Repurposing an Old Drug: A Study on the Potential Pharmacological Effects of Metformin

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ABSTRACT

Serving as a conventional first-line agent against type 2 diabetes mellitus (T2DM), metformin has been fully verified for its safety and efficacy, but its potential pharmacological effects have been continuously explored in recent years. In contrast to the lengthy cycle and high expenses of de novo drug R&D, "old drugs for new uses" has become an efficient path to explore the new value of drugs. Combining the progress of relevant domestic and foreign research in recent years, this article systematically summarizes various potential pharmacological effects of metformin, such as hypoglycemic, anti-aging and anti-tumor effects, and elaborates on its mechanism of action. This research result provides a reference basis for the subsequent in-depth research and clinical transformation of this drug, and has significant academic value.

Keywords: Metformin, Pharmacology, T2DM.

1. INTRODUCTION

1.1 Research background and Research Significance

Diabetes is a complex chronic endocrine disease. With socioeconomic development and the enrichment of people's diets, the number of diabetes patients in China has continued to grow rapidly in recent years. According to the 2025 national diabetes epidemiological survey, the prevalence population aged 20-79 years in China amounts to 116.14 million, ranking first in the world. The adult prevalence rate is 11.9%-12.8%, an increase of about 1.2 percentage points compared with 2021, of which T2DM accounts for 90% of all diabetic patients. However, diabetes treatment guidelines from various countries, led by the American Diabetes Association (ADA) as well as the World Health Organization (WHO) essential medicines list, clearly state that metformin remains an important first-line treatment drug for T2DM. As a drug that has been used clinically for more than half a century, metformin has been applied to new fields due to recent research findings that it also has other beneficial effects. This not only ensures the safety of the drug but also avoids the lengthy process of new drug development and screening. Most candidate drugs fail during clinical trials and enormous R&D investments often end up with no successful commercialization. In contrast, repurposing existing medicines takes full advantage of established safety profiles from decades of clinical use, drastically cutting overall investment costs, thus emerging as a popular research hotspot across global pharmaceutical research. Metformin is a typical example of "old drug, new use [1]". In addition to lowering blood glucose, it also has beneficial effects on anti-aging and tumor immunity [2].

2. STRUCTURE OF METFORMIN

Metformin originates from Galega officinalis and belongs to the biguanide class of derivatives. Its structure features a central carbon atom connected to two guanidine groups, with two methyl groups attached to the central carbon and no chiral center. In recent years, it has attracted widespread academic attention due to its potential anti-tumor effects [3].

3. GLUCOSE-LOWERING EFFECT

Metformin acts the first-line therapeutic drug for treating T2DM, and its core advantage lies in its ability to avoid inducing hypoglycemia, particularly suitable for obese patients. It exerts its hypoglycemic effects primarily through two major pathways: suppression of hepatic gluconeogenesis and accelerated glucose uptake in peripheral tissues [4].

The liver is the primary organ responsible for gluconeogenesis. Under fasting or starvation conditions, the liver could synthesizes glucose from lactate, glycerol, and amino acids to maintain blood glucose stability. In patients with T2DM, hyperactive hepatic gluconeogenesis is one of the main contributors to fasting hyperglycemia. The suppression of hepatic

gluconeogenesis occurs mainly via two mechanisms: the adenosine monophosphate-activated protein kinase (AMPK) pathway and non-AMPK pathways. When intracellular adenosine monophosphate (AMP) levels increase, liver kinase B1 (LKB1) is activated. LKB1 directly phosphorylates the α subunit at threonine 172 (Thr172), thereby activating AMPK [5]. This promotes the translocation of glucose transporters to the hepatocyte membrane and enhances the activity of insulin receptors in liver cells. In the non-AMPK pathway, metformin inhibits complex I of the mitochondrial electron transport chain (METC), causing decreased ATP synthesis and higher AMP levels. As a result, the key gluconeogenic enzyme fructose-1,6-bisphosphatase is inhibited while allosterically stimulates the critical glycolytic enzyme phosphofructokinase, preventing glycerol and lactate from being converted into blood glucose [6].

Furthermore, defective glucose absorption and metabolism in peripheral tissues, especially skeletal muscle and fat cells, is a key characteristic of insulin resistance in T2DM patients. Metformin facilitates glucose absorption in these tissues and optimizes overall glucose utilization. It activates AMPK, promoting the expression and membrane localization of glucose transporter type 4 (GLUT4) and accelerating glucose entry into cells. In part, it may also act through the protein kinase C (PKC) pathway, subsequently activating LKB1 and synergizing with the AMPK pathway [4].

