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A BRIEF INSIGHT INTO THE MECHANISM OF ACTION, REPURPOSING POTENTIALS AND PHARMACOGENOMICS OF METFORMIN

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Review articl

ABSTRACT

Metformin remained the mainstay of treatment of type 2 diabetes mellites (T2DM) for decades. Its complex mechanism of action gives it a great repurposing potential. It acts through activating adenosine monophosphate activated kinase (AMPK), inhibits hepatic gluconeogenesis, acts through redux related mechanisms, improves insulin sensitivity, modulates gut microbiota, inhibits tissue lipolysis and have other complex anticancer benefits. Individual patients' responses to metformin vary widely. This is due to a combination of genetic, environmental and metabolic factors. Pharmacogenomics research open the way to personalized medicine via investigating genes those control metformin's pharmacokinetics and pharmacodynamics such as SLC22 family (SLC22A1, SLC22A2, SLC22A3). Genetic variations may develop in form of single nucleotide polymorphisms (SNPs) or exons mutations. Detecting these genetic variations in order to predict good responders to metformin may not be cost effective if traditional genotyping assay methods were used, however, overlapping pool sequencing methods could be cost effective since they process multiple samples together. In conclusion, pharmacogenetic research on metformin might improve its use and repurposing if cost effective genotyping methods were carefully clinically implicated.

KEY WORDS: Metformin, Diabetes Mellites, Pharmacokinetics and Pharmacodynamics .

INTRODUCTION

Metformin which is an old drug, has remained the mainstay of therapy in the treatment of type 2 diabetes mellites for decades (1). It belongs to the biguanides family of oral antidiabetic medications which natural analogues were responsible for the therapeutic effects of the *Galega officinalis* (French Lilac) which used in the past to treat symptoms associated with type 2 DM (2). Unlike other members of the biguanides family which had been withdrawn from clinical practice (3), metformin is still keeping its place on the WHO essential drug list (4).

Mechanism of action of metformin:

The particular site of action or the exact mechanism of Metformin action is not yet well known, since complex and different mechanisms are involved and are still being actively investigated. The complexity of its mechanism of action gives it great potential for repurposing. In the following statements, the actions of metformin might be simply classified to several categories of action:

1. *Acts through activating Adenosine Monophosphate activated Protein Kinase (AMPK):*
   This is the primary and most famous mechanism via which metformin performs its action. It works through activating AMPK pathway, which is a signaling pathway which in turn plays crucial roles regulating energy utilization and glucose metabolism (3, 5, 6).
2. *Acts through inhibiting hepatic gluconeogenesis:*
   Uncontrolled hepatic gluconeogenesis is an important mechanism that elevates blood glucose in DMT2 patients in presence of insulin resistance. Metformin has the ability to suppress hepatic gluconeogenesis (7) through different pathways such as its possible ability for the induction of GCN5 and SIRT1 genes (8).
3. *Acts through redox related mechanisms:*
   These mechanisms include manipulating redux balance in a way that counter act the oxidative stress associated with T2DM and other mechanisms of mitochondrial interactions. One of them is the mitochondrial complex I that contributes to glucose lowering effects of metformin (7, 9, 10).
4. *Improves Insulin Sensitivity:*
   Metformin improves insulin sensitivity in peripheral tissues, facilitating better glucose uptake in different tissues such as muscle, liver and adipose tissues. This improvement in insulin sensitivity results in better utilization of glucose since it is also associated with increased glycogen production in muscle and liver (11-14).
5. *Modulates gut microbial flora (microbiota):*
   Metformin affects gut microbial flora population and diversity in a way which may play a role in its glucose-lowering effects and its inflammation reducing effect (15, 16).
6. *Other beneficial effects of metformin:*
   Metformin also Inhibits catecholamine induced adipose tissue lipolysis. This effect of metformin will reduces circulating free fatty acids (17) on the same time it did not inhibit exercise induced lipolysis (18).
7. *Anticancer effects of metformin:*
   A growing body of evidence indicates that metformin in vitro might significantly inhibit the proliferation and growth of several types of tumor cells (19, 20), these studied in vitro effects included several types of cancer cells such as bladder cancer (21), glioblastoma cells (22), prostate cancer cells (23, 24), breast cancer cells (25, 26), and Hypopharyngeal carcinoma cells (27). These anticancer effects in addition to the beneficial effects mentioned in the former point gives metformin a wide range of medical conditions for which it can be repurposed.

Variation in Individual Responses to Metformin:

The variation in individual responses to metformin, is not influenced by a single or simple factor. But, it is the result of a complex interactions between genetic, metabolic, and environmental factors, In addition to genetic variations in genes related to the pharmacokinetics and pharmacodynamics of the drug such as its transport or its metabolism.

Genetic Factors

Among different genes involved in the action of metformin, the SLC genes family attract substantial attention since they do code the transporters responsible for metformin excretion. They were linked to differences in drug response, as some variants in these genes are associated with better or reduced response to metformin (28, 29).

Metabolic Differences

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Metabolic profile of patients has distinct signatures in good and poor responders to metformin. The Good responders have higher levels of specific metabolites of sphingomyelins, acylcholines, and glutathione, and on the other hand the poor responders have increase in other metabolites from glucose metabolism and gut microbiota (30).

Influence of Environmental Factors:

In addition to the above-mentioned effect of inter-individual genetic and metabolic differences on the individual patients' response to metformin, environmental factors are still playing important role in figuring the therapeutic response in the recipients' patients. For instance, patient's gender, age, current medications and age which are all environmental factors illicit crucial effect on individual response to metformin (31). Moreover, response to metformin is also influenced by nutrient availability and oxygenation status at the cellular level (32).

Pharmacogenomics and Personalized Medicine

Personal response to metformin can be predicted from genetic information leveraged by molecular biotechnologies opening new horizons in the field of pharmacogenomics. With personal genetic information in hand, personalized treatment plan can then be designed for each patient. Then metformin (or any other medicine) can be prescribed for patients with anticipated good response and alternative therapy prescribed for patients with predicted poor response (33-35).

Most studies investigating the pharmacogenomics of metformin primarily focused on genes related to metformin pharmacokinetics and pharmacodynamics those encoding molecules engaged in the transport, metabolism and action of the drug. The variations focused on are primarily single nucleotide polymorphisms (SNPs) in these genes.

However, both, SNPs or mutations in SLC22 family genes such as SLC22A1, SLC22A2, SLC22A3 can affect the individual's response to metformin. For instance, the SNP rs12194182 in SLC22A3 helps achieving lower HbA1C in response to metformin therapy (36) while mutation exon 2 rs683369 (G>C) affect fasting blood glucose levels (37).

Clinical Implications

Several genes have been detected in genome-wide association studies those are associated with metformin response. However, these studies emphasized the importance of studying diverse cohorts to understand genetic variability in populations (38). Up to now, variations in the SLC22A1 can be depended on to predict response to metformin helping in establishing better personalized response (39).

Traditional genotyping assay methods such as real-time Polymerase Chain Reactions (real-time PCR) and Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) can be effectively used to screen for SLC22A1 variants. However, these individual sample processing methods are expensive, thus, they might not cost effective, especially in the context of T2DM (39, 40). On the other hand, methods those process group of samples instead of individual samples such as overlapping pool sequencing methods can be an alternative way to detect SLC22A1 variants with reduced cost (41)

In conclusion, metformin which is an old antidiabetic drug has a complex mechanism of action and is still effectively used to treat T2DM. The

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complexity of metformin's mechanism increase its repurposing potentials while the complexity of genetic variations those control the response to its actions opens the horizons towards precise individualized medicine.

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