REVIEW ARTICLE

The Sulfonylurea Controversy: More Questions From the Heart

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Myocardial ischemia and infarction are associated with substantially increased morbidity and mortality among patients with diabetes mellitus. Although many factors contribute to the increased morbidity and mortality, in patients with non–insulin-dependent (type II) diabetes mellitus, one contributor may be the use of sulfonylurea drugs, the most widely used oral hypoglycemic agents. Such a possibility, which first arose over a 25 years ago when it was observed that patients taking sulfonylurea drugs had increased cardiovascular mortality, has recently resurfaced after the discovery that sulfonylureas act by inhibiting adenosine triphosphate (ATP)-sensitive potassium channels. In the pancreas, inhibition of ATP-sensitive potassium channels induces release of insulin; but in the heart, inhibition of these channels prevents ischemic preconditioning, an endogenous cardioprotective mechanism that protects the heart from lethal injury. This review outlines the current understanding of the molecular and cellular pharmacodynamics of sulfonylurea drugs and discusses the potential clinical consequences of inhibition of ATP-sensitive potassium channels in the heart of diabetic patients with cardiac disease in whom the use of sulfonylureas may be harmful.

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by a sulfonylurea drug inhibits flux of K⁺ through the channel pore, depolarizing the plasmalemma and inducing release of insulin (Fig. 1).

**Heart.** 
K<sub>ATP</sub> channels are also abundantly distributed within the sarcolemmal membrane of cardiac cells (22). In an individual cardiomyocyte, there are estimated to be ~5,000 channels/cell (12,22). Opening of only a fraction of K<sub>ATP</sub> channels can have a profound effect on cardiac excitability (12). Sulfonylurea drugs also inhibit cardiac K<sub>ATP</sub> channels (29,30) and have been used extensively to better understand the function of these channels in the heart, although the efficacy with which sulfonylureas inhibit channel opening appears to be determined by the metabolic state of the cardiac cell (30–33).

Under physiologic conditions, cardiac K<sub>ATP</sub> channels remain closed because of their high sensitivity toward intracellular ATP, present at high levels within cardiomyocytes (12). During myocardial ischemia, ATP can no longer prevent the opening of K<sub>ATP</sub> channels. Although a discrepancy exists between the millimolar levels of ATP present within a cardiac cell and the micromolar sensitivity of the channel toward ATP-induced channel inhibition (12), a number of intracellular factors act to reduce the sensitivity of the channel toward ATP. These include nucleotide diphosphates, acidosis, lactate production, disruption of the cytoskeleton, phosphotransfer reactions and entry of the channel into ligand-insensitive conformational states (12,34–39). Although the precise role of K<sub>ATP</sub> channels in the heart is not fully understood (12), opening of cardiac K<sub>ATP</sub> channels initiates ischemic preconditioning and alters cellular excitability during ischemia.

**Figure 1.** K<sub>ATP</sub> channels. Targets of action of sulfonylurea drugs in the pancreatic beta-cell. Sulfonylurea drugs induce release of insulin by inhibiting K<sub>ATP</sub> channels present in the cell membrane of pancreatic beta-cells. In the presence of high blood glucose levels, glucose is transported into the cytosol of the pancreatic beta-cell, where it promotes synthesis of intracellular ATP, which blocks K<sub>ATP</sub> channels and prevents K⁺ efflux through the channel pore, leading to membrane depolarization and opening of voltage-sensitive Ca²⁺ channels, which allows influx of calcium and, in turn, release of insulin through exocytosis.

**Sulfonylureas Impair Ischemic Preconditioning**

Ischemic preconditioning is now recognized as a powerful, endogenous mechanism by which the heart can protect itself from lethal ischemic insult (13). The phenomenon was first described over a decade ago, when it was found that exposure of the myocardium to brief episodes of mild myocardial ischemia “preconditioned” the myocardium, markedly reducing the impact of subsequent prolonged ischemia (40). In the absence of ischemic preconditioning, complete occlusion of a major coronary artery leads to myocardial infarction (Fig. 2, top). However, the preconditioned myocardium, by virtue of its increased resistance to ischemic insult, is less vulnerable, which translates to a reduction in infarct size (Fig. 2, middle).

Although the cellular mechanisms by which ischemic preconditioning protects the myocardium during ischemic insults are only partially understood, ischemic preconditioning protects the myocardium independently of an increase in coronary collateral flow (13,40–42). Evidence for the role of the K<sub>ATP</sub> channel in ischemic preconditioning comes from the finding that the beneficial effect of ischemic preconditioning can be mimicked, at least in certain species, by endogenous openers of...
Ischemic preconditioning has been repeatedly demonstrated in the human heart (13,57–60). Us- ing sequential balloon inflations during coronary angioplasty, it has been possible to demonstrate a large infarct size.

