Anti-Diabetic Drugs.

Learning Objectives.

At the end of this course, you should be able to :

1. list the main groups of oral anti-diabetic drugs;
2. give a brief description of the pharmacological action of these drugs;
3. understand the mechanisms by which these drugs bring about hypoglycaemia;
4. give the common side effects encountered with these drugs;
5. list which drugs interact with oral anti-diabetic drugs.

Diabetes mellitus affects up to 6% of the UK population, although it is estimated that around half of these individuals remain undiagnosed. It occurs equally in both sexes but varies with age and race. The ethnic group at highest risk is the Pima Indians in North America with a 50% prevalence of diabetes. Other high-risk groups include the Afro-Caribbean and Asian populations, who are at four times the risk for developing diabetes than Caucasians.

Approximately 10% of the population over the age of 65 years, and 16% of Asians in the same age group in the UK, have diabetes. This racial and age effect, along with the potential for a Western lifestyle to generate a more sedentary and obese population, leads to significant differences in the size of the problem in different countries.

Comparison of type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes
Peak age of onset	12 years	60 years
UK prevalence	0.25%	5-7% (10% in >65yrs)
Aetiology	Autoimmune beta cell destruction	Combination of insulin resistance and beta cell dysfunction
Initial presentation	Polyuria, polydipsia and weight loss with ketoacidosis	Hyperglycaemic symptoms but often with complication of diabetes (no ketoacidosis)
Treatment	Insulin from outset	Diet, oral hypoglycaemic agents and/or insulin

Previously known as insulin dependent diabetes mellitus (IDDM), or juvenile-onset diabetes, Type 1 DM disorders are characterized by an absolute deficiency of insulin resulting from cell-mediated autoimmune destruction of the beta cells of the pancreas. Islet cell autoantibodies, autoantibodies to insulin, anti-GAD (glutamic acid decarboxylase) antibodies and anti-tyrosine phosphatase antibodies (Anti-IA-2 antibodies) are present in 90% of patients. If all four antibodies are present in a non-diabetic individual, they have an 88% chance of developing Type 1 within the subsequent ten years.

Although a genetic predisposition is suggested, environmental triggers are also important as not all patients with pancreatic auto-antibodies develop diabetes.

Type 2 was previously known as non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes. These patients usually exhibit insulin resistance and a relative insulin deficiency. Most patients with this form of diabetes are older and obese, and it is known that obesity itself produces relative insulin resistance. Blood insulin levels are usually normal or elevated. Despite this, serum glucose levels are higher in relation to the level of insulin.

Genetic predisposition to develop Type 2 diabetes is much stronger compared to Type 1 diabetes. However, the mechanisms are still not fully understood.

A number of other forms of diabetes can result from genetic defects of beta cell function, often characterised by hyperglycaemia at an early age. This autosomal dominant group of disorders is referred to as maturity-onset diabetes of the young (MODY). They arise from genetic mutations such as a defect on chromosome 20q resulting in altered activity of the hepatic nuclear factor (HNF) 4α gene(*MODY 1*), a defect in the glucokinase gene (*MODY 2*), and gene mutations that alter HNF-1α activity (*MODY 3*)

Genetic defects of insulin action are a rarer cause of diabetes. Leprechaunism, with characteristic facial features, is usually fatal in early childhood, and Rabson-Mendenhall syndrome, characterised by abnormalities of teeth and nails and pineal gland hyperplasia, are two examples. Any disease of the exocrine pancreas, such as pancreatitis, pancreatic trauma and pancreatic carcinoma, can result in diabetes if it is of sufficient severity to destroy the pancreas.

Endocrine diseases that result in hormone production antagonistic to insulin may also result in diabetes. Examples are Cushing's syndrome (cortisol), acromegaly (growth hormone) and phaeochromocytoma (adrenaline).

Drugs such as thiazide diuretics may precipitate diabetes in susceptible individuals, while nicotinic acid and glucocorticoids impair insulin action. Infections such as congenital rubella, Coxsackie B and cytomegalovirus have been implicated in the development of diabetes. Additionally, genetic syndromes such as Down's, Turner's and Wolfram's are also associated with diabetes.

Gestational diabetes mellitus is defined as any degree of glucose intolerance with the onset or first recognition of pregnancy.

