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Diabetes Mellitus

Introduction-Pathophysiology-Treatment

"**Solution-Pharmacy"** always try to make a notes on all those topics which are equally important to social life and for student's examination point of view. To make an effective notes we take reference of many standard books and online sources, and then after having idea we make our own diagram by converting theory into either flowchart or images. Solution believes that images and videos are powerful tools to make a concept clear and it became easy for anyone to memorize it or visualise it.

Introduction

In the current scenario life style has been changed, and so the disease/disorder occurring rate has been also changed accordingly. Diabetes is one of those disorder that is associated with life style (Except family history) Diabetes is a condition in which our body cell fails to utilize the sugar from circulating blood and thus it is not available for the use by cells and hence the level of sugar (Glucose) increase in blood and this is called blood sugar. This looks so simple in a first look but it's that much easy and simple way for occurrence of diabetes. There are many causes for diabetes and that may be associated with various backgrounds. As we have stated earlier that this is due to inability of body to utilize the available glucose from blood so it is classified as a metabolic disorder. (Refer Solution's 200 definition notes) glucose level is also written as- glycemia and if the level of glucose increase from normal level it is called- Hyper + glycaemia. The abnormal range is when the fasting plasma glucose level is more than 200 mg/dL or 200 mg/dL 2 hours after 75 grams oral glucose intake.

Types of Diabetes mellitus

Type 1 (Insulin dependent) or juvenile onset- Lets understand the type 1 diabetes, it is also known as- insulin dependent diabetes. Insulin dependent = a person is dependent on external insulin to metabolize the glucose of his/her body to make the level of glucose normal. In this type of diabetes there is destruction of Beta cell in pancreatic islet. As insulin is secreted from Beta cell of pancreas, it is logical that there will be no more secretion of insulin if this beta cell get destroyed due to any reason, so that particular person will have to arrange the insulin from any external sources, here oral hypoglycaemic drugs will not work because there is insensitivity of Beta cell for that drug as they are destructed. The main cause of this type of diabetes is autoimmunity, when antibody of our body destroy Beta cell by confusion, this result in type 1 diabetes, if the cause is antigen

than this cause is termed as- type 1A and if there is no Beta cell antibody that is called type 1B.

Note- This type of diabetes is less common and generally not associated with genetic transmission.

