Ischemia in Type 2 Diabetes: Tissue Selectivity of Sulfonylureas and Clinical Implications

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Sulfonylureas act by inhibition of β-cell adenosine triphosphate–dependent potassium (K_{ATP}) channels after binding to the sulfonylurea subunit 1 receptor (SUR1). However, K_{ATP} channels are also expressed in cardiac and vascular myocytes coupled to different receptor subtypes. These are thought to be involved in adaption of vascular tone and myocardial contractility. This brief review is intended to assess the interactions between sulfonylureas and extrapancreatic K_{ATP} receptors in type 2 diabetic patients. Different models addressing the possible influence of sulfonylureas on vascular function are discussed.

SULFONYLUREA derivatives are the most commonly used oral antihyperglycemic drugs in the treatment of type 2 diabetes.[1] Their popularity is based on their ease of administration, reliable effectiveness, and lack of symptomatic side effects other than hypoglycemia. Type 2 diabetic patients are known to be particularly susceptible to ischemic heart disease. There has been some concern that certain sulfonylureas might worsen clinical outcomes in these patients,[2] although definitive clinical evidence is lacking. Glibenclamide has been repeatedly shown to interact with sulfonylurea receptors in the cardiovascular system, whereas no such interaction has been demonstrated for newer sulfonylureas like gliclazide.

ADENOSINE TRIPHOSPHATE–DEPENDENT POTASSIUM CHANNELS: THE TARGET OF SULFONYLUREA ACTION

Sulfonylureas stimulate insulin release from pancreatic β cells via binding to a sulfonylurea receptor (SUR1) and subsequent closure of an adenosine triphosphate–dependent potassium (K_{ATP}) channel, resulting in β-cell depolarization.[3] However, K_{ATP} channels are not only found in β cells, but also in myocardial and vascular smooth muscle cells. In these cells, hypoxia and/or ischemia trigger(s) opening of the normally closed K_{ATP} channels, which consequently leads to hyperpolarization. This in turn results in shortening of the action potential in myocardium[4] and relaxation in vascular smooth muscle cells followed by vasodilation.[5] These mechanisms are therefore important determinants of protection against ischemia. In experimental situations, it has been shown that blockade of K_{ATP} channels by certain sulfonylureas worsens ischemic injury.[6]

Cloning and sequencing of K_{ATP} channel genes resulted in the concept of the molecular composition of the different K_{ATP} channels.[7] It is now well known that plasma membrane K_{ATP} channels consist of 2 different structural subunits: an inwardly rectifying potassium channel subunit, which forms the pore (Kir6.x), and a sulfonylurea receptor (SURX) as the regulatory subunit.[8] These subunits assemble as a hetero-octamer with 4:4 stoichiometry.[9]

A different sulfonylurea receptor subunit of the K_{ATP} channel is found in β cells (SUR1), myocardium (SUR2A), and vascular smooth muscle (SUR2B). Much of the research on sulfonylurea receptors has been done in cloned K_{ATP} channels using voltage-clamp methods. In these models, glibenclamide shows a similar, high-affinity blockade of the β cell and extrapancreatic K_{ATP} channels, whereas a newer sulfonylurea like gliclazide exhibits no high-affinity blockade of extrapancreatic K_{ATP} channels.[10] These findings have been confirmed in whole cells and tissue.[11,12] Based on these differences, glibenclamide, at therapeutic concentrations, is thought to exert a strong effect on the vasculature, whereas gliclazide does not.[11] In addition, glibenclamide has been shown to severely impair the activity of the potassium channel opener nicorandil, which is frequently used as an antianginal agent.[13] In contrast, gliclazide displayed no interference whatsoever with nicorandil's action on vascular smooth muscle and the cardiac myocyte.

DISTINCT EFFECTS OF SULFONYLUREAS ON VASCULAR REACTIVITY

In the absence of hemodynamically significant stenoses in large conduit arteries, blood flow to target organs is regulated at the level of local resistance vessels.[14] Therefore, adequate function of resistance vessels is mandatory to guarantee sufficient substrate (ie, oxygen) supply. Dysfunction of resistance arteries by means of reduced endothelium-dependent[15] or metabolic[16] vasodilation or reduced flow reserve[17] is thought to reflect an early reversible stage in the development of vascular disease.[18,19] Additionally, impaired reactivity of coronary resistance vessels has been shown to be associated with exercise-induced ischemia in subjects free of macrovascular coronary artery disease.[20] Recently, endothelial dysfunction in patients with moderate coronary artery disease was found to be accompanied by myocardial perfusion defects.[21] In the coronary circulation, adequate vasodilator reserve[22] is believed to be crucial to substrate supply under conditions of increased demand, and limitations of vascular reserve in patients with coronary artery disease have recently been shown to contribute to postprandial angina pectoris.[23] Reactive hyperemia (RH), as a measure of resistance vessel function, is determined by a variety of metabolic factors like nitric oxide,[24] or adenosine, cyclo-oxygenase products, and myogenic relaxation,[25] but also K_{ATP} channels.[26]

