PATHOPHYSIOLOGY OF ENDOCRINE SYSTEM (DIABETES)

For Class- B.Pharmacy 2nd Semester

Subject- Pathophysiology (BP204T)

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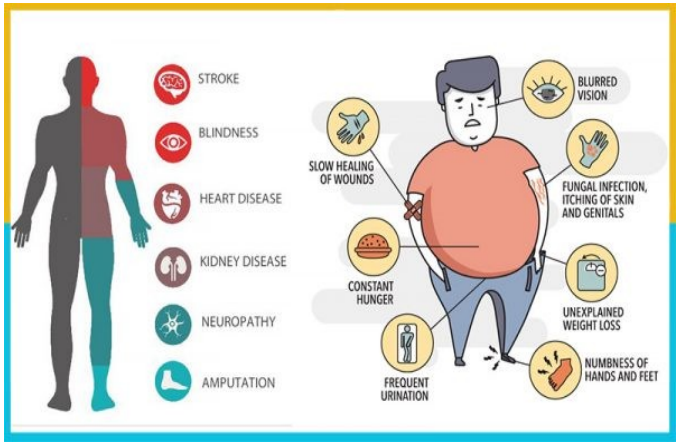
DIABETES MELLITUS

INTRODUCTION

Diabetes is a lifelong (chronic) disease and is a group of metabolic disorder characterized by high levels of sugar in blood (hyperglycemia). It is caused due to deficiency of insulin or resistance to insulin or both. Insulin is secreted by β-cells of pancreas to control blood sugar levels. Blurry visions, excess thirst, fatigue, frequent urination, hunger, weight loss are some of the symptoms commonly seen in diabetic patients.