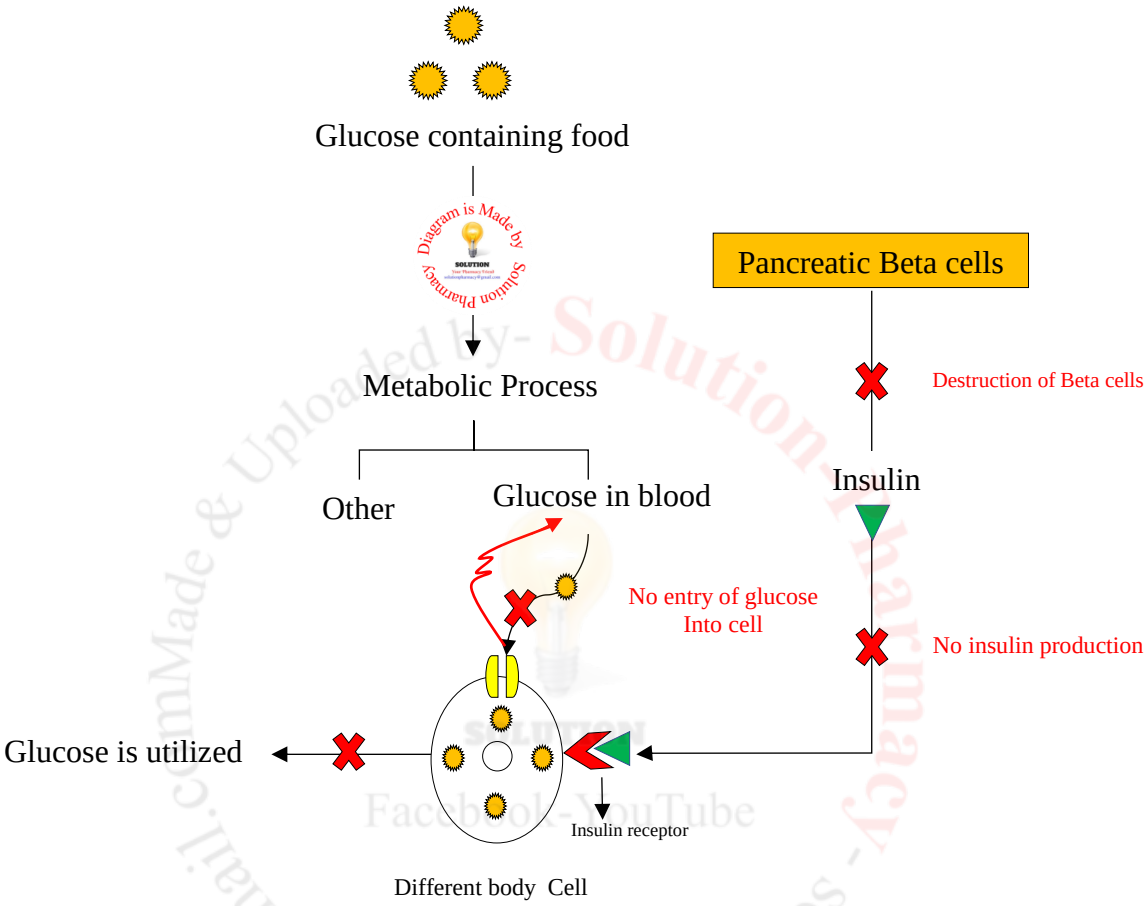
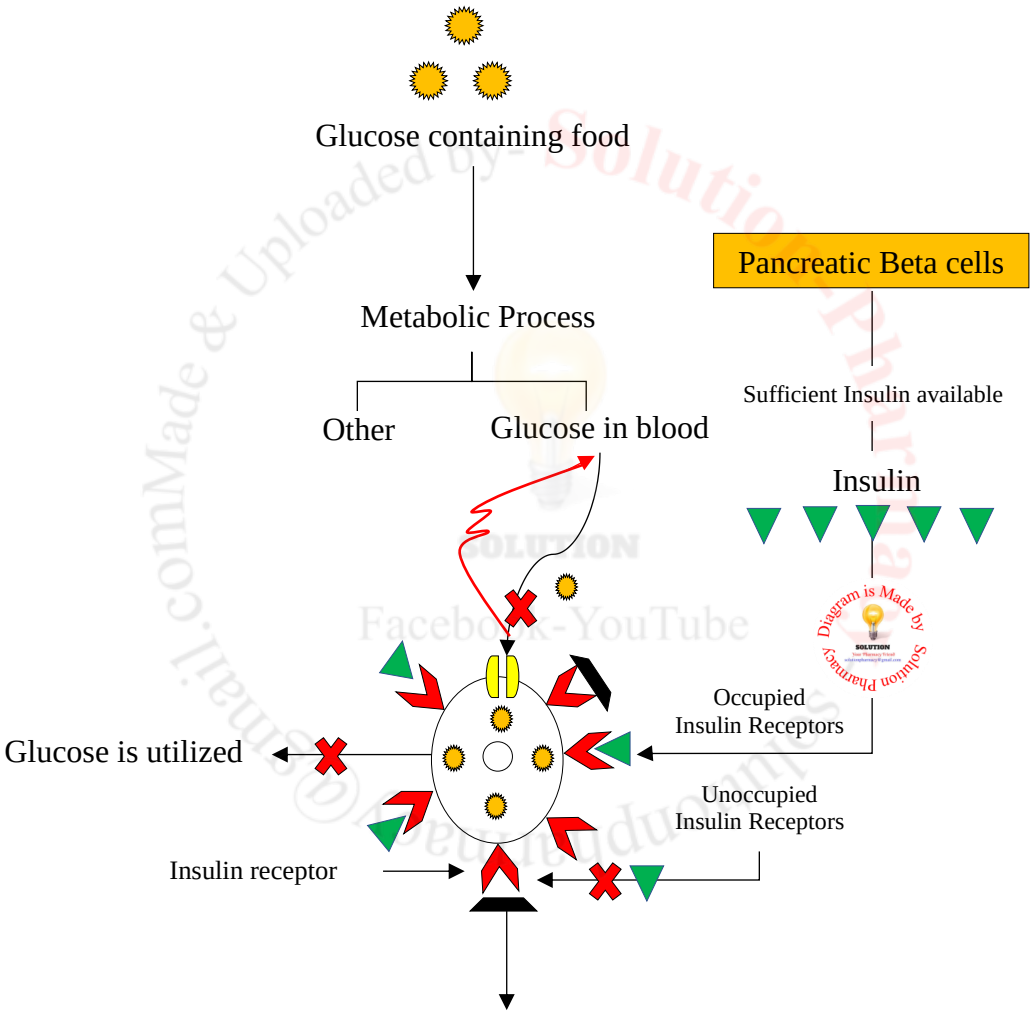


Diagram- A possible pathophysiology of Type- I (Insulin dependent) * Made by- Solution-Pharmacy

Cause of type 1 diabetes- In our body a normal and constant level of insulin is being secreted and it increase when any individual take a meal, this demand of insulin is increased and then fulfilled by beta cell of pancreases, this control the lipolysis, proteolysis, and glycogenolysis. However in the case of type 1 diabetes there is no functional beta cell and that person is not able to maintain the basal level of insulin nor respond to circulating fuels. The development and progression of neuropathy, nephropathy and retinopathy are directly related with the extend of glycaemic control.

Type 2 diabetes (Non-insulin dependent)- this type of diabetes is also known as maturity onset diabetes mellitus. In this type person is not dependent on external source of insulin to control his/her blood glucose level, although there is either low level of insulin in his blood or there is any type of resistance in insulin

receptor, that's why the glucose is not properly metabolized and then he has to take such medicine which will either increase the secretion of insulin or will reduce the resistance in insulin binding with its respective receptors. In this type there is no loss or only small reduction in beta cells, although insulin circulation level is little low, normal or even high, there is also no anti beta cell antibody. This type of diabetes have very powerful chances to carry forward to the next generation or may show family history episode. About 90% of the people have this type of diabetes.



