Sulfonylurea and non-sulfonylurea hypoglycemic agents: pharmacological properties and tissue selectivity

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Abstract

ATP-sensitive K⁺ (Kₐᵣᵢₜ) channels play many important roles in cellular functions, including control of membrane excitability of skeletal muscle and neurons, K⁺ recycling in renal epithelia, cytoprotection in cardiac ischemia, and insulin secretion from pancreatic β-cells. Kₐᵣᵢₜ channels are composed of pore-forming inwardly rectifying potassium channel (Kir6.2 or Kir6.1) subunits and sulfonylurea receptor (SUR1, SUR2A, or SUR2B) subunits. Kir6.2 or Kir6.1 subunits conjoined with a SUR subunit constitute the various tissue-specific Kₐᵣᵢₜ channels with distinct pharmacological properties. Both sulfonylureas and non-sulfonylurea hypoglycemic agents are used in treatment of type 2 diabetes mellitus. While the sulfonylurea receptor (SUR) is the target molecule of all of these hypoglycemic agents, the binding sites differ according to the moiety containing in the agent, and alter the pharmacological properties. In addition, chronic exposure of pancreatic β-cells to the various agents affects the agent-specific sensitivities differently.

Here we distinguish differences in pharmacological profile among the various hypoglycemic agents that reflect their chemical composition. We also suggest possible risk in the use of certain hypoglycemic agents in patients with ischemic heart disease.

Keywords: Hypoglycemic agent; Kₐᵣᵢₜ channel; Binding site; Pharmacological structure; Tissue selectivity

1. Introduction

ATP-sensitive K⁺ (Kₐᵣᵢₜ) channels are present in many tissues, including pancreatic β-cells [1], heart [2], and vascular smooth muscle [3]. Kₐᵣᵢₜ channels play important roles in various cellular functions such as secretion and muscle contraction by linking cell metabolism to membrane potential [4]. Kₐᵣᵢₜ channels are comprised Kir (Kir6.1 or Kir6.2) subunits that form the K⁺-selective channel pore and SUR (SUR1 or SUR2) subunits that are receptors of sulfonylureas [5]. Coexpression of Kir6.2 and SUR1 in mammalian cell line (COS-1 cells) by using lipofection method forms Kₐᵣᵢₜ channels with properties similar to those in native pancreatic β-cells [5]. It is generally accepted that Kir6.2/SUR2A, Kir6.2/SUR2B, and Kir6.1/SUR2B form cardiac and skeletal muscle type, smooth muscle...
Tissue-specific $\mathrm{K}_{\text{ATP}}$ channels. $\mathrm{K}_{\text{ATP}}$ channels are comprised Kir subunits that form the $\mathrm{K}^+$-selective ion channel pore and SUR subunits, which are receptors of sulfonylureas.

<table>
<thead>
<tr>
<th>Type of $\mathrm{K}_{\text{ATP}}$ channel</th>
<th>$\alpha$ subunit</th>
<th>$\beta$ subunit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic $\beta$-cell type</td>
<td>Kir6.2</td>
<td>SUR1</td>
</tr>
<tr>
<td>Cardiac and skeletal muscle type</td>
<td>Kir6.2</td>
<td>SUR2A</td>
</tr>
<tr>
<td>Smooth muscle type</td>
<td>Kir6.2</td>
<td>SUR2B</td>
</tr>
<tr>
<td>Vascular smooth muscle type</td>
<td>Kir6.1</td>
<td>SUR2B</td>
</tr>
</tbody>
</table>

The $\mathrm{K}_{\text{ATP}}$ channels in pancreatic $\beta$-cells are critical in the regulation of both glucose-induced and sulfonylurea-induced insulin secretions [9,10]. Recently, the non-sulfonylurea insulinotropic agents nateglinide and mitiglinide (KAD-1229) were shown to inhibit pancreatic $\beta$-cell type $\mathrm{K}_{\text{ATP}}$ channel by binding to SUR1 [11]. Nateglinide and mitiglinide are structurally unrelated to the sulphonylureas. As the sulfonylurea receptors (SUR1, SUR2A and SUR2B) are widely distributed in various tissues, determination of tissue specificity of the various hypoglycemic drugs that act through the sulfonylurea receptors is crucial in predicting side effects of therapy in diabetic patients.

Here we demonstrate various tissue specificities of the hypoglycemic agents by evaluating their chemical structure. We also suggest the potential risk of inhibition of the cardioprotective effects via the $\mathrm{K}_{\text{ATP}}$ channel by hypoglycemic agents in ischemic heart diseases.

2. Pharmacological structure and binding sites on SUR1

$\mathrm{K}_{\text{ATP}}$ channels are found in many tissues. The SUR subunits confer sensitivity to the hypoglycemic agents differing, reflected in the various responses to the therapeutic drugs. There are two binding sites for glibenclamide in SUR1 [12], one a tolbutamide-binding site and the other a benzamide-binding site (Table 2, Fig. 1). Recently, the cytosolic loop between transmembrane (TM) 5 and TM6 on SUR1 has been shown to play a key role in formation of the N-terminal component of the glibenclamide binding site, and the cytosolic loop between TM15 and TM16 is the determinant for the C-terminal component of this binding site [13].

Glibenclamide comprises both sulfonylurea and benzamide moieties, which might contribute to the long washout time, while tolbutamide contains only the sulfonylurea moiety, and nateglinide, which has neither of these but is thought to bind to the same site as tolbutamide (Table 2) [14].

