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ADAPT: ADIPOKINES AS DRUG TARGETS FOR ADVERSE EFFECTS OF ADIPOSE TISSUE

*J.RISY NAMRATHA, D.RAVI SANKAR REDDY, K.PRADEEP
Department of Pharmaceutical Chemistry, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur.
***Corresponding author:** Mail Id: r.namratha747@gmail.com

ABSTRACT

Adipose tissue is a white tissue and is part of the adipose organ, which consists of two functionally distinct tissues – brown and white adipose tissue. Brown adipose tissue is specialized for heat production by non-shivering thermogenesis. In white adipose tissue, the stored triacylglycerols(TAG) provide a long-term fuel reserve for the animal. Adipose tissue is an active secretory organ, sending out and responding to signals that modulate appetite, energy expenditure, insulin sensitivity, endocrine and reproductive systems, bone metabolism and inflammation and immunity. Adipose tissue produces and releases a variety of pro-inflammatory and anti-inflammatory factors, including the adipokines leptin, adiponectin, resistin, and visfatin, as well as cytokines and chemokines, such as TNF-α, IL-6, monocyte chemoattractant protein 1, and others. A Proinflammatory molecule produced by adipose tissue participates in the development of insulin resistance and the increased risk of cardiovascular disease associated with obesity.

KEY WORDS: TNF-α (Tumour necrosis factor - α), IL-6 (Interleukin -6), thermogenesis (liberation of heat), TAG (Triacylglycerols).

1.INTRODUCTION

Adipose tissue found throughout the body as areolar connective tissue (Kershaw and Flier,2004). It is an active secretory organ, sending out and responding to signals that modulate appetite, energy expenditure, insulin sensitivity, endocrine and reproductive systems, bone metabolism and inflammation and immunity. Adipose Tissue is a loose fibrous connective tissue packed with many cells called "Adipocytes" that are specialized for storage of triglycerides more commonly referred to as "fats". Adipocytes releases a large number of bioactive mediators, proteins called “Adipokines” also called as “Chemical Messengers (Mac Dougald,2007)” and associated with several complex age-associated chronic diseases. These include inflammatory mediators, angiogenic proteins, and metabolic regulators. Adipokines are thought to influence multiple processes including glucose and fatty acid metabolism, insulin sensitivity, and adipocyte differentiation. They are also thought to serve as mediators linking obesity, inflammation, immunity and other obesity-related disease.

Members include: Leptin, Adiponectin, Resistin, Chemerin, Interleukin-6 (IL-6), Plasminogen activator inhibitor-1 (PAI-1), Retinol binding protein 4 (RBP4), Tumor necrosis factor-alpha (TNFα), Visfatin.

Adipokines for Insulin sensitivity

Leptin: Adipocytes are the most important source of leptin, and circulating leptin levels directly co-relate with adipose tissue mass (Maffei,1995) and is structural similar with the cytokine family. Other tissues also express Leptin, including placenta, ovaries, skeletal muscle, stomach, pituitary and liver (Muoio and Lynis,2002).

Biological role: Leptin controls appetite, energy expenditure and protects T lymphocytes from apoptosis and regulates T-cell proliferation and activation. Its principal target is the central nervous system.

Receptors: The Leptin receptor (OB-R or Lep-R) is a large single membrane protein that belongs to cytokine class-1 receptors and certain isoforms are identified. Of them, OB-Rb is the major signalling isoform expressed throughout the beta cells, enterocytes and endothelial smooth muscle (Ghilardi,1996). OB-Re plays a prominent role in development of leptin resistance in peripheral tissues and OB-Ra involves in the transport of leptin across the blood-brain barrier.

Functions: 1.Leptin controls appétite and energy expenditure.

2.It regulates immune cells, pancreatic beta cells, adipocytes, muscle and blood cells, so acts as an endocrine and paracrine factor for regulation of puberty.

3.It affects maternal and placental functions, modifies insulin sensitivity, prevents lipid depositon and also treats obese patients (Heymsfield,1999).

