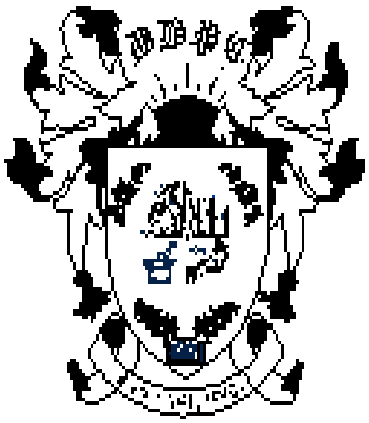
PIOGLITAZONE AND GLIMEPIRIDE- OVERVIEW

Jagdish L Kakadiya, Dr. Nehal J Shah

**Department of Pharmacology, Dharmaj degree Pharmacy College,
Petlad-Khambhat road, Dharmaj,
Dist: Anand, Gujarat, India.**



ADDRESS FOR CORRESPONDENCE

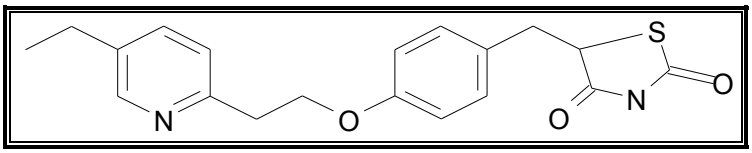
Mr. Jagdish L. Kakadiya
Dharmaj degree pharmacy college,
Amrapali Township, Petlad-Khambhat road,
Dharmaj, Dist: Anand-388430,
Gujarat, India.
jagdishkakadiya@yahoo.co.in

PIOGLITAZONE

DESCRIPTION

Pioglitazone is a member of the thiazolidinedione group of drugs developed for the treatment of type 2 diabetes mellitus, a disorder associated with a number of metabolic abnormalities that include impaired insulin secretion and insulin resistance. Insulin resistance leads to decreased glucose utilization by the peripheral tissues and increased hepatic glucose output. The thiazolidinedione act by sensitizing the liver and peripheral tissues to the effects of insulin, which results in improved insulin- mediated glucose disposal.

Pioglitazone is a member of the thiazolidinedione group of drugs developed for the treatment of Type 2 diabetes meDiavista oral tablets contain 15 mg or 30 mg of the agonist for peroxisome proliferator-activated receptor-gamma, 5-(4-[2-(5-ethylpyridin-2- yl) ethoxy] benzyl) thiazolidine-2, 4-dione, which has the following structural formula:



PHARMACODYNAMIC PROFILE:

The thiazolidinedione have been shown to bind with high affinity to than activate the nuclear peroxisome proliferators activated receptor gamma (PPAR-γ). Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α (1, 2). It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the lipidic, muscular tissues and in the liver. As a result, Pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated haemoglobin in the bloodstream. Although not clinically significant, Pioglitazone decreases the level of triglycerides and increases that of high-density lipoproteins (HDL) without changing low-density lipoproteins (LDL) and total cholesterol in patients with disorders of the lipid metabolism, although statins are the drug of choice for this.

More recently, Pioglitazone and other active TZDs have been shown to bind to the outer mitochondrial membrane protein mitoNEET with affinity comparable to that of pioglitazone for PPARγ (3, 4). The PPARs are member of the steroid receptor family and are thought to be involved in the modulation of the expression of a number of genes coding for proteins involved in glucose and lipid metabolism. PPAR-γ activation also stimulates differentiation of preadipocytes and bone marrow stromal cells into mature adipocytes. Most of the changes induced by the thiazolidinedione appear to be orchestrated via the activation of this receptor. Studies show that Pioglitazone stimulates stimulates the uptake of glucose and fatty acids into cells by promoting the synthesis and expression of cellular glucose and fatty acid transporters.

MECHANISM OF ACTION:

Pioglitazone is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. It is decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.

Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Since Pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Shown **Figure 1**

(a) Schematic representation of the domain structure of PPARγ, denoting the location of several of the natural mutations and polymorphisms which have been identified in the human receptor. F360L and R397C in PPARγ1 correspond to the F388L and R425C mutations in PPARγ2.

