



Antiaging Effects of Metformin; Mechanism of Regeneration of Cells

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ABSTRACT

Aging is a time-dependent inevitable process, in which cellular homeostasis is affected, which has an impact on tissue function. This represents a risk factor for the development of numerous non-transmissible diseases. In consequence, the scientific community continues to search for therapeutic measures capable of improving quality of life and delaying cellular aging. At the center of this research is metformin, a widely used drug in Type 2 Diabetes Mellitus treatment that has a reduced adverse effects profile. Furthermore, there is evidence that this drug has beneficial health effects that go beyond its anti-hyperglycemic properties. Among these effects, its geronto-protection capability stands out. There is growing evidence that points out to an increased life expectancy as well as the quality of life in model organisms treated with metformin. Therefore, there is an abundance of research centered on elucidating the mechanism through which metformin has its anti-aging effects. Among these, the AMPK, mTORC1, SIRT1, FOXO, NF.κB and DICER1 pathways can be mentioned. Furthermore, studies have highlighted the possibility of a role for the gut microbiome in these processes. The next step is the design of clinical essays that have as a goal evaluating the efficacy and safety of metformin as an anti-aging drug in humans to create a paradigm in the medical horizon. The question being if metformin is, in fact the new anti-aging therapy in humans.

Keywords: Metformin, Type 2 diabetes mellitus, Ageing, Anti-aging drugs, Cellular regeneration, Autophagy.

INTRODUCTION

Metformin is the most priority treatment especially in Type-2 diabetes. It belongs to the drug class biguanide hypoglycemic. Metformin discovery work had been started from plant *Galega officinalis* in the 17th century and was first launched in 1920's in France by Jean Sterne by adding ammonia group in Galegine [1]. Galgine was the active compound used for the treatment of diabetes like symptoms. Later in 1950's metformin was first approved for use against diabetes and also recognized in European countries and approved in United States in 1995 (Figures 1 and 2).

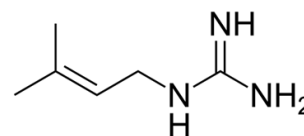


Figure 1: Structure of Galegine.

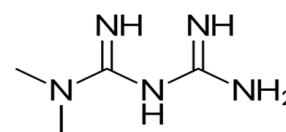


Figure 2: Structure of Metformin.

Metformin has very good tolerance and drug profile. This is the reason it is used globally for glucose uptake in diabetes type 2. Furthermore, it is getting focus of scientists and there is literature increasing day by day explaining its potential use in the treatment of multiple disorders alongside diabetes [2-4]. Many studies provide adept knowledge for its therapeutic effects in cancer, autoimmune disease, neuro-degenerative diseases and even helps in the regeneration of body cells that leads to explain its anti-aging effects [5-7] (Figure 3).

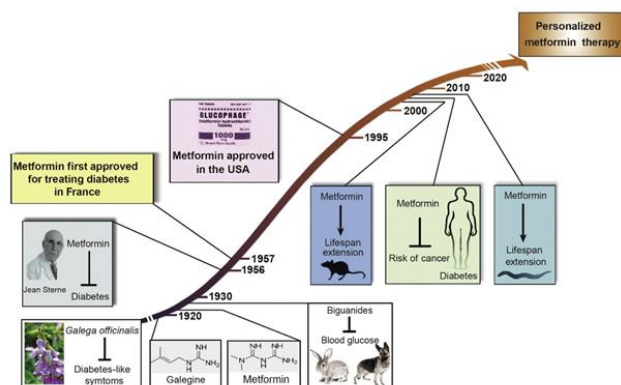


Figure 3: Evolutionary eras in the journey of super drug, Metformin.

Owing to its anti-aging mechanisms, metformin stimulates microbiota that in term are helpful in the promotion of growth cells and hence improves health [8,9]. Because of multiple actions of metformin the exact mechanism of action of metformin is unknown yet. However the present review focuses on the anti-aging effects of metformin and possible underlying mechanisms.

LITERATURE REVIEW

Mechanism of action of metformin

Metformin is the drug indicated as the first-line medical care of T2 Diabetes. This sort of polygenic disorder is most often diagnosed and is characterised by symptom including hyperglycemia resulting in insulin resistance and reduced internal secretion of insulin. This antidiabetic drug acts principally *via* inhibition of hepatic gluconeogenesis. Its anti-hyperglycemic influence is additionally mediated by a rise of hepatic insulin sensitivity and absorption of aldohexose in muscles [10,11]. Mitochondria appear to be a major target for metformin. Its principal performance is adenosine triphosphate (ATP) synthesis by biological process. This method leads to production of energy through oxidization of nutrients that make an electron gradient across the mitochondrial inner membrane. Such a gradient is employed as a supply of energy that enables

adenosine triphosphate synthesis, this transportation of ions is an exothermic reaction [12].