Regulation: Leptin gene expression is regulated in the context of hormonal and nutritional status. Plasma leptin levels are markedly lowered by fasting or dieting and are rapidly recovered during refeeding (Frederich,1995). Leptin expression may be increased and decreased by the actions of insulin, glucose, glucocorticoids, TNFα and beta-adrenoceptor agonists, androgens, thiazolidinediones, and cigarette smoking (Margetic,2002) respectively.

Effects: Leptin deficiency is associated with reduced inflammation in models of autoimmune disease and also with increased susceptibility to bacterial and viral infections.

Adiponectin: Adiponectin is the Adipokine that circulates at the highest levels. Adiponectin expressed by mature Adipocytes during Adipocytes differentiation. The adiponectin molecule is composed of a globular and a collagenous domain. Collagenous domain is responsible for building secondary and tertiary structure and globular domain is responsible for mediating Adiponectin effects.

Biological role: The main role involves in regulation of insulin sensitivity (Beltowski,2003). Adiponectin levels are significantly reduced in patients with type II diabetes without relating to obesity. Adiponectin reduces the production and activity of TNF-α (Masaki,2004). Adiponectin appears to act as an anti-inflammatory molecule.

Receptors: The effects of Adiponectin are mediated by two receptors (Yamauchi,2003), these receptors are identified on muscle cells (AdipoR1) and on liver cells (AdipoR2). These receptors mediate in activation of AMP kinase, PPAR-α activation and glucose uptake and fatty acid oxidation.

Functions: 1. Adiponectin acts as anti-atherogenic, anti-angiogenic and anti-proliferative agent.

2. It also plays a major role in breast, endometrial and prostate cancer.

Regulation: Adiponectin itself controls in metabolic stress conditions and also regulates exogenous factors such as dietary response and also by TNFα. Adiponectin regulation was inhibited by catecholamines, glucocorticoids, cytokines, prolactin, growth hormone and androgens.

Effects: Adiponectin suppress proliferation and activation of immune cells and the secretion of inflammatory cytokines such as TNF-α in the atherogenic process. A low adiponectin level develops atherosclerosis and cardiovascular diseases in obese patients.

Metabolism of Leptin and Adiponectin: Proteins can fundamentally influence lipid metabolism in several target tissues. Similarly, Adipokines, the proteins secreted by adipose tissue cause alterations in carbohydrate and lipid metabolism(Fig: 1). Leptin treatment of pancreatic islets causes an increase in fatty acid oxidation, decreases triacylglycerol content and also reduces lipogenic effects of insulin. The insulin-induced increase in triacylglycerol synthesis and decrease in fatty acid oxidation are reduced by simultaneous administration of leptin (Muoio,1999).

Leptin in adipocytes inhibits the synthesis of ACC, an enzyme essential (and rate-limiting) in the conversion of carbohydrates to long chain fatty acids and Adiponectin increases fatty acid oxidation and reduces glucose synthesis in liver results in insulin resistance.

