic nephropathy is defined as a clinical syndrome characterized by the development of persistent proteinuria, systemic hypertension, and declining renal function in subjects with diabetes mellitus. It is the leading cause of end-stage renal disease in developed countries and leads to a heavy burden of dialysis and transplantation. The risk of premature death in patients with diabetic nephropathy is increased by the factor of 40-100, and other complications such as retinopathy and neuropathy cluster in these patients (Borch-Johnsen et al., 1985). Diabetic nephropathy may develop in 30%-40% patients with diabetes mellitus (Andersen et al., 1983). Progression of diabetic nephropathy can be described in the following stages, a) Renal
hemodynamic alterations (hyperfiltration) and structural changes, b) Microalbuminuria

Renal Hemodynamic Alterations

Glomerular hyperfiltration is a common diagnosis of diabetes mellitus and is often accompanied by renal hypertrophy and increased renal plasma flow. Intraglomerular hypertension is consequent upon hyperfiltration that leads to mesangial expansion and basement membrane thickening. These features can be the hallmarks of diabetic glomerulosclerosis. A wide variety of growth factors and cytokines have been implicated in the etiology of glomerular hyperfiltration which include insulin like growth factor-1 (IGF-1) (Flyvberg et al., 1988), TGF-β (Wolf et al., 1992), atrial natriuretic peptide (ANP) (Sharma et al., 1996), thromboxane A₂ (Dunn et al., 1986), nitric oxide (Tolins et al., 1993) and angiotensin II (Anderson et al., 1993).

Glomerular Structural Changes

Diabetic nephropathy in humans presents several structural changes that are characterized by early hypertrophy of both glomerular and tubulointerstitial elements, thickening of the glomerular basement membrane, progressive accumulation of extracellular matrix components in the glomerular mesangium, and less well recognized lesions such as tubulointerstitial fibrosis and renal arteriosclerosis (Mauer et al., 1984; Osterby et al., 1988; Ziyadeh et al., 1989; Steffes et al., 1992).

Microalbuminuria

Once microalbuminuria is established the trend is one of increasing proteinuria until overt nephropathy develops. The normal urinary protein excretion rate is up to 300 mg/24 hr, of which about 10% is albumin, equivalent to an albumin excretion rate of 20 μg/min. Albumin excretion rates of 20-200 μg/min, equivalent to a urine albumin creatinine ratio (ACR) of 10-25 mg/mmol, are defined as microalbuminuria (also called as incipient nephropathy) as these levels are not detectable by conventional urine dipstick analysis. The onset of microalbuminuria is highly significant since its presence predicts the development of overt renal disease in both type 1 and type 2 diabetes (Viberti et al., 1982; Mogensen, 1984).

Overt Nephropathy

Proteinuria is generally regarded as a marker for the degree of glomerular damage. Albumin excretion rates above 200 μg/min or 300 mg/day (equivalent to an ACR of > 25 mg/mmol) are dipstick positive and defined as overt nephropathy. This is
usually associated with a relentless loss of glomerular filtration rate (by 1-24 ml/min per year) until end stage renal failure necessitates dialysis or renal transplantation. The rate of progression of microalbuminuria and overt nephropathy is heavily influenced by blood pressure control, glycemic control and the use of angiotensin converting enzyme (ACE) inhibitors (Remuzzi and Bertani, 1990).

**Diabetic Neuropathy**

Neuropathy is the most frequent symptomatic complication of diabetes and potentially one of the most devastating. Diabetic neuropathy has been reported to affect more than 50% of patients with a history of diabetes of more than 25 years duration, making it one of the most common diseases affecting the nervous system. Neurologic complications occur equally in type 1 and type 2 diabetes. Diabetes with chronic hyperglycemia appears to be the most important risk factor for the development of neuropathy. Male sex, smoking, retinopathy, microalbiminuria and alcoholism are other factors which are considered to be risk factors for development of diabetic neuropathy. Diabetic neuropathy can be classified into a) symmetric/asymmetric b) diffuse or focal and c) progressive/reversible.

**Pathogenesis of Diabetic Neuropathy**

The pathogenesis of diabetic neuropathy is multifactorial. The various pathogenic factors are interrelated and together contribute to the development and progression of syndrome (Stevens et al., 1995). Three mechanisms which are involved in causing peripheral nerve degeneration in diabetic patients are hyperglycemia, local nerve ischemia and neurotrophic factor deficiency.

In diabetes chronic hyperglycemia leads to accumulation of sorbitol intracellularly which produces a reciprocal decrease in levels of myoinositol and taurine to the point that they become insufficient for normal intracellular metabolism. Myoinositol and taurine depletion has been associated with reduced Na⁺/K⁺ adenosine triphosphate activity and reported to slow down in nerve conduction velocity (Green, 1992). Sorbitol accumulation also reported to reduce nicotinamide-adenine dinucleotide phosphate (NADPH) and glutathione stores in the cell. Hyperglycemia is also reported to promote formation of reactive oxygen species by auto oxidation of glucose and formation of advanced glycation end products (Hunt et al., 1988). Local nerve ischemia is one of the common features seen in diabetic neuropathy. Reduction in nerve blood flow is reported in diabetic animals and patients. Reduction in blood flow leads to
ischemia, and is reported to cause oxidative stress in nerve leading to increased production of reactive oxygen species which in turn is one of the causative factors for nerve injury. Deficiency of nerve growth factor is also one of the causes for diabetic neuropathy. Nerve growth factors are involved in the development maintenance and regulation of responsive element of the nervous system (Hellweg and Hartung, 1990).

Management of Diabetic Neuropathy

The most important step in the management of any diabetic neuropathy is strict glycemic control. Management of pain associated with diabetic neuropathy are being treated these days by few drugs. Tricyclic antidepressants are used in conditions of parasthesias. Topical capsaicin is used in conditions of burning pain. Gabapentin is generally used treating pain associated with mono neuropathies. Focal neuropathies are treated using carbamazapine. Many other approaches for treating diabetic neuropathy are in either experimental stage or in clinical trials. The promising among them are aldose reductase inhibitors, gamma linolenic acid, gangliosides, aminoguanidine, N acetyl carnitine, myoinosital, ACE inhibitors, calcium channel blockers and nerve growth factors.

A continuous search for drugs useful in neuropathy is being explored since few decades. The promising effects are seen from nerve growth factors, brain derived neuropathic, Neurotrophin NT-3 and NT-4/5, Insulin like growth factor IGF-II and glia cell derived neurotrophic factor. Clinical trials of recombinant human nerve growth factor are ongoing.

Biochemistry and Molecular Cell Biology of Diabetic Complications

Diabetes-specific microvascular disease is a leading cause of blindness, renal failure and nerve damage and diabetes-accelerated atherosclerosis leads to increased risk of myocardial infarction, stroke and limb amputation. Four main molecular mechanisms have been implicated in glucose-mediated vascular damage. All seem to reflect a single hyperglycemia-induced process of overproduction of superoxide by the mitochondrial electron-transport chain (Brownlee, 2001).

Mechanisms of hyperglycemia-induced damage

Four main hypotheses about how hyperglycaemia causes diabetic complications have generated a large amount of data, as well as clinical trials based on specific inhibitors of these mechanisms. The four hypotheses are
• Increased polyol pathway flux
• Increased advanced glycation end product (AGE) formation
• Activation of protein kinase C (PKC) isoforms
• Increased hexoseamine pathway flux

A common element linking hyperglycemia-induced damage

Specific inhibitors of aldose reductase activity, AGE formation, PKC activation and hexoseamine pathway each ameliorate various diabetes-induced abnormalities in cell culture and animal models, there has been no apparent common element linking the four mechanisms of hyperglycemia-induced damage. The recent discovery that each of the four different pathogenic mechanisms reflects a single hyperglycemia-induced process suggest over production of superoxide by mitochondrial electron transport chain. Many studies have shown that diabetes and hyperglycaemia increase oxidative stress, but neither the underlying mechanism nor the consequences for other pathways of hyperglycemic damage were known. In glucose metabolism, when the electrochemical potential difference generated by the proton gradient across the inner mitochondrial membrane is high, the lifetime of superoxide- generating electron-transport intermediates such as ubiquinol is prolonged. There seems to be a threshold value above which superoxide production is markedly increased. Hyperglycemia increases the proton gradient above threshold value as a result of over production of electron donors by the TCA cycle. This in turn, causes a marked increase in the production of the superoxide by endothelial cells. Over expression of manganese superoxide dismutase (MnSOD), the mitochondrial form of superoxide dismutase, abolishes the signal generated by reactive oxygen species, and over expression of uncoupling protein-1 (UCP-1) collapses the proton electrochemical gradient and prevents hyperglycemia-induced overproduction of reactive oxygen species.