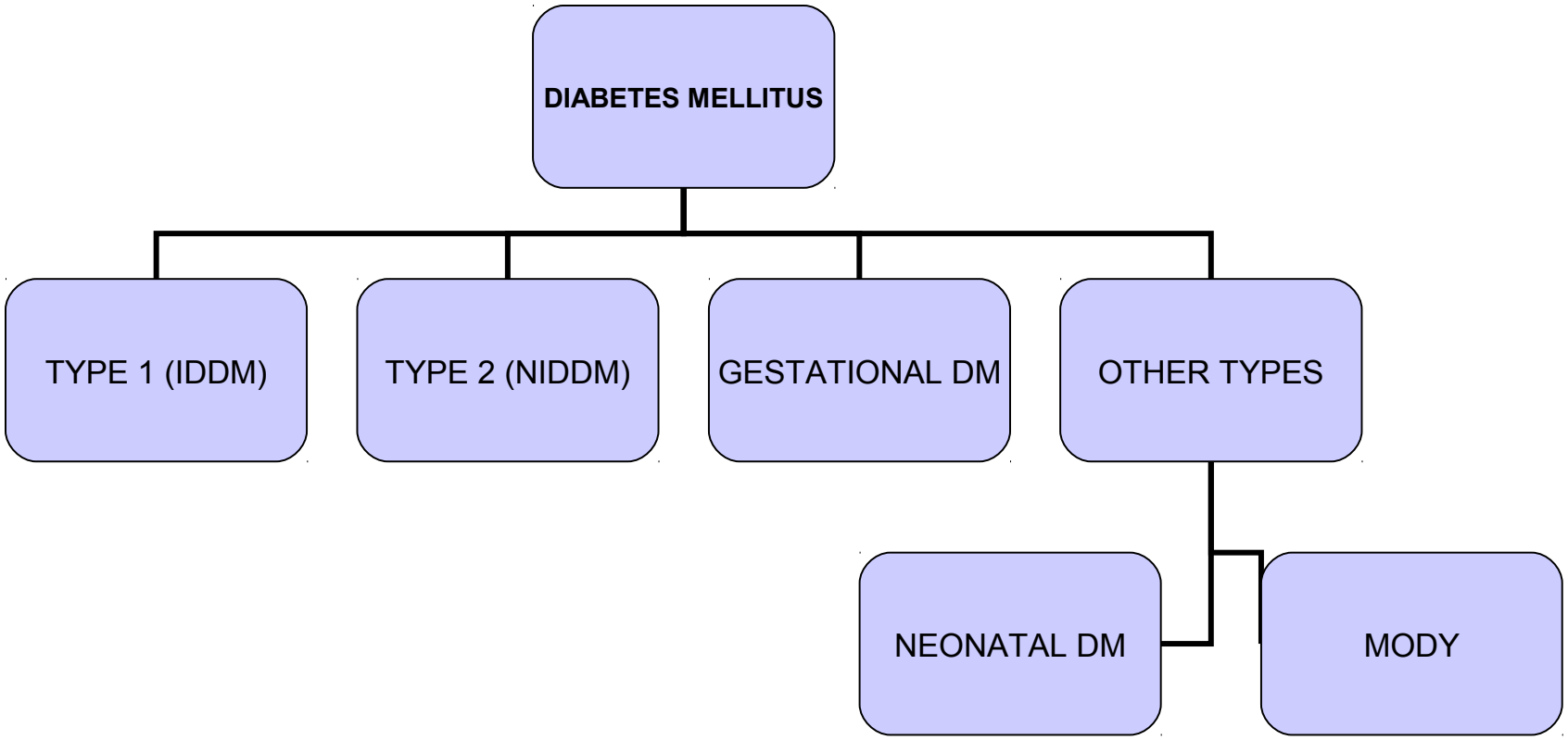
Diabetes

SIGN AND SYMPTOMS OF DIABETES MELLITUS



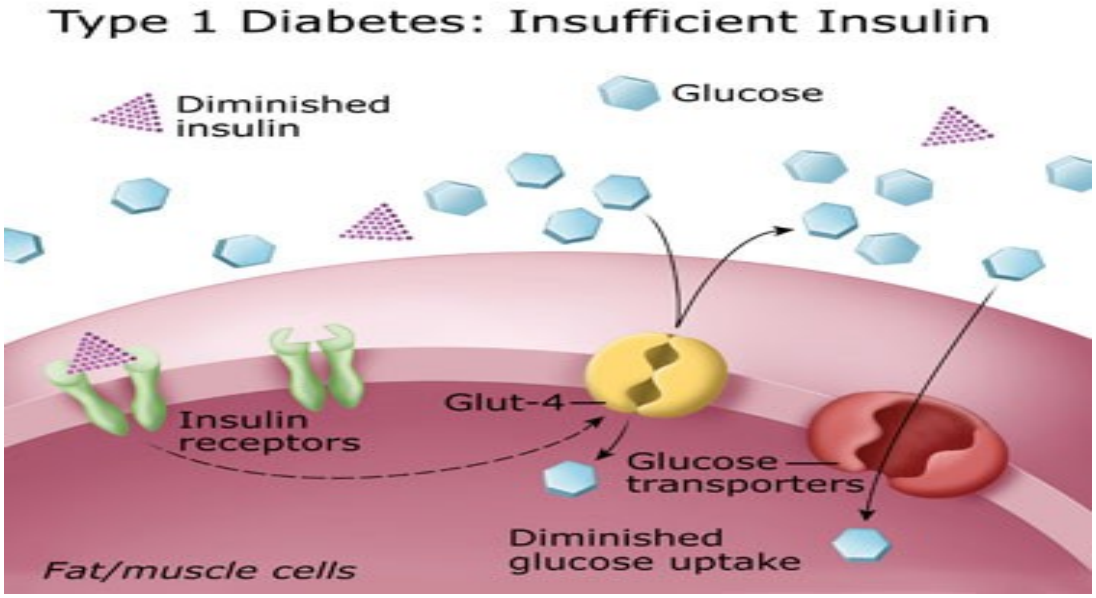
- Increased Thirst
- Frequent Urination
- Unexpected Weight Loss
- Increased Fatigue
- Blurred Vision
- Numbness And Tingling ,Especially In Your Feet And Hands
- Slow Healing Sores
- Red , Swollen ,Tender Gums
- Skin Itchy
- Irritability

TYPES OF DIABETES MELLITUS



TYPE 1 DIABETES MELLITUS (IDDM)

- T1D, also called as the insulin-dependent diabetes mellitus (IDDM), manifests due to the autoimmune damage of the β-cells which then leads to the suppression or cessation of insulin production. T1D is also called the “juvenile diabetes’’ People with Diabetes Type 1 are unable to produce insulin. Most patients with Diabetes Type 1 developed the condition before the age of 40. Approximately 15% of all people with diabetes have Type 1.



Risk Factors For Type 1 DM

- **The presence of damaging immune system cells that make auto antibodies:-**Sometimes family members of people with type 1 diabetes are tested for the presence of diabetes auto antibodies. If you have these auto antibodies, you have an increased risk of developing type 1 diabetes. But, not everyone who has these auto antibodies develops type 1.

