PHARMACOLOGY

Pharmacology of Endocrine System: Insulin, Oral Hypoglycemics and Glucagons

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Diabetes

Diabetes mellitus is defined as a group of metabolic disorders which lead to hyperglycemia, glycosuria, polyurea and polydipsia. Ketosis occurs in severe form of diabetes mellitus. Diabetes can be divided into two main forms; type 1 and type 2. In type 1 diabetes immunological destruction of beta cells of pancreatic islets occurs, although idiopathic form has also been recognized. There is severe or absolute deficiency of insulin in type 1 diabetes mellitus. Although more common at a younger age (usually less than 30 years), it can occur at any age. In type 2 diabetes the patients develop resistance to insulin action, decreased insulin secretion or increased glucose in body.

Other types of diabetes mellitus exist which can be divided into type 3 diabetes, where elevated blood glucose levels could be because of various other specific causes, non pancreatic diseases, drug therapy etc. Type 4 diabetes also known as gestational diabetes mellitus is defined as occurrence of abnormalities in blood glucose levels noted for the first time during pregnancy.

Criteria for Diagnosis of Diabetes (From American Diabetic Association)

Symptoms (glycosuria, polyurea and polydipsia) of diabetes with random blood glucose concentration > 200mg/dl, Fasting plasma glucose > 126 mg/dl (atleast 8 hr of fasting), 2 hr plasma glucose > 200 mg/dl during an oral glucose tolerance test after ingesting 75mg of glucose.

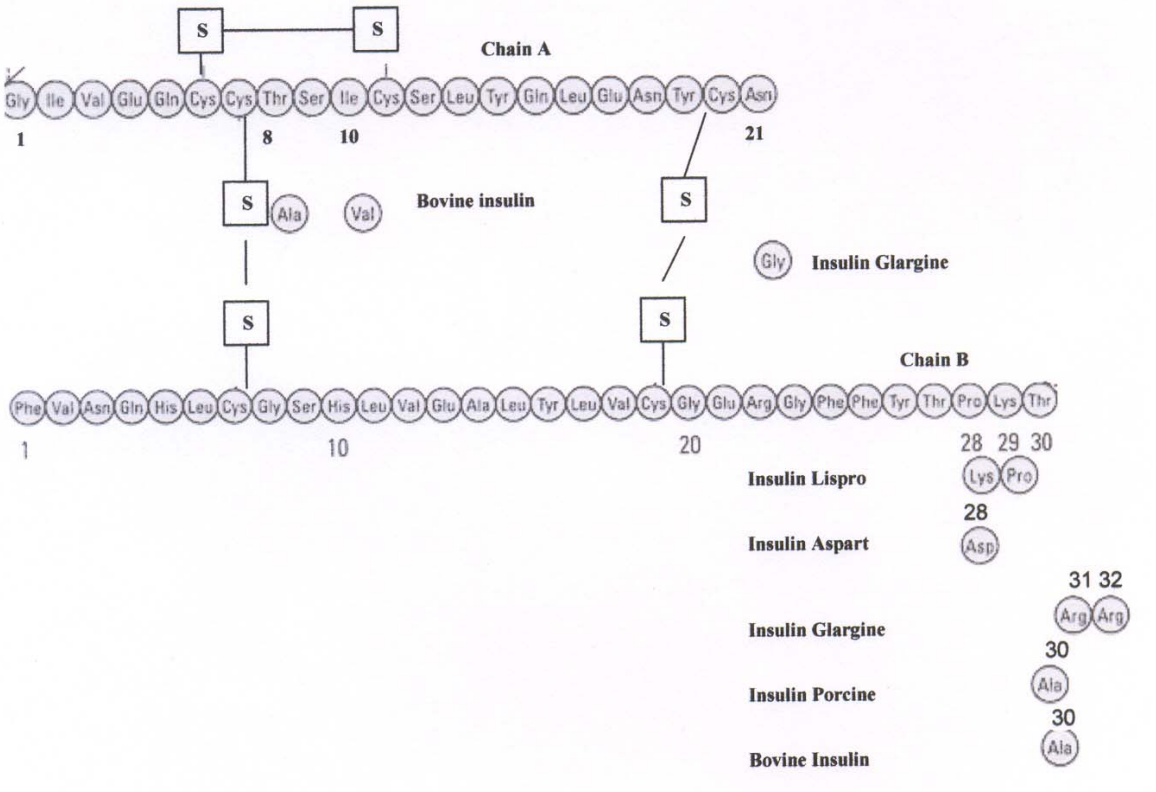

Fig1. Structure of Insulin

The main stay of treatment of diabetes is insulin. It was discovered by Banting and Best in 1923. Natural insulin is formed from cleavage of a 110 amino acid preproinsulin. Removal of 24 amino

acid amino terminal from preproinsulin leads to formation of 86 amino acid proinsulin. The proinsulin is processed within the golgi apparatus and packaged into granules. Further division of proinsulin leads to formation of 31 amino acid C-peptide and 51 amino acid insulin with removal of 4 basic amino acids. The 51 amino acid insulin is composed of two chains; chain A (21 amino acids) and chain B (30 amino acids). Both C-peptide and insulin are stored in the beta cells of the pancreas and secreted together on receipt of the right signal.