Inhibition of hyperglycemia induced mitochondrial superoxide by MnSOD or UCP-1 completely prevents an increase in polyol pathway flux, increased intracellular AGE formation, increased PKC activation and an increase in hexoseamine pathway activity in endothelial cells. Overexpression of UCP-1 or MnSOD corrects a variety of hyperglycemia-induced phenotypes in target cells of diabetic complications. In cultured glomerular mesangial cells, overexpression of MnSOD suppresses the increase in collagen synthesis induced by high glucose. In dorsal root ganglion (DRG) neurons from both wild type and MnSOD+/- mice, over expression of MnSOD decreases
hyperglycemia-induced programmed cell death, and in embryonic rat DRG neurons, over expression of UCP-1 inhibits cleavage of programmed cell death effector caspase. In aortic endothelial cells, over expression of either UCP-1 or MnSOD completely blocks hyperglycemia-induced monocyte adhesion.

The discovery that each of the four main mechanisms implicated in the pathogenesis of diabetic complications reflects a single hyperglycemia-induced process provides a new conceptual framework for future observation, general areas are of great importance to a more complete understanding of the molecular and cell biology of diabetic complications are, hyperglycemic memory, genetic determinants of susceptibility to both microvascular and macrovascular complications and interruption of overproduction of super-oxide dismutase (Brownlee, 2001).
3.3.1.3 Therapeutic Interventions in Diabetes Mellitus

Treatment in diabetes mellitus involves various drugs, other than drugs diet management and physical exercise are essential to control and maintain glycemic levels in conditions of diabetes.

Diet

The management of glycemic levels in conditions of diabetes involves coordination of various factors, among them, diet control, physical exercise and drugs play important role. For patients with diabetes, carbohydrates should comprise 50-55% of daily calorie allowance. This should be mainly in the form of complex rather than simple carbohydrates that is less digested starches in preference to mono or disaccharides. Higher intakes of carbohydrate, in the absence of a sufficient increase in fiber, may aggravate hypertriglycerideremia and are not generally recommended. High-starch, low-fat dieting improves insulin-mediated glucose metabolism (Himsworth, 1933). However, there are data on the effect of that type of diet on in vivo insulin action in IDDM patients. Various studies have shown that caloric restriction and weight reduction improve insulin sensitivity, insulin binding and glucose tolerance in obese, non-insulin-dependent diabetics (Olefsky, 1976; Beck-Nielsen, 1978; Beck-Nielsen et al., 1979; Beck-Nielsen et al., 1980). The glucose tolerance has been reported to be improved in non-obese, mild diabetics on a high carbohydrate, isocaloric diet (Brunzell et al., 1971). Kolterman et al (1979) have also shown that a high carbohydrate diet can appreciably enhance in vivo insulin sensitivity in healthy subjects after only 2 weeks, despite a concurrent decline in insulin receptor number. These observations thus indicate that a high carbohydrate diet can enhance insulin sensitivity by stimulating post receptor steps of insulin action. However, contrary evidence has also been provided i.e. a low carbohydrate diet can improve oral glucose tolerance and increase tissue sensitivity to insulin in non-insulin-dependent diabetics (Beck-Nielsen et al., 1980).

Physical Exercise

Regular physical activity is of potential benefit to many patients with diabetes. It should be encouraged wherever possible as an integral component of other lifestyle changes that is nutritional modification, avoidance of cigarettes and moderate alcohol consumption, benefits of regular exercise include, weight control, improved glycemic control, and improved cardiovascular risk profile. Exercise has beneficial effects on body
weight particularly when combined with caloric restriction, maintenance of fat free mass sustains resting-energy expenditure as adiposity is reduced. Physical exercise improves glycemic control in patients with type 2 diabetes this appears to be mediated via increased glucose disposal independently of the action of insulin on phosphoinositide-3-phosphate activity. Increased translocation of GLUT-4 glucose transporters in skeletal muscle improves glucose uptake after periods of exercise. Lowering of plasma total cholesterol and triglycerides, increased HDL-cholesterol, lower blood pressure and improved fibrinolysis via lower plasminogen activator inhibition-1 levels are some of the benefits associated with physical exercise in condition of diabetes.

**Exercise in the prevention of type 2 diabetes**

Exercise has the capacity to ameliorate several components of the insulin-resistance syndrome. Diet and exercise, alone or in combination, reduces the proportion of individuals with impaired glucose tolerance progressing to type 2 diabetes. Activities which raise the pulse moderately from its resting rate to sub maximal levels are necessary. The best modalities of exercise, ideally taken in combination are, aerobic endurance activities which include walking, running, cycling, swimming, aerobics etc. resistance training include low-intensity, high volume circuit training.

Diabetic patient's physiology will be altered during exercise and patients with metformin, acarbose or thiazolidinediones as monotherapy are not at risk of hypoglycemia, however, patients receiving sulphonylureas or insulin may have to reduce or omit their medication depending on the intensity and duration of the exercise. Trained athletes have normal or supernormal glucose tolerance despite plasma insulin responses that are slightly lower than those of untrained individuals (Lohmann et al., 1978; LeBlanc et al., 1979). Acute submaximal exercise is associated with an increase in insulin binding to monocytes and erythrocytes from untrained patients with IDDM (Pederson et al., 1980). These two observations suggest that physical activity has a beneficial effect on insulin sensitivity both in normal and diabetic subjects. A significant (~30%) improvement in insulin-mediated glucose uptake has also been observed after 9-wk of regular physical training in normal weight, sedentary healthy volunteers, on obese subjects and in patients with NIDDM as measured with the insulin clamp technique (DeFronzo and Ferrannini, 1982).
Drugs

Diabetes being a metabolic disease is primarily controlled by physical exercise and diet, however these two appear to have significant effect on glycemic control, they are insufficient to get the glycemic levels to a desired extent. Pharmacotherapeutic measures are hence becomes essential in maintaining near normal glycemic levels in diabetes. The drugs used in diabetes include insulins, sulfonylureas, biguanides, glitinides, thiazolidinediones and alpha glucosidase inhibitors.