Clinical evidence for sulfonylurea-induced impairment of ischemic preconditioning. Ischemic preconditioning has been demonstrated repeatedly in the human heart (13,57–60). Using sequential balloon inflations during coronary angioplasty or intermittent aortic cross-clamping during coronary artery bypass graft surgery, it has been possible to demonstrate a decrease in clinical indicators of ischemia severity, such as intensity of ischemic pain, extent of ST segment deviation from baseline and severity of regional wall abnormalities by echocardiography, as well as improved recovery of myocardial function after cardiac surgery (13,58–60). In other studies, the presence of angina before myocardial infarction has been associated with reduced infarct size, preservation of ventricular function and lower in-hospital mortality (61–63). Ischemic preconditioning is also believed to be the basis for the “warm-up” phenomenon, first described by Heberden (64) in the 18th century, in which patients experience more severe angina pain during initial exercise that decreases in intensity with subsequent exercise (65). This phenomenon has also been observed in patients undergoing serial exercise testing (66). In contrast, loss of the preconditioning response has consistently been observed in the presence of sulfonylurea drugs (13,60,67). Such findings demonstrate that in humans, ischemic preconditioning can be induced and has a cardioprotective effect that is abolished by sulfonylurea drugs.

However, not all studies have found unequivocal evidence for ischemic preconditioning in the human heart (68–71). One explanation for this is the presence of numerous confounding variables in clinical practice. In particular, determination of infarct size in humans by means of currently available clinical tools lacks specificity (72), which is necessary to allow precise demonstration of the cardioprotective effect of ischemic preconditioning. In addition, it is apparent that a narrow window exists for the development of ischemic preconditioning, leading to difficulties in the standardization of preconditioning protocols for the clinical evaluation of the efficacy of this cardioprotective phenomenon. Such factors could have contributed to the inconsistent results found to date in studies trying to determine the full potential of ischemic preconditioning in clinical practice (67–71).

At the cellular level, it is also becoming increasingly apparent that the interaction between sulfonylurea drugs and cardiac K_ATP channels is complex. Recent work investigating the determinants of K_ATP channel opening under ischemic conditions and K_ATP channel inhibition by sulfonylureas has found that the action of sulfonylureas is not uniform, but is governed by factors such as nucleotide diphosphates, lactate, and H⁺, as well as the channel microenvironment and operative condition (33,73–75). Thus, inhibition of the K_ATP channel is not simply determined by the mere presence of inhibitory ligands (39,76,77), and the outcome of the action of sulfonylureas on cardiac cells may vary depending on the cellular metabolic state (78). These findings further highlight the difficulties faced in establishing the signaling role of K_ATP channels in preconditioning and in predicting the consequences of K_ATP channel inhibition by sulfonylurea drugs in the human heart.

Sulfonylurea Drugs Also Affect Cardiac Excitability

The electrophysiologic consequence of cardiac K_ATP channel opening may be both proarrhythmic and antiarrhythmic (79,80). This apparent paradox can, at least in part, be explained through understanding the role played by K_ATP channels in determining the duration of the cardiac action potential in the ischemic myocardium. In the absence of myocardial ischemia, cardiac action potential duration is determined by changes, with respect to time, in the vector sum of
inward and outward currents flowing through sarcolemmal ion channels. Under this circumstance, ion conductance through $K_{ATP}$ channels does not contribute to the action potential because the channel is inhibited by high levels of intracellular ATP. However, with myocardial ischemia, intracellular ATP is no longer able to inhibit $K_{ATP}$ channel opening. Under this condition, $K^+$ efflux through $K_{ATP}$ channels is sufficient to induce significant shortening of the action potential duration (79–81), which could have two (opposing) consequences: 1) Shortening of the action potential duration reduces the influx of Ca$^{2+}$ into the cell through voltage-gated Ca$^{2+}$ channels because these channels now open for a shorter period. In turn, the decrease in intracellular Ca$^{2+}$ accumulation reduces the likelihood of abnormal arrhythmias caused by “triggered activity” arising from Ca$^{2+}$-dependent delayed afterdepolarizations (82–84). 2) Shortening of the action potential duration alters the refractoriness of the myocardium, which could result in an increased occurrence of arrhythmias caused by reentrant mechanisms, such as ventricular fibrillation (85–87). By preventing shortening of the action potential duration through inhibition of $K_{ATP}$ channel opening during ischemia, sulfonylureas may, on the one hand, increase intracellular Ca$^{2+}$, because these channels now open for a shorter period. In turn, the decrease in intracellular Ca$^{2+}$ accumulation reduces the likelihood of abnormal arrhythmias caused by “triggered activity” arising from Ca$^{2+}$-dependent delayed afterdepolarizations (82–84). 2) Shortening of the action potential duration alters the refractoriness of the myocardium, which could result in an increased occurrence of arrhythmias caused by reentrant mechanisms, such as ventricular fibrillation (85–87). By preventing shortening of the action potential duration through inhibition of $K_{ATP}$ channel opening during ischemia, sulfonylureas may, on the one hand, increase intracellular Ca$^{2+}$, because these channels now open for a shorter period. In turn, the decrease in intracellular Ca$^{2+}$ accumulation reduces the likelihood of abnormal arrhythmias caused by “triggered activity” arising from Ca$^{2+}$-dependent delayed afterdepolarizations (82–84). 2) Shortening of the action potential duration alters the refractoriness of the myocardium, which could result in an increased occurrence of arrhythmias caused by reentrant mechanisms, such as ventricular fibrillation (85–87). By preventing shortening of the action potential duration through inhibition of $K_{ATP}$ channel opening during ischemia, sulfonylureas may, on the one hand, increase intracellular Ca$^{2+}$, because these channels now open for a shorter period. In turn, the decrease in intracellular Ca$^{2+}$ accumulation reduces the likelihood of abnormal arrhythmias caused by “triggered activity” arising from Ca$^{2+}$-dependent delayed afterdepolarizations (82–84).