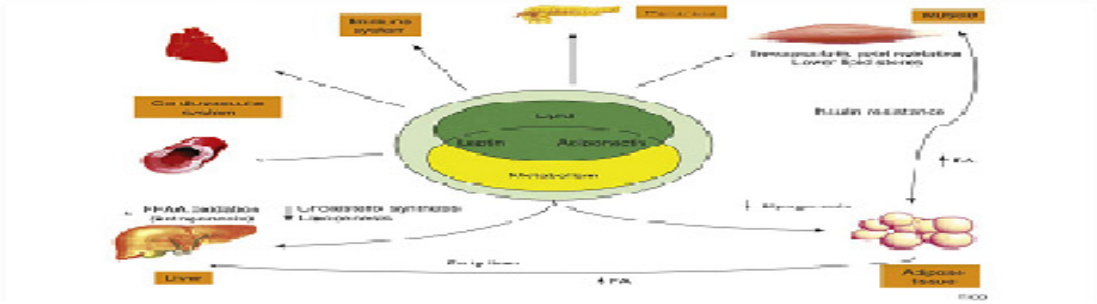

Figure: 1 Metabolism of Leptin and Adiponectin pathway

Signalling pathway: The Leptin and Adiponectin signalling pathway involved in the control of lipid metabolism. Leptin and Adiponectin cause phosphorylation of AMPK, which in turn phosphorylates ACC, inactivating it. Leptin and adiponectin thus inhibits malonyl CoA synthesis, leading to increased mitochondrial import and consumption of fatty acids leads to oxidation of fatty acids (Fig: 2). Leptin receptor, LEP-Rb has the long cytoplasmic domain that is necessary for transduction of the leptin signal (Fruhbeck,2006), receives mainly through JAK-STAT signalling pathways which involve JAK-2 phosphorylating tyrosine in the cytoplasmic domain of the receptor. Replacing the intracellular tyrosine of LEP-Rb with a serine residue prevents STAT3 activation and results in hyperphagia, obesity and impaired thermo regulation. Leptin directly stimulates phosphorylation and activation of the α-2 catalytic sub unit of AMP-activated protein kinase (AMPK) in skeletal muscle, increasing phosphorylation of Acetyl-CoA carboxylase (ACC) and fatty acid oxidation (Zhang,2009). Lipase levels are more immediately controlled by cellular levels of cAMP, means Leptin like glucagon and catecholamines, might stimulate lipolysis primarily by increasing cAMP concentrations.

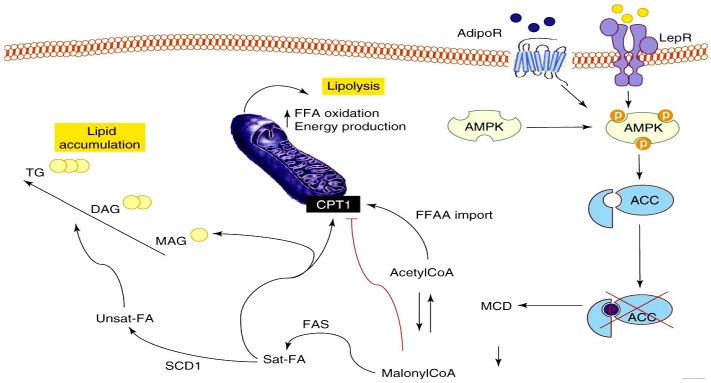

Figure: 2 Signalling pathway of Leptin and Adiponectin

Adipokines for Insulin resistance

Resistin: Resistin, a novel factor which is cysteine rich peptide secreted by adipocytes with an impact on insulin sensitivity proposed a pathogenic sequence of adipocyte-obesity-insulin resistance (Shuldiner,2001).

Biological role: Resistin plays a major role in inflammatory processes that involved in atherosclerosis and also in reversible conversion of α-helical to β-sheet conformation as a direct function of protein-protein interaction (Aruna,2003). Resistin acts through insulin receptors.

Function: Resistin related to insulin sensitivity and co-relates with pubertal development. **Regulation:** Resistin induces endothelial cell proliferation, migration, angiogenesis, forms plaque and thrombosis by facilitating inflammation in the lesion.

Signalling pathway: Similar to Adiponectin, Resistin also acts by AMPK pathway,. It involves in inhibition of AMPK signalling which results in decrease in sensitivity of Insulin and increases glucose production (Fig: 3).