Oxygen radicals, e.g. reactive oxygen species (ROS), are created in mitochondria, which can be hepatotoxic for cells and cause damage to DNA, macromolecule and super molecule like lipids and fats. It is a reason behind aerobic stress and mitochondrial pathology and dysfunction. Mitochondrial damage has been reported to be associated with resistance of internal secretion of insulin in tissues like skeletal muscles, liver, fat, heart and pancreas [13-15]. The wide accepted mechanism of action of Metformin is stimulation of adenosine monophosphate (AMP)-activated macromolecular enzyme the protein kinase (AMPK) [16,17]. AMPK is activated by high levels of ratio between adenosine triphosphate and adenosine diphosphate in metabolic stress conditions together with deficiency of oxygen level and blood glucose [18-30] (Figure 4).

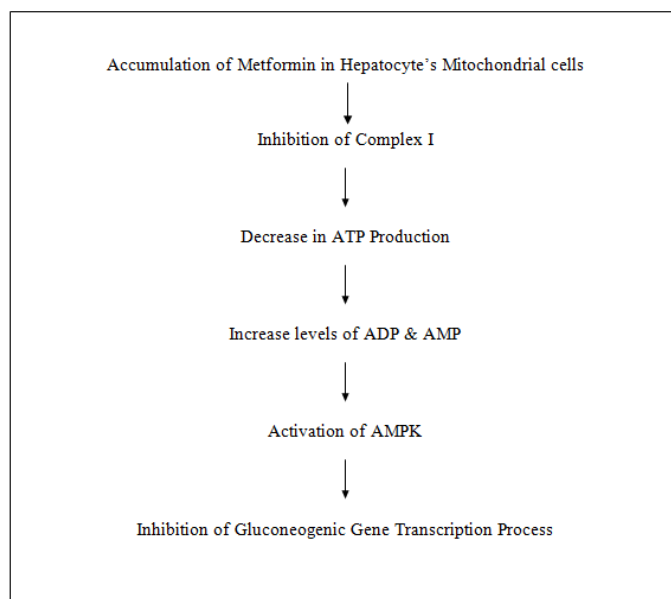


Figure 4: Flow chart showing activity of Metformin.

Uncertainty in the actions of metformin as an anti-aging therapy in humans

Despite the effects of metformin to reduce aging process there are sides by risks of adverse drug reactions that have been observed in the population taking therapy of metformin [31,32]. These side effects include nausea, diarrhea, vomiting, indigestion, abdominal discomfort etc. However these side effects may be diminished with the passage of time or may be minimized by taking drug with food and gradual increase in dose [33,34].

Furthermore metformin has variable effects in different populations. However this point is unclear whether its effects as anti-aging are similar for those with diabetes type 2 and without diabetes [35-37] (Figure 5).

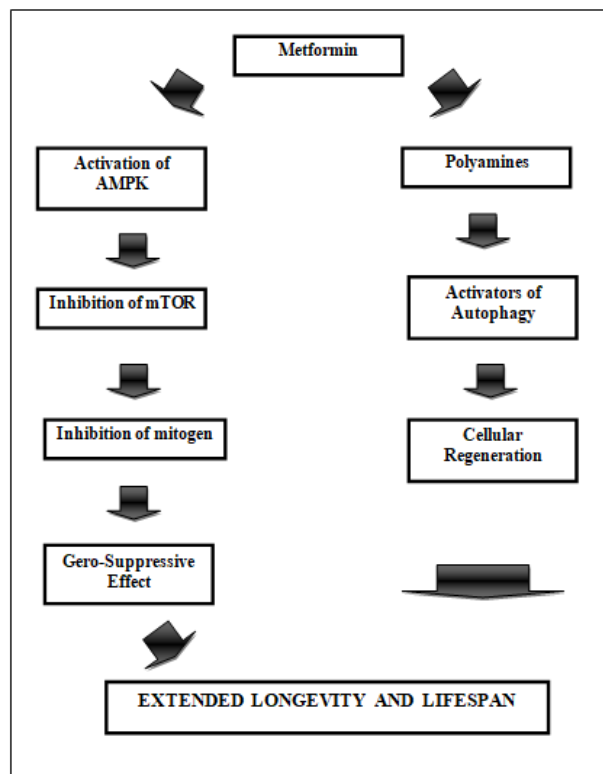


Figure 5: Metformin role in gero-suppression and autophagy.

CONCLUSION

Metformin has over sixty years history of its safe use as hypoglycemic agent against diabetes type 2. It has also been reported for its safe effects in neurodegenerative diseases, cancer and cellular degeneration. These mechanisms support its use as anti-aging therapy in different populations. Aging is a heterogeneous process and different population reacts differently in this regard. However, further studies and large scale, multi-centered, randomized, placebo controlled trials are necessary to explain the anti-aging effects of metformin. We also recommend that individual precision approaches may also be necessary for the clinical trials of metformin as anti-aging. For better results of these trials we should have accurate and better biomarkers which could clearly indicate the pathology of aging process in different population and correlate with favorable effects on the improvement of life span and longevity.

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