Of note, although the potential effects of sulfonylurea drugs on triggered activity are theoretically interesting, the clinical relevance of this action is questionable in the setting of acute myocardial ischemia, where reentry is believed to be the major cause of fatal, early (Harris phase I) arrhythmias (91). Indeed, thus far only an antiarrhythmic action of sulfonylureas has been demonstrated in humans during myocardial ischemia (92,93). In some (90,94) but not all (95) studies, sulfonylurea drugs have also been reported to alter the ST segment and T wave configuration on the rest electrocardiogram (ECG) during acute myocardial ischemia. Specifically, the magnitude of ST segment elevation and early peaking of the T wave during experimentally induced myocardial infarction was significantly reduced after pretreatment with glyburide (94). Such a property of sulfonylurea drugs acting on the ischemic myocardium could therefore decrease the sensitivity of the ECG as a diagnostic tool in some patients with acute myocardial infarction.

**Structure of $K_{ATP}$ Channels: Implications for Future Use of Sulfonylurea Drug Therapy?**

The structural components of the $K_{ATP}$ channel have only recently been determined (20,25). The $K_{ATP}$ complex is a heteromultimer formed by assembly of two subunits: an inwardly rectifying potassium channel (Kir6.2) and the SUR (Fig. 3) (20,25,28,96–99). Kir6.2 is the presumed pore-forming subunit responsible for $K^+$ conductance, which when intact can function only when coexpressed with the SUR subunit, the latter serving a regulatory role and as the binding site for sulfonylurea drugs (20,25,96). In the absence of SUR, Kir6.2 can conduct $K^+$ only after deletion of its carboxy terminal domain (100). One potentially important discovery, made recently, is the tissue-specific heterogeneity of the SUR subunit, which exists in several isoforms named SUR1, SUR2A, and SUR2B (20,25,28,96,97,101). The SUR1 isoform, when heterologously coexpressed and coassembled with Kir6.2, reconstitutes the pancreatic $K_{ATP}$ channel (20,25,96,98,99). Cardiac (SUR2A) and vascular (SUR2B) sulfonylurea receptors are structurally different from their pancreatic analog (97,101,102). One area of intense research is to understand more fully the structural and functional differences between pancreatic and cardiac isoforms of $K_{ATP}$ channels (96,97,103), to determine whether sufficient differences exist to allow development of sulfonylurea compounds that interact exclusively with the pancreatic $K_{ATP}$ channel, leaving the cardiac channel unaffected. “Selective” targeting of pancreatic $K_{ATP}$ channels by “beta-cell–selective sulfonylureas” could represent a new strategy in the pharmacologic management of diabetic patients with ischemic heart disease. However, it should be pointed out that the SUR subunit has also been reported to be capable of functionally interacting with inwardly rectifying $K^+$ channels other than Kir6.2, suggesting that additional ion channels may also be targeted by sulfonyl-
urea drugs (104). The functional importance of such interactions in intact cardiomyocytes is not yet known.

Conclusions

It is apparent that sulfonylurea drugs have important actions within the cardiovascular system that go beyond their ability to induce release of insulin. In diabetic patients with myocardial ischemia, sulfonylurea drugs may be harmful by preventing endogenous cardioprotective mechanisms to act, leading to enhanced cell death and arrhythmias caused by delayed afterdepolarizations. In contrast, sulfonylurea drugs may also prevent reentrant arrhythmias, such as ventricular fibrillation, during ischemia. Until newer, more tissue-selective sulfonylurea drugs become available, physicians caring for patients with non-insulin-dependent diabetes mellitus and ischemic cardiac disease should consider the complex effects of sulfonylurea drugs acting within the ischemic myocardium.

At this time, many unresolved questions remain regarding the basic properties of the $K_{ATP}$ channel, its role under pathophysiologic conditions (is it a “bad,” or a “good” channel?) and the cardiovascular consequences of $K_{ATP}$ channel inhibition by sulfonylurea drugs. With increasing understanding of the molecular properties of the $K_{ATP}$ channel (20) and the consequences of disruption of $K_{ATP}$ channel function (105), at least some of these questions may be answered. At the clinical level, sufficient data on the effect of sulfonylureas on clinical outcomes, on which to base recommendations for the use of these drugs in diabetic patients, are still lacking (13,106,107).

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References