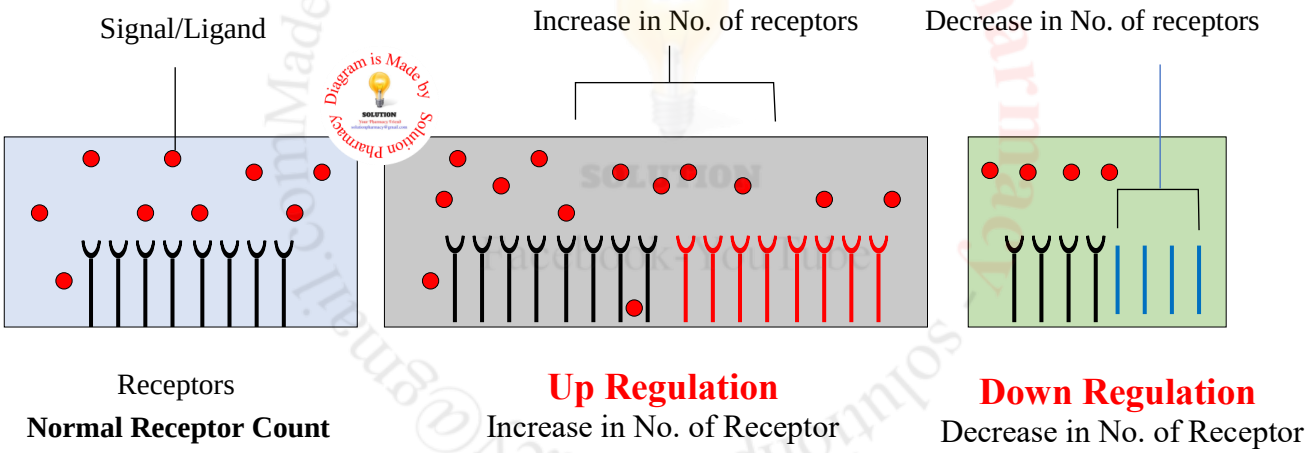
That's why insulins are not able to bind in receptors and glucose is not entering into cell

Diagram- A possible pathophysiology of Type- II * Made by- Solution-Pharmacy

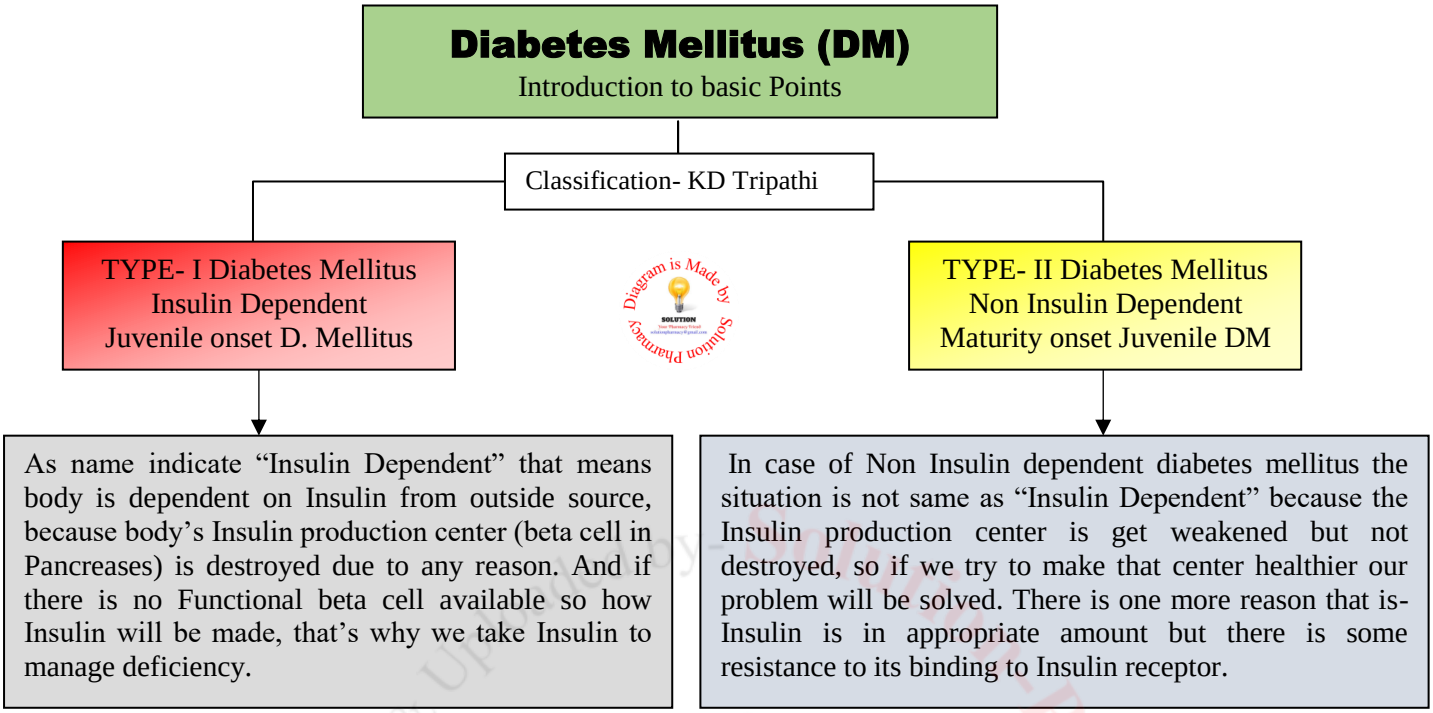
Causes of type 2 diabetes- There are few important causes of type 2 diabetes-

1. This type of diabetes is just because of improper secretion of insulin from beta cell so that they are not properly responsive to small amount of glucose entry, they only response when there is high amount of glucose in blood.
2. **Reduction in the sensitivity of peripheral tissue for insulin**. Reduction in insulin receptor as we have tried to explain in above diagram, the reduction in number of receptor is called down regulation. It is basically seen in hyperlipidaemic people.
3. Excess of hyperglycaemic hormone like **glucagon** and obesity which cause **insulin deficiency** because they counter the action of each other. Hyper glucagon means high glucose and less insulin efficiency. Most of the patients insulin resistance and beta cell deficiency both result into type 2 diabetes which is modulated by genetic and environmental factors.

