Glucose Homeostasis Regulated by Pancreatic Mechanisms and Study of Anti-Diabetic drugs

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***Abstract*- Regulation of blood sugar levels is highly complex mechanism. Various hormones and secretions help in order to keep check on levels of glucose. Pancreas plays the major role in almost all of the mechanisms. Hormonal reverse countering regulations like Insulin and Glycogen based on feedback mechanism controls the glucose homeostasis. The mechanism of insulin and glycogen mediated response is vital to maintain glucose homeostasis. The Pancreatic secretions are very much prone to the abnormalities and disturbances. The irregularities in the pancreatic regulation mechanisms results in diseases associated with glucose regulation such as Dysglycemia and Diabetes. The pancreatic regulation mechanisms carried out in body are significant to carry out furthermore studies for remedies. The understanding of ongoing mechanisms associated with glucose homeostasis also enable us to target specific level for therapeutic purposes. Particular actions of drug and their help in regulating blood sugar level will be discussed further.**

***Index terms*- Glucose Homeostasis, Insulin, Glucagon, Diabetes, Metformin, Canagliflozin**

1.INTRODUCTION

Pancreatic mechanisms help in the maintenance of glucose homeostasis. The pancreatic secretions like Insulin and Glucagon plays key role in regulation of normal blood glucose level. The cells producing these substances requires gene expression. The mechanism involved in stimulation of pancreatic cells to release specific hormone according to the need of body like release of insulin during elevation of blood sugar and release of glucagon during lowering of blood sugar. How these complex processes control the sugar level is studied here. The mechanism and working of insulin and glucagon is complex involving feedback systems. The Production of these hormones by gene expression is complex process. These mechanism are too much complex that irregularities can occur at any stage. Those abnormalities are discussed here along with the Anti-diabetic drugs. Anti-Diabetic drugs work by varied mechanism controlling the glucose level when insulin, glucagon and other regulators failed to do so. Anti-diabetic drugs and their action on target tissues discussed here from activation of specific enzymes and cytosolic components to the inhibition of transporters. The drugs like Metformin from Biguanides class and Canagliflozin from SGLT-2 inhibitors are discussed.

1. Pancreatic Secretions:

Pancreas is an important gland in the body which functions as both endocrine and exocrine. Here in Glucose homeostasis the endocrine functions of pancreas are utilized. The maintenance of blood sugar by means of hormonal regulation mechanisms like Insulin and Glucagon. The pancreatic secretions play key role in control of glucose homeostasis by increasing or lowering the blood glucose.

The irregularities in levels of blood glucose causes triggers in feedback system controlling. In increased glucose state stimulate the release of insulin from pancreatic βcells [1]. Similarly but in reverse order when glucose level in blood decreases the Glucagon is released from α cells of pancreas that help to convert glycogen into glucose.

Table 1.0 Cell Types in Pancreatic Islets their proportion and secretion

Types of cell	Proportion	Secretion
1. α cells	17%	glucagon
2. β cells	70%	insulin
3. δ cells	7%	somatostatin