(b) Addition of ligand (L) to the DNA-bound PPARγ-RXR heterodimer promotes recruitment of a transcriptional 'coactivator' protein complex, which in turn modulates the transcription of target genes regulating different physiological processes.

(c) Dominant negative human PPARγ mutants retain the ability to heterodimerize with RXR on DNA, but fail to bind ligand and recruit transcriptional coactivators. Instead they recruit a 'corepressor' protein complex, leading to silencing of target gene transcription.

The mechanisms through which TZDs might help to stabilise beta-cell function are as yet unclear. Possible mechanisms include direct or indirect reductions in lipotoxicity, prevention of decreases in beta-cell mass via an effect on reducing apoptosis and reduced secretary demand, as well as a possible contribution from a reduction in glucotoxicity.

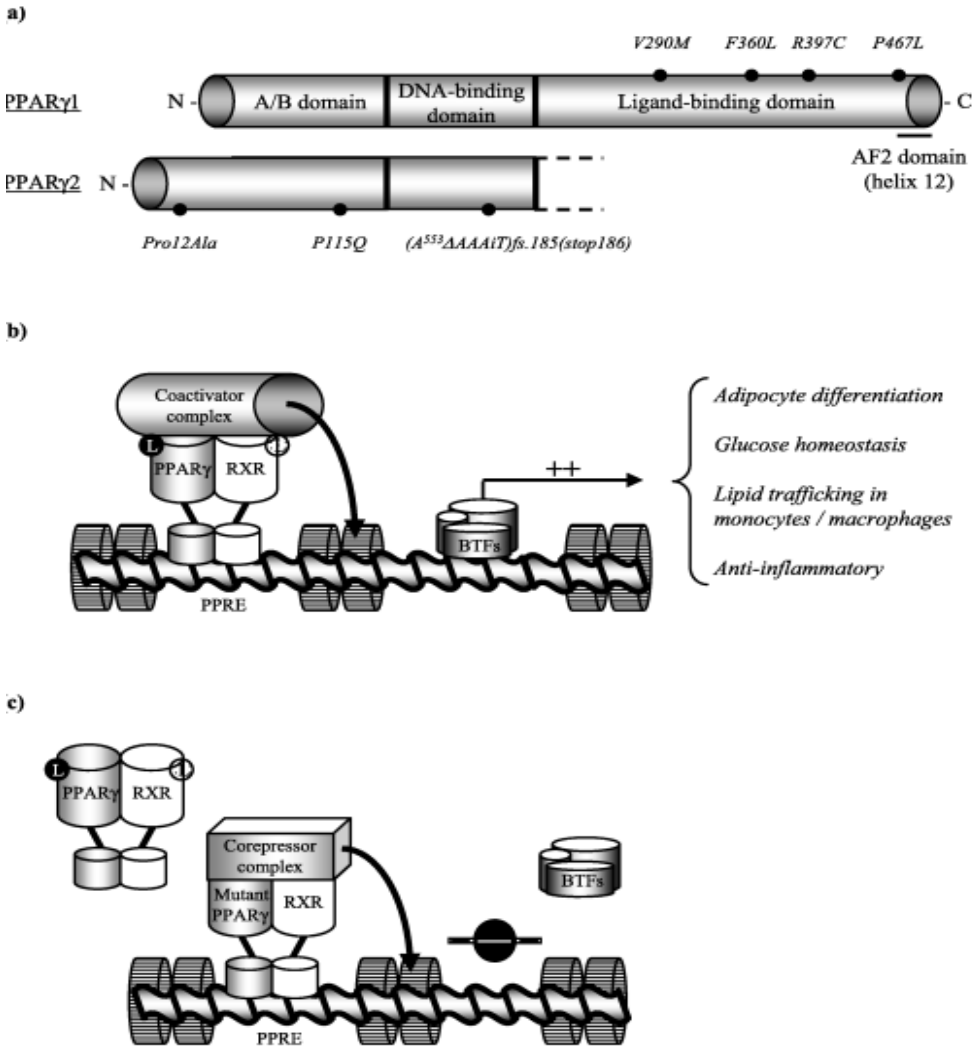


Figure 1

Transcriptional regulation by PPARγ

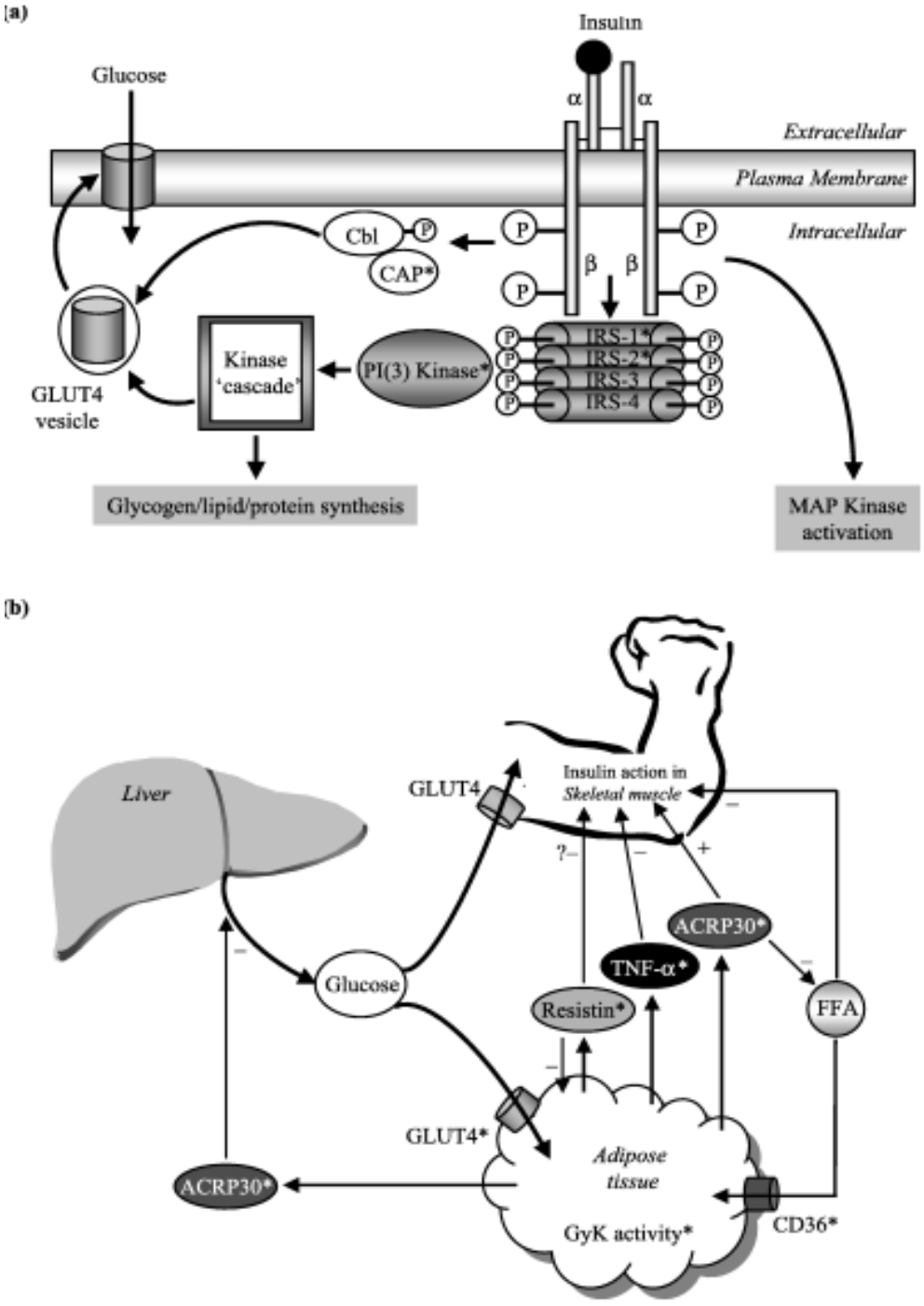


Figure 2

Potential sites of regulation by PPARγ in mammalian Glucose homeostasis

(a) At the cellular level, insulin stimulated glucose uptake is mediated by GLUT4, a specific glucose transporter. Activation of PI(3)K (phosphatidylinositol-3-OH kinase) promotes trafficking of GLUT4 containing vesicles from intracellular sites to the plasma membrane. In addition phosphorylation of Cbl (c-Cbl protooncogene), which associates with CAP (c-Cbl-associated protein), provides a second signal that acts in parallel with the PI (3) K pathways to augment this process. Molecules which are potential targets for regulation by PPARγ are asterisked.