- **Dietary factors**:- A number of dietary factors have been linked to an increased risk of type 1 diabetes, such as low vitamin D consumption; early exposure to cow's milk or cow's milk formula; or exposure to cereals before 4 months of age. However, none of these factors has been shown to cause type 1 diabetes.

- **Race:-.**Type 1 diabetes is more common in whites than in other races

- **Geography:-** Certain countries, such as Finland and Sweden, have higher rates of type 1 diabetes.

TYPE 2 DIABETES MELLITUS (NIDDM)

- Non insulin dependent diabetes mellitus (NIDDM),

  maturity onset diabetes mellitus

  There is no loss or moderate reduction in beta cell mass(30-40%); insulin in circulation is low , normal or even high. Over 90% cases are types 2 DM.
  The majority of people with Type 2 have developed the condition because they are overweight. Type 2 generally appears later on in life, compared to Type 1. Type 2 is the most common form of diabetes. In the case of insulin resistance, the body is producing the insulin, but insulin sensitivity is reduced and it does not do the job as well as it should do. The glucose is not entering the body's cells properly, causing two problems:

- **A build-up of glucose in the blood.**

- **The cells are not getting the glucose they need for energy and growth.**

RISK FACTORS FOR TYPE 2 DM

- **Obesity:-** The number one risk factor for type 2 diabetes is obesity. Greater weight means a higher risk of insulin resistance because fat interferes with the body's ability to use insulin. The number of children being diagnosed with type 2 diabetes has also risen.

- **Sedentary lifestyle**:- A sedentary lifestyle is damaging to health and bears responsibility for the growing obesity problems." Inactivity and being overweight go hand in hand towards a diagnosis of type 2. Muscle cells have more insulin receptors than fat cells, so a person can decrease insulin resistance by exercising. Being more active also lowers blood sugar levels by helping insulin to be more effective.

- **Unhealthy eating habit**:- People who have been diagnosed with type 2 diabetes are overweight. Unhealthy eating contributes largely to obesity. Too much fat, not enough fiber and too many simple carbohydrates all contribute to a diagnosis of diabetes. Eating right is can turn the diagnosis around and reverse or prevent Type 2.

- **Family history and genetics:-** If you have a relative who has/had diabetes your risk might be greater. The risk increases if the relative is a close one - if your father or mother has/had diabetes your risk might be greater than if your uncle has/had it

GESTATIONAL DIABETES MELLITUS

- Gestational diabetes only happens during pregnancy. It means you have high blood sugar levels, but those levels were normal before you were pregnant. If you have it, you can still have a healthy baby with help from your doctor and by doing simple things to manage your blood sugar also called blood glucose. After your baby is born, gestational diabetes usually goes away. Gestational diabetes makes you more likely to develop type 2 diabetes, but it won't definitely happen.

Gestational diabetes

CAUSES OF GESTATIONAL DM

- During pregnancy, the placenta (responsible for supplying oxygen and nutrients from mother to the developing baby) makes hormones that can lead to a buildup of glucose in your blood.
  Usually, your pancreas can make enough insulin to handle that. If not, your blood sugar levels will rise and can cause gestational diabetes.
- **Risk factors for gestational diabetes mellitus**
- **Age:-** Women older than age 25 are at increased risk.
- **Family or Personal History**:- Your risk increases if you have prediabetes -a precursor to type 2 diabetes — or if a close family member, such as a parent or sibling, has type 2 diabetes. You're also at greater risk if you had gestational diabetes during a previous pregnancy, if you delivered a very large baby or if you had an unexplained stillbirth.
- **Weight: -**Being overweight before pregnancy increases your risk.
- **Race:-** For reasons that aren't clear, women who are black, Hispanic, American Indian or Asian are more likely to develop gestational diabetes.

OTHER TYPES OF DM

- **Maturity onset diabetes of the young (MODY)** :- MODY is a rare form of diabetes which is different from both Type 1 and Type 2 diabetes, and runs strongly in families. MODY is caused by a mutation (or change) in a single gene. If a parent has this gene mutation, any child they have, has a 50 per cent chance of inheriting it from them. If a child does inherit the mutation they will generally go on to develop MODY before they're 25, whatever their weight, lifestyle, ethnic group etc.