In addition, accumulating evidence has demonstrated that metformin can reshape the gut microbiota. The gut microbiota, a sophisticated microbial ecosystem residing, consisting of abundant bacteria, fungi and other microbial species, serves as a crucial environmental factor closely associated with human health. It participates in the whole process of human growth and development, physiological metabolism, as well as the occurrence and progression of various diseases. Metformin exerts hypoglycemic effects via regulating gut microbes, mainly by preserving intestinal barrier integrity and boosting the production of short-chain fatty acids [7] (SCFAs). Furthermore, the regulatory effects of metformin on gut microbiota vary depending on the host's dietary patterns and health conditions. A high-fat diet profoundly alters the intestinal microbial composition in rodents. Metformin reduces bacterial diversity in mice fed a high-fat diet [8], while it poses no significant impact on those with a regular diet. In mouse models of high-fat diet-induced obesity and insulin resistance, metformin decreases lipopolysaccharide (LPS) levels and protects intestinal barrier function. As an endotoxin located in the cell wall of Gram-negative bacteria, LPS is released upon bacterial lysis and triggers widespread non-specific inflammatory responses in the body. Lee identified that Akkermansia muciniphila has been one of the most dominant single bacterial species in the human intestinal tract. Its population is negatively correlated with serum glucose levels [9] and it is important to maintain mucosal integrity. It can also restrict translocation of pro-inflammatory LPS and ameliorate glycemic metabolism. Relevant studies have shown that its population tends to decline remarkably among patients with insulin resistance and newly diagnosed T2DM [10]. Notably, metformin treatment markedly enriches the abundance of phylum Verrucomicrobia, genus Akkermansia, and Akkermansia muciniphila, thereby contributing to glycemic improvement.

4. ANTI-AGING EFFECT

Metformin has been shown to have the potential to delay aging in models such as C. elegans, drosophila, and rodents [11], and it can reduce mortality in diabetic patients. Nevertheless, it remains uncertain whether metformin can retard aging and alleviate age-related tissue damage in primates. In a 40-month study by Yuanhan Yang et al. [12], the geroprotective effect of metformin on adult male cynomolgus monkeys confirmed that metformin delays age-related phenotypes at the whole-organism level. The researchers developed an innovative monkey aging clock using whole-tissue transcriptomics, DNA methylomics, plasma proteomics, and metabolomics, and applied it to evaluate the effect of metformin on aging. This included comprehensive physiological, imaging, histological, and molecular assessments. The results showed that aging indicators were significantly slowed, and the plasma protein age was reversed by an average of 6.41 years. At the single-cell level with high-precision aging clock assessment, this drug effectively inhibited the cellular aging process across multiple neural cell populations in the brain aging process of various neural cells in the brain. The overall biological age of the frontal lobe of the brain was reversed by 5.90 years, and inhibitory neurons, excitatory neurons, microglia, oligodendrocytes, etc., all showed significant rejuvenation. It can be considered that metformin has significant neuroprotective effects, which help protect brain architecture and strengthen cognitive performance. The anti-aging effects of metformin on neurons are mainly mediated via the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Its core mechanism is as follows: metformin activates the Nrf2 pathway, increases the nuclear localization level of phosphorylated Nrf2, relieves the inhibition of KEAP1, upregulates antioxidant target genes such as HO-1, NQO-1, SOD3, GPX2, and GPX1, and reduces intracellular reactive oxygen species (ROS). Furthermore, it decreases the levels of cellular senescence markers, such as the proportion of SA-β-gal positive cells, and restrains the production of cell cycle arrest proteins such as p21. It repairs nuclear membrane integrity by increasing Lamin B2 expression and reducing abnormal protein aggregation, such as amyloid β (Aβ) and cytoplasmic aggregates. In addition, it enhances neuronal plasticity by promoting dendritic extension, maintaining synaptic connections, and improving the function of the prefrontal cortex and related

cognitive regions. The researchers also performed positive and negative validation of the Nrf2 pathway: after knocking down Nrf2, metformin could no longer alleviate hNeuron aging. Constructing the Nrf2 E82G mutant, which can continuously activate Nrf2, ultimately autonomously reversed hNeuron aging, with an effect superior to metformin treatment alone, and there was no additive effect when the two were combined.

5. ANTI-CANCER EFFECT

In recent years, with the progress of research, metformin is reported to have promising effects against tumor growth. Here, breast cancer, prostate cancer, and lung cancer are taken as examples to discuss its mechanisms of action. Evidence suggests that insulin promotes cell proliferation and survival, while tumor cells frequently show high expression of insulin receptors. Increased insulin levels are linked to higher risks of numerous cancers, including breast cancer, colorectal cancer, and prostate cancer.