Management.
Whilst Type 1 patients are always treated with insulin, Type 2 patients have a different management strategy. Initially, diet modification and exercise are the first line, unless they are significantly symptomatic, when a sulphonylurea may be used short term. As the disease worsens, patients may require oral hypoglycaemic agents and possibly insulin therapy.

Oral hypoglycaemic agents

The oral hypoglycaemic agents are classed into a small number of groups :
    Sulphonylureas eg glibenclamide, tolbutamide
    Biguanides eg metformin
    Prandial glucose regulators eg repaglinide
    Alpha glucosidase inhibitors eg acarbose
    Thiazolidinediones eg pioglitazone

These agents are similar in their ability to lower blood glucose, but there are some differences which may influence the choice for specific individuals. Sulphonylureas reduce microvascular complications (retinopathy) but not cardiovascular outcomes, and although metformin, a biguanide, is no better than sulphonylureas in reducing the blood glucose of obese Type 2 patients, it has proved to so far be the only drug that lowers overall mortality and the incidence of stroke or myocardial infarction.

The general side effects of the oral hypoglycaemic agents (except metformin) are weight gain and/or hypoglycaemia. Elderly patients with renal impairment should avoid long-acting sulphonylureas such as glibenclamide in view of the risk of severe hypoglycaemia and, possibly, death.

Lactic acidosis is a serious, rare complication of metformin. Patients at particular risk are those with tissue hypoxia (e.g. uncontrolled heart failure or liver failure) and renal impairment. Metformin should also be temporarily discontinued in patients who are undergoing radiological studies requiring contrast due to the deleterious effect of contrast media on renal function.

Insulin and oral agent mixtures

After diet, exercise and oral therapy, insulin may be added to the treatment regimen. Oral hypoglycaemic agents can be used for glycaemic control during the day, and pre-bed intermediate-acting insulin for glycaemic control overnight. Metformin is a good oral hypoglycaemic for this combination as it reduces insulin requirements and body weight.

1. Sulphonylureas

Sulfonylureas were developed by chemist Marcel Janbon and co-workers as a result of a chance observation. The group were studying sulfonamide antibiotics (used to treat typhoid), and discovered that the compound, sulfonylurea, induced hypoglycemia. First generation sulphonylureas include tolbutamide and chlorpropamide. Of these two, only tolbutamide is still in use. Second generation drugs include glibenclamide, glipizide, and gliclazide. They are pharmacologically more potent that the first generation drugs, but in practice their hypoglycaemic effect is very similar to the first tolbutamide.

Mechanism of action

Their principle action is on the beta cells of the pancreas, increasing the release of insulin. Receptors with a high affinity for sulphonylureas exist on the ATP-sensitive potassium (K) channels. The drugs bind to these channels on the cell membrane of pancreatic beta cells. This inhibits the escape of potassium from the cell causing the electric potential over the cell membrane to become more positive. This depolarization opens voltage-gated calcium channels, allowing the influx of calcium. The rise in intracellular calcium leads to increased movement of insulin-containing granules within the cell as they relocate to, and bind with, the cell membrane, releasing their contents, and therefore increasing the release of insulin.

There is some evidence that sulfonylureas also sensitise beta cells to glucose, that they limit glucose production in the liver, that they decrease the breakdown and release of fatty acids by adipose tissue (lipolysis), and decrease clearance of insulin by the liver.

Pharmacokinetics

These drugs are well absorbed, reaching peak plasma concentration usually within 3 hours. They all are strongly plasma protein-bound (albumin), and can interact with other drugs such as salicylates and sulphonamides because of this. Most sulphonylureas are excreted via the kidneys in urine, so their actions can be enhanced in those with renal disease, or in the elderly.

These drugs may also cross the placenta and can act on fetal beta cells resulting in severe hypoglycaemia at birth, so their use is contraindicated during pregnancy.

Various sulfonylureas have differing pharmacokinetics. Longer-acting sulfonylureas with active metabolites can induce hypoglycemia over a longer period of time, helping to achieve glycaemic control when tolerated by the

patient. The shorter-acting agents may not control blood sugar levels adequately.

Due to varying half-life, some drugs have to be taken twice (e.g. tolbutamide) or three times a day rather than once (e.g. glimepiride). The short-acting agents may have to be taken about 30 minutes before eating to achieve maximum efficacy.