Considering their pharmacological structure, these hypoglycemic agents would be categorized at least four groups: the group containing SU moiety, benzamide moiety, both, and neither (Table 2). These variations in moiety of the agent are reflected in the various pharmacological properties and differing tissue specificities.

3. $\mathrm{K}_{\text{ATP}}$ channel inhibition by hypoglycemic agents

$\mathrm{K}_{\text{ATP}}$ channel inhibition by the various drugs was compared (Table 3). Inhibition of the $\mathrm{K}_{\text{ATP}}$ channel by tolbutamide and gliclazide is highly tissue-specific for the pancreatic $\beta$-cell. Glibenclamide (benzamide moiety) and glimepiride (benzamide-like moiety) inhibits the activity of the cardiac and skeletal muscle type $\mathrm{K}_{\text{ATP}}$ channel (Kir6.2/SUR2A) and the smooth
Table 2
Putative binding sites for hypoglycemic agents

<table>
<thead>
<tr>
<th>Moieties</th>
<th>Binding site on SUR1</th>
<th>Tolbutamide-binding site</th>
<th>Benzamide-binding site</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzamide moiety</td>
<td>Meglitinide</td>
<td>Tolbutamide, gliclazide,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU moiety</td>
<td></td>
<td>acetohexamide, tolazamide,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU moiety + benzamide</td>
<td></td>
<td>glyclopyramide, chlorpropamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-) like moiety</td>
<td>Glibenclamide, glimepiride (?)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Repaglinide</td>
<td>Nateglinide, mitiglinide</td>
<td></td>
<td>Glyburide</td>
</tr>
</tbody>
</table>

Considering their pharmacological structure, these hypoglycemic agents would be categorized at least four groups, SU, benzamide, both, and neither.

Table 3
The comparison of K_ATP channel inhibition by the various drugs

<table>
<thead>
<tr>
<th></th>
<th>Glibenclamide</th>
<th>Tolbutamide</th>
<th>Gliclazide</th>
<th>Glimepiride</th>
<th>Nateglinide</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Kir6.2/SUR1</td>
<td>2–7 nM</td>
<td>5–30 µM</td>
<td>~50 nM</td>
<td>~3 nM</td>
<td>~100 nM</td>
</tr>
<tr>
<td>(2) Kir6.2/SUR2A</td>
<td>~50 nM</td>
<td>~1.7 µM</td>
<td>~7 nM</td>
<td>~7 nM</td>
<td>~1 µM</td>
</tr>
<tr>
<td>(3) Kir6.2/SUR2B</td>
<td>~50 nM</td>
<td>~0.9 nM</td>
<td>~1.2 mM</td>
<td>~8 nM</td>
<td>~100 nM</td>
</tr>
<tr>
<td>(4) Kir6.1/SUR2B</td>
<td>~1 µM</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Inhibition of the K_ATP channel by tolbutamide and gliclazide is highly tissue-specific.

muscle type K_ATP channel (Kir6.2/SUR2A). Nateglinide, which has a structurally unrelated SU moiety as well as a benzamide moiety, also inhibits cardiac and skeletal muscle type K_ATP channels (Kir6.2/SUR2A) and smooth muscle type (Kir6.2/SUR2B) at 1 µM and 100 nM, respectively. But it is still controversial since several reports indicate that therapeutic concentrations of nateglinide may selectively inhibit pancreatic type K_ATP channel. Since the cardiac and skeletal muscle type K_ATP channels plays a crucial cardioprotective role in ischemic heart diseases, the similarity in IC50 to that of pancreatic type K_ATP channels might indicate the latent risk in treating patients with diabetes and ischemic heart disease with certain hypoglycemic agent.

4. Protective effect of K_ATP channels in ischemic heart disease

Pharmacological clues to the mechanism of ischemic preconditioning have accumulated recently. Suzuki et al. demonstrated that sarcolemmal K_ATP channels function prominently in modulating ischemia/reperfusion injury, using a Kir6.2 knockout mouse [15]. Lee and Chou compared the impact of diabetes mellitus and therapy with the different sulfonylureas on cardioprotective effects in diabetic patients undergoing coronary angioplasty [16]. In their study, myocardial ischemia after coronary angioplasty was evaluated in 20 nondiabetic and 23 diabetic patients chronically taking either glibenclamide or glimepiride, and the results indicate that diabetes mellitus and sulfonylureas can both act to inhibit the activation of K_ATP channels in patients undergoing coronary angioplasty. The degree of inhibition assessed by metabolic and electrocardiographic parameters is less severe during treatment with glimepiride than with glibenclamide. On the other hand, the sulfonylureas did not have an adverse effect on cardiovascular outcome in patients with type 2 diabetes in the report from UK Prospective Diabetes Study (UKPDS) Group [17].

In addition to the cardiac type K_ATP channel, the K_ATP channel of the mitochondrial inner membrane (mitoK_ATP channel) also may play an important role in cardioprotection. Since glibenclamide also inhibits these mitoK_ATP channels, it may be risky to treat patient with type 2 diabetes and ischemic heart
disease with high-dosage glibenclamide. Further studies are required to determine whether other hypoglycemic agents inhibit mitoK\textsubscript{ATP} channels.

5. Conclusion

The different moieties of the various hypoglycemic agents may be reflected in their different pharmacological properties and tissue specificities. While tolbutamide and gliclazide are highly tissue-selective, glibenclamide might reduce the cardioprotective effect of K\textsubscript{ATP} channels. Further studies of the effects of other hypoglycemic agents on extra-pancreatic tissues and mitoK\textsubscript{ATP} channels are required to evaluate their proper use in the treatment of diabetes.

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References