Review

Sulfonylurea derivatives in cardiovascular research and in cardiovascular patients

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Abstract

Sulfonylurea derivatives are hypoglycemic drugs frequently used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). In the β-cell sulfonylureas act by blocking ATP-sensitive potassium channels (K.ATP channels). In several organ systems, including the cardiovascular system, sulfonylurea receptors and functional K.ATP channels have been identified. In the heart their role is not clear; an endogenous cardioprotective effect has been suggested. There is no doubt that K.ATP channels are effectively blocked by sulfonylureas. In the last decade sulfonylureas have been widely used as a pharmacological tool in experimental cardiac research. Blockade of K.ATP channels is the proposed cellular mechanism of action for all sulfonylurea-related effects. However, other membrane currents are affected as well. In addition, myocardial metabolism is modified by sulfonylurea pretreatment. Hence, it should seriously be questioned whether these drugs are suitable in assessing involvement of cardiac K.ATP channels in, for example, ischemia-related events. The detrimental effects of sulfonylureas in experimental studies on myocardial ischemia have led to speculation whether the widespread use of these drugs in patients with NIDDM, most often suffering from accompanying ischemic heart disease, should be reconsidered. However, a review of the clinical literature reveals that the most consistent finding is a lower incidence of ventricular arrhythmias associated with the use of glibenclamide, while no excess mortality has been shown for this agent in NIDDM with ischemic heart disease. Despite some direct effects on systemic and coronary vasculature, there are, at present, no firm clinical data on the basis of which sulfonylurea derivatives should be withheld from the cardiac patient.

Keywords: Sulfonylureas; Diabetes; Potassium channel, ATP-sensitive; Arrhythmias; Myocardial infarction; Myocardial ischemia

1. Introduction

Sulfonylurea derivatives are hypoglycemic drugs frequently used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). The mode of action of sulfonylures on the β-cell has been elucidated and involves blockade of the ATP-sensitive potassium channels (K.ATP channels). The β-cell sulfonylurea receptor has been purified and cloned [1]. In itself the sulfonylurea receptor (named SUR1) does not possess ion-conducting properties, but together with an inwardly rectifying K⁺ channel (called Kir 6.2) it forms K⁺ channels with characteristics closely resembling functional pancreatic K.ATP channels [2]. Sulfonylurea receptors and functional K.ATP channels have been identified in several organ systems and their role and function in physiological and pathophysiological states has been described in many of them. In mitochondrial membranes of various tissues, including myocardium, K.ATP channels are also expressed [3–5]. On the molecular level a second type of (sarcolemma) sulfonylurea receptor, designated SUR2, has been identified, with the highest expression levels in cardiac and skeletal muscle [6,7]. A further subdivision has been described with the demonstration of a SUR2 subtype, designated SUR2A, exclusively expressed in heart and skeletal muscle and SUR2B, ubiquitously expressed in these and other extrapancreatic tissues.

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myocytes revealed that the efficacy of glibenclamide-induced inhibition of myocardial K.ATP channels is, compared to pancreatic β-cells, relatively low with a half-maximal inhibition concentration (IC50) in the order of 5–10 μM [20,21]. Although lower values for cardiac K.ATP channels have been reported as well [22], the affinity for pancreatic K.ATP channels is presumably 3 orders of magnitude higher [15,18,23,24]. In line with these findings are the functional characteristics, including a higher affinity for glibenclamide in the same order of magnitude of SUR1 as of SUR2 [6]. Of particular relevance to the question whether myocardial K.ATP channel block is involved in the sulfonylurea-related deleterious effects is the observation that its efficacy to block the channel is increased by a reduction in pH [25] and is reduced after prolonged metabolic stress [20,26].

K.ATP channels are not the only cardiac ionic channels inhibited by sulfonylureas. Recently, glibenclamide has been demonstrated to block the cAMP-activated chloride conductance (ICl, cAMP) [27]. The Hill coefficient for the effect on ICl, cAMP and on K.ATP channels is roughly similar, but the effective concentration range is considerably higher (half-maximal inhibition of ICl, cAMP ± 30 μM [27] compared to 5–10 μM for half-maximal inhibition of K.ATP channels) (see above). Glibenclamide also blocks the cystic fibrosis transmembrane conductance regulator, another chloride channel, expressed in the heart with unknown function. The blocking action was irreversible with half-maximal inhibition in a concentration range comparable to affect ICl, cAMP [28]. It is not known whether factors pertinent to ischemia modify the glibenclamide sensitivity of these currents.