Downregulation- An example of downregulation is the cellular decrease in the number of receptors to a molecule, such as a hormone or neurotransmitter which reduces the cell's sensitivity to the molecule. This is an example of a locally acting (negative feedback) mechanism



Upregulation-An example of upregulation is the response of liver cells exposed to such xenobiotic molecules as dioxin In this situation, the cells increase their production of cytochrome P450 enzymes which in turn increases their degradation of these molecules



Basic comparative study of Type 1 and type 2 Diabetes

Profile	Insulin Dependent	Non-Insulin Dependent
Insulin production	Body is not in condition to make sufficient Insulin	Body can make sufficient Insulin
Status of Beta cell	Destruction of Beta cell	No loss or Destruction of Beta cell
Cause	Autoimmune disorder	(1) Abnormality of glucose-receptor (2) Reduced sensitivity of peripheral tissue for Insulin (3) Excess of hyperglycemic hormones
Treatment	Insulin from external sources	Oral hypo glycemic Drugs

Common sign and symptoms of diabetes mellitus

1. Polyphagia- Feeling of excessive hunger
2. Polydipsia- Excessive thrust
3. Polyurea- Excessive urine excretion
4. Blurred vision- Accumulation of glucose particles in eye side*
5. Fatigue- Due to excretion of glucose and its unviability due to receptor unavailability of lack of insulin secretion.
6. Increase time for wound healing
7. Lack of interest in physical activity and unusual weight loss
8. Sign- gathering of ants around urine excretion site
9. Possibility to occur glaucoma
10. Frequent infection, such as gums or skin infection

Risk factor	Complication
Weight (Obesity)	Cardiovascular disease
Physical inactivity	Nerve damage
Family history	Kidney damage
Race	Eye damage
Age	Foot damage
Gestational diabetes	Skin complications
Polycystic disease	Hearing impairment
High blood pressure	Alzimer disease
Abnormal cholesterol & triglyceride	Depression
Heavy consumption of cafeteria diet	Irritability

Important points about Insulin (KD Tripathi- 8th Edition)

1. Insulin is secreted by beta cell of pancreas islet cells as a single chain peptide preproinsulin, from which 24 AAs are first removed to form proinsulin.
2. It was discovered in 1921 by Banting and best
3. It was first obtained in crystalline form in 1926 and chemical structure was worked out in 1956 by Sanger.
4. Insulin is two chain polypeptide with 51 amino acids. Molecular weight is about 6000
5. The A chain of insulin is having 21 and B chain is having 30 amino acids
6. The A and B chain are bound together with 02 disulphide bonds.
7. There is a minor difference in human, pork and beef insulin, hence pork insulin is more homologues to human insulin.
8. Assay of insulin is done by measuring blood sugar depression in rabbits or by potency to induce hypoglycaemic convulsion in mice.

9. 1mg of international standard of insulin is equal to- 28 units.
10. Plasma insulin can be measured by the radioimmunoassay or enzyme immunoassay.
11. Under basal condition about 1U insulin is secreted per hour by human pancreas.
12. Secretion of insulin is regulated by- chemical, hormonal and neural mechanism.
13. Other nutrient other than glucose which may evoke or initiate insulin secretions are- amino acids, fatty acids, and ketone bodies.
14. A number of hormones- GH, corticosteroids, thyroxin modify insulin release.
15. Pancreas have 03 cells- Alpha, Delta and Beta. Their percentage is 25%, 5-10% and remaining is for beta cells respectively.
16. Glucagon evoke the release of insulin as well as of somatostatins.
17. Insulin inhibit glucagon secretion
18. Amylin inhibit the release of glucagon through central site of action of brain.
19. Adrenergic alpha$_2$ receptor activation decrease insulin secretion.
20. Adrenergic Beta$_2$ stimulation increase insulin release.

