European Journal of Pharmacology 803 (2017) 103–111

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Metformin-like antidiabetic, cardio-protective and non-glycemic effects of naringenin: Molecular and pharmacological insights

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ARTICLE INFO

Keywords:
AMP-activated protein kinase
Diabetes
Naringenin
Metformin

ABSTRACT

Metformin is a widely used drug for the treatment of type 2 diabetes (T2D). Its blood glucose-lowering effects are initially due to inhibition of hepatic glucose production and increased peripheral glucose utilization. Metformin has also been shown to have several beneficial effects on cardiovascular risk factors and it is the only oral antihyperglycaemic agent thus far associated with decreased macrovascular complications in patients with diabetes.

Adenosine Monophosphate Activated-Protein Kinase (AMPK) is a major cellular regulator of lipid and glucose metabolism. Recent evidence shows that pharmacological activation of AMPK improves blood glucose homeostasis, lipid profiles, blood pressure and insulin-resistance making it a novel therapeutic target in the treatment of T2D. Naringenin a flavonoid found in high concentrations as its glycone naringin in citrus fruits, has been reported to have antioxidant, antiatherogenic, anti- dyslipidemic and anti-diabetic effects. It has been shown that naringenin exerts its anti-diabetic effects by inhibition of gluconeogenesis through upregulations of AMPK hence metformin-like effects. Naringin has further been shown to have non-glycemic affects like metformin that mitigate inflammation and cell proliferation. This review evaluates the potential of naringenin as anti-diabetic, anti-dyslipidemic anti-inflammatory and antineoplastic agent similar to metformin and proposes its further development for therapeutic use in clinical practice.

1. Introduction

It is estimated that 642 million people globally and 34.2 million people in sub-Saharan Africa will be diagnosed with diabetes by 2040 (Aguiree et al., 2015). Diabetes end-points such as ketoacidosis, neuropathy, retinopathy, nephropathy and cardiovascular diseases contribute to increased morbidity and mortality not only in the developed but also more devastatingly so in the developing countries. These end-points result from all types of diabetes including Type 2 Diabetes (T2D) which is the most common in adults but is now increasingly being encountered in adolescents (Mary Anne Koda-Kimble et al., 2009). In the past 3 decades, metformin has been recommended as the first-line therapy for T2D in the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the American Association of Clinical Endocrinologists (AACE) treatment guidelines, respectively (Nathan et al., 2006; Garber et al., 2016). Metformin appears to decrease the risk of diabetes-related morbidity and mortality in overweight diabetic patients, but unlike insulin or its secretagogues, it is not associated with weight gain or hypoglycaemic incursions (Viollet et al., 2012). The United Kingdom Prospective Diabetes Study (UKPDS) reported that metformin therapy decreases the risk of macrovascular and microvascular complications of diabetes (UKPDS Group, 1998; Holman et al., 2008). However, despite significant gains with metformin as monotherapy in T2D, a considerable number of patients fail to achieve optimum glycemic control and are either maintained on metformin with insulin or insulin secretagogues, or switched to insulin monotherapy. Furthermore, some patients are intolerant to metformin (Dujic, 2015) or may have developed end-point diabetes complications such as heart or renal failure for which metformin is controversially contra-indicated due to perceived risk of lactic acidosis (Anabtawi and Miles, 2016). In recent times, there appears to be accumulating published evidence in medical literature supporting the efficacy of plant-derived bioflavonoids in the management of degenerative diseases such as diabetes (Vitale et al., 2016). Citrus fruit-derived flavonoid, naringin or its aglycone naringenin have been shown to

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http://dx.doi.org/10.1016/j.ejphar.2017.03.042
Received 12 January 2017; Received in revised form 16 March 2017; Accepted 17 March 2017
Available online 18 March 2017

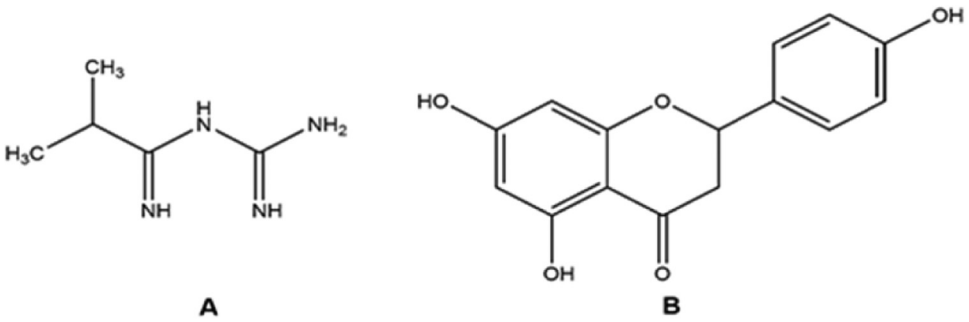

Fig. 1. Chemical structures of A: metformin and B: naringenin. ChemDraw, PerkinElmer®.

have antidiabetic, antidyslipidemic and cardioprotective effects (Owira and Ojewole, 2010; Xulu and Owira, 2012; Ren et al., 2016; Sharma et al., 2015; Bai et al., 2014; Alam et al., 2014). This review examines the similarities between pharmacological effects of naringenin and metformin in diabetes and cardiovascular diseases and provides evidence why it should be incorporated as adds-on therapy or substitute to metformin in clinical practice.