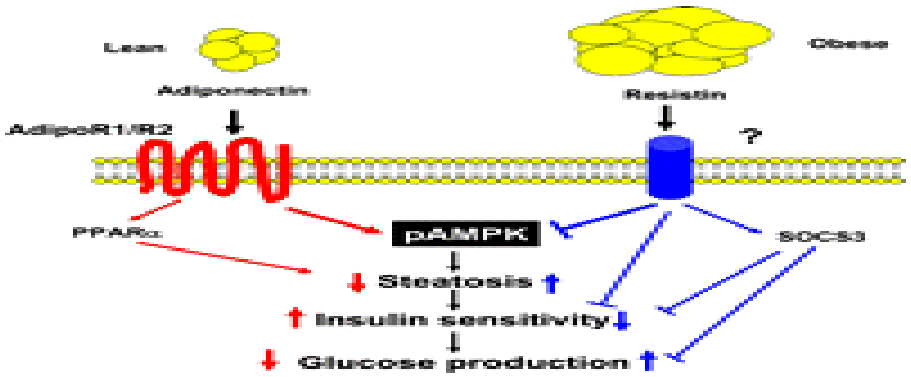

Figure: 3 Resistin Signalling pathway

Regulation: Resistin is controlled by nutritional and hormonal conditions and are low in fasting conditions (Rajala,2004). The tissue level of resistin is decreased by insulin and cytokines such as TNFα, endothelin-1 and dexamethasone, and increased by growth and gonadal hormones and DHEA (Kochan and Karbowska,2004), hyperglycaemia, male gender, and some pro-inflammatory cytokines, such as IL-6 and lipopolysacharide.

Effects: Resistin can be induced by endotoxin and cytokines. In diabetic patients, Resistin levels correlate with inflammatory markers and are even predictive for the development of cardiovascular disease (Reilly,2005). Over expression of Resistin in adipose tissue (Kim,2004) causes elevation of serum levels. Resistin inhibits adipogenesis and it also affects endothelial cell proliferation.

TNF-α (Tumour Necrosis Factor- α): TNF-α is a multipotential cytokine with several immunologic functions. It is produced and released from adipocytes and its enhanced expression associated to induction of insulin resistance was reported in obese subjects. In adipose tissue TNF-α is also engaged in stimulation of lipolysis and apoptosis. Probably TNF-α activates transcription factor NF-kappa β that leads to increased production of cytokines and increases oxidative stress while adiponectin inhibits this factor.

Interleukin-6: Interleukin-6 is a cytokine having multiple effects, secreted by immune cells, fibroblasts, endothelial cells, skeletal muscle and adipose tissue. This pro-inflammatory cytokine is increased in subjects with obesity and insulin resistance and may be regarded as a predictive factor for Type-II diabetes and myocardial infarction. Induction of insulin resistance by IL-6 could be mediated by suppression of insulin receptor signal transduction in hepatocytes.

Novel Adipokines: The identification and characterization of Novel Adipokines provides novel molecular targets for the development of treatment strategies for obesity and related diseases. The identified Novel Adipokines are Chemerin, Vaspin and Omentin.

Chemerin: Chemerin is a recently discovered chemo attractant protein that serves as a ligand for the G-protein coupled receptor. Active chemerin is abundant in ovarian cancer patients and arthritic patients. Chemerin mRNA level was most highly expressed in white adipose tissue, liver, and placenta with intermediate expression in the ovary. White adipocytes serve as both a primary source of Chemerin secretion as well as a target for autocrine/paracrine Chemerin signalling (Prusty,2002).

Role of Chemerin: Chemerin is highly expressed in adipocytes and has modulator effects on the expression of adipocyte genes and involves in lipid and glucose metabolism. It also plays role in mediating recruitment of expressing cells in macrophages to adipose tissue. In Adipocytes, Chemerin may have consequences for alterations in systemic metabolism and lipid homeostasis.

Effects : Chemerin may oppose the lipolytic action of catecholamines through the reduction of intracellular cAMP levels. IBMX, a PDE3 inhibitor, induces lipolysis by blocking the degradation of cAMP. The inability of chemerin to inhibit IBMX-stimulated lipolysis also suggests the antilipolytic mechanism lies at a point upstream of cAMP production.

VASPIN (Visceral Adipose tissue-derived Serine Protease INhibitor): In general, increased abdominal visceral fat is associated with insulin resistance, type 2 diabetes, and coronary heart disease. Reduction of visceral fat mass by omentectomy has significant positive and long-term effects on glucose metabolism, insulin sensitivity, and metabolic profiles in obese subjects. Vaspin, isolated from visceral white adipose tissue, highly expressed when obesity and insulin plasma concentrations reach a peak (Thorne,2002).