Insulins

Treatment with insulin is a must for type 1 diabetic patients, however in patients with type 2 diabetes use of insulin is essential when diet, physical exercise and oral antidiabetic agents fail to maintain glycemic levels. In conditions of type 2 diabetes there is reluctance to use insulin earlier due to mode of administration, unwanted side effects of insulin and need to monitor blood glucose levels frequently. The direct effect of insulin on peripheral insulin resistance is controversial. Several studies (Garvey et al., 1985) have shown that intensive insulin treatment for several weeks produced a 72% increase in the maximal rate of insulin-stimulated glucose uptake by peripheral tissues. Karmeli et al (1987) in a study described that insulin therapy for 8 days in streptozotocin diabetic rats was associated with a threefold increase in glucose transport activity in the intact adipose cell compared with control and with about a six fold increase when compared with cells isolated from diabetic rats. Several groups of investigators have looked at the effects of CSII on in vivo insulin action in IDDM patients. In these reports peripheral tissue sensitivity to insulin has been studied with the euglycemic insulin clamp at one or more steady-state plasma insulin concentrations (Lager et al., 1983; Yki-Jarvinen and Koivisto, 1984; Simonson et al., 1985). Near normalization of glycemia and normalization of plasma concentration of insulin-antagonistic hormones and FFA with CSII partially corrected but did not restore to normal the insulin-stimulated glucose disposal to peripheral tissues. In one study the prepump basal glucose production in the liver was elevated but showed a significant fall during pump treatment (Yki-Jarvinen and Koivisto, 1984), whereas in another study the prepump basal hepatic glucose output was normal and showed no change during CSII (Simonson et al., 1985). Insulin binding to adipocytes and blood cells is unaltered and the basal glucose transport and metabolism in adipocytes are further suppressed during CSII (Pederson et al., 1986).
CSII causes a decrease of basal hepatic glucose output. In vivo studies also indicate an increment but not a normalization of peripheral insulin sensitivity. The improved peripheral glucose clearance seems to reflect an increase of glucose utilization in muscle tissue because in vitro studies have failed to demonstrate any beneficial effects of CSII on insulin-mediated adipocyte glucose processing. It is hypothesized that the CSII-induced increase of glucose turnover in skeletal muscles may at least in part be secondary to the lower plasma levels of FFA, which increases the glucose oxidation by enhancing the activity of pyruvate dehydrogenase.

Use of insulin in these days are made convenient by introduction of longer acting insulins, insulin which are released at constant rate, new devices for insulin administration have also attracted use of insulin in diabetic patients. In near future one can anticipate the availability of pulmonary administration of insulin. The developments in last one decade in insulin formulations have made patients willingness to use insulin in a greater way as compared to previous decades.

Though insulin being a wonderful drug which controls hyperglycemia, it has the side effects of hypoglycemia and weight gain. Hypoglycemia can be avoided on proper dosing of insulin. Diabetic patients with obesity should reduce insulin usage and can be supplemented with metformin to avoid weight gain.

**Sulfonylureas**

Sulfonylureas have remained as mainstay drugs in antidiabetic therapy for almost three decades. The mode of action of sulfonylureas involves inhibition of $K_{ATP}$ channels initiating insulin secretion. These drugs can be used only in patients with type 2 diabetes having functional beta cells for endogenous insulin production. Sulfonylureas are known to produce their antidiabetic activity by both pancreatic and extra pancreatic actions. Sulfonylureas act on pancreatic islets and produce insulin secretion and hence maintain glycemic levels. Since long time sulfonylureas are known to possess extra-pancreatic actions (Feldman and Lebovitz, 1969). When administered acutely, these agents cause a prompt increase in insulin secretion, which can be demonstrated both in vivo (Yalow et al., 1960; Feinglos and Lebovitz, 1980) and in vitro (Gotfredsen, 1986). This stimulatory effect is observed in both the presence and absence of glucose and is exerted on both the early and late phases of insulin secretion (Gotfredsen, 1976).
The effect of glibenclamide treatment on insulin-mediated glucose disposal was studied in C-peptide-negative IDDM patients by applying the euglycemic insulin clamp (Pernet et al., 1985). At a physiological steady-state plasma insulin concentration the glucose disposal rate to peripheral tissues increased by 35%. However, with chronic sulfonylurea treatment basal and insulin stimulated plasma insulin levels return to normal or below (Reaven and Dray, 1957; Sheldon et al., 1966; Chu et al., 1968; Varsano-Aharon et al., 1970; Duckworth et al., 1972; Barnes et al., 1974; Dunbar and Foa, 1974), yet glucose tolerance remains improved. The study by Duckworth et al. (1972) exemplified the findings of prolonged sulfonylurea therapy. After 6 month therapy with gliburide in seven patients with NIDDM, the fasting plasma glucose levels decreased to normal without any change in plasma insulin levels and glucose tolerance also improved considerably despite a slight decrease in plasma insulin response. This improvement in glucose tolerance was maintained at 12 months in the face of even greater (40%) reduction in the plasma insulin response.

The increase in tissue sensitivity to insulin induced by these agents appears to be related to enhanced glucose uptake by peripheral tissue (Feldman and Lebovitz, 1969; Fengeglos and Lebovitz, 1980) as well as greater efficacy of insulin in inhibiting hepatic glucose production (Tarding and Schambage, 1958; Kaldor and Pogatsa, 1960). In addition, recent evidence indicates that the improvement in insulin sensitivity may be mediated, at least in part, by an increase in insulin binding to membrane receptors in a variety of tissues, including liver cells (Fengeglos and Lebovitz, 1978), human fibroblasts (Prince and Olefsky, 1980) and circulating monocytes from patients with NIDDM (Olefsky et al., 1973; Beck-Nielsen et al., 1979). The precise mechanism of action of sulfonylureas on tissue sensitivity to insulin under in vivo conditions, however, is not known. It has been suggested that these agents may increase the number of insulin receptors by slowing down receptor degradation.

Following the release of UKPDS (1998) study report, which implicated tolbutamide in increased mortality secondary to cardiovascular events, a sharp decline in the use of first generation sulfonylureas like acetohexamide, chlorpropamide, tolbutamide and tolazamide. However second generation sulfonylureas like glyburide, glipizide and glimeperide have exhibited favorable side effects and hence have contributed to their renewed use. Overt hypoglycemia is the most significant side effect associated with sulfonylurea treatment. Glipizide and glimepride are associated with
lower incidence of weight gain and thus may not be optimal for choice for obese patients.

**Biguanides**

Metformin is the only drug under this class which is clinically used for diabetes treatment. Metformin works by reducing hepatic glucose output through inhibition of gluconeogenesis and to lesser extent, enhancing insulin sensitivity in hepatic and peripheral tissues as well as by limiting gastrointestinal glucose absorption (DeFronzo, 1999; Iannello, 2000). Metformin also increases glucose utilization by intestine, primarily via nonoxidative metabolism. This results in extra lactate production, which is taken up by liver and used as a gluconeogenic substrate. Unlike sulfonylureas, it does not stimulate insulin secretion, or does it aggravate hyperinsulinaemia or cause hypoglycemia or weight gain (Iannello, 2000). Its more prominent effect in type 2 diabetic patients is on postprandial hyperglycemia. It is considered as a first-line agent particularly in obese and/or hyperlipidaemic type 2 diabetic patients (Lefebvre and Scheen, 1992). Biguanides have been shown to lower insulin needs in IDDM patients and in a short-term study with the euglycemic clamp at a single steady-state plasma insulin level, an 18% improvement in glucose utilization of peripheral tissues was demonstrated in metformin-treated IDDM (Gin et al., 1985).

Metformin unlike phenformin does not bear risk of lactic acidosis. Other effects of metformin include a reduction in plasma triglyceride levels and low density lipoprotein levels. Metformin is unusual among the oral antidiabetic drugs as it does not produce weight gain, but rather few cases show reduction in body weight in diabetic subjects. A rare but important side effect associated with metformin treatment is lactic acidosis.

**Thiazolidinediones**

Thiazolidinediones are PPARγ agonists. This is an orphan member of nuclear hormone super family that mediates adipocyte differentiation and modulates insulin sensitivity through regulation of gene expression. Rosiglitazone and pioglitazone are the two drugs under this class which are in clinical use. Thiazolidinediones reduce fasting hyperglycemia and insulinaemia by improving insulin sensitivity in skeletal muscles, adipose tissue and hepatocytes, while normalizing a wide range of metabolic abnormalities associated with insulin resistance. They activate the peroxisome proliferator activated receptor gamma (PPARγ) which acts in conjunction with the
retinoid X receptor by de-repression to increase transcription of certain insulin sensitive genes (Henry, 1997; Spiegelman, 1998). Reported effects include (a) decrease in plasma triglyceride, FFA and LDL cholesterol levels and increase in plasma HDL cholesterol, (b) increased expression of glucose transporters GLUT-1 and GLUT-4, (c) activation of glycolysis in hepatocytes, (d) antagonism towards some of the effects of TNF-α, (e) decrease in blood pressure, (f) inhibition of vascular smooth muscle cell proliferation and hypertrophy, (g) enhanced endothelium-dependent vasodilation and (h) antioxidant action (Iannello, 2000). Thiazolidinediones do not stimulate insulin secretion, but they improve the secretory response of β cells to insulin secretagogues. Thiazolidinediones increase insulin sensitivity in fat and muscle tissues and to a lesser extent inhibit hepatic glucose production. Both drugs in this class show decrease in triglyceride levels. There is no risk of hypoglycemia with this class of agents. Significant weight gain has been reported with this class of agents, which cause a severe concern for their use in diabetes. These drugs should not be used in patients who show liver dysfunction.