Some sulfonylureas are metabolised by the cytochrome P450 system in the liver. Inducers of this enzyme system (eg rifampicin) can therefore increase the clearance of sulfonylureas. In addition, because some sulfonylureas are bound to plasma proteins, use of drugs that also bind to plasma proteins can release the sulfonylureas from their binding places, leading to increased clearance.

Side effects

Generally these drugs are well-tolerated, but they are known to stimulate the appetite, and therefore induce weight-gain. Additional known side-effects include gastrointestinal disturbance, headache, and hypersensitivity reactions. Very rarely, bone marrow damage can occur.

Second-generation sulfonylureas have increased potency compared to the first-generation, and have decreased side effects but are more expensive. Among the second-generation agents gliclazide and glimepiride offer the best protection against coronary artery disease whilst it is possible that glyburide and glipizide may increase the risk of myocardial infarction.

Drug Interactions

A number of drugs increase the actions of sulphonylureas, and can cause clinical effects. NSAIDs, coumarins, alcohol, MAOIs, some antibitoics (sulphonamides, trimethoprim, chloramphenicol), and some anitfungals (miconazole, fluconazole), have all been reported to produce severe hypopglycaemia in combination with sulphonylureas. This is most likely due

to either competition for plasma protein binding sites, or competition for metabolising enzymes.

Drugs that decrease the action of sulphonylureas include corticosteroids, and the thiazide and loop diruetics (bendrofluazide, frusemide, bumetanide).

2. Biguanides.

This group of drugs are derived from the plant *Galega officinalis* (French Lilac), and it's hypoglycaemic properties were first studied scientifically in the late 1920's. The only drug currently used in this class is Metformin. Biguanides are actively hypoglycaemic, and require functioning beta-cells (and therefore endogenous insulin), although their mechanism of action is not yet properly understood. They increase glucose uptake in skeletal muscle, they also affect glucose absorption, and hepatic glucose production.

History

Metformin was first described in the scientific literature in 1922 by Emil Werner and James Bell as a side product in the synthesis of *N,N*-dimethylguanidine, but it was not until 1929 that Slotta and Tschesche investigated its sugar-lowering potential in rabbits. However, this finding was forgotten as other guanidine analogs, such as the synthalins, took centre stage, and were then overshadowed by insulin.

French diabetologist, Jean Sterne, studied the antihyperglycemic properties of galegine, a toxic extract of *Galega,* and from1956 onwards Sterne investigated several biguanide analogs for the treatment of diabetes; his interest in biguanides was at least partly prompted by anecdotal reports from the previous decade, when metformin (under the name flumamine) was used as a treatment for influenza and was serendipitously found to have an hypoglycemic effect in humans. Sterne was first to try metformin on humans for the treatment of diabetes. He coined the name "Glucophage" for

the drug and published his results in 1957. However, his report was soon followed by trials of phenformin and buformin, which were more potent and thus adopted for clinical use.

Phenformin and Buformin were withdrawn from clinical use in the 1970s, after which metformin 're-discovered'. Metformin was first marketed in France in 1979, but it was not until 1995 that it received a US licence for use in Type 2 Diabetes as Glucophage. Since this time, generic formulations have become available.

Mechanism of action

Metformin improves hyperglycemia primarily through its suppression of hepatic glucose production. In most patients with Type 2 the rate of gluconeogenesis is three times the non-diabetic rate, but the use of metformin reduces this by around one third. This occurs via activation of AMP-activated protein kinase (AMPK), an hepatic enzyme with a central role in insulin signaling, as well as control of glucose and fat metabolism. If AMPK is activated then there is an inhibitory effect on the production of glucose by hepatocytes. Whilst it is known that metformin activates AMPK, the mechanism by which this occurs remains unclear, although it may be linked with the increase in cytosolic adenosine monophosphate (AMP) levels which occurs with metformin.

Metformin also increases insulin sensitivity, encourages the peripheral uptake of glucose, increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilisation of glucose may be due to improved insulin binding to insulin receptors. AMPK probably also plays a role, as metformin administration increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 (an insulin receptor) translocation, resulting in insulin-independent glucose uptake.

