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REVIEW ARTICLE

Mechanism of Action of Oral Antidiabetic Drugs

Dr. Nirmalya Roy (Corresponding author)*
Kingshuk Bhattacharjee (Co-author)**

*Associate Professor, Dept. of Medicine, KPC Medical College
**Independent Medical Writer

Abstract:

Type 2 diabetes mellitus (T2DM) is one of the major health problems witnessed in the 21st century, with increasing rates of obesity and unhealthy lifestyle both driving up the number of patients affected and also reducing the age at diagnosis. Drugs that lower the blood glucose level are warranted in patients with type 2 diabetes to reduce symptoms and the risk of long-term complications. Oral antidiabetic drugs (OADs) are by definition the starting point of pharmalogical treatment of type 2 DM when diagnosed at lower HbA1c levels (<9%). The modes of action of the currently available OADs are diverse having their action on various organs responsible for T2DM. A sound knowledge of the mode of action provides an opportunity to "tailor treatment" to the likely heterogeneous pathogenetic mechanism or condition as per the patients' individual needs. This review article aims to provide information about the OADs in current use in a form that a clinician may find useful in choosing among the plethora of glucose-lowering agents.

Keywords: ***Oral antidiabetic drugs, Mechanism of action, Type 2 Diabetes Mellitus.***

Case Vignette 1:

A 45 year old woman, a known type 2 diabetes mellitus (T2DM) case for last 10years. Her BMI is 32 kg/m^2. She is currently on metformin 1 gram twice daily (bid). She loves to eat, scared of needle. Her glycaemic profile is HbA1c 8%, fasting plasma glucose (FPG) - 160 mg/dL and post prandial plasma glucose (PPPG) - 210 mg/dL. Preferred DPP4i over SGLT2i because she suffered from repeated episodes of urinary tract infection.

Case Vignette 2:

A 48 year old T2DM diagnosed recently during health check-up with fasting plasma glucose (FPG) - 180 mg/dL and post prandial plasma glucose (PPPG) – 235mg/dL and HbA1c of 8.2%. He was diagnosed with fatty liver on USG. He denied any history of alcohol use. Liver function tests (LFTs) within normal limits. Serum creatinine - 1.6 mg/dL. Pioglitazone would be a good choice.

Case Vignette 3:

An elderly female aged 78 years complaints of 'Gas' for last one year. Her creatinine is 1.7mg/dl, fasting plasma glucose (FPG) -180mg/dl and post prandial plasma glucose (PPPG) – 280 mg/dL. She is coming for treatment for first time as she needs a cataract surgery. She weighs 45 kg with prior history of fracture three years back. Her

cataract surgery would be free of cost if done within 10 days. Sulphonylureas could help her in achieving the glycemic targets rapidly.

In order to solve the aforementioned cases, the current paper shall discuss about mechanism of action of currently available oral antidiabetic agents (OADs), which would be helpful for a clinician in choosing an appropriate oral OADs in their regular practice.

Introduction

Type 2 diabetes is a one of the major health problem witnessed in the 21st century, with increasing rates of obesity and unhealthy lifestyle both driving up the number of patients affected and also reducing the age at diagnosis.[1] Drugs that lower the blood glucose level are warranted in patients with type 2 diabetes to reduce symptoms and the risk of long-term complications.[1] This review article aims to provide information about the OADs in current use in a form that a clinician may find useful in choosing among the plethora of glucose-lowering agents. This information may form part of patient education when first prescribing OADs, or when changing their present regimen. It may also help a clinician to give answers to questions asked by patients about "their difficulties".

Oral antidiabetic drugs

Oral antidiabetic drugs (OADs) should be considered when glycaemic and weight targets are not met with diet and lifestyle changes alone. Patients should be reassured that the need for pharmacological therapy is not a failure on their part and should understand that the maximal benefits from drugs will only be achieved if they continue to make strenuous efforts at lifestyle modification. The various classes of OADs are discussed below emphasizing on their diverse mechanism of actions.[1]