Troglitazone the first among the thiazolidinediones introduced into clinical use demonstrated significant liver dysfunctions (Gitlin et al., 1998; Neuschwander-Tetri et al., 1998; Vella et al., 1998), hence it was withdrawn from clinical use. Though newer compound, rosiglitazone does not appear to be hepatotoxic, it is contraindicated in patients with history or sign/symptoms of liver disease and its use requires monitoring of liver function test. Other issues such as fluid retention, haemodilution, an increase in plasma cholesterol and other effects of PPAR-γ stimulation are under investigation. Significant weight gain has been reported with this class of agents, which cause a severe concern for their use in diabetes.

**Glitinides**

Repaglinide, netaglinide and meglitinide, are the drugs in this class of antidiabetic agents, these drugs are structurally different from traditional sulfonylureas, but shows chemical resemblance to the nonsulfonylurea moiety of the glibenclamide molecule. These drugs binds to the ATP-dependent potassium channel at a site distinct from the sulphonylureas, furthermore in contrast to glibenclamide, these will not enter the beta cell to stimulate exocytosis of insulin containing secretory granules. Glitinides requires the presence of glucose, in contrast to sulphonylureas which will stimulate insulin release in the absence of glucose. In contrast to sulphonylureas, glitinides do not
stimulate calcium dependent exocytosis. Unlike commonly used sulfonylureas, glitinides have a very quick onset of action and a short half-life. Some potential advantages of this class of agents include a greater decrease in postprandial glucose and decreased risk of hypoglycemia.

Glitinides are effective when used as both monotherapy and in combination with metformin. Glitinides is taken with meals with the aim of controlling post-prandial hyperglycemia. Glitinides is generally well tolerated with only minor adverse effects, no significant drug interactions have been reported, glitinides has also shown a lower risk of hypoglycemia when compared with sulphonylureas, which makes it attractive option for older patients at highest risk.

**Alpha Glucosidase Inhibitors**

Alpha glucosidase are found in the brush border cells that line small intestine, these enzymes cleaves more complex carbohydrates into sugars. Alpha glucosidase inhibitors inhibit breakdown and subsequent absorption of carbohydrates from the gut following meals. Acarbose, miglitol and voglibose are the drugs under this category. α-glucosidase inhibitors reduces the carbohydrate absorption from the gastrointestinal tract by inhibiting the action of the enzyme complex α-glucosidase in the brush border of the small intestine, postprandial increase in blood glucose is therefore reduced. Enhanced secretion of the incretin hormone glucagon-like peptide-1 from the small intestine may represent an additional mode of action. The major impact of these drugs is on postprandial hyperglycemia.

In a study of patients with impaired glucose tolerance, acarbose decreased postprandial plasma glucose and insulin concentrations and improved insulin sensitivity. Serious adverse effects of acarbose are rare, systemic absorption of the parent drug and its metabolites is low. Hypoglycemia is not a risk factor if the drug is used as monotherapy. However, tolerability is limited by gastrointestinal side-effects. Clinical studies have generally demonstrated lower efficacy of acarbose with sulphonylureas or biguinides. Acarbose may be combined with sulphonylureas, metformin or insulin. Miglitol is a competitive and reversible inhibitor with shorter duration of action than acarbose, in contrast to acarbose, the drug is absorbed and excreted unchanged by the kidneys. Reductions in post-prandial hyperglycemia have been reported in patients with type 2 diabetes. Miglitol may be useful when combined with sulfonylureas. Miglitol has
similar gastrointestinal side effects as that of acarbose. Voglibose, a potent inhibitor of sucrase, has been studied in patients with type 2 diabetes. In the same way as acarbose, voglibose reportedly stimulates release of the incretin glucagon-like peptide-1 from the intestine. The significant side effect associated with α-glucosidase inhibitors includes abdominal discomfort, flatulence and diarrhea. These agents should be avoided in patients with liver cirrhosis.
3.3.1.4 New Drug Targets for Type 2 Diabetes and Metabolic Syndrome

Several new therapeutic approaches are studied these days for diabetes treatment which include reduction of excessive glucose production by liver, mechanisms to augment glucose-stimulated insulin secretion, specific molecular targets in the insulin signalling pathway and newer approaches for net improvement in insulin action. The developments in these areas are briefly summarized below.

Reducing excessive hepatic glucose production

Liver plays a critical role in regulation of endogenous glucose production by gluconeogenesis and glycogenolysis. Increased rates of hepatic glucose production are largely responsible for the development of overt hyperglycemia (DeFronzo et al., 1992). Glucagon receptor antagonists are one among the targets for reduction of hepatic glucose production. Inhibition of hepatic glycogen phosphorylase has proven to reduce elevated glycemic levels in rodent models of diabetes (Treadway et al., 2001). Inhibition of glucose 6-phosphatase and fructose-1, 6-bisphosphatase is other mechanism by which one can reduce hepatic glucose production (Zhang and Moller, 2000). Reducing excessive glucose production even though appears attractive it has some limitations as it can cause hypoglycemia, accumulation of triglycerides and increased plasma lactate levels.

Enhancing glucose stimulated insulin secretion

In conditions of diabetes, a reduction in the ability of glucose to stimulate insulin secretion from pancreatic β cells is observed. The failure of β cells to compensate for insulin secretion under insulin resistance conditions leads to overt hyperglycemia which may be associated with defective β cell function (Porte, 1990). In such conditions two targets which are explored which produce glucose stimulated insulin secretion are gut derived peptide hormones like glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 agonists have shown to produce antidiabetic effect and are also found to suppress energy intake in humans. Drugs belonging to GLP-1 class appear to reach for clinical use in near future (Knudsen, 2004). Although GLP-1 and GIP have strong potential as chronic therapies for diabetes, both are subject to rapid aminoterminal degradation by dipeptidylpeptidase-IV (DP-IV). To overcome such disadvantage of short duration of action of GLP-1 and GIP, DP-IV inhibitors have been developed which have demonstrated increased duration of GLP-1 action and hence antidiabetic activity (Weber, 2004).
Targeting the insulin signalling pathway

Many studies have shown multiple defects in insulin signalling can lead to insulin resistance, among which impaired activation of insulin receptor tyrosine kinase and reduced activation of insulin stimulated phosphotidylinositol-3-OH kinase (PI-3 kinase) appears to be affected. A number of molecular targets are being investigated as ways of enhancing insulin-mediated signal transduction which include PTP-1B inhibitors, glycogen synthase kinase inhibitors, protein kinase C inhibitors and insulin receptor activators. The discovery of a small-molecule natural product derivative that mediates selective activation of the insulin receptor has shown significant antidiabetic activity. Several studies have shown PTP-1B inhibitors, produce antidiabetic activity by enhancing insulin sensitivity (Moller, 2001). Glycogen synthase kinase has a clear role in opposing the effect of insulin, by inhibiting the activation of glycogen synthase and the subsequent accumulation of glycogen in muscles. Studies with selective GSK-3 inhibitors have shown to augment insulin action and prevent diabetes (Weston, 2001).

Targeting lipotoxicity

In conditions of diabetes many studies have shown, lipotoxicity occurs due to accumulation of triglycerides and long-chain fatty acyl-CoA in liver and muscle which causes reduction in insulin mediated metabolic activity. The accumulation of triglycerides in islets leads to impaired insulin secretion. Several therapeutic targets are explored for correcting lipotoxicity and hence improve insulin mediated metabolic action leading to maintain glycemic levels in diabetes. The targets which are explored under such category include AMP-activated protein kinase (AMPK), acetyl-CoA carboxylase (ACC), adipocyte-related complement protein 30 (Acrp 30), PPARγ and PPARα modulators.

