® Postepy Hig Med Dosw (online), 2017; 71: 170-175
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 2016.06.12
Accepted: 2016.11.25
Published: 2017.03.02

Metformin – its potential anti-cancer and anti-aging effects

Metformina – potencjalne działanie przeciwnowotworowe i przeciwstarzeniowe

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Summary

The generally accepted mechanism of metformin's effect is stimulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK). AMPK is directly activated by an increase in AMP:ATP ratio in metabolic stress conditions including hypoxia and glucose deprivation. Lately, many novel pathways, besides AMPK induction, have been revealed, which can explain some of metformin's beneficial effects. It may help to identify new targets for treatment of diabetes and metabolic syndrome. Moreover, metformin is now attracting the attention of researchers in fields other than diabetes, as it has been shown to have anti-cancer, immunoregulatory and anti-aging effects. The aim of this review is to describe the potential anti-cancer and anti-aging properties of metformin and discuss the possible underlying mechanisms.

Keywords: metformin • cancer • aging • AMPK • mTOR

Full-text PDF: http://www.phmd.pl/fulltxt.php?ICID=1232528
DOI: 10.5604/01.3001.0010.3801
Word count: 1574
Tables: –
Figures: 2
References: 57

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Introduction

Metformin is a biguanide derivative widely used in clinical practice as an anti-diabetic drug. It inhibits hepatic gluconeogenesis and triggers glucose uptake in skeletal muscles [50,52]. The drug is well tolerated and safe with known pharmacokinetics [50,52]. Because of its properties, metformin is presently the first-line drug for the treatment of type 2 diabetes (T2D). Interestingly, there is a quickly growing body of literature demonstrating its potential in the therapy of multiple disorders other than diabetes, [33,43,52]. Many epidemiologic analyses have reported that metformin may improve prognosis of cancer patients and also may prevent tumor initiation [18,51]. Moreover, there is evidence suggesting that metformin acts as an anti-aging factor and modulates the microbiota, promoting health [45]. Thus, metformin is currently being investigated for new applications. The precise mechanisms of metformin's action have not been entirely explained yet, but many pathways may be involved. The present review focuses on potential anti-aging and anti-cancer properties of metformin and discusses possible underlying mechanisms.

Mechanisms of metformin action

Metformin is the drug indicated as the first-lime therapy of T2D. This type of diabetes is the most frequently diagnosed and is characterized by hyperglycemia resulting from insulin resistance and reduced insulin secretion. Metformin acts mostly via inhibition of hepatic gluconeogenesis. Its anti-hyperglycemic influence is also mediated by an increase of hepatic insulin sensitivity and absorption of glucose in muscles [27,45].

Mitochondria seem to be a significant target for metformin. Its principal function is ATP synthesis by oxidative phosphorylation. This process results in production of energy through oxidation of nutrients that create an electron chemical gradient across the mitochondrial inner membrane. Such a gradient is used as a source of energy that allows ATP synthesis, transport of ions and heat production [56]. Oxygen radicals, e.g. reactive oxygen species (ROS), are also produced in mitochondria, which may be toxic for cells and cause DNA, protein and lipid damage. It is a cause of oxidative stress and mitochondrial dysfunction. Mitochondrial dysfunction has been reported to be related to insulin resistance in tissues such as skeletal muscles, liver, fat, heart and pancreas [26,34,54].

The widely accepted mechanism of metformin action is stimulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) [50,56]. AMPK is activated by an increase in AMP:ATP ratio in metabolic stress conditions including hypoxia and glucose deficiency [24]. Thus, AMPK can act as an indicator of energy levels in cells [14]. In hepatocytes metformin accumulates within the mitochondrial matrix and targets complex I of the mitochondrial respiratory chain [42,53]. Once complex I is inhibited, it results in a reduction of ATP production and an increase in ADP and AMP levels, which leads to AMPK activation [25,42,53]. AMPK inhibits gluconeogenic gene transcription. Moreover, it inhibits lipogenesis, which improves insulin sensitivity [20,21,31,45]. Mitochondrial stress may also influence tissue metabolism independently of AMPK stimulation [28].

Recently, some new pathways, besides AMPK activation, were discovered, which can explain the additional positive properties of metformin. The decrease in cellular energy level can directly inhibit the gluconeogenic process. Moreover, increased AMP leads to inhibition of adenylate cyclase, resulting in lowering of cAMP production. As a result the activity of PKA (protein kinase A) and its targets, such as CREB (cyclic AMP response element binding), are inhibited. Metformin stops the activity of mGPD (glycerol-3-phosphate dehydrogenase) as well. In turn it prevents glycerol usage in gluconeogenesis. The cytosolic redox state is increased, which reduces the use of lactate as a gluconeogenic substrate [13,35,45,48].