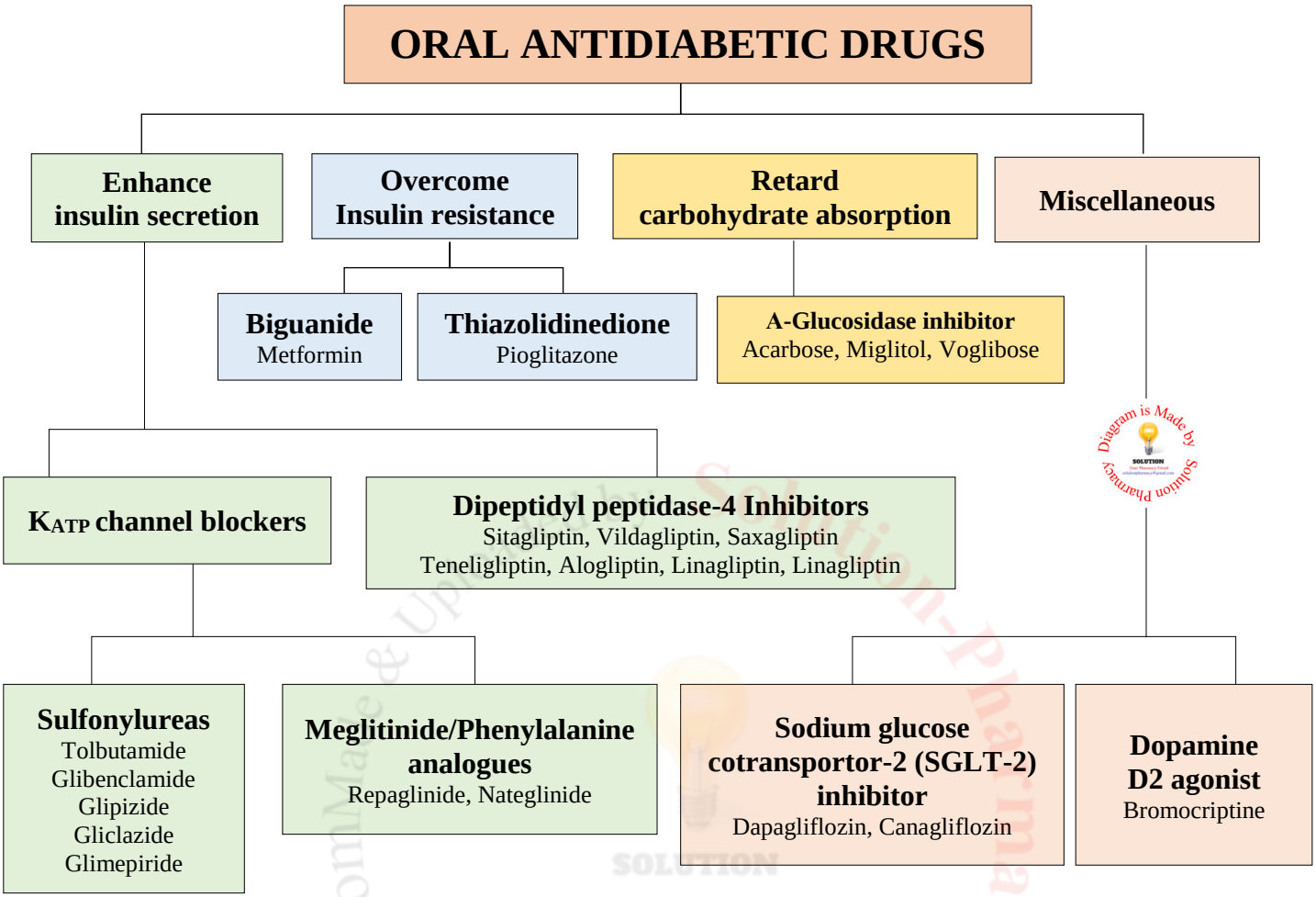
Types of insulin preparations-

1. **Regular (Soluble Insulin)** – it is buffered neutral pH solution of unmodified insulin stabilized by small amount of zinc. Peak action is produced only after 2-3 hours and action continues up to 6-8 hours.
2. **Lente insulin (Insulin-Zinc suspension)** it has 02 main types- (1) with large particles is crystalline and practically insoluble in water (Ultralente) it is long acting and (2) smaller particles and amorphous (Semilente) is short acting. There 7:3 ratio is called "Lente insulin" and it is intermediate acting.
3. **Isophane (Neutral protamine Hagedorn insulin)-** Protamine is added in a quantity just enough to complex all insulin molecule.
4. **Human insulin-** It was prepared in 1980, it has same amino acid sequence as of human. This was produced by the recombinant DNA technology using ***E-Coli***. Proinsulin recombinant bacterial (prb) and in yeast-precursor yeast recombinant (pyr) or by enzymatic modification of porcine insulin (emp)

Drug interaction with insulin

1. Beta adrenergic blocker prolong hypoglycaemia by inhibiting compensatory mechanism .
2. Thiazide, furosemide, corticosteroids, oral contraceptives, salbutamol, nifedipine tends to rise blood sugar and reduce effectiveness of insulin.
3. Acute ingestion of alcohol can precipitate hypoglycaemia by depleting hepatic glycogen.
4. Lithium, high dose aspirin and theophylline may also accumulate hypoglycaemia by enhancing insulin secretion.

