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Review

A preclinical overview of metformin for the treatment of type 2 diabetes

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ABSTRACT

Type 2 diabetes (T2D) is the most common type of diabetes mellitus and is mainly characterized by insulin resistance, β-cell dysfunction, and elevated hepatic glucose output. Metformin is a first-line antihyperglycemic agent that works mainly by regulating hepatic glucose production and peripheral insulin sensitivity. Metformin has been clinically applied for more than half a century, although the underlying pharmacological mechanisms remain elusive. This current review mainly focused on the development history of metformin and related preclinical studies on structural modification, pharmacological mechanisms for treatment of T2D, toxicology, pharmacokinetics, and pharmaceutics. The pharmacological function of metformin in lowering hyperglycemia suggests that multi-targeting could be an effective strategy for the discovery of new anti-diabetic drugs. A number of discoveries have revealed the pharmacologic mechanisms of metformin; however, precise mechanisms remain unclear. Deeper investigations on the biological features of metformin are expected to provide more rational applications and indications of this evergreen anti-T2D agent, which will in turn help to better understand the complicated pathogenesis of T2D.

1. Introduction

Diabetes mellitus is a metabolic disorder that occurs when the body cannot produce enough insulin or cannot use insulin effectively, leading to consistent hyperglycemia [1]. Currently, over 451 million people worldwide are suffering from diabetes, and the International Diabetes Federation projects have warned that this number will increase to nearly 693 million by 2045 [2]. Type 2 diabetes (T2D) is one of the most common type of diabetes mellitus, accounting for more than 90% of the cases [3]. The number of people afflicted with T2D is growing rapidly worldwide. T2D is mainly characterized by insulin resistance, β-cell dysfunction, and elevated hepatic glucose output [4]. Chronic hyperglycemia, which resulted from T2D, produces severe complications, including retinopathy, nephropathy, neuropathy, atherosclerosis, and heart diseases [5,6].

T2D can be initially improved by exercise and diet regulation [3]. However, if the blood glucose level is not adequately managed to a normal state using these measures, medications are needed. Patients prefer oral medication to injection in T2D therapy; thus, oral hypoglycemic agents are increasing in demand [7]. Currently, many available clinical anti-T2D drugs remain limited by their efficacy, tolerability, and side effects, such as weight gain and hypoglycemia [3]. Nonetheless, the popularity of new anti-T2D drugs in the last few years has increased the number of choices for patients. Some glucose-lowering drugs that can both inhibit hepatic gluconeogenesis and improve insulin sensitivity exist in the market, but they have equivocal pharmacological mechanisms, among which is metformin [8]. The specific mechanisms underlying the pharmacological functions of metformin

Abbreviations: aPKC, atypical protein kinase C; CBP, CREB binding protein; ChREBP, carbohydrate response element-binding protein; CREB, cAMP response element-binding protein; CRTC2, CREB-regulated transcription coactivator 2; FA, fatty acid; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; G6Pase, glucose-6-phosphatase; HbA1c, glycosylated hemoglobin; KLF15, Krüppel-like factor 15; MATE, multidrug and toxin extrusion; OCTs, organic cation transporters; PC, pyruvate carboxylase; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, PPAR-γ coactivator 1α; PK, pyruvate kinase; PKA, protein kinase A; PPAR-γ, peroxisome proliferator-activated receptor-γ; SHP, small heterodimer partner; SIKs, salt-inducible kinases; SIRT1, sirtuin 1; SREBP-1c, sterol regulatory element binding protein-1c; T2D, type 2 diabetes

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remain unclear; however, a number of reports have confirmed its multiple-target effects in reducing hepatic glucose production and intestinal glucose absorption, promoting pancreatic β-cell functions, and improving insulin sensitivity [9,10]. Clinically, metformin is widely used for treating T2D, particularly in overweight and obesity [11,12]. Metformin has been approved for initial therapy by the American Diabetes Association and European Association of the Study of Diabetes largely due to its low price, safety profile, and potential cardiovascular protection [13,14]. Deeper pharmacological studies on metformin are expected to provide more rational applications and indications of this evergreen anti-T2D agent, which in turn may help better inspect the complicated pathogenesis of T2D. The current review focused on the preclinical study of metformin for the treatment of T2DM, including the history, structural modification, pharmacological mechanisms against hyperglycemia, toxicological studies, pharmacokinetics, and pharmaceutics. This study has expanded the understanding of metformin and highlighted the importance of new anti-T2DM drug research based on the structure and mechanisms of metformin.