Biguanides

The biguanide, metformin is the first-line agent of choice. It is at least weight neutral and may help with weight loss. Its main mode of action is to inhibit hepatic glucose output. It does not increase circulating insulin levels, stimulate appetite or cause hypoglycaemia.[1] In addition, in the UKPDS, overweight patients given metformin had a better outcome than those receiving other therapies. (Effect of intensive glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34).[2] The full details of mechanism of action of metformin is not known. The primary effect is to reduce hepatic glucose production through activation of the enzyme AMP-activated protein kinase (AMPK). Other mechanisms of action includes impairment of renal gluconeogenesis, slowing of glucose absorption from the gastrointestinal tract, increased glucose to lactate conversion by intestinal cells, direct stimulation of glycolysis in tissues, increased glucose removal from blood and reduction of plasma glucagon levels.[3] Thedrug has a good safety record, but should not be used in renal failure (serum creatinine > 1.5 mg/dL in men and > 1.4 mg/dL in women), or severe heart and liver failure because of the risk of lactic acidosis.[3] Minor abnormalities in liver function tests or stable, treated heart failure should not preclude its use. It can be used in combination with sulphonylureas or thiazolidinedione.[4] If mild side-effects do occur as the dosage is increased, it is worthwhile persevering with treatment as they often subside. However, in some patients, the dosage may have to be reduced or the drug stopped completely. Given that metformin does not cause hypoglycaemia, patients should take the maximum dose they can tolerate.[3]

Sulphonylureas

Sulphonylureas (SUs) can be used as first-line therapy, particularly in thin patients or those unable to take metformin, or can be used in combination with metformin orthiazolidinedione.[3,4] They bind to specific receptors on the pancreatic beta-cell, stimulating insulin release and thus may cause hypoglycaemia and weight gain. It acts by binding to the sulfonylurea receptor (SUR) resulting in inhibition of potassium efflux causing depolarisation. Opening of voltage gated calcium channel raises intracellular calcium triggering insulin secretion. Unlike older SUs, glimepiride has some special characteristics with respect to its binding to sulphonylureas- receptors on the β cells. The older SUs bound strongly with the SU receptors and caused a continuous release of insulin from the β cells. Whereas, glimepiride has a high association/ dissociation rate at the SUR; therefore, only the required amount of insulin is released rapidly and not continuously. This is also termed as "switch on-switch off mechanism" of glimepiride.[3,4] Furthermore, as compared with glibenclamide, glimepiride has a 3-fold higher rate of binding to the SUR, a 3-fold lower affinity to SUR and a 9-fold faster rate of dissociation from the SUR. The brisk action of glimepiride at the SUR provides the various benefits as compared to older SUs namely reducing the risk of hypoglycemia, preserving the beta cells and thus it prevents early secondary failure to SUs, lesser risk of weight gain and avoiding the potentially atherogenic effects of hyperinsulinaemia. To try to match blood insulin levels

with food absorption, these agents should be taken 20–30 minutes before eating, as with injected insulin. Begin with a low starting dosage and increase every one to three months to the minimum dosage that achieves appropriate glycaemic control. Unlike older SUs like glibenclamide, glimepiride also has another extra-pancreatic action that protects the heart during periods of decreased blood supply. This is called cardio-protective effect of glimepiride. Older SUs like glibenclamide bind to all 3 types of SUR receptors and close the ATP sensitive potassium channels in cardiac and smooth muscles as well, thereby interfering with ischaemic preconditioning and predisposing the heart to myocardial infarction. Ischaemic preconditioning is the normal process by which the heart prepares itself to face an ischaemia (decreased blood supply). The mechanism of ischaemic preconditioning that occurs in a normal heart involves opening of ATP-sensitive potassium channels on the heart muscle cells when there is decreased blood supply to the heart. This prevents the change in polarity within the heart muscle cells, thereby preventing the opening of calcium channels on the heart muscle cells. Decreased entry of calcium into the heart muscle cells prevents their contraction and therefore decreases the workload on the heart. When the workload on the heart decreases, the requirement of blood supply to the heart muscles also decreases and hence death of heart muscles (myocardial infarction or heart attack) due to lack of blood supply is prevented. Different types of sulfonylurea receptors are present of ATP sensitive potassium channels found in the beta cells, heart muscle cells and smooth muscle cells. Incontrast to older sulfonylureas, glimepiride selectively acts on SUR-1 receptors on the β cells, hence ATP sensitive potassium channels remain open in the cardiac cells and ischaemic preconditioning is not hampered and myocardial infarction is prevented.[4] The other commonly used second generation sulfonylurea is the gliclazide. It has a similar mechanism of action as glimepiride, however it has few additional benefits to confer owing to the amino aza bicyclo-octane ring.[5,6] The unique free radical scavenging property of the gliclazide is due to the presence of aminoazabicyclo-octane ring, which is not found on other sulfonylureas. This unique antioxidant properties ensure direct cardiovascular protection, mainly through inhibition of oxidation of LDL-C, reduction in platelet reactivity, and decreased free radical production.[5,6]

