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Review Article

Pharmacogenomics of Insulin Secretagogues in Pharmacodynamics, Pharmacokinetics and Adverse Reactions

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Abstract

Insulin secretagogues, including sulfonylureas and glinides, are prevailingly used to manage type 2 diabetes mellitus to ameliorate hyperglycemia. Although they have been wildly 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 variations and genetic polymorphisms with drug responses, which is expected to establish the correlated assays for personalized medication. 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

Abbreviations

ABCB1: ATP Binding Cassette Subfamily B Member 1; *ABCC8*: ATP Binding Cassette Subfamily C Member 8; ADR: Adverse Reaction; AUC: Area Under Curve; BCRP: Breast Cancer Resistance Protein; *CDKAL1*: CDK5 (Cyclin-Dependent Kinase 5) Regulatory Subunit Associated Protein 1-like 1; CDKN2A/2B: Cyclin Dependent Kinase Inhibitor 2A/2B; *CYP2C9*: Cytochrome P450, Family 2, Subfamily C, Polypeptide 9; *CYP2D6*: Cytochrome P450, Family 2, Subfamily D, Polypeptide 6; *CYP3A4*: Cytochrome P450, Family 3, Subfamily A, Polypeptide 4; FPG: Fasting Plasma Glucose; GoDARTS: Genetics of Diabetes Audit and Research Tayside Study; GWAS: Genome Wide Association Study; HbA1c: Glycated Hemoglobin; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance; *IGF2BP2*: Insulin Like Growth Factor 2 MRNA Binding Protein 2; *IRS-1*: Insulin Receptor Substrate 1; K_{ATP}: ATP-sensitive Potassium Channels; *KCNJ11*: Potassium Inwardly-rectifying Channel, Subfamily J, Member 11; *KCNQ1*: Potassium Voltage-gated Channel Subfamily Q Member 1; MRP1: Multidrug Resistance-Associated Protein 1; *NAMPT*: Nicotinamide Phosphoribosyltransferase; NeuroD1: Neuronal Differentiation 1; NIDDM: Non Insulin-dependent Diabetes Mellitus; *NOS1AP*: Nitric Oxide Synthase 1 Adaptor Protein; OGTT: Oral Glucose Tolerance Test; PAX4: Paired Box 4; PD: Pharmacodynamics; PK: Pharmacokinetics; PPG: Postprandial Plasm Glucose; SLC30A8: Solute Carrier Family 30, Member 8; *SLCO1B1*: Solute Carrier Organic Anion Transporter Family, Member 1B1; SLCO2B1: Solute Carrier Organic Anion Transporter Family, Member 2B1; SNP: Single Nucleotide Polymorphism; SU: Sulfonylurea; SUR-1: Sulfonylurea Receptor 1; T2DM: Type 2 Diabetes Mellitus; *TCF7L2*: T-Cell-Specific Transcription Factor 4; UCP2: Uncoupling Protein 2

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 prevailingly 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

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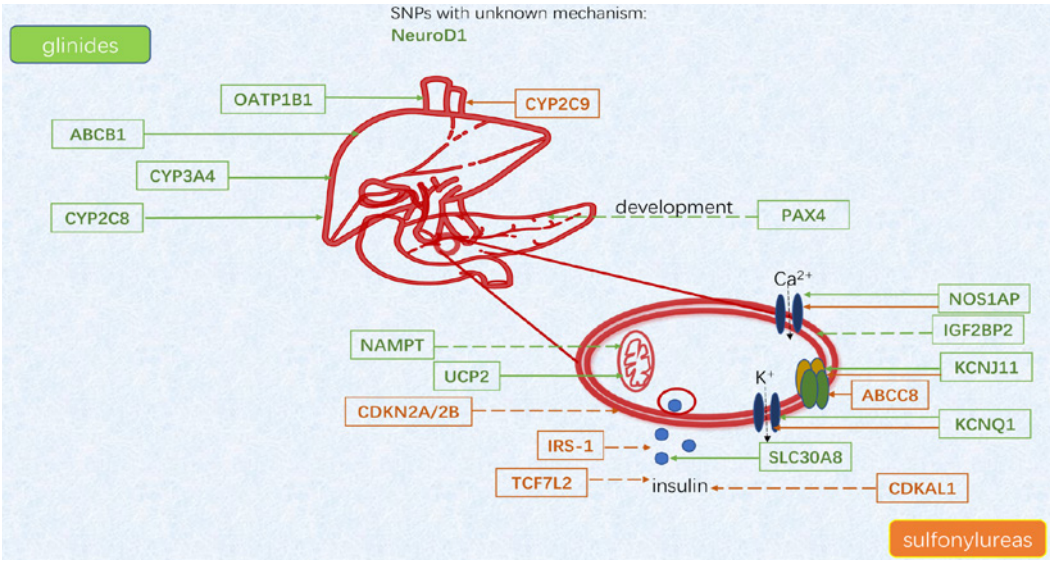

Figure 1: Pharmacogenomics of sulfonylureas and glinides in pharmacokinetics, pharmacodynamics and adverse reactions. Green color refers to glinides and orange color refers to sulfonylureas. The solid lines refer to direct effects and the dotted lines refer to indirect or unknown effects. These polymorphisms cover several certain tissues like liver and pancreas. The specific SNPs of mentioned genes are showed entirely in Supplementary Table 1.

and pharmacodynamics, and eventually leads to the variation of the drug therapeutic efficacy and side effects between individuals [2].

