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A reappraisal on metformin

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ABSTRACT

This review investigates the different biological effect of Metformin (MET) in different conditions. MET is an oral antidiabetic drug used for the treatment of type 2 diabetes mellitus (T2DM) particularly in overweight people. The main mechanism of action of the MET is inhibition of hepatic glucose production and reduction of insulin resistance. In addition to its antidiabetic effects, MET is also found to be related with the risk for development of several human solid cancers types such as colorectal, breast and pancreas cancer in the diabetic patients. Nowadays according to some researches, MET is believed to decrease or prevent aging and mortality. Moreover, clinical and experimental evidence has shown that MET has beneficial effects in patient with obesity, polycystic ovarian syndrome and Alzheimer's disease. Recent studies have shown that activation of adenosine monophosphate-activated protein kinase (AMPK) by MET can explain its beneficial metabolic effects. In this manuscript, a reevaluation of mechanisms as well as pharmacokinetic properties, genetic variants of transporters, drug-drug interactions, side effects and potential clinical benefits of MET have been reviewed.

1. Introduction

Diabetes mellitus (DM) is the most widespread metabolic disease and it becomes a heavy burden of public health systems (Ke et al., 2016). According to World Health Organization (WHO) Global report on diabetes in 2016, the number of people with diabetes has increased from 108 million in 1980 to 422 million in 2014 (World Health Organization Grod, 2017). International Diabetes Federation (IDF) says that 1 in 11 adults have diabetes in the world and the number of people with diabetes is estimated that there will be 642 million in 2040 (IDF Diabetes Atlas, 2017). Especially it has seen to diabetes prevalence has risen more rapidly low- and middle-income countries, compared to in high-income countries (World Health Organization Grod, 2017).

Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) are the types of DM. T1DM, insulin-dependent diabetes mellitus, occurs when the pancreas fails to produce enough insulin for glucose metabolism. T2DM, non-insulin-dependent diabetes mellitus, is a chronic condition characterized by increased blood glucose levels as a result of resistance to the action of insulin. It begins with insulin resistance, a condition in which cells fail to respond to insulin properly (WHO Diabetes Fact Sheet RN, 2017). T2DM can lead to numerous micro and/or macrovascular complications and may cause substantial disability (Charokopou et al., 2015). As long as the disease progresses, a lack of insulin may also develop (Chandalia and Das, 2012). Deteriorations of beta cell function and insulin resistance are two fundamental pathophysiologic defects of T2DM. Recent studies suggest that beta cell dysfunction develops before onset of T2DM (Saisho, 2015). It was noticed that greater glycemic variability and poorer glycemic control because of β-cell dysfunction may result in increased risk of diabetic disorders. It has been proven that at the time when T2DM was established, the loss of beta cell function was shown to reduce by 50% and this decline of beta cell function progressed over time, although traditional antihyperglycemic therapy had been applied (Wajchenberg, 2007). In order to postpone the progress of disease, new therapies are required to persistently act on beta cell failure and insulin resistance (Ke et al., 2016).

The medical history of metformin (MET) goes back to the use of *Galega officinalis* (the French lilac) extracts, which was utilized in Chinese medicine and also in medieval Europe to treat halitosis and polyuria (Bailey and Day, 1989; Witters, 2001). Later, in France, it was also described that MET is used to treat symptoms of diabetes until the early 1930s (Parturier and Hugnot, 1935). According to researchers in the late 1800s, *Galega officinalis* was rich in guanidine, which had hypoglycemic properties in animals. Thus, the anti-diabetic action of plants was explained (Watanabe, 1918). However, galegine, an isoprenyl derivative, was used in the treatment of diabetes in humans in the 1920s due to its fewer side effects compared to guanidine, whereas the clinical usage of guanidine was determined to be toxic (Muller and Rheinwein, 1927). In the same period, MET that is dimethyl biguanide was also synthesized and has strong effects on lowering blood glucose

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levels *in vivo* (Hesse and Taubmann, 1929). However, since insulin was discovered during the same decade, its clinical application for treatment of diabetes was hindered. In addition to MET, the more potent biguanide derivatives called as phenformin and buformin used clinically to treat T2DM (Bailey and Day, 2004). In the 1950s, Jean Sterne a physician at the Hospital Laennec and Aron Laboratories in Paris independently investigated biguanides as antidiabetic agents and determined MET was the best option for clinical development called "Glucophage" (glucose eater) (Fischer and Ganellin, 2010). Initially, the latter drugs were more widely used; yet, in the 1970s, phenformin and buformin were correlated with life-threatening lactic acidosis (Nattrass and Alberti, 1978). In 1994, MET was approved for use in the United States. The American Diabetes Association and the European Association for the Study of Diabetes have suggested it as the first line oral treatment for T2DM since 2009 (Thomas and Gregg, 2017).

MET is the most widely used an oral antihyperglycemic drug for the treatment of T2DM today. It has also other beneficial effects beyond glycemic control, especially on several disorders such as cancer, aging, Alzheimer's disease, polycystic ovarian syndrome, and obesity due to its different biological properties (Maniar et al., 2017). Nowadays, in addition to its use in diabetes, it is being searched for its role on these subjects.

The aim of this review is to reevaluate the mechanisms and pharmacokinetic properties, genetic variants of transporters, drug-drug interactions, side effects, and give more detailed information about potential clinical benefits of MET in terms of aforementioned major diseases.