In non-cardiac tissue effects on other ion channels/currents have been described. Whereas in pancreatic β-cells sulfonylureas seem to be rather specific, with no effects at relevant dosages on other K+ channels [29], glibenclamide has been shown to inhibit a voltage-gated, Ca2+- and ATP-independent K+ current in the human neuroblastoma cell line SH-SY5Y (cells expressing several properties of noradrenergic neurons) [30]. In vascular smooth muscle cells glibenclamide (10 μM) has been shown to modulate the L-type Ca2+ channel current (both an increase and a decrease have been described, depending on the presence of the agonist BAY K-8644) [31] and to abolish, at the single channel level, the potassium channel opener-induced increase in the Ca2+-activated K+ channel [32]. In contrast, in isolated smooth muscle cells from rabbit portal vein glibenclamide did not affect the Ca2+-activated K+ channel [33]. In the same preparation glibenclamide inhibited the potassium channel opener-induced block of the oscillatory outward current [33]. This current is believed to be elicited by Ca2+ release from an intracellular store. The modulating effects of both the potassium channel opener pinacidil and glibenclamide suggest an effect on the kinetics of calcium release from these stores, which putatively represent the sarcoplasmatic reticulum (SR). A similar con-

2. Effects on membrane currents

There can be no doubt that sulfonylurea derivatives effectively block myocardial K.ATP channels. The most widely used representative glibenclamide (glyburide) is one of the most potent sulfonylureas [18]. Clinically, in patients on glibenclamide a wide concentration range is encountered (0–1.5 μM/L; mean 0.5 μM/L) [19]. In vitro experiments on isolated guinea-pig and rat ventricular
clusion has been reached by Chopra et al. who described a direct action of KATP channel modulators (including glibenclamide in concentrations > 1 μM) on intracellular calcium stores in cultured airway smooth muscle of the rabbit [34]. Indeed, in skeletal muscle Ca2+ transport across the SR membrane is influenced by the state of K+ channels in the SR membrane [35]. KATP channels may be involved in this process.

3. Effects on myocardial energy metabolism

Sulfonylureas affect myocardial energy metabolism. In aerobic rat hearts tolbutamide (in clinically relevant dosages) markedly stimulated glycogenolysis, glucose uptake and utilization and at the same time decreased fatty acid metabolism [36,37]. The latter effect is due to direct inhibition of mitochondrial carnitine palmitoyltransferase, which is the key regulatory enzyme in fatty acid oxidation [38]. Alternatively, it may be speculated that blockade of mitochondrial KATP channels, with, compared to the sarcosomal KATP channel, roughly similar affinity for sulfonylureas [4], is involved. As a result of stimulation of anaerobic glycolysis lactate production is increased, prior to any metabolic challenge [39,40], and within 30 min glycogen levels may decrease by 30% [36,37]. Due to these effects the contribution of glucose metabolism to ATP synthesis is greatly enhanced by tolbutamide [36,37]. These effects, which are independent of insulin, are even more pronounced in diabetic hearts [37].

Observations that lactate production is inhibited during myocardial hypoxia [20] and myocardial ischemia [41] may reflect the reduced glycan content prior to the experimental event.

4. Impact on sulfonylurea action during metabolic inhibition

Glibenclamide-sensitive effects during metabolic inhibition include hypoxia- and ischemia-related action potential shortening, a rise in the extracellular potassium concentration ([K+]o), a decrease in incidence of arrhythmias and the occurrence of preconditioning. The question now to address is whether it is possible that the sulfonylurea-induced effects on membrane currents other than the KATP channel or on myocardial glucose and free fatty acid metabolism are of any relevance to these effects. It may be argued that the relatively high concentrations needed to affect other currents preclude any non-KATP channel mediated effect. However, as mentioned before, with regard to the blocking efficacy of glibenclamide, it has been shown that intracellular pH sensitizes the channel to glibenclamide [25]. Similar effects might be present for any other sulfonylurea-mediated effect.