Clinical use

The main use for metformin is in the management of Type 2 diabetes particularly in obese patients with insulin resistance – metformin is known to suppress appetite, unlike sulphonylureas. It also does not cause weight gain, and may produce minor weight loss. Metformin also modestly reduces LDL and triglyceride levels.

Moreover, metformin is the only anti-diabetic drug that has been proven to protect against the cardiovascular complications of diabetes. This was first shown in the United Kingdom Prospective Diabetes Study, a large study of overweight patients with diabetes.

Pharmacokinetics

Metformin slowly absorbed, and orally has 50–60% bioavailability. Peak plasma concentrations are reached within one to three hours of taking immediate-release metformin, and between four and eight hours with extended-release formulations. The plasma protein binding of metformin is almost zero, therefore almost 100% of the drug is free to be active. Metformin is not metabolised, but cleared by renal tubular secretion and excreted unchanged in the urine.

Adverse effects

The most common adverse effect of metformin is gastrointestinal upset, including diarrhea, cramps, nausea, vomiting and increased flatulence; metformin is more commonly associated with gastrointestinal side effects than most other anti-diabetic drugs. The most serious potential side effect of metformin use is lactic acidosis; this complication is very rare, and seems limited to people with impaired liver or kidney function.

Metformin has also been reported to reduce the blood levels of thyroid-stimulating hormone in patients with hypothyroidism, and, in men, lutenizing hormone and testosterone. The clinical significance of these changes is still unknown.

Gastrointestinal - Gastrointestinal upset can cause severe discomfort for patients; it is most common when metformin is first administered, or when the dose is increased. The discomfort can often be avoided by beginning at a low dose and increasing the dose gradually. Gastrointestinal upset after prolonged, steady use is less common.

Long-term use of metformin has been associated with increased homocysteine levels (associated with increased cardio-vascular disiase), and malabsorption of vitamin B_{12}. Higher doses and prolonged use are associated with increased incidence of B_{12} deficiency.

Lactic acidosis - The most serious potential adverse effect of biguanide use is lactic acidosis. Phenformin, another biguanide, was withdrawn from the market because of an increased risk of lactic acidosis. However, metformin is safer than phenformin, and the risk of developing lactic acidosis is not increased by the medication so long as it is not prescribed to known high-risk groups.

Lactate uptake by the liver is diminished with metformin administration because lactate is a substrate for hepatic gluconeogenesis, a process which metformin inhibits. In healthy individuals, this slight excess is simply cleared by other mechanisms (including uptake by the kidneys, when their function is unimpaired), and no significant elevation in blood levels of lactate occurs. When there is impaired renal function, clearance of metformin (and lactate) is reduced and the drug may accumulate, leading to lactic acidosis. Because metformin decreases liver uptake of lactate, any condition which may precipitate lactic acidosis is a contraindication to its use. Common causes of increased lactic acid production include alcoholism, heart failure, and respiratory disease (due to inadequate oxygenation of tissues); the most common cause of impaired lactic acid excretion is kidney disease.

It has also been suggested that metformin increases production of lactate in the small intestine; this could potentially contribute to lactic acidosis in patients with risk factors. However, the clinical significance of this is unknown, and the risk of metformin-associated lactic acidosis is most commonly attributed to decreased hepatic uptake rather than increased intestinal production.

Interactions

Cimetidine causes an increase in the plasma concentration of metformin by reducing clearance of metformin by the kidneys; both metformin and cimetidine are cleared from the body by tubular secretion, and both may compete for the same transport mechanism. There is also some evidence that the antibitoic, cefalexin, increases metformin concentrations by a similar mechanism.

Contraindications

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders, lung disease and liver disease. Heart failure has long been considered a contraindication for metformin use, although a 2007 systematic review showed metformin to be the only anti-diabetic drug that was not associated with harm in people with heart failure.

It is recommended that metformin be temporarily discontinued before any radiographic study involving iodinated contrast (such as a contrast-enhanced CT scan or angiogram), as contrast dye may temporarily impair kidney function, indirectly leading to lactic acidosis by causing retention of metformin in the body. It is recommended that metformin be resumed after two days, assuming kidney function is normal.