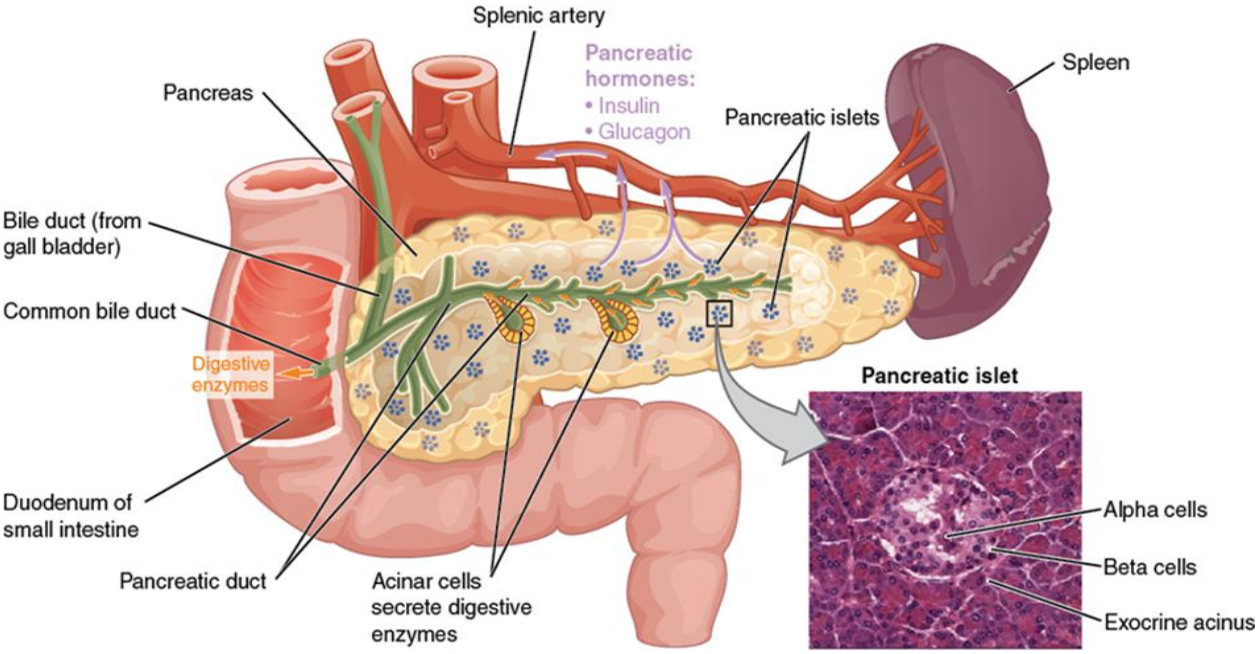

Fig 1.0 Pancreas and surrounding organs [2]

2. INSULIN

2.1 Insulin Production:

Insulin is synthesised in the β cells of pancreatic islets of Langerhans. βcells constitute 70 percent of total pancreatic islet cells [3]. Insulin is a hormone which is responsible for entry of glucose in the cells. The clusters of cells present in the pancreas produces different hormones based on the levels of blood sugar in body [4]. This blood sugar level is under check of feedback mechanism which enables the cells of pancreatic islets to inhibit or to stimulate secretion of particular hormones.

Insulin is 51-residue anabolic protein containing two chains bonded by disulphide bonds. It is produced from precursor called as proinsulin [5]. The gene produced mRNA is translated in single chain precursor called as preproinsulin. The terminal peptides are removed during insertion into endoplasmic reticulum to give proinsulin [6]. This proinsulin undergoes action by endopeptidases and generates insulin and free C peptide which are packed in secretory granules. When the βcells are stimulated, the insulin is secreted by exocytosis and get diffused into pancreatic islets. Only insulin is taken up C peptide has no significant activity [6]

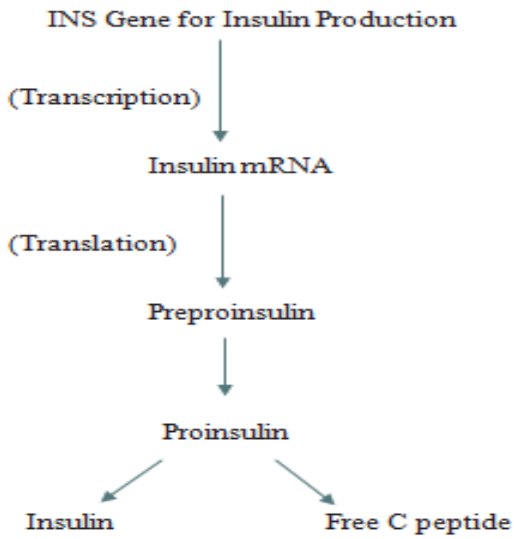

Fig 2.1 Stepwise production of insulin from INS gene

2.2 Release of Insulin:

Blood sugar levels are under constant check by negative feedback system. The stimulus for secretion of insulin is elevated blood sugar levels. During 24 hours of the day the levels of blood glucose fluctuates [7]. The receptors are present in the βcells of pancreas detect this change and act accordingly to decrease the glucose level if it is elevated and vice versa. Pancreatic cells contain secretory granules containing Insulin and Free C peptides. The GLUT

transporter present on the surface of pancreatic cells allows intake of glucose into cells. This glucose undergoes pathway of glycolysis and TCA cycle producing large amount of ATP. These ATP molecules close the ATP sensitive Potassium Channels. This process creates membrane depolarisation resulting into opening of Voltage gated Calcium Channels [8]. Calcium (Ca+) ions influx occurs and at the same time Insulin Vesicles previously produced by INS gene are released into Blood vessels ultimately carrying it to portal vein.

