Pharmacological Reports 69 (2017) 959–970

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Therapeutic molecules against type 2 diabetes: What we have and what are we expecting?

Ashwini Kumar[a], Sudhanshu Kumar Bharti[b], Awanish Kumar[a,*]

[a] Department of Biotechnology, National Institute of Technology Raipur, Raipur, Chhattisgarh, India
[b] Department of Biochemistry, Patna University, Patna, Bihar, India

ARTICLE INFO

Article history:
Received 5 January 2017
Received in revised form 5 April 2017
Accepted 6 April 2017
Available online 9 April 2017

Keywords:
Type 2 diabetes
Conventional anti-diabetics
Novel anti-diabetics
Promising therapeutics

ABSTRACT

World Health Organization (WHO) has identified diabetes as one of the fastest growing non-communicable diseases with 422 million patients around the world in 2014. Diabetes, a metabolic disease, is characterized primarily by hyperglycemia which results in various macrovascular and microvascular complications like cardiovascular disease and neuropathies which can significantly deteriorate the quality of life. The body either does not manufactures enough insulin (type 1 diabetes or T1DM) or becomes insensitive to physiologically secreted insulin or both (type 2 diabetes or T2DM). The majority of the diabetic population is affected by type 2 diabetes. Currently, hyperglycemia is treated by a broad range of molecules such as biguanides, sulfonylurea, insulin, thiazolidinediones, incretin mimetics, and DPP-4 inhibitors exerting different mechanisms. However, new drug classes have indeed come in the market such as SGLT-2 inhibitors and other are in the experimental stages such as GPR 40 agonists, GSK-3 inhibitors, GK activators and GPR21 inhibitors which definitely could be anticipated as safe and effective for diabetes therapy. This article reviews the general approach to currently approved therapies for type 2 diabetes and focusing on novel approaches that could be a panacea and might be useful in the future for diabetes patients.

Contents

* Corresponding author.
E-mail addresses: drawanishkr@gmail.com, awanik.bt@nitrr.ac.in (A. Kumar).

http://dx.doi.org/10.1016/j.pharep.2017.04.003
1734-1140/

Introduction

Four hundred twenty-two (422) million diabetic patients were reported worldwide by WHO in the year 2014 [1]. Diabetes mellitus is a group of metabolic disease primarily diagnosed by hyperglycemia and resultant microvascular complications like nephropathy, retinopathy, neuropathy and major macrovascular events like cardiovascular disorders, stroke and peripheral vascular complications [2]. Diabetes is classified mainly into two types *viz.* type 1 diabetes mellitus (T1DM) which is an auto-immune condition whereby the β cells of the pancreas are destroyed and type 2 diabetes mellitus (T2DM) which accounts for the major form of diagnosed diabetes. A third form known as gestational diabetes mellitus (GDM) is often reported in the case of pregnancy and in most cases disappears post-partum while other diabetes types include monogenic diabetes syndromes that include maturity-onset diabetes of the young or MODY [2,3]. Therapeutic molecules used currently to treat hyperglycemia include Metformin (biguanide), Sulfonylureas (Insulin secretagogues), Thiazolidinediones (TZDs), α-glucosidase inhibitors (AGI), Incretin analogs, Dipeptidyl Peptidase–4 (DPP-4) inhibitors [4]. The experimental candidates discussed in this review include GPR-40 agonists, GSK-3β inhibitors, GK activators and amylin analogs.

Metformin, a biguanide, is considered as the first line of treatment for T2DM since it is the safest molecule present against T2DM [5]. It primarily targets the hepatic gluconeogenesis and improves insulin resistance. Sulfonylureas, though as old as biguanide, are associated with the adverse drug reaction of hypoglycemia which could be very severe at times [4]. Thiazolidinediones appeared as a revolutionary molecule but a few molecules were withdrawn due to severe adverse cardiac effects [4]. The available TZDs are still present with those effects but to a lesser extent than the withdrawn molecules. AGIs are considered safe as the most frequent ADRs associated with them is diarrhea and gastrointestinal discomfort, but it is safe from hypoglycemic effect. The next in the line are incretin analogs or incretin mimetics which, through their action in the gut, stimulate insulin release from the pancreas. Their close relative DPP-4 inhibitors inhibit the enzyme DPP-4 which breaks down the physiological incretins and thus helps in elongating the period of physiological insulin release aided by incretins. But the major ADRs reported with the later two groups are pancreatitis, cardiac effect and joint pains [4].