Classification- KD Tripathi

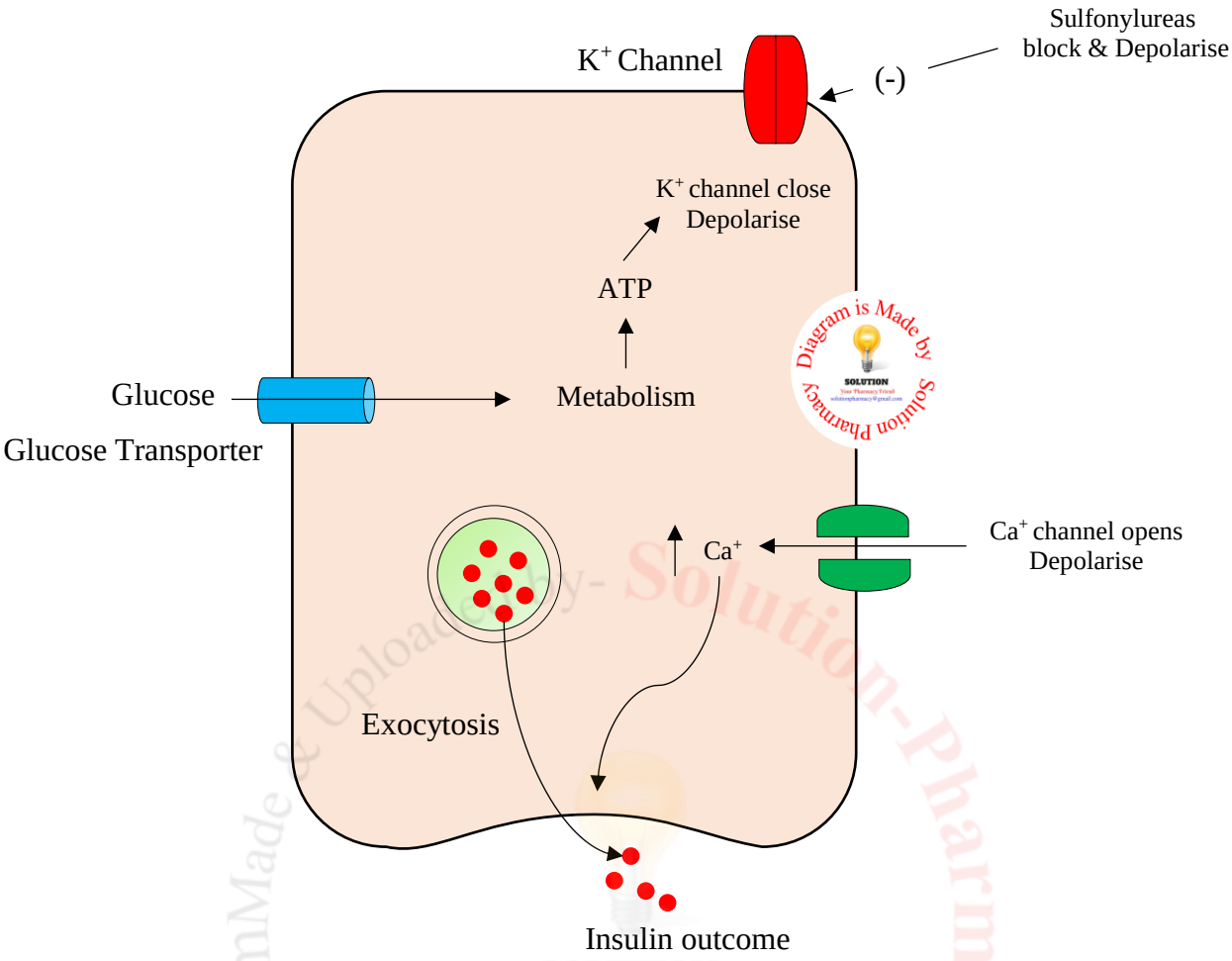


Sulfonylureas-

These are the examples of insulin secretagogues, because they promote insulin secretion from beta cells.

Mechanism of action- the mechanism of action of Sulfonylureas has been converted into following points, so that this may be easy to memorise (Ref- Lippincott, 5th Ed. 307 & KD Tripathi 8th Ed.294)

1. Sulfonylureas bind to a specific "Sulfonylureas receptors" located on the pancreatic beta cells membrane and evoke a brisk release of insulin.
2. Stimulation of insulin release from the beta cell of pancreas by blocking the ATP sensitive K^+ channels, which result into a depolarization and Ca^+ influx.
3. Reduction in hepatic glucose production
4. Increase in the peripheral insulin sensitivity
5. After the few months of administration, the illuminance action of Sulfonylureas decline probably due to down regulation of sulfonylureas receptors on beta cell, but important in glucose tolerance is maintained.



Mechanism of action of Sulfonylureas

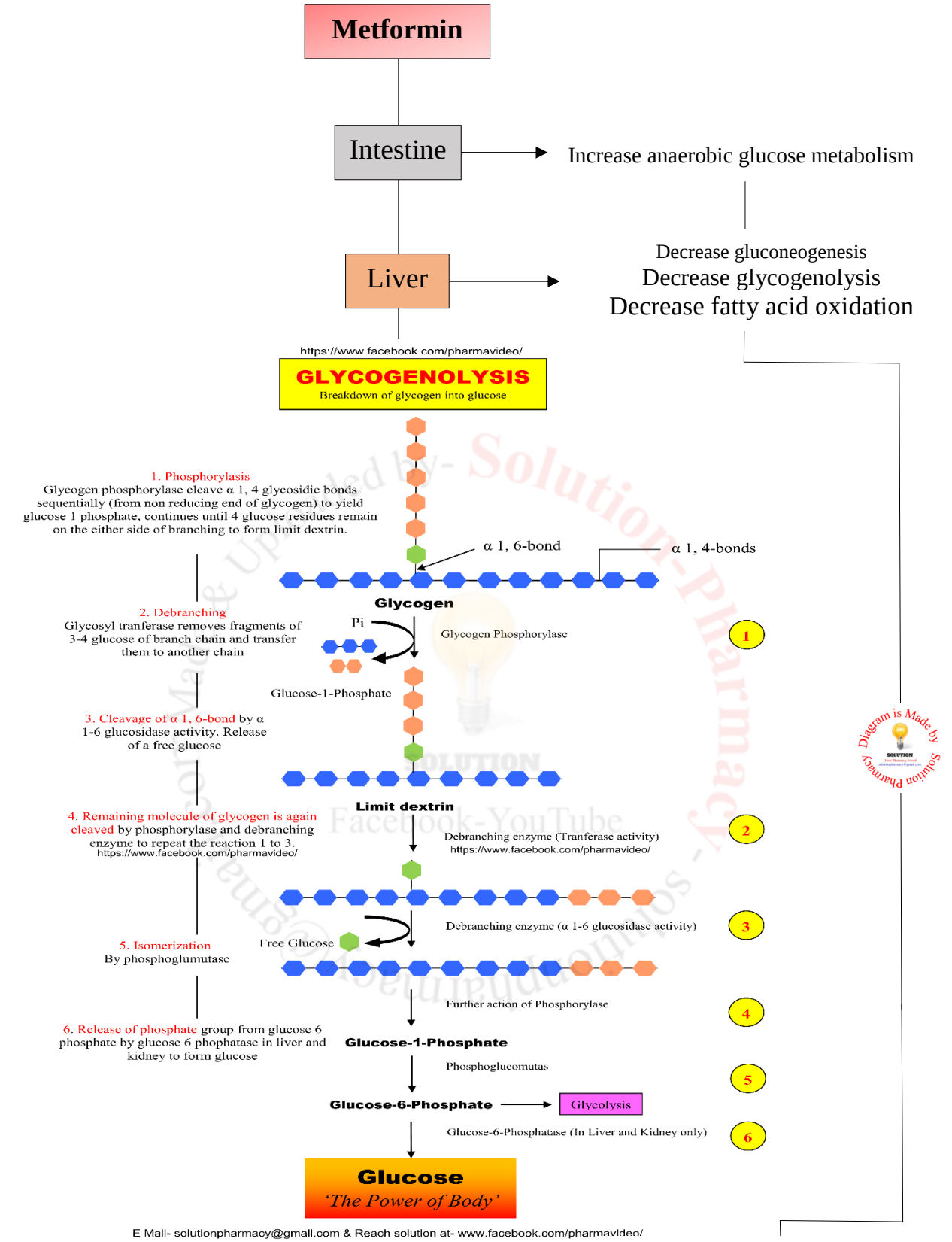
Diagram is made by- Solution-Pharmacy with Reference- Katzung- 11th Ed (Google Search)