3. Prandial glucose regulators

These agents potentiate the post-prandial secretion of insulin. There are currently two drugs in this class :

> Repaglinide - may be given as monotherapy for patients who are not overweight or for those in whom metformin is contra-indicated or not tolerated, or it may be given in combination with metformin.

> Nateglinide - In combination with metformin

Like sulfonylureas, these drugs stimulate cells in the pancreas to produce insulin. Repaglinide is unusual in that it has a rapid onset of action and a short duration of action. When taken just prior to meals, it promotes the release of insulin that normally occurs with meals and is responsible for preventing blood glucose levels becoming high. It has been shown to lower HbA1c levels by between 1.6% and 1.9%. Repaglinide is taken immediately before a meal, or 15 to 30 minutes before a meal. It should be taken with every meal up to 4 times a day.

Mechanism of action
Repaglinide stimulates the release of insulin from pancreatic beta-cells by inhibition of potassium efflux, resulting in closure of ATP-regulated K+ channels. This results in depolarisation of the cell and subsequent opening of calcium channels, leading to influx of calcium into the cells, which causes release of insulin. It is suggested that repaglinide and glibenclamide probably regulate these ATP-sensitive K+ channels via different binding sites on the beta-cell.

Pharmacokinetics
Repaglinide is rapidly absorbed from the GI tract and reaches maximum plasma concentration approximately 1 hour after taken orally, and is at least 98% protein bound. It is extensively metabolised in the liver with only a very small proportion of the unchanged drug appearing in the urine. Its metabolites do not contribute to the glucose-lowering effect of the drug.

The major metabolites of repaglinide are excreted mainly into the bile. Concurrent administration with food did not appear to alter the absorption of repaglinide significantly in healthy volunteers. Age does not appear to have a significant effect on repaglinide pharmacokinetics in normal ubjects, however clearance is reduced in elderly Type 2 patients. Pharmacokinetic studies in patients with mild/moderate and severe renal impairment, those on haemodialysis as well as patients with hepatic impairment indicate an increased exposure to the drug in these patient groups.

Adverse Effects

The most frequently reported adverse events are hypoglycaemia, upper respiratory tract infections, rhinitis, back pain, diarrhoea, nausea, constipation, arthralgia, headache, and sinusitis. There is also the potential for weight gain. There have been isolated reports of increases in liver enzymes most cases were mild and transient. Hypersensitivity reactions can occur as itching, rashes and urticaria.

Drug Interactions

Repaglinide is metabolised in the liver by an enzyme called CYP3A4. Drugs that affect this enzyme may affect the blood levels of repaglinide and thus alter its glucose lowering effect. The metabolism of repaglinide may be prevented by ketoconazole, itraconazole, fluconazole, erythromycin, and clarithromycin. As a result, blood levels of repaglinide rise and there is an enhanced glucose-lowering effect. Dangerous hypoglycemic reactions can occur.

The elimination of repaglinide may be increased with drugs that increase levels of CYP3A4 in the liver, such as barbiturates, carbamazepine, and rifampin. This can result in lower blood levels of repaglinide and hyperglycemia.

Some drugs increase blood sugar and therefore reverse the effects of repaglinide. Such drugs include amphetamines, glucorticoids such as

prednisone, oestrogens, isoniazid, phenothiazines such as chlorpromazine, phenytoin, decongestants, and thyroid drugs.

Contra-Indications

These drugs are not used in the management of Type 1 diabetes, or in patients with diabetic ketoacidosis, with or without coma. They are also avoided during pregnancy and lactation, and are not used in the management of children. Because of their mechanism of metabolism, their use is avoided in patients with renal or hepatic impairment, and also in patients whose medication includes drugs which inhibit or induce cytochrome P450.

Precautions

Repaglinide should only be prescribed if poor blood glucose control and symptoms of diabetes persist despite dieting, exercise and weight reduction. Repaglinide can produce hypoglycaemia, this risk is increased when treatment is combined with metformin. Although repaglinide acts through a distinct binding site, use in secondary failure to other insulin secretagogues has not been investigated. Trials of combination therapy with insulin, thiazolidenediones, other insulin secretagogues, or acarbose, have not been performed. At times of stress it may be necessary to discontinue repaglinide and treat with insulin on a temporary basis.