AMPK is activated in response to reduced cellular energy charge. In turn, ACC, a key AMPK substrate, is inactivated in response to phosphorylation. AMPK activation with an adenosine analogue, AICAR has been shown to produce several beneficial effects, including inhibition of hepatic glucose output and increased muscle glucose uptake (Winder and Hardie, 1999). Studies with metformin have shown the reduction in hepatic glucose output involve AMPK activation (Zhou et al., 2000). Taken together, the beneficial effects of AMPK activation by AICAR and metformin in reducing glucose output by liver, it can be considered as viable target for diabetes. Acrp30 or adiponectin have demonstrated to have antidiabetic effect by reducing glucose, triglyceride and free
Adiponectin is also shown to enhance hepatic insulin action (Berg et al., 2001). Recombinant adiponectin derivatives or small molecule Acrp 30 mimetic compounds could be envisaged as new therapeutic approaches.

PPARs are ligand activated transcription factors which offer a promising therapeutic approach to metabolic syndrome. PPARγ is predominant molecular target for insulin-sensitizing thiazolidinedione drugs. PPARα is the molecular target for the fibrate class of lipid lowering drugs. Dual activators of PPARγ and PPARα have shown promising antidiabetic activity associated with antihyperlipidemic effect, considering the added advantage of dual activators of PPARγ and PPARα over alone PPARγ activators, many compounds in the class have been developed and have shown good antidiabetic effect. Many drugs under this class have reached late stage clinical trials and can be anticipated to come into clinical use in near future (Henke, 2004).

The category of targets mentioned above are few among many which are presently undergoing investigations to get drugs useful in conditions of diabetes. Since many drugs introduced in recent times have failed to possess enough safety aspects, the development of agents with greater therapeutic effect and least safety concerns are the prime objective of the day. Having such objectives the development of drugs is getting delayed as it needs to ensure enough safety before it can reach for clinical use.
3.3.2 Obesity

The World Health Organization (1995) defines overweight and obesity in terms of body mass index as presented in table 1. Body mass index is a proxy for fatness calculated from the formula:

Weight (kg)/height (m)$^2$.

Table 1.

<table>
<thead>
<tr>
<th>Range</th>
<th>Body mass index (kg/m$^2$)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>19-25</td>
<td>0</td>
</tr>
<tr>
<td>Over weight</td>
<td>25-30</td>
<td>1</td>
</tr>
<tr>
<td>Obesity</td>
<td>30-40</td>
<td>2</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td>40 and more</td>
<td>3</td>
</tr>
</tbody>
</table>

The distribution of excess adipose tissue is closely linked to the development of the major risk factors associated with obesity. Vague (1956) pointed out the strong association between android (upper body or truncal) obesity and the development of type 2 diabetes. Truncal obesity, sometimes referred to as ‘apple shaped’ is significantly more strongly associated with the development of risk factors than gynoid (gluteo-femoral or pear shaped) obesity. Android obesity is now recognized as a feature of syndrome of insulin resistance or syndrome X, which includes compensatory hyperinsulinaemia, dyslipidemia, hypertension, glucose intolerance, a procoagulant tendency and accelerated atheroma formation (Reaven, 1988).

Obesity and overweight are associated with an increased risk of developing type 2 diabetes, hypertension, coronary artery disease, stroke, gall bladder disease and certain cancers (Jung, 1997). Obesity is linked to genetic and familial influences. Studies in Denmark have given substance to there being a genetic component to obesity (Stunkard et al., 1986; Sorensen et al., 1989). It is reported that the primary cause of obesity lie in environmental and behavioural change (Prentice and Jebb, 1995). Children of families where one or both parents are obese are certainly at increased risk of becoming obese themselves (Guillaume et al., 1993).

Understanding obesity needs to known about adipose tissue. Adipose tissue is a type of loose connective tissue made up of adipocytes surrounded by a matrix of collagen fibers, blood vessels, fibroblasts and immune cells. There are basically two types of adipose tissue namely white and brown, of which white predominates in
humans. Brown adipose tissue makes up a small percentage of total body fat, it is more abundant in infants but is present in adults as well. In brown adipose tissue the fat cells as well as the blood vessels have an extensive sympathetic innervation of some fat cells but the principal sympathetic innervation is on blood vessels. Extensive sympathetic innervation is responsible for activating diet induced thermogenesis which in turn plays a part in energy regulation. Reduced sympathetic activation of brown adipose tissue is a feature of most models of obesity (Stock, 1998). White adipocytes have only a single large droplet of white fat, whereas brown fat cells contain several small droplets of fat (Gannong, 1999).

Intra-abdominal fat accumulation is often indicative of a constellation of risk factors which include insulin resistance and hyperinsulinaemia, hypertension, dyslipidaemia, and lowered HDL-cholesterol which markedly increases an individual’s risk of developing coronary heart disease. The lipids in cells are of two main types first type lipids are structural lipids, which are an inherent part of the membranes and other parts of cells and neutral fat, which is stored in the adipocytes of the fat depots. While neutral fat is mobilized during starvation, structural lipid is preserved. In non-obese individual, fat depots make up about 15% of body weight in men and 21% in women. Adipose tissue is not an inert mass but is actually involved in metabolism and energy homeostasis as well as having endocrine and paracrine functions. In addition it influences autonomic and immune function (Flier and Spiegelman, 1996; Mohammed-Ali et al., 1998).

Adipocytes secrete a range of substances with autocrine, paracrine and endocrine functions. Leptin, adiponectin and resistin are secreted by adipose tissues which have an influence on endocrine functions and in turn in obesity.

**Leptin**

It was discovered in 1994 and is secreted mainly by adipose tissue although low levels have been detected in the placenta, skeletal muscle, gastric and mammary epithelia and brain (Friedman and Halaas, 1998). Circulating leptin levels are high in obese individuals and low in lean people. Females tend to have higher leptin levels than males, probably as a result of an inhibitory effect by androgens. Synthesis of leptin is higher in subcutaneous than visceral fat. Deficiency of leptin results in hyperphagia, decreased energy expenditure and morbid obesity. Injection of leptin into the brain reduces food intake and reduces energy stores as fat. These findings led to the concept of leptin as an
anti-obesity hormone. However, the high levels of leptin found in obese people clearly
do not prevent its development. Also, clinical trials of injected leptin have yielded
disappointing results. This has led to the concept of leptin resistance. It has been found
that the CSF levels of leptin are considerably lower than serum levels in obese people
(Shwartz et al., 2000). Thus failure to cross blood brain barrier could be a contributory
factor to leptin resistance.

Leptin exerts its effects on the hypothalamus via a signaling system involving
neuropeptide Y (NYP) and agouti-related protein (AGRP) which stimulate food intake
and melanocyte stimulating hormone (MSH) and cocaine and amphetamine related
transcript which reduce food intake. Thus an imbalance or failure of the signaling system
could also be contributory to leptin resistance. It is reported that leptin signals the brain
information about the size of the body’s energy stores and switch between the fed and
fasted states (Flier, 1998). Leptin has so far yielded disappointing results, knowledge
about its signalling system has stimulated research into manipulating this for therapeutic
purposes. Leptin also acts on the endocrine system, including the hypothalamo-pituitary
axis and influences the production of growth hormone and prolactin. It also activates the
sympathetic nervous system and is involved in blood pressure regulation, brain and bone
development, haematopoiesis and wound healing (Ahima and Flier, 2000). An
alternative hypothesis on the role of leptin is that of controlling the deposition of fat,
preventing its harmful accumulation in tissues such as the heart, liver and kidneys.