Insulin secretion

There are various regulators of insulin secretion, glucose being the key regulator. Others include amino acids, ketones, various nutrients, gastrointestinal hormones and neurotransmitters. Glucose levels > 70mg/dl lead to secretion of insulin. Glucose and other nutrients when taken orally are more effective in causing insulin secretion than when given intravenously indicating the involvement of gastrointestinal hormones or chemical signals 'incretins' from the gut in secretion of insulin.

Step1. First step involves entry of glucose into the pancreatic beta cell by the GLUT2 glucose transporter.

Step2. After entry glucose is phosphorylated by glucokinase to glucose 6 phosphate (G6P) in cytoplasm of beta cell.

Step3. G6P undergoes glycolysis to generate ATP.

Step4. ATP generated here leads to inhibition of ATP sensitive K^+ ion channels. ATP sensitive K^+ channel has two proteins.

Step5. Inhibition of K^+ channels induces beta cell membrane depolarization, which in turn leads to opening of voltage dependent Ca^{2+} channels. Ca^{2+} enters the cells and leads to release of insulin.

Distribution and Metabolism

Approximately 50% of the insulin released into the portal venous circulation is degraded by the liver. Rest enters the systemic circulation where it binds to the insulin receptor and stimulates the tyrosine kinase activity. Half life of natural insulin is 5-6min in normal subject and in uncomplicated diabetics. Normal pattern of insulin secretion after a meal shows a rapid rise in the level of insulin in portal circulation, followed by parallel but smaller rise in peripheral circulation. Metabolism of insulin occurs primarily in liver, kidney and muscle.

Mechanism of Action of Insulin

After reaching the target cell insulin binds to its receptor. Insulin receptor is a transmembrane glycoprotein composed of two alpha subunits and two beta subunits linked by disulphide bonds forming a beta-alpha-alpha-beta tetramer.

After insulin binds to the receptor, insulin-receptor complex is internalized and undergoes autophosphorylation. This leads to activation of tyrosine kinase activity, which in turn leads to activation of various MAP kinases and phosphoinositol phosphate 3 kinase (PI3 kinase) (Fig 2).