2. Physical-chemical characteristics of metformin and naringenin

Metformin, a synthetic 3-(diaminomethylidene)−1,1-dimethylguanidine is developed from guanides derived from *Galega officinalis* or the "French Lilac" or "Goat ruce" (Bailey and Day, 1989) and formulated as gastro-dispersible tablets of 500 mg of metformin HCl with high water solubility (Fig. 1). Metformin is transported in an electrogenic manner into enterocytes or hepatocytes by Organic Cation Transporter Protein 1 (OCT 1) and/or Multidrug and Toxin Extrusion transporters (MATE) but is not metabolised and is eliminated unchanged in the kidneys through OCT 1/2 and MATE (Markowicz-Piasecka et al., 2016; He and Wondisford, 2015). After absorption from the intestines, plasma concentrations drop from 40 to 70 μM in the hepatic portal vein to 10–40 μM post hepatic uptake at therapeutic doses in both humans and experimental animals (Wilcock and Bailey, 1994). Dosage formulations such as immediate-release, extended-release or delayed-release preparations are clinically available to maximise efficacy and reduce gastrointestinal symptoms (Davidson and Howlett, 2004; Buse et al., 2015).

On the other hand, naringenin (4′, 5, 7-trihydroxyflavanone 7-rhamnoglucoside) like all flavonoids has a chemical structure based on a 15-carbon skeleton consisting of two benzene rings (A and B) linked via a heterocyclic pyrane ring (C) (Fig. 1) (Kumar and Pandey, 2013). Upon ingestion, naringin is hydrolysed by intestinal bacterial naringinase complex to its aglycone naringenin which appears to be biologically more potent (Alam et al., 2014; Ribeiro and Ribeiro, 2008a,b). Naringenin has poor water solubility and the mechanisms by which it crosses plasma membranes are not fully understood as yet but it is known to be extensively metabolised by hepatocytes to its glucuronides and sulphates which are renally excreted (Alam, and Lin et al., 2014, 2014), (Fig. 2). Absorption of naringin as a compound is minimal. However, orally administered naringin is systematically available as naringenin, its aglycone (Alam et al., 2014, Ribeiro and Ribeiro, 2008a,b Lin et al., 2014). Our current data yet to be published indicate that the apparent pharmacological effects of naringin could actually be due to naringinenin. Naringin is rapidly converted to naringenin whether administered orally or IV by either intestinal bacterial or hepatic metabolism, respectively. Variability in bioavailability of orally administered drugs is not a new phenomenon in pharmacokinetics as metformin in its clinical formulations is also equally affected by this process (Wilcock and Bailey, 1994). Furthermore, naringin/naringenin is not yet clinically formulated into dosage forms. This is an area of still ongoing research.

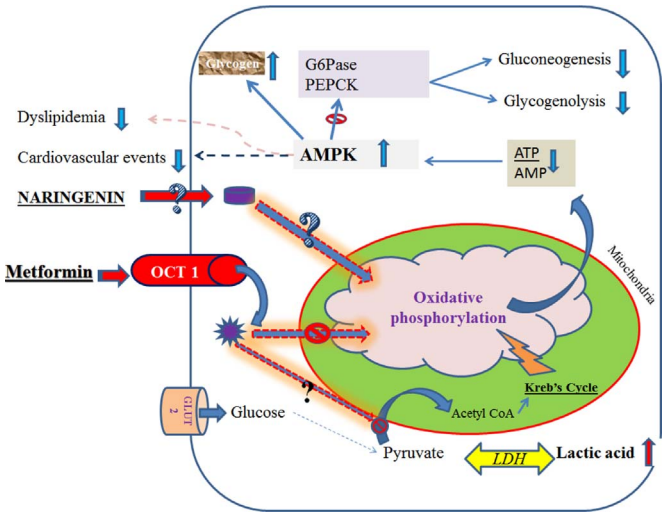

Fig. 2. Known and proposed mechanisms of action of metformin and naringenin in hepatocytes. AMP (Adenosine Monophosphate Protein); AMPK (Adenosine Monophosphate-Activated Protein Kinase); ATP (Adenosine Triphosphate); PEPCK (Phosphoenol-Pyruvate Carboxykinase); G6Pase (Glucose 6-Phosphatase); OCT 1 (Organic Cation Transporter 1); GLUT 2 (Glucose Transporter 2); LDH (Lactate Dehydrogenase).

However, despite the striking structural dissimilarities between metformin and naringenin (Fig. 1), it is intruguing that 2 compounds with diverse chemical structures could possess such pontently similar pharmacological properties. What is known however, is that naringenin like all flavonoids has powerful antioxidant properties (Alam et al., 2014) but it is also now emerging that some non-glycemic pharmacological effects of metformin could be attributed to its antioxidant potential (Yang et al., 2016; Diniz et al., 2016; Obi et al., 2016; Singh, 2016). Could this be the common link to their strikingly similar pharmacological effects? Reduced oxidative stress is known to protect pancreatic β-cells from hyperglycemia-induced apoptosis, diminished insulin secretion and also improve insulin signaling and hence improve glycemic control. So despite structural chemical diversity, the observed pharmacological effects of both metformin and naringenin could be mediated by antioxidant effects as the only property they share in common.

3. Pharmacological effects of metformin and naringenin

Upon its entry into hepatocytes, metformin directly inhibits Electron Transport Chain (ETC) complex 1 which is the rate-limiting step leading to a decrease in both cytosolic and mitochondrial ATP/ADP ratio and concomitant increase in AMP/ATP ratio which allosterically activates Adenosine Monophosphate-Activated Protein Kinase (AMPK) (Fig. 2), (Quinn et al., 2013; Cai et al., 2009). This leads to inhibition of gluconeogenesis by inactivation of transcription of key regulatory enzymes, Phosphoenol-Pyruvate Carboxykinase