Review Article

Pharmacogenomics of Insulin Secretagogues in Pharmacodynamics, Pharmacokinetics and Adverse Reactions

Yu-jie Li1, Zuowei Li2, Wanjin Hong1,2* and Liang-cheng Li1*

1State Key Laboratory of Cellular Stress Biology, Fujian Provincial Key Laboratory of Innovative Drug Target Research, School of Pharmaceutical Sciences, Xiamen University, Xiamen, Fujian, 361102, China
2Institute of Molecular and Cell Biology (IMCB), 61 Biopolis Drive, Singapore, 138673, Singapore
*Corresponding author: Liang-Cheng Li, Associate Professor, State Key Laboratory of Cellular Stress Biology, Fujian Provincial Key Laboratory of Innovative Drug Target Research, School of Pharmaceutical Sciences, Xiamen University, Xiamen, Fujian, 361102, China

Wanjin Hong, Professor, State Key Laboratory of Cellular Stress Biology, Fujian Provincial Key Laboratory of Innovative Drug Target, School of Pharmaceutical Sciences, Xiamen University, Xiamen, 361102, China

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Abstract

Insulin secretagogues, including sulfonylureas and glinides, are prevailingy used to manage type 2 diabetes mellitus to ameliorate hyperglycemia. Although they have been widely used in clinic for many years and exhibited acceptable efficacy, however, the response to these drugs varies among individuals, which is partly due to the genetic factors that affect the pharmacokinetics, pharmacodynamics and adverse reactions of the drugs. Pharmacogenomics, is to expound the relationship between the genetic polymorphisms and drug responses, which is expected to provide information for personalized medicing. In this article, we review and discuss current pharmacogenomics researches on insulin secretagogues, and wish to provide useful data and idea to improve the utilization of these drugs in clinic.

Keywords: Pharmacogenomics; Insulin secretagogues; Pharmacokinetics; Pharmacodynamics; Adverse reactions

Introduction

Diabetes mellitus has already been a global pandemic and there have been nearly half a billion people suffering from this disease worldwide [1]. With hyperglycemia as the main symptom, diabetes is a serious, chronic condition with dysfunction of glucose, lipid and protein metabolism. The main categories of diabetes are type 1, type 2 and gestational diabetes mellitus. While, Type 2 Diabetes Mellitus (T2DM) is the most common type without clear pathogenesis, which is prevalently managed by healthy diets and lifestyle, combined with medication if necessary. Insulin secretagogues, including sulfonylureas and glinides, are drugs that can promote the insulin secretion of islet β-cells to ameliorate hyperglycemia. However, as these medicines are getting more and more extensively used in clinic, some deficiencies emerged: a) interindividual differences of drug efficacy are conspicuous when receiving the same therapy; b) the adverse reactions are severe and unpredictable. Therefore, the studies of pharmacogenomics are the key to understand these problems for better managing the use of these drugs.

Pharmacogenomics is a conception focused on not only the
relationship between genetic polymorphism and the efficacy of drugs but also the whole genome and drug development. The polymorphism of coding genes responsible for drug metabolizing enzymes, transporters and drug targets will influence their pharmacokinetics and pharmacodynamics, and eventually leads to the variation of the drug therapeutic efficacy and side effects between individuals [2].

To maximize the efficacy and minimize the adverse reactions of medication, it is essential to implement precise medication, which relies on the study of pharmacogenomics. Here, as shown in Figure 1 and Supplementary Table 1, studies of pharmacogenomics on insulin secretagogues, sulfonylureas and glinides, which were published in PubMed between 1999-2020, were searched and cataloged. We are expected to contribute to establishing corresponding assays for personalized medicine and providing information for clinical practice to improve the quality of life and cure rate of T2DM patients.

The efficacy of drugs is a combination of both pharmacokinetics and pharmacodynamics, the changes of pharmacokinetic parameters always lead to the variation of pharmacodynamics, such as the changes of HbA1c, FPG, insulin levels and so on. So, it is difficult to distinguishing whether the effect is caused by pharmacodynamic or pharmacokinetic changes and most of studies not defined clearly. Here, we discuss the pharmacogenomic effects on insulin secretagogues in pharmacodynamics/pharmacokinetics and adverse reactions.