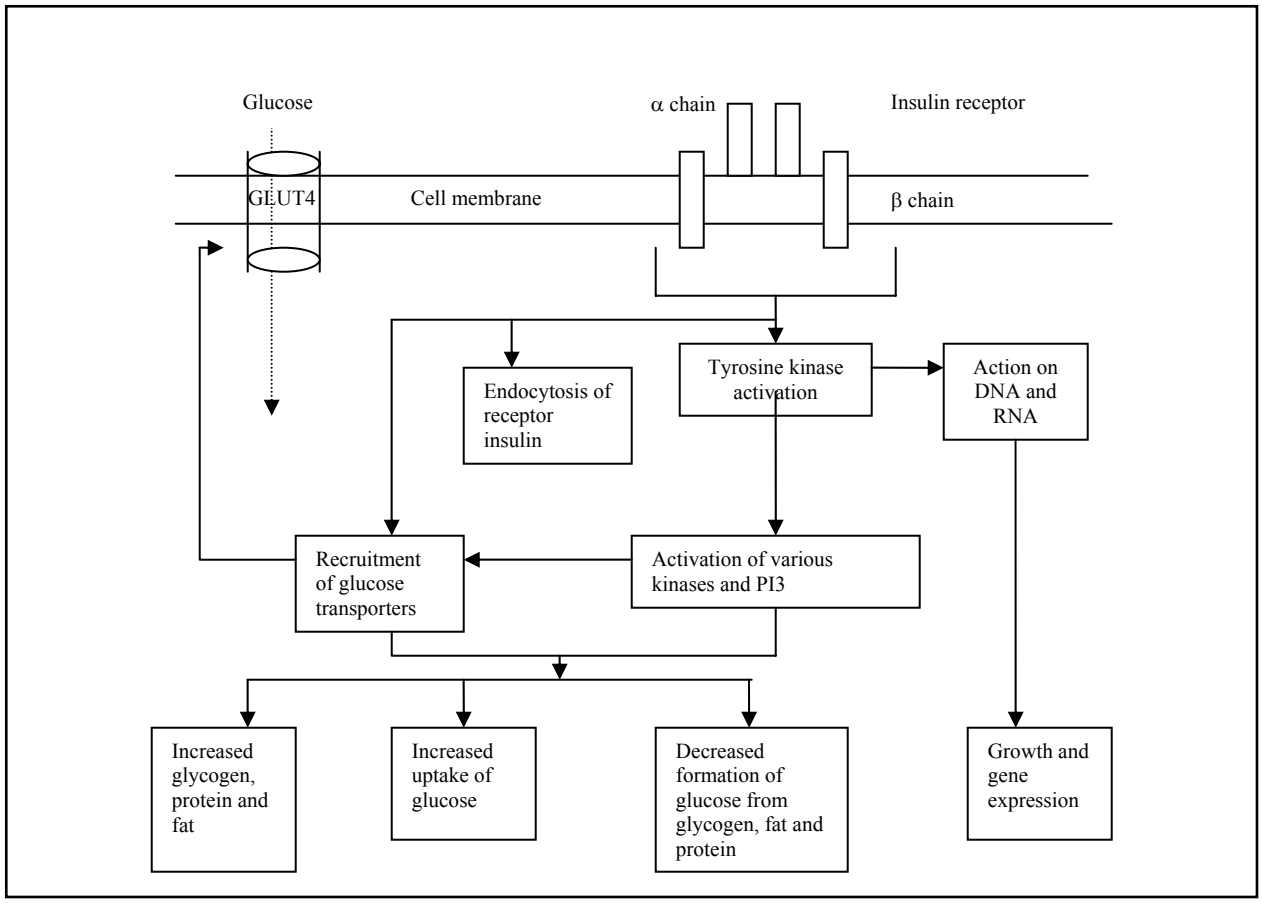

Fig2: Mechanism of Action of Insulin

Cellular Actions

Insulin is an anabolic hormone having main actions on liver, muscle and fat cells. Its chief actions include uptake and storage of glucose, amino acids and fatty acids and inhibition of catabolism.

Effects on carbohydrate metabolism: In liver it inhibits glycogenolysis and gluconeogenesis while stimulating glycogen synthesis. It also increases glycolysis. In muscle it increases the uptake of glucose via GLUT 4 transporter and stimulates glycogen synthesis and glycolysis. In adipose tissue insulin increases glucose uptake by GLUT 4 transporters.

Effects on fat metabolism: It increases fatty acid and triglyceride synthesis in adipose tissue and liver. It inhibits the lipolysis and opposes the lipolytic action of adrenaline, growth hormone and glucagon.

Effect on protein metabolism : It increases the uptake of amino acids into muscle and increases protein synthesis. Insulin inhibits the breakdown of amino acids.

Other effects : It increases the transport of potassium, calcium, nucleosides and phosphate into the cells.

Table 1: Summary of insulin actions

Metabolism	Liver cells	Muscle cells	Adipose cells
Carbohydrate	↑↓Gluconeogenesis ↓ Glycogenolysis ↑ Glycolysis ↑ Glycogenesis	↑ Glucose uptake ↑ Glycolysis ↑ Glycogenesis	↑ Glucose uptake ↑ Glycerol synthesis
Fat	↑ Lipogenesis ↓ Lipolysis	-	↑Synthesis of triglycerides ↑ Fatty acid synthesis ↓ Lipolysis
Protein	↓ Protein breakdown	↑ Amino acid uptake ↑ Protein synthesis	-

Insulin Therapy

Various preparations of insulin can be classified according to their duration of action into rapid, short, intermediate and long acting and by their various species of origin e.g. Human insulin (prepared by DNA recombinant technology), Porcine insulin (differs from human insulin by only one amino acid alanine instead of threonine in position 30 in B chain), and Bovine insulin (differs from human insulin in having alanine and valine in place of theronine and isoleucin in position 8 and 10 in chain A). The initial insulin preparations contained lot of impurities and were replaced by porcine monocomponent insulin having very little impurities. Human insulin and monocomponent insulin are less antigenic, more stable, show less insulin resistance and less lipodystropy but are more expensive.

1. Short and Rapid Acting Insulins

Regular insulin: is soluble crystalline zinc insulin. Its effect sets in 30 min and peaks between 2 and 3 hr and lasts for up to 6-7 hr. It should be injected 30- 45 min before meal. Besides subcutaneous route of administration it can be given intravenously and intramuscularly.

A number of insulin analogue are available which retain their monomeric configuration and hence are more rapidly absorbed. These agents have a fast onset and short duration of action. These short acting agents should be injected 15 minutes before meals as compared to atleast 30 minutes interval for regular insulin. They are absorbed three times faster than human insulin from subcutaneous site. These analogues include:

Insulin Lispro: is produced by recombinant technology, differs from human insulin in two amino acid position at B 28 (**ly**sine) and B29 (**pro**line). This difference makes them less prone to self associate and form dimmers.

Insulin Aspart: differs by amino acid at B 28 (**aspart**ic acid).This reduces the propensity of self association to even less than lispro, though clinically efficacy of both the agents has been found to be similar.

Insulin Glulisine: this also has an amino acid change at B29 by glutamic acid and lysine at B23. It also has a low self association and fast dissociation into monomers characteristics.

2. Intermediate Acting Insulins

Lente insulin (Insulin Zn suspension): lente insulin is a mixture of 30% semilente (insulin with Zn ions in acetate buffer with rapid onset of action) and 70% ultralente (poorly soluble crystalline insulin that has delayed onset and prolonged action). So this combination of two insulins gives relatively rapid onset (1-2 hr) with long duration of action (18-24 hr).

Neutral Protamine Hagedorn or isophane insulin (NPH): combination of protamine and insulin in ratio of 1:10 by weight forming an isophane complex. After injecting the proteolytic enzymes degrade protamine to enable absorption of insulin. It has onset of action and duration of action similar to lente insulin. Neutral protamine insulins containing insulin lispro (NPL) and insulin aspart (NPA) are also available.

3. Long acting insulin

Ultralente (Extended insulin zinc suspension): it has a very slow onset and a prolonged and relatively flat peak of action. It provides low basal concentration through out the day.

Protamine Zn Insulin suspension: is no longer used because of its unpredictable nature.