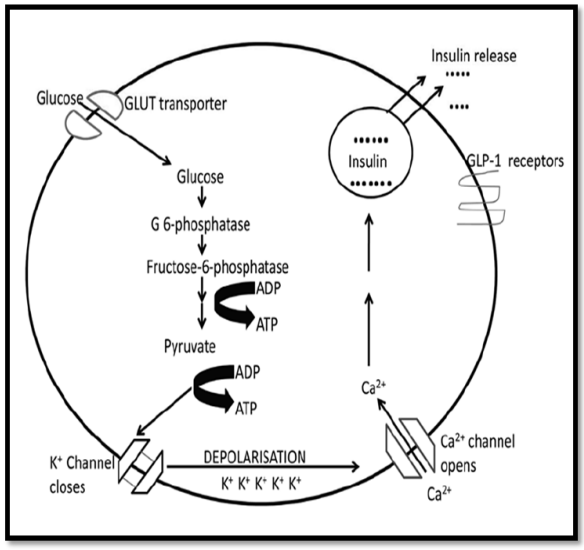

Fig 2.2 Glucose triggering secretion of Insulin in pancreatic cell shown in above diagram. Source: [8]

2.3 Insulin Mediated Glucose Regulation:

The process of reduction of blood glucose involves diffusion of excess sugar in blood into cells. This is achieved by an increased translocation of insulin dependent glucose carriers called as GLUT [9]. The GLUT-4 is found in skeletal muscles and varied cells of body like hepatocytes and adipocytes. The movement of glucose is bidirectional but in presence of insulin metabolically active insulin sensitive tissues glucose is transported from exterior to the interior of the cell [10].

Table 2 Glucose Transporters and their Target locations

Glucose Transporter	Target
1. GLUT-1 (Insulin Independent)	RBCs and Brain
2. GLUT-2 (Insulin Independent)	Kidney, Liver and Intestine.
3. GLUT-3 (Insulin Independent)	Neurons and Small Intestine
4. GLUT-4 (Insulin Dependent)	Muscles, Heart and Adipose Tissue

Insulin receptor (IR) is present on the cell surface is Tyrosine Kinase. Insulin Regulator Substrate is phosphorylated and binding sites opens up [11]. After that the glucose can go to different metabolic pathways in the cell like MAP Kinase signalling pathway where it is utilised for cell growth and proliferation. If glucose enters into PI3K pathway it will lead to formation of products like lipids, proteins and glycogen.

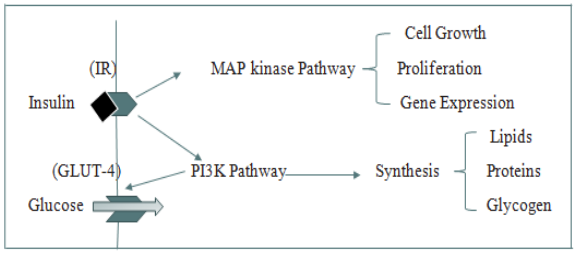

Fig 2.3 Insulin Regulated Glucose Intake and its further processing.

3.GLUCAGON

3.1 Production of Glucagon:

Glucagon is secreted by the α-cells of the islets of Langerhans of the pancreas which opposes the action of insulin [12]. The free running production of it is suppressed by a peptide hormone co secreted with insulin, amylin. As soon as the glucose level in plasma recedes, the successive reduction in the secretion of amylin alleviates its suppression of the α cells which further allows the secretion of glucagon [13]

Glucagon is a 29-amino acid peptide hormone which is produced from the proglucagon, a precursor, and can be converted into many other related peptide hormones. The further processing of proglucagon is carried out by the enzymes prohormone convertase 1/3 (PC1/3) and prohormone convertase 2 (PC2), respectively. In the pancreas, PC2 converts proglucagon to glucagon, glicentin-related pancreatic polypeptide (GRPP), intervening peptide 1 (IP1), and major proglucagon fragment (MPGF) whereas conversion of proglucagon in the intestine and the brain is carried out by PC1 which leads to the formation of glucagon-like peptide 1 (GLP-1) and

glucagon-like peptide 2 (GLP-2) oxyntomodulin, intervening peptide 2 (IP2), and glicentin [14]