- **Neonatal diabetes:-** Neonatal diabetes is a form of diabetes that is diagnosed under the age of nine months. It's a different type of diabetes than the more common Type 1 diabetes as it's not an autoimmune condition (where the body has destroyed its insulin producing cells).

DIAGNOSE TEST FOR DIABETES MELLITUS

- **Tests for type 1 and type 2 diabetes**

- **Glycated hemoglobin (A1C) test**

  This blood test, which doesn't require fasting, indicates your average blood sugar level for the past two to three months. It measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells.

  The higher your blood sugar levels, the more hemoglobin you'll have with sugar attached. An A1C level of 6.5 percent or higher on two separate tests indicates that you have diabetes. An A1C between 5.7 and 6.4 percent indicates prediabetes (A condition in which blood sugar is high but not high enough to be type 2 diabetes) Below 5.7 is considered normal.

If the **A1C** test results aren't consistent, the test isn't available, or you have certain conditions that can make the A1C test inaccurate — such as if you're pregnant or have an uncommon form of hemoglobin (known as a hemoglobin variant) — your doctor may use the following tests to diagnose diabetes:

- **Random blood sugar test.**

  A blood sample will be taken at a random time. Regardless of when you last ate, a random blood sugar level of 200 milligrams per deciliter (mg/dL) — 11.1 millimeters per liter (mmol/L) — or higher suggests diabetes.

- **Fasting blood sugar test.**

  A blood sample will be taken after an overnight fast. A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, you have diabetes.

- **Oral glucose tolerance test**.

  For this test, you fast overnight, and the fasting blood sugar level is measured. Then you drink a sugary liquid, and blood sugar levels are tested periodically for the next two hours.

  A blood sugar level less than 140 mg/dL (7.8 mmol/L) is normal. A reading of more than 200 mg/dL (11.1 mmol/L) after two hours indicates diabetes. A reading between 140 and 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) indicates prediabetes.

TESTS FOR GESTATIONAL DIABETES MELLITUS

Your doctor will likely evaluate your risk factors for gestational diabetes early in your pregnancy:

- **Initial glucose challenge test :-** You'll begin the glucose challenge test by drinking a syrupy glucose solution. One hour later, you'll have a blood test to measure your blood sugar level. A blood sugar level below 140 mg/dL (7.8 mmol/L) is usually considered normal on a glucose challenge test, although this may vary at specific clinics or labs.

  If your blood sugar level is higher than normal, it only means you have a higher risk of gestational diabetes.

- **Follow-up glucose tolerance testing:-** For the follow-up test, you'll be asked to fast overnight and then have your fasting blood sugar level measured. Then you'll drink another sweet solution — this one containing a higher concentration of glucose — and your blood sugar level will be checked every hour for a period of three hours.

  If at least two of the blood sugar readings are higher than the normal values established for each of the three hours of the test, you'll be diagnosed with gestational diabetes.

TREATMENT FOR ALL TYPES OF DIABETES

Healthy eating :- Contrary to popular perception, there's no specific diabetes diet. You'll need to center your diet on more fruits, vegetables, lean proteins and whole grains — foods that are high in nutrition and fiber and low in fat and calories — and cut down on saturated fats, refined carbohydrates and sweets. In fact, it's the best eating plan for the entire family. Sugary foods are OK in a while, as long as they're counted as part of your meal plan.