Insulin Glargine: it is an ultra long acting insulin with peak less action. It is formed by attaching two arginine molecules to the carboxy end of the B chain and substitution of asparagine at the A21 position. It has an acidic pH of 4 and is a clear solution but precipitates out in neutral pH thus slowing the absorption after being injected. It is given as a once daily dose. It should not be mixed with other insulins.

Various preparation of Insulin: see Table 2

Table 2. Various insulin preparations

TYPES OF INSULIN	Onset	Peak	Duration
Rapid-Acting Insulins *These are clear insulin with neural pH and contain small amount of Zn to improve their shelf life.*			
Insulin injection Regular	30- 60 min	2- 4 hr	6-8 hr
Insulin lispro (insulin analog)	5-15 min	within 1 hr	3- 5 hr
Insulin aspart (insulin analog)	10- 20 min	within 1 hr	3-5 hr
Intermediate-Acting Insulins			
Isophane insulin	1—2 hr	6—12 hr	18—24 hr
Insulin zinc suspension	1—2.5 hr	6—12 hr	18—24 hr
Long-Acting Insulins			
Insulin glargine	1-1.5hr	none, maximum effect 4-5 hr	11-24 hr
Extended insulin zinc suspension (Ultralente)	4-8 hr	8—20 hr	24—48 hr

Mixed Insulins			
Isophane insulin suspension + Regular insulin 70/30	30-60 min then 1-2 hr	2-4 hr then 6-12 hr	6-8 hr then 18-24 hr
Isophane insulin suspension+ Regular insulin 50/50	30-60min then 1-2 hr	2-4 hr then 6-12 hr	6-8 hr then 18-24 hr
High-Potency Insulin			
Insulin injection concentrated (Regular 500)			24 hr

Unitage

For all therapeutic purposes doses and concentration of insulin are expressed in units. One unit of insulin is equal to the amount required to reduce the concentration of blood glucose in a fasting rabbit to 45mg/dl. Most commercial preparations of insulin are supplied in solution or suspension at concentration of 100unit/ml, which is 3.6 mg of insulin per ml. It is also available in a more concentrated solution for 500unit/ ml for patients resistant to normal doses.

Mixing Insulins

If the patient is to receive regular insulin and NPH insulin, or regular and lente insulin, the clarification must be taken whether two separate injections are to be given or if the insulins may be mixed in the same syringe. If the two insulins are to be given in the same syringe, the short acting insulin (regular or lispro) is drawn into the syringe first. Although short acting insulin preparation (regular, insulin lispro or insulin aspart) can be mixed with their intermediate acting neutral protamine insulins and are available as prefilled pen devices, lente or ultralente should not be mixed with short acting insulin preparations. Even small amounts of intermediate- or long-acting insulin, if mixed with the short-acting insulin, can bind with the short-acting insulin and delay its onset. Regular insulin is clear, whereas intermediate- and long-acting insulins are cloudy. The clear insulin should be drawn up first. When insulin lispro is mixed with longer-acting insulin, the insulin lispro is drawn up first.

Insulin Dosage and Regimens

In a normal person about 18-40 units of insulin are produced per day, half of this is secreted in response to meals and half in basal state to take care of hepatic output of glucose. There is no fixed dose of insulin. It has to be titrated from patient to patient. The aim therefore is to bring down blood glucose levels to normal and to normalize other metabolic disturbances as seen in diabetes mellitus. The average dose of insulin is generally 0.6-0.7 u/kg/day. The most common route of insulin administration is subcutaneous (s.c), although is can be given intramuscularly (i.m) injection; all short acting insulins can be given intravenously (i.v) but regular insulin is preferred, as it is cheaper. No other preparation can be given i.v. The total dose of insulin can be divided into basal and post prandial requirements. Regular/ lispro insulin is given before meals to take care of post prandial rise in blood glucose concentration while intermediate acting or long acting preparation are given to take care of basal hepatic output of glucose. Portable percutaneous injections are available to facilitate multiple subcutaneous injections of insulin.

They contain premixed NPH and regular insulin in a ratio of 70%/30% and 50%/ 50%; neutral protamine lispro (NPL) / lispro as 75% / 25% and 50 % / 50%; neural protamine aspart (NPA)/ aspart insulin as 70%/ 30%, respectively.

The mixtures of short acting and intermediate or long acting insulin preparations can be given before breakfast and before dinner. These are known as split mixed regimens. Insulin can also be administered by subcutaneous insulin pumps.

Inhalation insulin: This novel formulation of human recombinant insulin, an alternative to injectable form, is supplied as a powder in 1 and 3 mg dose blisters. It was approved for treatment of adult patients with diabetes mellitus for the control of hyperglycemia in Janunary 2006. Insulin inhalation powder differs from regular human insulin by its rapid onset of action (to be administered within 10min before meal). The use of inhalation insulin in patients with underlying lung disease such as asthma and COPD, is not recommended. In smokers, the systemic insulin exposure from inhalational insulin formulation is about 2 to 5 fold higher than in non-smokers. As such inhalation insulin formulation is contraindicated in patients who smoke or who have discontinued smoking fewer than 6 months prior to initiating therapy. The most commonly reported adverse events reported with insulin powder include hypoglycemia, chest pain, dry mouth, otitis media and respiratory events (cough, dyspnea, pharyngitis, increased sputum epistaxis, decreased pulmonary function).