These novel properties of metformin are now attracting the attention of researchers in fields other than diabetes, as the drug has been reported to have anti-cancer, immunoregulatory and anti-aging effects [33,43,52]. Such new mechanisms of metformin are described in detail below.

Metformin influences longevity

Two different mechanisms are described as the primary causes of aging. The first one – the ROS theory – refers to cumulative DNA damage caused by ROS, the by-products of oxidative phosphorylation. The second one is the TOR theory, and it is connected with constitutive stimulation of mitogen – and nutrient-sensing mTOR/S6 signaling [23]. The cellular pathways upstream of mTOR such as the IGF-1/GH axis, MAPK, AKT, and PI3K are the targets for aging inhibition. They may be stimulated by mitogens, growth factors, sugars and amino acids. On the other hand, calorie restriction, mimetics such as 2-deoxy--Dglucose and blockers of mitogens and growth factors such as somatotropin and IGF-1 may suppress mTOR signaling pathways [4,5,8]. It is supported by the fact that the mutations reducing growth hormone (GH) and IGF-1 signaling in mammals are associated with a prolonged lifespan [6,7]. The specific inhibitor rapamycin may directly inhibit the kinase activity of mTOR. It is widely reported that rapamycin has gero-suppressive effects such as extending the lifespan, preventing age-related disorders or reducing costs of patient care [11,17]. AMPK activation leads to indirect inhibition of mTOR; thus metformin as an AMPK activator is shown to have gero-suppressive effects [41]. Extended longevity and lifespan were shown in experiments with mice fed with metformin and rapamycin [2,3]. The use of metformin as an anti-aging drug has been recently suggested based on its wide application in clinical practice as well as its well-known pharmacokinetics and acceptable toxicity [3].

Among gero-suppressive mechanisms the activation of autophagy plays a significant role as well [46,55]. The process is induced by nutrient deficiency that leads to subcellular membrane rearrangement. As a result, double-membraned autophagosomes enclosing cytoplasmic constituents and organelles are formed [39,46]. Autophagy protects the nutrient supply and the proper function of cell organelles [28]. Genes involved in regulation of autophagy are critical for longevity of different organisms from yeasts, flies and nematodes up to mice. It was also reported that induction of autophagy may extend the lifespan [17]. Polyamines are the most effective activators of autophagy, and induction of this process is associated with suppression of signaling along the IGF and mTOR pathways [40,49] Thus, inhibitors of these pathways such as rapamycin or metformin can be activators of autophagy [36]. Anti-aging effects of metformin are presented in Fig. 1.

Metformin exhibits anti-cancer effects

Recently, it was widely proposed that metformin could be protective against neoplastic diseases. The anti-