**Pharmacogenomics of Sulfonylureas**

Sulfonylureas are recommended by the American Diabetes Association and European Association as second-line agents following metformin monotherapy failure because of the lower cost and good HbA1c-lowering capacity. Sulfonylureas decrease HbA1c levels by facilitating pancreatic β-cell to secrete insulin. They bind to ATP-sensitive potassium channels (K_{ATP}) channels of β-cells, make plasma membrane depolarization, then calcium influx into the cells to trigger insulin release. As a kind of insulin secretagogues, at least 30% functional β-cell remaining intact is necessary for sulfonylureas therapy. According to the Genetics of Diabetes Audit and Research in Tayside, Scotland (GoDARTS) study, the failure of sulfonylureas therapy is up to 42.6% due to genetic variations [3]. Besides, there are many adverse reactions, the most severe one is hypoglycemia.

**Pharmacogenomics and pharmacokinetics/pharmacodynamics of sulfonylureas**

Sulfonylureas are transported by plasma membrane protein SLCO2B1 and then eliminated mainly by hepatic metabolism. MRP1 and BCRP may participate in the transportation of glyburide [4]. However, there is no study showing that the SNPs of MRP1 and BCRP are related with therapeutic effects. Sulfonylureas such as glipizide, glimepiride and tolbutamide are mostly metabolized by the cytochrome p450 2C9 (CYP2C9) in the liver. However, CYP3A4 and CYP2C9 contribute to metabolism of glimepiride by 50% and 30% respectively. A Genetics of Diabetes Audit and Research Tayside Study (GoDARTS) conducted by Zhou et al. [5] revealed that two CYP2C9 variants--*2 (rs1799853) and *3 (rs1057910) are associated with lower enzyme activity and slower metabolism of sulfonylureas. The results suggest that individuals carrying two copies of a loss-of-function allele (*2/*2 or *2/*3 or *3/*3) were 3.4 times (P=0.0009) more likely to achieve a treatment HbA1c level <7% than ones with two wild-type CYP2C9 alleles. Furthermore, *2 and *3 allele carriers were less likely to experience treatment failure with sulfonylurea monotherapy (P=0.04). In conclusion, CYP2C9*2 and *3 are kinds of loss-function alleles associated with slower metabolism and higher level of sulfonylurea concentration in the plasma which leads to less failure in view of pharmacokinetics, and better response to sulfonylureas treatment.

It has been clearly known that sulfonylureas target on K_{ATP} which consist of four SUR-1 and four inward-rectifier potassium ion channels respectively encoded by ABCC8 and KCNJ11. The
It was showed that Glucose (FPG) can be used to test the effect of genetic variants and efficacy of gliclazide. Generally, the decrease of Fasting Plasma T2DM patients investigated the association between genetic variants and rs5219, rs5210, rs5215 respectively [6].

common variants SNPs of ABCC8 and KCNJ11 are rs757110 and rs5219, rs5210, rs5215 respectively [6]. KCNJ11 and ABCC8 are located on chromosome 11 and only 5 kb away from each other, they are linkage disequilibrium inheritance. Mutations of KCNJ11 and ABCC8 were proved to cause neonatal diabetes by reducing secretion of insulin. A study by Feng et al. [7] on 1268 Chinese T2DM patients investigated the association between genetic variants and efficacy of gliclazide. Generally, the decrease of Fasting Plasma Glucose (FPG) can be used to test the effect of genetic variants. It was showed that ABCC8 rs 757110 and KCNJ11 rs 5210 were significantly associated with decreasing FPG (P=0.002). Individuals carrying Ala/Ala genotype significantly had obvious decrease of FPG (P<0.001) compared to wild-type (Ser/Ser) after 8 weeks of gliclazide treatment. Besides, individuals carrying Ser/Ala or Ala/Ala genotype significantly had decrease of 2-h plasma glucose (plasma glucose in 2 hours after OGTT) (P=0.001 and P=0.003). There were many studies that investigated the relationship between ABCC8/KCNJ11 and the response to sulfonylureas treatment on different ethnic population, however, some of them were contradictory to each other, which might be impacted by different gene frequencies in different ethnic population or derisory sample size.