A 1 mg blister of inhalable insulin is approximately equivalent to 3 IU of s.c. injected regular human insulin. A 3 mg blister of inhalable insulin is approximately equivalent to 8 IU of s.c. injected regular human insulin.

Indication for the use of insulin

(i). All patients with type I diabetes mellitus.

(ii). Patients of type 2 diabetes mellitus who fail to respond to intervention of diet, exercise and or oral antidiabetic agents.

(iii). Patients who develop diabetes mellitus during pregnancy (gestational diabetes) or after surgical removal of pancreas.

(iv). In the treatment of severe form of diabetes mellitus including diabetes ketoacidosis and hyperglycemic non ketotic diabetic coma.

(v). Insulin is also used in combination with glucose to treat hypokalemia, as insulin produces a shift of potassium from the blood into the cells.

Diabetic ketoacidosis (DKA) and Nonketotic hperosmolar state (NKHS)

These are acute complications of diabetes. DKA is primarily seen in patients of type I diabetes and NKHS is seen in patients of type 2 diabetes mellitus. Both of these complications are associated with absolute or relative insulin deficiency, volume depletion and altered sensorial.

DKA is associated with various clinical and laboratory changes. Nausea and vomiting are two prominent symptoms. Others include acetone breath, altered rhythm of respiration, lethargy and coma. DKA results due to insulin deficiency and relative increase of hormone like glucagon,

catchecolamine, cortisol and growth hormone. Therefore there is increase in glucose production from liver and impaired uptake of this increased glucose in to muscle due to deficient insulin. Ketone body production is increased due to increased rate of lipolysis from the adipocytes and liver producing ketones from the fatty acids. Management of patients of DKA includes intravenous rehydration, insulin and monitoring of various metabolic and electrolyte abnormalities. The insulin preparation of choice is regular insulin which can be administered in a dose of 0.1- 0.2U /kg i.v followed by infusion of insulin at the rate of 0.1U / kg/hr till blood glucose level comes down to 300mg/dl. To correct dehydration 0.9% saline is infused till condition of patient is stabilized. This is followed by infusion of 1/2N saline. Once blood glucose falls to 300mg/dl, 5% dextrose is added to the intravenous fluids. To correct the hypokalemia and acidosis, potassium chloride and sodium bicarbonate, respectively can be added to intravenous fluid. An antibiotic may be required to treat infection.

Adverse reactions to insulin

Hypoglycemia: may result from a delay in taking meal, unaccustomed physical exercise (exercise increases the uptake of glucose without insulin) or by mistake a larger dose of insulin has been given. If mild, it can be treated by taking glucose orally. However, if severe it may require intravenous administration of glucose or glucagon injection in a dose of 1 mg subcutaneously or intravenously.

Insulin allergy: it is an intermediate type of hypersensitivity reaction leading to local or systemic urticaria. It is less likely to occur with monocomponent or human insulin preparation.

Insulin resistance: If insulin requirement is more than 200 units/day, insulin resistance is said to have developed. It may be:

Acute: It develops rapidly and could be precipitated by infection, trauma, stress, use of steroids etc. Treatment involves treating the precipitating cause and administration of higher dose of insulin.

Chronic: It is generally due to formation of antibodies and can be managed by changing to monocomponent or human insulin.

Lipoatrophy and lipohypertrophy: lipoatrophy of subcutaneous fatty tissue occurs at the site of injection. It is due to local immunological reaction and not seen with monocomponent or human insulin. Incidence of lipoatrophy or hypertrophy can be minimised by changing the site of injection frequently.

Insulin edema: there may be short lasting dependent edema

Drug interaction with glucose metabolism and insulin

Alcohol can enhance hypoglycemia by inhibiting the production of glucose (gluconeogenesis) from liver. Oral antidiabetic drugs can exacerbate insulin induced hypoglycemia. Adrenergic receptor blocking drugs lead to increased risk of hypoglycemia as they inhibit the effect of catecholamines on glycogenolysis and gluconeogenesis. They inhibit the release of insulin from pancreas. They can also mask the signs of hypoglycemia by inhibiting the expression of increase sympathetic activity. Pentamidine initially increases release of insulin from pancreatic cell and then later causes diabetes by destroying these cells. Salicylates lead to hypoglycemia by

enhancing insulin secretion and peripheral utilization of glucose. They have been shown to inhibit I-kappa-kinase B in high doses (4-6gms). Besides these agents angiotensin-converting enzyme inhibitors, lithium, sulphonamides, Ca^{2+} ions can also produce hypoglycemia and enhance insulin action while glucocorticoids, diuretics, diazoxide, phenytoin, Ca^{2+} channel blockers and clonidine can cause hyperglycemia and antagonize insulin action.

New Molecules

Exenatide: Exenatide is the first in a new class of synthetic molecules known as incretin mimetics. Exenatide possess similar activity to the naturally occurring hormone GLP-1, which when released in response to food binds to its receptors on pancreatic beta cells and releases insulin. It has also been shown to slow gastric emptying, inhibits production of glucose by the liver and appears to suppress appetite and helps weight loss. The FDA in 2005 approved exenatide as an adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycaemic control. Its principal drawback includes need to be injected and nausea on use.