2. History of metformin

Metformin (Fig. 1) has been clinically used for more than a half century [8]. Structurally, it is a dimethylbiguanide-type compound designed to reduce the adverse effects of galegine-like compounds derived from *Galega officinalis* [15]. Guanidine is traced to the use of *Galega officinalis* in medieval Europe and possesses hypoglycaemic activity in animals, but it is highly toxic in clinical use [16]. To reduce the side effects of guanidine, some kinds of glucose-lowering biguanides were synthesized in the 1920s, including metformin, phenformin, and butformin (Fig. 1) [17]. The hypoglycaemic activity of metformin was first investigated by Jean Sterne, who performed its clinical research and published the results in 1957 [15]. Phenformin and buformin were withdrawn from clinical use in the 1970s because of their lactic acidosis toxicities, although these two agents exhibited even more potent activities than metformin [18]. The lactic acidosis toxicities of these two biguanide derivatives ever limited the application of metformin, but later on, accumulating evidence, such as its efficient antihyperglycemic effects without overt hypoglycemia or weight-gain side effects, have largely supported the clinical usage of metformin [19]. The United Kingdom Prospective Diabetes Study demonstrated that the early use of metformin could reduce cardiovascular mortality in overweight and obese T2D patients [20]. Metformin was finally approved by the Food and Drug Administration for T2D in 1994 [10]. In fact, metformin is currently used as a medication not only for T2D treatment, but also for treating some other metabolic disorders including polycystic ovary syndrome [8].

3. Structural modification of metformin

The synthetic route of metformin is very simple [21]. Metformin hydrochloride, the most frequently used type of metformin in clinic, is synthesized from dicyanodiamide and dimethylammonium chloride through a simple cyano addition reaction (Fig. 1) [22]. Interestingly, the hydrophilic character of metformin is commonly known to hinder its ability to cross cell membranes via a rapidly passive diffusion thus leading to a slow absorption [23], but a few reports on the structural modification of metformin exist. It is tentative to think that the rationally structural modification of metformin seems to be not simple just because the structure of metformin is simple. This simple structural feature may impose limitations on structural modification, thereby causing difficulties in the structure-activity relationship studies on metformin.

Prodrug is a precursor chemical compound of the parent drug. It is pharmacologically inactive but can be transformed into an active form through a normal metabolic process in vivo [24]. The microwave-assisted synthetic lipophilic sulfenamide prodrugs of metformin improve the permeability and passive absorption of highly water-soluble metformin [25] and improve oral absorption and bioavailability [26]. Sulfonamide prodrugs of metformin that are bioactivated by glutathione-S-transferase enhance the oral absorption of metformin [27]. Therefore, the prodrug strategy is expected to reduce the clinical dosage of metformin and decrease its adverse effects, although the clinical safety of these prodrugs needs to be further investigated.

4. Pharmacological mechanisms of metformin against hyperglycemia

Metformin is widely used for treating T2D with high efficiency in reducing fasting and postprandial blood glucose and lowering glycosylated hemoglobin (HbA1c) in patients [8]. Metformin turns out to be a multi-target agent, although its molecular mechanisms in the treatment of T2D remain debatable [3]. Results have indicated that metformin improves glucose metabolisms predominantly in the liver, muscle, fat, pancreas, and intestine (Fig. 2). The hypoglycemic effect of metformin is closely related to its capabilities in suppression of hepatic glucose production and intestinal glucose absorption, and promotion of β-cell functions and insulin sensitivity [9,11,28].

4.1. Metformin reduces hepatic glucose production

Increasing evidence from clinical studies and pharmacological assays in cell- and animal-based investigations has suggested that the primary function of metformin is to decrease hepatic glucose production, which is largely attributable to its ability in inhibiting gluconeogenesis through multiple pathways (Fig. 3) [11,19,29].

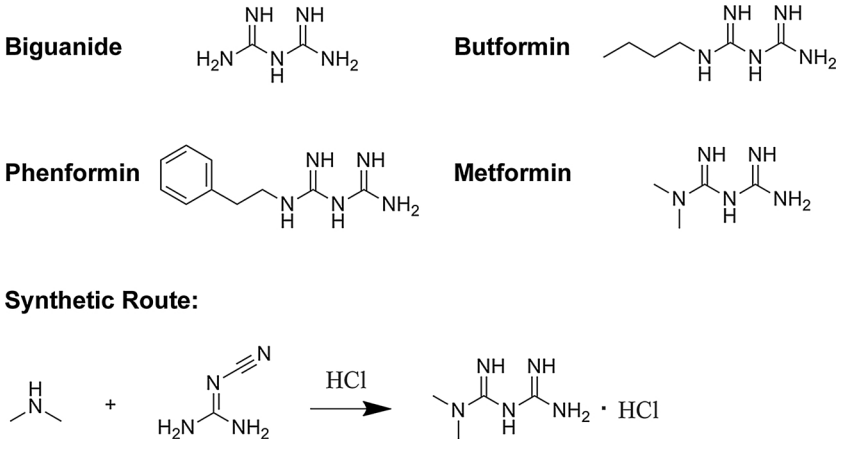

Fig. 1. Metformin is a derivative of biguanide.
Chemical structures of biguanide, butformin, phenformin, and metformin. Metformin is a derivative of biguanide. The synthetic route for the preparation of metformin hydrochloride is briefly indicated. The reaction of dicyanodiamide with dimethylammonium chloride generates metformin through a cyano addition reaction.