Glycemic Effects Linked to Unique Mechanism of Action of Sulfonylureas

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Abstract
Sulfonylureas (SUs) are insulin secretagogues that are widely used in the management of type 2 diabetes mellitus (T2DM). The primary mechanism of action (MoA) involves the stimulation of insulin release from pancreatic islet β cells by binding to sulfonylurea receptors (SURs) and inhibition of ATP-sensitive potassium (KATP) channels. In addition to pancreatic β cells, KATP channels are also present in other cells such as cardiomyocytes and vascular smooth muscle cells. Opening of the plasma membrane KATP channels in cardiomyocytes shortens the action potential and, thereby, decreases the cardiac workload. Different sulfonylureas have different binding affinities to SURs, and this mainly differs based on the duration and onset of action, and their clearance. Modern SUs such as glimepiride possess beneficial pancreatic, extra-pancreatic, and cardiovascular effects. Here we will discuss the glycemic effects of SUs, specifically linked to their unique mechanism of action.

Molecular Mechanism of Sulfonylurea Action
Sulfonylureas (SUs) are insulin secretagogues widely used in the management of type 2 diabetes mellitus (T2DM). The primary mechanism of action (MoA) of SU involves the stimulation of insulin release from pancreatic islet β cells by binding to sulfonylurea receptors (SURs) and inhibition of ATP-sensitive potassium (KATP) channels.1-3

Sulfonylurea mediated increase in plasma insulin levels ensues via two pathways: (i) stimulation of insulin secretion by β cells, and (ii) a decrease in hepatic insulin clearance. The latter effect occurs mainly after the increase in insulin secretion has taken place.3

During the first month of SU therapy, a rapid increase in the levels of insulin and insulin response to glucose takes place, leading to lowered blood glucose. Following this period, baseline and stimulated insulin levels are reduced compared to those measured at the start, although the glucose levels stay unaltered.2

Sulfonylurea Receptor and KATP Channel: Clinical Implications
The KATP channels are made up of hetero-octameric complex of four Kir.2 subunits and four regulatory sulfonylurea receptor (SUR) subunits and possesses both low- and high-affinity SU binding sites. Clinically, sulfonylureas exert their secretory activity in pancreatic islet beta cells possibly by binding to the high affinity binding sites and blocking the KATP channels.2 Findings from various in vivo studies demonstrate that, at therapeutic concentrations, SUs cause secretion of insulin in a glucose-dependent manner.4,5

Of the three isoforms of SUR (viz. SUR1, SUR2A, and SUR2B), SUR1 is expressed at higher levels in pancreatic islets β cells. It is also present in brain tissue. SUR2A is expressed largely in skeletal and heart muscles, whereas SUR2B is expressed in other tissues, such as vascular smooth muscle cells. (Table 1)4,6

When SUs bind to one or both SUR1 sites, the inhibition of flow of K+ within the β-cell causes cell membrane depolarization, thus pulling out the electric screen that inhibits diffusion of calcium into the cytosol. Increased calcium flow to β cells leads to the shrinkage of the filaments of actomyosin, resulting in insulin exocytosis (Figure 1).1,2

By binding to cardiac SURs, SUs contribute to inhibition of ischemic preconditioning, leading to adverse cardiovascular outcomes. This could occur, since KATP channels in myocytes shorten the action potential to decrease the cardiac workload. Furthermore, K+ ATP channels in vascular smooth muscle cells control relaxation and vasodilatation, providing an endogenous protective mechanism during episodes of reperfusion and ischemia.4,7

Different SUs have different binding affinities to SURs, and this mainly differs based on the duration and onset of action, and their clearance.4,5 For example, glimepiride and gliclazide maintain ischemic myocardial

Table 1: Types and functions of Sulfonylurea receptors (SURs)4-6

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Kir6 subunit</th>
<th>Kir6.1 subunit</th>
<th>Nucleotide affinity</th>
<th>Primary function</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUR1</td>
<td>Kir6.2</td>
<td>Brain; pancreas</td>
<td>High</td>
<td>Pancreatic ß-cells: Regulating insulin release</td>
</tr>
<tr>
<td>SUR2A</td>
<td>Kir6.2</td>
<td>Skeletal and heart</td>
<td>Low</td>
<td>Myocardial cells: Regulating action potential duration</td>
</tr>
<tr>
<td>SUR2B</td>
<td>Kir6.2 and Kir6.1</td>
<td>Heart; eye; brain; cerebellum; colon</td>
<td>Intermediate to high</td>
<td>Smooth muscle cells, including vasculard: Regulating action potential duration and vasodilation</td>
</tr>
</tbody>
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preconditioning, but glibenclamide appears to prevent it. Glimepiride binds to a specific 65-kDa protein site on the $K_{ATP}$ channel of pancreatic $\beta$ cells and inhibits SUR complex. Glimepiride exhibits lower binding affinity (2- to 3-fold) to SURs, as well as a higher rate of association (2.5- to 3-fold) and dissociation (8- to 9-fold) from the receptor, compared to glibenclamide. The distinct binding sites and unique receptor interactions of glimepiride result in lower inhibition of $K_{ATP}$ channels, contributing to a reduced risk of hypoglycemia compared to conventional SUs.\(^9\)

**Extrapancreatic Effects Exerted by Sulfonylureas**

Modern SUs such as glimepiride exhibit several extrapancreatic effects, apart from glycemic control, and thereby contribute to better clinical outcomes. These extrapancreatic effects include inhibition of metabolic clearance rate of insulin, inhibition of glucagon secretion from pancreatic $\alpha$-cells, insulin sensitization, increased adiponectin levels, antioxidative and angiogenetic effects, and preservation of ischemic preconditioning.\(^{10,11}\)

**Conclusion**

Modern SUs are insulin secretagogues that promote the release of insulin from pancreatic $\beta$ cells by binding to SURs and inhibiting $K_{ATP}$ channels. They exhibit extrapancreatic effects and contribute to better clinical outcomes and could be considered a panacea in diabetes care.

**Conflict of Interest**

AB is an employee of Sanofi India. All other authors report no conflicts of interest.

**References**