2. Methods

2.1. Strategy, inclusion and exclusion criteria of the review

During the literature review, key words and index/subject terms related to the topic were searched in at least publication titles, article titles, article abstracts, and author names. In this literature review, all important publications were taken into consideration by utilizing the peer-reviewed journals, non-peer reviewed literature, and expert reports and examinations. In the context of the review, a total of 120 source references covering the main characteristics and the various clinical impacts, benefits, and outcomes on specific disorders such as cancer, neurology, endocrine, metabolism, and aging of MET was included in the study. While there was no specific exclusion criterion in the study, mostly the publications of 2005 and later were considered.

3. Physicochemical and pharmacokinetic properties of metformin

MET has been synthesized in 1922, and involves the reaction of dimethylamine hydrochloride (1) and 2-cyanoguanidine (2) (Werner and Bell, 1922). (Fig. 1).

The acid dissociation constant values (pKa) of MET is 11.5. Due to its alkaline characteristic, the absorption of MET is higher in alkaline environment. As a consequence its high solubility and low permeability, MET is a class III drug according to the Biopharmaceutics Classification System (BCS) (Kim et al., 2014). Because of the low lipophilicity, MET cannot pass through the cell membranes rapidly by passive diffusion. In the present, there are different bioavailability studies that researchers aim to invent more lipophilic derivatives of MET for better oral absorption and bioavailability (Graham et al., 2011).

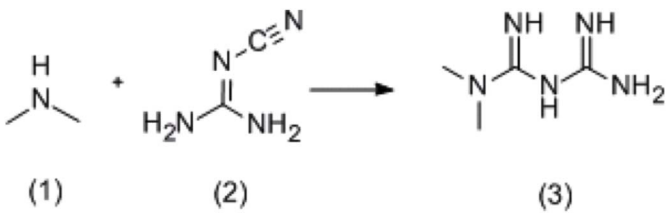

Fig. 1. Chemical synthesis of metformin (Werner and Bell, 1922).

MET is absorbed dominantly from the small intestine (Graham et al., 2011), but this absorption is slow and it is not entirely (Stage et al., 2015; Holguín et al., 2011). The oral bioavailability of 0.5–1.5 g MET is 50–60% (Holguín et al., 2011) and its maximum plasma concentration occurs 2–3 h after dosage (Stage et al., 2015). The half-life of MET is 6.2 h and effects of MET continues for 8–12 h (Drugbank, 2016). MET is rapidly distributed following absorption and it does not bind to plasma proteins. It is not metabolized in the liver and it is excreted without changing in the urine without metabolic change (Graham et al., 2011). It is filtrated freely by glomerular secretion (Stage et al., 2015). The population mean for renal clearance (CLR) is 510 ± 130 ml/min and it is also secreted in the proximal tubules (Graham et al., 2011).

The principal route of MET elimination is active tubular secretion in the kidney. MET is widely distributed into body tissues including intestine, liver, and kidney by organic cation transporters (Graham et al., 2011). These transporters which play a role in the transport of MET, are organic cation transporters (OCTs), multidrug and toxin extrusion transporters (MATEs), and plasma membrane monoamine transporter (PMAT) (Stage et al., 2015).

The intestinal absorption of MET may be primarily mediated by PMAT, which is encoded by gene SLC29A4, and expressed on the luminal side of enterocytes (Zhou et al., 2007). Currently there are no in-vivo data regarding the role of PMAT in the disposition and pharmacological effect of MET. OCT3 (gene SLC22A3) is also expressed on the brush border of the enterocytes and it may contribute to MET uptake (Graham et al., 2011; Muller et al., 2005). In addition, OCT1 (gene SLC22A1), which is expressed on the basolateral membrane and cytoplasm of the enterocytes, may ease the transfer of MET into the interstitial fluid (Muller et al., 2005). The hepatic uptake of MET is mediated primarily by OCT1 and possibly by OCT3. Both of these transporters are expressed on the basolateral membrane of hepatocytes (Graham et al., 2011; Takane et al., 2008; Chen et al., 2010; Nies et al., 2009). In OCT1-deficient mice, the hepatic MET concentration in the liver was significantly lower when compared to the control mice. As a result, it is realized that OCT1 is essential for the hepatic uptake of MET (Shu et al., 2007). Moreover, the glucose-lowering effects of MET were completely prohibited in the OCT1-deficient mice. Also, MET is a good substrate for human multidrug and toxin extrusion 1, MATE1 (encoded by the gene SLC47A1) and MATE2-K (gene SLC47A2) (Takane et al., 2008; Tsuda et al., 2009a; Sato et al., 2008; Tanihara et al., 2007). MATE1 is highly revealing, in the liver, kidney, and skeletal muscle (Otsuka et al., 2005), and may contribute toward the excretion of MET from both the liver and the kidney. However, the role of MATE1 in hepatic secretion has been questioned, as biliary excretion of MET seems to be insignificant in humans (Graham et al., 2011). Data from a mouse study about MATE1 suggest that, at least in rodents, biliary excretion of MET occurs (Ito et al., 2010). The uptake of MET from circulation into renal epithelial cells is primarily expedited by OCT2 (gene SLC22A2) (Takane et al., 2008), which is expressed predominantly at the basolateral membrane in the renal tubules. Renal excretion of MET from the tubule cell to the lumen is mediated through MATE1 and MATE2-K (Tsuda et al., 2009a, 2009b; Sato et al., 2008; Ito et al., 2012). MATE1 and MATE2-K are expressed in the apical membrane of the renal proximal tubule cells, and studies in healthy individuals suggest that they contribute to the renal excretion of MET (Kusuhara et al., 2011). Furthermore, P-gp (gene ABCB1) and BCRP (gene ABCG2) are involved in the efflux of metformin across placental apical membranes (Hemauer et al., 2010).

4. Mode of action of metformin

The mode of action of MET is different from other classes of oral antihyperglycemic agents (Sanders et al., 2007). The ability of MET to