To maximize efficacy of medication and minimize the adverse reactions, 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-lowing capacity. Sulfonylureas decrease HbA1c levels by facilitating pancreatic β-cell to secrete insulin. They bind to K_{ATP} channels of β-cells, make 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 sever 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 ATP-sensitive potassium channels (K_{ATP}) which consist of four SUR-1 and four inward-rectifier potassium ion channels respectively encoded by *ABCC8* and *KCNJ11*. The 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 5kb 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* rs757110 and *KCNJ11* rs5210 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] illuminated 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-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 trail was FPG levels after 6 months sulfonylureas treatment in different genotypes of *CDKAL1* rs7756992. Adjusted the change of FPG (ΔFPG) 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), while HbA1c levels were not significantly different. Besides, sulfonylureas doses among three genotype groups were significantly different (P=0.032) and the GG genotype received obviously lower dose compared to AA (P=0.015). In a dominant genetic model, carriers of the G-allele (AG+GG) achieved significantly lower FPG levels in comparison with patients with AA genotype (P=0.013). Moreover, a study of relationship between variants of rs7754840 and sulfonylureas resistance was conducted by Soltani et al. [12] in Iranian T2DM patients. There was a significant association between GG genotype and higher risk of sulfonylureas resistance (OR 2.250, P=0.046). Rs10946398 was verified to have association with the progress of T2DM but haven't been proved to have association with response to sulfonylureas treatment [10].

KCNQ1 (Potassium Voltage-Gated Channel, KQT-Like Subfamily, Member 1) is wildly expressed in many tissues which plays a role in K+ channel function. Meanwhile, previous GWAS studies in different ethnic population have proved that *KCNQ1* has a relationship with T2DM. The mutation of *KCNQ1* might lead to impaired insulin secretion. Schroner et al. [13] illustrated ΔFPG was significantly different among three genotypes (TT, TG and GG) of rs163184 in *KCNQ1* (P=0.017). In a recessive genetic model, carriers of T allele achieved significant lower FPG levels compared with GG genotype (P=0.033). ΔFPG was significantly higher in TT+TG group than in GG group (P=0.016). Li et al. [14] expounded the association between rs2237892/rs2237895 and modified-release gliclazide effect in Chinese T2DM patients. In rs2237892 variant, carriers of TT genotype exhibited higher 2-h glucose levels after 16 weeks of sulfonylureas gliclazide MR (modified-release gliclazide) treatment (P=0.044). whereas, in rs2237895 variant, the ΔHbA1c 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 ΔFPG 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 Ca^{2+} levels. Since sulfonylurea promotes insulin secretion by increasing intracellular Ca^{2+} 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 impaired 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_{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 rs7903146), *CDKAL1* (rs7754840, rs10946398, rs7756992), *KCNQ1* (rs2237892 and rs2237895), CDKN2A/2B (rs10811661), *NOS1AP* (rs10494366) and *IRS-1* (Gly972Ala), polymorphisms of which are associated with the therapeutic effect of sulfonylureas by

influencing the FPG.

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 [20]. Dujic et al. [21] also clarified that variants of *CYP2C9* were associated with nearly three-fold higher odds of hypoglycemia (OR 2.81, P=0.009) and better response to SU treatment (P=0.003) only in patients carrying the POR*1/*1 genotype.

To summarize, the adverse reaction is mainly caused by the excessive concentration of sulfonylureas in the plasma, and it is closely correlated with drug metabolism. The slow metabolizers have better response to sulfonylureas, but on the other hand, they may have more chances of suffering from hypoglycemia.

Pharmacogenomics of Glinides

Like sulfonylureas, glinides consisting of nateglinide, repaglinide and mitiglinide are also insulin secretagogues which targeting at K_{ATP} channels of β-cells but with different binding sites. It is wildly 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], and mitiglinide is 0.17-1.1% in reducing HbA1c [23]. Although, glinides are wildly 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 *SLCO1B1* and then transformed into inactive metabolites via *CYP2C8* and *CYP3A4* [24, 25]. But glinides sometimes can be pumped out by *ABCB1* which will reduce the concentration of drug in target cells. Glinides are metabolized mainly by hepatic cytochrome P450 (*CYP450*). E.g. repaglinide is metabolized by *CYP2C8* and *CYP3A4* [26], while nateglinide is primarily metabolized by *CYP2C9* and to a lesser extent by *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 absorbs repaglinide and nateglinide from the plasma into hepatocytes. Carriers with CC or CT genotype of rs4149056 in *SLCO1B1* had greater AUC than others with TT genotype due to the less transport activity [28,34-37].

ABCB1 (ATP Binding Cassette Subfamily B Member 1) or *MDR1* is efflux 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)/*CYP3A4* (*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_{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 *TCF7L2* 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) than AA homozygotes, while T allele of rs4402960 carriers displayed an enhanced effect than GG homozygotes (P<0.01) [44].

UCP2 (Uncoupling Protein 2), also refer to *SLC25A8*, is related

to glucose-stimulated insulin secretion. Rs659366 is associated with the effect of repaglinide according to Wang et al. [33,45] A allele was associated with smaller decrease in FPG (P<0.05) and HbA1c (P<0.05) levels compared to GG genotype.

NAMPT (Nicotinamide Phosphoribosyltransferase) encodes systemic NAD biosynthetic enzyme that regulates insulin secretion. Variant rs11977021 has influences on repaglinide efficacy through FPG, PPG and HbA1c levels as evidenced by a study by Shang et al. [46].

To summarize, like sulfonylureas, glinides also target on K_{ATP} 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* (rs290287), *SLC30A8* (rs13266634 and rs16889462), *IGF2BP2* (rs1470579 and rs4402960), *UCP2* (rs659366) and *NAMPT* (rs11977021) 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 *ABCC8*, *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 drugs' 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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