Transcription Factor 7 Like 2 (TCF7L2) is one of the earliest genes with many SNPs and is proved to be associated with development of T2DM. It participates in the secretion, proliferation and apoptosis of pancreatic β-cells as well as the synthesis and process of insulin. Rs7903146 is one of the most studied SNPs of TCF7L2 and is associated with therapeutic effect of sulfonylureas. A GoDARTS study conducted by Pearson et al. [8] illustrated that in rs12255372 variant T/T genotype was less likely to respond to sulfonylureas (OR 1.95, P=0.005) compared with wild-type G/G. Similarly, in rs7903146 variant T/T genotype was less likely to respond to sulfonylureas (OR 1.73, P=0.015) compared with wild-type C/C, although its effect was not as strong as rs12255372. This study consisted of 579 patients treated by sulfonylureas for 12 months. Also, Schroner et al. [9] proved that individuals carrying genotype CC of rs7903146 would have obvious reduction of HbA1c (P=0.003) and FPG (P=0.031) in 6 months of sulfonylureas treatment compared with genotype CC.

CDKAL1 (cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-1 like 1) can modulate insulin secretion despite the mechanism is yet to be defined. It has several SNPs, like rs7754840, rs10946398, rs7756992 associated with therapeutic response to sulfonylureas [10]. Schroner et al. [11] conducted a study on 101 T2DM patients who have failed to achieve glycemic control on metformin monotherapy. The end of the trial was FPG levels after 6 months sulfonylures treatment in different genotypes of CDKAL1 rs7756992. Adjusted the change of FPG (∆FPG) was significantly higher in the AG+GG compared to the AA group (1.48±1.51 vs. 1.02±1.33 mmol/l, p=0.022), whereas, in rs7756992 variant, the ∆FPG was much higher in CC group (P=0.024) compared with AC group. Compared with the C allele, the odds ratio for treatment success among carriers of the rs2237892 T allele was 2.533 (P=0.007); and the rs2237895 C allele was associated with a 2.360-fold decrease in HbA1c compared with the A allele (P=0.009).

The variation of CDKN2A/2B (Cyclin Dependent Kinase Inhibitor 2A/2B) was verified to cause dysfunction of pancreatic β-cells among different population. There was a significant difference in FPG 4 weeks later and ∆FPG among T/T, T/C and C/C genotypes in rs10811661 (P=0.025 and P=0.008). Carriers of C allele might have higher response to sulfonylureas according to Ren et al. [15].

NOS1AP (nitric oxide synthase 1 adaptor protein) is involved in the regulation of intracellular Ca2+ levels. Since sulfonylurea promotes insulin secretion by increasing intracellular Ca2+ concentration, Becker et al. [16] conducted a study to illuminate the relationship between NOS1AP and response to sulfonylureas on 619 participants. In participants with the TG or GG genotype at rs10494366 in NOS1AP, glibenclamide was less effective in reducing glucose levels. The mortality rates were also higher compared with glibenclamide users with the TT genotype. In tolbutamide and glimepiride users, patients with the TG and GG genotype were associated with a reduced mortality rate.

The Gly972Ala polymorphism of IRS-1 (insulin receptor substrate-1) was proved to have association with improved glucose-stimulated insulin secretion and resulted in the relative deficiency of insulin [17]. In a study conducted by SESTI et al. [18], the genotype frequency of the Arg972 IRS-1 variant was 8.7% among diabetic patients well controlled with oral therapy and 16.7% among patients with secondary failure to sulfonylurea (OR 2.1, P=0.01).