Omentin: Omentin was identified as a novel Adipokine predominantly secreted by visceral stromal vascular cells. This enhances insulin-mediated glucose uptake in human subcutaneous and omental adipocytes, while increasing Akt/PKB phosphorylation. The plasma concentration of Omentin in human plasma decreased in patients with Type-1 Diabetes Mellitus and not affected by glucose ingestion. Omentin plasma levels and Omentin gene expression in Visceral Adipose Tissue are decreased in obesity.

Adverse effects of Adipose tissue by effecting Adipokines (figure: 4): Obesity, Obesity induced diabetes, Obesity induced immunity-inflammation, Atherosclerosis, Cardio vascular disease, Asthma, Cancer, Rheumatoid arthritis

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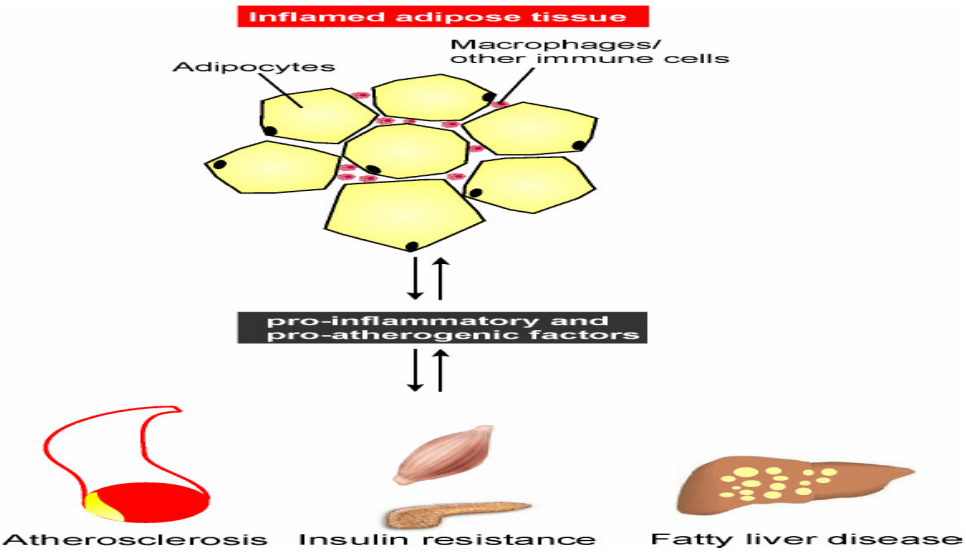
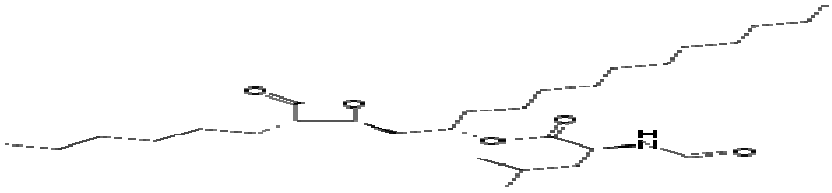


Figure: 4 Adipose tissue adverse effects

Anti-Obese Drugs

Orlistat: Also known as tetrahydrolipstatin is a drug to treat obesity. It is the saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium, *Streptomycin toxytricini*.



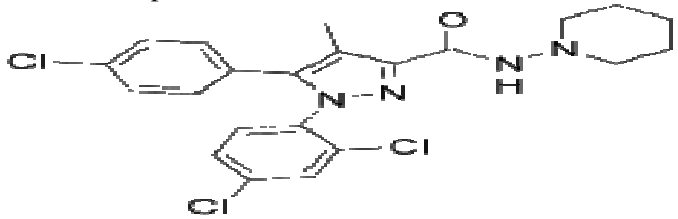
IUPAC NAME:(*S*)-(*S*)-1-((2*S*,3S)-3-hexyl-4-oxooxetan-2-yl)tridecan-2-yl)2-formamido-4-methylpentanoate.