Metformin (Overcome insulin resistance category)

Metformin is the only currently available biguanide and comes under the class of insulin sensitizer. It increase the glucose uptake and use by target site, thereby decreasing insulin resistance. It defers from Sulfonylureas in that it doesn't promote insulin secretion so hyper insulinemic is not a problem.

Mechanism of action along with important points.

1. It supress hepatic glycogenesis and glucose output from liver. This is the major action responsible for lowering the blood glucose level in diabetes.
2. Enhance insulin mediated glucose uptakes and disposal in skeletal muscle and fat. Insulin resistance shown by type 2 diabetes is solved. This translate into-
   (a) Glycogen storage in skeletal muscle
   (b) Reduce lipogenesis in adipose tissue and enhance fatty acid oxidation
   (c) Interfere with mitochondrial respiratory chain and promote peripheral glucose utilization through anaerobic glycolysis.



Possible mechanism of action of metformin.

Acarbose

Acarbose is a complex oligosaccharide which reversibly inhibit alpha-glucosidase, the main and final enzyme for the digestion of carbohydrate in small intestine mucosa. It slows down and decrease the digestion and absorption of starch or other polysaccharides and sucrose. Apart from this the GLP-1 release is prompted which may increase this effect (Decreasing of digestion) postprandial glycaemia is decreased without significant increase in insulin level. It is a mild antihyperglycemic and not a hypoglycaemic, which may be used as adjuvant of diet