**Adiponectin**

It is secreted exclusively by adipocytes, their levels are decreased in obesity, type
2 diabetes and coronary artery disease. It inhibits vascular smooth muscle proliferation
and expression of various adhesion molecules. The lower levels found in obesity could
be contributory to the increased risk of cardiovascular diseases (Ahima and Flier, 2000).

**Resistin**

It was discovered in 2001 (Steppan et al., 2001). The molecular links between
obesity and type 2 diabetes have been elusive, yet the links are strong as 80 % of people
with type 2 diabetes are obese. One of the fundamental defects in type 2 diabetes is
insulin resistance. The increased storage of triglycerides in adipose tissue in obesity is a
factor for insulin resistance. The insulin resistance in liver, skeletal muscle and other
body parts are not known to certainty yet. Non esterified fatty acids and TNF-α secreted by adipocytes as factors for insulin resistance. Experiments done by Steppan et al. (2001) showed treatment with thiazolidinediones to differentiated adipocytes reverses insulin resistance, in the process it expresses a messenger called resistin, which is involved in insulin resistance. They also showed that resistin suppresses insulin's ability to stimulate the uptake of glucose by adipocytes, whether it is able to do this in liver, muscle and other tissues awaits elucidation with further studies.

**Choice of drug in conditions of obesity**

Presently two drugs are used in the treatment of obesity they are orlistat and sibutramine.

**Orlistat**

It is a novel drug for the treatment of obesity in conjunction with a mildly hypocaloric diet in patients with a BMI 30 kg/m² or BMI > 28 kg/m² with associated risk factors. Mechanism of action of orlistat involves inhibition of the action of pancreatic lipase in the process of digesting fat that approximately 30% of dietary fat is unabsorbed and subsequently excreted from the body, thereby reducing the amount of energy available to the body. It is reported that treatment with orlistat to obese patients in long term trials have shown less weight regainment than those of placebo (Zavarol, 1998; Davidson et al., 1999; Finer et al., 2000). Another study showed patients treated with orlistat produced significant reduction in glycosylated haemoglobin, fasting glucose, dose reduction in sulfonylurea, reduction in total cholesterol, LDL-cholesterol, triglyceride and apolipoprotein B (Hollander et al., 1998). In patients with obesity and type 2 diabetes treatment with orlistat produced a significant reduction in body weight, insulin resistance and improved cardiovascular profile (Dimitor et al., 2000). Some of the contraindications associated with orlistat are chronic malabsorption syndrome, cholestasis. Adverse effects of orlistat include spotting from the rectum, fatty oily stools, fecal urgency, bloating and abdominal discomfort.

**Sibutramine**

It is one of the drugs used in obesity these days. Sibutramine offers three types of benefit in weight management like enhancement of weight loss, improvement in weight maintenance and reduction in comorbidities. The mechanism of action of sibutramine involves two complimentary physiological effects, first it promotes and prolongs satiety after eating thereby reduces food intake, including snack consumption. Secondly it
stimulates energy expenditure and limits the decline in metabolic rate that normally accompanies weight loss (Stock, 1997). Sibutramine has two fold pharmacological actions in that it is a monoamine reuptake inhibitor, and is particularly effective in blocking the reuptake of both serotonin and noradrenaline.

Treatment with sibutramine causes a dose related weight loss (Weintraub et al., 1991). Clinical studies have demonstrated the weight loss effect produced by sibutramine (Jones and Heath, 1996). The results of the STORM trial which involved sibutramine treatment to obese subjects showed weight loss and a significant reduction in triglycerides, VLDL-cholesterol, C peptide and uric acid (James et al., 2000). Treatment with sibutramine in patients with both obesity and type 2 diabetes have shown significant weight loss and decreased fasting blood glucose and glycosylated haemoglobin levels (Finer et al., 2000). Another study with sibutramine which involved patients with obesity and diabetic subjects with insulin resistance produced reduction in fasting glucose levels, improved insulin sensitivity and weight loss without much change in free fatty acids levels (McLaughlin, 2001). Adverse effects of sibutramine include dry mouth, anorexia, constipation, insomnia, hypertension, anxiety, blurred vision etc.

Orlistat and sibutramine are imperfect but nonetheless valuable additions to the armamentarium of the clinician faced with trying to combat the impact on health of the burgeoning epidemic of obesity.

New drugs for the treatment in obesity is currently needed, it is worth to consider few mechanisms that can alter the storage of body fat and its distribution. Bray (1998) explained few aspects to be considered in search of new drugs for obesity which include reduction in food intake, blockade of food absorption, reduction in gastric emptying, stimulation of thermogenesis, increase in fat or protein metabolism of storage and to moderate the central controller.
3.3.2.2 New Drug Targets for Obesity

Weight loss occurs when an organism is in negative energy balance that is, energy expenditure is greater than intake, and this endpoint can be achieved by decreasing food intake or by increasing energy expenditure, the combination of these two mechanisms, by both dieting and doing more exercise, will result in additive, and possibly even synergistic, reductions in body weight. Mechanisms for reducing body weight currently being exploited include reduction of food intake, inhibition of lipid absorption from the gut, enhancement of energy expenditure, mobilization of adipocyte fat stores and prevention of lipogenesis. Sites of action for novel anti-obesity drugs, therefore, include the brain, the gastrointestinal system, adipose tissue, liver and skeletal muscle (Cheetam et al., 2004).

The novel targets for obesity can broadly be divided into two major types they are targets which modulate hypothalamic functions and those that act peripherally. The targets which modulate hypothalamic functions and in turn useful in obesity include monoamines like 5-HT₂C agonists, 5-HT₅ antagonists, Histamine H₃ antagonists and Cannabinoid CB₁ receptor antagonists. Neuropeptides like MCH₁ antagonists, MC₄ agonists, Neuropeptide Y₂ agonists, and periphery brain signals like leptin agonists and fatty acid synthesis inhibitors. Peripheral targets for novel obesity drugs include thyroid hormone β₃ receptor agonists, 11β-HSD inhibitors and PGC-1α activators (Cheetam et al., 2004).

Hypothalamic targets for novel anti-obesity drugs

Serotonergic drugs

Serotonergic agents include fenfluramine, its dextrorotatory stereoisomer dexfenfluramine, fluoxetine, and sertraline. These agents act by causing release or by inhibiting reuptake of serotonin (5-HT, 5-hydroxytryptamine), and by stimulating hypothalamic 5-HT₁B/D and 5-HT₂C receptors (Toubro and Astrup, 1997; Mayer and Walsh, 1998). Fenfluramine and dexfenfluramine no longer constitute a clinical option for obesity today. SSRIs have been shown to induce weight loss via suppression of appetite (Ward et al., 1999) they may also improve insulin sensitivity (Maheux et al., 1997). The 5-HT₂C is one of the 5-HT receptors which are involved in energy regulation. Several lines of evidence show that 5-HT₂C receptors, which are restricted to CNS, contribute to the anorectic properties of non-selective serotonergic agonists (Curzon et al., 1997). High affinity 5-HT₂C receptor agonist, such as m-chlorophenylpiperazin
the dexfenfluramine metabolite norfenfluramine, have appetite-suppressant actions that are blocked by 5-HT$_{2C}$ receptor antagonist. Mice with targeted disruptions of this receptor have increased food consumption and develop late onset and type 2 diabetes, despite normal responses to exogenous leptin administration. This indicates that 5-HT$_{2C}$ receptors might not be in the direct path of leptin action. 5-HT$_{2C}$ receptor agonists like APD-356 and BVT 933 have shown promising effect in conditions of obesity. 5-HT$_{6}$ antagonist BVT 5182C have also shown promising effects in conditions of obesity (Cheetam et al., 2004).