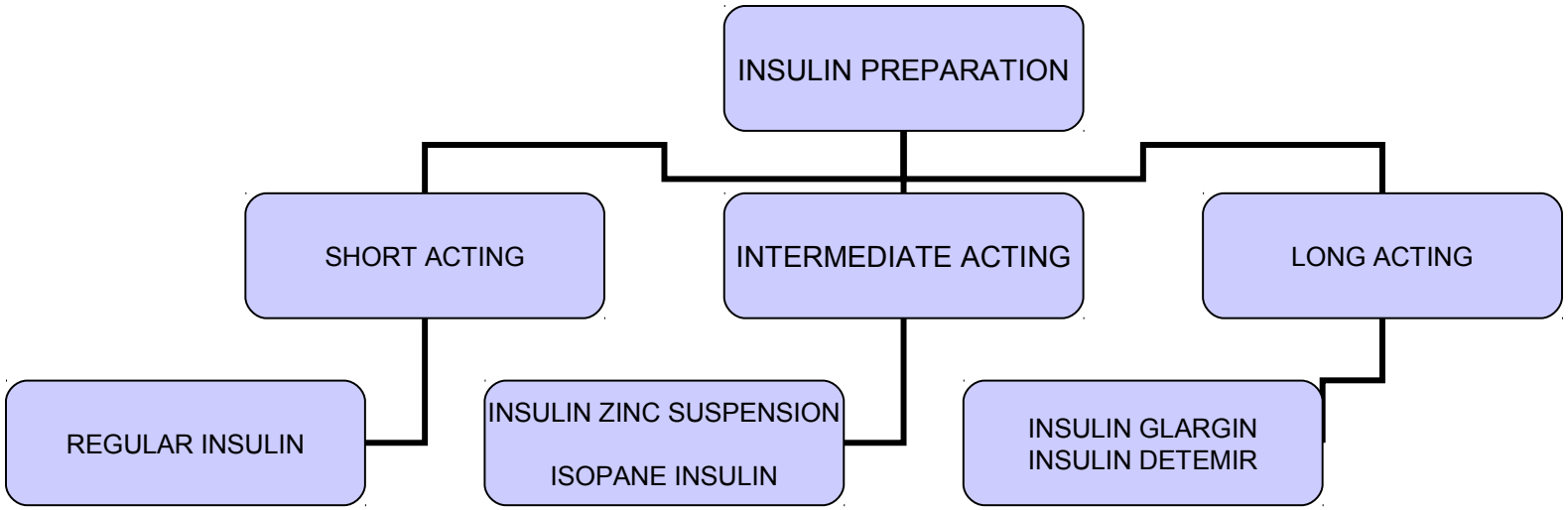
Physical activity :- Everyone needs regular aerobic exercise, and of the three hours of the test, you'll be diagnosed with gestational diabetes.
people who have diabetes are no exception. Exercise lowers your blood sugar level by moving sugar into your cells, where it's used for energy. Exercise also increases your sensitivity to insulin, which means your body needs less insulin to transport sugar to your cells.

TREATMENTS FOR TYPE 1 DIABEES MELLITUS

- **Insulin :-** People with type 1 diabetes need insulin therapy to survive. Many people with type 2 diabetes or gestational diabetes also need insulin therapy.

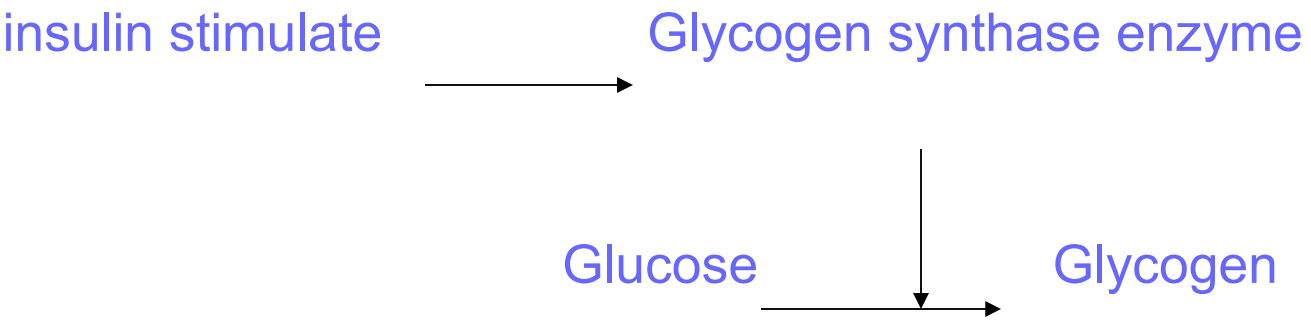
Insulin is usually given subcutaneously either by injections or by an insulin pump Research of other routes of administration is underway. In acute-care settings, insulin may also be given intravenously. In general, there are three types of insulin, characterized by the rate which they are metabolized by the body. They are rapid acting insulin's, intermediate acting insulin's and long acting insulin's.