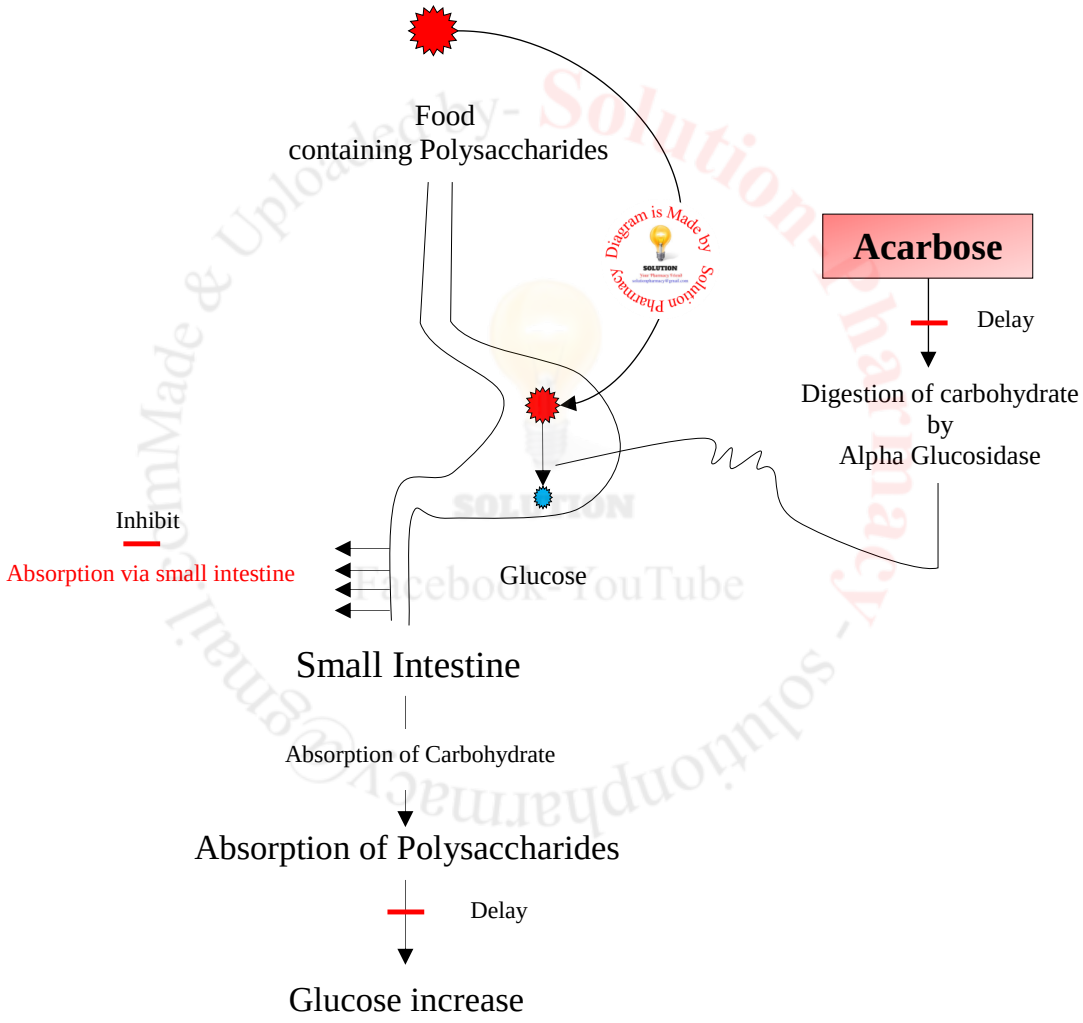


Diagram-Possible mechanism of action of Acarbose. Diagram by- Solution-Pharmacy

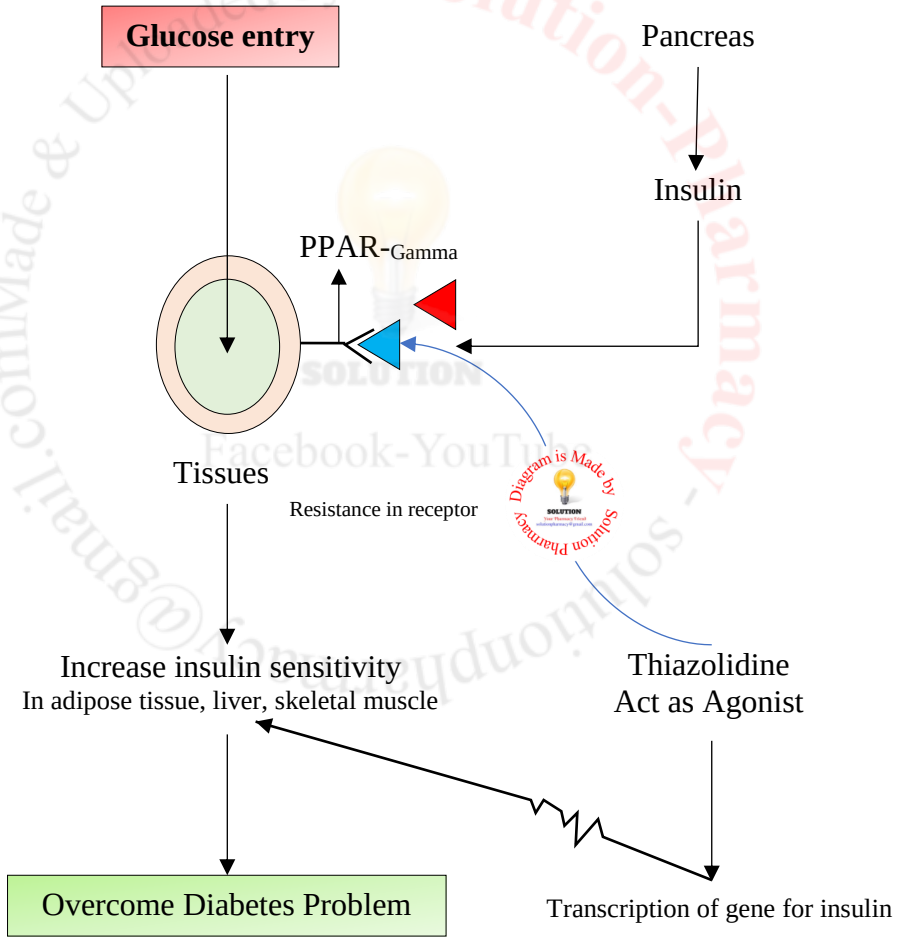
* No reference is available for this diagram. Solution has converted theory into diagram

Thiazolidinediones

Thiazolidinediones are also insulin sensitizers. The two members of this class are pioglitazone and rosiglitagine. Although insulin is required for their action, the TZDs do not promote its release from beta cells, so hyper-insulinemia is not a risk.

Mechanism of action

The TZDs lower insulin resistance by acting as agonist for the peroxisome proliferator -activated receptor-gamma, a nuclear hormone receptor. Activation of PAPAR-$_{gamma}$ regulate the transcription of several insulin responsive gene, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle.



Thiazolidine- Possible mechanism of action (Diagram made by Solution-Pharmacy)

References-

1. KD Tripathi, essential of medical pharmacology-8th edition.
2. Lippincott- Illustrated reviews of pharmacology- 6th edition.
3. Solution-Pharmacy- Facebook

Platform	Direct Link (Only for PDF)
Website	https://pushpendrakpatel.wixsite.com/solution
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