**Histaminergic drugs**

Histamine appears to be involved in the central processes governing satiety and hunger perception. Intracerebroventricular (i.c.v.) administration of histamine suppresses food consumption in animals (Clineschmidt and Lotti, 1973; Tuomisto and Eriksson, 1979; Machidori et al., 1992), and histamine antagonists increase food intake in the early light period (Sakata et al., 1988; Ookuma et al., 1989). There are 3 histamine receptors namely H$_1$, H$_2$ and H$_3$ receptors, H$_1$ and H$_2$ receptors are located postsynaptically, and the H$_3$ receptor is located presynaptically. Feeding behaviour modification is predominantly mediated via H$_1$ and H$_3$ histamine receptors (Sakata et al., 1997). The H$_1$ receptor agonist 2-(3-trifluoromethylphenyl) histamine, suppresses feeding behaviour in the rat (Lecklin et al., 1998). Similarly, H$_1$, receptor antagonists induce feeding during the early light cycle (Sakata et al., 1988). Activation of the presynaptic H$_3$ receptor can inhibit the release of other neurotransmitters, including noradrenaline, 5-HT, and acetylcholine (Schlicker et al., 1989; Fink et al., 1990; Clapham and Kilpatrick, 1992), and by doing so, may be expected to affect feeding behaviour via these mechanisms. Recent data suggest that the H$_3$ receptor may also regulate the activity of orexigenic peptides in the hypothalamus. For example, thioperimide, an H$_3$ receptor antagonist, was shown to suppress neuropeptide Y (NPY) and peptide-YY-induced food intake in the rat (Itoh et al., 1998; Itoh et al., 1999). Other feeding pathways thought to be regulated by the histaminergic system are those involving bombesin/gastrin releasing peptide (GRP) and amylin (Merali and Banks, 1994; Lutz et al., 1996b; Kent et al., 1997), and histamine neurones may themselves be targets for leptin in feeding behaviour (Morimoto et al., 1999; Yoshimatsu et al., 1999).
Cannabinoid CB₁ receptor antagonists  

Cannabinoid receptors are broadly divided into CB₁ and CB₂ receptors. Anandamide, the endogenous agonist of cannabinoid receptor, activates both the known cannabinoid receptors CB₁ and CB₂ (Rinaldi-Carmona et al., 1996). CB₁ receptor is predominantly localised to the brain, including the hypothalamus, where it is expressed both in neurons and in astrocytes (Guzman and Sanchez, 1997). CB₁ receptor is mainly involved in regulating energy balance. CB₂ receptor is largely expressed peripherally, and does not appear to be involved in regulating energy balance. Studies in rodents have shown that a cannabinoid receptor agonist, D-9-tetrahydrocannabinol, stimulates food intake and activates the hypothalamic-pituitary-adrenal axis. Anandamide stimulation of nocturnal feeding in the rat is blocked by a CB₁ antagonist SR141716 (Williams and Kirkham, 1999), but not by CB₂ antagonists, suggesting that CB₁ is the feeding receptor. Various studies have shown that CB₁ receptor antagonists to have beneficial effects on obesity. Some of the studies which show beneficial effects of CB₁ receptor antagonists in obesity are described below. Peripheral administration of CB₁ antagonist SR141716 (3 mg/kg) suppressed chow and sucrose-pellet feeding in rats, suggesting that the endogenous cannabinoid system exerts a positive feeding drive. NPY-induced sucrose drinking (but not water intake) is also inhibited by SR141716 (Arnone et al., 1997). Another study compared the effect of SR141716 in high-fat-fed versus high-carbohydrate-fed obese Zucker rats (Arnone et al., 1999). Over a 12-day period, SR141716 reduced food intake in the high-fat-fed rats, and this was accompanied by a reduction in body weight gain. Studies mentioned above suggested the concept that CB₁ receptor antagonists may selectively reduce the intake of palatable food is therapeutically attractive. CB₁ receptor antagonist SR141716 or remonabant is in phase III clinical trials and has shown promising effects and in a very short time may reach the market for obesity treatment. Other CB₁ receptor antagonists which have shown promising effect in conditions of obesity include SLV-319 (Cheetam et al., 2004).

Melanin-concentrating hormone antagonists  

Melanin-concentrating hormone (MCH) is a 19 amino acid cyclic peptide. Studies have shown MCH peptide levels are elevated in fat/fat mice (Rovere et al., 1996). Increased expression of MCH under conditions of altered energy balance, therefore, is consistent with a physiological role for MCH in nutritional control. Neuroanatomical and immunohistochemical localization of MCH to hypothalamic
regions associated with feeding, as well as regulation of MCH mRNA expression by neural pathways that control energy homeostasis, further support a physiological involvement of MCH in feeding regulation and energy balance (Tritos and Maratos-Flier, 1999). MCH knockout mice are hypophagic, have increased metabolic rate, and are lean. They have decreased circulating leptin, which presumably is a consequence of their lean phenotype (Shimada et al., 1998). The findings from MCH can surely suggest that it can be a good target for drugs useful in obesity. MCH₁ receptor antagonists like T-226296 have shown promising effects in conditions of obesity (Cheetam et al., 2004).

**MC₄ agonists**

The melanocortins are peptides derived from a larger precursor protein, pro-opiomelanocortin (POMC), that encodes α-, β-, and γ-MSH, as well as adrenocorticotrophic hormone and β-endorphin. Many studies have indicated the dependence of POMC expression on a functional leptin system. POMC levels are reduced in ob/ob (Thornton et al., 1997) and db/db mice (Mizuno et al., 1998), as well as in hypoleptinaemic situations, such as fasting (Schwartz et al., 1997) or MCH knockout mice (Shimada et al., 1998). Central administration of melanocortin agonists has been shown to increase energy expenditure (Cowley et al., 1999). Peripheral tissues, notably muscle and adipose tissue, may also play a role in MSH-induced changes in energy homeostasis, specifically thermogenesis and lipogenesis (Moussa and Claycombe, 1999). Melanocortin receptors (MCRs) are G-protein-coupled receptors (Cone et al., 1996). Melanocortin receptors are 1 to 5 of which MC₄ receptor appears to be a suitable target for obesity. MC₄ receptor knockout mice show no response to the anorectic effect of leptin, placing this pathway as an important downstream target of leptin action. Long-term suppression of MC₄ receptor function, via knockout of the receptor (Huszar et al., 1997) or its antagonism with HS014 (Kask et al., 1999), causes hyperphagia and obesity. This suggests a role for the melanocortin system in the chronic regulation of energy homeostasis. MC₄ agonists like PGE-657022 have shown significant beneficial effects in obesity (Cheetam et al., 2004).

**Neuropeptide Y₂ agonists**

NPY is a 36 amino acid peptide, it is believed to perform neurotransmitter or neuromodulator roles in both central and peripheral nervous systems. Central administration of NPY stimulates feeding in a variety of species, with only agouti-related protein (AgRP) among hypothalamic peptides matching it in the power of this effect
NPY not only stimulates feeding, but it elicits a number of other endocrine and metabolic responses that increase the storage of energy as fat (Gehlert, 1999). In particular, it stimulates insulin secretion, reduces sympathetic nervous system activity in brown adipose tissue, and lowers metabolic rate. Repeated central administration or chronic infusion of NPY increases 24-hr energy intake, and this, together with a reduction in metabolic rate, promotes weight gain and obesity (Stanley et al., 1989; Paez and Myers, 1991; Beck et al., 1992). Again, this suggests that NPY antagonists may have most utility when leptin levels are low. For most obese patients, this is likely to be when they are already adhering to a low-energy diet. Y1 knockout did display a marked reduction in fast-induced feeding, and both knock-outs caused some reduction in the feeding response to NPY (Marsh et al., 1998; Pedrazzini et al., 1998). However, Y2 receptor knockout has been found to develop increased food intake, body weight, and fat deposition, consistent with the view that this receptor plays a presynaptic role in inhibiting NPY release in the hypothalamus (Naveilhan et al., 1999). Thus, the ideal NPY receptor ligand might be one that not only antagonises both Y1 and Y5 receptors (Flynn et al., 1999a; Flynn et al., 1999b; Inui, 1999; Sun and Miller, 1999), but also stimulates Y2 receptors. Studies with antagonists also support a role for both Y1 and Y5 receptors. Y1 antagonist BIBP 3226 inhibits NPY-stimulated feeding (Haynes et al., 1998; Kask et al., 1998; Morgan et al., 1998; Iyengar et al., 1999). Two potent Y5 antagonists that are selective relative to antagonism of other NPY receptors have been described. L-152,804 inhibited feeding driven by the selective Y5 agonist bovine PP, but not that driven by NPY. It also had no effect on natural feeding in db/db mice or fa/fa rats (Gehlert, 1999; Kanatani et al., 2000). In contrast, CGP 71683A antagonised NPY-, fasting-, and streptozotocin-driven feeding, and natural feeding in lean rats. Body weight remained suppressed over 28 days of daily injection of CGP 71683A (Criscione et al., 1998). Antagonism of NPY remains a tantalizing target, but it appears difficult to find a developable compound with a suitable pharmacology, and it has yet to be demonstrated that such a compound can reduce obesity in animals, let alone humans. A particular challenge will be to demonstrate anti-obesity activity in situations where leptin levels are high and NPY release is low (Widdowson et al., 1999). NPY2 agonists like AC162352 have shown promising effect in conditions of obesity (Cheetam et al., 2004).
**Leptin**