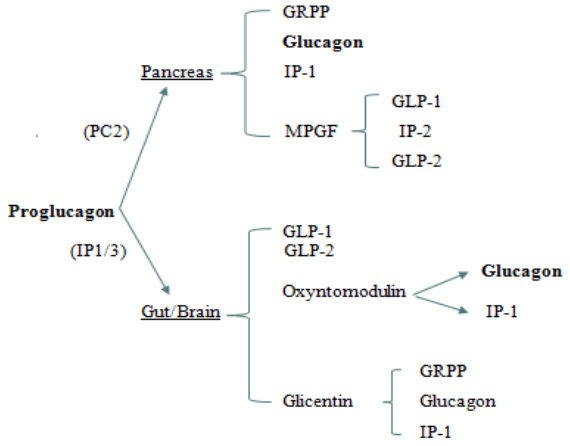

Fig 3.1 Production of Glucagon from Proglucagon

3.2 Action of Glucagon:

The Glucagon is released from pancreatic cells when the glucose level drops below the normal range. The glucagon receptor called as (GCGR) a type of GPCR G-Protein Coupled Receptors has major role in regulation of blood glucose levels [15]. Glucagon after binding to receptor leads to chain of processes involving utilization of ATP. The cAMP produced in the process activates the PKA, PKA phosphorylates PPK and inactivates Glycogen Synthase [16]. After this Cascade process breakdown of glycogen starts by action of phosphorylase. In this manner the glucose levels are increased back to normal.

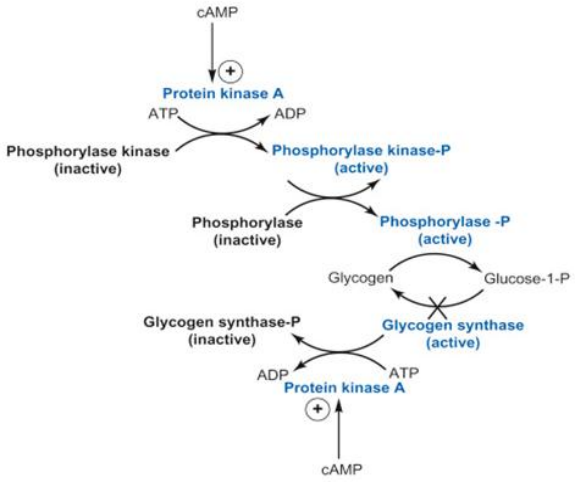

Fig 3.2 Cascade Action of Glucagon [16]

4 IRREGULARITIES IN BLOOD GLUCOSE HOMEOSTASIS

Regulation of normal blood glucose is complex mechanisms evolving multistep processes. The irregularities can occur in production of insulin and glucagon as well as their secretion from pancreatic cells. Abnormalities can occur in the cellular receptors that help insulin and glucagon to regulate glucose.

Disorder	Complications	Change in Glucose level
Glycosuria	Excretion of glucose through urine	increases
Hyperglycaemia	body does not produce or use enough insulin,	increases
Hyperinsulinism	Insulin resistance	decreases
Hypoglycaemia	Increased insulin in body	Decreases

Table 3 Disorders related in glucose irregularities.

Diabetes Mellitus:

Diabetes mellitus is an endocrine disease common in aged people. It is characterized by high serum glucose concentration and disturbances of carbohydrate and lipid metabolism [17]. Some of complications like hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state also occurs to patients. The complications such as coronary and cerebral vascular disease, blindness, chronic kidney disease, complicated infections, and amputations are present in a much higher incidence in diabetics than in no diabetics [18]. Diabetes is frequently ranked as one of the five major chronic diseases that account for a significant proportion of our health care spending [19].

TYPE 1

Type 1 diabetes occurs due to the cells that produce insulin (beta cells) are damaged. In type 1 diabetes, the pancreas makes little or no insulin, so sugar cannot get into the body's cells for use as energy [19]. People with type 1 diabetes must use insulin injections to control their blood glucose [20]. Diabetes can occurs at any age but it is the common form of diabetes in people under age 30.

TYPE 2

The pancreas produces insulin regularly, but sometimes it doesn't produce amount required, or produced insulin doesn’t work properly. This type occurs most often in people who are over 40 years old but can occur even in childhood if there are risk factors present [21]. Type 2 diabetes may sometimes be controlled with a combination of diet, weight management and exercise [21].

5 ANTI-DIABETIC DRUGS

Drugs used to treat diabetes mellitus are referred as Anti-Diabetic Drugs. They do so by controlling blood glucose level either bringing it down from elevated condition or to increase it if it lowers. These medications are administered mostly by oral route with some exceptions like insulin which is administered intravenously. Division of Oral Anti-Diabetic drugs is as follows.

