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METFORMIN: MOLECULAR MECHANISMS OF ACTION BEYOND THE HYPOGLYCAEMIC EFFECT

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Abstract
Metformin, the main drug for the treatment of type 2 diabetes mellitus, has a multifaceted mechanism of action, which includes inhibition of gluconeogenesis in the liver and increased peripheral glucose uptake and tissue sensitivity to insulin. The compound also has antioxidant and cardioprotective properties, reducing the risk of cardiovascular complications in diabetes. Accumulated data indicate its potential in cancer prevention and therapy, and metformin is a promising multifunctional agent for the comprehensive treatment of type 2 diabetes mellitus.

Introduction

Metformin is a first-line drug for the treatment of type 2 diabetes and is traditionally used to control glycaemia in diabetes. However, experimental and clinical studies show that metformin has pleiotropic activity that is not consistent with the hypoglycaemic effect of the drug. At the molecular level, treatment targets important regulators of cellular metabolism and causes activation of adenosine monophosphate-activated protein kinase (AMPK), changes in mitochondria, and suppression of inflammatory signalling pathways. These actions form the basis for possible cardioprotective, anti-inflammatory, and antiproliferative effects. Thus, the analysis of non-glycaemic factors underlying the action of metformin is important in scientific and clinical literature.

The purpose of this article is to analyse the molecular mechanisms of metformin's action beyond its hypoglycaemic effect.

Materials and Methods:

Analysis of scientific studies cited in the PubMed, Cyberleninka, and National Library of Medicine databases.

Results

Metformin: pharmacology, mechanisms of action, and clinical significance

Metformin, an antidiabetic drug, was approved by the US Food and Drug Administration (FDA) in 1994 for the treatment of type 2 diabetes. [2[Metformin, which has been used in clinical practice for the treatment of non-insulin-dependent diabetes mellitus associated with insulin resistance (DM) (currently

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classified as type 2 DM) for over 60 years, belongs to the biguanide group and is the only representative of this class of drugs recommended for the treatment of type 2 DM. [1]

Mechanism of antihyperglycaemic action

The hypoglycaemic efficacy of metformin is mainly due to a reduction in glucose production by the liver, which primarily leads to a decrease in basal (fasting) glucose levels. However, metformin also has a hypoglycaemic effect by enhancing anaerobic glucose metabolism in the intestine and enhancing insulin-stimulated peripheral glucose uptake. Blood glucose concentrations gradually decrease during the first 1-2 weeks of metformin therapy and then when the dose is titrated.

Studies of isolated mitochondria, submitochondrial particles, mitochondrial membranes, and isolated mitochondrial respiratory chain have shown that the reduction in gluconeogenesis by metformin in hepatocytes may also be associated with moderate and transient inhibition of the mitochondrial respiratory chain complex I. Inhibition of mitochondrial complex I by metformin, which prevents the synthesis of mitochondrial adenosine triphosphate (ATP), leads to an increase in adenosine monophosphate (AMP) levels in the cell. Subsequently, AMP binds to one of the AMPK subunits, making it more susceptible to LKB1 phosphorylation. Activated AMPK increases the liver's sensitivity to insulin and switches hepatocytes from anabolic pathways, such as gluconeogenesis, fatty acid and protein synthesis, to catabolic pathways, such as glycolysis and fatty acid oxidation, consuming less energy and restoring energy balance. By improving insulin signalling and insulin sensitivity, metformin increases glucose uptake and utilisation in skeletal muscle, thereby regulating glycaemic control in people with dysglycaemia. In turn, increasing the sensitivity of adipose tissue to insulin with metformin inhibits lipolysis and reduces the release of free fatty acids [FFA] from adipocytes and their accumulation in the liver and other organs [4].