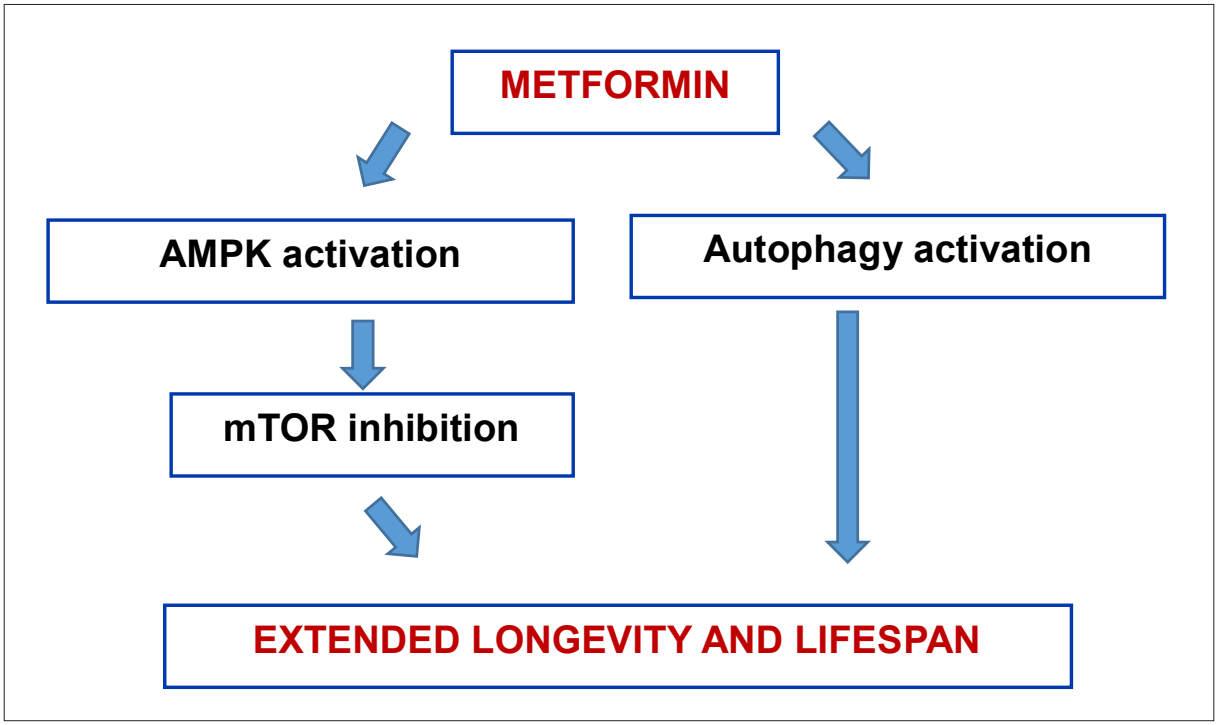

Fig. 1. Anti-aging effects of metformin

-cancer activities of metformin are associated with both indirect and direct effects of this drug. The indirect mechanisms result from general modifications of blood glucose and insulin levels, which could influence the survival of cancer cells [52]. It is reported that insulin and insulin-like growth factor 1 (IGF-1) can promote tumorigenesis by stimulating the proliferation of epithelial cells [44,45]. Decreasing the insulin level as a result may prevent such neoplastic activity. Metformin can also affect the inflammatory processes that are reported to play a significant role in tumor progression. Blocking of transcription factor nuclear factor-κ B (NF-κ B) activity mediated by metformin results in reduced secretion of pro-inflammatory cytokines [38]. Additionally, metformin has been reported to activate the immune response to cancer cells [45]. For example, it has been found that the drug improved the effectiveness of an experimental anti-cancer vaccine that was mainly mediated by activation of memory T cells [43]. The direct anti-cancer effects of metformin are connected with AMPK-dependent and AMPK-independent mechanisms [52]. These are summarized in Fig. 2.

AMPK-dependent mechanisms of metformin's anti-cancer effects

The activation of the AMPK pathway may be significantly involved in the anti-cancer mechanisms of metformin's action. A key consequence of AMPK activation is inhibition of mTOR signaling – the major regulator of cell growth and proliferation [22]. It was also reported that metformin can act as an anti-folate drug [15,16]. Similarly to anti-folate chemotherapeutics, this mechanism damaging the metabolism of folates leads to inhibition of cancer cell proliferation. The cell cycle regulation via interactions with classical oncogenes and tumor suppressors, which may be induced by AMPK, is considered as the next mechanism responsible for anti-cancer properties of metformin. Experimental research provides evidence that metformin down-regulates c-MYC in an AMPK-dependent manner in breast cancer cell lines [12]. AMPK has also been found to target p53 and induces cell-cycle arrest by Ser15 phosphorylation of p53 protein [14,29].

AMPK-independent mechanisms of metformin's anti-cancer effects

AMPK-independent mechanisms can also explain the anti-cancer mechanism of metformin action. The drug can inhibit cell DNA damage by preventing ROS generation by complex I [1]. Furthermore, metformin can induce activation of mTORC1 in the absence of AMPK [30]. Some research provides evidence that the anti-neoplastic effect of metformin is mediated by AMPK-independent inhibition of cyclin D1, which is an important regulator of the cell cycle [9]. Such inhibition is reported to be connected with p53-dependent up-regulation of REDD1 that is a result of the DNA damage response [10]. It was shown that metformin up-regulates apoptosis and autophagy in esophageal squamous cell carcinoma, which leads to reduction of tumor growth [19]. This was mediated by inactivation of the Stat3 (signal transducer and activator of transcription 3)-Bcl2 pathway. This pathway is only marginally deteriorated by AMPK knockdown, which indicates a rather limited con-