Leptin is the product of the OB gene, which is secreted as a 146 amino acid protein, primarily from white adipose tissue. It is a 4-helix bundle protein, similar to a number of cytokines, and its receptor is a Class I cytokine receptor. Leptin plays roles in neuroendocrine, reproductive, haematopoietic, and metabolic regulation, but its role in the regulation of energy balance, in which it influences both food intake and energy expenditure, remains the subject of the most intensive research (Dallongeville et al., 1998). There are two key questions concerning the leptin system as a target. The efficacy of leptin or a leptin mimetics and stimulation of the leptin system. The potential of leptin as a drug, or the leptin system as a target, was brought into question when it was discovered that obese people tend to have raised plasma leptin levels (Considine et al., 1996). There is a wide variation in the plasma leptin level for any degree of obesity, and low leptin levels in relationship to body fat content appear to make some, although not a major, contribution to the incidence of obesity (Scholz et al., 1996; Montague et al., 1997; Ravussin et al., 1997; Hager et al., 1998; Lindroos et al., 1998). However, many workers have concluded that if obese people have raised leptin levels compared with lean people, then they must be obese because they are “leptin-resistant” This logic is an example of a correlation being interpreted as cause and effect. It seems to ignore the point that if leptin plays a role in signalling body fat content, its level must be raised in obese people, unless their obesity is due to low leptin levels. It is logic that demands that all obesity must be due either to inadequate leptin secretion or to leptin resistance. Thus, the rapid recent increase in the incidence of obesity in affluent societies due to readily available, energy dense food and lack of exercise is largely ascribed to “leptin resistance”. The concept of leptin resistance arises from a parallel with the insulin resistance of type 2 diabetes, in which high blood glucose and insulin occur together in the early stages of the disease. Lethal yellow (Ay/a) obese mice, which have high leptin levels, are resistant to both central and peripheral leptin. However, if these mice are made even more obese by introducing the mutant ob gene, they become sensitive to leptin (Boston et al., 1997). The explanation is almost certainly that the mice now lack leptin. Leptin resistance in humans, therefore, may be more often a consequence than a cause of obesity. Various clinical studies have shown moderate weight loss on leptin treatment in obese subjects, however the weight loss is not significantly greater as compared to sibutramine or orlistat the drugs which are in market for obesity. Leptin
itself is no longer being developed because adequate weight loss was not separable from injection site reactions, but leptin mimetics may yet have potential in some subjects.

Obese subjects who adhere to a low-energy diet and whose leptin level is low can be provided with a fragment or modified form of leptin (mutein, chimera, or covalently modified leptin) that has a longer duration of action or some other pharmaceutical advantage over leptin. Various fragments from the C-terminal end of leptin reduce food intake in rodents (Samson et al., 1996; Fruhbeck et al., 1998). In conclusion, the leptin system is a valid target for antiobesity drugs and leptin resistance, and the problems encountered with leptin itself may have been over emphasized. The leptin receptor itself is the target that probably would provide drugs with the best benefit to side effects ratio, but activating this receptor with nonpeptides is a difficult task.

**β₃-adrenoceptor agonists**

β₃-Adrenoceptor agonists were first described in 1983 (Arch and Ainsworth, 1983), and their molecular target, the seven-transmembrane G-protein-coupled β₃-adrenoceptor, was cloned 6 years later (Emorine et al., 1989), making it one of the first of the new wave of molecular targets for antiobesity drugs arising from the genomics revolution. Therefore, it is disappointing that a β₃-adrenoceptor agonist is not closer to the market. Nevertheless, the rationale for this approach remains strong. First-generation β₃-adrenoceptor agonists were selected on the basis of their thermogenic and anti-obesity activities in rats and mice. In obese rodents, they produce good weight loss (or prevent weight gain) because they increase metabolic rate. There may be an initial reduction in food intake (Tsujii and Bray, 1998), but no effect on total intake is detectable over a few days or longer (Arch et al., 1984). All the weight lost is fat, and when given with food, there may be an increase in body protein (Choo et al., 1990; Arch et al., 1991). Lean animals, which have little fat to start with, lose very little body weight. They resist weight loss in three ways: they have a smaller thermogenic response to β₃-adrenoceptor agonists; their metabolic rate falls below control levels when plasma levels of the β₃-adrenoceptor agonist are low; and if net thermogenesis still occurs, they increase their food intake (Arch et al., 1991). Both low nonesterified fatty acid and low leptin levels may play a role in this resistance (Wilson et al., 1986; Trayhurn et al., 1996; Grujic et al., 1997; Ghorbani and Himms-Hagen, 1998).

In addition to their anti-obesity activity, β₃-adrenoceptor agonists elicit marked improvements in insulin sensitivity in obese and insulin-resistant rodents. Such effects
are seen at doses below those that elicit significant anti-obesity activity. The thermogenic, anti-obesity and anti-diabetic effects of \( \beta_3 \)-adrenoceptor agonists in rodents are achieved without significant cardiovascular effects, lowering of blood potassium or tremor, because they lack potency or efficacy at rodent \( \beta_1 \)- and \( \beta_2 \)-adrenoceptors. Unfortunately, clinical experience with the first-generation compounds has been less encouraging. Although some compounds have been shown to be thermogenic, to produce weight loss with conservation of protein, or to improve insulin action, efficacy generally has been associated with \( \beta_1 \)- or \( \beta_2 \)-adrenoceptor-mediated side effects.

Despite the failure of the first-generation compounds in humans, their effects on metabolic rate and insulin action suggest that the \( \beta_3 \)-adrenoceptor is a valid target. It might be argued that the beneficial effects of BRL-26830, BRL-35135, and ZD-2079 were due to stimulation of \( \beta_1 \)- or even \( \beta_2 \)-adrenoceptors. Indeed, 60% of the thermogenic effects of BRL-35135 was blocked with the \( \beta_1 \)/\( \beta_2 \)-adrenoceptor antagonist nadolol. Nevertheless, the remaining activity does appear to be mediated by the \( \beta_3 \)-adrenoceptor (Wheeldon et al., 1994). Moreover, CL-316,243 did not elicit side effects via \( \beta_1 \) or \( \beta_2 \)-adrenoceptors in humans, suggesting that all of its activity is mediated by the \( \beta_3 \) adrenoceptor.

\( \beta_1 \)-and \( \beta_2 \)-adrenoceptors appear similar between humans and rodents, selectivity for \( \beta_3 \) adrenoceptors are low in humans. These findings have led a number of pharmaceutical companies to use human cloned \( \beta \)-adrenoceptors to seek better agonists for humans. Although a number of highly selective compounds have been identified, it has proved extremely difficult to combine the pharmacology with good oral bioavailability.

The above list of targets and the drugs modifying such targets have demonstrated significant beneficial effects in obesity. In near future one can anticipate few drugs which modulate above discussed targets to enter for clinical use.