Pramlintide (Islet Amyloid Polypeptide analogue): Pramlintide is a synthetic analog of human amylin, a naturally occurring hormone that is made in the beta cells of the pancreas. Amylin and insulin work together with glucagon, to maintain normal glucose concentrations. Pramlintide acts as an amylinomimetic agent, has the following effects: 1) slowing of gastric emptying; 2) prevention of the postprandial rise in plasma glucagon; and 3) satiety leading to decreased caloric intake and potential weight loss. Clinical studies demonstrate that pramlintide, a self-administered injection given prior to meals, helps patients achieve lower blood glucose (sugar) after meals, leading to less fluctuation during the day, and better long-term glucose control as compared to patients taking insulin alone. On an average, patients in these studies used less mealtime insulin and also had a reduction in body weight compared to patients taking insulin alone.

Pramlintide injection was approved in 2005 for the following indication:

1. Type 2 diabetes, as an adjunct treatment in patients who use meal time insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.

2. Type 1 diabetes, as an adjunct treatment in patients who use meal time insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.

Pramlintide is not intended for all patients with diabetes. It is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. Other adverse effects include GI disturbances and nausea, which disappear over time as the doses are titrated.

Oral Antidiabetic Drugs

1.Insulin Sectretagogues :

- Sulfonylureas,
- Meglitinides, D-Phenylalanine Derivatives

2.Biguanides

3.Thiazolidinediones

4. ά Glucosidase Inhibiotrs

Sulfonylureas

They are sulfonamide derivatives and are divided into first and second generation sulfonylureas. First generation comprises of tolbutamide, acetohexamide, tolazamide and chlorpropamide. The second group, which are also more potent include glibenclamide (glyburide), glipizide, gliclazide and glimepride.

Table 1. Pharmacokinetic of oral hypoglycemics

First generation (Relative potency)	Tolbutamide (1)	Chlorpropamide (6)	Tolazamide (3)	Acetohexamide (2.5)
Absorption	Well absorbed	Well absorbed	Slowly absorbed	Well absorbed
Distribution Metabolism	Metabolized in liver, short half life 4-5hr. Metabolites less active than parent compound Safe in elderly	Metabolized in liver, half life of 32-40 hr It increases release of ADH and leads to water retention and hyponatremia	Slow onset, half life of 5-7 hr	Short t 1/2 but active metabolites which have 2.5times activity, half life 4-7 hr
Duration of action	6-12 hr	50- 60 hr	10-14 hr	10-14 hr
Excretion	Metabolites excreted renally	20-30% excreted unchanged in urine	Metabolites excreted renally	Metabolites excreted in urine

Second generation	Glibenclamide (150)	Glipizide (75-150)	Glimepiride (350)
Metabolism	Metabolized by liver, Short half life of 4-6 hr, active metabolite with low hypoglycemic activity	Short half life of 2-4 hr, inactive metabolites	Metabolized by liver, short half life of 5-8hr, but substantially excreted in bile
Duration of action	Slow hypoglycemic activity 10-24 hr; give once daily	Fast acting 10- 24 hr; given once daily	Approved for once daily use , and use in renal dysfunction 12-24 hr
Contraindication	Type1 diabetes, advance liver and renal dysfunction (except glimepiride), sulfa drug allergy		

Mechanism of Action: They cause hypoglycemia by stimulating insulin release from pancreatic beta cells by binding to the ATP sensitive K^+ channel and inhibiting it. Reduced K^+ conductance lead to membrane depolarization which allows Ca^{2+} to enter the cell and then insulin is released. They also decrease the hepatic clearance of insulin whereby increasing insulin level in the body. They also stimulate the secretion of somatostatin and suppress glucagon. They also have extra pancreatic actions.

Adsorption, Fate and Excretion : All sulfonylureas are well absorbed from the gastrointestinal tract. Food and hyperglycemia may retard their absorption. They are largely bound to plasma protein (90-99%). They are metabolized mainly in liver; some metabolites are active and then excreted in urine. Hence they should be used cautiously in patients in hepatic and renal dysfunction.

Adverse Effects : First generation sulfonylureas produce more side effect then the second generation drugs. First generation have high tendency to cause hypoglycemia in patients. This is higher in elderly patient with renal and hepatic insufficiency and on taking a longer acting sulfonylurea like chorpropamide. Many drugs potentiate the effect of sulfonylureas by inhibiting their metabolism and excretion. Some also displace them from protein binding and transiently increase their free concentration e.g sulfonamide, clofibrate, salicylates, etc. Other side effects include nausea and vomiting, cholestatic jaundice, agranulocytosis, aplastic and hemolytic anemia, generalized hypersensitivity reactions and dermatological reactions. Disulfiram like reaction can develop with chlorpropamide which can also cause water retention and dilutional hyponatremia. All sulfonylureas are contraindicated in type 1 diabetes, advance liver and kidney disease and sulfa drug allergy. Glimepiride may however be used in patients of renal dysfunction as it is excreted in bile.