Mechanism of action: Orlistat acts by inhibiting gastric and pancreatic lipases, the enzymes that break down of triglycerides in the intestine. When lipase activity is blocked, triglycerides from the diet are not hydrolyzed into absorbable free fatty acids, and are excreted undigested. This results in decrease of cholesterol synthesis.

Uses: Orlistat decreases Type II diabetes in an obese population. Long-term use of Orlistat leads to modest reduction in blood pressure.

Side effects: The primary side effects include steatorrhea, faecal incontinence and frequent or urgent bowel movements and the unpleasant side-effects are observed when taken with high fat meal.

Rimonabant: Rimonabant, a neurokinin-3 and selective cannabinoid (CB1) receptor antagonist, is currently being researched and developed.



IUPAC NAME: N-piperino5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3 carboxamide

Mechanism of action: Rimonabant is the first in a new class of agents that act by selectively blocking the Cannabinoid-1 receptors with resultant central and metabolic peripheral effects, thereby decreasing food intake. CB-1 receptors are present both in the CNS as well as in certain peripheral tissues.

Uses: Rimonabant is used mainly to quit smoking, to reduce ethanol- and opiate addiction and to improve short-term memory.

Adverse effects: The adverse effects of Rimonabant are upper respiratory tract infections, nausea, dizziness and diarrhoea.

Exenatide: Exenatide is a medication for the treatment of Diabetes Mellitus Type-II in Obese patients. It displays biological properties similar to human glucagon-like peptide 1 (GLP-1), a regulator of Glucose metabolism and Insulin secretion.

H–His–Gly–Glu–Gly–Thr–Phe–Thr–
Ser–Asp–Leu–Ser–Lys–Gln–Met–
Glu–Glu–Glu–Ala–Val–Arg–Leu–
Phe–Ile–Glu–Trp–Leu–Lys–Asn–
Gly–Gly–Pro–Ser–Ser–Gly–Ala–
Pro–Pro–Pro–Ser–NH_2

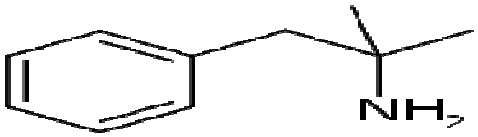
Mechanism of action: Exenatide slows down gastric emptying and thus decreases the rate at which meal-derived glucose appears in the bloodstream and has a prolonged effect to reduce appetite. Thus it reduces the liver fat present in patients with type 2 diabetes.

Uses: It is used to control glycemic control in obese patients with Type-II Diabetes.

Side effects: Exenatide cause sour stomach, belching, diarrhoea and heartburn.

Stimulants

Phentermine: Phentermine, a contraction of "phenyl-tertiary-butylamine", is an appetite suppressant of the phenethylamine class. It is a non-amphetamine stimulant.



IUPAC NAME: 2-methyl-1-phenylpropan-2-amine

Mechanism of action: Phentermine acts on the hypothalamus portion of the brain to stimulate the adrenal glands to release nor-epinephrine, a neurotransmitter or chemical messenger (an adipokine, leptin) that signals reducing hunger. Phentermine also cause fat cells to break down stored fat, results in decrease of cholesterol content but the principal basis of efficacy is hunger-reduction.

Uses: Phentermine is used for the short term treatment of obesity.

Adverse effects: The adverse effects of Phentermine are Lactic acidosis, Hypertension and Irritability.

PPAR's (Peroxisome Proliferative Activated Receptors): A family of drugs that activate certain proteins in the body called peroxisome proliferator-activated receptors (PPARs). Three PPAR forms are commonly known, PPAR α, PPAR β, PPAR γ. The PPAR agonists can help to improve blood glucose levels and levels of blood lipids (fats and cholesterol) and reduces risk of atherosclerosis as they regulate the expression of genes that affect blood lipid metabolism, the generation of adipocytes (fat cells), and blood glucose control. The main role of PPAR's is to govern obesity-induced inflammation in adipose tissue(fig.5).