Continuous research in the field of diabetes has given many novel targets such as GPR-40, GSK-3β, Glucokinase (GK), GPR 21 and a few others. We would like to mention here that diabetes is clinically diagnosed primarily with two basic parameters *viz.* fasting plasma glucose (≥126 mg/dl) and HbA1c (≥6.5). This review covers brief information about the currently available antidiabetic drugs and other molecules those are in pipeline and clinical trials.

Therapeutic approach in T2DM

Diabetes management usually starts with lifestyle and dietary management. The routine is followed by initial oral anti-diabetic (OADs) followed by subcutaneous insulin injections (if hyperglycemia persists even after administration of OADs). The most prescribed conventional OADs are biguanides, sulfonylureas, AGIs and thiazolidinediones followed by basal or intense insulin if hyperglycemia remains uncontrolled. According to the treatment protocol outlined by American Diabetes Association (ADA), metformin is usually the first medicine recommended for T2DM, if not contraindicated and if tolerated. If monotherapy OADs are not able to maintain the blood glucose and HbA1c level after 3 months of treatment, a combination of OADs is often considered. In dual-therapy too, metformin usually remains one of the drugs. If still, significant symptoms persist, basal insulin can be initiated. The dual or triple therapy and initiation of insulin depend upon several other factors such as age, weight, eating schedule, working habits *etc*. New molecules such as incretin analogs, DPP-4 inhibitors, and SGLT-2 inhibitors have been marketed for last few years. The detailed outlined treatment protocol by ADA has been mentioned in the Reference number [6]. It would be a good mention here that we may expect many more molecules such as GPR-40 agonists and GPR 21 inhibitors in the coming decade as they are in different research phases. In this review article, the general approach to the treatment of type 2 diabetes (Fig. 1), focusing on currently approved therapies and novel approaches that have a potential to be used in the future are discussed in detail.

Current or conventional therapeutic molecules

Biguanides

Among all the molecules of biguanide family, metformin is the most prescribed drug as the first-line treatment of hyperglycemia in T2D. Its primary target is hepatic gluconeogenesis. In addition, it also increases the insulin sensitivity in hepatocytes and muscle cells decreasing post-prandial glucose increment and decrease the plasma free fatty acid by 30% which in turn increases insulin sensitivity [6]. Metformin has also shown to reduce body weight and possesses cardio-protective effects by lowering high triglyceride. The American Diabetes Association recommends metformin as most preferable first-line therapy for T2D based on the fact that it does not cause hypoglycemia even on long dosing and may reduce the risk of cardiovascular events due to diabetes [6,7]. One of the studies indicated that long-term metformin therapy is associated with vitamin B_{12} deficiency [8]. Early biguanides were associated with rare but potentially fatal advert effect known as lactic acidosis, which is characterized by elevated blood lactate concentration (>45 mg/dL), decreased blood pH (<7.35) and an electrolyte imbalance leading to tissue hypoxia [9]. Biguanides target hepatic gluconeogenesis mainly from lactate, alanine and pyruvate thus building up lactate. The most appropriate mechanism believed till date is the activation of AMP-activated protein kinase or AMPK protein. A part from the hepatic gluconeogenesis, metformin is said to decrease intestinal glucose absorption and increases the glucose uptake by skeletal muscle and adipocytes. It has also been reported that metformin antagonizes the action of glucagon resulting in suppressed glucose production. Another major beneficial effect due to AMPK activation is seen with a decrease of circulation triglyceride and free fatty acid. Metformin activated AMPK actually phosphorylates and inhibits acetyl-CoA carboxylase enzyme (ACC) and improves the lipid metabolism in hepatocytes. This improvement of lipid metabolism in hepatocytes significantly improves glucose uptake and metabolism. Thus, metformin also stabilizes the lipid profile in diabetic patients