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Review Article

Role of Metformin in Infection

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Abstract

Metformin is the most extensively used type II diabetes drug which has shown probable usages in other disease domain in the capacity of an anticancer, anti-ageing, weight management, cardioprotective, neuroprotective etc. It has also been observed that metformin use is associated with reduced risk of hospital acquired infections. It has shown to be potent against multiple numbers of pathogens, which expand metformin scope from anti-diabetic to an anti-infective agent.

Discussion

French lilac, a perennial herb, was used during the Middle Ages or maybe earlier in managing diabetes. Guanidine saws isolated from G. officinalis which was shown to lower blood glucose level in the animal but found to be toxic. Metformin is one of the biguanide, first synthesized in 1929 and developed clinically in the late 1950s and was named Glucophage - "glucose eater". In 1994 it got FDA approval and became generic in 2002 making it one of the widely used and most affordable diabetes treatments. Metformin the most extensively used 1st line therapy for type II diabetes has distinguishable its application in dissimilar disease indication of late. The simple biguanide used for treating non-insulin-dependent diabetes mellitus reduces glucose production and uplift insulin mediated glucose uptake and this in turn decline glucose production. Metformin is unalike chemically and pharmacologically from groups of oral antidiabetic class of chemicals. Metformin is obtained in a one pot reaction by heating dimethylamine hydrochloride and 2-cyanoguanidine [1,2].

The laboratory method of preparation of Metformin is pretty simple and the yield is around 96%. An equimolar quantity of dimethylamine and 2-cyanoguanidine, when dissolved in toluene with cooling a concentrated solution is obtained to which an equimolar amount of HCl is added to obtained metformin hydrochloride. However, Metformin Hydrochloride in a pure form, which is substantially free from impurities like melamine and cyanoguanidine, can be prepared in one pot. The dimethylamine hydrochloride is prepared in situ by purging dimethylamine gas into the water followed by treatment with HCl to get dimethylamine hydrochloride. Excess water is removed by distillation under vacuum followed by azeotropic distillation using xylene. Finally dicyandiamide (DCDA) is added into the flask and the reaction mass is heated up to 135-140^{0}C for 5-10 hours to attained complete conversion. On completion of the reaction metformin is extracted into water and concentrated and cooled followed by centrifugation and finally a methanol wash resulted in pure metformin. Metformin lowers the glucose level and in turn improves insulin sensitivity [3]. Its epistasis effect has drawn much attention.

The common side effect associated with metformin treatment is mild gastric reflux which can be addressed by adjusting the doses basically starting a low dose and then increasing slowly. Another side effect lactic acidosis caused by metformin is rare. Many clinical benefits and minor side effect has made this antihyperglycemic agent a preferred combination drugs with other oral agents. It has been shown to decrease food intake [4] and body weight [3] in some studies. Moreover, this drug can positively influence lipid profile [3,5] and fatty liver [6], modulate inflammatory markers [7,8] and possibly reduce cancer risk [9] and of late in tuberculosis treatment [10].

Guanidines were isolated from goat's-rue, in the early 20th century and concede that it could lower blood glucose level in the animal but found to be toxic. Chemists started to have an alternate approach to make this compound more tolerable by bonding two guanidine together, forming biguanidine. The laboratory synthesis of metformin was first established in the year 1929. Jean Sterne, a French physician clinically developed it in the late 1950 and coined its name as Glucophage (glucose eater).

Phenformin and buformin, the other two biguanidine were also produced during the same time but withdrawn as both were associated with an unacceptably high incidence of lactic acidosis which was proven fatal.

Enough studies on metformin have been carried out in terms of its safety and efficacy. It was one of the landmark studies by UKPDC (United Kingdom Prospective Diabetes Study) [11] which placed metformin on the global map. This study has shown that Type II diabetic people who were under metformin treatment and who were obese and overweight lived longer and had fewer heart attacks than those under insulin or sulfonylurea treatment. Metformin got approved by FDA in 1994, assuring access to the rising star of diabetes to Americans. It became generic in the year 2002, making it one of the least expensive diabetic treatments.