Meglitinides (glinides)

Meglitinides analogues belongs a family of insulin secretagogues which stimulate insulin secretion by inhibiting ATP-sensitive potassium channels of the beta-cell membrane via binding to a receptor distinct from that of sulphonylureas (SUR1/KIR 6.2).[7] Repaglinide and nateglinide are absorbed rapidly, stimulate insulin release within a few minutes, are rapidly metabolised in the liver and are mainly excreted in the bile.[7] Therefore, following pre-prandial administration of these drugs, insulin is more readily available during and just after the meal. This leads to a significant reduction in postprandial hyperglycaemia without the danger of hypoglycaemia between meals.[7] The short action of these compounds and biliary elimination makes repaglinide and nateglinide especially suitable for patients with type 2 diabetes mellitus who would prefer to have a more flexible lifestyle, because of unplanned eating behaviour (e.g. geriatric patients) or in whom one of the other first-line antidiabetic drugs, i.e. metformin, is strictly contraindicated.

Thiazolidinedione

The exact mode of action of the thiazolidinedioneis not known. They bind to the peroxisome proliferator activated receptor (PPAR)-gamma nuclear receptor and increase the transcription of many genes, including some that regulate metabolism. Activation of PPAR- γ leads to the increased transcription of various proteins regulating glucose and lipid metabolism. These proteins amplify the post-receptor actions of insulin in the liver and peripheral tissues, which leads to improved glycaemic control with no increase in the endogenous secretion of insulin. The expression of PPAR-γ is high in adipose tissue and skeletal muscle. PPAR- γ activation stimulates differentiation of adipocytes which is conversion of pre-adipocytes into mature adipocytes. They also cause partial activation of PPAR-α leading to increase in high density lipoproteins (HDL) and reduction of triglycerides (TG). Increases uptake of fatty acid into the adipose tissue. Pioglitazone induced adipogenesis and alterations in adipocyte morphology, results in the development of smaller and more insulin-sensitive cells and hence it reduces insulin resistance by this effect. The net result is improvement in 'insulin sensitivity', the body responding more efficiently to circulating insulin levels. Pioglitazone reduces hyperinsulinaemia, hyperglycaemia and hypertriglyceridemia. Pioglitazone has been shown to increase insulin receptor expression in adipocytes and hepatocytes. Expression of glucose transporter proteins GLUT 1 and GLUT 4 are increased.[8,9] These agents can cause fluid retention and peripheral oedema and are contraindicated in significant heart failure. Risks of liver toxicity, seen in the first-generation drug of this class, seem

low, so that three monthly liver function tests, which were recommended initially, now seem unnecessary. The drug is taken once a day, with meals, beginning with the lower dosage and increasing as needed. Use as single agent is not recommended, not because the drugs are not effective, but on the grounds of cost.[8,9] There is also no longterm data showing that treatment with the thiazolidinedione reduces the incidence of complications of diabetes, although it seems unlikely that they would not. They should therefore be added to therapy with metformin or sulphonylureas, when treatment goals are not met on the maximum tolerated dosage of these agents. The full glucose lowering effects of these drugs are not seen for at least one month. If metformin or a sulphonylureas are stopped and a thiazolidinedione substituted, glucose control may actually deteriorate temporarily. It is thus important to discuss this with patients when the drug is first started.[10,11]