TYPES OF INSULIN USED IN THE TREATMENT OF THE TYPE 1 DM



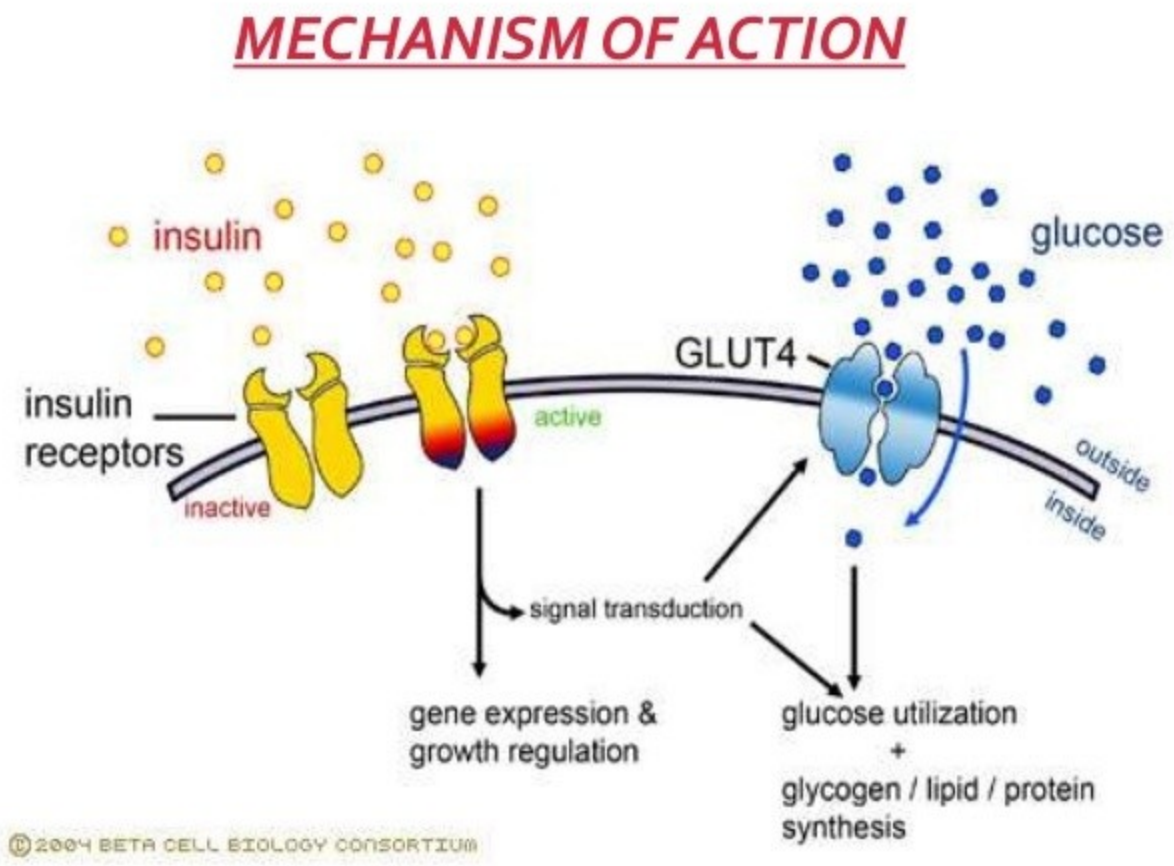
ACTIONS OF NSULIN

- It helps in the transportation of glucose across the cell membrane.
- Insulin activate GLUT-4 (Transporter of glucose) as a result of that glucose transportation occur across the cell.
- It helps in the formation of glycogen;



- Insulin inhibit the phosphorylase enzyme which convert the glycogen into glucose.

MECHANISM OF ACTION OF INSULIN (IDDM)



TREATMENT FOR TYPE 2 DM (NIDDM)

Oral diabetes medications are used in the treatment of type 2 diabetes Medicines within this category fall within one of several classes, including;

A) Enhance insulin secretion

1) sulfonylureas (KATP channel blocker)

First generation- Tolbutamide

Second generation- Glibenclamide,Glipizide

2) Meglitinide/Phenylalanine analogues

Repaglinide,Nateglinide

3) Glucagon like pepetide -1 (GLP1) Receptor Agonist (Injectable Drugs)

Excenatide, Liraglutide

4) Dipeptidyl Peptidase -4 (DPP4) Inhibitors

Sitagliptin , vildagliptin

B) Overcome insulin resistance

1) Biguanide (Ampk Activator)