Particularly the shortening of the action potential and the increased K+ efflux are widely believed to result from hypoxia/ischemia-induced activation of KATP channels. This belief is almost exclusively based on the sulfonylurea sensitivity of these phenomena (see Refs. [16] and [42]). However, for example, with regard to the hypoxia-induced action potential shortening a variety of other currents might be involved, including Icl, cAMP as has been suggested previously [43]. Indeed, modulation of the extracellular chloride concentration and addition of chloride channel blockers (which are devoid of any effect on the KATP channel current) attenuate the early hypoxia-induced shortening of the action potential [44]. Hence, potentially the glibenclamide-induced blockade of Icl, cAMP may be involved in the attenuation of the hypoxia-related action potential shortening. The observation that the forskolin-induced shortening of the action potential is reversed by glibenclamide [27] corroborates this suggestion. The 3–6-fold difference in effective blocking concentration would preclude glibenclamide-induced block of Icl, cAMP being involved, but these values have been obtained in normoxic conditions. Although in later stages of metabolic deprivation the glibenclamide KATP channel block becomes less efficient [20,26], no information is available on the blocking efficacy of other currents in similar conditions. We have previously noted that the observed time-delay for the channel to open in response to hypoxia [45], ischemia [46] or metabolic inhibition [47] is indeed difficult to reconcile with involvement of KATP channels in early action potential shortening [42].

In addition to theoretical considerations precluding a causative role for any K+ channel in determining increased K+ efflux, the latter arguments also hold for a potential role of KATP channels in explaining increased K+ efflux [42]. Further, the observation that glibenclamide might prevent hypoxia-induced K+ efflux by ±50%, which occurred in the absence of any change in action potential duration, also suggests that the sulfonylurea effect on K+ efflux is not related to KATP channels [48]. Pivotal to an alternative explanation for the sulfonylurea-induced effects on K+ accumulation might be the reduced levels of glyco- gen after pretreatment with sulfonylurea derivatives (see above). Such an effect will reduce glycolytic activity during the subsequent ischemic episode. This may result in less lactate production and in less intracellular acidification. Attenuation of intracellular acidification has been shown to be associated with less K+ accumulation [49]. Indeed, ischemia-induced [41] and hypoxia-induced lactate efflux [20] has been reported to be attenuated after glibenclamide pretreatment and we have observed an inverse linear relationship between the pre-ischemic lactate production by glibenclamide and the effect on extracellular potassium [Wilde et al., unpublished observations]. In addition, 3P-nuclear magnetic resonance spectroscopy during
global ischemia in glycogen-depleted hearts (by other means, including which preconditioning) revealed less intracellular acidification than in control hearts [50,51]. Extracellular acidification is not affected by glibenclamide in a variety of species where it does attenuate the ischemia-induced early rise in extracellular potassium [40], but this might well be a too crude measure for (anaerobic) glycolytic activity. Lactate has been shown to reduce action potential duration [52], which in itself may involve K.ATP channel activation [53]. Hence, the sulfonylurea-induced decrease in lactate efflux may serve as an alternative explanation for the related attenuation of action potential shortening.

The favorable effects of sulfonylureas on the arrhythmias during acute ischemia may relate to attenuation of the action potential shortening and the attenuation of the rise in \([K^+]_o\). Particularly slowing of conduction, which is closely related to \([K^+]_o\), is considered to play a key role in arrhythmogenesis in early ischemia.

With regard to preconditioning, two sulfonylurea-induced effects can be regarded as seriously confounding factors in explaining the modulatory effects of preconditioning: (1) the effects on metabolism discussed above and (2) the possible modulation of adenosine release, which seems to be a critical mediator of preconditioning. In general, preconditioning, which also leads to reduced glycogen content prior to the index ischemic period, is abolished by sulfonylureas (see Ref. [10]). Pre-ischemic reduction in glycogen content protects the heart from subsequent prolonged ischemia, in terms of myocardial injury (i.e., preconditioning) [54]. However, the concomitant sulfonylurea-induced prolonged action potential during ischemia may outweigh this effect and therefore not lead to attenuation of ischemic damage. Finally, glibenclamide has been shown to influence adenosine release. Experimental results are controversial; ischemia-related adenosine release in rabbits was not influenced by glibenclamide [55], but in rats the 5'-nucleotidase-mediated adenosine release was reduced by glibenclamide (in a concentration-dependent manner; EC_{50} = 10 \mu M) [56]. Because the adenosine release during ischemia invoked in the occurrence of preconditioning is mediated by the enzyme 5'-nucleotidase [57], any sulfonylurea effect on this pathway will have an impact on preconditioning.

In summary, in addition to blocking K.ATP channels there are many other effects of sulfonylureas. Since these effects might have impact on, probably all, ischemia-related events, the suitability of these drugs for assessment of involvement of cardiac K.ATP channels has been seriously questioned. Careful selection of the concentration might provide useful information. However, in the absence of relevant data on, for example, the blocking efficacy of glibenclamide on other currents in pathophysiological conditions, the statement that sulfonylureas cannot be used at all to serve this purpose might even be correct. Likewise, the use of glibenclamide to prove involvement of K.ATP channels in vascular smooth muscle has been questioned [58].