Table 4 Classification of Anti-Diabetic Drugs [22]

Class of Drug	Mechanism of action	Example
1. Insulin	Increasing Glucose uptake in cells	Intravenous Insulin
2.Sulphonylureas	Increasing insulin Secretion from β cells	Glimepiride
3.Meglitinides	Increasing insulin Secretion from β cells	Nateglinide
4. Biguanides	Reducing Hepatogluconeogenesis	Metformin
5.GLP-1 agonists	Stimulation of GLP-1 Receptor	Exenatide, Albiglutide
6.DPP-4 inhibitors	Inhibition of GLP-1 degradation and elevating Glucose dependent insulin secretion	Saxaglipti n
7.Thiazolidinedione	Reducing Insulin Resistance by Stimulation of PPARs	Pioglitazone
8.Amylin analogues	Reducing release of glucagon	Pramlintide

5.1 Metformin:

5.1.1 General Information

Metformin belongs to class Biguanides in antihyperglycemic agents. It is used in type 2 Diabetes to lower the blood glucose without causing hypoglycemia [23]. It is an Organic drug with simple structure freely soluble in water but insoluble in Acetone, Ether or Chloroform [24].It was first described in 1922 by Emil Werner and James Bell and it's sugar lowering action was studied in rabbits by Slotta and Tschesche in 1929 [24]. Metformin is used in the treatment of type 2 diabetes which can be used alone or with other drug classes like sulfonylureas, thiazolidinedione and various hypoglycemic agents [25]. Metformin is also causes weight loss and it is preferred in patients of overweight conditions with Type 2 Diabetes.

Table 5 General Information of Metformin

Drug Name:	Metformin
IUPAC Name:	3-(diaminomethylidene)-1,1-dimethylguanidine
Chemical formula:	C4H11N5.
Biological Half-life:	6.2 Hours [26]

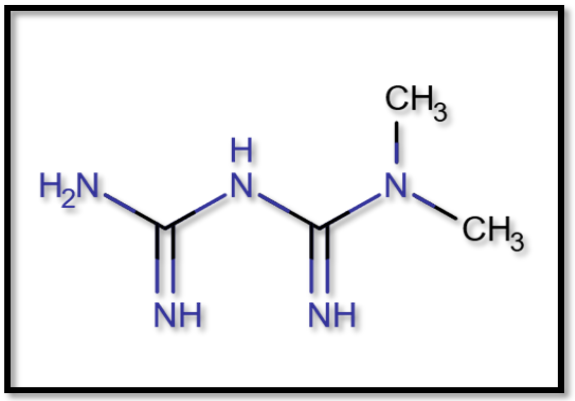

Fig 5.1 Structure of Metformin

5.1.2 Action of Metformin:

Metformin works on multiple target sites like Liver, Kidney and Intestine. Metformin when taken orally it acts on cellular receptors called as OCT-1 (exclusively present in liver) and OCT-2 is present in renal tubules where it helps uptake of metformin from circulation [27]. Metformin after entering into the liver it accumulates inside the mitochondria [28]. Metformin causes inhibition of Complex I in mitochondria which results into suppression of ATP production [29]. As result of respiratory chain inhibition suppression of ATP production along with changes in NAD+: NADH ratio decreases gluconeogenesis [30]. Metamorfin decreases the amount of enzyme Phosphoenolpyruvate carboxylase (PEPCK) and Glucose-6-phosphatase [31]. After entering into the hepatic cells, Metformin activates the primary upstream kinase of AMPK called as LKB1. Activation of LKB1 leads to phosphorylation of AMPK. This AMPK when phosphorylated results in cytosolic sequestering of TORC2. This TORC2 makes CREB inefficient to transcribe PGC1a, as a results low PGC1a expression lowers the levels of PEPCK and Glucose-6-phosphate. Finally leading to decrease in hepatogluconeogenesis.