To summarize, sulfonylureas are metabolized by CYP2C9 and CYP2C9, and the SNP *2 and *3 are associated with less treatment failure. The target of sulfonylureas is K\textsubscript{ATP}, which is encoded by ABCC8 and KCNJ11, and the variants rs757110 and rs5219, rs5210, rs5215 are related to varying decrease of FPG. There are other genes regulating the pharmacodynamic pathways, like TCF7L2 (rs12255372) and ABCC8 (rs757110 and rs5219, rs5210, rs5215 respectively [6].
repaglinide and mitiglinide are also insulin secretagogues which closely correlated with drug metabolism. The slow metabolizers have 2.81, P=0.009) and better response to SU treatment (P=0.003) only in associated with nearly three-fold higher odds of hypoglycemia (OR). E.g. repaglinide is metabolized by (CYP450)

Pharmacogenomics and adverse reactions of sulfonylureas

One of the most severe adverse reaction of sulfonylureas therapy is hypoglycemia, which occurs about 1.8% patients every year. The cause of hypoglycemia is the slower metabolism of sulfonylureas. Carriers with variants CYP2C9*2 and CYP2C9*3 are slow metabolizers, resulting in higher concentration of sulfonylureas in their plasma than wild type. The higher the drug levels in the plasma are, the more chances of causing adverse reaction. The association between CYP2C9*2/*3 and the risk of sulfonylurea-induced hypoglycemia was elucidated successively by A. Holstein et al. in 2004 [19] and 2010 CYP2C9

It is widely used to control hyperglycemia after meals because of the rapid acting, that’s why it is called prandial glucose regulator. The hypoglycemia can be avoided by monotherapy of glinides, and when combined with metformin, glinides can stabilize glucose levels and reduce the dose of insulin. Nateglinide and repaglinide are effective in reducing the HbA1c levels by 0.4-0.8% and 1% respectively in T2DM [22,23]. Although, glinides are widely used in clinic because of the safety and efficacy, like other antidiabetic agents, however, the therapeutic effect of glinides also has interindividual difference and the failure of treatment up to 40%

Pharmacogenomics of Glinides

Like sulfonylureas, glinides mainly consisting of nateglinide, repaglinide and mitiglinide are also insulin secretagogues which targeting at K_\(\text{ATP}\) channels of β-cells but with different binding sites. It is widely used to control hyperglycemia after meals because of the rapid acting, that’s why it is called prandial glucose regulator. The hypoglycemia can be avoided by monotherapy of glinides, and when combined with metformin, glinides can stabilize glucose levels and reduce the dose of insulin. Nateglinide and repaglinide are effective in reducing the HbA1c levels by 0.4-0.8% and 1% respectively in T2DM [22,23]. Although, glinides are widely used in clinic because of the safety and efficacy, like other antidiabetic agents, however, the therapeutic effect of glinides also has interindividual difference and the failure of treatment up to 40%

Pharmacogenomics and pharmacokinetics of repaglinide

Taking repaglinide as an example, as a kind of hydrophilic agents, repaglinide is first taken up from the blood to hepatocytes by and SLCO1B1 and then transformed into inactive metabolites via CYP3A4 and CYP2D6 respectively [27].

Variants of CYP2C8 and CYP3A4 have an impact on clearance rates of repaglinide, carriers with CYP2C8*1/*1 had greater AUC than others with CYP2C8*1/*3 in Caucasians population [28-30] and CYP3A4*1/*18 was associated with lower elimination rate (44.0%) than CYP3A4*1/*1 in Malaysian population [31]. However, for nateglinide, CYP2C9*3 displayed significantly reduction in clearance and higher AUC [32,33] while CYP2D6*4 and CYP2D6*5 showed no significant effect on nateglinide clearance [32].

SLCO1B1 or OATP1B (Solute Carrier Organic Anion Transporter Family Member 1B1) is influx transporter that pump repaglinide out of cells to decrease the concentration in target cells. For repaglinide, T allele of rs2032582 in MDR1 was associated with higher levels of repaglinide which signified higher response (P=0.007) [38].

To summarize, the variants of CYP2C8 (*3)/CYP3A44 (*18), SLCO1B1 (rs4149056) and ABCB1 (rs2032582) impact the pharmacokinetics of glinides to vary the concentration in plasma and targets sits.

Pharmacogenomics and pharmacodynamics of repaglinide

Both sulfonylureas and repaglinide act on K_\(\text{ATP}\) channels, so the effects of variants may be similar to some extent although they target at different subunits of the channels.