5. NIDDM, sulfonylurea derivatives and cardiac disease

NIDDM patients are at increased risk of cardiovascular morbidity and mortality [59,60]. In these patients sulfonylureas have always been the cornerstone of oral therapy [61], despite the early report of the University Group Diabetes Program which suggested an association between tolbutamide therapy and an increased risk of cardiovascular mortality [62]. However, shortly after its appearance this report became extensively criticized for methodological and statistical reasons [63–65]. The results of 7 other epidemiological studies performed in the 1970s were contradictory and not conclusive either [66]. Later Rytter et al. retrospectively compared patients with IDDM to those with NIDDM with respect to the prevalence and mortality of acute myocardial infarction [60]. They found a significantly higher mortality rate from acute myocardial infarction in NIDDM patients treated with oral hypoglycemic agents than in NIDDM patients treated with insulin (50 vs 9.1%; distribution of hypoglycemic agents not specified). This difference could not be explained by better in-hospital metabolic control in the insulin-treated patients. However, the pre-hospital metabolic state, a determinant of outcome in this study, was not reported for the two groups [60]. In another analysis of diabetic patients presenting with myocardial infarction, sulfonylurea treatment did not influence hospital outcome in terms of morbidity (pump failure) and mortality [67]. In this study prior metabolic control, assessed by glycylated glucose, did not predict outcome either. Finally, Ulvenstam et al. reported on the long-term follow-up of diabetic men who survived a first myocardial infarction [68]. Only a trend towards a higher mortality among patients treated with sulfonylureas compared to those on insulin (IDDM an NIDDM) was found [68]. The interpretation of the results concerning the subgroups mentioned above is hampered by the small number of patients and the lack of sufficient data on clinical variables, such as metabolic control, infarction size and concomitant treatment.

The discovery of the mode of action of sulfonylureas (blockade of pancreatic B-cell K.ATP channel) and of the presence of K.ATP channels in the heart and vascular tissue eventually gave rise to new discussions on the clinical implications of the use of these agents in cardiovascular patients [15–17]. These discussions were largely based on experimental data showing significant interaction of sulfonylureas with the cardiovascular system. Most of these, predominantly negative, data have been reviewed by Smits and Thien [17] and by Leibowitz and Cerasi [15] and will not be repeated here. We will focus on studies evaluating the (direct) cardiovascular effects of sulfonylureas in man. In reviewing these data the principle interest is not
whether the sulfonylurea-related effects are mediated by K-ATP channel block or not. As argued by Smits and Thien [17], plasma sulfonylurea concentrations in man on chronic treatment may well be sufficient to block vascular and cardiac K-ATP channels.

6. Direct cardiovascular effects of sulphonylureas in man

6.1. Vascular tone

Whereas in different experimental models sulfonylureas have been shown to interfere with coronary vascular smooth muscle relaxation, there are no such data in man. In a study by Nahser et al. [69], evaluating maximal coronary flow reserve and metabolic coronary vasodilation in diabetic and non-diabetic patients, no difference was found between diabetic patients on insulin treatment and those on sulfonylurea derivatives. This study, however, was not designed to investigate the effects of these agents on coronary flow characteristics. Furthermore, on the day of the experiment oral hypoglycemic agents were withheld, probably resulting in serum levels too low to elicit any effect.

More data are available on the peripheral vascular effects of sulfonylureas in man. The acute effects of glibenclamide on baseline flow and hyperemic response to arterial occlusion in the human calf were studied recently [70]. After oral ingestion of 7.5 mg glibenclamide there was a significant decline in baseline flow (30 and 42% of control value after 1 and 2 h) and in peak reactive flow (22, 30 and 28% of control value after 1, 2 and 3 h), and an increase in the duration of the hyperemic response after 2 and 3 h. Total reactive hyperemic volume was not significantly influenced by glibenclamide. Placebo did not cause significant changes in any of these parameters [70]. In another study it was demonstrated that the vasodilator effect of diazoxide was significantly reduced by concomitant infusion of glibenclamide [71]. An important finding in these two studies is the fact that glibenclamide is able to elicit measurable vascular effects at therapeutic serum levels (250 ng/ml = 0.5 μM) [19,72]. Taking into account the high degree of binding to serum albumin (> 99%) [73], the serum levels of free glibenclamide in these studies were lower than the threshold value for inhibition of the effect of potassium channel openers on vascular activity (25 ng/ml = 0.05 μM) in the experimental model [74]. These findings [70,71] might have clinical implications for NIDDM patients with coronary disease treated with sulfonylureas. However, it should be emphasized that these studies dealt with healthy volunteers and that there might be different sensitivities for glibenclamide in coronary and peripheral smooth muscle K-ATP channel receptors. In addition, by design only the acute effects of the drugs were investigated, but it has been demonstrated that glibenclamide induced an increase of the relative changes in systemic vascular resistance index also after 4 weeks of treatment whereas metformin, a biguanide, unrelated to sulfonylureas, had no effect [75].