Clinical Efficacy

Blocks mitochondrial glycerol -3-phosphate dehydrogenase, which plays a key role in the glycerophosphate shuttle mechanism, leading to a deficiency of the oxidised form of nicotinamide adenine dinucleotide (coenzyme NAD+) and suppression of gluconeogenic reactions, including the conversion of lactate to pyruvate [5]

Great interest in the pharmacological properties of metformin arose after the results of the UKPDS were obtained. It showed that metformin administration in a group of patients with T2DM and excess weight led to a significant and substantial reduction in diabetes-related deaths by 42%, overall mortality by 36%, and myocardial infarction by 39% compared to the control group, where only traditional diet therapy was used as treatment [6]

Antioxidant properties

Antioxidant action Oxidative stress plays an important role in the pathogenesis of a wide range of cardiovascular diseases, including IHD and CHF, which often occur as comorbidities in patients with T2DM. Metformin acts as an antioxidant through several mechanisms, including: 1) direct scavenging of hydroxyl radicals that have a toxic effect on tissues; 2) enhancement of the endogenous antioxidant system by increasing the activity of antioxidant enzymes: glutathione reductase, catalase, and superoxide dismutase; 3) reduction of NADPH oxidase production [7].

Antitumour potential

Accumulated data indicate that metformin inhibits the growth, survival and metastasis of various types of tumour cells, including breast, liver, bone, pancreatic, endometrial, colon, kidney and lung cancer cells [8] Metformin activates AMPK, which leads to the inhibition of mTOR signalling, resulting in impaired protein synthesis and suppressed cell growth and proliferation. For example, cross-talk between G protein-coupled receptors (GPCRs) and insulin receptor signalling systems can be inhibited by metformin: this may contribute to the inhibition of pancreatic cancer proliferation. P53 is considered a critical tumour suppressor gene in human cancer. Studies have shown that p53 is involved in the anti-cancer effects of metformin. Metformin activates AMPK and then induces p53 phosphorylation, preventing cell invasion and metastasis. (ii) Metformin also inhibits mTORC1, a key regulator of cell growth that can integrate intracellular and extracellular stimuli, in an AMPK-independent manner. In addition, metformin suppresses mitochondrial complex I, thereby preventing the formation of reactive oxygen species (ROS) and further reducing DNA damage, suppressing cancer development. Previous studies have also suggested that metformin may suppress cancer development by activating autophagy and apoptosis via an AMPK-independent pathway. [9]

Discussions

The dominant agent for the treatment of type 2 diabetes (T2D) is metformin, which has been in medical practice for over 60 years. It works by inhibiting hepatic gluconeogenesis, enhancing peripheral glucose uptake, and stimulating anaerobic glucose metabolism in the intestine at several levels. At the molecular level, metformin partially inhibits mitochondrial complex I and causes an increase in intracellular AMP production and AMPK activation. As a result, the sensitivity of the liver and peripheral tissues to insulin increases, lipolysis in adipose tissue decreases, and the accumulation of free fatty acids decreases, leading to better glycaemic control [3,4,5]. Metformin therapy in patients with T2D and overweight has been shown to be associated with a significant reduction in diabetes-related mortality, overall mortality, and myocardial infarction risk based on clinical studies such as the UKPDS, confirming its important role not only in glycaemic control but also in reducing cardiovascular risk [6]. Metformin also has antioxidant effects, i.e., it can directly scavenge free radicals and increase the activity of endogenous antioxidant enzymes and reduce the production of NADPH oxidase, which is particularly important for preventing cardiovascular complications in individuals with T2D [7]. Accumulated data also suggest that metformin has an antitumour effect. It inhibits the growth of a number of cancer cells and reduces their survival by stimulating AMPK, inhibiting mTORC1, phosphorylating p53, limiting the formation of reactive oxygen species in cells, and enhancing autophagy and apoptosis. These effects can be modulated by AMPK, but also independently of it, which opens up possibilities for the use of metformin to prevent or treat cancer [8,9]. Thus, metformin is a multifunctional compound with hypoglycaemic, cardioprotective, antioxidant, and possibly antitumour effects, representing an important drug in response to T2D and providing a basis for future research in medicine.

Conclusions

Metformin is an effective drug for the treatment of type 2 diabetes mellitus, lowering blood glucose by improving insulin sensitivity and suppressing gluconeogenesis. It also exhibits antioxidant and

cardioprotective effects, which reduce the risk of cardiovascular complications. In addition, metformin has potential antitumour activity, which expands its therapeutic possibilities.

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