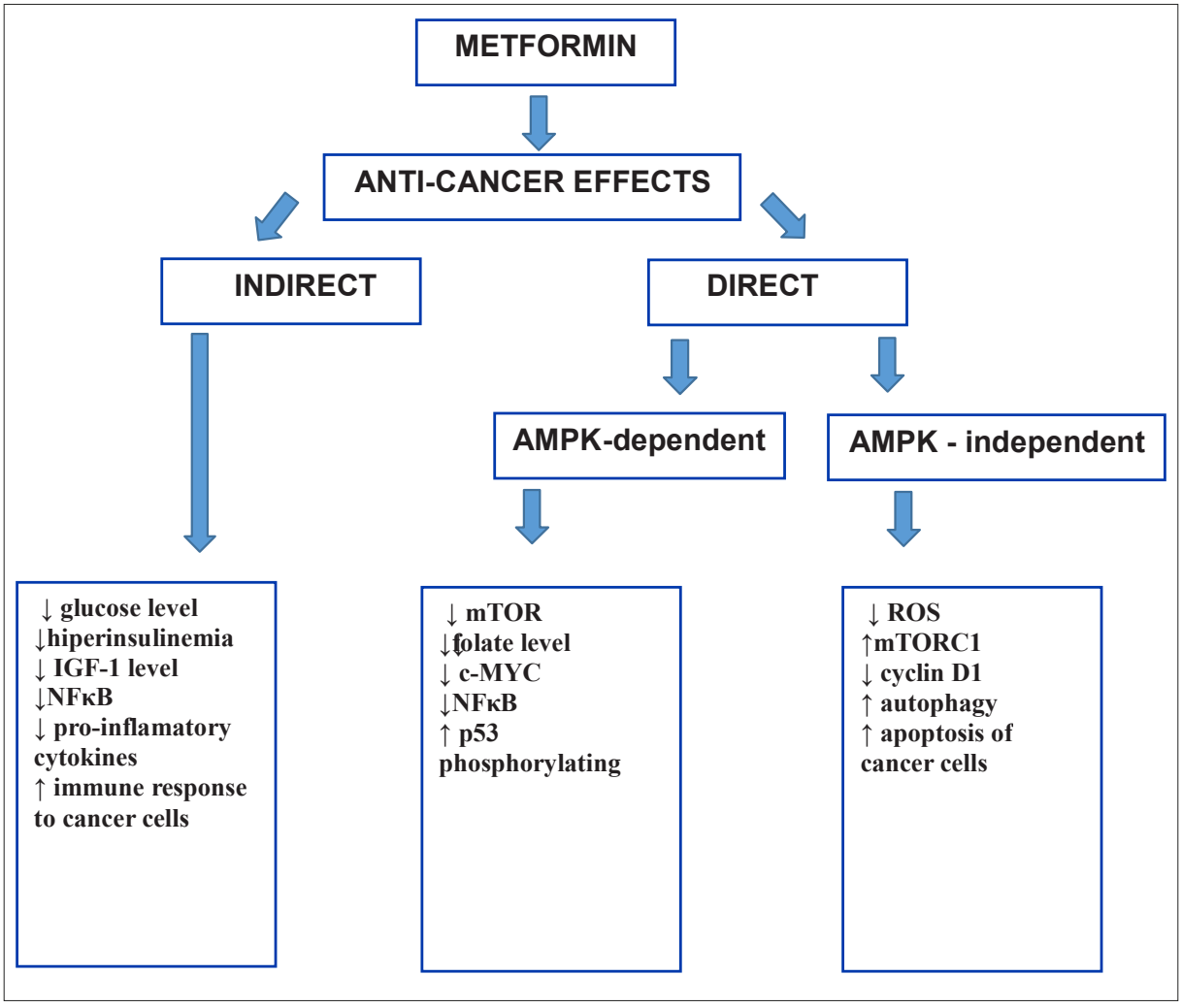

Fig. 2. Anti-cancer effects of metformin

tribution of AMPK. It was also reported that metformin reduced glucose uptake in lung cancer and breast cancer cells. Inhibition of such an energy source leads finally to mitochondrial depolarization and programmed cell death [32,47].

Conclusions

Metformin is currently approved for treatment of T2D, but its therapeutic potential in the treatment of other diseases was recently reported. In particular, the anti-cancer and anti-aging effects of metformin seem to be promising. There are a number of mechanisms reported to be responsible for these effects, which have been described in this review. However, further studies in this subject are still required, and numerous mechanisms must still be explained.

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The authors have no potential conflicts of interest to declare.