(b) At the physiological level, hepatic glucose production and skeletal muscle glucose disposal are subject to regulation by a number of adipocyte derived factors (adipokines). It is probable that ambient blood glucose levels reflect, at least in part, the balance that exists between factors which impair insulin action (e.g. TNF-α , FFA, resistin) and those with insulin-sensitizing effects (e.g. ACRP30). GyK acts to reduce FFA release through promotion of triglyceride synthesis. Molecules whose expression or secretions are regulated by PPARγ are asterisked. GLUT4, CD36, ACRP30 and GyK are positively regulated and TNFα and resistin negatively regulated by the receptor.

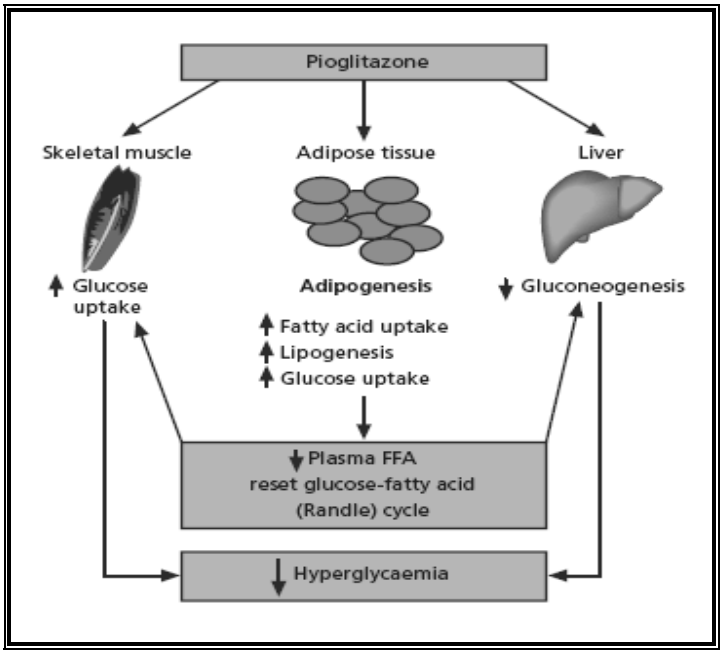


Figure 3

Mechanism of antihyperglycaemic effect of pioglitazone

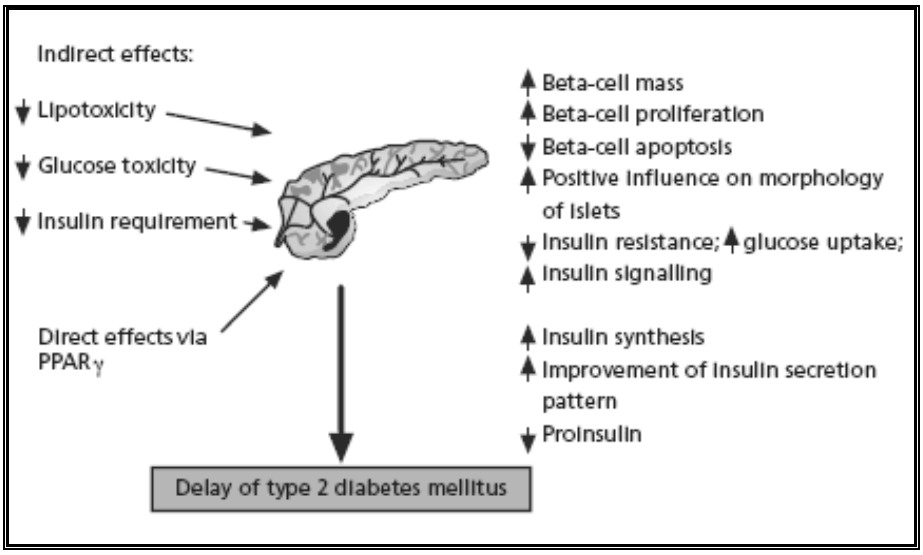


Figure 4

Possible mechanism of action of TZDs on beta-cell

And beneficial effects

PHARMACOKINETICS AND DRUG METABOLISM

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both Pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption:

Oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution:

The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (> 99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism:

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of Pioglitazone) and M-III (keto derivative of Pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extra-hepatic CYP1A1. In vivo studies of pioglitazone in combination with P450 inhibitors and substrates have been performed. Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination:

Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

INDICATIONS

Pioglitazone is used for the treatment of diabetes mellitus type 2 (previously known as non-insulin-dependent diabetes mellitus, NIDDM) in monotherapy and in combination with sulfonylurea, metformin, or insulin. Pioglitazone has also been used to treat non-alcoholic steatohepatitis (fatty liver), but this use is presently considered experimental.

CONTRAINDICATIONS

Pioglitazone cannot be used in patients with a known hypersensitivity to pioglitazone, other thiazolidinediones or any of components of its pharmaceutical forms. It is ineffective and possibly harmful in diabetes mellitus type 1 and diabetic ketoacidosis. Its safety in pregnancy, lactation (breastfeeding) and people under 18 is not established.

SIDE EFFECTS

The risk of hypoglycemia is low in the absence of other drugs that lower blood glucose. Pioglitazone can cause fluid retention and peripheral edema. As a result, it may precipitate congestive heart failure (which worsens with fluid overload in those at risk). It may cause anemia. Mild weight gain is common due to increase in subcutaneous adipose tissue. Patients on pioglitazone had a slightly increased proportion of upper respiratory tract infection, sinusitis, headache, myalgia and tooth problems.

A meta-analysis released subsequently showed that pioglitazone reduced the number of ischemic cardiac events rather than increase the risk, but increases CHF, a common class effect of the TZD. Therapy with pioglitazone raised HDL, and lowered triglyceride and hsCRP, these are all beneficial effects on risk factors for coronary artery disease, however to date, and no oral anti-diabetic drug has been shown to reduce the risk of cardiovascular complications.

CARDIOVASCULAR EFFECTS:

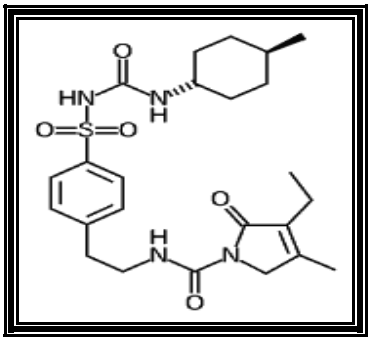
Pioglitazone 20 mg/kg/day for 7 weeks prevented the development of hypertension and reduced plasma insulin levels in rats fed diets with high fat or glucose content. The same doseage of Pioglitazone for 4 weeks significantly reduced fasting postprandial plasma insulin levels and systolic and mean blood pressures in spontaneously hypertensive rats. Pioglitazone has been

shown to possess direct insulin independent vasorelaxant properties. Addition of Pioglitazone at 0.1 mg/kg to feed given to SHR for 6 weeks decreased mean systolic blood pressure and significantly attenuated contractile responses of mesenteric arterial and aortic tissue to arginine vasopressin and noradrenaline. At a daily dosage of 22 mg/kg, Pioglitazone prevented increases in blood pressure seen in rats given a normal or high fructose diet.

GLIMEPIRIDE

DESCRIPTION

Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder formulated into tablets of 1-mg, 2-mg, and 4-mg strengths for oral administration, 3-ethyl-4-methyl- N-(4 -[N-((1r,4r)-4-methyl cyclohexyl carbamoyl) sulfamoyl] phenethyl)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide, which has the following structural formula:



Glimepiride is the first third-generation sulfonylurea, and is very potent.

MECHANISM OF ACTION:

Glimepiride lowers the blood glucose level by stimulating pancreatic beta cells to produce more insulin and by inducing increased activity of intracellular insulin receptors.