Glibenclamide has been shown to reduce vasodilation induced by diazoxide (a potassium channel opener) after intravenous administration,[27] as well as basal perfusion and peak, post-ischemic, RH in human skeletal muscle resistance arteries after oral admin-

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0026-0495/03/5208-1001$30.00/0
doi:10.1016/S0026-0495(03)00211-7

istration.[26] In addition, glibenclamide prevents ischemic preconditioning in humans.[28] Ischemic preconditioning refers to the fact that a brief period of ischemia leads to a less severe and subsequently more prolonged episode of ischemia. Gliclazide, although it exerts no action on the cardiovascular system, has so far not been investigated with regard to this aspect.

In humans, the effects of sulfonylurea derivatives on resistance vessel function have mostly been studied in healthy volunteers using intravenous or acute oral administration.[26,27,29,30] Only a few recent studies have addressed the clinically more relevant question of possible cardiovascular interactions after chronic administration of sulfonylureas in type 2 diabetic patients.[31,32] In 2 of these trials, Abbink et al investigated the effects of chronic treatment with oral antidiabetic drugs on vascular reactivity in type 2 diabetic patients.[31,32] Their major findings are that chronic treatment with glibenclamide, glimepiride, metformin, or acarbose had no effect on the vasodilator response to diazoxide (a K_{ATP} channel opener), acetylcholine, dipyridamole, or ischemia. These results seem not to support the existence of relevant differences with regard to post-ischemia vascular response between different sulfonylureas or between sulfonylurea and metformin or acarbose, respectively. Moreover, the observations appear to be in agreement with results from the United Kingdom Prospective Diabetes Study (UKPDS), which showed no higher risk for the development of macrovascular complications in patients chronically treated with glibenclamide, compared with metformin.[33] These studies, however, did not take into account the pharmacokinetics of sulfonylureas, and determined vascular reactivity only at one time point following acute dosage. Thus, the time-dependent effects after administration of the drugs were not investigated.

We recently investigated the effects of acute and chronic treatment with glibenclamide and gliclazide on postischemic vascular reactivity in type 2 diabetes patients. In accordance with Abbink et al, we found no drug influence on the steady state before dosing. However, preliminary results show that after acute administration during chronic sulfonylurea treatment, glibenclamide—but not gliclazide—significantly reduced postischemic vasodilation.[34]

POTENTIAL CLINICAL IMPLICATIONS

Type 2 diabetes patients have an increased risk of cardiovascular complications, associated with a higher morbidity and mortality than a nondiabetic population with coronary artery disease.[35] Sulfonylureas have been used in the treatment of type 2 diabetes for more than 50 years, and are still the most common treatment approach. However, there has been some concern about possible adverse cardiovascular effects with certain sulfonylureas. This possibility was first suggested in the context of the University Group Diabetes Program (UGDP), where patients on sulfonylureas apparently showed a higher cardiovascular mortality than patients on diet alone.[2] However, the study was discredited because of its inadequate design and methods, and other studies failed to show an increased cardiovascular risk for sulfonylureas.

Recent data from the UKPDS showed that intensified treatment with glibenclamide did not result in any specific long-term disadvantages with regard to macrovascular complications compared with insulin or chlorpropamide.[36] However, the UKPDS did not ascertain the effect of glibenclamide on type 2 diabetic patients with acute coronary syndromes or in those patients at high risk for myocardial infarction. In this context, it is noteworthy that glibenclamide was repeatedly shown to interact with vascular as well as myocardial K_{ATP} channels in clinical studies, thereby reducing ischemia-mediated vasodilation[26] and abolishing ischemic preconditioning.[28,37] Gliclazide, in contrast, has no comparable effects. Furthermore, gliclazide, due to its antioxidant capacity, appears to possess an intrinsic vasoprotective potential.[38-41] The benefit of these properties independent of blood glucose lowering for patients at risk for cardiovascular disease needs to be evaluated in future clinical studies.

CONCLUSION

Data from our group, as well as others, indicate that, in patients with type 2 diabetes, glibenclamide, but not gliclazide, results in reduction in K_{ATP} channel–mediated vascular reactivity. This difference is most probably based on a different binding behavior to the SUR family of receptors, and may have important implications in diabetic patients with inducible myocardial ischemia, since, contrary to glibenclamide, gliclazide exerts a selective action on the pancreatic β-cell SUR receptors. However, further clarification of the potential clinical significance of the different properties of sulfonylureas can only arise from head-to-head studies in appropriate populations, such as subjects with stable effort-induced ischemia or acute coronary syndromes, since, in both conditions, K_{ATP} channel opening mediates important defense mechanisms.

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