Rs2237892/rs2237895 of KCNQ1 [39], rs10494366 of NOS1AP [40] and rs5219 of KCNJ11 [41] were found associated with effect of both repaglinide and sulfonylureas. The relationship between sulfonylureas and aforementioned variants was already shown previously and the effects were same. It is remarkable that variant rs10494366 of NOS1AP was significantly correlated with relieving insulin resistance. It was reported that the variant of rs10494366 and repaglinide treatment had an interaction effect only in HOMA-IR (P=0.013), indicating that TT genotype may associated with insulin resistance. There was a significant difference in the response rate to repaglinide treatment between the E and K alleles of rs5219 in KCNJ11 (68% vs. 82%, P=0.0324).

Rs290287 is a SNP of TCFC12 that is associated with response to repaglinide according to Yu et al. [42]. The study exhibited that TT homozygotes showed greater efficacy on the levels of fasting insulin, triglycerides and low-density lipoprotein cholesterol than C allele carriers.

SLC30A8 or ZnT-8, encoding a zinc transporter, is expressed at a high level only in the pancreas whose variants are certainly associated with developing type 2 diabetes mellitus. It pumps zinc into vesicles of insulin from endochylema and takes part in insulin secretion. Two of its variants-rs13266634 and rs16889462 were also correlated with repaglinide treatment. T allele of rs13266634 and GA genotype of rs16889462 both showed enhanced response to repaglinide according to Wu et al. [43].

IGF2BP2 (Insulin like Growth Factor 2 MRNA Binding Protein 2) regulates the translation of IGF-2, which plays an important role in growth and insulin signaling. Rs1470579 and rs4402960 are identified to be associated with the effect of repaglinide treatment. C
allele carriers had lower effects of repaglinide treatment on reducing FPG (P<0.05) and PPG (P<0.05) but on different subunits. Therefore, the same variants (rs2237892/ rs2237895 of KCNQ1, rs10494366 of NOS1AP and rs5219 of KCNJ11) also have influence on the therapeutic effect of glinides. The pharmacodynamics of glinides is relevant to the synthesis and secretion of insulin, the development of pancreatic islets and the insulin signaling. The correlated genes like TCF7L2 contribute to varying FPG/PPG or HbA1c levels.

Pharmacogenomics and adverse reactions of glinides

Because of the shorter half-life of glinides, there is lower risk of treatment-related hypoglycemia. But compared with sulfonylureas, glinides have more chances of having weight gain [47]. Although there is no study directly probing the association between adverse reactions and glinides treatment, we still can make a hypothesis that hypoglycemia may be associated with higher concentration of drug in the plasma due to slower elimination of drugs. Therefore, the individuals with decreased function of CYP450 (slow metabolizer) are likely have more chances of developing hypoglycemia during the treatment. As for weight gain, there still remains controversy.

Conclusion and Future Perspective

Insulin secretagogues are widely used in clinic to control hyperglycemia, but their adverse reactions and individual variation still can’t be neglected. Sulfonylureas and glinides are recommended as second-line medicines, likely because of more adverse reactions such as hypoglycemia. The diagnosis of genotypes of patients is also essential for personalized medicine. Sulfonylureas are mostly metabolized by CYP2C9 and CYP3A4, patients with decreased function of these genes will have better effects with lower dosage but the chances of hypoglycemia are also increased at the same time. Moreover, variants of ABCG8, KCNJ11, TCF7L2, CDKAL1, KCNQ1, CDKN2A/2B, NOS1AP and IRS-1 are significantly associated with the response to sulfonylureas by impacting the pharmacodynamics.

As for glinides, although they are safer than sulfonylureas, but their treatment failure can’t be neglected. Except variants of KCNQ1, NOS1AP, TCF7L2 and KCNJ11 are both associated with response to sulfonylureas and glinides, IGF2BP2, UCP2 and NAMPT are correlated with pharmacodynamics of repaglinide as they play important roles in drug’s efficacy. Furthermore, the main metabolic enzymes such as CYP2C8 and CYP3A4 also contribute to therapeutic efficacy and adverse reaction by regulated drug concentration in the plasma.

In conclusion, there is still a long way to explicitly define the relationship between genetic variation and therapeutic effect of medications. Only by conducting more GWAS studies, to deep understanding the effect of genetic variation on drug action, we can design individualized therapy, which will improve therapy efficacy and decrease adverse reactions.

Declaration

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