Meglitinides

These are benzoic acid derivatives and unrelated to sulfonylureas. Repaglinide is the drug of this class. But like sulfonylureas, repaglinide increases insulin secretion by inhibiting ATP dependent K^+ channels in pancreatic cells. It is rapidly absorbed from the intestines and has a fast onset of action. Peak effect comes within 1 hr and duration of action is 5-8 hr. Because of this it is mainly used to control post prandial rise in blood glucose concentration. It is metabolized by hepatic CYP3A4 and renal tissue. Therefore needs caution in patients with hepatic and renal insufficiency.

D-Phenylalanine Derivatives

Nateglinide is a D-phenylalanine derivative and is effective orally. Like sulfonylureas and repaglinide, nateglinide stimulates insulin secretion by inhibiting ATP sensitive K^+ channels in pancreatic cells. Nateglinide is primarily metabolized in liver by CYP 2C9, 3A4 system and therefore dose adjustment is needed in patients with hepatic insufficiency. No dosage adjustment is needed in renal failure.

Therapeutically nateglinide is primarily used for controlling postprandial hyperglycemia in patients of type 2 diabetes mellitus and it produce even fewer episodes of hypoglycemia than other secretagogues as its ability to release insulin is markedly decreased in presence of normoglycemia.

Biguanides
Metformin and phenformin are the two biguanides used for treating hyperglycemia. Phenformin was withdrawn in 1970s for its association with lactic acidosis.

Mechanism of Action: Metformin is an antihyperglycemic agent and does not cause hypoglycemia as it does not lead to release of insulin. It also has no significant effect on other counter regulatory hormones like glucagon and cortisol or somatostatin. It primarily causes decrease in hepatic glucose production (↓ gluconeogenesis) and increasing insulin action in muscle and fat. These actions are mediate by activation of cellular kinase, AMP-activated protein kinase. It may also decrease uptake of glucose from small intestines.

Absorption, Fate and Excretion: Drug is primarily absorbed from small intestines. It does not bind to plasma proteins and excreted unchanged in urine.

Adverse Effect: Patients with renal and hepatic dysfunction, history of lactic acidosis , cardiac failure, chronic hypoxic lung disorder should not be given metformin because of increased risk of lactic acidosis. Acute side effects that can occur with metformin include diarrhea, abdominal pain, nausea , metallic taste, and anorexia. Intestinal absorption of B12 and folate is decreased with chronic metformin therapy.

Therapeutic status of oral anti diabetic agents: These drugs are used in patients with type 2 diabetes who have some residual pancreatic cell function, who cannot achieve euglycemia by non pharmacological interventions like regulation of diet and exercise alone. They are used in patients whose age is above 40 yr at the onset of the disease, duration of disease is less than 5 yr, and fasting blood glucose concentration is less than 200mg/dl. Patients should be slightly obese. However, biguanides are preferred in very obese patients as they cause loss of weight. These agents can be used effectively in 80% of the properly selected patients. All sulfonylureas are metabolized in liver and eliminated renally. So dose must be adjusted in patients with hepatic and renal dysfunction. Risk of hypoglycemia is higher with long acting first generation sulfonylureas such as chlorpropamide, so use in elderly is not preferred. Long acting second generation sulfonylureas like glimepiride causes hypoglycemia in only 2-4% of patients as compared to glyburide and glipizide (15-19%). Risk of drug-drug interaction is also higher with first generation sulfonylureas especially in elderly patients on polypharmacy.

Secretagogues like nateglinide and repaglinide are short acting (1 to 1.5 hr) agent with rapid onset of action (0.5 – 1 hr). Repaglinide is mainly metabolized by liver and eliminated in bile. It is useful in patients with renal dysfunction as no dose modification is required. No improvement in efficacy is seen in patients given combination of sulfonylureas and other secretagogues.

Thiazolidinediones
They are clofibrate derivatives which include troglitazone, pioglitazone, ciglitazone and rosiglitazone. Troglitazone was withdrawn from the market due to hepatoxicity.

Mechanism of Action: Thiazolidinediones are selective agonist for nuclear peroxisomal proliferator activated receptor-γ (PPAR- γ)These drugs binds to PPAR- γ, which activates genes that regulate carbohydrate and fat metabolism. They require insulin to be present for their action as they principally increase insulin sensitivity. They also may decrease glucose production by

liver. They increase the uptake of glucose into muscle and fat by increasing the expression of specific transporters. Affinity for pioglitazone for PPAR- γ is 10-15 fold and rosiglitazone has 100 - 200 times more affinity, as compared to troglitazone. Long term side effects include mixed effect on the lipid profile.

Absorption, Fate and Excretion: Given in a once a day dose these agent are absorbed within 2 hours but it takes week for their effect to set in. They are highly protein bound and metabolized in liver by the CYP enzyme system. Pioglitazone is metabolized predominantly by CYP3A4and rosiglitazone by CYP2C8 enzyme system

Adverse Effect : No case of hepatic failure has been reported with pioglitazone and rosiglitazone. But most frequent adverse event reported with both these agents include weight gain, fluid retention and edema. Other adverse events also reported but of lower frequency include upper respiratory tract infection, sinusitis and headache.

Long term use of these agents has been associated with development of cancer in various tissues in animal models and such possibility has not been ruled out in human.