5.1 Breast Cancer

Breast cancer is one of the most prevalent malignant tumors in women. Its incidence worldwide has been on the rise since the 1970s, now with approximately 2.3 million new cases and 672,000-854,000 deaths each year, making it a major threat to women's health. It is resulted from the uncontrolled multiplication of epithelial cells in the mammary gland. A growing number of clinical researches have shown that insulin not only promotes tumorigenesis through direct mitogenic effects on breast epithelial cells, but also by regulating insulin-like growth factor (IGF), sex hormones, and adipokines, all of which promote the occurrence of breast cancer [13]. Metformin inhibits breast cancer through AMPK-dependent and non-AMPK-dependent pathways [14]. The AMPK-dependent pathway involves metformin inhibiting mitochondrial complex I in cancer cells, reducing ATP availability and upregulating the AMP/ATP ratio, thereby activating the glycolytic pathway and LKB1, activating AMPK, inhibiting mTOR signaling, activating P70S6K and PS6, promoting cell apoptosis, and inhibiting protein synthesis. In the non-AMPK pathway, metformin lowers systemic insulin levels. It reduces mitogenic stimulation through the insulin and IGF-1 pathways. By lowering blood glucose levels and the IGF-1 ratio, it inhibits the PI3K/AKT/mTOR signaling pathway, thereby suppressing tumor proliferation [15].

5.2 Prostate Cancer

Prostate cancer (PCa) represents the most prevalent male cancer and ranks as the second primary cause of cancer-high mortality in males [16]. The research about PCa have risen slightly during these years, and some pharmacologists have noted that metformin may help prevent and treat prostate cancer [17]. Jessica Whitburn et al. investigated [18], on one hand, the direct effect of metformin is mediated through AMPK activation, similar to the mechanism described above for breast cancer inhibition. On the other hand, the indirect one is realized through the suppression of gluconeogenesis in the liver. Hepatic AMPK is activated restrains the transcription of key gluconeogenic enzyme genes and promotes glucose absorption in muscle cells, leading to decrease both blood glucose and insulin levels [19]. Lower systemic insulin levels then cause the inhibition of the PI3K pathway, which is critically involved in cell growth, proliferation, differentiation, and migration, which is the second major driver of prostate cancer growth, ultimately reducing tumor incidence.

5.3 Lung Cancer

Globally, lung cancer is the most common cancer and it also stands among the leading causes of death from malignant tumors in both men and women. In China, new lung cancer cases account for 1/3 of the global total, with non-small cell lung cancer (NSCLC) dominating, accounting for 80%-85% [20]. Based on Zhang's meta-analysis [21], the use of metformin has the potential to decease the risk of lung cancer significantly. Currently, the mainstream anti-lung cancer pathways are still the activation of AMPK and suppression of IGF pathway mentioned above. However, Antouin Levy et al. [22] found that other two ways to eliminate lung cancer, one is to increase the amount of CD8+ tumor-infiltrating lymphocytes (TILs), the other is to activate the ATM-checkpoint kinase 2 (Chk2) pathway, thereby promoting cell apoptosis.

6. DISCUSSION AND CONCLUSION

Metformin has a long history of clinical application and serves as a well-established pharmaceutical agent for T2DM. However, its therapeutic effects on diseases other than T2DM have always received widespread attention in the academic community. More and more studies have confirmed that metformin has potential anti-cancer effects, and recently its anti-aging effects have also been discovered. However, most current medication cases only involve diabetic patients, and the anti-aging effect has only been demonstrated in primates. Future research needs to further verify and clarify the effects of metformin on patients with different diseases, especially non-diabetic patients. Conventional cytotoxic anticancer drugs

clinically available fail to selectively target malignant cells. They damage normal body tissues alongside tumor elimination, frequently inducing adverse reactions such as myelosuppression, alopecia, nausea and vomiting. Metformin with low adverse effects provides a promising adjuvant therapeutic option to ease the drawbacks of traditional chemotherapy, but the dosage, treatment duration, and target population in non-diabetic patients still require extensive clinical research. Finally, the synergistic effects of metformin with first-line therapies for certain diseases and their underlying mechanisms, as well as potential drug interactions, warrant further investigation.

In summary, this review analyzes and discusses the glucose-lowering effect of metformin, its anti-aging effect, and its inhibitory effects on various cancers such as breast cancer and prostate cancer. Its main mechanisms include AMPK pathway-mediated glucose lowering; Nrf2 pathway-mediated neuronal antioxidation and anti-aging; and activation of AMPK with inhibition of mTOR signaling to suppress cancer cell growth. Therefore it expected to be further developed and applied as a novel therapeutic agent for tumor treatment. However, as a first-line treatment for T2DM, the feasibility of using metformin in non-diabetic individuals with cancer still requires further validation.

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