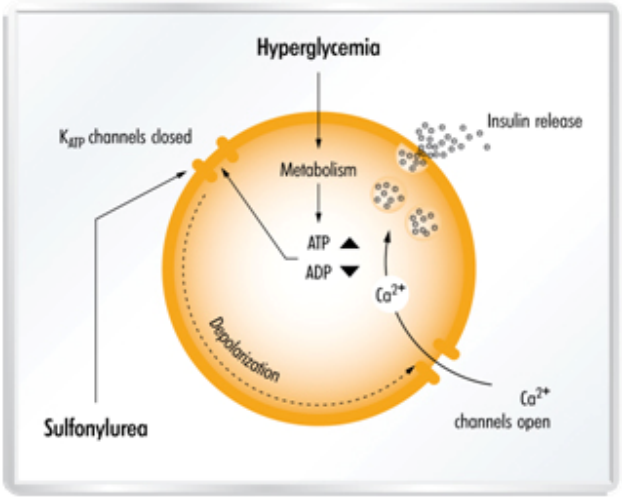


Figure 5

Mechanism of action of Glimepiride

PHARMACODYNAMICS

The primary mechanism of action of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extra pancreatic effects may also play a role in the activity of sulphonylureas such as Glimepiride.

PHARMACOKINETICS

Absorption

After oral administration, Glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes mellitus (NIDDM) have shown significant absorption of Glimepiride within 1 hour after administration and peak drug levels (C max) at 2 to 3 hours. When Glimepiride was given with meals, the mean T max (time to reach C max) was slightly increased (12%) and the mean C max and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

Distribution

After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

Excretion

When 14 C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in faeces and M1 and M2 (predominant) accounted for about 70% of that recovered in faeces. No parent drug was recovered from urine or faeces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

INDICATIONS

Glimepiride is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with non insulin-dependent (Type 2) diabetes mellitus (NIDDM) whose hyperglycaemia cannot be controlled by diet and exercise alone. Glimepiride may be used concomitantly with metformin when diet, exercise, and glimepiride or metformin alone do not result in adequate glycaemic control. Glimepiride is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycaemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycaemic agent. Combined use of glimepiride and insulin may increase the potential for hypoglycaemia.

CONTRAINDICATIONS

Glimepiride is contraindicated in patients with Known hypersensitivity to the drug. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

SIDE EFFECTS

Nausea or upset stomach may occur. If any of these effects persist or worsen, notify your doctor or pharmacist promptly. Tell your doctor immediately if any of these highly unlikely but very serious side effects occur: yellowing eyes or skin, stomach/abdominal pain, dark urine, unusual tiredness or weakness, easy bleeding or bruising, signs of infection (e.g., fever, persistent sore throat), mental/mood changes, unusual or sudden weight gain, seizures. This medication can cause low blood sugar (hypoglycemia). This effect may occur if you do not consume enough calories (from food, juices, fruit, etc.). The symptoms include chills, cold sweat, blurred vision, dizziness, drowsiness, shaking, rapid heart rate, weakness, headache, fainting, tingling of the hands or feet, or hunger. It is a good habit to carry glucose tablets or gel to treat low blood sugar. If you are in a situation where you don't have these reliable forms of glucose, eat a quick source of sugar such as table sugar, honey, or candy, or drink a glass of orange juice or non-diet soda to quickly raise your blood sugar level. Tell your doctor immediately about the reaction. To help prevent hypoglycemia, eat meals on a regular schedule and do not skip meals. Symptoms of high blood sugar (hyperglycemia) include thirst, increased urination, confusion, drowsiness, flushing, rapid breathing, or fruity breath odor. If these symptoms occur, tell your doctor immediately.

REFERENCES

1. Gillies PS, Dunn CJ (August 2000). "Pioglitazone". Drugs 60 (2): 333–43; discussion 344–5.
2. Smith U (September 2001). "Pioglitazone: mechanism of action". Int J Clin Pract Suppl (121): 13–8.
3. Colca JR, McDonald WG, Waldon DJ, Leone JW, Lull JM, Bannow CA, Lund ET, Mathews WR (2004). "Identification of a novel mitochondrial protein ("mitoNEET") cross-linked specifically by a thiazolidinedione photoprobe". Am. J. Physiol. Endocrinol. Metab. 286 (2): E252–60.
4. Paddock ML, Wiley SE, Axelrod HL, Cohen AE, Roy M, Abresch EC, Capraro D, Murphy AN et al. (2007). "MitoNEET is a uniquely folded 2Fe 2S outer mitochondrial membrane protein stabilized by Pioglitazone". Proc. Natl. Acad. Sci. U.S.A. 104 (36): 14342–7.