4. Alpha glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs) inhibit the absorption of carbohydrates from the gut and may be used in the treatment of patients with Type 2 diabetes or impaired glucose tolerance. There is currently no evidence that AGIs are beneficial to prevent or delay mortality or micro/macrovascular complications in Type 2 diabetes. Its beneficial effects on glycated haemoglobin are comparable to metformin or thiazolidinediones, and probably slightly inferior to the sulphonylureas. For patients with impaired

glucose tolerance AGIs may prevent, delay, or even mask the occurrence of Type 2 diabetes.

Examples of alpha-glucosidase inhibitors include:

- Acarbose
- Miglitol
- Voglibose

Even though the drugs have a similar mechanism of action, there are subtle differences between acarbose and miglitol. Acarbose is an oligosaccharide, whereas miglitol resembles a monosaccharide. Miglitol is fairly well-absorbed by the body, as opposed to acarbose. Moreover, acarbose inhibits pancreatic alpha-amylase in addition to alpha-glucosidase.

Mechanism of action

Alpha-glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates, specifically alpha-glucosidase enzymes in the brush border of the small intestines. The membrane-bound intestinal alpha-glucosidases hydrolyse oligosaccharides, trisaccharides, and disaccharides, to glucose and other monosaccharides in the small intestine.

Acarbose also blocks pancreatic alpha-amylase in addition to inhibiting membrane-bound alpha-glucosidases. Pancreatic alpha-amylase hydrolyses complex starches to oligosaccharides in the lumen of the small intestine.

Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drugs therapies is to decrease current blood glucose levels, whilst the long term effect is a small reduction in HbA1c levels.

AGIs must be taken at the start of main meals to have maximal effect. Their effects on blood sugar levels following meals will depend on the amount of

complex carbohydrates in the meal. In addition, these drugs may be useful in managing the obese Type 2 patient.

Side effects & precautions

Since alpha-glucosidase inhibitors prevent the degradation of complex carbohydrates into glucose, the carbohydrates will remain in the intestine. In the colon, bacteria will digest the complex carbohydrates, thereby causing gastrointestinal side effects such as flatulence and diarrhea. Since these effects are dose-related, it is generally advised to start with a low dose and gradually increase the dose to the desired amount. Voglibose, in contrast to acarbose, is thought to have fewer of these side effects, and is also more economical compared to acarbose.

If a patient using an alpha-glucosidase inhibitor suffers from an episode of hypoglycemia, the patient should eat something containing monosaccharides, such as glucose tablets. Since the drug will prevent the digestion of polysaccharides (or non-monosaccharides), non-monosaccharide foods may not effectively reverse a hypoglycemic episode in a patient taking an alpha-glucosidase inhibitor.

Drug Interactions

AGIs reduce serum digoxin concentrations. Digestive enzymes and intestinal adsorbents, such as charcoal, should not be taken at the same time as the alpha-glucosidase inhibitors, as they will decrease their efficacy. Miglitol decreases the bioavailability of propanolol and ranitidine.

5. Thiazolidinediones

The thiazolidinediones (or 'glitazones') are one of the newer classes of drugs for the treatment of Type 2 diabetes. They bind to peroxisome proliferator-activated receptor gamma (PPARγ) in adipocytes to promote adipogenesis and fatty acid uptake, although this occurs in peripheral rather than visceral fat. By reducing circulating fatty acid concentrations and lipid availability in liver and muscle, the drugs improve the patient's sensitivity to insulin.

Thiazolidinediones favourably alter concentrations of the hormones secreted by adipocytes, particularly adiponectin. They increase total body fat and have mixed effects on circulating lipids.

Thiazolidinediones have several biological actions. Although the precise mechanism by which the thiazolidinediones improve insulin sensitivity is still not completely understood, a large part of their action is thought to be mediated by changes in body fat and its distribution.

History

The discovery of thiazolidinediones occurred in Japan. The first compound, ciglitazone, improved glycaemic control in animal models of insulin resistance, but its mechanism of action was poorly understood and toxicity prevented trials in humans. Other compounds were subsequently developed with less toxicity in animals, and two important findings led to a rapid increase in understanding of their mode of action. These findings were that thiazolidinediones bind avidly to peroxisome proliferator-activated receptor gamma (PPARγ), and that they improve insulin sensitivity in parallel with a major change in fat metabolism, including a substantial reduction in circulating free fatty acids.