6.2. Myocardial ischemia and preconditioning

Although the effect of sulfonylureas at therapeutic levels on the human coronary vasculature remains to be determined, some evidence that human myocardium is sensitive to such levels of glibenclamide already exists. The oral administration of 10 mg glibenclamide, prior to the procedure, abolished the attenuation of ST-segment shift at a second balloon inflation during coronary angioplasty [76]. Inhibition of collateral circulation recruitment by glibenclamide as a possible explanation for this finding was very unlikely (based on angiographic assessment), suggesting a direct myocardial effect of glibenclamide on ischemic preconditioning. Also in an in vitro model using right atrial trabeculae glibenclamide prevented ‘ischemic’ preconditioning [77]. Since preconditioning is thought to protect the myocardium against subsequent ischemic events, resulting in less extensive myocardial infarction and better clinical outcome [78,79], the use of glibenclamide might have deleterious effects in patients with repetitive myocardial ischemia treated with this agent.

6.3. Arrhythmias

In various experimental models of acute ischemia pre-treatment with sulfonylureas proved antiarrhythmic during myocardial ischemia [16]. Clinical data seem to corroborate these results. In a randomized crossover study in NIDDM (glibenclamide versus metformin), glibenclamide significantly reduced the incidence of ventricular premature complexes and ventricular tachycardia during (spontaneous) transient myocardial ischemia [80]. Glibenclamide did not alter the ischemic burden nor did it interfere with non-ischemia-related arrhythmias [80]. In a study on NIDDM patients suffering from acute myocardial infarction, ventricular fibrillation (VF) occurred significantly less frequently in the glibenclamide-treated group than in NIDDM patients treated otherwise and than in non-diabetics (1.7 vs 7.9 and 9.9%, respectively) [81]. Although demographic, clinical and treatment parameters were comparable in the three groups, there was a much higher mortality rate in the non-glibenclamide treated diabetic patients, which was related to the higher incidence of heart failure in this group [81]. This finding suggests the presence of an unknown confounder, prompting cautious interpretation of the data from this study. On the other hand, recently presented data from a large retrospective study on patients with acute myocardial infarction, similarly showed that the rate of VF in patients on glibenclamide was lower than that for diabetics on gliclazide or insulin [82]. In this study, in contrast to the former study [81], VF rate was the same as that of non-diabetics [82].
Studies involving first-generation sulfonylureas in diabetics with an acute myocardial infarction provided variable results. A trend towards a higher incidence of early VF was shown in diabetics on oral treatment (mainly sulfonylureas), as compared to those treated with insulin or diet alone (12 vs 3 and 7%, respectively) [83]. In a similar study comparing these three groups no difference in primary VF incidence was observed at all [84]. In both studies time from onset of symptoms to hospital admission, a critical factor when it comes to the incidence of primary VF, was however not reported.

6.4. Other effects

Some investigators reported a positive inotropic effect of sulfonylureas [85,86], whereas others failed to confirm this finding [87,88]. In vitro studies showed evidence for beneficial effects of certain sulfonylurea derivatives on cardiovascular risk factors such as platelet aggregation and fibrinolysis [15,66]. However, the clinical relevance of these effects is unclear.

7. Summary

In summary, the most consistent finding concerning the cardiac effects of sulfonylurea derivatives in NIDDM with ischemic heart disease is the lower incidence of ventricular arrhythmia associated with the use of glibenclamide, while no excess mortality has been shown for this agent. The effect of blockade of myocardial preconditioning by this agent has still to be evaluated with respect to clinical end-points. It should be noted that in the older studies an excess of cardiovascular mortality in diabetics using sulfonylureas was an inconsistent finding and that in those studies virtually only first-generation agents were used. Furthermore, the findings of those studies might not be applicable to current clinical practice. Based on the direct effects described above there are, at present, no firm clinical data on the basis of which sulfonylurea derivatives should be withheld from the cardiac patient.

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