It has been shown by various studies that AMPK signalling pathways is the key actuator of various metabolic pathways and it's a mechanistic knob of cellular energy homeostasis. Metformin activates this AMPK pathway by elevating phosphorylation at the Thr172 site. A high concentration of metformin has shown to inhibit the complex

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I of the mitochondrial ETC (Electron Transport Chain) which in turn lead to uplifted ADP/ATP and AMP/ATP ratios [12].

Metformin mode of action has been gestated in three different modes

Mechanism of action through AMPK and mTORC1

Supratherapeutic concentration of metformin leads to inhibition of complex I of the mitochondrial ETC, which in turn elevate AMP concentration and supress glucogenesis by inhibiting cAMP/PKA pathway. The elevated AMP: ATP ratio is the result of activation of AMPK pathway by allosteric activation AMPK protein. AMPK is the upstream target of mTOR. AMPK promotes catabolic response whereas mTOR promotes anabolic response. AMPK suppress mTORC1 activity by directly phosphorylating TSC2 tumour suppressor and mTORC1 binding subunit raptor and in turn down regulate pathways involving protein synthesis, cell survival, cell growth and proliferation [13].

Mechanism of action through LKB1

In this classical model metformin in its therapeutic concentration acts via tumour suppressor gene serine-threonine kinase LKB1 which is an upstream kinase activate AMPK pathway by phosphorylating it. AMPK pathway activation initiates autophagy and leads to inhibition of glucose production [14] via phosphorylation of the proteins CBP and CRTC2.

Mechanism of action through AXIN

The inhibition of transmembrane protein ATPase is accomplished at the therapeutic concentration of metformin which increases AMP/ATP ratio and activates AMPK via allosteric activation and also promote AXIN-LKB1_ATPase, which ultimately leads to inhibition of mTORC1 [15].

Use of Metformin in Infection and avoid of Resistance

Pseudomonas aeruginosa pathogen affects patients with suppressed immunity. This leads to a number of infections including pneumonia, diabetic foot and urinary tract infections. Antibiotics are used to treat bacterial infection. However due to developed resistance and lack of new antibiotics, it is now a bare necessity to develop new therapeutic approaches to overcome antibiotic resistance. This can be addressed by interfering with the virulence of bacteria. Targeting virulence makes no stress on bacterial growth and can avoid the emergence of resistance. Many studies have shown that biofilm can shield pathogen from phagocytosis and also increase tolerance to drug treatment. The higher tolerance towards drug treatment is due to the result of slower growth rate and lower metabolic activity.

Metformin has been shown to be a novel quorum sensing inhibitor in PAO1 which encouraged it to be used as an anti-virulence agent in treatment of Pseudomonas aeruginosa infection [16]. Hydrolytic enzymes produce by Pseudomonas aeruginosa facilitate the spread of bacteria inside the host tissues and thereby developed resistance to host immunity. Some studies have reflected light on inhibition capacity of metformin on hemolysine, elastase and protease to different extents.

The Intervention of Metformin increase mitochondrial ROS (mROS) production which in turn turnoff mitochondrial complex 1 (NADH dehydrogenase) [17] resulting in phagosome lysosome fusion and ultimately promote bacterial killing. Metformin has also shown to induce CD4 and CD8 T cells in the lung of mice infected with Mtb. Accumulation of CD4 and CD8 cells contribute towards the control of Mtb infection [10].

An in vitro and in vivo study by Chiaki Kajiwara et al has shown the immunomodulatory character of metformin in L. pneumophila infection. It has been demonstrated that metformin reduces the intracellular growth of bacteria via the AMPK pathway through mTOR activation [18].

Conclusion

Some research findings have suggested metformin to be potent against multiple numbers of pathogens, which expand metformin scope from anti-diabetic to anti-infective agent. The mechanistic pathways by which Metformin works have been discussed above. It should be studied in the clinical trial set up and implemented as an adjunct therapy in different hospital acquired infections if found efficacious.

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