Alpha Glucosidase inhibitors

The Alpha-glucosidase inhibitor (AGIs) prevents the digestion of carbohydrate in the small intestine. Large carbohydrates in the food have to be broken down to simple sugars (like glucose) before they can be absorbed into the blood from the intestine. Alpha glucosidases are a group of enzymes, attached to the brush border of the intestine, that break down larger carbohydrates (like complex starches, oligosaccharides and disaccharides) to glucose. AGIs competitively inhibit alpha glucosidase and delay the absorption of glucose from the intestine, thereby reducing the postprandial plasma glucose peaks. It therefore reduces postprandial blood glucose more than fasting levels. Its use is limited by gastrointestinal side-effects and it is probably less effective in reducing HbA1c than all the other agents. It may, however, be of limited use when metformin and thiazolidinedione are contraindicated. Because of its mode of action, it is taken at meals, with the first mouthful of food.[12]

DPP4 Inhibitors

Glucagon-like peptide-1 (GLP-1) are released by intestinal L-cells in response to ingested food. GLP-1 is rapidly and extensively inactivated by an enzyme called dipeptidyl peptidase-4 (DPP4).[13] The kinetics of the inactivation process were explored both in healthy subjects as well as type 2 diabetes mellitus (T2DM) patients, all of whom were given the active amide GLP-1(7–36) (administered subcutaneously or intravenously).[13] In all instances, the active amide was rapidly attacked at its N-terminus by dipeptidyl peptidase-4 (DPP-4), leaving the inactive metabolite GLP-1(9–36) and giving the active amide a half-life of only 1–2 minutes.[14] Early on in the development of DPP-4 inhibitor therapy, it was hypothesized that inhibition of DPP-4 may enable endogenous GLP-1 to avoid inactivation, augment the deficient incretin response seen in T2DM, and improve metabolic control across the multiple defects associated with the disorder. Such hopes were the impetus for an exploratory trial in which 12 healthy subjects fasted overnight and then ate a standardized breakfast 30 minutes after receiving single oral doses of placebo or the active drug NVP-DPP728.[14] The active drug increased the subjects' plasma levels of prandial active GLP-1, with concomitant reduction in prandial glucose exposure. These findings, reported in the year 2000, were the first to provide direct evidence that inhibition of DPP-4 could be a viable pharmacologic approach for potentiating the activity of endogenous GLP-1 in humans.[15] Post–meal ingestion, GLP-1 and GIP are released from the small intestine and are rapidly degraded by the enzyme DPP-4. Inhibition of DPP-4 prevents the breakdown of GLP-1 and GIP and enhances glucose-stimulated insulin secretion (incretin action). GLP-1 and GIP act on the pancreatic β-cell to increase insulin release. GLP-1 also acts on the β-cell to suppress glucagon release and ultimately suppress hepatic glucose production. Together, the increased cellular glucose uptake and the decreased hepatic glucose output offer physiologic glucose control. GLP-1 also acts to cause satiety and by delaying gastric emptying.[15]

Bromocriptine

Timed-release bromocriptine, a sympatholytic dopamine D_2 receptor agonist, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes. This centrally acting anti-diabetic agent has a novel mechanism of action. is believed to augment low hypothalamic dopamine levels and inhibit excessive sympathetic tone within the central nervous system (CNS), resulting in a reduction in post-meal plasma glucose levels due to enhanced suppression of hepatic glucose production. Bromocriptine has not been shown to augment insulin secretion or enhance insulin sensitivity in peripheral tissues (muscle). Addition of bromocriptine to poorly controlled type 2 diabetic patients treated with diet alone, metformin, sulfonylureas, or thiazolidinedione produces a 0.5–0.7 decrement in HbA1c. It has been found to reduce plasma glucose, triglyceride, and free fatty acid (FFA) levels; and in a prospective 1-year study reduced cardiovascular events.[16] The drug is absorbed quickly after ingestion. The

maximum concentration is achieved within 60 minutes in fasting and 120 minutes in fed state. It has to be started at 0.8 mg and up titrated to 4.8 mg.