Metformin

2)Thiazolidinediones (PPARalpha Activator

Pioglitazine

C) Miscellaneous Antidiabetic Drugs

1) Alpha glucosidase inhibitors

Acarbose , Miglitol

2) Amylin Analogue

Pramlintide

3)Dopamine D2 Receptor Agonist

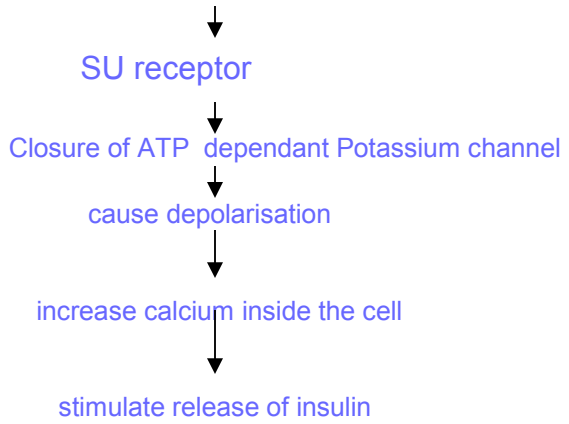
Bromocriptine

4) Sodium Glucose Cotransport 2 Inhibitors

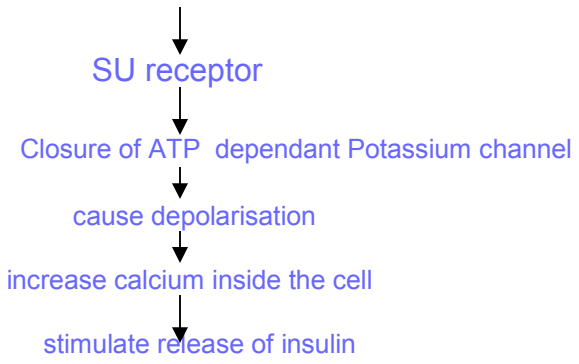
Dopagliflozin

MECHANISM OF ACTION

1)Sulphonyl urease:- Sus → SU Drugs



2) Meglitinide Analogues:- Sus → Meglitinide drugs



- GLP1 Receptor Agonist:- Food in GIT → Glucose → GLP1 ← liraglutide

  ↓

  Act on beta cell

  ↓

  Increase the insulin release

- DPP4 Inhibitors :- sitagliptin

  DPP 4 ⊘

  GLP1 → Inactivate peptide (Degrade)

HERBAL DRUG TREATMENT FOR DIABETES

- Acacia arabica
- Achyranthes aspera
- Allium sativum (garlic)
- Allium cepa: (onion)
- Azadirachta indica
- Tinospora cordifolia: (Guduchi)
- Cinnamon
- Bitter Melon
- Fenugreek
- Gymnema

NEW ANTI DIABETIC DRUGS

- **New Drug Treatments for Type 1 and Type 2 Diabetes**

- **NN1250/Insulin Degludec/Tresiba**

NN1250/Insulin Degludec is being developed by Novo Nordisk and has reached phase 3 clinical trials. This is a completely neutral, soluble, and subcutaneous ultra-long-acting new-generation insulin that lasts for over 24 hours. This insulin is designed for basal insulin treatment of both type 1 and type 2 diabetes mellitus.

- **LY2405319**

LY2405319 is a new drug being developed by Eli Lilly. The drug is in a new class of treatments known as FGF21 analogues. FGF21 stands for fibroblast growth factor 21, which is a hormone in the body that stimulates glucose uptake of adipose cells (fat cells). In initial phase 1 human studies, the drug has shown beneficial effects on blood lipid levels, blood glucose levels and reduction in body weight.

LIFESTYLE FOR TYPE 1 AND TYPE 2 DM

- **Identify yourself:-** Wear a tag or bracelet that says you have diabetes. Keep a glucagon kit nearby in case of a low blood sugar emergency — and make sure your friends and loved ones know how to use it.
- **Pay attention to your feet:-**Wash your feet daily in lukewarm water. Dry them gently, especially between the toes. Moisturize with lotion, but not between the toes. Check your feet every day for blisters, cuts, sores, redness or swelling. Consult your doctor if you have a sore or other foot problem that doesn't start to heal on its own.
- **Keep your blood pressure and cholesterol under control:-** Eating healthy foods and exercising regularly can go a long way toward controlling high blood pressure and cholesterol. Medication may be needed, too.
- **Take care of your teeth:-** Diabetes may leave you prone to gum infections. Brush and floss your teeth at least twice a day. And if you have type 1 or type 2 diabetes, schedule dental exams at least once a year. Consult your dentist right away if your gums bleed or look red or swollen.