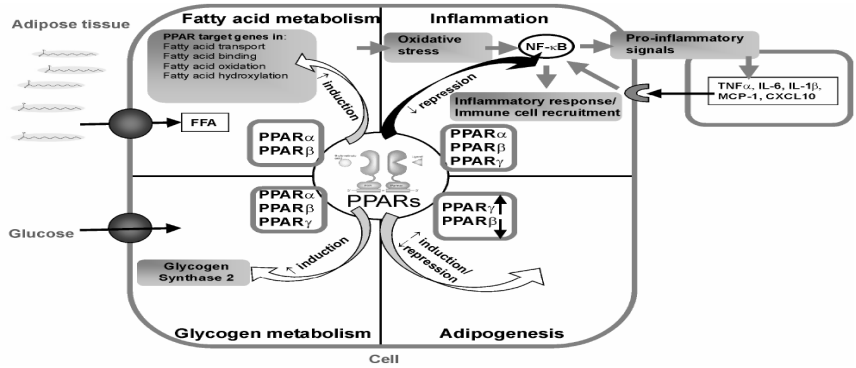
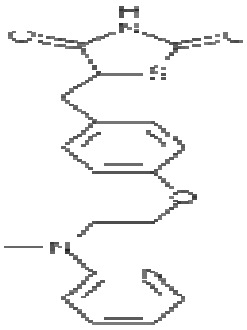
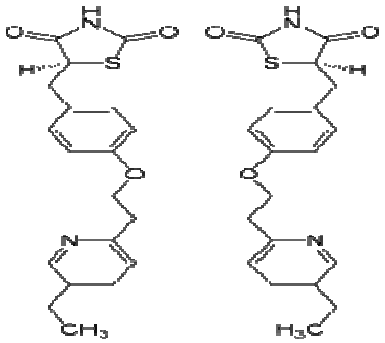


Figure:5 Role of PPAR's

Thiazolidinediones (TZD) or PPAR Agonists: Rosiglitazone, Pioglitazones are the PPAR agonists acts as an Anti-diabetic drug in the Thiazolidinedione class of drugs.



Rosiglitazone



Pioglitazone

Mechanism of action: These acts by binding to the PPAR receptors in fat cells and make them more responsive to insulin by increasing the adiponectin levels and decreasing leptin levels. They reduce glucose, fatty acid, and insulin blood concentrations.

Uses: PPAR's plays a major role in anti-inflammatory action. Thiazolidinediones acts as targets of Obesity induced inflammatory effects.

Adverse effects: PPAR's cause Cardiac risk factor, Bone fracture and Eye damage.

Future Prospects:

- ✓ The characterisation of regulation of adipocytokine secretion may help to modulate the adipocyte secretory function.
- ✓ Evaluation of the relevance of a defective leptin transport system across the blood-brain barrier and the signalling pathway in obesity.
- ✓ Role of Leptin administration on tumourigenesis should be investigated by the use of tissue specific leptin receptor antagonists and leptin synthesis blockers.
- ✓ Resistin levels whether associated with inflammatory markers related to atherosclerosis are being studied under clinical trials.
- ✓ Elucidation of mechanism of action and regulation of adiponectin levels, particularly in identifying its receptor antagonists for obesity related disorders.
- ✓ Current research has identified an increasing number of adipocyte-secreted factors and more yet to be discovered.

2.SUMMARY AND CONCLUSION

The Adipose tissue, an endocrine organ, produces adipocytes that stores adipokines. Leptin and Adiponectin, plays a major role as insulin sensitisers where as Resistin acts as insulin resistance. Novel adipokines are also identified which involves in regulating the functions of adipose tissue. The dysfunction of this adipose tissue leads to altered levels of these adipokines, results in many metabolic disorders. Of them, Obesity is the most common effect associated with health problems like insulin resistance and type II diabetes, atherosclerosis, degenerative disorders and various types of cancer. To treat these diverse effects of Adipokines and their physiological role results in development of new therapeutic approaches. Besides Obesity, metabolic disorders are also well characterised and therapeutically treated.

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