Colesevelam

It was initially developed as a lipid lowering agent rather anti-diabetic agents. However, among many bile acid Sequesterants (BAS) it is the only BAS which has been extensively tested as an anti-diabetic agents. As the class suggests, it is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase, and increasing the number of hepatic LDL receptors. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. Serum TG levels may increase or remain unchanged. It is not yet known how Colesevelam works to help control blood sugar in people with type 2 diabetes. However, it is clear that the drug works within the digestive tract, since it is not absorbed into the rest of the body. Its mechanism of action is not explained properly, however potential routes includes action on the farnesoid x receptor (present in the liver and intestine) and G-protein coupled bile salt receptor (TGR-5). It has also been found to have an effect on the incretin system. The main advantage of colesevelam is that it is not being systemically absorbed and thus not contraindicated in patients with renal or hepatic impairment or heart failure.[17]

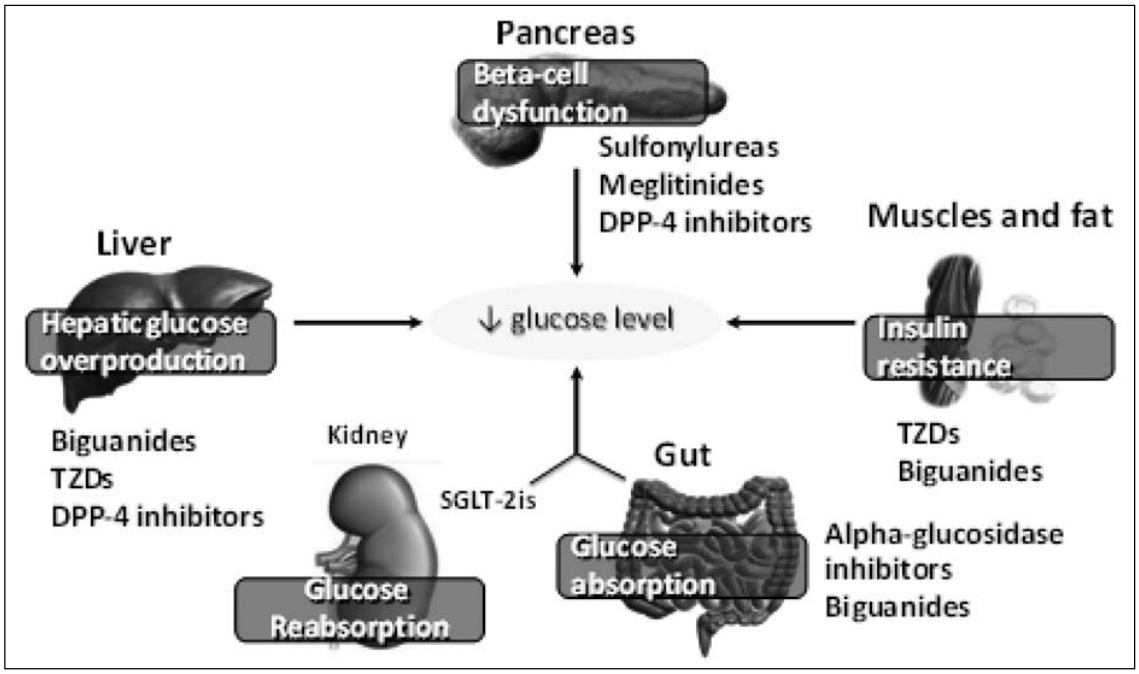
SGLT-2 Inhibitors

In a healthy individual, normally all filtered glucose is reabsorbed. Sodium glucose co-transporters 2 (SGLT-2) inhibitors are highly specific for the kidney and SGLT2 transporter. It works by blocking the reabsorption of glucose (blood sugar) by the kidney, increasing glucose excretion, and lowering blood glucose levels in diabetics who have elevated blood glucose levels. The effectiveness is independent of insulin. This mechanism of action is independent of insulin so this could be a benefit for someone who is having insulin resistance.[18]

Conclusion

OADs are by definition the starting point of pharmalogical treatment of type 2 DM when diagnosed at lower HbA1c levels (<9%). The modes of action of the currently available OHAs are diverse having their action on various organs responsible for T2DM. A sound knowledge of the mode of action provides an opportunity to "tailor treatment" to the

Figure 1 | *Sites of Action of Different Oral hypoglycemic Agents used in Management of Type 2 Diabetes Mellitus*



Adapted from *Ann Intern Med*. 1999; 131: 281–303 and Williams Textbook of Endocrinology. 10th ed. Philadelphia: WB Saunders; 2003:1427–1483

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"Educating the mind without educating the heart is no education at all."

— Aristotle