ά-Glucosidase Inhibiotrs (acarbose, miglitol)

ά-glucosidase enzyme is responsible for breaking down complex oligosaccharide into simple monomer. It is located on the brush border of intestinal cells. These monomeric units like glucose and fructose are absorbed. By inhibiting this enzyme the absorption of glucose into blood stream is decreased. Acarbose and miglitol are competitive inhibitors of this enzyme and reduce post postprandial rise of glucose. Miglitol is 6 times more potent than acarbose. They are approved for both mono and combination therapy.

Adverse Effects: Prominent adverse events include flatulence, diarrhea and abdominal pain, which results from undigested carbohydrate in the intestines.

New Molecules

Sitagliptin phosphate : It is an orally active dipeptidyl peptidase-4 (DPP-4) inhibitor available for the treatment of type 2 diabetes. Sitagliptin phosphate has been approved as monotherapy and as an add-on therapy to either of two other types of oral anti diabetic medications, metformin or thiazolidinediones, to improve blood glucose control in patients with type 2 diabetes when diet regulation and exercise are not enough. Sitagliptin enhances a natural body system called the incretin system, which helps to regulate glucose by affecting the beta cells and alpha cells in the pancreas. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), are released by the intestine through out the day. However, their levels are increased in response to meals. By inhibiting the DPP-4 enzyme, sitagliptin significantly increases the levels of active incretin hormones leading to increase in the synthesis and release of insulin from the pancreatic beta cells and decreasing the release of glucagon from the pancreatic alpha cells.

Sitagliptin is well absorbed from the gastrointestinal tract with no interaction with food. It is eliminated by kidneys. The recommended dose is 100mg once daily. No dosage adjustment is needed for patients with mild to moderate hepatic insufficiency or in patients with mild renal insufficiency. Its safety in pediatric age group and nursing mothers has not been established.

Glucagon

Glucagon is a single chain polypeptide containing 29 amino acids. It is synthesized in the cells of the islet of Langerhans from preproglucagon. It plays an important role in the regulation of glucose and ketone body metabolism.

The major regulators of glucagon secretion include dietary glucose, insulin, amino acids, and fatty acid. Glucose and fatty acids inhibit glucagon secretion while amino acids stimulate its release. Glucose and amino acids are more effective in modulating glucagon secretion when taken orally indicating a role of some gastrointestinal hormone in this effect. Somatostatin also inhibits glucagon secretion. Glucagon is mainly metabolized in the liver, kidney, plasma and its site of action. It has a short half life of only 3 to 6 minutes.

Glucagon receptors are present on the plasma membrane of target cells. It is a G protein coupled receptor linked to adenyl cyclase. It exhibits a stimulatory effect on adenyl cyclase leading to increased production of cyclic AMP. Glucagon enhances glycogenolysis and inhibits glycogen synthesis leading to hyperglycemia. At higher concentration it increases lipolysis in adipose tissue, increases the force of cardiac contraction and relaxes gastrointestinal tract.

Therapeutic Uses: Clinically used glucagon is obtained from bovine and porcine pancreas.
(i). Its main use is in the treatment of severe hypoglycemia. It is given in a dose of 1 mg intravenously or intramuscularly. Once hepatic stores of glycogen are depleted, glucagon will be ineffective. Hence it should be administered as early as possible.

(ii). Because of its relaxant effect on the gastrointestinal(GI) tract it is used for radiographic examination of upper and lower GI tract in barium and retrograde iliography; MRI of GI tract; for treatment of spasm associated with acute diverticulitis and sphincter of Oddi; impaction of oesophagus and intussusceptions and to distinguish obstructive and hepatocellular jaundice.

(iii). It has been used for diagnoses of pheochromocytoma since it causes release of catecholamines from pheochromocytoma.

(iv). As a cardiac stimulant for the treatment of shock. It is less likely to produce arrhythmias as compared to sympathomimetic agents.

Suggested Reading

1. Triplett CL, Reasner CA, Isley WL. Diabetes Mellitus. In : Dipiro JT, Tolbert RL, Yee GC, Mateke GR, Welf BG, Posey LM, editors. Pharmacotherapy. 6ed, New York: Mcgraw Hill 2005.p. 1333-67.
2. Nichols WK. The Pancreatic hormone. In: Gennara AR, editor. Remington: The science and Practice of Pharmacy Volume II 20th ed, Maryland: Lippincott William & Willikins 2000. p. 1370-78.
3. Cheatham B, Kahn CR. Insulin action and the insulin signaling network. Endocr Rev 1995; 16: 117-42.
4. Ebert R, Creutzfedt W. Gastrointestinal peptide and insulin secretion. Diabetes Metab Rev 1987; 3: 1 -26.
5. Davis SN. Insulin, oral hypoglycemic agents, glucagon and the pharmacotherapy of exocrine pancreas. In: Bronton LL, Lazo JS, Parker KL. Goodman and Gillman's The Pharmacological Basic of Therapeutics 11thed. NewYork: McGraw Hill 2006.p.1613-45.
6. http://www.fda.gov/cder/foi/label/2005/021332lbl.pdf (accessed on 3 Dec 2006)
7. http://www.fda.gov/cder/foi/label/2005/021773lbl.pdf (accessed on 3 Dec 2006)
8. http://www.fda.gov/cder/foi/label/2006/021868lbl.pdf (accessed on 3 Dec 2006)