Three compounds - troglitazone, pioglitazone and rosiglitazone - have entered clinical practice and there has been a steadily increasing understanding of the multiple biological effects of these drugs.

Unfortunately, troglitazone caused uncommon but serious liver toxicity, leading to its withdrawal from use.

Mechanism of action

PPARγ is a member of a family of nuclear receptors and is expressed in many tissues, including colon, skeletal muscle, liver, heart and activated macrophages, but is most abundant in adipocytes.

Thiazolidinediones are selective agonists of PPARγ. When activated by a ligand, such as a thiazolidinedione, PPARγ binds to a retinoic acid receptor to form a heterodimer. This binds to DNA to regulate the genetic transcription and translation of a variety of proteins involved in cellular differentiation and glucose and lipid metabolism.

One result of PPARγ activation is enhanced differentiation and proliferation of pre-adipocytes into mature fat cells, particularly in non-visceral (peripheral or subcutaneous) fat depots. There is an upregulation of enzymes/transporters in adipocytes to facilitate their uptake of fatty acids. Most of these consequences of PPARγ stimulation are not seen in visceral adipocytes, even though these cells have abundant PPARγ receptors. Visceral adipocytes are also metabolically quite different to peripheral adipocytes in other ways, for example they are less responsive to insulin and more responsive to catecholamines. Increased fatty acid storage in subcutaneous adipocytes results in a 'lipid-steal' phenomenon, leading to lower circulating fatty acids and reduced concentrations of triglycerides in muscle and liver. Studies in animals and humans have shown that thiazolidinediones only improve insulin action (and glycaemic control in diabetes) in the presence of insulin resistance. This may be explained by the fact that the effects of these drugs on lipid redistribution are only beneficial if there is excess tissue lipid availability. The 'lipid-steal' effect of thiazolidinediones may therefore be a major contributor to improved insulin action in muscle (enhanced glucose utilisation) and liver (reduced hepatic glucose output), as the direct effects of PPARγ stimulation in muscle and liver are unclear.

The thiazolidinediones do not increase insulin secretion, but actually acutely reduce insulin levels, which may be a consequence of improved insulin sensitivity and/or reduced circulating fatty acids (as fatty acids stimulate insulin secretion). In the longer term, thiazolidinediones arrest the decline in ß-cell function that occurs in Type 2 diabetes, perhaps by protecting the ß-cell from lipotoxicity. The thiazolidinediones are of no use in Type 1 diabetes.

Side effects

Given the effect of the thiazolidinediones on adipocyte differentiation and proliferation, particularly in peripheral adipocytes, it is not surprising that an adverse effect of thiazolidinedione treatment is a gain in weight and peripheral fat mass. In fact, there tends to be a correlation between increasing peripheral fat and clinical improvement in insulin sensitivity and glycaemia in Type 2 diabetes. On the other hand, visceral fat, which appears far more metabolically 'harmful' than peripheral fat, is not increased and may decrease with thiazolidinedione therapy.

An adverse effect, which may preclude the use of the thiazolidinediones in patients with moderate to severe cardiac failure, is fluid retention. This is an important effect, which may result in peripheral oedema, particularly in patients taking concomitant insulin therapy (which may itself cause some increase in interstitial fluid). An increase in plasma volume results in a small drop in haemoglobin concentrations due to haemodilution. This is rarely clinically significant.

Pharmacokinetics

The thiazolidinediones are rapidly absorbed and reach peak concentrations within a few hours. Steady-state is usually reached within one week, but perhaps because of the importance of fat redistribution, the full benefit may take 4 - 12 weeks to become evident. Rosiglitazone and pioglitazone are strongly protein bound in the circulation, predominantly to albumin.

Drug interactions

No significant drug interactions have been reported with the thiazolidinediones, but it should be noted that in combination with the sulfonylureas, hypoglycaemia may occur due to the combination of enhanced insulin sensitivity (thiazolidinediones) and enhanced insulin secretion (sulfonylureas). Thiazolidinediones are metabolised by the cytochrome P450 system, but conventional doses do not affect the activity of those enzymes. Caution should still be exercised when using thiazolidinediones in combination with drugs metabolised by these enzymes.