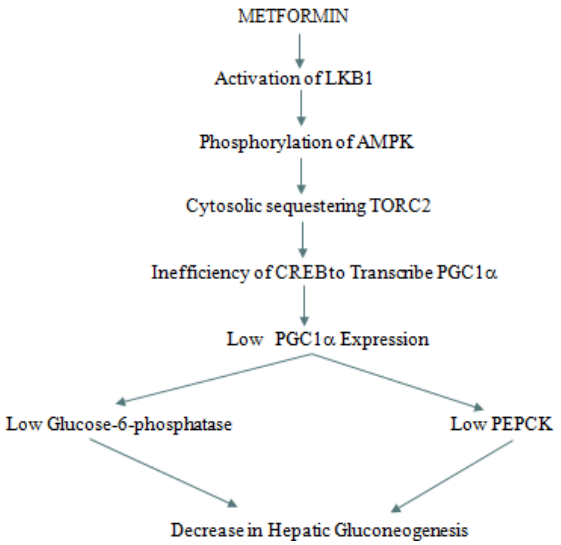

Fig 5.2 Action of metformin to decrease hepatic Gluconeogenesis

5.2 Canagliflozin:

5.2.1 General Information:

Canagliflozin is Sodium-Glucose Co-transporter 2 (SGLT -2) inhibitor which mainly acts on kidney to lower glucose reabsorption. It comes under class of SGLT-2 inhibitor. It is an ant diabetic drug approved to administer for prevention of cardiovascular complications in T2DM [32]. It is an Organofluoric compound containing C-glycosyl compound and thiophene member and used in hemihydrate form [33]. Mitsubishi Tanabe Pharma developed this drug and it is currently marketed by Janssen [34].

Table 6 General Information of Canagliflozin

Drug Name:	Canagliflozin
Chemical Formula:	$C_{24}H_{25}FO_5S$
Biological half-life:	100mg = 10.6 Hours, 300mg = 13.1 Hours [35]

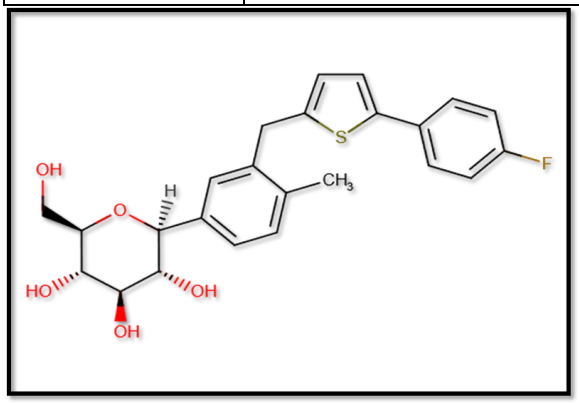

Fig 5.3 Structure of Canagliflozin [36]

5.2.2 Action of Canagliflozin:

Canagliflozin is SGLT-2 inhibitor which specifically works to reduce the glucose reabsorption. This results in increased glucose excretion from urine and lowers the glucose levels [37]. Mainly a SGLT-2 inhibitor causes DKA (Diabetic Ketoacidosis). The Normal functioning of SGLT-2 is inhibited and the reabsorption of glucose from proximal tubules of nephron is impacted negatively by this inhibition. In this manner the SGLT-2 inhibitors increases glucose excretion and lowers the blood glucose levels.

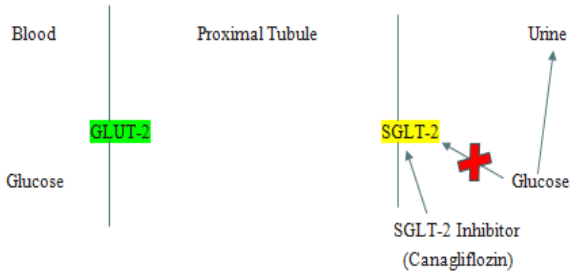

Fig 5.4 Mechanism of SGLT-2 Inhibitor (Canagliflozin)

6. CONCLUSION

Pancreatic is an important gland for regulation of glucose homeostasis. Its secretions like Insulin and Glucagon plays important role in maintaining blood glucose levels. There are different mechanisms involved in body to regulate blood sugar. These mechanisms are triggered when the glucose levels delflect from regular levels either elevated or lowered. The production of the glucose homeostatis regulating substances mainly takes part in pancreas but they act on different targets. Action of insulin on glucose transpoters and action of glucagon on glycogen production and breakdown regulates the action. There are various abnormalities associated with glucose homeostatsis the major among them is Diabetes. Anti-Diabetic drugs are used as medications to treat the condition. Those drugs are classified based on their action and targets. The drugs like metformin and Canagliflozin works to reduce the blood sugar levels. Their mechanism are complex and different. Where the metformin act on gene express resulting in reduction of hepatogluconeogenosis on the other hand canagliflozin inhibits renal reabsorption of glucose.

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